Journal of Medicinal Chemistry

Article

pubs.acs.org/jmc

Structure–Activity Relationships and Pharmacophore Model of a Noncompetitive Pyrazoline Containing Class of GluN2C/GluN2D Selective Antagonists

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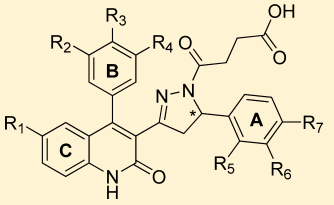
Supporting Information

ABSTRACT: Here we describe the synthesis and structure–activity relationship for a class of pyrazoline-containing dihydroquinolone negative allosteric modulators of the NMDA receptor that show strong subunit selectivity for GluN2C- and GluN2D-containing receptors over GluN2A- and GluN2B-containing receptors. Several members of this class inhibit NMDA receptor responses in the nanomolar range and are more than 50-fold selective over GluN1/GluN2A and GluN1/GluN2B NMDA receptors, as well as AMPA, kainate, GABA, glycine, nicotinic, serotonin, and purinergic receptors. Analysis of the purified enantiomers of one of the more potent and selective compounds shows that the *S*-enantiomer is both more potent and more selective than the *R*-enantiomer. The *S*-enantiomer had an IC_{50} of 0.17–0.22 μM at GluN2D- and GluN2C-containing receptors, respectively, and showed over 70-fold selectivity over other NMDA receptor subunits. The subunit selectivity of this class of compounds should be useful in defining the role of GluN2C- and GluN2D-containing receptors in specific brain circuits in both physiological and pathophysiological conditions.



INTRODUCTION

Glutamatergic neurotransmission through ionotropic glutamate receptors is the primary means of excitatory synaptic transmission in the mammalian central nervous system (CNS). The receptor family comprises the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA), *N*-methyl-D-aspartate (NMDA), and kainate receptors.[1,2] NMDA receptors are widely expressed in the CNS and are thought to be involved in a range of important physiological processes including axonal guidance, synaptic plasticity, and memory formation.[2−5] NMDA receptors are also thought to play an important role in pathophysiological conditions including Parkinson's disease, schizophrenia, depression, and ischemia.[2,6−8]

NMDA receptors mediate the slow component of excitatory synaptic transmission and require the binding of both glutamate and glycine for channel activation. Glycine binds to the GluN1 subunits, which have eight splice variants encoded by a single gene.[9−11] The GluN2 subunits (GluN2A–D) bind glutamate and are encoded by four distinct genes.[12] The GluN2 subunits control many of the functional and pharmacological properties of the receptor, including agonist EC_{50}, single channel open time and open probability, and deactivation time course following removal of glutamate.[2,13−17] NMDA receptor deactivation time course determines the time course for the slow, Ca^{2+}-permeable component of synaptic transmission.[18] Typically, NMDA receptors are blocked by extracellular Mg^{2+} at resting membrane potentials, and the requirements of the glutamate release and depolarization-induced relief of Mg^{2+} block have led to the idea that the NMDA receptors act as coincidence detectors in the brain.[19,20] The Mg^{2+} IC_{50} and the kinetics of block and unblock also vary according to the GluN2 subunit.[21]

The GluN1 subunits are expressed throughout the CNS, but GluN2 subunit composition and expression vary during development and anatomically.[8,22−28] The spatially restricted expression patterns, together with distinct functional and pharmacological differences imparted by the GluN2 subunits, make NMDA receptor subunit selective modulators of therapeutic interest for several neurological disorders, including stroke, schizophrenia, treatment-resistant depression, and Parkinson's disease.[7,8,25,29] Subunit selectivity will restrict modulator actions to brain regions that express the subunit of interest, potentially limiting side effects that occur as a result of global NMDA receptor blockade.

We previously have described the discovery, preliminary SAR of 25 compounds, and pharmacological mechanism of a representative member of the dihydroquinolone pyrazoline (DQP) class of GluN2C/D subunit-selective antagonists.[30] In our previous study, the most potent analogue, DQP-1105, had an IC_{50} of 2.7 μM at GluN2D-containing NMDA receptors and was 41-fold selective over GluN2B-containing receptors (Figure 1A).[30] In this report we provide an extensive exploration of the

Received: May 2, 2013

dx.doi.org/10.1021/jm400652r | J. Med. Chem. XXXX, XXX, XXX–XXX

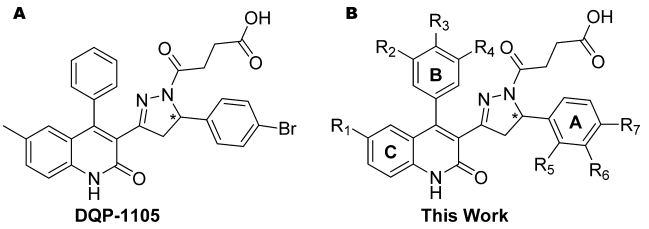


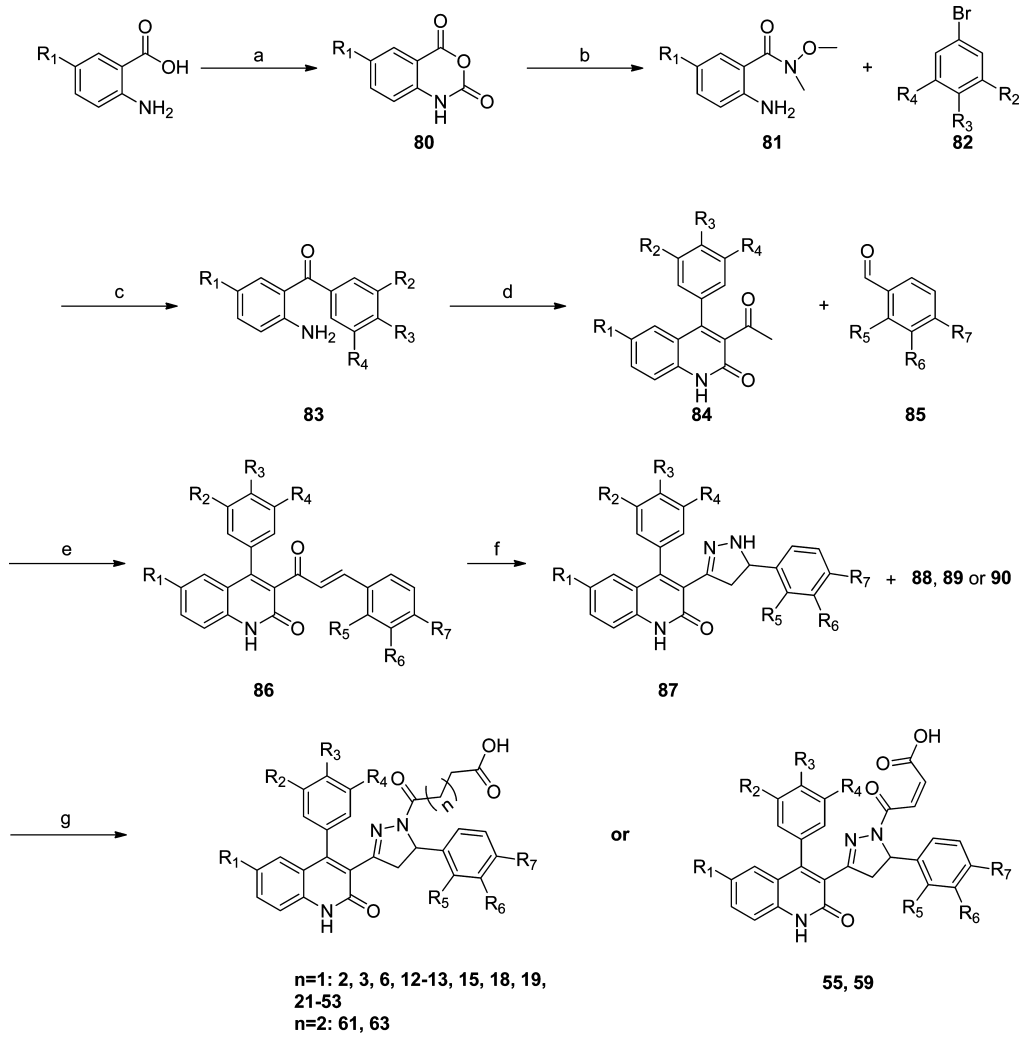
Figure 1. Previously reported best-in-class compound and representative structure for SAR: (A) structure of previously reported representative compound DQP-1105;[30] (B) structure of a general analogue with numbered substituents.

SAR, confirmation of mechanism of action, off-target analysis, an analysis of the stereoselectivity for a representative member of the class, and data regarding metabolic stability and potential for blood–brain barrier (BBB) penetration. These efforts have yielded potent and selective analogues as well as insights into the pharmacophore for these pyrazoline-containing compounds.

RESULTS

Chemistry. The structure–activity relationship around the quinolone pyrazoline core was probed by testing the potency and selectivity of analogues that contained a variety of aromatic substitutions in combination with perturbations of the acyl chain moiety (Figure 1B). A representative synthesis of these analogues is shown in Scheme 1. Briefly, anthranilic acids were reacted with triphosgene under standard conditions to yield the isatoic anhydride derivatives **80**. These compounds were then converted, via the Weinreb amide **81** and a subsequent lithium halogen exchange reaction with aryl bromides **82**, to the appropriate benzophenones, **83**.[31] The substituted quinolone core was accessed by condensation of **83** with ethyl acetoacetate using microwave irradiation, yielding compound **84**. The resultant methyl ketone underwent base-catalyzed condensation with an appropriate arylaldehyde, **85**, yielding the α,β-unsaturated ketone compounds **86**. These intermediates could be treated with hydrazine monohydrate in ethanol, utilizing microwave irradiation, to yield the pyrazoline-containing compounds typified by **87**. The pyrazoline amine was then functionalized with succinic anhydride (**88**), glutaric

Scheme 1. Synthesis of Dihydroquinolone Pyrazoline Derivatives[a]



[a](a) Anhydrous THF, triphosgene (warning, triphosgene is toxic; see Experimental Section), reflux; (b) EtOH, Weinreb's HCl salt, reflux; (c) anhydrous THF, *n*-butyllithium, −78 °C; (d) ethyl acetoacetate, DMF, 4 Å molecular sieves, 180 °C, microwave; (e) 4:3 EtOH/H_2O (0.05 M), 0 °C to rt; (f) hydrazine monohydrate, EtOH, 110 °C, microwave; (g) anhydrous THF, 4 Å molecular sieves, 165 °C, microwave.

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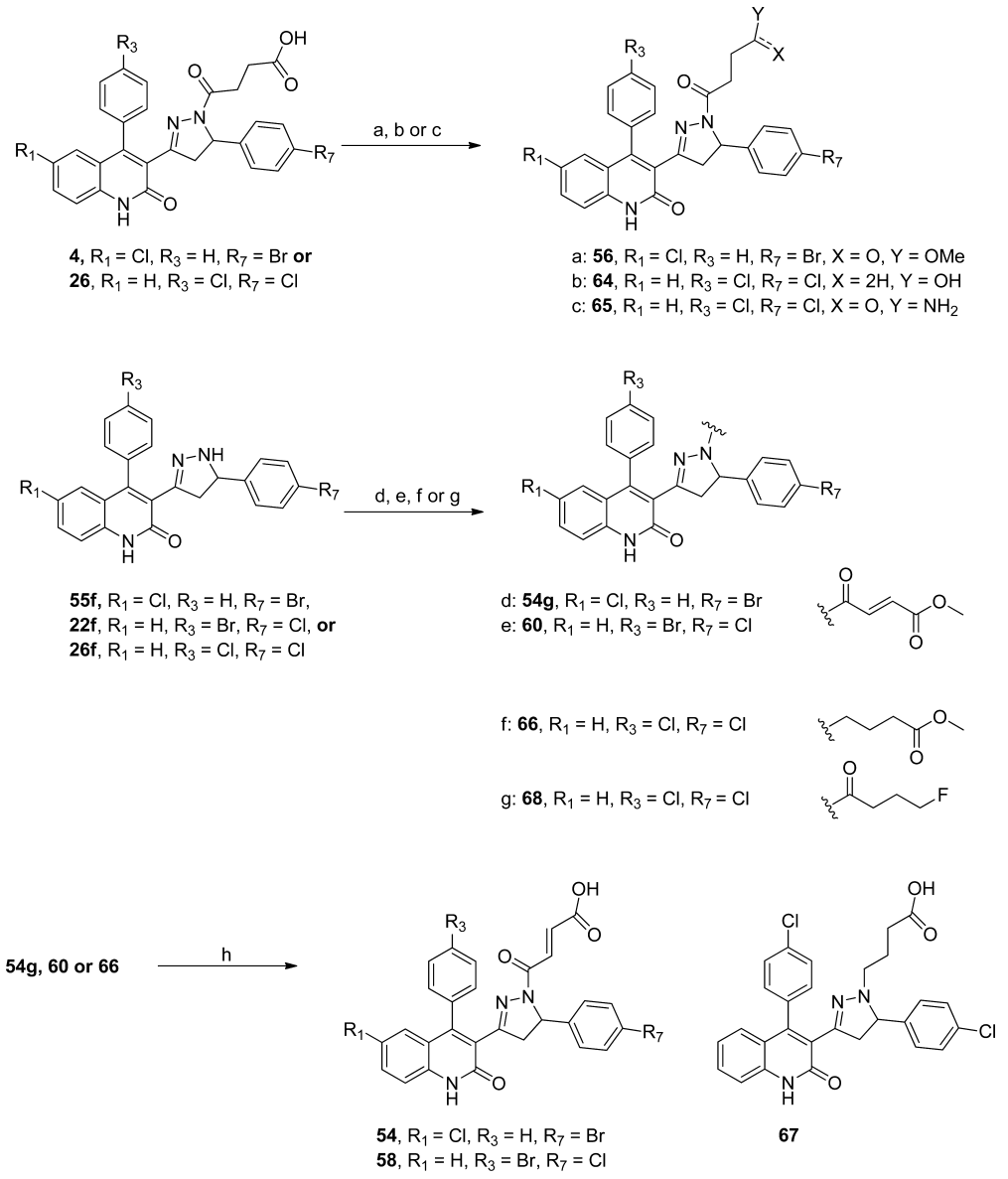
Scheme 2. Modifications to the Acyl Chain[a]



[a](a) HCl, MeOH; (b) BH_3−Me_2S, anhydrous THF, 0 °C; (c) EDCI, DMAP, NH_3 in dioxane (0.5M), THF; (d) EDCI, DMAP, (*E*)-4-methoxy-4-oxobut-2-enoic acid; (e) anhydrous THF, (*E*)-methyl 4-chloro-4-oxobut-2-enoate, 4 Å molecular sieves, 165 °C, microwave; (f) methyl 4-oxobutanoate, BH_3−Me_2S, THF; (g) EDCI, DMAP, 4-fluorobutanoic acid, DCM; (h) NaOH, EtOH/H_2O.

anhydride (**89**), or maleic anhydride (**90**) to yield the fully saturated or cis double bond acyl chain derivatives (Scheme 1).

Standard esterification conditions from compound **4** yielded the saturated monomethyl ester analogue **56** (Scheme 2). Reduction of the acid in compound **26** with BH_3−DMS led to the primary alcohol containing compound, **64**; a coupling reaction with compound **26** and NH_3 gave the primary amide compound **65** (Scheme 2). The unsaturated fumaric esters could be accessed under standard amide coupling conditions using (*E*)-4-methoxy-4-oxobut-2-enoic acid and compound **55f**, yielding compound **54g**, or with acylation of **22f** using (*E*)-methyl 4-chloro-4-oxobut-2-enoate, yielding compound **60** (Scheme 2). Additionally, the acyl chain was replaced with the alkyl chain by reacting the pyrazoline derivative **26f** and methyl 4-oxobutanoate under reductive amination conditions to give compound **66** (Scheme 2). Monofluorobutyrate **68c** (Scheme S1) was synthesized in three steps and also coupled to compound **26f**, yielding **68** as an isostere of the hydroxyl-containing compound **64** (Scheme 2).[32,33] The ester containing compounds **54g**, **60**, and **66** could be saponified under basic conditions yielding the target scaffolds **54**, **58**, and **67** (Scheme 2). All compounds were assayed for activity using two-electrode voltage clamp recordings from *Xenopus laevis* oocytes recombinantly expressing the desired NMDA receptor subtypes (see Experimental Section).

A-Ring Substituent Optimization. We first evaluated the effect of substituents on the A-phenyl ring (Figure 1B) by holding the chlorine substitution on the quinolone core constant and evaluating the substitutions shown in Table 1 and Table S1. At the A-ring, 4-substituted phenyl derivatives resulted in the best potency and selectivity. This observation led to the identification of **5** (Table 1), with a nitro group at R_7, which was the most potent para-substituted analogue at GluN2D-containing receptors compared to the unsubstituted

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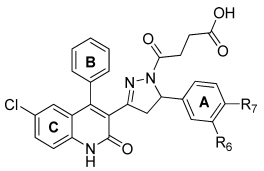
Table 1. Evaluation of A-Ring Para and Ether Substitutions[a]



					IC_{50} (μM)			
DQP	R_6	R_7	(2A IC_{50})/(2D IC_{50})	(2B IC_{50})/(2D IC_{50})	GluN2A	GluN2B	GluN2C	GluN2D
1	H	H			NE	NE	86	88
2	H	F	9	6	128	87	23	14
3	H	Cl			NE	NE	5.5	4.5
4	H	Br		7	NE	22	3.6	3.1
5	H	NO_2	85	42	91	45	0.9	1.1
6	H	COOH			NE	NE	NE	NE
7	H	COOMe			NE	NE	93	32
8	H	CF_3	20	13	80	54	5	4.1
9	H	OMe	9	9	197	187	28	21
10	H	NMe_2			NE	NE	39	19
11		-OCH_2O-		4	NE	90	23	23

[a]IC_{50} values were obtained by fitting the Hill equation to the average composite concentration−effect curves (see Experimental Section). Data are from 7−18 oocytes between 2−4 frogs. NE indicates less than 30% inhibition at 100 μM.

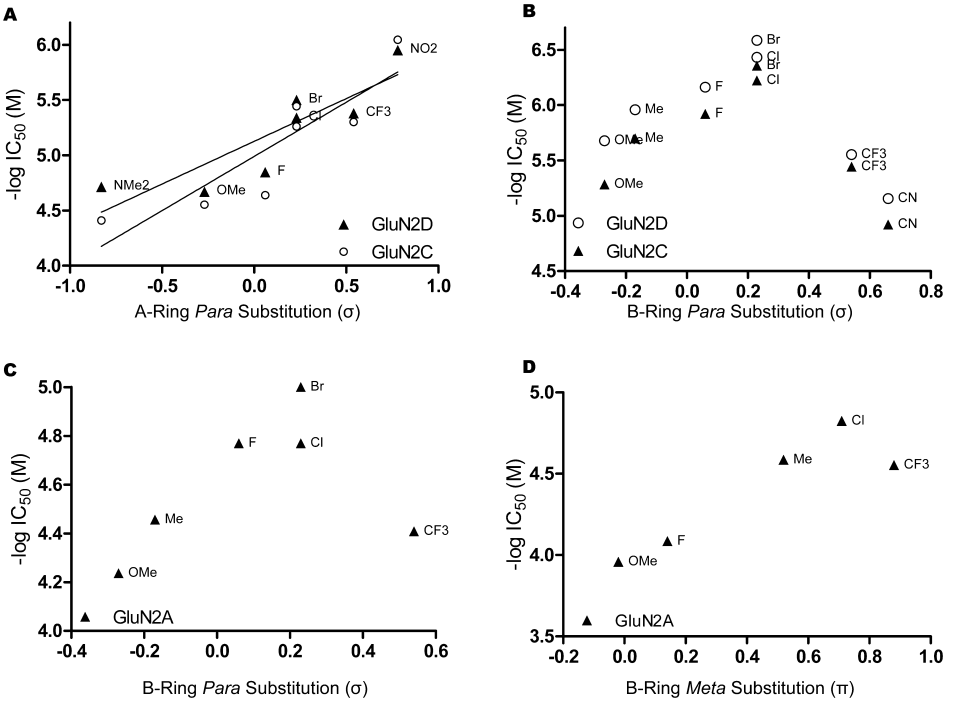


Figure 2. Evaluation of substituent effects for A- and B-ring modifications. (A) The σ substituent constants of the para-substituted A-ring analogues vs activity show a correlation for GluN2C- and GluN2D-containing receptors, when the R_1 position of the C-ring is substituted with chloro: GluN2D $r^2 = 0.82$, $p < 0.05$ Pearson two-tailed correlation analysis; GluN2C $r^2 = 0.84$, $p < 0.05$ Pearson two-tailed correlation analysis; compounds **2**−**5** and **8**−**10**). (B) The analysis of the para-substituents on the B-ring as a function of activity at GluN2C- and GluN2D-containing receptors appears parabolic with respect to the σ substituent constants, with an optimal value close to that of the chloro and bromo substitutions (compounds **29**−**33**). (C) The analysis of the para-substituents at GluN2A-containing receptors shows a similar parabolic relationship as observed at the GluN2C- and GluN2D-containing receptors when the activity is plotted as a function of the σ substituent constants (compounds **29**−**33**). (D) The analysis of the substituent effects appears parabolic with respect to the π substituent constants for B-ring meta-substituted compounds at GluN2A-containing receptors, suggesting an optimal hydrophobicity close to that of the chloro substitution. Substituent constants were obtained from the same source (compounds **34**−**39**).[35]

A-ring, compound **1** (1.1 μM vs 88 μM, respectively, Table 1). Realizing the substantial liabilities associated with the nitro group, we explored bioisosteres of the substitution, replacing this group with a carboxylic acid **6** (Table 1) which showed no activity. By contrast, the methyl ester **7** (Table 1) remained active but had decreased potency at GluN2D-containing receptors (32 μM vs 1.1 μM). Interestingly, sp^3 hybridization is tolerated but not preferred, as can be seen with the

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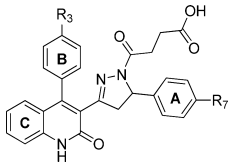
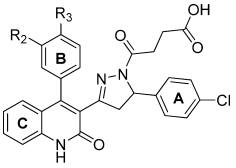
Table 2. A- and B-Ring Modifications[a]



					IC_{50} (μM)			
DQP	R_3	R_7	(2A IC_{50})/(2D IC_{50})	(2B IC_{50})/(2D IC_{50})	GluN2A	GluN2B	GluN2C	GluN2D
21	Br	Br	33	59	13	23	0.71	0.39
22	Br	Cl	34	79	10	23	0.56	0.29
23	Br	F	12	26	34	75	3.8	2.9
24	Br	H	7	12	64	113	10	9.1
25	Cl	Br	37	67	19	34	0.95	0.51
26	Cl	Cl	48	50	21	22	0.77	0.44
27	Cl	F	14	26	47	90	4.1	3.4
28	Cl	H	4	13	49	143	13	11

[a]IC_{50} values were obtained by fitting the Hill equation to the average composite concentration−effect curves (see Experimental Section). Data are from 8−18 oocytes between 2−3 frogs. Compound **26** is shown in Table 4 for comparison.

Table 3. B-Ring Modifications[a]



					IC_{50} (μM)			
DQP	R_2	R_3	(2A IC_{50})/(2D IC_{50})	(2B IC_{50})/(2D IC_{50})	GluN2A	GluN2B	GluN2C	GluN2D
29	H	F	36	98	21	57	1.0	0.58
26	H	Cl	48	50	21	22	0.77	0.44
30	H	Me	24	30	33	42	2.5	1.4
31	H	OMe	27	33	62	75	5	2.3
32	H	CN	22		156	NE	12	7
33	H	CF_3	10	14	29	39	3.6	2.8
34	F	H	67	101	46	70	1.1	0.69
35	Cl	H	20	43	20	43	2.1	1.0
36	Me	H	13	37	24	71	4.0	1.9
37	OMe	H	24	34	110	152	7.8	4.5
38	CN	H			NE	NE	19	13
39	CF_3	H	11	18	28	47	3.4	2.6

[a]IC_{50} values were obtained by fitting the Hill equation to the average composite concentration−effect curves (see Experimental Section). Data are from 6−14 oocytes between 2−3 frogs. NE indicates less than 30% inhibition at 100 μM. Data for **26** are presented in Table 2 and repeated here to facilitate comparisons with data.

trifluoromethyl-containing compound **8** (IC_{50} = 4.1 μM, GluN2D, Table 1). Although substitution at any of the three available positions on the A-ring is tolerated, substitution at either the R_5 or R_6 position showed no improvement in potency or selectivity with any of the analogues tested (**12**−**20**, **71**; Table S1). Similarly, analogues with the A-ring replaced with furan, thiophene, and pyridine substituents were evaluated and were inactive (Table S2).

A manual Hansch analysis, similar to that of the Topliss approach, was employed to better understand the physicochemical properties governing potency.[34] Analysis of the steric, σ, and π substituent effects for the A-ring suggests that only the para-σ contribution is directly associated with the IC_{50} values at the GluN2C- and GluN2D-containing NMDA receptors (compounds **2**−**5** and **8**−**10**, Table 1 and Figure 2A).[34,35]

B-Ring Substituent Optimization. We next modified the B-ring substituents with the aim of understanding the substituent effects at the meta- and para-positions (Figure 1B).[34] The *p*-bromo substitutions at the A- and B-rings in compound **21** showed enhanced potency at GluN2C- and GluN2D-containing receptors, with IC_{50} values of 0.71 and 0.39 μM, respectively (Table 2). Interestingly, this compound also showed less selectivity for GluN2D- over GluN2A-containing receptors (33-fold) compared to GluN2B-containing receptors (59-fold), suggesting that a more favorable interaction with GluN2A-containing receptors had been formed (Table 2).

Co-varying A-ring para-substituents with the *p*-bromo B-ring substitution allowed us to determine that the *p*-chloro A-ring substitution was optimal for potency (**22**−**24**, Table 2). A similar trend was observed using the *p*-chloro substitution on the B-ring while co-varying the A-ring substituents (**25**−**28**,

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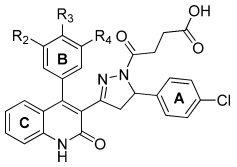
Table 4. B-Ring Disubstitution[a]



						IC_{50} (μM)			
DQP	R_2	R_3	R_4	(2A IC_{50})/(2D IC_{50})	(2B IC_{50})/(2D IC_{50})	GluN2A	GluN2B	GluN2C	GluN2D
40	F	Cl	H	23	53	12	28	0.91	0.53
41	Cl	F	H	19	34	19	34	1.4	1.0
42	Cl	Cl	H	8	22	7.7	20	0.79	0.91
43	F	F	H	32	108	21	71	0.78	0.66
44	F	H	F	26	123	21	100	1.1	0.81
45	Cl	H	Cl	8	19	5.5	13	0.78	0.70

[a]IC_{50} values were obtained by fitting the Hill equation to the average composite concentration−effect curves from oocyte recordings (see Experimental Section). Data are from 8−15 oocytes between 2 frogs.

Table 2). Therefore, this *p*-chloro substitution on the A-ring was used for further SAR elaboration. We varied substituents at the meta- and para-position of the B-ring which identified numerous analogues that were highly potent and selective (Table 3). Notably, the *p*-fluoro containing compound **29** and the *m*-fluoro containing compound **34** were both potent congeners that showed over 90-fold selectivity for GluN2D- over GluN2B-containing receptors; compound **34** also showed 67-fold selectivity over GluN2A-containing receptors (Table 3).

The Hansch evaluation of the para-σ substituent effects at the B-ring shows a seemingly parabolic relationship when compared to potency for only GluN2A-, GluN2C-, and GluN2D-containing receptors (compounds **26** and **29**−**33**, Table 3, Figure 2B,C), with an optimal σ value corresponding to the bromo and chloro substitutions at all three receptors. At the meta-position of the B-ring, the correlation between the potency and the hydrophobic π value for substitutions also appears parabolic at GluN2A-containing receptors (compounds **34**−**39**, Table 3, Figure 2D). The decrease in potency at GluN2A-containing receptors observed with compound **39**, which was meta-substituted with the CF_3 group (Table 3 and Figure 2D), could be a result of steric clashes with the receptor or, as was observed with the para-σ substituents, could suggest that the optimal hydrophobicity at the GluN2A-containing receptors is attained with the *m*-chloro substitution.

From this analysis of meta- and para-substitutions, we hypothesized that combining an optimal para-substitution for potency at GluN2D-containing receptors with a meta-substitution that was less active at GluN2A-containing receptors might improve selectivity. Both Cl and F substitutions gave optimal potency and selectivity when monosubstituted on the B-ring, leading us to co-vary these groups (Table 4). We synthesized compound **40**, which has a *m*-fluoro and *p*-chloro substitution pattern on the B-ring. This compound maintained potency but did not increase selectivity (Table 4). Several other compounds that were disubstituted on the B-ring exhibited submicromolar potency at GluN2D-containing receptors, but all showed modest selectivity over GluN2A-containing receptors (**41**−**45**, Table 4).

C-Ring Substitutions with Optimized A- and B-Ring Substituents. We next made a series of substitutions to the C-ring on the quinolone core (Table S3). Beginning with a methyl group at R_1 (Figure 1B) in combination with either the *p*-chloro or the *m*-fluoro substitution on the B-ring, we synthesized compounds **46** and **47**, which decreased the potency compared to the more favorable compounds with only B-ring and A-ring substitutions (Table S3). Interestingly, the modifications showed variability with regard to the relative selectivity for GluN2A- over GluN2B-containing receptors, suggesting that there remains room in this portion of the binding pocket for potential optimization of selectivity (compounds **48**−**53**, Table S3).

Acyl-Chain Perturbations. We subsequently evaluated a series of perturbations to the acyl chain of the pyrazoline nitrogen (Table 5). Restricting the conformation to a cis-configuration with the maleate derivative maintained similar potency to the parent compound in each instance tested (**55** and **59** vs **4** and **22**, respectively, Table 5). The *trans*-configuration in the fumaric containing derivative **58** was the most potent compound identified but was no more selective over GluN2A- or GluN2B-containing receptors than the saturated derivative **22** (Tables 5 and 2). The succinic ester containing compound **56** was inactive, as was the fumaric ester **60** (Table 5). We also evaluated glutaric-containing derivatives such as compound **61** (Table 5), which showed potencies similar to that of the succinic derivative **22** (Tables 5 and 2) at all receptors tested, suggesting that the length of the acyl chain is not crucial for activity.

The primary alcohol containing compound **64** retained similar activity as that of the parent compound **26** at GluN2C- and GluN2D-containing receptors (IC_{50} of 1.7 and 0.69 μM, respectively) while improving selectivity over GluN2A-containing receptors to 90-fold (Table 5). The primary amide derivative of the succinate acyl chain in compound **65** retained activity but showed decreased potency and selectivity compared to the alcohol and acid moieties (Table 5). Replacing the amide linkage to the pyrazoline with the alkyl derivative in compound **67** slightly diminished potency at GluN2D-containing receptors over the parent compound **26** but maintained selectivity over the other receptor subtypes (Tables 5 and 2). The monofluoro isostere of the hydroxyl group in compound **64** was tested with compound **68** (Table 5). While this compound retained the ability to accept a hydrogen bond, it was inactive.

Stereochemical Preference of a Representative Analogue. Finally, we evaluated the selectivity and potency of purified enantiomers for a representative member of this class of compounds. The enantiomers of the racemic final product **26** were separable via reverse phase chiral chromatography

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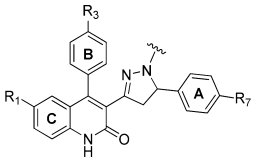
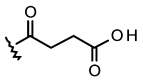
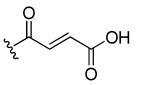
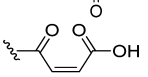
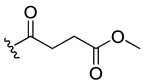
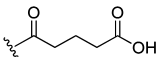
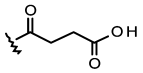
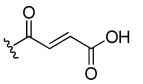
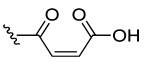
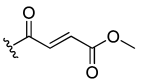
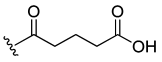
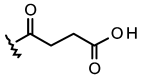
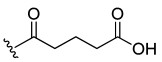
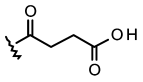
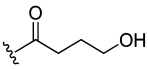
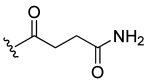
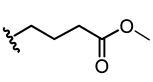
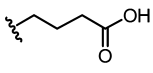
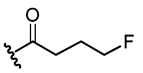
Table 5. Acyl Chain Perturbations[a]



DQP-	R_1	R_3	R_7	Acyl Chain	2A IC_{50} / 2D IC_{50}	2B IC_{50} / 2D IC_{50}	GluN2A IC_{50} (μM)	GluN2B IC_{50} (μM)	GluN2C IC_{50} (μM)	GluN2D IC_{50} (μM)
4	Cl	H	Br		-	7	NE	22	3.6	3.1
54	Cl	H	Br		-	-	NE	NE	2.1	1.4
55	Cl	H	Br		15	7	74	37	8.9	5
56	Cl	H	Br		-	-	NE	NE	NE	NE
57	Cl	H	Br		20	23	78	90	6.4	4.0
22	H	Br	Cl		34	79	10	23	0.56	0.29
58	H	Br	Cl		23	63	4.3	12	0.20	0.19
59	H	Br	Cl		21	30	12	17	1.0	0.57
60	H	Br	Cl		-	-	NE	NE	59	95
61	H	Br	Cl		33	91	10	29	0.6	0.32
5	Cl	H	NO_2		85	42	91	45	0.9	1.1
63	Cl	H	NO_2		10	8	109	92	10	11
26	H	Cl	Cl		48	50	21	22	0.77	0.44
64	H	Cl	Cl		90	48	62	33	1.7	0.69
65	H	Cl	Cl		31	18	34	20	2.0	1.1
66	H	Cl	Cl		-	-	NE	NE	NE	NE
67	H	Cl	Cl		34	31	58	53	3	1.7
68	H	Cl	Cl		-	-	NE	NE	NE	NE

[a]IC_{50} values were obtained by fitting the Hill equation to the average composite concentration−effect curves (see Experimental Section). Data are from 5−24 oocytes between 2−4 frogs. NE indicates less than 30% inhibition at 100 μM. Data for compounds **4**, **22**, **5**, and **26** were presented in preceding tables and are shown here for comparison.

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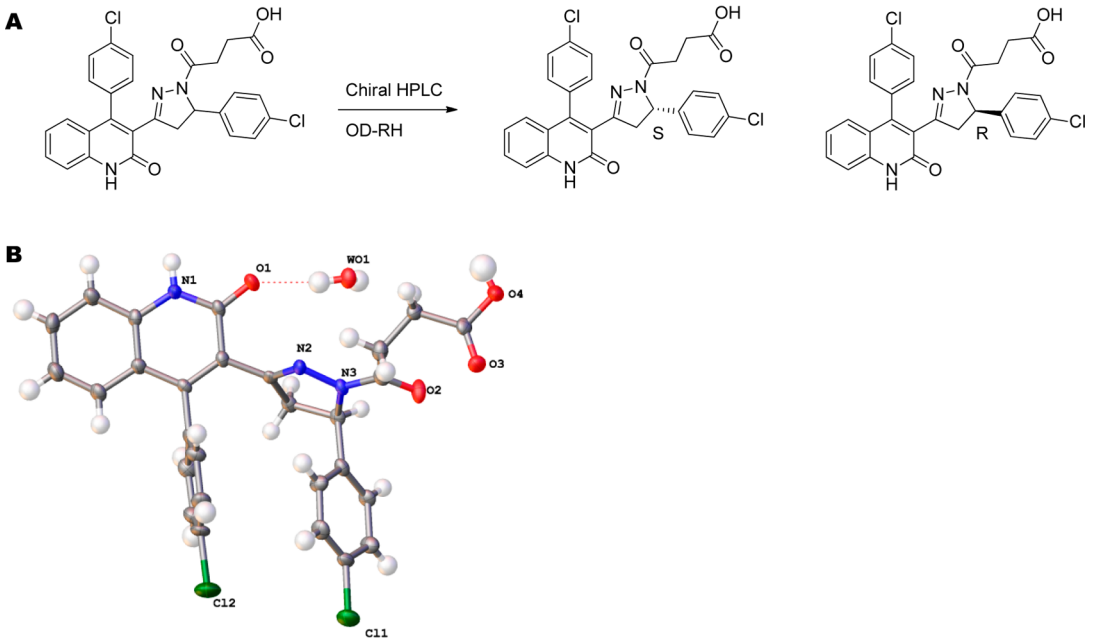

Figure 3. Separation of enantiomers. (A) The enantiomers of the final compound, **26**, could be separated using reverse phase chiral chromatography (see Experimental Section). (B) The crystal structure of the inactive enantiomer, **70** (Table 6), was solved using X-ray diffraction and has the *R* configuration.

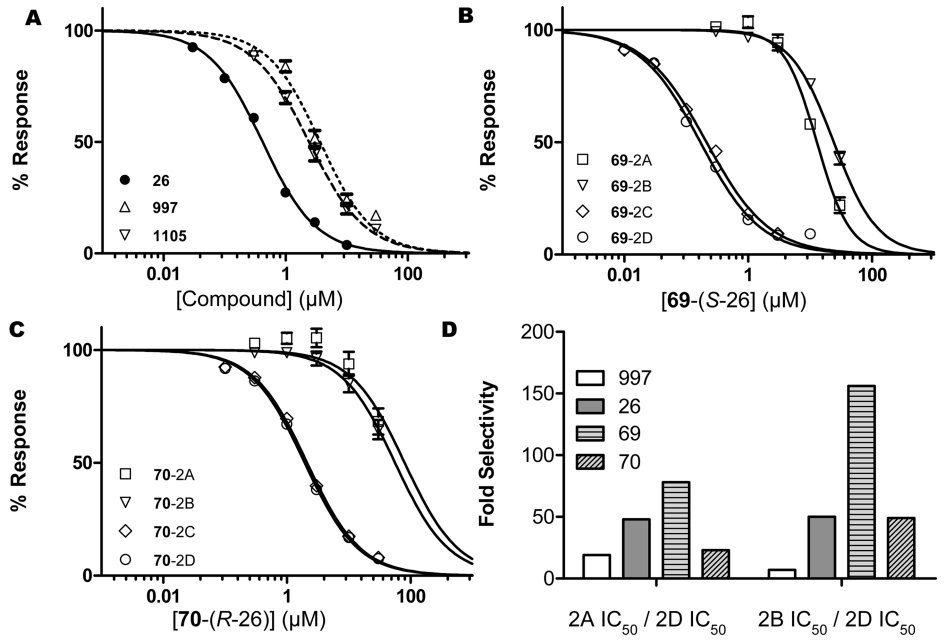

Figure 4. Improvements in selectivity and potency. (A) The potency of the racemic compounds at GluN2D-containing receptors was improved 10-fold over the previous members in the class. (B) The potency of the *S*-enantiomer of compound **26**, compound **69**, is 2-fold more potent than the racemic mixture at GluN2D-containing receptors, while the potency at GluN2A- and GluN2B-containing receptors is unaffected, making it more selective for GluN2C- and GluN2D-containing receptors. (C) The potency of the *R*-enantiomer of compound **26**, compound **70**, at GluN2C- and GluN2D-containing receptors is diminished compared to the racemate **26**, making it less selective over GluN2A- and GluN2B-containing receptors. (D) Bar graph showing the fold-selectivity improvements attained through SAR. Data for compounds **997** and DQP-1105 (A, D) are previously published and shown here for comparison.[30]

using an OD-RH column (Figure 3, see Experimental Section). Absolute stereochemistry of the second peak to elute during the enantiomeric resolution was assigned using X-ray crystallography as the *R*-enantiomer (**70**) (Figure 3, see Experimental Section). Evaluation of the purified enantiomers showed that the *S*-enantiomer (**69**) is 11-fold more potent at GluN2D-containing receptors (IC_{50} = 0.17 μM) than the *R*-enantiomer **70** (IC_{50} = 1.9 μM; Figure 4 and Table 6). In addition, **69** shows enhanced selectivity for GluN2C- and GluN2D- over GluN2A- and GluN2B-containing receptors compared to the racemic **26** and the *R*-enantiomer **70** due to the enhanced potency at the GluN2D-containing receptors (Figure 4 and Table 6).

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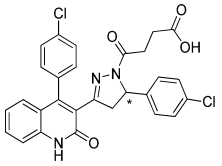
Table 6. Stereoselectivity for the Purified Enantiomers of Compound 26[a]



DQP	R_2	R_4	(2A IC_{50})/(2D IC_{50})	(2B IC_{50})/(2D IC_{50})	IC_{50} (μM) GluN2A	GluN2B	GluN2C	GluN2D
26	Cl	Cl	48	50	21	22	0.77	0.44
69 (*S*-**26**)	Cl	Cl	78	156	13	26	0.22	0.17
70 (*R*-**26**)	Cl	Cl	23	49	45	52	2.1	1.9

[a]IC_{50} values were obtained by fitting the Hill equation to the average composite concentration−effect curves (see Experimental Section). Data are from 8−17 oocytes between 2−4 frogs. Data for compound **26**, which were presented in preceding tables, are shown here for comparison.

Table 7. Off-Target Responses for Compounds 26 and 58[a]

receptor	agonist (μM)	**26** $I_{test}/I_{control}$ (mean ± SEM, %)	**26** *N*	**58** $I_{test}/I_{control}$ (mean ± SEM, %)	**58** *N*
GluN1/GluN2A	100 glutamate, 30 glycine	89 ± 4.2*	14	89 ± 2.2*	12
GluN1/GluN2B	100 glutamate, 30 glycine	79 ± 2.9*	12	98 ± 1.9	12
GluN1/GluN2C	100 glutamate, 30 glycine	21 ± 1.2*	14	26 ± 1.5*	11
GluN1/GluN2D	100 glutamate, 30 glycine	14 ± 1.6*	13	14 ± 1.6*	13
GluA1	100 glutamate	97 ± 2.2	6	99 ± 1.1	6
GluA2	100 glutamate	98 ± 0.8	3	96 ± 0.9*	4
GluA3	100 glutamate	99 ± 0.3	4	100 ± 1.1	4
GluA4	100 glutamate	96 ± 1.3	3	97 ± 1.5	4
GluK1	100 glutamate	97 ± 1.0	3	100 ± 4.4	3
GluK2	100 glutamate	97 ± 1.1	4	97 ± 0.6*	4
GluK2/GluK5	100 glutamate	97 ± 1.3	3	95 ± 1.8	3
serotonin 5-HT_{3A}	3 serotonin	95 ± 1.5*	4	95 ± 1.2*	4
$GABA_A$ $\alpha\beta_1\beta_2\gamma$2s	20 GABA	97 ± 2.7	4	95 ± 3.1	4
$GABA_C$ $(\rho 1)^{(human)}$	2 GABA	99 + 2.1	4	97 + 0.6*	4
glycine α_1	50 glycine	101 ± 1.6	4	99 ± 1.0	4
nicotinic $\alpha_1\beta_1\gamma\delta^{(mouse)}$	1 acetylcholine	94 ± 1.2*	6	98 ± 0.7	7
nicotinic $\alpha_4\beta_2^{(human)}$	10 acetylcholine	79 ± 4.2*	6	82 ± 1.7*	5
nicotinic $\alpha_3\beta_4^{(human)}$	10 acetylcholine	77 ± 2.7*	7	87 ± 2.2*	5
nicotinic $\alpha_7^{(human)}$	300 acetylcholine	82 ± 9.4	3	64 ± 7.3*	3
nicotinic $\alpha_9\alpha_{10}$	100 acetylcholine	67 ± 4.6*	3	72 ± 4.7*	4
purinergic $P2_{X2}^{(human)}$	9 ATP	113 ± 1.8*	5	100 ± 0.9	4
purinergic $P2_{X2}^{(rat)}$	9 ATP	97 + 1.2*	5	96 + 1.0*	4

[a]Agonist-evoked currents were recorded from the receptors listed using the *Xenopus laevis* oocyte expression system under two-electrode voltage clamp (V_{hold} = −30 to −60 mV) in the absence and presence of 3 μM **26** or 3 μM **58**. The cDNA origin used was rat unless otherwise indicated (paired *t*-test, (*) $p < 0.05$).

Mechanism and Site of Action. A previous study of a representative member suggested that this class of compounds inhibits NMDA receptor function in a voltage-independent and noncompetitive manner.[30] We confirmed this mechanism for compound **58**. Inhibition of GluN1/GluN2D responses by 1 μM **58** was not surmounted by increasing both glutamate and glycine from 30 μM to 3 mM (4.1 ± 0.58% of control in 30 μM, 3.1 ± 0.50% of control in 3 mM; n = 6, unpaired t test), implying that the compound is noncompetitive at the glutamate and glycine binding sites. Moreover, inhibition produced by 1 μM **58** was not significantly different at −40 or +30 mV (4.9 ± 1.3% and 4.8 ± 1.2% of control, respectively, n = 8, Student's t test, p = 0.93), suggesting that the receptor blockade by this more potent compound is also voltage-independent. We also examined whether these more potent analogues interacted with the binding site first identified for both the previously described DQP-1105 (Figure 1A) and the quinazolin-4-one (QNZ), QNZ-46.[30,36] Mutations to the wild type GluN2D receptor (Q801Y, L705F, and A752V), previously shown to decrease sensitivity of the GluN2D receptor to blockade by either DQP-1105 and/or QNZ-46 in the membrane proximal region of the bi-lobed ligand binding domain encoded by the S2 region of the polypeptide chain, were evaluated.[30,36] A test of the effectiveness of racemic **26** revealed that these mutants each significantly reduced the degree of inhibition, consistent with this compoundnicotinic acetylcholine receptors, which exhibited acting at a similar site as DQP-1105 and QNZ-46 (Figure S1).

Evaluation of Off-Target Effects. We next evaluated the off-target actions for the racemic compounds **26** and **58** in a series of two-electrode voltage-clamp recordings using recombinant ligand-gated ion channels expressed in *Xenopus* oocytes (Table 7, see Experimental Section). Compounds **26** and **58** were tested at 3 μM on the AMPA receptors (GluA1−

dx.doi.org/10.1021/jm400652r | J. Med. Chem. XXXX, XXX, XXX−XXX

4), kainate receptors (GluK1−2 and GluK2/GluK5), the serotonin receptor ($5HT_{3A}$), the γ-aminobutyric acid receptors ($GABA_A$ and $GABA_C$), the glycine receptor (glycine α1), nicotinic acetylcholine receptors comprising $\alpha_1\beta_1\delta\gamma$, $\alpha_3\beta_4$, $\alpha_4\beta_2$, α_7, or α_9/α_{10}, and purinergic $P2_{X2}$ receptors. Of the ion channel classes evaluated, compounds **26** and **58** altered agonist-induced currents by less than 10%, with the exception of the nicotinic acetylcholine receptors, which exhibited 13−33% inhibition (Table 7).

We also tested the actions of racemic compounds **26** and **58** at 5 μM on 42 different ion channels, G-protein-coupled receptors, and transporters via the National Institute of Mental Health (NIMH) psychoactive drug screening program (PDSP; Supporting Information Table S4). The primary binding assay demonstrated that compounds **26** and **58** had a minimal effect on the receptors and transporters, with initial screens showing inhibition of three receptors by **26** ($5HT_6$, H_2, κ-opioid) and four receptors by **58** ($5\text{-}HT_{1E}$, $5\text{-}HT_6$, κ-opioid, μ-opioid). For both compounds, the K_i values at these receptors were greater than 10 μM on all receptors. The data collected from both the two-electrode voltage-clamp experiments and the PDSP demonstrate the utility of this class of compounds as selective inhibitors of the GluN2C- and GluN2D-containing NMDA receptors.

Plasma Stability, Aqueous Solubility, BBB Penetration, and Human Liver Microsomal Stability. Three of the more potent analogues **58**, **26**, and **64** were evaluated for plasma stability. The compounds showed minimal degradation in human, rat, and mouse plasma over a two hour time-course (Figure S2). The aqueous solubility of compound **26** was evaluated in oocyte recording buffer using nephelometry and assessed to be soluble at >80 μM (see Experimental Section and Supporting Information p S8).

The topological polar surface area (TPSA) of the carboxylic acid compounds was calculated to be outside the optimal range (<90 Å^2) for blood−brain barrier (BBB) penetration.[37] However, reduction of the acid to the alcohol moves the properties of this class closer to a typical range for CNS penetration (**64**, 102.0 Å^2, QikProp).[37] In order to assess the potential for BBB penetration, compounds **26** and **64** were selected for evaluation in the MDR1-MDCK permeability assay which has been demonstrated to accurately predict BBB penetration because of the overexpression of P-glycoprotein (P-gp) and high transepithelial electrical resistance of the cell line (Table 8).[38] As was anticipated with the carboxylic acid containing **26**, the potential for BBB penetration was low (Table 8). The results for the hydroxyl-containing compound **64** also suggested low BBB potential; however, the permeability coefficient (P_{app}(A−B)) was much closer to the recommended 3.0×10^{-6} cm/s (**64**, P_{app}(A−B) = 2.46×10^{-6} cm/s) than that of the carboxylic acid containing compound (**26**, P_{app}(A−B) = 0.47×10^{-6} cm/s), suggesting that efflux may be problematic with this congener.[38] In order to evaluate an analogue with lower TPSA, the monofluoro-containing compound **68** (Table 5, TPSA = 79.08 Å^2, QikProp) was assessed in the MDR1-MDCK assay and was classified as being highly brain penetrable (P_{app}(A−B) = 3.88×10^{-6} cm/s; P_{app}(B−A) = 9.52×10^{-6} cm/s; Table 8).[38]

Table 8. MDR1-MDCK Permeability[a]

test compd	direction	recovery (%)	P_{app} (10^{-6} cm/s) 1	2	av	efflux ratio
64	A to B	43	2.45	2.48	2.46	26
	B to A	73	66.2	62.7	64.5	
26	A to B	73	0.47	0.47	0.47	55
	B to A	76	33.4	17.9	25.6	
68	A to B	43	4.51	3.24	3.88	2.5
	B to A	67	9.32	9.72	9.52	

[a]The P_{app} and efflux ratio were calculated as described in the Experimental Section. Compounds displaying $P_{app} < 3.0 \times 10^{-6}$ cm/s and an efflux ratio of >10 are interpreted to have a low potential for crossing the BBB. Compounds with $P_{app} > 3.0 \times 10^{-6}$ cm/s and an efflux ratio of <10 are expected to have high brain penetration.[38]

The same compounds were also evaluated for metabolic stability using human liver microsomes. While the carboxylic acid containing **26** showed minimal degradation over the 60 min assay, the hydroxyl-containing derivative **64** had a half-life of 13 min (Table 9). The half-life of the monofluoro compound, **68**, was determined to be 35 min in the human liver microsomal assay (Table 9). These data suggest that the acyl chain is a candidate for further optimization of desirable pharmacokinetic properties.

DISCUSSION AND CONCLUSION

This study describes the development of potent, selective, and soluble negative allosteric modulators for GluN2C- and GluN2D-containing NMDA receptors that act on the membrane proximal lobe of the GluN2 glutamate binding domain. We describe here several compounds with IC_{50} values in the 100−500 nM range that show 50- to 200-fold selectivity over GluN2A- and GluN2B-containing receptors. We have taken a classical approach to the SAR, allowing proposal of features for a hypothetical pharmacophore.

The A-ring substituents that were explored directly correlate potency with the para-σ substituent coefficients at only GluN2C- and GluN2D-containing receptors, when R_1 was substituted with chloro (Figures 2A and 5A). While we maintained selectivity with many of the analogues, our results suggest that there is a conserved portion of the binding pocket among GluN2A-, GluN2C-, and GluN2D-containing receptors with respect to the para-position of the B-ring; the electronic effects relative to the σ substituent coefficient show similar trends when plotted as a function of potency (Figure 2B,C and Figure 5A). We visualized the electron density of these analogues by carrying out Hartree−Fock calculations using the 6-31G* basis set. While several of the analogues substituted at the para-position of the B-ring could theoretically accept a hydrogen bond, only the bromo- and chloro-containing compounds (**26** and **21**) exhibit an accessible deficiency of electron density at the terminal position of the substitutions. We hypothesize that the apparent σ hole found at the bromo and chloro atoms could enhance potency by forming a halogen bond with an oxygen electron donor at the receptors (Figure 5B).[39,40] Furthermore, the SAR has revealed that rigidifying the acyl chain in the trans-conformation can enhance potency at the GluN2D-containing receptors, while the length of the chain was found not to be crucial for activity (Figure 5A). The finding that the hydroxyl-containing compound **64** (Table 5) retains both potency and selectivity suggests that the charge on the carboxylic acid is not crucial for either property. While it would be ideal to interpret these data in the context of the receptor, no high quality crystallographic data exist for the region of the LBD where these compounds are thought to act, making docking studies challenging.

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Table 9. Human Microsomal Stability

	% remaining of initial						
test compd	0 min	10 min	20 min	30 min	60 min	half-life[a] (min)	CL_{int}[b] ((mL/min)/mg protein)
64	100	52	31	24	6.5	13	0.110
26	100	101	100	115	86	>60	<0.02
68	100	67	49	49	39	35	0.040

[a]Half-life was calculated based on $t_{1/2} = 0.693/k$, where k is the elimination rate constant based on the slope of the natural logarithm percent remaining versus incubation time. [b]Intrinsic clearance (CL_{int}) was calculated on $CL_{int} = k/P$, where k is the elimination rate constant and P is the protein concentration in the incubation.

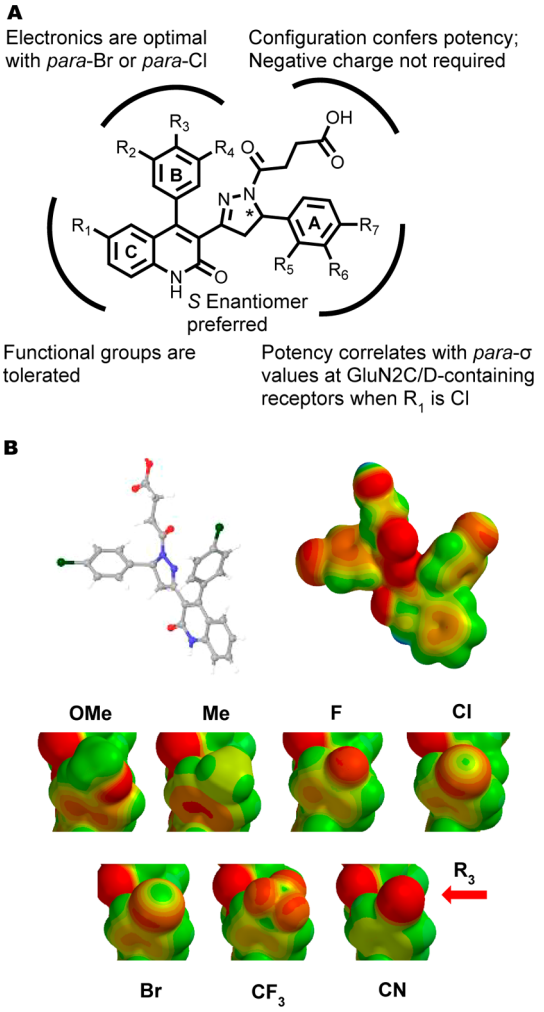

Figure 5. Pharmacophore model and electrostatic potential maps of para-B-ring modifications. (A) The para-substitution of the A-ring shows correlation between the σ substituent constants and activity at GluN2C/D-containing receptors, when R_1 is a chlorine. The length and configuration of the acyl chain is flexible, with the trans-configuration improving potency. B-ring modification shows an optimal para-σ coefficient close to that of chloro and bromo substitutions for GluN2A-, GluN2C-, and GluN2D-containing receptors, suggesting a conserved nature of the binding interaction at each of the three receptors. The C-ring substitutions explored are consistent with this portion of the molecule interacting with a hydrophobic pocket and could allow for improvements in selectivity. (B) The electrostatic potential maps of the para-B-ring modifications evaluated are shown. Only the Cl and Br substituents show significant electron deficiency at the termini of the substituents, suggesting that a potential halogen bond could be responsible for the improved potency of these compounds.

We expect that a reduction in molecular weight in conjunction with further optimization of the topological polar surface area will be required to obtain optimal BBB penetration and pharmacokinetic properties. However, the improvements in potency and selectivity suggest that this class of compounds should be useful as pharmacologic probes to evaluate the contributions of the GluN2C- and GluN2D-containing NMDA receptors in normal and pathophysiologic processes in isolated systems.

The GluN2C- and GluN2D-NMDA receptor subunits remain understudied largely because of a lack of potent and selective pharmacological tools. However, these NMDA receptor subunits reside in a number of brain regions that are highly relevant for neurological disease. For example, expression of functional GluN2D in the subthalamic nuclei raises the possibility that GluN2D-selective inhibitors could attenuate neuronal firing rate and alter firing patterns in subthalamic neurons, which could be of utility in Parkinson's disease.[22,24,26,28,41−44] In addition, expression of GluN2D-containing receptors in substantia nigra pars compacta neurons raises the possibility that GluN2D-selective antagonists might possess neuroprotective properties in Parkinson's disease by diminishing Ca^{2+} influx into the dopaminergic substantia nigra pars comapcta neurons, which may lead to neuronal death.[8,45] GluN2C is expressed widely in the cerebellum and has also been suggested to have a role in both emotional learning and schizophrenia.[46−48] The compounds described here could therefore be tools with which to evaluate GluN2C- and GluN2D-containing receptor function in specific circuits implicated in these conditions.

EXPERIMENTAL SECTION

Biology. Two-Electrode Voltage-Clamp Electrophysiology. The Emory University Institutional Animal Care and Use Committee approved all protocols involving the use of animals. *Xenopus laevis* oocytes were isolated and maintained as previously described.[36] The cDNAs for the desired NMDA receptor subunits (GenBank accession numbers U11418 and U08261; GluN1, D13211; GluN2A, U11419; GluN2B, M91563; GluN2C, L31611; GluN2D) were obtained from Drs. S. Heinemann (Salk Institute), S. Nakanishi (Kyoto University), and P. Seeburg (University of Heidelberg). Preparation of cRNA, injection of oocytes with RNA, and two-electrode voltage clamp recordings have been described elsewhere.[30,36,49] Briefly, oocytes were placed in a perfusion chamber with recording solution comprising (in mM) 90 NaCl, 1 KCl, 0.5 $BaCl_2$, 0.005 EDTA, and 10 HEPES, with pH adjusted to 7.4 with NaOH at 23 °C. The glass electrodes used had tip resistances of 0.5−2.0 MΩ and were filled with 0.3−3.0 M KCl. Compounds were made as 20 mM stock solutions in DMSO and diluted to final concentrations in recording solution (final DMSO was 0.1−0.05% v/v). The current recordings were performed using a Warner OC-725B or -C amplifier at a holding potential of −40 mV.

Subunit selectivity was determined by recording from various ligand-gated ion channels expressed in *Xenopus laevis* oocytes as previously described.[50] The cDNA encoding $GABA_A$, $GABA_C$, and

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glycine receptor cDNAs were provided by Dr. Weiss (University of Texas Health Science Center at San Antonio). Nicotinic acetylcholine and 5-HT_{3A} serotonin receptor cDNAs were provided by Drs. Papke and Heinemann (University of Florida and Salk Institute), and purinergic receptor cDNA was provided by Dr. Hume (University of Michigan). The glutamate receptors GluA1−4, GluK1, and GluK2 were activated by 100 μM glutamate. GluK1 and GluK2 expressing oocytes were incubated for 5 min in 1 mg/mL concanavalin A prior to recording. The GluK2/5 receptor was activated with 100 μM AMPA (2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propanoic acid). The $GABA_A$ and $GABA_C$ receptors were activated by 20 and 2 μM γ-aminobutyric acid, respectively. Acetylcholine was used activate the nicotinic acetylcholine $\alpha_1\beta_1\delta\gamma$ (1 μM), $\alpha_3\beta_4$ (10 μM), $\alpha_2\beta_4$ (10 μM), α_7 (300 μM), $\alpha_9\alpha_{10}$ (10 μM) receptors. The glycine α_1 and 5-HT_{3A} currents were evoked by 50 μM glycine receptor and 3 μM serotonin, respectively. The human and rat $P2_{X2}$ purinergic receptors were activated with 9 μM adenosine triphosphate.

The receptor binding profiles (Supporting Information Table S2) and K_i determinations for compounds **26** and **58** were generously provided by the National Institute of Mental Health psychoactive drug screening program, Contract HHSN-271-2008-025C (NIMH PDSP). The NIMH PDSP is directed by Bryan L. Roth M.D., Ph.D. at the University of North Carolina at Chapel Hill and Project Officer Jamie Driscoll at NIMH, Bethesda, MD, U.S. Data were collected using 5 μM **26** and **58**.

MDR1-MDCK Permeability. Cell monolayers were grown to confluence on collagen-coated, microporous, polycarbonate membranes in 12-well Costar Transwell plates. The permeability assay buffer was Hanks' balanced salt solution containing 10 mM HEPES and 15 mM glucose at pH 7.4. The buffer in the receiver chamber also contained 1% bovine serum albumin. The dosing solution concentration in the assay buffer was 5 μM for each compound tested. The cell monolayers were dosed on the apical side (A to B) or basolateral side (B to A) and incubated at 37 °C with 5% CO_2 in a humidified incubator. Samples were taken from the donor and receiver chambers at 120 min. Each determination was performed in duplicate. All samples were assayed by LC−MS/MS using electrospray ionization. The apparent permeability (P_{app}) and percent recovery were calculated as follows.

$$P_{app} = (dC_r/dt)V_r/(AC_A) \quad (1)$$

$$\text{percent recovery} = 100 \times [(V_rC_r^{final}) + (V_dC_d^{final}) + (V_dC_d^{final})]/(V_dC_N) \quad (2)$$

where dC_r/dt is the slope of the cumulative concentration in the receiver compartment versus time in μM s^{-1}, V_r is the volume in the receiver compartment in cm^3, V_d is the volume in the donor compartment in cm^3, A is the area of the insert (1.13 cm^2 for 12-well Transwell), C_A is the average of the nominal dosing concentration and the measured 120 min donor concentration in μM, C_N is the nominal concentration of the dosing solution in μM, C_r^{final} is the cumulative receiver concentration in μM at the end of the incubation period, and C_d^{final} is the concentration of the donor in μM at the end of the incubation period. The MDR1-MDCK permeability assays were performed by Absorption Systems.

Human Liver Microsomal Stability. Human liver microsomes were obtained from XenoTech. The reaction mixture was prepared with 0.5 mg/mL human liver microsomes, 100 mM potassium phosphate (pH 7.4), 5 mM magnesium chloride, and 1 μM test compound. The reaction mixture was incubated in a shaking water bath at 37 °C for 3 min prior to the addition of NADPH (1 mM). Testosterone was run simultaneously in a separate vessel as a control. Then 100 μL aliquots were taken at 0, 10, 20, 30, and 60 min for both test compound and testosterone. The aliquots were combined immediately with 400 μL of ice cold 50/50 acetonitrile/deionizd H_2O containing 0.1% formic acid and internal standard to terminate the reaction. The samples were then mixed and centrifuged to precipitate microsomal proteins. All samples were assayed by LC−MS/MS using electrospray ionization and multiple reaction monitoring, and the peak area responses to internal standard of the compounds at each time point were compared to the peak area response at time 0 to determine the percent compound remaining. The human liver microsomal stability assays were performed by Absorption Systems.

Data Analysis. Potency of compounds was assessed by fitting the composite concentration−response curve obtained from the average of multiple recordings with the equation

$$\text{response} = 100/\{1 + [(\text{inhibitor concentration})/IC_{50}]^N\} \quad (3)$$

where IC_{50} is the concentration of compound that is required to inhibit the response half-maximally and N is the Hill slope. Saturating conditions were assumed to give complete inhibition. Data for compounds that did not inhibit the steady-state current by at least 30% were not fit by the above equation and are designated as NE in the data tables.

Chemistry. Commercial vendors provided compounds **4**, **5**, **9**−**11**, **14**, **16**, **17**, **20**, **57**, and **62**, which are not described below and which were ≥90% purity, as provided by the vendor or determined independently as below. All reagents were obtained from commercial suppliers and used without further purification unless otherwise noted. Reaction progress was monitored by thin layer chromatography (TLC) on precoated glass plates (silica gel 60 F254, 0.25 mm). Proton, carbon, and fluorine NMR spectra were recorded on INOVA-400 (400 MHz), VNMRS 400 (400 MHz), UNITY-600 (600 MHz), or INOVA-600 (600 MHz) instrument. Proton and carbon spectra were referenced to the residual solvent peak, while fluorine spectra were referenced to trifluoroacetic acid residual peak. The Emory University Mass Spectrometry Center collected mass spectral data on either a VG 70-S Nier Johnson or JEOL instrument. Compound purity was assessed by reverse phase liquid chromatography using an Agilent Zorbax, 3.5 μm, XD B-C18 column, 4.6 mm × 50 mm (254 nm), or by elemental analyses, performed by Atlantic Microlab Inc. Purity for all compounds synthesized and tested was at or above 95% unless otherwise noted. Flash chromatography was performed on a Teledyne ISCO Combiflash Companion with prepackaged disposable normal phase silica columns.

Computational Analysis. Energy minimized conformations of the compounds being analyzed were generated using the OPLS_2005 force field in MacroModel (*MacroModel*, version 9.9; Schrödinger, LLC: New York, NY, 2011). The TPSA approximations were obtained from QikProp (*QikProp*, version 3.4; Schrödinger, LLC: New York, NY, 2011) using energy minimized conformations, as above. The Hartree−Fock calculations were carried out using the neutral compounds and the 6-31G* basis set in Spartan '10 (*Spartan '10*; Wavefunction, Inc.: Irvine, CA). The equilibrium geometry at the ground state in vacuum was calculated. For visualization purposes, the energy range in the electrostatic potential maps was limited from −100.00 to 280.00 kJ/mol.

Separation and X-ray Crystallography of Enantiomers. Separation of the final compounds used for biological testing from the racemic **26** was obtained using a ChiralPak OD-RH 30 mm × 250 mm, 5 μm column using the following conditions: flow rate 10 mL/min, injection volume 4−6 mL (2 mg/mL), 60% acetonitrile (0.1% formic acid)/40% H_2O (0.1% formic acid); **69** t_R = 21.8; **70** t_R = 25.1 min. The enantiomeric excess (ee) of the enantiomers **69** and **70** was determined using an Agilent 1200 HPLC pump on a ChiralPak OD-RH column (4.6 mm × 150 mm, 5 μm) using the following conditions: flow rate 0.5 mL/min, injection volume 10 μL, 60% acetonitrile (0.1% formic acid)/40% H_2O (0.1% formic acid); **69** (*S*-**26**, $[\alpha]_D^{20}$ −34.0 (c = 0.32, chloroform), t_R = 7.47 min, 100% ee. **70** (*R*-**26**) $[\alpha]_D^{20}$ + 36.0 (c = 0.25, MeOH), t_R = 8.79 min, 98% ee. Optical rotation data were collected using a Perkin-Elmer 314 instrument. The proton NMR spectrum was identical to that of racemic **26** for each enantiomer. Single crystals of the second peak to elute from the separation of racemic **26** (**70** t_R = 25.1 min) were grown by slow evaporation of a solution of the compound in a mixture of methanol and water. Crystal data for $C_{28}H_{23}Cl_2N_3O_5$ (M = 552.39): 1.124 × 0.087 × 0.056, orthorhombic, space group $P2_12_12_1$ (No. 19), a =

dx.doi.org/10.1021/jm400652r | J. Med. Chem. XXXX, XXX, XXX−XXX

8.0529(5) Å, b = 10.2097(5) Å, c = 31.2978(13) Å, V = 2573.2(2) Å^3, Z = 4, μ(Mo Kα) = 0.315 mm^{-1}, D_{calc} = 1.490 g/mm^3, temperature 173 K. Intensity data were collected on a Bruker APEX II CCD diffractometer with monochromated Mo Kα radiation (λ = 0.710 73 Å) at 173 K in the 2θ range 2.6−53.4°. The user interface Olex2 was used for the crystallographic calculations and crystal structure visualization.[51] The structure was solved with Superflip by charge flipping and refined by least-squares minimization using SHELXL.[52,53] A total of 15 745 reflections were measured ($2.602 \leq 2\theta \leq 53.41$), while 5408 unique data (R_{int} = 0.124) were used in the refinements. The final R_1 was 0.0590 ($I > 2\sigma(I)$) and the weighted R value wR2 was 0.0874 (all data).

General Procedure for the Synthesis of Acylated Quinolone Pyrazoline Products. Procedure G. In an appropriately sized microwaveable vessel, the pyrazol-3-ylquinolin-2(1*H*)-one intermediate (1.00 equiv) was dissolved in anhydrous tetrahydrofuran (THF) (0.15 M) with 4 Å molecular sieves present. The appropriate anhydride (1.00 equiv) was added. The solution was microwaved (Biotage Initiator) with stirring for 20 min at 165 °C. The THF was removed under vacuum, and the organics were dissolved in dichloromethane (DCM), washed three times with acidified (pH 2, HCl) brine, dried over magnesium sulfate, filtered, concentrated under reduced pressure, and subjected to flash column chromatography using a 0−10% MeOH/DCM gradient unless otherwise noted.

4-[3-(6-Chloro-2-oxo-4-phenyl-1,2-dihydroquinolin-3-yl)-5-(4-fluorophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl]-4-oxobutanoic Acid (2). Compound **2** was prepared according to general procedure G using succinic anhydride (**88**) (0.062 g, 0.622 mmol) and **2f** (0.260 g, 0.622 mmol). After removal of the THF, the residue was dissolved in hot EtOAc and small portions of hexanes were added until a solid began to form. The solid was filtered and column-chromatographed using 0−10% MeOH/DCM, and the title compound was obtained as a yellow solid. Yield 0.236 g, 73.2%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.42 (s, 1H), 12.15 (s, 1H), 7.68−7.38 (m, 6H), 7.27 (d, J = 7.4 Hz, 1H), 7.04 (td, J = 8.8, 2.4 Hz, 2H), 6.93 (d, J = 2.5 Hz, 1H), 6.85−6.76 (m, 2H), 5.35−5.30 (m, 1H), 3.80−3.67 (m, 1H), 2.83−2.74 (m, 1H), 2.48−2.39 (m, 2H), 2.34−2.25 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.59, 168.66, 160.13, 152.45, 149.96, 138.39, 137.34, 134.56, 131.25, 129.47, 128.51, 127.55, 126.09, 124.64, 120.68, 117.65, 115.26, 115.05, 58.24, 45.23, 28.92, 28.59, 28.22. ^{19}F NMR (376 MHz, DMSO-d_6) δ −116.13 to −116.20 (m). HRMS (m/z): [M − H]$^-$ calcd for $C_{28}H_{20}ClN_3O_4F$, 516.11319; found, 516.11246. Anal. Calcd for $C_{28}H_{21}ClN_3O_4F$: C, 64.93; H, 4.09; N, 8.11. Found: C, 61.01; H, 4.22; N, 7.15. HPLC 85% MeOH/H_2O (0.1% formic acid) t_R = 0.95 min; >95% purity; 75% ACN/H_2O (0.1% formic acid) t_R = 0.72 min; >95% purity.

4-[3-(6-Chloro-2-oxo-4-phenyl-1,2-dihydroquinolin-3-yl)-5-(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl]-4-oxobutanoic Acid (3). Compound **3** was prepared according to general procedure G using **87** (0.046 g, 0.460 mmol) and **3f** (0.200 g, 0.460 mmol). The title compound was obtained by removing the THF, dissolving the crude mixture into hot EtOAc, and adding small portions of hot hexanes until a yellow precipitate formed. The mixture was allowed to cool and filtered to give the title compound as a yellow solid. Yield 0.187 g, 76.0%. ^{1}H NMR (400 MHz DMSO-d_6) δ 12.42 (s, 1H), 12.15 (s, 1H), 7.64 (dd, J = 8.7, 2.5 Hz, 1H), 7.61−7.38 (m, 5H), 7.27 (d, J = 7.9 Hz, 3H), 6.94 (d, J = 2.5 Hz, 1H), 6.79 (d, J = 8.2 Hz, 2H), 5.33 (dd, J = 12.1, 4.7 Hz, 1H), 3.75 (dd, J = 18.5, 12.0 Hz, 1H), 2.78 (dd, J = 18.4, 4.7 Hz, 1H), 2.49−2.23 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.55, 168.67, 160.09, 152.42, 149.96, 141.13, 137.32, 134.54, 131.59, 131.24, 129.47, 128.57, 128.46, 128.37, 127.38, 126.13, 126.06, 124.56, 120.66, 117.64, 58.29, 45.12, 28.57, 28.23. HRMS (m/z): [M + H]$^+$ calcd for $C_{28}H_{22}Cl_2N_3O_4$, 534.09819; found, 534.09774. Anal. Calcd for $C_{28}H_{21}Cl_2N_3O_4 \cdot 0.40H_2O$: C, 62.09; H, 4.06; N: 7.76. Found: C, 61.90; H, 4.13; N: 7.64.

4-[1-(3-Carboxypropanoyl)-3-(6-chloro-2-oxo-4-phenyl-1,2-dihydroquinolin-3-yl)-4,5-dihydro-1*H*-pyrazol-5-yl]benzoic Acid (6). Compound **6** was prepared according to general procedure G using **87** (0.045 g, 0.451 mmol) and **6f** (0.200 g, 0.451 mmol). The solvent was removed, and the product was obtained by dissolving in hot EtOAc and adding hexanes until a solid began to precipitate. The solution was cooled and the product filtered to yield a white solid. Yield 0.040 g, 16.3%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.42 (bs, 3H), 7.79 (d, J = 8.0 Hz, 2H), 7.64 (dd, J = 8.7, 2.4 Hz, 1H), 7.60−7.41 (m, 5H), 7.27 (d, J = 7.4 Hz, 1H), 6.96−6.82 (m, 3H), 5.39 (dd, J = 12.0, 4.8 Hz, 1H), 3.79 (dd, J = 18.4, 12.2 Hz, 1H), 2.79 (dd, J = 18.4, 4.7 Hz, 1H), 2.61−2.37 (m, 2H), 2.30 (t, J = 6.9 Hz, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 173.51, 172.19, 168.72, 167.04, 160.09, 152.41, 149.99, 146.92, 137.33, 134.56, 131.25, 129.68, 129.55, 129.51, 128.52, 128.48, 128.38, 126.12, 126.07, 125.54, 124.53, 120.68, 117.65, 58.71, 45.12, 28.53, 28.22. HRMS (m/z): [M + Na]$^+$ calcd for $C_{29}H_{22}ClN_3O_6Na$, 566.10893; found, 566.10923. HPLC 85% MeOH/H_2O (0.1% formic acid) t_R = 0.71 min; >95% purity; 75% ACN/H_2O (0.1% formic acid) t_R = 0.53 min; >95% purity.

4-{3-(6-Chloro-2-oxo-4-phenyl-1,2-dihydroquinolin-3-yl)-5-[4-(methoxycarbonyl)phenyl]-4,5-dihydro-1*H*-pyrazol-1-yl}-4-oxobutanoic Acid (7). Compound **7** was prepared according to general procedure G using **87** (0.055 g, 0.546 mmol) and **7f** (0.250 g, 0.546 mmol). The title compound was purified using flash chromatography (2−10% MeOH/DCM), followed by precipitation from hot EtOAc using hot hexanes. Yield 0.040 g, 13.1%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.38 (s, 1H), 12.06 (s, 1H), 7.84−7.72 (m, 2H), 7.64−7.35 (m, 6H), 7.22 (d, J = 7.4 Hz, 1H), 6.87 (d, J = 8.4 Hz, 3H), 5.36 (dd, J = 12.3, 4.6 Hz, 1H), 3.90−3.69 (m, 4H), 2.74 (dd, J = 18.5, 4.6 Hz, 1H), 2.51−2.33 (m, 2H), 2.30−2.21 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.53, 168.77, 165.96, 160.10, 152.43, 150.02, 147.43, 137.34, 134.59, 131.29, 129.44, 128.41, 126.14, 125.76, 124.50, 120.67, 117.67, 58.68, 52.16, 45.09, 28.52, 28.22. HRMS (m/z): [M + Na]$^+$ calcd for $C_{30}H_{24}ClN_3O_6Na$, 580.12458; found, 580.12484. Anal. Calcd for $C_{30}H_{24}ClN_3O_6 \cdot 0.80H_2O$: C, 62.95; H, 4.51; N, 7.34. Found: C, 63.04; H, 4.55; N, 7.36.

4-{3-(6-Chloro-2-oxo-4-phenyl-1,2-dihydroquinolin-3-yl)-5-[4-(trifluoromethyl)phenyl]-4,5-dihydro-1*H*-pyrazol-1-yl}-4-oxobutanoic Acid (8). Compound **8** was prepared according to general procedure G using **87** (0.043 g, 0.427 mmol) and **8f** (0.200 g, 0.427 mmol). The title compound was obtained after flash chromatography (2−10% MeOH/DCM) followed by trituration from EtOAc as a yellow solid. Yield 0.030 g, 12.4%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.42 (s, 1H), 12.04 (s, 1H), 7.65 (dd, J = 8.7, 2.4 Hz, 1H), 7.61−7.40 (m, 7H), 7.26 (d, J = 7.4 Hz, 1H), 6.99 (d, J = 8.0 Hz, 2H), 6.93 (d, J = 2.3 Hz, 1H), 5.43 (dd, J = 12.2, 4.7 Hz, 1H), 3.79 (dd, J = 18.5, 12.2 Hz, 1H), 2.80 (dd, J = 18.6, 4.7 Hz, 1H), 2.60−2.40 (m, 2H), 2.29 (t, J = 6.8 Hz, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 174.14, 169.46, 160.72, 153.09, 150.68, 147.32, 138.01, 135.23, 131.92, 130.09, 129.22, 129.12, 129.05, 126.88, 126.79, 126.72, 126.05, 125.13, 121.31, 118.31, 59.19, 45.74, 29.19, 28.89. HRMS (m/z): [M + H]$^+$ calcd for $C_{29}H_{22}ClN_3O_4F_3$, 568.12455; found, 568.12554. $C_{29}H_{21}ClN_3O_4F_3 \cdot 0.07$EtOAc; HPLC 85% MeOH/$H_2O$ (0.1% formic acid) t_R = 1.1 min; >95% purity; 75% ACN/H_2O (0.1% formic acid) t_R = 0.86 min; >95% purity.

4-[3-(6-Chloro-2-oxo-4-phenyl-1,2-dihydroquinolin-3-yl)-5-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl]-4-oxobutanoic Acid (9). Compound **9** was prepared according to general procedure G using **87** (0.058 g, 0.582 mmol) and **9f** (0.250 g, 0.582 mmol). After removal of the THF, the title compound was obtained by dissolving the crude mixture into hot EtOAc and adding small portions of hot hexanes until a yellow precipitate formed. The mixture was allowed to cool and filtered to give the title compound as a yellow solid. Yield 0.132 g, 42.8%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.40 (s, 1H), 12.16 (s, 1H), 7.64 (dd, J = 8.9, 2.4 Hz, 1H), 7.60−7.49 (m, 3H), 7.45 (d, J = 8.7 Hz, 1H), 7.43−7.38 (m, 1H), 7.29 (d, J = 7.0 Hz, 1H), 6.93 (d, J = 2.5 Hz, 1H), 6.82−6.66 (m, 4H), 5.24 (dd, J = 12.1, 4.6 Hz, 1H), 3.89−3.62 (m, 4H), 2.78 (dd, J = 18.3, 4.6 Hz, 1H), 2.45 (t, J = 7.0 Hz, 2H), 2.27 (t, J = 6.9 Hz, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 173.58, 168.49, 160.14, 158.22, 152.39, 149.86, 137.30, 134.58, 134.31, 131.22, 129.42, 128.57, 128.43, 128.35, 126.77, 126.09, 126.02, 124.74, 120.71, 117.63, 113.71, 58.47, 55.10, 45.27, 28.63, 28.24. HRMS (m/z): [M + Na]$^+$ calcd for $C_{29}H_{24}ClN_3O_5Na$, 552.12967; found, 552.13018. Anal. Calcd for

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$C_{29}H_{24}ClN_3O_5 \cdot 1.00H_2O$: C, 63.56; H, 4.78; N, 7.67. Found: C, 63.68; H, 4.57; N, 7.59.

4-[3-(6-Chloro-2-oxo-4-phenyl-1,2-dihydroquinolin-3-yl)-5-(3-fluorophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl]-4-oxobutanoic Acid (12). Compound **12** was prepared according to general procedure G using **87** (0.120 g, 1.20 mmol) and **12f** (0.500 g, 1.20 mmol). After removal of the THF, the title compound was obtained by precipitation from EtOAc using hexanes, as a yellow solid. Yield 0.380 g, 62%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.42 (s, 1H), 12.15 (s, 1H), 7.65 (dd, J = 8.7, 2.6 Hz, 1H), 7.53 (m, 2H), 7.44 (m, 3H), 7.26 (d, J = 7.0 Hz, 2H), 7.03 (t, J = 8.7 Hz, 1H), 6.93 (d, J = 2.3 Hz, 1H), 6.64 (dd, J = 12.3, 8.8 Hz, 2H), 5.35 (dd, J = 12.3, 4.4 Hz, 1H), 3.75 (dd, J = 18.6, 12.1 Hz, 1H), 2.81 (dd, J = 17.7, 4.7 Hz, 1H), 2.60−2.23 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.57, 168.75, 163.36, 160.94, 160.12, 152.47, 149.98, 144.95, 144.88, 137.33, 134.56, 131.25, 130.52, 130.45, 129.40, 128.56, 128.42, 128.38, 128.29, 126.14, 126.07, 124.53, 121.50, 120.65, 117.65, 114.00, 113.79, 112.34, 112.13, 58.41, 45.14, 28.53, 28.20. HRMS (m/z): $[M - H]^-$ calcd for $C_{28}H_{20}ClN_3O_4F$; 516.11319; found, 516.11239. Anal. Calcd for $C_{28}H_{21}ClN_3O_4F \cdot 0.40H_2O$: C, 64.93; H, 4.09; N, 8.11. Found: C, 64.11; H, 4.03; N, 7.94. HPLC 85% MeOH/H_2O (0.1% formic acid) t_R = 0.97 min; >95% purity; 75% ACN/H_2O (0.1% formic acid) t_R = 0.73 min; >95% purity.

4-[3-(6-Chloro-2-oxo-4-phenyl-1,2-dihydroquinolin-3-yl)-5-(3-chlorophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl]-4-oxobutanoic Acid (13). Compound **13** was prepared according to general procedure G using **87** (0.046 g, 0.460 mmol) and **13f** (0.200 g, 0.460 mmol). After removal of the THF, the title compound was obtained by precipitating from EtOAc using hexanes, as a yellow solid. Yield 0.156 g, 63.4%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.39 (s, 1H), 12.04 (s, 1H), 7.64−7.57 (m, 1H), 7.56−7.34 (m, 5H), 7.27−7.17 (m, 3H), 6.97−6.87 (m, 2H), 6.68 (d, J = 6.8 Hz, 1H), 5.29 (dd, J = 12.2, 4.8 Hz, 1H), 3.71 (dd, J = 18.5, 12.0 Hz, 1H), 2.84−2.73 (m, 1H), 2.50−2.32 (m, 2H), 2.25 (t, J = 6.7 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.55, 168.78, 152.53, 150.00, 144.54, 137.35, 134.62, 133.05, 130.47, 129.37, 128.60, 128.45, 127.14, 126.15, 125.51, 124.51, 124.11, 120.64, 58.40, 45.10, 28.53, 28.18. HRMS (m/z): $[M + Na]^+$ calcd for $C_{28}H_{21}Cl_2N_3O_4Na$; 556.08013; found, 556.07988. Anal. Calcd for $C_{28}H_{21}Cl_2N_3O_4 \cdot 0.20H_2O$: C, 61.68; H, 4.10; N, 7.71. Found: C, 61.74; H, 4.27; N, 7.32.

4-[3-(6-Chloro-2-oxo-4-phenyl-1,2-dihydroquinolin-3-yl)-5-(3-methoxyphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl]-4-oxobutanoic Acid (15). Compound **15** was prepared according to general procedure G using **87** (0.029 g, 0.29 mmol) and **15f** (0.13 g, 0.29 mmol). The title compound was purified using flash chromatography (2−10% MeOH/DCM) and isolated as a yellow solid. Yield 0.090 g, 58.7%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.41 (s, 1H), 12.08 (s, 1H), 7.64 (dt, J = 8.8, 2.1 Hz, 1H), 7.58−7.42 (m, 4H), 7.39 (d, J = 7.3 Hz, 1H), 7.27 (d, J = 7.3 Hz, 1H), 7.13 (t, J = 7.9 Hz, 1H), 6.93 (d, J = 2.2 Hz, 1H), 6.77 (dd, J = 8.2, 2.4 Hz, 1H), 6.59 (s, 1H), 6.32 (d, J = 7.7 Hz, 1H), 5.27 (dd, J = 12.0, 4.7 Hz, 1H), 3.77−3.63 (m, 4H), 2.85 (dd, J = 18.4, 4.7 Hz, 1H), 2.48−2.36 (m, 2H), 2.28 (t, J = 6.8 Hz, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 173.54, 168.64, 160.16, 159.25, 152.47, 149.91, 143.75, 137.32, 134.64, 131.21, 129.59, 129.15, 128.59, 128.48, 128.37, 128.30, 126.09, 124.56, 120.68, 117.63, 117.39, 112.37, 111.35, 58.88, 54.98, 45.23, 28.56, 28.22. HRMS (m/z): $[M - H]^-$ calcd for $C_{29}H_{23}ClN_3O_5$, 528.13317; found, 528.13351. Anal. Calcd for $C_{29}H_{23}Cl_1N_3O_5 \cdot 0.70H_2O$: C, 64.32; H, 4.54; N, 7.76. Found: C, 64.38; H, 4.67; N: 7.67.

4-[3-(6-Chloro-2-oxo-4-phenyl-1,2-dihydroquinolin-3-yl)-5-(2-chlorophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl]-4-oxobutanoic Acid (18). Compound **18** was prepared according to general procedure G using **87** (0.046 g, 0.460 mmol) and **18f** (0.200 g, 0.460 mmol). After removal of the THF, the title compound was obtained by precipitation from EtOAc using hexanes, as a yellow solid. Yield 0.136 g, 55.3%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.40 (s, 1H), 12.13 (s, 1H), 7.63 (dd, J= 8.6, 1.6 Hz, 1H), 7.56−7.49 (m, 2H), 7.45−7.41 (m, 4H), 7.26 (t, J = 7.6 Hz, 1H), 7.19−7.15 (m, 2H), 6.93 (s, 1H), 6.41 (d, J = 7.4 Hz, 1H), 3.87 (dd, J=18.4, 12.4 Hz, 1H), 2.75 (dd, J = 18.2, 4.7 Hz, 1H), 2.60−2.54 (m, 1H), 2.46−2.32 (m, 2H), 2.39−2.30 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.55, 168.78, 160.02, 152.56, 150.10, 138.66, 134.68, 131.27, 130.52, 129.36, 128.78, 128.37, 128.58, 126.13, 125.90, 124.33, 120.66, 117.64, 56.40, 44.20, 28.43, 28.22. HRMS (m/z): $[M + Na]^+$ calcd for $C_{28}H_{21}Cl_2N_3O_4Na$, 556.08013; found 556.08038. Anal. Calcd for $C_{28}H_{21}Cl_2N_3O_4 \cdot 0.30H_2O$: C, 62.30; H, 4.03; N, 7.78. Found: C, 62.27; H, 4.32; N, 7.49.

4-[5-(2-Bromophenyl)-3-(6-chloro-2-oxo-4-phenyl-1,2-dihydroquinolin-3-yl)-4,5-dihydro-1*H*-pyrazol-1-yl]-4-oxobutanoic Acid (19). Compound **19** was prepared according to general procedure G using **87** (0.063 g, 0.627 mmol) and **19f** (0.300 g, 0.627 mmol). After removal of the THF, the title compound was obtained by precipitation from EtOAc and hexanes, as a yellow solid. Yield 0.140 g, 38.6%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.41 (s, 1H), 12.05 (s, 1H), 7.64 (dd, J = 8.9, 2.5 Hz, 1H), 7.59 (d, J = 7.5 Hz, 1H), 7.53 (p, J = 7.6 Hz, 2H), 7.42 (dd, J = 11.1, 7.9 Hz, 3H), 7.26−7.15 (m, 3H), 6.93 (d, J = 2.3 Hz, 1H), 6.39−6.32 (m, 1H), 5.48 (dd, J = 12.1, 4.6 Hz, 1H), 3.87 (dd, J = 18.3, 12.0 Hz, 1H), 2.73 (dd, J = 18.4, 4.6 Hz, 1H), 2.62−2.51 (m, 1H), 2.49−2.28 (m, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.53, 168.76, 160.06, 152.42, 150.11, 140.19, 137.33, 132.58, 131.25, 129.08, 128.41, 126.12, 124.30, 120.64, 117.63, 58.69, 44.33, 28.41, 28.21. HRMS (m/z): $[M + Na]^+$ calcd for $C_{28}H_{21}ClBrN_3O_4Na$; 600.02962, found 600.02945. Anal. Calcd for $C_{28}H_{21}ClBrN_3O_4$: C, 58.10; H, 3.66; N, 7.26. Found: C, 54.48; H, 3.54; N, 6.55. HPLC 85% MeOH/H_2O (0.1% formic acid) t_R = 1.17 min; >95% purity; 75% ACN/H_2O (0.1% formic acid) t_R = 1.17 min; >95% purity.

4-{5-(4-Bromophenyl)-3-[4-(4-bromophenyl)-2-oxo-1,2-dihydroquinolin-3-yl]-4,5-dihydro-1*H*-pyrazol-1-yl}-4-oxobutanoic Acid (21). Compound **21** was prepared according to general procedure G using **87** (0.057 g, 0.573 mmol) and **21f** (0.300 g, 0.573 mmol). There was a yellow solid present in the reaction vessel which was filtered, dried, and determined to be the title compound. Yield 0.320 g, 90%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.30 (s, 1H), 12.18 (s, 1H), 7.75 (d, J = 8.2 Hz, 1H), 7.66 (d, J = 8.2 Hz, 1H), 7.58 (t, J = 7.8 Hz, 1H), 7.48−7.39 (m, 3H), 7.36 (d, J = 8.1 Hz, 1H), 7.22 (d, J = 8.1 Hz, 1H), 7.15 (t, J = 7.7 Hz, 1H), 7.03 (d, J = 8.2 Hz, 1H), 6.74 (d, J = 7.9 Hz, 2H), 5.33 (dd, J = 11.8, 4.4 Hz, 1H), 3.74 (dd, J = 18.7, 12.1 Hz, 1H), 2.76 (dd, J = 18.5, 4.4 Hz, 1H), 2.65−2.39 (m, 2H), 2.39−2.30 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.52, 168.65, 160.14, 152.69, 149.89, 141.52, 138.55, 134.40, 131.73, 131.45, 131.24, 130.82, 127.63, 127.28, 123.41, 122.41, 121.82, 120.09, 119.07, 115.59, 58.28, 45.14, 28.49, 28.23. HRMS (m/z): $[M - H]^-$ calcd for $C_{28}H_{20}Br_2N_3O_4$, 619.98260; found, 619.98231. Anal. Calcd for $C_{28}H_{21}Br_2N_3O_4$: C, 53.96; H, 3.40; N, 6.74. Found: C, 52.23; H, 3.67; N, 5.55. HPLC 85% MeOH/H_2O 0.1% formic acid) t_R = 1.2 min; >95% purity; 75% ACN/H_2O (0.1% formic acid) t_R = 0.84 min; >94% purity.

4-{3-[4-(4-Bromophenyl)-2-oxo-1,2-dihydroquinolin-3-yl]-5-(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl}-4-oxobutanoic Acid (22). Compound **22** was prepared according to general procedure G using **87** (0.105 g, 1.04 mmol) and **22f** (0.500 g, 1.044 mmol). After removal of the THF, the residue was partitioned between EtOAc and acidified brine. The organics were washed three times, dried over magnesium sulfate, and concentrated under vacuum. The title compound was obtained after column chromatography using 10% MeOH/DCM. Yield 0.240 g, 39.7%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.29 (s, 1H), 12.05 (s, 1H), 7.74 (dd, J = 8.1, 2.2 Hz, 1H), 7.65 (dd, J = 8.1, 2.2 Hz, 1H), 7.58 (t, J = 7.6 Hz, 1H), 7.42 (d, J = 8.3 Hz, 1H), 7.36 (dd, J = 8.1, 2.3 Hz, 1H), 7.34−7.25 (m, 2H), 7.22 (dd, J = 8.2, 2.3 Hz, 1H), 7.15 (t, J = 7.6 Hz, 1H), 7.03 (d, J = 8.1 Hz, 1H), 6.85−6.75 (m, 2H), 5.35 (dd, J = 11.9, 4.4 Hz, 1H), 3.73 (dd, J =18.4, 12.1 Hz, 1H), 2.76 (dd, J = 18.6, 4.4 Hz, 1H), 2.65−2.42 (m, 2H), 2.34 (t, J = 6.7 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.54, 168.69, 160.17, 152.70, 149.90, 141.10, 138.58, 134.42, 131.61, 131.45, 131.27, 130.84, 128.34, 127.30, 123.44, 122.42, 119.08, 115.60, 58.23, 45.16, 28.48, 28.23. HRMS (m/z): $[M - H]^-$ calcd for $C_{28}H_{20}BrClN_3O_4$, 576.03312; found, 576.03267. Anal. Calcd for $C_{28}H_{21}BrClN_3O_4 \cdot 0.50H_2O$: C, 57.21; H, 3.77; N, 7.15. Found: C, 57.02; H, 3.72; N, 7.05.

dx.doi.org/10.1021/jm400652r | J. Med. Chem. XXXX, XXX, XXX−XXX

4-{3-[4-(4-Bromophenyl)-2-oxo-1,2-dihydroquinolin-3-yl]-5-(4-fluorophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl}-4-oxobutanoic Acid (23). Compound **23** was prepared according to general procedure G using **87** (0.054 g, 0.541 mmol) and **23f** (0.250 g, 0.541 mmol). The title compound, a yellow solid, was obtained after purifying using flash chromatography (0−10% MeOH/DCM). Yield 0.100 g, 32.9%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.29 (s, 1H), 12.11 (s, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.66 (d, J = 8.2 Hz, 1H), 7.58 (t, J = 7.7 Hz, 1H), 7.43 (d, J = 8.3 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.23 (d, J = 8.2 Hz, 1H), 7.15 (t, J = 7.6 Hz, 1H), 7.05 (t, J = 8.9 Hz, 3H), 6.83 (dd, J = 8.4, 5.2 Hz, 2H), 5.35 (dd, J = 12.0, 4.4 Hz, 1H), 3.72 (dd, J = 18.5, 12.0 Hz, 1H), 2.78 (dd, J = 18.4, 4.4 Hz, 1H), 2.65−2.43 (m, 2H), 2.34 (t, J = 6.7 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.56, 168.64, 160.16, 152.71, 149.87, 138.56, 138.36, 134.42, 131.69, 131.46, 131.24, 130.86, 127.46, 127.38, 127.29, 123.47, 122.43, 121.80, 119.08, 115.59, 115.18, 114.96, 58.15, 45.26, 28.50, 28.23. ^{19}F NMR (376 MHz, DMSO-d_6) δ −116.06 to −116.19 (m). HRMS (m/z): [M + H]$^+$ calcd for $C_{28}H_{22}BrFN_3O_4$, 562.07722; found, 562.07669. Anal. Calcd for $C_{28}H_{21}BrFN_3O_4$: C, 59.80; H, 3.76; N, 7.47. Found: C, 50.97; H, 3.55; N, 6.00. HPLC 75−95% MeOH/H_2O (0.1% formic acid) t_R = 0.89 min; >95% purity; 75% ACN/H_2O (0.1% formic acid) t_R = 0.67 min; >95% purity.

4-{3-[4-(4-Bromophenyl)-2-oxo-1,2-dihydroquinolin-3-yl]-5-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl}-4-oxobutanoic Acid (24). Compound **24** was prepared according to general procedure G using **87** (0.023 g, 0.23 mmol) and **24f** (0.100 g, 0.23 mmol). The title compound was obtained after purifying using flash chromatography (0−10% MeOH/DCM) as an off-white solid. Yield 0.110 g, 86%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.29 (s, 1H), 12.20 (s, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.67−7.54 (m, 2H), 7.47−7.34 (m, 2H), 7.23 (d, J = 5.4 Hz, 4H), 7.15 (t, J = 7.6 Hz, 1H), 7.03 (d, J = 8.3 Hz, 1H), 6.77 (d, J = 6.7 Hz, 2H), 5.32 (dd, J = 11.8, 4.7 Hz, 1H), 3.75 (dd, J = 18.2, 11.9 Hz, 1H), 2.77 (dd, J = 18.3, 4.5 Hz, 1H), 2.62−2.41 (m, 2H), 2.33 (t, J = 6.7 Hz, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 173.54, 168.57, 160.17, 152.68, 149.84, 142.25, 138.54, 134.42, 131.74, 131.40, 131.25, 131.16, 130.84, 128.36, 127.28, 127.03, 125.33, 123.55, 122.39, 121.77, 119.11, 115.57, 58.87, 45.39, 28.54, 28.24. HRMS (m/z): [M − H]$^-$ calcd for $C_{28}H_{21}BrN_3O_4$, 542.07209; found, 542.07235. Anal. Calcd for $C_{28}H_{22}BrN_3O_4$: C, 61.89; H, 3.89; N, 7.73. Found: C, 56.02; H, 4.02; N, 6.78. HPLC 95% MeOH/H_2O (0.1% formic acid) t_R = 0.91 min; >95% purity; 65% ACN/H_2O (0.1% formic acid) t_R = 0.70 min; >95% purity.

4-{5-(4-Bromophenyl)-3-[4-(4-chlorophenyl)-2-oxo-1,2-dihydroquinolin-3-yl]-4,5-dihydro-1*H*-pyrazol-1-yl}-4-oxobutanoic Acid (25). Compound **25** was prepared according to general procedure G using **87** (0.031 g, 0.31 mmol) and **25f** (0.150 g, 0.31 mmol). The title compound was obtained after purifying using flash chromatography (0−10% MeOH/DCM) as an off-white solid. Yield 0.048 g, 27%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.30 (s, 1H), 7.64−7.48 (m, 2H), 7.42 (t, J = 7.9 Hz, 5H), 7.28 (d, J = 8.2 Hz, 1H), 7.15 (t, J = 7.6 Hz, 1H), 7.02 (d, J = 8.1 Hz, 1H), 6.74 (d, J = 8.0 Hz, 2H), 5.33 (dd, J = 11.9, 4.4 Hz, 1H), 3.72 (dd, J = 18.5, 12.0 Hz, 1H), 2.79−2.69 (m, 1H), 2.53−2.36 (m, 2H), 2.32 (t, J = 6.9 Hz, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 174.14, 169.65, 160.19, 152.36, 149.87, 141.71, 138.60, 133.96, 133.25, 131.59, 131.44, 131.23, 130.56, 128.37, 127.64, 127.26, 123.65, 122.43, 120.06, 119.18, 115.66, 58.23, 45.12, 30.27, 29.69. HRMS (m/z): [M + H]$^+$ calcd for $C_{28}H_{22}BrClN_3O_4$, 578.04767; found, 578.04719. Anal. Calcd for $C_{28}H_{21}BrClN_3O_4$·1.20H_2O: C, 56.01; H, 3.93; N, 7.00. Found: C, 56.02; H, 4.02; N, 6.78.

4-{5-(4-Chlorophenyl)-3-[4-(4-chlorophenyl)-2-oxo-1,2-dihydroquinolin-3-yl]-4,5-dihydro-1*H*-pyrazol-1-yl}-4-oxobutanoic Acid (26). Compound **26** was prepared according to general procedure G using **87** (0.046 g, 0.460 mmol) and **26f** (0.200 g, 0.460 mmol). The title compound was obtained after removing the THF under vacuum, precipitating from EtOAc with hexanes and further purification using flash chromatography (2−10% MeOH/DCM) as a yellow solid. Some compound was lost because of spillage. Yield 0.054 g, 22%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.29 (s, 1H), 12.06 (s, 1H), 7.65−7.55 (m, 2H), 7.52 (dd, J = 8.2, 2.3 Hz, 1H), 7.48−7.38 (m, 2H), 7.34−7.24 (m, 3H), 7.15 (t, J = 7.6 Hz, 1H), 7.03 (d, J = 8.1 Hz, 1H), 6.82 (d, J = 8.5 Hz, 2H), 5.35 (dd, J = 11.9, 4.5 Hz, 1H), 3.73 (dd, J = 18.5, 12.0 Hz, 1H), 2.77 (dd, J = 18.4, 4.4 Hz, 1H), 2.65−2.43 (m, 2H), 2.34 (t, J = 6.7 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.54, 168.67, 160.17, 152.72, 149.89, 141.09, 138.57, 134.04, 133.22, 131.59, 131.46, 130.55, 128.32, 127.31, 122.42, 119.15, 115.59, 58.21, 45.16, 28.47, 28.20. HRMS (m/z): [M + H]$^+$ calcd for $C_{28}H_{22}Cl_2N_3O_4$, 534.09819; found, 534.09787. Anal. Calcd for $C_{28}H_{21}Cl_2N_3O_4$: C, 62.93; H; 3.96; N, 7.86. Found: C, 62.38; H, 4.03; N, 7.73. HPLC 85% MeOH/H_2O (0.1% formic acid) t_R = 0.95 min; >95% purity; 75% ACN/H_2O (0.1% formic acid) t_R = 0.61 min; >95% purity.

4-{3-[4-(4-Chlorophenyl)-2-oxo-1,2-dihydroquinolin-3-yl]-5-(4-fluorophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl}-4-oxobutanoic Acid (27). Compound **27** was prepared according to general procedure G using **87** (0.029 g, 0.287 mmol) and **27f** (0.120 g, 0.287 mmol). The title compound was obtained after removal of the residual solvent, dissolving the crude material in DCM and washing 3× with acidified brine. The organics were collected, dried over magnesium sulfate, and concentrated to yield the title compound as a brown solid. Yield 0.085 g, 57%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.30 (s, 1H), 12.08 (s, 1H), 7.65−7.49 (m, 3H), 7.47−7.34 (m, 2H), 7.34−7.26 (m, 1H), 7.15 (t, J = 7.7 Hz, 1H), 7.10−7.00 (m, 3H), 6.88−6.80 (m, 2H), 5.35 (dd, J = 11.7, 4.3 Hz, 1H), 3.72 (dd, J = 18.1, 12.0 Hz, 1H), 2.78 (dd, J = 18.5, 4.3 Hz, 1H), 2.64−2.42 (m, 2H), 2.33 (t, J = 6.6 Hz, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 174.19, 169.29, 160.82, 153.38, 150.51, 139.22, 138.99, 134.70, 133.85, 132.08, 131.24, 128.97, 128.11, 128.05, 127.94, 124.20, 123.06, 119.81, 116.25, 115.76, 115.62, 58.80, 45.91, 29.16, 28.87. HRMS (m/z): [M − H]$^-$ calcd for $C_{28}H_{20}ClFN_3O_4$, 516.11319; found, 516.11362. Anal. Calcd for $C_{28}H_{21}ClFN_3O_4$·0.70DCM: C, 59.70; H, 3.91; N, 7.28. Found: C, 59.54; H, 4.15; N, 7.20.

4-{3-[4-(4-Chlorophenyl)-2-oxo-1,2-dihydroquinolin-3-yl]-5-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl}-4-oxobutanoic Acid (28). Compound **28** was prepared according to general procedure G using **87** (0.055 g, 0.550 mmol) and **28f** (0.220 g, 0.550 mmol). The title compound was obtained by filtering from DCM after removal of the THF in vacuo. Yield 0.204 g, 74%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.29 (s, 1H), 12.13 (s, 1H), 7.66−7.54 (m, 2H), 7.54−7.39 (m, 3H), 7.32−7.11 (m, 5H), 7.03 (d, J = 8.1 Hz, 1H), 6.77 (dd, J = 6.5, 3.0 Hz, 2H), 5.32 (dd, J = 11.9, 4.3 Hz, 1H), 3.75 (dd, J = 18.4, 12.1 Hz, 1H), 2.77 (dd, J = 18.3, 4.3 Hz, 1H), 2.64−2.39 (m, 2H), 2.33 (t, J = 6.6 Hz, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 173.55, 168.57, 160.17, 152.70, 149.84, 142.23, 138.54, 134.03, 133.17, 131.48, 131.40, 130.57, 128.33, 128.25, 127.28, 127.03, 125.33, 123.62, 122.39, 119.18, 115.57, 58.86, 45.39, 28.53, 28.23. HRMS (m/z): [M − H]$^-$ calcd for $C_{28}H_{21}ClN_3O_4$, 498.12261; found, 498.12276. HPLC 85% MeOH/H_2O (0.1% formic acid) t_R = 0.87 min; >95% purity; 75% ACN/H_2O (0.1% formic acid) t_R = 0.69 min; >95% purity.

4-{5-(4-Chlorophenyl)-3-[4-(4-fluorophenyl)-2-oxo-1,2-dihydroquinolin-3-yl]-4,5-dihydro-1*H*-pyrazol-1-yl}-4-oxobutanoic Acid (29). Compound **29** was prepared according to general procedure G using **87** (0.072 g, 0.718 mmol) and **29f** (0.300 g, 0.718 mmol). The title compound was obtained by filtering from DCM after removal of the THF in vacuo. Yield 0.210 g, 57%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.27 (s, 1H), 12.09 (s, 1H), 7.58 (t, J = 7.7 Hz, 1H), 7.43 (d, J = 7.6 Hz, 2H), 7.40−7.25 (m, 5H), 7.15 (t, J = 7.7 Hz, 1H), 7.04 (d, J = 8.2 Hz, 1H), 6.86 (d, J = 8.2 Hz, 2H), 5.34 (dd, J = 11.9, 4.6 Hz, 1H), 3.74 (dd, J = 18.5, 11.9 Hz, 1H), 2.79 (dd, J = 18.4, 4.6 Hz, 1H), 2.64−2.42 (m, 2H), 2.33 (t, J = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.54, 168.67, 160.21, 152.82, 150.17, 141.11, 138.53, 131.57, 131.44, 130.80, 128.30, 127.36, 123.62, 122.38, 119.40, 115.57, 115.31, 115.10, 58.21, 45.16, 28.50, 28.20. HRMS (m/z): [M + Na]$^+$ calcd for $C_{28}H_{21}ClFN_3O_4Na$, 540.10968; found, 540.10938. Anal. Calcd for $C_{28}H_{21}ClFN_3O_4$·0.90H_2O: C, 62.96; H, 4.30; N, 7.86. Found: C, 62.80; H, 4.06; N: 7.80.

4-[5-(4-Chlorophenyl)-3-(2-oxo-4-p-tolyl-1,2-dihydroquinolin-3-yl)-4,5-dihydro-1*H*-pyrazol-1-yl]-4-oxobutanoic Acid (30). Compound **30** was prepared according to general procedure G using **87** (0.060 g, 0.604 mmol) and **30f** (0.250 g, 0.604 mmol). The title

dx.doi.org/10.1021/jm400652r | J. Med. Chem. XXXX, XXX, XXX−XXX

compound was obtained as a yellow solid after purifying using flash chromatography (2−10% MeOH/DCM) followed by precipitation from EtOAc using hexanes. Yield 0.260 g, 84%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.24 (s, 1H), 12.08 (s, 1H), 7.57 (t, J = 7.5 Hz, 1H), 7.42 (d, J = 8.2 Hz, 1H), 7.36−7.21 (m, 5H), 7.18−7.04 (m, 3H), 6.84 (dd, J = 8.5, 2.3 Hz, 2H), 5.32 (dd, J = 11.9, 4.4 Hz, 1H), 3.68 (dd, J = 18.4, 12.0 Hz, 1H), 2.74 (dd, J = 18.4, 4.5 Hz, 1H), 2.63−2.39 (m, 5H), 2.31 (t, J = 6.7 Hz, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 173.55, 168.65, 160.25, 152.86, 151.26, 141.13, 138.55, 137.66, 132.18, 131.51, 131.28, 129.24, 128.79, 128.69, 128.54, 128.26, 127.45, 123.25, 122.23, 119.43, 115.52, 58.17, 45.20, 28.79, 28.60, 28.24, 20.90. HRMS (m/z): [M + H]$^+$ calcd for $C_{29}H_{25}ClN_3O_4$, 514.15281; found, 514.15260. Anal. Calcd for $C_{29}H_{24}ClN_3O_4\cdot0.80H_2O$: C, 65.92; H, 4.88; N, 7.95. Found: C, 65.86; H, 4.84; N, 7.75.

4-{5-(4-Chlorophenyl)-3-[4-(4-methoxyphenyl)-2-oxo-1,2-dihydroquinolin-3-yl]-4,5-dihydro-1*H*-pyrazol-1-yl}-4-oxobutanoic Acid (31). Compound **31** was prepared according to general procedure G using **87** (0.047 g, 0.465 mmol) and **31f** (0.200 g, 0.465 mmol). The title compound was obtained as a white solid by filtering from DCM after removal of the THF in vacuo. Yield 0.165 g, 67%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.05 (s, 1H), 12.24 (s, 1H), 7.57 (t, J = 7.7 Hz, 1H), 7.42 (d, J = 8.3 Hz, 2H), 7.38−7.06 (m, 6H), 7.01 (d, J = 8.5 Hz, 1H), 6.83 (d, J = 7.8 Hz, 3H), 5.33 (dd, J = 11.8, 4.4 Hz, 1H), 3.85 (s, 3H), 3.67 (dd, J = 18.4, 12.1 Hz, 1H), 2.78−2.53 (m, 2H), 2.41−2.22 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 175.22, 173.68, 168.75, 160.42, 160.28, 159.20, 152.91, 151.06, 141.19, 138.54, 131.50, 131.26, 131.01, 130.92, 130.00, 128.39, 128.24, 127.68, 127.44, 127.00, 123.52, 122.23, 119.66, 115.54, 113.68, 113.56, 58.16, 55.17, 45.24, 32.60, 28.76, 28.44. HRMS (m/z): [M + K]$^+$ calcd for $C_{29}H_{24}ClN_3O_5$, 568.10361; found, 568.10341. Anal. Calcd for $C_{29}H_{24}ClN_3O_5$: C, 65.72; H, 4.56; N, 7.92. Found: C, 57.27; H, 4.20; N, 6.50. HPLC 85% MeOH/H_2O (0.1% formic acid) t_R = 0.89 min; >95% purity; 75% ACN/H_2O (0.1% formic acid) t_R = 0.67 min; >95% purity.

4-{5-(4-Chlorophenyl)-3-[4-(4-cyanophenyl)-2-oxo-1,2-dihydroquinolin-3-yl]-4,5-dihydro-1*H*-pyrazol-1-yl}-4-oxobutanoic Acid (32). Compound **32** was prepared according to general procedure G using **87** (0.059 g, 0.588 mmol) and **32f** (0.150 g, 0.588 mmol). The title compound was obtained as a yellow solid after precipitation from EtOAc using hexanes followed by purification using flash chromatography with 10% MeOH/DCM as a yellow solid. Yield 0.150 g, 48.6%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.33 (s, 1H), 12.09 (s, 1H), 7.97 (ddd, J = 11.8, 7.7, 1.7 Hz, 2H), 7.64−7.56 (m, 2H), 7.50 (dd, J = 7.8, 1.7 Hz, 1H), 7.43 (d, J = 8.1 Hz, 1H), 7.35−7.27 (m, 2H), 7.14 (t, J = 7.7 Hz, 1H), 6.95 (dd, J = 8.2, 1.2 Hz, 1H), 6.89−6.84 (m, 2H), 5.35 (dd, J = 12.0, 4.4 Hz, 1H), 3.79 (dd, J = 18.5, 12.0 Hz, 1H), 2.89 (dd, J = 18.5, 4.5 Hz, 1H), 2.57−2.23 (m, 4H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 173.45, 168.70, 160.12, 152.50, 149.37, 140.99, 140.55, 138.61, 132.20, 131.62, 130.59, 130.50, 129.79, 128.37, 128.25, 127.32, 127.23, 123.18, 122.52, 118.75, 118.63, 115.65, 111.18, 58.30, 45.00, 28.77, 28.22. HRMS (m/z): [M − H]$^-$ calcd for $C_{29}H_{20}ClN_4O_4$, 523.11786; found, 523.11828. HPLC 85% MeOH/H_2O (0.1% formic acid) t_R = 0.67 min; 87% purity; 75% ACN/H_2O (0.1% formic acid) t_R = 0.89 min; 85% purity.

4-[5-(4-Chlorophenyl)-3-{2-oxo-4-(4-(trifluoromethyl)-phenyl)-1,2-dihydroquinolin-3-yl}-4,5-dihydro-1*H*-pyrazol-1-yl]-4-oxobutanoic Acid (33). Compound **33** was prepared according to general procedure G using **87** (0.039 g, 0.385 mmol) and **33f** (0.180 g, 0.220 mmol). The title compound was obtained after flash column chromatography using 0−10% MeOH/DCM and precipitation from EtOAc using hexanes as a yellow solid. Yield 0.125 g, 57.2%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.34 (s, 1H), 12.07 (s, 1H), 7.90 (d, J = 8.1 Hz, 1H), 7.85 (d, J = 8.1 Hz, 1H), 7.65 (d, J = 8.1 Hz, 1H), 7.65 (d, J = 8.1 Hz, 1H), 7.59 (t, J = 7.6 Hz, 1H), 7.53 (d, J = 8.1 Hz, 1H), 7.45 (d, J = 8.2 Hz, 1H), 7.26 (d, J = 8.2 Hz, 2H), 7.15 (t, J = 7.7 Hz, 1H), 6.98 (d, J = 8.1 Hz, 1H), 6.86 (d, J = 8.2 Hz, 2H), 5.36 (dd, J = 12.0, 4.6 Hz, 1H), 3.80 (dd, J = 18.4, 12.0 Hz, 1H), 2.91 (dd, J = 18.5, 4.8 Hz, 1H), 2.52−2.21 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.42, 168.68, 160.19, 152.58, 149.61, 141.06, 139.85, 138.62, 131.62, 130.35, 129.69, 128.31, 127.27, 125.20, 123.28, 122.54, 118.95, 115.63, 58.23, 45.04, 28.32, 28.05. ^{19}F NMR (376 MHz, DMSO-d_6) δ −61.595 (s). HRMS (m/z): [M − H]$^-$ calcd for $C_{29}H_{20}ClF_3N_3O_4$, 566.10999; found, 566.11036. Anal. Calcd for $C_{29}H_{21}ClF_3N_3O_4\cdot0.40H_2O$: C, 60.56; H, 3.82; N, 7.31. Found: C, 60.57; H, 4.00; N: 7.23.

4-{5-(4-Chlorophenyl)-3-[4-(3-fluorophenyl)-2-oxo-1,2-dihydroquinolin-3-yl]-4,5-dihydro-1*H*-pyrazol-1-yl}-4-oxobutanoic Acid (34). Compound **34** was prepared according to general procedure G using **87** (0.060 g, 0.598 mmol) and **34f** (0.250 g, 0.367 mmol). The title compound was obtained after precipitating from EtOAc using hexanes followed by flash column chromatography using 10% MeOH/DCM, as a yellow solid. Yield 0.190 g, 61.3%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.24 (s, 1H), 12.08 (s, 1H), 7.57 (t, J = 7.5 Hz, 1H), 7.42 (d, J = 8.2 Hz, 1H), 7.36−7.21 (m, 5H), 7.18−7.04 (m, 3H), 6.84 (d, J = 8.2 Hz, 2H), 5.32 (dd, J = 12.0, 4.5 Hz, 1H), 3.68 (dd, J = 18.5, 12.0 Hz, 1H), 2.74 (dd, J = 18.5, 4.5 Hz, 1H), 2.52−2.39 (m, 4H). ^{13}C NMR (100 MHz DMSO-d_6) δ 173.48, 168.60, 160.19, 149.62, 141.15, 138.53, 131.53, 131.45, 130.35, 128.37, 127.33, 127.16, 122.44, 119.07, 115.57, 58.27, 45.11, 28.79, 28.47, 28.18. ^{19}F NMR (376 MHz, DMSO-d_6) δ −113.29 to −113.63 (m). HRMS (m/z): [M + Na]$^+$ calcd for $C_{28}H_{21}ClFN_3O_4Na$, 540.10968; found, 540.11014. Anal. Calcd for $C_{28}H_{21}ClFN_3O_4\cdot0.90H_2O$: C, 62.96; H, 4.30; N, 7.87. Found: C, 63.04; H, 4.38; N, 7.55.

4-{5-(4-Chlorophenyl)-3-[4-(3-chlorophenyl)-2-oxo-1,2-dihydroquinolin-3-yl]-4,5-dihydro-1*H*-pyrazol-1-yl}-4-oxobutanoic Acid (35). Compound **35** was prepared according to general procedure G using **87** (0.069 g, 0.691 mmol) and **35f** (0.300 g, 0.691 mmol). The title compound was obtained as a yellow solid after flash column chromatography using 2−10% MeOH/DCM. Yield 0.170 g, 46.1%. ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.25 (s, 1H), 12.04 (s, 1H), 7.58−7.51 (m, 2H), 7.51−7.46 (m, 1H), 7.39 (d, J = 8.2 Hz, 1H), 7.36−7.32 (m, 1H), 7.25 (ddt, J = 7.1, 4.9, 2.5 Hz, 2H), 7.19 (d, J = 7.5 Hz, 1H), 7.12 (t, J = 7.7 Hz, 1H), 7.01−6.94 (m, 1H), 6.81−6.73 (m, 2H), 5.34−5.28 (m, 1H), 3.83−3.74 (m, 1H), 2.84−2.70 (m, 1H), 2.52−2.34 (m, 2H), 2.31−2.24 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.50, 168.64, 160.20, 152.66, 149.46, 141.16, 138.53, 137.44, 137.28, 133.18, 131.56, 131.47, 130.15, 130.00, 129.59, 128.49, 128.40, 127.29, 127.16, 123.43, 122.48, 119.17, 115.58, 58.30, 45.10, 28.78, 28.49, 28.19. HRMS (m/z): [M + Na]$^+$ calcd for $C_{28}H_{21}Cl_2N_3O_4Na$, 556.08013; found, 556.07990. Anal. Calcd for $C_{28}H_{21}Cl_2N_3O_4\cdot0.70H_2O$: C, 61.48; H, 4.13; N, 7.68. Found: C, 61.51; H, 4.11; N: 7.48.

4-{5-(4-Chlorophenyl)-3-[2-oxo-4-(*m*-tolyl)-1,2-dihydroquinolin-3-yl]-4,5-dihydro-1*H*-pyrazol-1-yl}-4-oxobutanoic Acid (36). Compound **36** was prepared according to general procedure G using **87** (0.060 g, 0.604 mmol) and **36f** (0.250 g, 0.604 mmol). The title compound was obtained as a yellow solid after flash column chromatography using 0−10% MeOH/DCM followed by precipitation from hot EtOAc and hexanes. Yield 0.240 g, 77.0%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.21 (s, 1H), 12.05 (s, 1H), 7.53 (t, J = 7.6 Hz, 1H), 7.42−7.27 (m, 3H), 7.27−7.17 (m, 2H), 7.16−7.06 (m, 2H), 7.00 (q, J = 10.2, 8.9 Hz, 2H), 6.80−6.67 (m, 2H), 5.33−5.23 (m, 1H), 3.80−3.62 (m, 1H), 2.76 (dd, J = 18.4, 4.6 Hz, 0.5H), 2.64 (dd, J = 18.5, 4.6 Hz, 0.5H), 2.57−2.34 (m, 5H), 2.31−2.18 (m, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 173.61, 173.54, 168.63, 168.57, 160.29, 152.88, 152.70, 151.33, 151.24, 141.25, 141.20, 138.52, 137.49, 137.43, 135.17, 135.03, 131.53, 131.30, 130.25, 128.84, 128.36, 128.32, 128.13, 127.50, 127.41, 127.34, 127.26, 126.39, 125.46, 123.16, 122.28, 119.42, 115.55, 115.51, 58.28, 58.23, 45.25, 28.90, 28.79, 28.67, 28.57, 28.35, 28.24, 28.14, 21.09, 21.02, 20.97, 20.91. HRMS (m/z): [M + H]$^+$ calcd for $C_{29}H_{25}ClN_3O_4$, 514.15281; found, 514.15263. Anal. Calcd for $C_{29}H_{24}ClN_3O_4\cdot1.50H_2O\cdot0.06$EtOAc: C, 64.29; H, 5.07; N, 7.69. Found: C, 64.65; H, 4.90; N, 7.29.

4-{5-(4-Chlorophenyl)-3-[4-(3-methoxyphenyl)-2-oxo-1,2-dihydroquinolin-3-yl]-4,5-dihydro-1*H*-pyrazol-1-yl}-4-oxobutanoic Acid (37). Compound **37** was prepared according to general procedure G using **87** (0.070 g, 0.698 mmol) and **37f** (0.300g, 0.698 mmol). The title compound was obtained as a yellow solid after flash column chromatography using 0−10% MeOH/DCM. Yield 0.090 g, 24.3%. ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.23 (s, 1H), 12.03 (s, 1H), 7.57 (t, J = 7.8 Hz, 1H), 7.48−7.35 (m, 2H), 7.32−7.21 (m, 2H),

dx.doi.org/10.1021/jm400652r | J. Med. Chem. XXXX, XXX, XXX−XXX

7.18−7.12 (m, 1H), 7.09 (t, J = 8.3 Hz, 2H), 6.95 (d, J = 9.9 Hz, 1H), 6.85−6.72 (m, 3H), 5.37−5.30 (m, 1H), 3.84−3.64 (m, 4H), 2.83−2.72 (m, 1H), 2.60−2.51 (m, 2H), 2.31 (t, J = 7.1 Hz, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 173.52, 168.60, 160.26, 159.03, 152.90, 150.95, 141.24, 141.19, 138.52, 138.50, 136.50, 136.46, 131.56, 131.48, 131.33, 131.31, 129.43, 129.38, 128.35, 128.21, 128.14, 127.46, 127.43, 127.19, 123.24, 123.14, 122.32, 121.65, 120.70, 119.31, 119.27, 115.51, 115.13, 114.02, 113.88, 113.58, 58.25, 55.26, 54.99, 45.30, 45.19, 28.59, 28.22. HRMS (m/z): [M + H]$^+$ calcd for $C_{29}H_{25}ClN_3O_5$, 530.14773; found, 530.14715. Anal. Calcd for $C_{29}H_{24}ClN_3O_5$: C, 65.72; H, 4.56; N, 7.93. Found: C, 65.52; H, 4.72; N, 7.97.

4-{5-(4-Chlorophenyl)-3-[4-(3-cyanophenyl)-2-oxo-1,2-dihydroquinolin-3-yl]-4,5-dihydro-1*H*-pyrazol-1-yl}-4-oxobutanoic Acid (38). Compound **38** was prepared according to general procedure G using **87** (0.021g, 0.212 mmol) and **38f** (0.090 g, 0.212 mmol). The title compound was obtained as a yellow solid after flash column chromatography using 0−10% MeOH/DCM. Yield 0.034 g, 31.0%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.35 (s, 1H), 12.10 (s, 1H), 8.04−7.91 (m, 1H), 7.84−7.67 (m, 2H), 7.65−7.55 (m, 2H), 7.43 (d, J = 8.2 Hz, 1H), 7.31 (d, J = 8.3 Hz, 2H), 7.16 (t, J = 7.7 Hz, 1H), 6.97 (d, J = 8.2 Hz, 1H), 6.82 (m, 2H), 5.40−5.32 (m, 1H), 3.96−3.81 (m, 1H), 2.87 (dt, J = 18.3, 4.1 Hz, 1H), 2.42 (d, J = 7.6 Hz, 2H), 2.35−2.26 (m, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 173.58, 173.42, 168.61, 160.13, 152.58, 148.90, 141.02, 138.54, 136.80, 136.70, 134.66, 133.48, 133.05, 132.18, 132.09, 131.73, 131.57, 129.51, 129.32, 128.47, 128.41, 127.34, 127.25, 127.04, 123.64, 123.53, 122.54, 119.03, 118.52, 115.59, 111.60, 111.40, 58.27, 45.03, 28.75, 28.32, 28.10. HRMS (m/z): [M − H]$^-$ calcd for $C_{29}H_{20}ClN_4O_4$, 523.11786; found, 523.11778. Anal. Calcd for $C_{29}H_{21}ClN_4O_4$: C, 66.35; H, 4.03; N, 10.67. Found: C, 63.97; H, 4.59; N, 9.39. HPLC 85% MeOH/H_2O (0.1% formic acid) t_R = 0.68 min; >95% purity; 75% ACN/H_2O (0.1% formic acid) t_R = 0.59 min; >95% purity.

4-[5-(4-Chlorophenyl)-3-{2-oxo-4-[3-(trifluoromethyl)-phenyl]-1,2-dihydroquinolin-3-yl}-4,5-dihydro-1*H*-pyrazol-1-yl]-4-oxobutanoic Acid (39). Compound **39** was prepared according to general procedure G using **87** (0.054 g, 0.53 mmol) and **39f** (0.250 g, 0.53 mmol). The title compound was obtained as a yellow solid using a 0−8% MeOH/DCM. Yield 0.073 g, 24%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.34 (s, 1H), 12.06 (s, 1H), 7.96−7.84 (m, 1H), 7.82−7.66 (m, 2H), 7.59 (t, J = 8.4 Hz, 2H), 7.44 (d, J = 8.3 Hz, 1H), 7.28 (d, J = 8.2 Hz, 1H), 7.23 (d, J = 8.1 Hz, 1H), 7.20−7.13 (m, 1H), 6.98 (d, J = 8.2 Hz, 0.5H), 6.92 (d, J = 8.2 Hz, 0.5H), 6.84 (d, J = 8.1 Hz, 1H), 6.76 (d, J = 8.0 Hz, 1H), 5.34 (dt, J = 12.2, 4.3 Hz, 1H), 3.95−3.70 (m, 1H), 3.00−2.74 (m, 1H), 2.54−2.23 (m, 4H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 173.40, 173.34, 168.62, 168.52, 160.20, 160.17, 152.67, 152.61, 149.38, 141.10, 141.03, 138.57, 136.57, 136.47, 133.59, 132.57, 131.60, 131.51, 129.50, 129.33, 129.15, 128.92, 128.49, 128.38, 128.30, 127.67, 127.25, 127.17, 127.13, 126.47, 125.07, 123.62, 123.45, 122.54, 122.36, 119.26, 119.11, 115.61, 58.26, 58.21, 45.12, 45.01, 28.37, 28.29, 28.19, 28.08. HRMS (m/z): [M + H]$^+$ calcd for $C_{29}H_{22}ClF_3N_3O_4$, 568.12455; found, 568.12417. Anal. Calcd for $C_{29}H_{21}ClF_3N_3O_4\cdot0.20H_2O$; C, 60.94; H, 3.77; N, 7.35. Found: C, 60.79; H, 3.96; N, 7.33.

4-{3-[4-(4-Chloro-3-fluorophenyl)-2-oxo-1,2-dihydroquinolin-3-yl]-5-(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl}-4-oxobutanoic Acid (40). Compound **40** was prepared according to general procedure G using **87** (0.040 g, 0.398 mmol) and **40f** (0.180 g, 0.398 mmol). The title compound was obtained after flash column chromatography using 0−10%MeOH/DCM as a yellow solid followed by precipitation from EtOAc and hexanes. Yield 0.096 g, 43.7%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.33 (s, 1H), 12.12 (s, 1H), 7.79−7.64 (m, 1H), 7.62−7.51 (m, 2H), 7.46−7.38 (m, 2H), 7.33−7.23 (m, 2H), 7.21−7.00 (m, 2H), 6.93−6.78 (m, 2H), 5.39 (dt, J = 12.1, 4.4 Hz, 1H), 3.85−3.72 (m, 1H), 2.91−2.79 (m, 1H), 2.66−2.39 (m, 2H), 2.34 (td, J = 7.0, 2.2 Hz, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 173.61, 173.47, 173.44, 168.68, 168.66, 168.09, 168.05, 160.11, 157.84, 156.19, 152.77, 152.70, 152.63, 148.67, 141.03, 140.99, 138.55, 136.45, 136.36, 136.30, 131.63, 131.57, 130.63, 130.53, 128.34, 128.28, 127.32, 127.21, 127.12, 127.00, 126.21, 123.57, 123.45, 122.54, 119.69, 119.58, 118.92, 117.28, 115.58, 58.28, 58.17, 45.15, 28.77, 28.39, 28.17. ^{19}F NMR (376 MHz, DMSO-d_6) δ −116.32 to −116.51 (m). HRMS (m/z): [M + K]$^+$ calcd for $C_{28}H_{20}Cl_2FN_3O_4K$, 590.04465; found, 590.04631. Anal. Calcd for $C_{28}H_{20}Cl_2FN_3O_4\cdot0.80H_2O\cdot0.10EtOAc$: C, 59.26; H, 3.92; N, 7.30. Found: C, 59.16; H, 4.21; N, 7.14.

4-{3-[4-(3-Chloro-4-fluorophenyl)-2-oxo-1,2-dihydroquinolin-3-yl]-5-(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl}-4-oxobutanoic Acid (41). Compound **41** was prepared according to general procedure G using **87** (0.040 g, 0.398 mmol) and **41f** (0.180 g, 0.398 mmol). The title compound was obtained after purifying using flash column chromatography using 0−10% MeOH/DCM as a yellow solid. Yield 0.120 g, 54.6%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.32 (s, 1H), 12.12 (s, 1H), 7.73−7.50 (m, 3H), 7.44 (dd, J = 8.2, 1.7 Hz, 2H), 7.29 (td, J = 8.8, 2.0 Hz, 2H), 7.17 (t, J = 7.6 Hz, 1H), 7.09−7.01 (m, 1H), 6.88 (dt, J = 8.6, 2.4 Hz, 2H), 5.38 (dd, J = 10.4, 4.6 Hz, 1H), 3.90−3.76 (m, 1H), 2.93−2.77 (m, 1H), 2.66−2.40 (m, 2H), 2.40−2.28 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.63, 173.48, 173.44, 168.68, 160.15, 155.93, 152.68, 152.60, 148.76, 148.72, 141.01, 138.50, 133.00, 132.90, 131.93, 131.62, 131.57, 131.50, 130.63, 130.51, 129.53, 128.39, 128.34, 127.38, 127.23, 127.11, 123.74, 123.66, 122.50, 119.77, 119.46, 119.24, 116.87, 116.66, 115.56, 58.25, 45.10, 28.78, 28.43, 28.38, 28.15. HRMS (m/z): [M + H]$^+$ calcd for $C_{28}H_{21}Cl_2FN_3O_4$, 552.08877; found, 552.09030. Anal. Calcd for $C_{28}H_{20}Cl_2FN_3O_4$: C, 60.88; H, 3.64; N, 7.61. Found: C, 58.29; H, 4.04; N, 6.66. HPLC 85% MeOH/H_2O (0.1% formic acid) t_R = 0.93 min; >95% purity; 75% ACN/H_2O (0.1% formic acid) t_R = 0.55 min; >95% purity.

4-{5-(4-Chlorophenyl)-3-[4-(3,4-dichlorophenyl)-2-oxo-1,2-dihydroquinolin-3-yl]-4,5-dihydro-1*H*-pyrazol-1-yl}-4-oxobutanoic Acid (42). Compound **42** was prepared according to general procedure G using **87** (0.043 g, 0.427 mmol) and **42f** (0.200 g, 0.427 mmol). The title compound was obtained after purifying flash column chromatography using 0−10% MeOH/DCM as a yellow solid. Yield 0.102 g, 42.0%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.31 (s, 1H), 12.10 (s, 1H), 7.83−7.70 (m, 1H), 7.63−7.54 (m, 2H), 7.46−7.37 (m, 2H), 7.32−7.22 (m, 2H), 7.16 (t, J = 7.7 Hz, 1H), 7.04 (t, J = 7.0 Hz, 1H), 6.87−6.80 (m, 2H), 5.37 (dd, J = 12.0, 4.3 Hz, 1H), 3.88−3.74 (m, 1H), 2.90−2.74 (m, 1H), 2.53−2.39 (m, 2H), 2.38−2.29 (m, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 174.04, 169.33, 160.76, 153.24, 149.13, 141.66, 139.20, 136.68, 132.40, 132.27, 132.19, 131.96, 131.08, 130.76, 129.73, 129.05, 128.98, 127.99, 127.83, 127.74, 123.18, 119.69, 116.23, 58.93, 45.75, 29.62, 29.11, 29.07, 28.86. HRMS (m/z): [M + H]$^+$ calcd for $C_{28}H_{21}Cl_3N_3O_4$, 568.05922; found, 568.06168. Anal. Calcd for $C_{28}H_{20}Cl_3N_3O_4\cdot0.80H_2O$: C, 57.66; H, 3.73; N, 7.20. Found: C, 57.70; H, 3.65; N: 6.94.

4-{5-(4-Chlorophenyl)-3-[4-(3,4-difluorophenyl)-2-oxo-1,2-dihydroquinolin-3-yl]-4,5-dihydro-1*H*-pyrazol-1-yl}-4-oxobutanoic Acid (43). Compound **43** was prepared according to general procedure G using **87** (0.0427 g, 0.427 mmol) and **43f** (0.200 g, 0.427 mmol). The title compound was obtained after flash column chromatography using 0−10% MeOH/DCM as a yellow solid. Yield 0.110 g, 68.8%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.31 (s, 1H), 12.13 (s, 1H), 7.63−7.52 (m, 3H), 7.46−7.39 (m, 1H), 7.35−7.28 (m, 1H), 7.29−7.23 (m, 2H), 7.20−7.10 (m, 1H), 7.06 (d, J = 8.2 Hz, 1H), 6.95−6.84 (m, 2H), 5.43−5.33 (m, 1H), 3.88−3.73 (m, 1H), 2.86 (dd, J = 18.5, 4.4 Hz, 1H), 2.66−2.29 (m, 4H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 174.08, 169.36, 160.79, 153.45, 149.53, 141.69, 139.20, 139.20, 132.28, 132.14, 128.99, 128.91, 127.98, 127.80, 124.26, 123.12, 119.83, 116.22, 58.92, 45.79, 29.07, 28.84. ^{19}F NMR (376 MHz, DMSO-d_6) δ −5.88 to −6.23 (m), −6.44 to −6.75 (m). HRMS (m/z): [M − H]$^-$ calcd for $C_{28}H_{19}ClF_2N_3O_4$, 534.10376; found, 534.10358. Anal. Calcd for $C_{28}H_{20}ClF_2N_3O_4\cdot0.40H_2O$: C, 61.92; H, 3.86; N, 7.74. Found: C, 61.76; H, 4.15; N, 7.52.

4-{5-(4-Chlorophenyl)-3-[4-(3,5-difluorophenyl)-2-oxo-1,2-dihydroquinolin-3-yl]-4,5-dihydro-1*H*-pyrazol-1-yl}-4-oxobutanoic Acid (44). Compound **44** was prepared according to general procedure G using **87** (0.041 g, 0.413 mmol) and **44f** (0.180 g, 0.413 mmol). The title compound as a yellow solid was obtained after purifying using flash column chromatography with 0−10% MeOH/DCM. Yield 0.133 g, 56.5%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.33 (s, 1H), 12.07 (s, 1H), 7.59 (t, J = 7.7 Hz, 1H), 7.47−7.33 (m, 2H), 7.29 (d, J = 8.2 Hz, 2H), 7.23 (d, J = 8.5 Hz, 1H), 7.17 (t, J = 7.6 Hz,

dx.doi.org/10.1021/jm400652r | J. Med. Chem. XXXX, XXX, XXX−XXX

1H), 7.08 (d, J = 8.0 Hz, 2H), 6.89 (d, J = 8.1 Hz, 2H), 5.40 (dd, J = 12.0, 4.6 Hz, 1H), 3.86 (dd, J = 18.4, 12.0 Hz, 1H), 2.90 (dd, J = 18.5, 4.6 Hz, 1H), 2.59−2.41 (m, 2H), 2.33 (t, J = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.65, 173.46, 168.64, 163.55, 163.43, 161.11, 160.95, 160.11, 152.68, 148.60, 141.09, 139.05, 138.95, 138.52, 131.58, 128.55, 128.40, 127.26, 127.13, 123.41, 122.57, 118.79, 115.58, 113.31, 113.12, 112.32, 112.12, 103.85, 58.30, 45.02, 28.80, 28.37, 28.15. ^{19}F (376 MHz, DMSO-d_6) δ −109.98 to −110.05 (m). HRMS (m/z): [M − H]$^-$ calcd for $C_{28}H_{19}ClF_2N_3O_4$, 534.10376; found, 534.10402. Anal. Calcd for $C_{28}H_{20}ClF_2N_3O_4 \cdot 0.50H_2O$: C, 61.71; H, 3.88; N, 7.71. Found: C, 61.52; H, 4.05; N, 7.42.

4-{5-(4-Chlorophenyl)-3-[4-(3,5-dichlorophenyl)-2-oxo-1,2-dihydroquinolin-3-yl]-4,5-dihydro-1*H*-pyrazol-1-yl}-4-oxobutanoic Acid (45). Compound **45** was prepared according to general procedure G using **87** (0.038 g, 0.384 mmol) and **45f** (0.180 g, 0.384 mmol). The title compound was obtained as a yellow solid after purifying using flash column chromatography with 0−10% MeOH/DCM. Yield 0.080 g, 36.6%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.33 (s, 1H), 12.10 (s, 1H), 7.84−7.71 (m, 1H), 7.64−7.56 (m, 2H), 7.51−7.39 (m, 2H), 7.29 (t, J = 7.3 Hz, 2H), 7.17 (t, J = 7.6 Hz, 1H), 7.06 (t, J = 6.9 Hz, 1H), 6.84 (d, J = 8.1 Hz, 2H), 5.39 (dd, J =12.0, 4.3 Hz, 1H), 3.89−3.75 (m, 1H), 2.85−2.67 (m, 1H), 2.64−2.30 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.46, 168.66, 160.11, 152.60, 152.53, 148.48, 141.01, 138.52, 136.01, 131.77, 131.59, 131.31, 131.11, 130.39, 130.13, 129.07, 128.40, 128.33, 127.35, 127.17, 127.06, 122.55, 119.02, 115.57, 58.24, 45.09, 28.43, 28.38, 28.17. HRMS calcd for $C_{28}H_{19}Cl_3N_3O_4$ [M − H]$^-$, 566.04466; found, 566.04483. Anal. Calcd for $C_{28}H_{20}Cl_3N_3O_4 \cdot 0.30H_2O$: C, 58.57; H, 3.62; N, 7.32. Found: C, 58.58; H, 3.75; N, 7.23.

4-{5-(4-Chlorophenyl)-3-[4-(4-chlorophenyl)-6-methyl-2-oxo-1,2-dihydroquinolin-3-yl]-4,5-dihydro-1*H*-pyrazol-1-yl}-4-oxobutanoic Acid (46). Compound **46** was prepared according to general procedure G using **87** (0.039 g, 0.39 mmol) and **46f** (0.175 g, 0.39 mmol). The title compound was obtained after flash column chromatography using 0−8% MeOH/DCM as a yellow solid. Yield 0.114 g, 53.3%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.18 (s, 1H), 11.79 (s, 1H), 7.56 (dt, J = 8.2, 2.3 Hz, 1H), 7.48 (dt, J = 8.2, 2.3 Hz, 1H), 7.41−7.34 (m, 2H), 7.30 (dd, J = 8.3, 2.2 Hz, 1H), 7.27−7.20 (m, 3H), 6.80−6.72 (m, 3H), 5.35−5.25 (m, 1H), 3.75−3.59 (m, 1H), 2.76−2.65 (m, 1H), 2.61−2.33 (m, 2H), 2.26−2.32 (m, 2H), 2.19 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.54, 168.64, 160.00, 152.85, 149.66, 141.10, 136.63, 134.07, 133.16, 132.79, 131.56, 131.48, 131.40, 130.53, 128.37, 128.30, 127.30, 126.53, 123.47, 119.05, 115.59, 58.18, 45.18, 28.47, 28.19, 20.58. HRMS (m/z): [M − H]$^-$ calcd for $C_{29}H_{22}Cl_2N_3O_4$, 546.09929; found, 546.09872. Anal. Calcd for $C_{29}H_{23}Cl_2N_3O_4 \cdot 0.50H_2O$: C, 62.49; H, 4.34; N, 7.54. Found: C, 62.44; H, 4.55; N 7.39.

4-{5-(4-Chlorophenyl)-3-[4-(3-fluorophenyl)-6-methyl-2-oxo-1,2-dihydroquinolin-3-yl]-4,5-dihydro-1*H*-pyrazol-1-yl}-4-oxobutanoic Acid (47). Compound **47** was prepared according to general procedure G using **87** (0.037 g, 0.37 mmol) and **47f** (0.160 g, 0.37 mmol). The title compound was obtained after flash column chromatography using 0−10% MeOH/DCM as a brown solid. Yield 0.094 g, 47.7%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.24 (s, 1H), 12.12 (s, 1H), 7.64−7.47 (m, 1H), 7.42 (d, J = 8.5 Hz, 1H), 7.40−7.32 (m, 2H), 7.32−7.22 (m, 3H), 7.11 (dd, J = 23.8, 8.5 Hz, 1H), 6.86−6.77 (m, 3H), 5.35 (dt, J = 12.5, 3.4 Hz, 1H), 3.80 (dd, J = 18.6, 12.1 Hz, 1H), 2.81 (dt, J = 18.5, 5.2 Hz, 1H), 2.53−2.39 (m, 2H), 2.31 (t, J = 6.8 Hz, 2H), 2.23 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 173.46, 168.57, 162.67, 161.11, 160.03, 152.88, 152.81, 149.39, 141.15, 137.59, 136.61, 132.77, 131.58, 131.52, 131.38, 130.25, 128.36, 128.20, 127.33, 127.15, 126.57, 126.52, 125.83, 124.79, 123.38, 123.30, 118.98, 116.66, 116.52, 115.57, 115.19, 115.05, 58.25, 45.16, 28.98, 28.47, 28.19, 20.61. ^{19}F NMR (376 MHz, DMSO-d_6) δ −113.28 to −113.50 (m). HRMS (m/z): [M − H]$^-$ calcd for $C_{29}H_{22}ClFN_3O_4$, 530.12884; found, 530.12883. Anal. Calcd for $C_{29}H_{23}ClFN_3O_4 \cdot 1.20H_2O$: C, 62.92; H, 4.62; N, 7.59. Found: C, 62.82; H, 4.37; N, 7.34.

4-{3-[6-Chloro-4-(4-chlorophenyl)-2-oxo-1,2-dihydroquinolin-3-yl]-5-(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl}-4-oxobutanoic Acid (48). Compound **48** was prepared according to general procedure G using **87** (0.038 g, 0.38 mmol) and **48f** (0.180 g, 0.38 mmol). The title compound was obtained as a yellow solid after flash column chromatography using 0−8% MeOH/DCM. Yield 0.033 g, 15.1%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.44 (s, 1H), 12.08 (s, 1H), 7.69−7.58 (m, 2H), 7.54 (dd, J = 8.2, 2.3 Hz, 1H), 7.44 (dd, J = 8.5, 2.7 Hz, 2H), 7.35−7.23 (m, 3H), 6.93 (d, J = 2.3 Hz, 1H), 6.85−6.76 (m, 2H), 5.35 (dd, J = 12.0, 4.4 Hz, 1H), 3.72 (dd, J = 18.5, 12.0 Hz, 1H), 2.76 (dd, J = 18.5, 4.4 Hz, 1H), 2.64−2.38 (m, 2H), 2.33 (t, J = 6.7 Hz, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 173.50, 168.71, 159.96, 152.33, 148.76, 141.00, 137.33, 133.52, 133.36, 131.61, 131.48, 131.38, 130.52, 128.52, 128.32, 127.27, 126.25, 125.91, 124.80, 120.43, 117.67, 58.25, 45.08, 28.47, 28.19. HRMS (m/z): [M + H]$^+$ calcd for $C_{28}H_{21}Cl_3N_3O_4$, 568.05922; found, 568.05881. Anal. Calcd for $C_{28}H_{20}Cl_3N_3O_4 \cdot 0.40H_2O$: C, 58.38; H, 3.64; N, 7.29. Found: C, 58.29; H, 3.73; N, 7.24.

4-{3-[6-Chloro-4-(3-fluorophenyl)-2-oxo-1,2-dihydroquinolin-3-yl]-5-(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl}-4-oxobutanoic Acid (49). Compound **49** was prepared according to general procedure G using **87** (0.035 g, 0.35 mmol) and **49f** (0.160 g, 0.35 mmol). The title compound was obtained as a yellow solid after flash column chromatography using 0−8% MeOH/DCM. Yield 0.039 g, 20.0%. ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.45 (s, 1H), 12.05 (s, 1H), 7.65 (dd, J = 8.8, 2.5 Hz, 1H), 7.63−7.53 (m, 1H), 7.45 (d, J = 8.8 Hz, 1H), 7.42−7.32 (m, 2H), 7.30 (d, J = 8.2 Hz, 1H), 7.29−7.25 (m, 1H), 7.19 (dd, J = 9.2, 2.1 Hz, 1H), 7.12 (d, J = 7.5 Hz, 1H), 6.94 (d, J = 2.4 Hz, 1H), 6.83 (dd, J = 11.9, 8.3 Hz, 2H), 5.36 (dt, J = 12.2, 4.6 Hz, 1H), 2.88−2.80 (m, 1H), 2.51−2.44 (m, 2H), 2.31 (t, J = 6.9 Hz, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 174.13, 169.33, 163.45, 161.82, 160.66, 153.02, 152.95, 149.14, 141.73, 137.95, 137.52, 132.03, 131.21, 129.05, 127.96, 127.78, 126.91, 126.57, 125.39, 125.30, 121.01, 118.31, 116.19, 58.96, 45.71, 29.12, 28.85. HRMS (m/z): [M − H]$^-$ calcd for $C_{28}H_{19}Cl_2FN_3O_4$, 550.07421; found, 550.07485. Anal. Calcd for $C_{28}H_{20}Cl_2FN_3O_4 \cdot 1.00H_2O$: C, 58.96; H, 3.89; N, 7.37. Found: C, 58.98; H, 3.78; N, 7.06.

4-{5-(4-Chlorophenyl)-3-[4-(4-chlorophenyl)-6-fluoro-2-oxo-1,2-dihydroquinolin-3-yl]-4,5-dihydro-1*H*-pyrazol-1-yl}-4-oxobutanoic Acid (50). Compound **50** was prepared according to general procedure G using **87** (0.035 g, 0.35 mmol) and **50f** (0.19 g, 0.42 mmol). The title compound was obtained after flash column chromatography using 0−10% MeOH/DCM as a yellow solid. Yield 0.151 g, 65.1%. ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.37 (s, 1H), 12.07 (s, 1H), 7.61 (dd, J = 8.2, 2.4 Hz, 1H), 7.56−7.41 (m, 4H), 7.34−7.25 (m, 3H), 6.85−6.78 (m, 2H), 6.71 (dd, J = 9.7, 2.9 Hz, 1H), 5.36 (dd, J = 12.0, 4.5 Hz, 1H), 3.73 (dd, J = 18.5, 12.1 Hz, 1H), 2.78 (dd, J = 18.5, 4.4 Hz, 1H), 2.62−2.54 (m, 1H), 2.53−2.40 (m, 1H), 2.33 (t, J = 6.7 Hz, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 173.48, 168.69, 159.89, 157.84, 156.25, 152.46, 149.03, 141.01, 135.30, 133.52, 133.45, 131.59, 131.40, 130.47, 128.48, 128.30, 127.28, 124.74, 119.94, 119.78, 119.61, 117.67, 117.62, 111.93, 111.77, 58.24, 45.07, 28.46, 28.18. ^{19}F NMR (376 MHz, DMSO-d_6) δ −120.13 to −120.29 (m). HRMS (m/z): [M − H]$^-$ calcd for $C_{28}H_{19}Cl_2FN_3O_4$, 550.07421; found, 550.07419. Anal. Calcd for $C_{28}H_{20}Cl_2FN_3O_4$: C, 60.88; H, 3.65; N, 7.61. Found: C, 60.16; H, 3.98; N, 7.28. HPLC 85% MeOH/H_2O (0.1% formic acid) t_R = 1.10 min; >95% purity; 75% ACN/H_2O (0.1% formic acid) t_R = 0.81 min; >95% purity.

4-{5-(4-Chlorophenyl)-3-[6-fluoro-4-(3-fluorophenyl)-2-oxo-1,2-dihydroquinolin-3-yl]-4,5-dihydro-1*H*-pyrazol-1-yl}-4-oxobutanoic Acid (51). Compound **51** was prepared according to general procedure G using **87** (0.041 g, 0.41 mmol) and **51f** (0.180 g, 0.41 mmol). The title compound was obtained after flash column chromatography using 0−10% MeOH/DCM as a yellow solid. Yield 0.076 g, 34.3%. ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.34 (s, 1H), 12.01 (s, 1H), 7.59−7.39 (m, 3H), 7.37−7.19 (m, 3H), 7.14 (t, J = 7.8 Hz, 1H), 7.07 (t, J = 7.2 Hz, 1H), 6.83−6.75 (m, 1H), 6.74−6.63 (m, 1H), 5.40−5.33 (m, 1H), 3.81 (dd, J = 18.5, 12.1 Hz, 2H), 2.85−2.75 (m, 1H), 2.46−2.36 (m, 2H), 2.27 (t, J = 7.0 Hz, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 173.47, 168.66, 162.80, 161.17, 161.11, 159.93, 157.85, 156.26, 152.52, 152.44, 148.77, 141.08, 137.08, 137.02, 136.97, 135.29, 131.62, 131.56, 130.55, 128.39, 127.39, 127.25, 127.21, 127.08, 125.75, 124.69, 124.59, 119.90, 119.83, 117.66, 116.65, 115.50, 115.36, 111.87, 58.36, 58.24, 45.07, 28.46, 28.18. ^{19}F NMR (376 MHz,

dx.doi.org/10.1021/jm400652r | J. Med. Chem. XXXX, XXX, XXX−XXX

DMSO-d_6) δ −112.89 to −113.28 (m), −120.04 to −120.29 (m). HRMS (m/z): [M − H]$^-$ calcd for $C_{28}H_{19}ClF_2N_3O_4$, 534.10376; found, 534.10345. Anal. Calcd for $C_{28}H_{20}ClF_2N_3O_4$: C, 62.75; H, 3.76; N, 7.84. Found: C, 61.88; H, 3.98; N: 7.67.

4-{5-(4-Chlorophenyl)-3-[4-(4-chlorophenyl)-6-methoxy-2-oxo-1,2-dihydroquinolin-3-yl]-4,5-dihydro-1*H*-pyrazol-1-yl}-4-oxobutanoic Acid (52). Compound **52** was prepared according to general procedure G using **87** (0.039 g, 0.39 mmol) and **52f** (0.180 g, 0.39 mmol). The title compound was obtained as a yellow solid after flash column chromatography using 0−10% MeOH/DCM. Yield 0.095 g, 43.4%. ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.19 (s, 1H), 12.09 (s, 1H), 7.61 (dd, J = 8.2, 2.4 Hz, 1H), 7.52 (dd, J = 8.2, 2.4 Hz, 1H), 7.42 (dd, J = 8.2, 2.3 Hz, 1H), 7.39 (d, J = 8.8 Hz, 1H), 7.32−7.25 (m, 4H), 6.82 (d, J = 8.5 Hz, 2H), 6.42 (d, J = 2.8 Hz, 1H), 5.34 (dd, J = 11.9, 4.5 Hz, 1H), 3.73 (dd, J = 18.4, 12.0 Hz, 1H), 3.60 (s, 3H), 2.77 (dd, J = 18.4, 4.4 Hz, 1H), 2.63−2.44 (m, 2H), 2.33 (t, J = 6.6 Hz, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 173.52, 168.66, 159.69, 154.24, 152.88, 149.28, 141.09, 134.02, 133.23, 133.15, 131.57, 131.42, 130.51, 128.39, 128.29, 128.12, 127.31, 123.95, 120.17, 119.68, 117.01, 109.05, 58.20, 55.32, 45.15, 28.48, 28.21. HRMS (m/z): [M − H]$^-$ calcd for $C_{29}H_{22}Cl_2N_3O_5$, 562.09420; found, 562.09430. Anal. Calcd for $C_{29}H_{23}Cl_2N_3O_5$: C, 61.71; H, 4.11; N, 7.44. Found: C, 61.47; H, 4.06; N, 7.36.

4-{5-(4-Chlorophenyl)-3-[4-(3-fluorophenyl)-6-methoxy-2-oxo-1,2-dihydroquinolin-3-yl]-4,5-dihydro-1*H*-pyrazol-1-yl}-4-oxobutanoic Acid (53). Compound **53** was prepared according to general procedure G using **87** (0.027 g, 0.27 mmol) and **53f** (0.120 g, 0.27 mmol). The title compound was obtained as a yellow solid after flash column chromatography using 0−10% MeOH/DCM. Yield 0.040 g, 27.7%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.21 (s, 1H), 7.64−7.48 (m, 1H), 7.43−7.07 (m, 6H), 6.87−6.77 (m, 2H), 6.45−6.40 (m, 1H), 5.40−5.30 (m, 1H), 3.87−3.74 (m, 2H), 3.60 (s, 3H), 2.83 (dt, J = 18.4, 5.2 Hz, 1H), 2.54−2.39 (m, 2H), 2.31 (t, J = 6.9 Hz, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 173.55, 168.62, 162.77, 162.71, 161.15, 161.08, 159.73, 154.23, 152.93, 152.85, 149.03, 141.16, 137.56, 137.51, 133.12, 131.59, 131.52, 130.38, 128.41, 128.32, 127.44, 127.26, 127.07, 125.78, 124.73, 123.87, 123.78, 120.06, 119.63, 116.98, 115.17, 109.18, 58.35, 58.17, 55.38, 55.20, 45.10, 28.49, 28.23. ^{19}F NMR (376 MHz, DMSO-d_6) δ −113.15 to −113.37 (m). HRMS (m/z): [M − H]$^-$ calcd for $C_{29}H_{22}ClFN_3O_5$, 546.12375; found, 546.12384. Anal. Calcd for $C_{29}H_{23}ClFN_3O_5$: C, 63.56; H, 4.23; N, 7.67. Found: C, 52.15; H, 3.91; N, 5.95. HPLC 85% MeOH/H_2O (0.1% formic acid) t_R = 0.809 min; >95% purity; 75% ACN/H_2O (0.1% formic acid) t_R = 0.625 min; >95% purity.

(*E*)-4-[5-(4-Bromophenyl)-3-(6-chloro-2-oxo-4-phenyl-1,2-dihydroquinolin-3-yl)-4,5-dihydro-1*H*-pyrazol-1-yl]-4-oxobut-2-enoic Acid (54). Compound **54** was prepared from **54g** (0.190 g, 0.322 mmol) and 1 M NaOH (1.22 mL, 1.22 mmol), which were stirred to give a yellow solution. After 4 h, 1 M HCl (1.22 mL) was added and a yellow solid precipitated. The solid was filtered and rinsed with water to give the title compound as a yellow solid. Yield 0.170 g, 92.0%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.03 (s, 1H), 12.46 (s, 1H), 7.66 (dd, J = 8.8, 2.4 Hz, 1H), 7.61−7.38 (m, 7H), 7.31 (dt, J = 5.6, 2.5 Hz, 1H), 7.26 (d, J = 15.7 Hz, 1H), 6.94 (d, J = 2.4 Hz, 1H), 6.78 (d, J = 8.3 Hz, 2H), 6.45 (d, J = 15.7 Hz, 1H), 5.45 (dd, J = 11.8, 4.5 Hz, 1H), 3.80 (dd, J = 18.7, 11.9 Hz, 1H), 2.88 (dd, J = 18.7, 4.5 Hz, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 167.81, 166.11, 160.30, 159.96, 155.82, 154.41, 150.24, 140.70, 137.39, 134.48, 132.67, 131.83, 131.42, 129.19, 128.63, 128.51, 128.36, 127.93, 127.83, 126.17, 126.05, 124.09, 120.60, 120.44, 117.66, 58.69, 58.63, 45.11. HRMS (m/z): [M − H]$^-$ calcd for $C_{28}H_{18}ClBrN_3O_4$, 574.01747; found, 574.01750. Anal. Calcd for $C_{28}H_{19}ClBrN_3O_4 \cdot 1.00H_2O$: C, 56.54; H, 3.56; N, 7.06. Found: C, 56.66; H, 3.76; N: 6.93.

(*Z*)-4-[5-(4-Bromophenyl)-3-(6-chloro-2-oxo-4-phenyl-1,2-dihydroquinolin-3-yl)-4,5-dihydro-1*H*-pyrazol-1-yl]-4-oxobut-2-enoic Acid (55). Compound **55** was prepared according to general procedure G using furan-2,5-dione (**90**) (0.061 g, 0.63 mmol) and **55f** (0.300 g, 0.63 mmol). The title compound was obtained after filtration from the cooled reaction medium and rinsed with THF. Yield 0.200 g, 55.3%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.69 (s, 1H), 12.41 (s, 1H), 7.64 (d, J = 8.7 Hz, 1H), 7.60− 7.36 (m, 7H), 7.25 (d, J = 7.2 Hz, 1H), 6.92 (s, 1H), 6.78 (d, J = 8.1 Hz, 2H), 6.40 (d, J = 12.1 Hz, 1H), 6.16 (d, J = 12.1 Hz, 1H), 5.37 (dd, J = 12.0, 4.9 Hz, 1H), 3.78 (dd, J = 18.5, 12.0 Hz, 1H), 2.79 (dd, J = 18.7, 4.8 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.77, 161.77, 160.01, 153.58, 150.11, 140.93, 137.36, 134.39, 131.31, 129.57, 129.46, 128.64, 128.43, 127.96, 126.16, 126.08, 124.26, 120.62, 120.29, 117.67, 58.43, 45.17. HRMS (m/z): [M − H]$^-$ calcd for $C_{28}H_{18}ClBrN_3O_4$, 574.01747; found, 574.01654. Anal. Calcd for $C_{28}H_{19}BrClN_3O_4$: C, 58.30; H, 3.32; N, 7.28. Found: C, 43.78; H, 3.00; N: 5.57. HPLC 85% MeOH/H_2O (0.1% formic acid) t_R = 1.18 min; >95% purity; 75% ACN/H_2O (0.1% formic acid) t_R = 1.06 min; >95% purity.

Methyl 4-[5-(4-Bromophenyl)-3-(6-chloro-2-oxo-4-phenyl-1,2-dihydroquinolin-3-yl)-4,5-dihydro-1*H*-pyrazol-1-yl]-4-oxobutanoate (56). Compound **56** was prepared from **56g** (0.400 g, 0.69 mmol) in the following manner. **56g** (0.400 g, 0.69 mmol) was dissolved in 6.9 mL of THF, and freshly prepared HCl (acetyl chloride added to methanol) in MeOH was added dropwise to the reaction vessel with stirring until TLC indicated completion. Upon completion, the THF was removed under vacuum, the residue dissolved in DCM, washed 3× with acidified brine, and column-chromatographed using a 0−10% MeOH gradient in DCM to give the title compound as a yellow solid. Yield 0.100 g, 24.4%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.42 (s, 1H), 7.64 (dd, J = 8.7, 2.4 Hz, 1H), 7.54−7.49 (m, 3H), 7.48−7.38 (m, 4H), 7.31−7.24 (m, 1H), 6.93 (d, J = 2.3 Hz, 1H), 6.77−6.70 (m, 2H), 5.31 (dd, J = 12.0, 4.6 Hz, 1H), 3.76 (dd, J = 18.5, 12.2 Hz, 1H), 3.59 (s, 1H), 3.54 (s, 2H), 2.79 (dd, J = 18.5, 4.6 Hz, 1H), 2.61−2.42 (m, 2H), 2.37 (t, J = 6.7 Hz, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 172.44, 168.37, 168.08, 160.09, 152.81, 152.61, 149.98, 141.49, 137.32, 134.58, 131.30, 129.45, 128.48, 128.36, 127.78, 127.67, 126.13, 126.01, 124.50, 120.65, 120.14, 117.65, 58.43, 58.30, 51.35, 51.24, 45.23, 45.08, 28.46, 27.96. HRMS (m/z): [M − H]$^-$ calcd for $C_{29}H_{22}ClBrN_3O_4$, 590.04877; found, 590.04851. Anal. Calcd for $C_{29}H_{23}ClBrN_3O_4$: C, 58.75; H, 3.91; N, 7.09. Found: C, 58.35; H, 4.08; N, 6.66.

(*E*)-4-{3-[4-(4-Bromophenyl)-2-oxo-1,2-dihydroquinolin-3-yl]-5-(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl}-4-oxobut-2-enoic Acid (58). Compound **58** was prepared from compound **60** using the following method. In a 50 mL round-bottomed flask, ethanol (28.2 mL), **60** (0.500 g, 0.850 mmol), and 1 M NaOH (3.22 mL, 3.22 mmol) were stirred to give a yellow solution. After 4 h, 1 M HCl (3.22 mL) was added and a yellow solid precipitated. The solid was filtered and rinsed with water. The resulting solid was dissolved in DCM, washed with brine, and the organics were dried over magnesium sulfate in vacuo. The title compound was obtained from column chromatography (0−10% MeOH in DCM) as an off-white solid. Yield 0.320 g, 65.6%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.98 (s, 1H), 12.28 (s, 1H), 7.71−7.51 (m, 3H), 7.48−7.19 (m, 6H), 7.12 (t, J = 7.6 Hz, 1H), 7.02 (d, J = 8.2 Hz, 1H), 6.85 (d, J = 8.2 Hz, 2H), 6.44 (d, J = 15.7 Hz, 1H), 5.45 (dd, J = 11.7, 4.4 Hz, 1H), 3.73 (dd, J = 18.7, 11.8 Hz, 1H), 2.89 (dd, J = 18.6, 4.4 Hz, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 168.08, 166.05, 160.24, 160.04, 154.75, 152.81, 152.77, 150.29, 140.25, 138.65, 134.49, 132.80, 131.95, 131.60, 131.36, 131.26, 130.74, 128.51, 127.55, 127.43, 122.92, 122.47, 121.84, 119.01, 115.61, 58.50, 45.19. HRMS (m/z): [M + H]$^+$ calcd for $C_{28}H_{20}ClBrN_3O_4$, 576.03202; found, 576.03294. Anal. Calcd for $C_{28}H_{19}ClBrN_3O_4 \cdot 0.40H_2O$: C, 57.58; H, 3.42; N, 7.19. Found: C, 57.46; H, 3.50; N, 7.23.

(*Z*)-4-{3-[4-(4-Bromophenyl)-2-oxo-1,2-dihydroquinolin-3-yl]-5-(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl}-4-oxobut-2-enoic Acid (59). Compound **59** was prepared according to general procedure G using **89** (0.061 g, 0.63 mmol) and **22f** (0.300 g, 0.630 mmol). The THF was removed under vacuum, and the resultant residue was dissolved in hot EtOAc. A yellow solid was present upon cooling which was filtered and determined to be the desired product. Yield 0.171 g, 47.3%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.74 (s, 1H), 12.30 (s, 1H), 7.75 (d, J = 8.3 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.58 (t, J = 7.9 Hz, 1H), 7.43 (d, J = 8.4 Hz, 1H), 7.32 (t, J = 8.6 Hz, 3H), 7.22 (d, J = 8.2 Hz, 1H), 7.15 (t, J = 7.8 Hz, 1H), 7.03 (d, J = 8.2 Hz, 1H), 6.87 (d, J = 8.1 Hz, 2H), 6.48 (d, J = 12.2 Hz, 1H), 6.20 (d, J = 12.1 Hz, 1H), 5.47−5.38 (m, 1H), 3.76 (dd, J = 18.8, 11.9 Hz, 1H),

dx.doi.org/10.1021/jm400652r | J. Med. Chem. XXXX, XXX, XXX−XXX

2.84−2.74 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.80, 161.77, 160.05, 153.90, 150.03, 140.50, 138.60, 134.27, 131.76, 131.69, 131.55, 131.28, 130.82, 129.68, 129.41, 128.36, 127.51, 127.32, 123.10, 122.47, 121.89, 119.04, 115.61, 93.88, 67.04, 58.28, 45.27, 25.15. HRMS (m/z): [M − H]$^-$ calcd for $C_{28}H_{18}ClBrN_3O_4$, 576.03202; found, 576.03371. Anal. Calcd for $C_{28}H_{19}ClBrN_3O_4 \cdot 0.60H_2O$: C, 57.23; H, 3.46; N, 7.15. Found: C, 57.22; H, 3.54; N, 6.91.

(*E*)-Methyl 4-{3-[4-(4-Bromophenyl)-2-oxo-1,2-dihydroquinolin-3-yl]-5-(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl}-4-oxobut-2-enoate (60). Compound **60** was prepared from **22f** (0.750g, 1.60 mmol) and (*E*)-methyl 4-chloro-4-oxobut-2-enoate (0.280 g, 1.90 mmol) using standard procedure G. The THF was removed under vacuum. The residue was dissolved in DCM and washed 3× with brine, and the organics were concentrated. The title compound was obtained as a yellow solid by flash chromatography using a 0−10% MeOH gradient in DCM. Yield 0.546 g, 59.0%. ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.32 (s, 1H), 7.70 (dt, J = 8.3, 1.9 Hz, 1H), 7.67 (dt, J = 8.1, 2.0 Hz, 1H), 7.60 (t, J = 7.8 Hz, 1H), 7.44 (d, J = 8.3 Hz, 1H), 7.37−7.32 (m, 3H), 7.30 (dt, J = 8.2, 2.0 Hz, 1H), 7.27−7.22 (m, 1H), 7.16 (t, J = 7.6 Hz, 1H), 7.08 (d, J = 8.2 Hz, 1H), 6.95 (d, J = 7.6 Hz, 2H), 6.53 (dd, J = 15.5, 1.0 Hz, 1H), 5.49 (dd, J = 11.6, 4.3 Hz, 1H), 3.86−3.73 (m, 4H), 3.03 (dd, J = 18.6, 4.2 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.13, 160.11, 159.92, 154.93, 150.40, 140.16, 138.71, 134.71, 133.36, 132.02, 131.69, 131.37, 131.30, 131.11, 130.80, 129.93, 128.65, 128.56, 127.57, 127.46, 122.77, 122.50, 121.77, 119.01, 115.63, 58.56, 52.16, 45.15. HRMS (m/z): [M + H]$^+$ calcd for $C_{29}H_{22}ClBrN_3O_4$, 590.04767; found, 590.04887. HPLC 85% MeOH/H_2O (0.1% formic acid) t_R = 1.56 min; >90% purity; 75% ACN/H_2O (0.1% formic acid) t_R = 1.39 min; >90% purity.

5-{3-[4-(4-Bromophenyl)-2-oxo-1,2-dihydroquinolin-3-yl]-5-(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl}-5-oxopentanoic Acid (61). Compound **61** was prepared according to general procedure G using **88** (0.071 g, 0.63 mmol) and **22f** (0.30 g, 0.63 mmol). Upon completion, the THF was removed under vacuum and the residue was dissolved in hot EtOAc. When the mixture was cooled, a yellow solid formed which was filtered, dried under vacuum, and determined to be the desired product. Yield 0.204 g, 54.9%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.29 (s, 1H), 12.09 (s, 1H), 7.77 (dd, J = 8.2, 2.1 Hz, 1H), 7.70 (dd, J = 8.2, 2.1 Hz, 1H), 7.58 (t, J = 7.7 Hz, 1H), 7.43 (d, J = 8.3 Hz, 1H), 7.36 (dd, J = 8.2, 2.2 Hz, 1H), 7.34−7.28 (m, 2H), 7.23 (dd, J = 8.1, 2.3 Hz, 1H), 7.15 (t, J = 7.6 Hz, 1H), 7.04 (d, J = 8.2 Hz, 1H), 6.86−6.76 (m, 2H), 5.36 (dd, J = 12.0, 4.4 Hz, 1H), 3.81−3.68 (m, 1H), 2.80 (dd, J = 18.7, 4.3 Hz, 1H), 2.40 (dt, J = 15.3, 7.4 Hz, 1H), 2.29−2.06 (m, 3H), 1.68−1.51 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.11, 169.29, 160.18, 152.73, 149.89, 141.29, 138.57, 134.59, 131.73, 131.64, 131.47, 131.30, 131.25, 130.88, 128.40, 127.31, 127.27, 123.41, 122.44, 121.77, 119.09, 115.60, 58.13, 45.10, 32.96, 32.58, 19.82. HRMS (m/z): [M + H]$^+$ calcd for $C_{29}H_{24}ClBrN_3O_4$, 592.06332; found, 592.06461. Anal. Calcd for $C_{29}H_{23}ClBrN_3O_4$: C, 58.75; H, 3.91; N, 7.09. Found: C, 58.47; H, 3.96; N, 6.91.

5-[3-(6-Chloro-2-oxo-4-phenyl-1,2-dihydroquinolin-3-yl)-5-(4-nitrophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl]-5-oxopentanoic Acid (63). Compound **63** was prepared according to general procedure G using glutaric anhydride (**89**) (0.077 g, 0.67 mmol) and **63f** (0.30 g, 0.67 mmol). The title compound was obtained after being dissolved in hot EtOAc followed by slow addition of hot hexanes to yield the title compound as a yellow solid. Yield 0.220 g, 58.4%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.44 (s, 1H), 12.12 (s, 1H), 8.12 (d, J = 8.3 Hz, 2H), 7.70−7.51 (m, 4H), 7.51−7.38 (m, 2H), 7.28 (d, J = 6.6 Hz, 1H), 7.07 (d, J = 8.5 Hz, 2H), 6.95 (d, J = 2.5 Hz, 1H), 5.50 (dd, J = 12.3, 4.8 Hz, 1H), 3.83 (dd, J = 18.6, 12.2 Hz, 1H), 2.86 (dd, J = 18.6, 4.9 Hz, 1H), 2.45−2.30 (m, 1H), 2.29−2.17 (m, 1H), 2.13 (t, J = 7.4 Hz, 2H), 1.65−1.45 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.07, 169.49, 160.10, 152.49, 149.59, 146.59, 137.35, 131.30, 129.39, 128.47, 126.68, 126.08, 124.34, 123.82, 120.63, 117.67, 58.32, 44.90, 32.94, 32.53, 19.70. HRMS (m/z): [M + H]$^+$ calcd for $C_{29}H_{24}ClN_4O_6$, 559.13789; found, 559.13826. Anal. Calcd for $C_{29}H_{23}ClN_4O_6$: C, 62.31; H, 4.15; N, 10.02. Found: C, 62.42; H, 4.39; N, 9.72.

4-(4-Chlorophenyl)-3-[5-(4-chlorophenyl)-1-(4-hydroxybutanoyl)-4,5-dihydro-1*H*-pyrazol-3-yl]quinolin-2(1*H*)-one (64). In a flame-dried 25 mL round-bottomed flask, **26** (0.300 g, 0.560 mmol) was dissolved in THF (10 mL) and cooled on an ice bath to 0 °C under nitrogen with stirring. BH_3−Me_2S (2.0 M in hexanes, 0.561 mL, 2 equiv) was added dropwise. The mixture was stirred for 30 min, quenched with MeOH, and the solvent was removed under vacuum. The resultant residue was dissolved in DCM, washed three times with brine, and the organics were combined, dried over magnesium sulfate, concentrated in vacuo, and column-chromatographed using a 0−8% gradient of MeOH in DCM to give the title compound as a yellow solid. Yield 0.063 g, 21.6%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.29 (s, 1H), 7.65−7.49 (m, 3H), 7.46−7.24 (m, 5H), 7.20−7.00 (m, 2H), 6.89−6.78 (m, 2H), 5.35 (dd, J = 12.0, 4.4 Hz, 1H), 4.45 (t, J = 5.2 Hz, 1H), 3.74 (dd, J = 18.5, 12.1 Hz, 1H), 3.41−3.27 (m, 2H), 2.80 (dd, J = 18.5, 4.5 Hz, 1H), 2.44−2.19 (m, 2H), 1.59−1.39 (m, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 169.82, 160.17, 152.52, 149.83, 141.31, 138.53, 134.18, 133.14, 131.58, 131.43, 131.39, 130.57, 129.11, 128.33, 127.28, 123.50, 122.41, 119.14, 115.57, 60.19, 58.10, 45.06, 30.14, 27.71. HRMS (m/z): [M + H]$^+$ calcd for $C_{28}H_{24}Cl_2N_3O_3$, 520.11892; found, 520.11993. Anal. Calcd for $C_{28}H_{23}Cl_2N_3O_3 \cdot 0.40H_2O$: C, 63.74; H, 4.55; N, 7.96. Found: C, 63.75; H, 4.33; N, 7.89.

4-{5-(4-Chlorophenyl)-3-[4-(4-chlorophenyl)-2-oxo-1,2-dihydroquinolin-3-yl]-4,5-dihydro-1*H*-pyrazol-1-yl}-4-oxobutanamide (65). In a flame-dried 25 mL round-bottomed flask, **26** (0.300 g, 0.560 mmol), 4-dimethylaminopyridine (0.069 g, 0.560 mmol), and *N*1-((ethylimino)methylene)-*N*3,*N*3-dimethylpropane-1,3-diamine (0.096 g, 0.618 mmol) were added to THF (11.23 mL) at 0 °C and stirred for 45 min. Ammonia (0.5 M in dioxane, 1.0 equiv, 1.1 mL) was added to the flask, and the reaction mixture was stirred overnight while being allowed to warm to room temperature. The reaction was quenched with dilute HCl (0.1 M), and the organics were removed under vacuum. The resultant residue was dissolved in DCM, washed 3× with brine, and the organics were dried over magnesium sulfate and concentrated in vacuo prior to column chromatography using a 0−8% MeOH gradient in DCM (0.1% Et_3N). The title compound was obtained as a white solid. Yield 0.019 g, 6.35%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.29 (s, 1H), 7.66−7.56 (m, 2H), 7.55−7.49 (m, 1H), 7.43 (d, J = 8.4 Hz, 2H), 7.28 (dd, J = 8.2, 4.4 Hz, 3H), 7.24 (s, 1H), 7.15 (t, J = 7.6 Hz, 1H), 7.03 (d, J = 8.2 Hz, 1H), 6.79 (d, J = 8.5 Hz, 2H), 6.73 (s, 1H), 5.34 (dd, J = 12.1, 4.5 Hz, 1H), 3.71 (dd, J = 18.4, 12.2 Hz, 1H), 2.72 (dd, J = 18.4, 4.5 Hz, 1H), 2.59−2.50 (m, 2H), 2.20 (t, J = 7.2 Hz, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 173.69, 169.78, 160.79, 153.18, 150.49, 141.85, 139.21, 134.63, 133.87, 132.22, 132.19, 132.09, 131.23, 128.99, 128.95, 127.94, 124.23, 123.07, 119.80, 116.24, 58.83, 46.27, 45.80, 29.94, 29.44. HRMS (m/z): [M + H]$^+$ calcd for $C_{28}H_{23}Cl_2N_4O_3$, 533.11417; found, 533.11517. HPLC 85% MeOH/H_2O (0.1% formic acid) t_R = 0.89 min; >90% purity; 75% ACN/H_2O (0.1% formic acid) t_R = 1.00 min; >95% purity.

Methyl 4-{5-(4-Chlorophenyl)-3-[4-(4-chlorophenyl)-2-oxo-1,2-dihydroquinolin-3-yl]-4,5-dihydro-1*H*-pyrazol-1-yl}-butanoate (66). In a 20 mL round-bottomed flask, **26f** (0.500 g, 1.151 mmol) and methyl 4-oxobutanoate (0.121 mL, 1.151 mmol) were dissolved in DCE (11.51 mL). The mixture was allowed to stir at room temperature for 4 h, and sodium triacetoxyborohydride (0.293 g, 1.381 mmol) was added in one portion. The reaction was monitored by TLC and HPLC−MS. Upon completion, the DCE was removed under vacuum. The residue was diluted with DCM and washed 3× with brine. The organics were concentrated, and the title compound was obtained from flash column chromatography using 0−10% MeOH in DCM and trituration of the compound from ether as a yellow solid. Yield 0.150 g, 24.4%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.22 (s, 1H), 7.55−7.45 (m, 3H), 7.40 (s, 1H), 7.34−7.26 (m, 5H), 7.22 (s, 2H), 7.13 (t, J = 7.6 Hz, 1H), 4.11 (dd, J = 13.6, 10.1 Hz, 1H), 3.62 (s, 3H), 3.41 (dd, J = 16.4, 10.1 Hz, 1H), 2.91−2.78 (m, 1H), 2.70−2.53 (m, 2H), 2.30−2.08 (m, 2H), 1.84−1.66 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.18, 162.94, 150.63, 146.34, 139.59, 138.08, 135.07, 134.23, 133.49, 131.12, 130.90, 129.08, 128.89, 128.51, 128.33, 127.82, 124.96, 122.96, 120.65, 116.18, 70.81, 52.20, 51.66, 46.60, 31.30, 23.04. HRMS (m/z): [M + H]$^+$ calcd for $C_{29}H_{26}Cl_2N_3O_3$, 534.13457;

dx.doi.org/10.1021/jm400652r | J. Med. Chem. XXXX, XXX, XXX−XXX

found, 534.13624. HPLC 85% MeOH/H_2O (0.1% formic acid) t_R = 2.35 min; >95% purity; 75% ACN/H_2O (0.1% formic acid) t_R = 2.09 min; >95% purity.

4-{5-(4-Chlorophenyl)-3-[4-(4-chlorophenyl)-2-oxo-1,2-dihydroquinolin-3-yl]-4,5-dihydro-1*H*-pyrazol-1-yl}butanoic Acid (67). In a 10 mL round-bottomed flask, compound **66** (0.100 g, 0.187 mmol) was dissolved in NaOH (0.711 mL, 0.711 mmol), H_2O (10.00 mL), and ethanol (6.24 mL). The mixture was stirred at room temperature for 4 h and monitored by TLC/LC−MS. Upon completion, HCl (0.711 mL, 0.711 mmol) was added, giving a bright yellow solid which was filtered, dissolved in DCM, and washed 3× with acidified (pH 2, HCl) brine. The organics were combined, dried over magnesium sulfate and concentrated *in vacuo*. The title compound was obtained by flash chromatography using 0−8% MeOH in DCM as a yellow solid. Yield 0.050 g, 51.3%. ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.16 (s, 1H), 11.92 (s, 1H), 7.59−7.49 (m, 3H), 7.42−7.37 (m, 3H), 7.35−7.29 (m, 4H), 7.13 (t, J = 7.6 Hz, 1H), 7.07 (d, J = 8.2 Hz, 1H), 4.03 (dd, J = 13.8, 10.2 Hz, 1H), 3.33 (dd, J = 16.4, 10.2 Hz, 1H), 2.73 (dd, J = 16.5, 13.8 Hz, 1H), 2.54−2.46 (m, 1H), 2.40−2.31 (m, 1H), 2.12−1.96 (m, 2H), 1.55−1.39 (m, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 174.25, 160.57, 148.75, 146.65, 140.21, 138.31, 135.02, 132.63, 131.86, 131.23, 131.19, 130.84, 130.75, 129.09, 128.44, 128.08, 127.81, 127.04, 125.16, 122.15, 119.31, 115.43, 69.48, 52.16, 46.06, 30.83, 22.35. HRMS (m/z): [M + H]$^+$ calcd for $C_{28}H_{24}Cl_2N_3O_3$, 520.11892; found, 520.11970. HPLC 85% MeOH/H_2O (0.1% formic acid) t_R = 1.33 min; >95% purity; 75% ACN/H_2O (0.1% formic acid) t_R = 0.98 min; >95% purity.

4-(4-Chlorophenyl)-3-[5-(4-chlorophenyl)-1-(4-fluorobutanoyl)-4,5-dihydro-1*H*-pyrazol-3-yl]quinolin-2(1*H*)-one (68). In a 10 mL round-bottomed flask, 4-fluorobutanoic acid **68g** (0.100 g, 0.943 mmol), DMAP (0.127 g, 1.037 mmol), and EDCI (0.199 g, 1.037 mmol) were dissolved in DCM (9.43 mL) which had been precooled to 0 °C. The mixture was stirred for 45 min prior to the addition of the **26f** (0.409 g, 0.943 mmol). The mixture was allowed to warm to room temperature and monitored by TLC. The reaction was quenched with 0.2 N HCl and extracted into DCM. The organics were washed 3× with brine, dried over magnesium sulfate, and concentrated. The title compound was obtained as a yellow solid after column chromatography using a gradient of 0−50% EtOAc in DCM as a yellow solid. Yield 0.050 g, 21.6%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.16 (s, 1H), 7.62−7.43 (m, 4H), 7.38 (d, J = 8.2 Hz, 1H), 7.34−7.16 (m, 5H), 7.02 (d, J = 8.3 Hz, 2H), 5.42 (dd, J = 11.8, 4.0 Hz, 1H), 4.44 (dtd, J = 47.3, 5.8, 1.7 Hz, 2H), 3.70 (dd, J = 18.2, 11.8 Hz, 1H), 3.15 (dd, J = 18.3, 4.1 Hz, 1H), 2.68−2.45 (m, 2H), 2.18−1.82 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.45, 162.91, 152.52, 151.98, 151.92, 140.41, 138.42, 135.43, 134.99, 133.97, 133.56, 132.00, 130.81, 130.72, 130.68, 130.36, 129.05, 128.96, 128.85, 128.73, 128.70, 128.04, 127.60, 127.52, 126.86, 123.47, 123.09, 120.36, 116.41, 84.06, 82.97, 59.35, 45.44, 29.91, 29.88, 25.69, 25.62, 25.56. ^{19}F NMR (282 MHz, $CDCl_3$) δ −220.53 (tt, J = 47.3, 26.3 Hz). HRMS (m/z): [M + H]$^+$ calcd for $C_{28}H_{23}Cl_2N_3O_2F$, 522.11459; found, 522.11462. HPLC 85% MeOH/H_2O (0.1% formic acid) t_R = 1.46 min; >95% purity; 75% ACN/H_2O (0.1% formic acid) t_R = 1.32 min; >95% purity.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details for the synthesis of all intermediates, solubility determination methods and data analysis, Table S1 with A-ring modifications, Table S2 with heteroaromatic C-ring substitutions, Table S3 with C-ring modifications, Table S4 with off-target data from NIMH-PDSP, Figure S1 showing mutant receptor responses, Figure S2 showing plasma stability, compound solubility, and Scheme S1 showing the synthesis of the monofluorobutyrate. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare the following competing financial interest(s): Several of the authors are co-inventors (T.M.A., D.C.L., S.F.T.) of Emory University owned patent-pending technology and have an equity position (D.C.L., S.F.T., J.P.S.), are board members (D.C.L.), or are paid consultants (S.F.T.) for a company that has licensed this technology.

■ ACKNOWLEDGMENTS

The authors thank the Emory Institute for Drug Development for performing the plasma stability assays, Dr. Terry W. Moore, Dr. Alexandra Orchard, and Eric Miller for helpful discussions and comments on the manuscript, Drs. Shaoxiong Wu and Fred Strobel for excellent core facility support, and Phuong Le and Jing Zhang for excellent technical assistance. This work was support by the National Institutes of Health (NIH-NINDS Grant NS071802 (T.M.A.) and Grants NS065371, NS036654 (S.F.T.)) and an NIH Graduate Training in the Pharmacological Sciences (Grant GM008602 (T.M.A.)), an NIH Translational Research in Neurology (Grant 5T32-NS007480-07 (K.M.V.)), the University of KwaZulu-Natal and the NRF (C.S.), and Lundbeck A/S and Pfizer Inc. research grants to Emory University.

■ ABBREVIATIONS USED

Ca^{2+}, calcium ion; Mg^{2+}, magnesium ion; ATD, amino-terminal domain; LBD, ligand-binding domain; DQP, dihydroquinolone pyrazoline; BH_3−DMS, borane−dimethylsulfide; NH_3, ammonia; μM, micromolar; mV, millivolt; QNZ, quinazoline-4-one; S2, segment 2; TPSA, topological polar surface area; P_{app}, permeability coefficient; MDR1-MDCK, multidrug resistance gene 1 Madin−Darby canine kidney; cRNA, complementary RNA; NaCl, sodium chloride; KCl, potassium chloride; $BaCl_2$, barium chloride; NaOH, sodium hydroxide; MΩ, megaohm; NIMH PDSP, National Institute of Mental Health psychoactive drug screening program; ACN, acetonitrile; EtOAc, ethyl acetate

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