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Multicomponent Strategy to Pyrazolo[3,4-*e*]indolizine Derivatives under Microwave Irradiation

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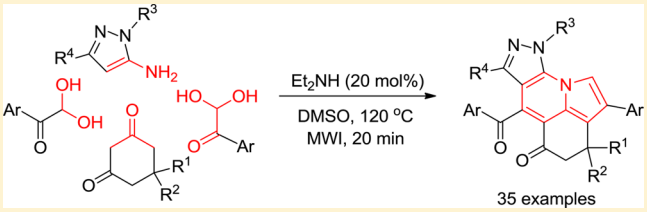
Supporting Information

ABSTRACT: A simple and efficient one-pot construction of pyrazolo[3,4-*e*]indolizine derivatives via a diethylamine-catalyzed three-component domino reaction of arylglyoxals, cyclic 1,3-diones, and 5-aminopyrazoles under microwave irradiation is described. In this one-pot transformation, seven bonds and two new rings are efficiently formed. This synthesis was confirmed to follow the group-assisted-purification (GAP) chemistry process, which can avoid traditional recrystallization or chromatography purification methods.



The indolizine nucleus is present in many natural products and biologically active compounds.[1] Many indolizine derivatives have important biological activities, including anti-inflammatory,[2] anti-HIV,[3] hypoglycemic,[4] 5-HT3 receptor antagonist,[5] H3 receptor antagonist,[6] antiacetylcholine,[7] CNS depressant,[8] and estrogen-receptor-binding activities,[9] and are used in drug discovery as L-type calcium channel blockers,[10] sPLA2 inhibitors,[11] and GSK-3β inhibitors (Figure 1).[12]

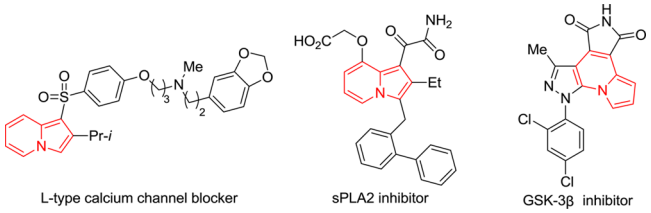


Figure 1. Examples of biological modulators containing indolizine skeleton.

Indolizine derivatives are also used as molecular probes because of their long-wavelength absorption and fluorescence with high quantum efficiency in the visible-light region.[13] The development of efficient, particularly convergent, methods for the rapid construction of indolizines with functional groups is therefore of considerable interest to organic and medicinal chemists. Typical molecular constructions of indolizines fall into two classes: (A) construction of a pyrrole ring from pyridine derivatives, including 1,3-dipolar cycloaddition of pyridinium *N*-methylides with electron-deficient alkenes or alkynes,[14] metal-catalyzed intramolecular cycloisomerizations of pyridines,[15] and domino reactions of pyridines;[16] and (B) construction of a pyridine ring from pyrrole derivatives.[17] However, these methods often suffer from limitations such as substrate complexity and low availability, and the use of expensive metal catalysts and multistage synthesis. Convenient and efficient methods for the construction of indolizine skeletons from simple and readily available starting materials are therefore important.

The creation of diverse and complex molecules with biological activities from readily available precursors is a challenging theme in synthetic chemistry for both academia and the pharmaceutical industry. One of the most promising approaches is based on multicomponent domino reactions (MDRs), which are defined as complex product formation via convergent processes involving three or more reactants that contribute significantly. These processes avoid the isolation and purification of intermediates, maximize the yield of the final product, minimize solvent waste, and enhance the greenness of the transformations. Consequently, MDRs have become a popular tool in the synthesis of complex heterocyclic molecules.[18] Recently, we developed a series of new MDRs that offer easy access to some nitrogen-containing heterocyclic skeletons of chemical and pharmaceutical interest.[19] In this study, we developed a novel MDR for the one-pot construction of indolizine skeletons from readily available starting materials under microwave irradiation. The attractive features of this MDR include the one-pot formation of up to seven bonds and two new rings (pyridine and pyrrole rings).

We initially selected the three-component domino reaction of phenylglyoxal monohydrate (**1a**), 5,5-dimethylcyclohexane-1,3-dione (**2a**), and 5-amino-3-methyl-1-phenylpyrazole (**3a**) as the model reaction for optimizing the reaction conditions. The reaction was conducted using a 2:1:1 mixture of **1a**, **2a**, and **3a** under different conditions (Table 1). The desired product **4a** was not obtained when the reaction was carried out in ethanol at 100 °C for 20 min under microwave irradiation and catalyst-free conditions (Table 1, entry 1). However, **4a** was obtained in

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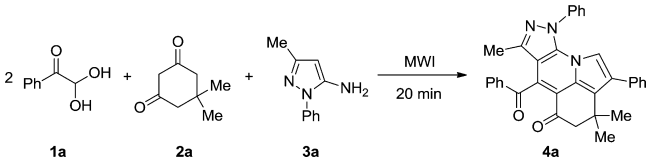
Table 1. Optimization of Reaction Conditions for Synthesis of 4a under Microwave Irradiation[a]



entry	solvent	base (mol %)	temp (°C)	yield[b] (%)
1	EtOH	–	100	NR
2	EtOH	Cs_2CO_3 (20)	100	15
3	EtOH	NaOH (20)	100	trace
4	EtOH	K_2CO_3 (20)	100	14
5	EtOH	pyridine (20)	100	trace
6	EtOH	piperidine (20)	100	33
7	EtOH	DMAP (20)	100	trace
8	EtOH	Et_3N (20)	100	17
9	EtOH	Et_2NH (20)	100	47
10	H_2O	Et_2NH (20)	100	trace
11	$HOCH_2CH_2OH$	Et_2NH (20)	100	49
12	DMF	Et_2NH (20)	100	42
13	CH_3CN	Et_2NH (20)	100	56
14	THF	Et_2NH (20)	100	18
15	DMSO	Et_2NH (20)	100	74
16	DMSO	Et_2NH (5)	100	20
17	DMSO	Et_2NH (10)	100	31
18	DMSO	Et_2NH (15)	100	65
19	DMSO	Et_2NH (25)	100	73
20	DMSO	Et_2NH (20)	110	73
21	DMSO	Et_2NH (20)	120	81
22	DMSO	Et_2NH (20)	130	77
23	DMSO	Et_2NH (20)	140	76

[a]Reactions were performed using **1a** (1 mmol), **2a** (0.5 mmol), **3a** (0.5 mmol), and diethylamine (0.1 mmol) in solvent (4 mL) under microwave irradiation. [b]The yields were determined by HPLC-MS.

15% yield when the reaction was conducted in the presence of Cs_2CO_3 (20 mol %) in ethanol (Table 1, entry 2). Several bases were evaluated in the reaction, including Cs_2CO_3, NaOH, K_2CO_3, pyridine, piperidine, DMAP, Et_3N, and Et_2NH; these were all added in a substoichiometric amount (20 mol %), and the reactions were carried out in ethanol at 100 °C for 20 min under microwave irradiation. The catalytic efficiency of Et_2NH was the highest (Table 1, entries 2–9). Various solvents were then evaluated to determine the impact of the solvent on the reaction yields. DMSO gave the best product yield (Table 1, entries 9–15). We then evaluated the amount of base required for this transformation. The results show that increasing the amount of Et_2NH from 5 to 20 mol % led to an increase in the yield from 20% to 74% (Table 1, entries 15–18). The use of 20 mol % Et_2NH in DMSO was identified as the most effective way of pushing this reaction toward completion; the addition of a larger amount of this base did not further improve the yield (Table 1, entry 19). Finally, the reaction was performed at different temperatures to determine the optimum reaction temperature. The reaction was conducted with 20 mol % Et_2NH in DMSO at 100, 110, 120, 130, and 140 °C, and the desired product **4a** was formed in yields of 74%, 73%, 81%, 77%, and 76% (Table 1, entries 15 and 20–23), respectively. These results show that the best reaction temperature was 120 °C. Taken together, the results of these screening experiments show that the optimum reaction conditions are 20 mol % Et_2NH in DMSO at 120 °C under microwave irradiation.

With the optimum reaction conditions in hand, we evaluated the scope of the transformation using various substituted phenylglyoxals **1**, cyclohexane-1,3-diones **2**, and 5-aminopyrazoles **3**. The results are summarized in Table 2. As shown in Table 2, methyl, phenyl, and cyclopropyl substituents on the pyrazole ring, and naphthalen-2-yl, thien-2-yl, and phenyl groups bearing either electron-withdrawing or electron-donating groups on the phenylglyoxal, were well tolerated under the reaction conditions, leading to the final products in satisfactory yields. Moreover, this synthesis follows the group-assisted-purification chemistry process,[20] which avoids the use of traditional chromatography or recrystallization purification methods. Pure products were obtained simply by filtration and washing the solid with a mixture of ethanol and water.

The structures of the products synthesized in the current study were determined using IR, ^{1}H NMR, and ^{13}C NMR spectroscopies and HRMS analysis. The structure of compound **4k** was confirmed by X-ray analysis (see Supporting Information).

On the basis of our results, we propose the mechanism shown in Scheme 1 for this novel four-component domino reaction. The Knoevenagel condensation of phenylglyoxal **1** with cyclohexane-1,3-dione **2** gives intermediate **A**. The subsequent Michael addition of 5-aminopyrazole **3** to **A** gives intermediate **B**, which undergoes an intramolecular nucleophilic addition reaction, followed by loss of water to form intermediate **E**. The Et_2NH-catalyzed condensation of **E** with **1** gives intermediate **F**, which undergoes a second intramolecular nucleophilic addition reaction and dehydration to form intermediate **I**. Finally, intermediate **I** undergoes Et_2NH-catalyzed dehydration to give the desired product **4**.

In conclusion, we have successfully developed an efficient, three-component domino reaction for the construction of functionalized indolizine skeletons under microwave irradiation. The key features of this new method are mild reaction conditions, readily available starting materials, high bond-forming efficiency, and environmental friendliness.

EXPERIMENTAL SECTION

General Methods. Microwave irradiation was carried out with Initiator 2.5 Microwave Synthesizers from Biotage, Uppsala, Sweden. The reaction temperatures were measured by an infrared detector (external sensor type) during microwave heating. Addition details on general methods are given in the Supporting Information.

Representative Synthesis for Compounds 4. Arylglyoxals **1** (1.0 mmol), cyclic 1,3-diones **2** (0.5 mmol), and 5-aminopyrazoles **3** (0.5 mmol) were placed in a 10 mL Inititator reaction vial, followed by Et_2NH (0.1 mmol) and DMSO (4 mL). The reaction vial was then sealed and prestirred for 15 s before being irradiated in the microwave (time, 20 min; temperature, 120 °C; absorption level, high; fixed hold time) until TLC (3:1 mixture of petroleum ether and ethyl acetate) revealed complete consumption of the starting materials. The reaction mixture was then cooled to room temperature to give a precipitate, which was collected by Büchner filtration. The solid material was then washed with a mixture of ethanol and water to afford the desired product **4**.

*6-(Benzoyl)-3,3,7-trimethyl-2,9-diphenyl-3,4-dihydropyrazolo-[3,4-b]pyrrolo[3,2,1-ij]quinolin-5(9H)-one (**4a**).* Yellow solid, 0.199 g, yield 78%; mp 247–249 °C; IR (KBr, ν, cm^{-1}) 2924, 2850, 1687, 1668, 1572, 1493, 1453, 1362, 1289, 1256, 1223, 1166, 1040, 984, 866, 844, 777, 744; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm) 7.97 (d, J = 7.2 Hz, 2H), 7.61–7.54 (m, 6H), 7.49–7.45 (m, 2H), 7.36 (s, 5H), 6.69 (s, 1H), 2.68 (s, 2H), 2.18 (s, 3H), 1.25 (s, 6H); ^{13}C NMR (100 MHz,

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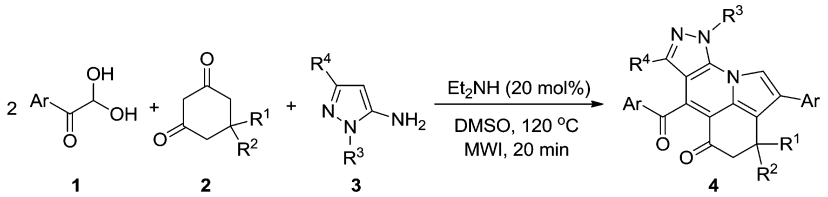
Table 2. Synthesis of Pyrazolo[3,4-*e*]indolizine Derivatives under Microwave Irradiation



1 2 3 4

entry	product	Ar	R^1	R^2	R^3	R^4	isolated yield (%)
1	**4a**	Ph	Me	Me	Ph	Me	78
2	**4b**	4-$MeOC_6H_4$	Me	Me	Ph	Me	77
3	**4c**	4-MeC_6H_4	Me	Me	Ph	Me	82
4	**4d**	4-ClC_6H_4	Me	Me	Ph	Me	71
5	**4e**	4-BrC_6H_4	Me	Me	Ph	Me	70
6	**4f**	Ph	Me	Me	Ph	Ph	70
7	**4g**	4-$MeOC_6H_4$	Me	Me	Ph	Ph	73
8	**4h**	4-MeC_6H_4	Me	Me	Ph	Ph	72
9	**4i**	4-ClC_6H_4	Me	Me	Ph	Ph	74
10	**4j**	4-BrC_6H_4	Me	Me	Ph	Ph	68
11	**4k**	Ph	Me	Me	Me	Ph	73
12	**4l**	4-ClC_6H_4	Me	Me	Me	Ph	69
13	**4m**	4-$MeOC_6H_4$	Me	Me	Me	Me	72
14	**4n**	4-MeC_6H_4	Me	Me	Me	Me	75
15	**4o**	4-ClC_6H_4	Me	Me	Me	Me	65
16	**4p**	4-BrC_6H_4	Me	Me	Me	Me	62
17	**4q**	3,4-$(CH_3)_2C_6H_3$	Me	Me	Ph	cyclopropyl	61
18	**4r**	4-$EtOC_6H_4$	Me	Me	Ph	cyclopropyl	64
19	**4s**	3,4-$OCH_2OC_6H_3$	Me	Me	Ph	cyclopropyl	62
20	**4t**	naphthalen-2-yl	Me	Me	Ph	Me	76
21	**4u**	naphthalen-2-yl	Me	Me	Ph	Ph	69
22	**4v**	3-ClC_6H_4	Me	Me	Ph	Me	70
23	**4w**	3,4-$(MeO)_2C_6H_3$	Me	Me	Ph	Me	70
24	**4x**	4-$EtOC_6H_4$	Me	Me	Ph	Me	75
25	**4y**	4-$EtOC_6H_4$	Me	Me	Ph	Ph	72
26	**4z**	3,4-$OCH_2OC_6H_3$	Me	Me	Ph	Me	77
27	**4a′**	3,4-$(CH_3)_2C_6H_3$	Me	Me	Ph	Me	73
28	**4b′**	2,5-$(CH_3)_2C_6H_3$	Me	Me	Ph	Me	69
29	**4c′**	4-EtC_6H_4	Me	Me	Ph	Me	76
30	**4d′**	4-*i*-PrC_6H_4	Me	Me	Ph	Me	76
31	**4e′**	thien-2-yl	Me	Me	Ph	Me	64
32	**4f′**	Ph	H	*n*-propyl	Ph	Me	67
33	**4g′**	4-$MeOC_6H_4$	H	*n*-propyl	Ph	Me	70
34	**4h′**	Ph	H	*i*-propyl	Ph	Me	62
35	**4i′**	4-MeC_6H_4	H	*i*-propyl	Ph	Me	64

$CDCl_3$, δ, ppm) 196.3, 146.8, 137.7, 137.2, 136.0, 135.8, 133.7, 130.2, 129.9, 129.5, 129.0, 128.8, 127.9, 127.4, 127.1, 120.6, 117.1, 111.5, 106.7, 56.6, 35.4, 30.1, 13.7; HRMS (ESI-TOF) m/z calcd for $C_{34}H_{27}N_3NaO_2$ 532.2001 $[M + Na]^+$, found 532.1972.

*6-(4-Methoxybenzoyl)-2-(4-methoxyphenyl)-3,3,7-trimethyl-9-phenyl-3,4-dihydropyrazolo[3,4-b]pyrrolo[3,2,1-ij]quinolin-5(9H)-one (**4b**).* Yellow solid, 0.219 g, yield 77%; mp 243−244 °C; IR (KBr, ν, cm^{-1}) 2958, 2934, 2837, 1678, 1656, 1577, 1526, 1493, 1435, 1166, 1106, 924, 863, 855, 752, 703; ^1H NMR (400 MHz, $CDCl_3$, δ, ppm) 7.94 (d, J = 7.2 Hz, 2H), 7.56 (s, 5H), 7.27−7.25 (m, 2H), 6.95−6.89 (m, 4H), 6.69 (s, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 2.68 (s, 2H), 2.19 (s, 3H), 1.25 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) 196.3, 194.8, 164.0, 159.0, 146.9, 131.3, 131.2, 130.5, 129.8, 129.5, 128.8, 127.9, 127.1, 114.1, 113.3, 111.5, 56.7, 55.5, 55.3, 35.3, 30.1, 13.6; HRMS (ESI-TOF) m/z calcd for $C_{36}H_{31}N_3NaO_4$ 592.2212 $[M + Na]^+$, found 592.2228.

*3,3,7-Trimethyl-6-(4-methylbenzoyl)-9-phenyl-2-(p-tolyl)-3,4-dihydropyrazolo[3,4-b]pyrrolo[3,2,1-ij]quinolin-5(9H)-one (**4c**).* Yellow solid, 0.220 g, yield 82%; mp 241−242 °C; IR (KBr, ν, cm^{-1}) 2955, 2922, 1681, 1654, 1572, 1492, 1384, 1175, 855, 821, 774; ^1H NMR (400 MHz, $CDCl_3$, δ, ppm) 7.86 (d, J = 8.0 Hz, 2H), 7.57−7.53 (m, 5H), 7.27 (s, 1H), 7.25−7.22 (m, 3H), 7.18−7.16 (m, 2H), 6.70 (s, 1H), 2.67 (s, 2H), 2.42 (s, 3H), 2.39 (s, 3H), 2.18 (s, 3H), 1.25 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) 195.8, 195.4, 146.3, 144.1, 137.3, 136.7, 135.5, 134.3, 132.3, 129.6, 129.4, 129.1, 129.0, 128.7, 128.6, 128.1, 126.6, 125.6, 120.0, 116.5, 111.0, 106.2, 56.2, 34.9, 29.6, 21.4, 20.7, 13.2; HRMS (ESI-TOF) m/z calcd for $C_{36}H_{31}N_3NaO_2$ 560.2314 $[M + Na]^+$, found 560.2301.

*6-(4-Chlorobenzoyl)-2-(4-chlorophenyl)-3,3,7-trimethyl-9-phenyl-3,4-dihydropyrazolo[3,4-b]pyrrolo[3,2,1-ij]quinolin-5(9H)-one (**4d**).* Yellow solid, 0.205 g, yield 71%; mp 270−271 °C; IR (KBr, ν, cm^{-1}) 2924, 2856, 1689, 1674, 1573, 1491, 1468, 1377, 1286, 1230, 1165, 1090, 1012, 984, 854, 827, 772, 727, 717; ^1H NMR (400 MHz, $CDCl_3$, δ, ppm) 7.91 (d, J = 8.4 Hz, 2H), 7.57 (s, 5H), 7.44 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 7.28 (s, 2H), 6.69 (s, 1H), 2.68 (s, 2H), 2.19 (s, 3H), 1.25 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) 196.2, 195.0, 146.6, 140.2, 137.6, 136.0, 135.6, 134.2, 133.6, 131.4, 130.2, 130.1, 129.5, 129.3, 128.2, 128.0, 127.1, 120.7, 117.1, 111.6, 56.5, 35.6, 30.1, 13.7; HRMS (ESI-TOF) m/z calcd for $C_{34}H_{26}Cl_2N_3O_2$ 578.1402 $[M + H]^+$, found 578.1396.

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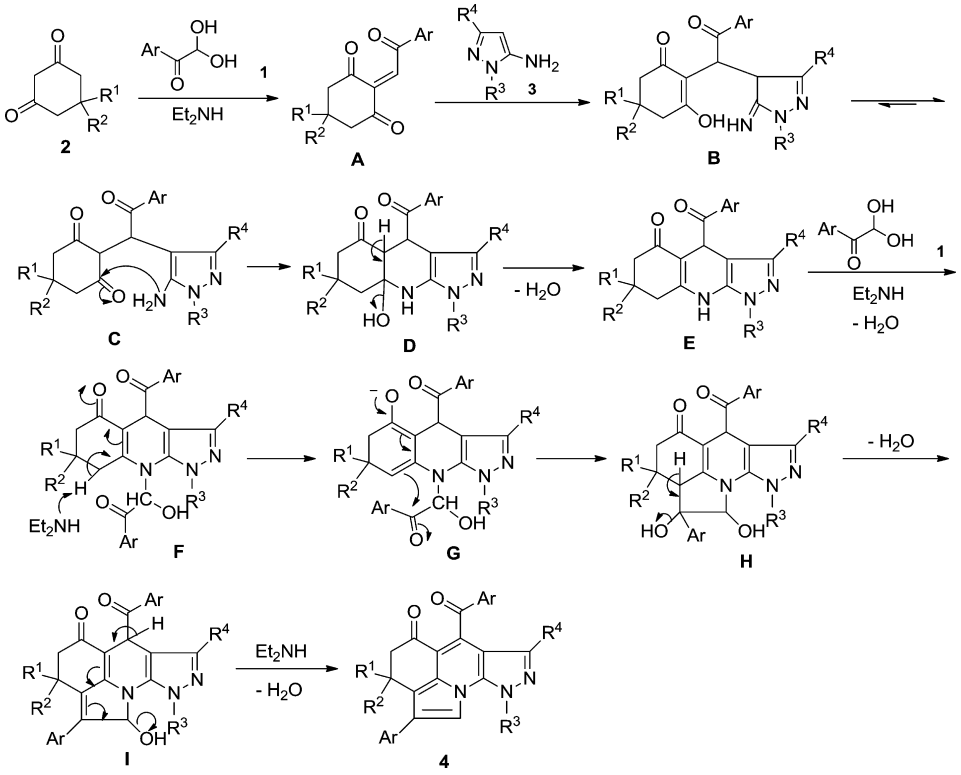
Scheme 1. Proposed Mechanism for the Synthesis of Compound 4



*6-(4-Bromobenzoyl)-2-(4-bromophenyl)-3,3,7-trimethyl-9-phenyl-3,4-dihydropyrazolo[3,4-b]pyrrolo[3,2,1-ij]quinolin-5(9H)-one (**4e**).* Yellow solid, 0.233 g, yield 70%; mp 286−287 °C; IR (KBr, ν, cm^{-1}) 2924, 2853, 1687, 1674, 1573, 1490, 1466, 1384, 1284, 1244, 1166, 1068, 1011, 984, 851, 826, 774, 721; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm) 7.83−7.82 (m, 2H), 7.61 (d, J = 8.0 Hz, 2H), 7.57 (s, 5H), 7.49 (d, J = 7.6 Hz, 2H), 7.21 (d, J = 7.2 Hz, 2H), 6.69 (s, 1H), 2.68 (s, 2H), 2.19 (s, 3H), 1.24 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) 196.2, 195.2, 146.6, 137.6, 136.0, 134.7, 132.2, 131.8, 131.1, 130.3, 130.1, 129.5, 129.0, 128.0, 127.1, 121.8, 120.7, 117.1, 111.5, 106.6, 56.5, 35.4, 30.2, 13.7; HRMS (ESI-TOF) m/z calcd for $C_{34}H_{26}Br_2N_3O_2$ 666.0392 $[M + H]^+$, found 666.0392.

*6-Benzoyl-3,3-dimethyl-2,7,9-triphenyl-3,4-dihydropyrazolo[3,4-b]pyrrolo[3,2,1-ij]quinolin-5(9H)-one (**4f**).* Yellow solid, 0.200 g, yield 70%; mp 282−283 °C; IR (KBr, ν, cm^{-1}) 3398, 3269, 3200, 2970, 2887, 2257, 1733, 1622, 1514, 1488, 1459, 1132, 1089, 958, 841, 723; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm) 7.65−7.62 (m, 4H), 7.57−7.56 (m, 3H), 7.44−7.42 (m, 1H), 7.37(s, 5H), 7.29−7.27 (m, 2H), 7.19−7.17 (m, 3H), 7.10−7.07 (m, 2H), 6.78 (s, 1H), 2.71 (s, 2H), 1.26 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) 196.3, 195.1, 150.6, 137.8, 137.1, 135.8, 133.0, 131.3, 130.3, 130.1, 130.0, 129.7, 129.5, 129.3, 128.8, 128.7, 128.2, 127.9, 127.7, 127.4, 127.2, 125.9, 121.0, 118.2, 111.8, 106.6, 56.8, 35.4, 30.1; HRMS (ESI-TOF) m/z calcd for $C_{39}H_{29}N_3NaO_2$ 594.2157 $[M + Na]^+$, found 594.2135.

*6-(4-Methoxybenzoyl)-2-(4-methoxyphenyl)-3,3-dimethyl-7,9-diphenyl-3,4-dihydropyrazolo[3,4-b]pyrrolo[3,2,1-ij]quinolin-5(9H)-one (**4g**).* Yellow solid, 0.230 g, yield 73%; mp 294−295 °C; IR (KBr, ν, cm^{-1}) 2924, 2853, 1886, 1654, 1597, 1567, 1491, 1464, 1383, 1250, 1164, 1028, 980, 846, 776, 720; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm) 7.66−7.65 (m, 2H), 7.60−7.55 (m, 5H), 7.28−7.27 (m, 2H), 7.23−7.20 (m, 3H), 7.13−7.09 (m, 2H), 6.91 (d, J = 8.4 Hz, 2H), 6.76−6.74 (m, 2H), 6.73 (s, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 2.72−2.68 (m, 2H), 1.25 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) 196.3, 193.6, 163.4, 159.1, 150.7, 137.8, 135.9, 131.4, 131.3, 131.1, 130.7, 130.1, 130.0, 129.7, 129.5, 128.9, 128.6, 127.9, 127.7, 127.2, 121.0, 117.9, 113.5, 113.3, 111.7, 106.5, 56.9, 55.4, 55.3, 36.5, 35.4; HRMS (ESI-TOF) m/z calcd for $C_{41}H_{33}N_3NaO_4$ 654.2369 $[M + Na]^+$, found 654.2398.

*3,3-Dimethyl-6-(4-methylbenzoyl)-7,9-diphenyl-2-(p-tolyl)-3,4-dihydropyrazolo[3,4-b]pyrrolo[3,2,1-ij]quinolin-5(9H)-one (**4h**).* Yellow solid, 0.216 g, 72%; mp >300 °C; IR (KBr, ν, cm^{-1}) 3381, 3269, 3203, 2949, 2884, 2267, 1751, 1682, 1513, 1444, 1302, 1252, 1134, 1092, 855, 822, 782, 699; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm) 7.66−7.64 (m, 2H), 7.57−7.53 (m, 5H), 7.25 (s, 2H), 7.21−7.17 (m, 5H), 7.11−7.07 (m, 4H), 6.74 (s, 1H), 2.69 (s, 2H), 2.40 (s, 3H), 2.35 (s, 3H), 1.19 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) 196.3, 194.7, 150.6, 143.8, 137.8, 137.2, 135.9, 134.9, 132.8, 131.4, 130.1, 130.0, 129.7, 129.5, 129.2, 129.0, 128.9, 128.6, 127.7, 127.3, 126.0, 120.9, 118.0, 111.7, 106.5, 56.9, 35.4, 30.9, 21.8, 21.2; HRMS (ESI-TOF) m/z calcd for $C_{41}H_{33}N_3NaO_2$ 622.2470 $[M + Na]^+$, found 622.2465.

*6-(4-Chlorobenzoyl)-2-(4-chlorophenyl)-3,3-dimethyl-7,9-diphenyl-3,4-dihydropyrazolo[3,4-b]pyrrolo[3,2,1-ij]quinolin-5(9H)-one (**4i**).* Yellow solid, 0.236 g, yield 74%; mp >300 °C; IR (KBr, ν, cm^{-1}) 2924, 2825, 1960, 1663, 1565, 1462, 1378, 1293, 1235, 981, 845, 776, 722; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm) 7.67−7.65 (m, 2H), 7.61−7.58 (m, 3H), 7.54 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 7.29−7.27 (m, 2H), 7.25−7.23 (m, 3H), 7.18−7.11 (m, 4H), 6.74 (s, 1H), 2.71 (s, 2H), 1.25 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) 196.2, 193.9, 150.5, 139.4, 137.6, 135.8, 135.5, 134.1, 133.7, 131.4, 130.2, 130.0, 129.7, 129.5, 128.8, 128.2, 128.1, 127.8, 127.2, 125.5, 121.1, 118.2, 111.8, 106.5, 56.7, 35.4; HRMS (ESI-TOF) m/z calcd for $C_{39}H_{28}Cl_2N_3O_2$ 640.1559 $[M + H]^+$, found 640.1543.

*6-(4-Bromobenzoyl)-2-(4-bromophenyl)-3,3-dimethyl-7,9-diphenyl-3,4-dihydropyrazolo[3,4-b]pyrrolo[3,2,1-ij]quinolin-5(9H)-one (**4j**).* Yellow solid, 0.247 g, yield 68%; mp >300 °C; IR (KBr, ν, cm^{-1}) 2953, 1689, 1662, 1565, 1446, 1289, 1228, 1169, 1069, 1048, 982, 843, 774, 755; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm) 7.66−7.65 (m, 2H), 7.61−7.58 (m, 3H), 7.52−7.46 (m, 4H), 7.40 (d, J = 8.4 Hz, 2H), 7.24−7.21 (m, 3H), 7.18−7.11 (m, 4H), 6.73 (s, 1H), 2.71 (s, 2H), 1.25 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) 196.2, 194.0, 150.5, 137.6, 135.9, 135.7, 134.6, 131.8, 131.6, 131.1, 130.2, 130.1, 130.0, 129.7, 129.5, 129.2 128.9, 128.2, 128.1, 127.8, 127.2, 125.4, 121.8, 121.1, 118.2, 111.8, 106.5, 56.7, 35.4; HRMS (ESI-TOF) m/z calcd for $C_{39}H_{28}Br_2N_3O_2$ 728.0548 $[M + H]^+$, found 728.0563.

*6-Benzoyl-3,3,9-trimethyl-2,7-diphenyl-3,4-dihydropyrazolo[3,4-b]pyrrolo[3,2,1-ij]quinolin-5(9H)-one (**4k**).* Yellow solid, 0.186 g, yield

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73%; mp 252−253 °C; IR (KBr, ν, cm^{-1}) 2924, 2852, 1682, 1670, 1601, 1577, 1454, 1385, 1270, 1256, 1232, 1168, 1020, 984, 920, 856, 839, 770, 754; ^1H NMR (400 MHz, $CDCl_3$, δ, ppm) 7.74 (s, 1H), 7.54 (d, J = 7.6 Hz, 2H), 7.51−7.49 (m, 2H), 7.45−7.38 (m, 4H), 7.24−7.18 (m, 3H), 7.08 (s, 4H), 4.42 (s, 3H), 2.69 (s, 2H), 1.28 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) 196.2, 195.1, 148.9, 137.0, 136.8, 135.8, 132.9, 131.5, 130.3, 129.9, 129.8, 129.6, 128.7, 128.5, 128.1, 128.0, 127.7, 127.6, 126.5, 120.9, 117.7, 110.5, 106.4, 56.7, 38.4, 30.1; HRMS (ESI-TOF) m/z calcd for $C_{34}H_{27}N_3NaO_2$ 532.2001 $[M + Na]^+$, found 532.1998.

6-(4-Chlorobenzoyl)-2-(4-chlorophenyl)-3,3,9-trimethyl-7-phenyl-3,4-dihydropyrazolo[3,4-b]pyrrolo[3,2,1-ij]quinolin-5(9H)-one (**4l**). Yellow solid, 0.199 g, yield 69%; mp 281−283 °C; IR (KBr, ν, cm^{-1}) 2924, 2853, 1686, 1670, 1604, 1583, 1458, 1381, 1265, 1162, 1089, 984, 851, 757, 723; ^1H NMR (400 MHz, $CDCl_3$, δ, ppm) 7.73 (s, 1H), 7.46−7.42 (m, 6H), 7.20−7.18 (m, 3H), 7.11−7.08 (m, 4H), 4.43 (s, 3H), 2.68 (s, 2H), 1.26 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) 196.1, 193.8, 148.8, 139.3, 136.7, 135.3, 134.2, 133.8, 131.5, 131.3, 130.0, 129.6, 128.7, 128.6, 128.5, 128.3, 127.8, 126.0, 121.0, 117.7, 110.5, 106.4, 59.3, 56.5, 39.8, 38.4, 35.4, 34.2, 29.7; HRMS (ESI-TOF) m/z calcd for $C_{34}H_{26}Cl_2N_3O_2$ 578.1402 $[M + H]^+$, found 578.1398.

6-(4-Methoxybenzoyl)-2-(4-methoxyphenyl)-3,3,7,9-tetramethyl-3,4-dihydropyrazolo[3,4-b]pyrrolo[3,2,1-ij]quinolin-5(9H)-one (**4m**). Yellow solid, 0.183 g, yield 72%; mp 230−231 °C; IR (KBr, ν, cm^{-1}) 2972, 2941, 1678, 1656, 1598, 1572, 1498, 1436, 1304, 1266, 1250, 1189, 1174, 1033, 1024, 953, 946, 879, 854, 838, 781, 744; ^1H NMR (400 MHz, $CDCl_3$, δ, ppm) 7.86 (s, 2H), 7.65 (s, 1H), 7.40−7.38 (m, 2H), 6.98−6.89 (m, 4H), 4.32 (s, 3H), 3.87 (s, 3H), 3.85 (s, 3H), 2.65 (s, 2H), 2.06 (s, 3H), 1.26 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) 196.3, 194.7, 163.9, 159.1, 144.9, 136.9, 131.2, 130.4, 129.9, 129.3, 127.9, 126.7, 120.3, 116.3, 114.0, 113.4, 110.2, 106.4, 56.6, 55.5, 55.3, 37.9, 35.3, 30.1, 13.4; HRMS (ESI-TOF) m/z calcd for $C_{31}H_{29}N_3NaO_4$ 530.2056 $[M + Na]^+$, found 530.2041.

3,3,7,9-Tetramethyl-6-(4-methylbenzoyl)-2-(p-tolyl)-3,4-dihydropyrazolo[3,4-b]pyrrolo[3,2,1-ij]quinolin-5(9H)-one (**4n**). Yellow solid, 0.178 g, yield 75%; mp 255−256 °C; IR (KBr, ν, cm^{-1}) 2924, 2852, 1688, 1669, 1601, 1582, 1496, 1458, 1383, 1248, 1174, 821, 804, 725, 711; ^1H NMR (400 MHz, $CDCl_3$, δ, ppm) 7.79 (d, J = 7.6 Hz, 2H), 7.67 (s, 1H), 7.37 (d, J = 7.6 Hz, 2H), 7.23−7.21 (m, 4H), 4.30 (s, 3H), 2.64 (s, 2H), 2.43 (s, 3H), 2.39 (s, 3H), 2.05 (s, 3H), 1.27 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm) 196.3, 195.8, 144,8, 144.5, 137.2, 136.9, 134.7, 132.8, 130.1, 129.9, 129.6, 129.5, 129.0, 128.7, 126.5, 120.3, 116.4, 110.3, 106.4, 56.6, 40.9, 37.9, 35.3, 30.9, 30.1, 21.8, 21.3, 13.4; HRMS (ESI-TOF) m/z calcd for $C_{31}H_{29}N_3NaO_2$ 498.2157 $[M + Na]^+$, found 498.2165.

6-(4-Chlorobenzoyl)-2-(4-chlorophenyl)-3,3,7,9-tetramethyl-3,4-dihydropyrazolo[3,4-b]pyrrolo[3,2,1-ij]quinolin-5(9H)-one (**4o**). Yellow solid, 0.168 g, yield 65%; mp 248−249 °C; IR (KBr, ν, cm^{-1}) 2924, 2852, 1684, 1673, 1602, 1582, 1460, 1383, 1250, 1203, 1171, 1092, 1014, 986, 870, 835, 800, 726, 757, 713; ^1H NMR (400 MHz, $CDCl_3$, δ, ppm) 7.83 (d, J = 8.4 Hz, 2H), 7.68 (s, 1H), 7.41 (s, 5H), 7.39 (s, 1H), 4.32 (s, 3H), 2.65 (s, 2H), 2.05 (s, 3H), 1.26 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) 196.1, 194.9, 144.7, 140.1, 136.9, 135.5, 134.2, 133.7, 131.5, 130.1, 129.9, 129.2, 128.4, 128.2, 125.9, 124.2, 120.5, 116.5, 110.4, 106.3, 56.3, 40.9, 37.9, 35.3, 30.1, 13.4; HRMS (ESI-TOF) m/z calcd for $C_{29}H_{24}Cl_2N_3O_2$ 516.1246 $[M + H]^+$, found 516.1245.

6-(4-Bromobenzoyl)-2-(4-bromophenyl)-3,3,7,9-tetramethyl-3,4-dihydropyrazolo[3,4-b]pyrrolo[3,2,1-ij]quinolin-5(9H)-one (**4p**). Yellow solid, 0.187 g, yield 62%; mp 277−279 °C; IR (KBr, ν, cm^{-1}) 2924, 2854, 1686, 1603, 1581, 1460, 1384, 1286, 1269, 1248, 1206, 1173, 1070, 1009, 985, 833, 721; ^1H NMR (400 MHz, $CDCl_3$, δ, ppm) 7.75 (d, J = 8.0 Hz, 2H), 7.76 (s, 1H), 7.57 (d, J = 7.6 Hz, 4H), 7.36 (s, 1H), 7.34 (s, 1H), 4.32 (s, 3H), 2.65 (s, 2H), 2.06 (s, 3H), 1.26 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) 196.1, 195.1, 144.8, 136.9, 135.8, 134.7, 132.2, 131.8, 131.2, 130.2, 129.9, 128.9, 128.5, 125.9, 121.9, 120.6, 116.6, 110.3, 106.3, 56.3, 41.0, 38.0, 35.3, 30.2, 13.5; HRMS (ESI-TOF) m/z calcd for $C_{29}H_{24}Br_2N_3O_2$ 604.0235 $[M + H]^+$, found 604.0232.

7-Cyclopropyl-6-(3,4-dimethylbenzoyl)-2-(3,4-dimethylphenyl)-3,3-dimethyl-9-phenyl-3,4-dihydropyrazolo[3,4-b]pyrrolo[3,2,1-ij]-quinolin-5(9H)-one (**4q**). Yellow solid, 0.181 g, yield 61%; mp 275−276 °C; IR (KBr, ν, cm^{-1}) 2924, 2855, 1681, 1657, 1602, 1574, 1489, 1385, 1295, 1246, 1208, 1172, 1129, 1100, 1057, 1022, 829, 808, 777, 723; ^1H NMR (400 MHz, $CDCl_3$, δ, ppm) 7.81 (s, 1H), 7.67−7.65 (m, 1H), 7.53 (s, 5H), 7.20−7.08 (m, 4H), 6.66 (s, 1H), 2.67 (s, 2H), 2.32−2.28 (m, 12H), 1.64 (s, 1H), 1.25 (m, 6H), 0.99 (s, 1H), 0.79 (s, 1H), 0.62 (s, 1H), 0.41 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) 196.5, 196.4, 151.7, 143.2, 137.9, 137.1, 136.1, 135.8, 135.3, 131.5, 130.2, 129.9, 129.8, 129.4, 129.1, 127.6, 127.2, 127.0, 126.5, 120.3, 116.9, 111.4, 107.4, 56.7, 35.3, 30.1, 19.9, 19.8, 19.5, 8.6; HRMS (ESI-TOF) m/z calcd for $C_{40}H_{37}N_3NaO_2$ 614.2783 $[M + Na]^+$, found 614.2793.

7-Cyclopropyl-6-(4-ethoxybenzoyl)-2-(4-ethoxyphenyl)-3,3-dimethyl-9-phenyl-3,4-dihydropyrazolo[3,4-b]pyrrolo[3,2,1-ij]-quinolin-5(9H)-one (**4r**). Yellow solid, 0.200 g, yield 64%; mp 264−265 °C; IR (KBr, ν, cm^{-1}) 2924, 2853, 1674, 1663, 1601, 1572, 1493, 1463, 1385, 1263, 1244, 1168, 1116, 1048, 984, 829, 775, 702; ^1H NMR (400 MHz, $CDCl_3$, δ, ppm) 7.96 (d, J = 8.0 Hz, 2H), 7.56 (s, 5H), 7.28 (s, 1H), 7.24 (s, 1H), 6.95−6.90 (m, 4H), 6.66 (s, 1H), 4.13−4.05 (m, 4H), 2.70 (s, 2H), 1.75−1.72 (m, 1H), 1.47−1.44 (m, 6H), 1.26 (s, 6H), 1.05 (s, 1H), 0.80 (s, 1H), 0.57 (s, 1H), 0.41 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) 196.4, 196.1, 163.3, 158.4, 151.7, 137.9, 135.9, 131.4, 131.2, 130.5, 129.8, 129.4, 127.2, 121.5, 120.4, 116.76, 114.4, 113.8, 111.4, 107.4, 63.8, 63.5, 56.8, 35.3, 30.1, 14.9, 14.7, 8.5, 7.9, 6.8; HRMS (ESI-TOF) m/z calcd for $C_{40}H_{37}N_3NaO_4$ 646.2682 $[M + Na]^+$, found 646.2669.

2-(Benzo[d][1,3]dioxol-5-yl)-6-(benzo[d][1,3]dioxole-5-carbonyl)-7-cyclopropyl-3,3-dimethyl-9-phenyl-3,4-dihydropyrazolo[3,4-b]-pyrrolo[3,2,1-ij]quinolin-5(9H)-one (**4s**). Yellow solid, 0.193 g, 62%; mp 290−292 °C; IR (KBr, ν, cm^{-1}) 2924, 2862, 1672, 1668, 1601, 1578, 1483, 1463, 1387, 1256, 1161, 1048, 984, 828, 712; ^1H NMR (400 MHz, $CDCl_3$, δ, ppm) 7.54 (s, 6H), 7.48 (d, J = 7.6 Hz, 1H), 6.82−6.78 (m, 4H), 6.62 (s, 1H), 6.06 (s, 2H), 5.99 (s, 2H), 2.68 (s, 2H), 1.73−1.68 (m, 1H), 1.26 (s, 6H), 1.03 (s, 1H), 0.81 (s, 1H), 0.61 (s, 1H), 0.47 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) 196.4, 194.5, 152.2, 151.6, 147.1, 147.0, 137.8, 132.4, 129.9, 129.4, 129.3, 128.7, 127.2, 126.1, 123.6, 120.4, 111.5, 110.7, 108.1, 107.8, 102.0, 56.7, 41.0, 35.3, 30.1, 30.0, 8.5, 7.8, 6.9; HRMS (ESI-TOF) m/z calcd for $C_{38}H_{29}N_3NaO_6$ 646.1954 $[M + Na]^+$, found 646.1934.

6-(2-Naphthoyl)-3,3,7-trimethyl-2-(naphthalen-2-yl)-9-phenyl-3,4-dihydropyrazolo[3,4-b]pyrrolo[3,2,1-ij]quinolin-5(9H)-one (**4t**). Yellow solid, 0.232 g, yield 76%; mp 272−274 °C; IR (KBr, ν, cm^{-1}) 2924, 2851, 1674, 1625, 1569, 1495, 1385, 1287, 1270, 1246, 1182, 1127, 1018, 1002, 821, 778, 752; ^1H NMR (400 MHz, $CDCl_3$, δ, ppm) 8.34 (s, 1H), 8.21 (d, J = 8.4 Hz, 1H), 7.97 (d, J = 8.8 Hz, 1H), 7.90−7.83 (m, 5H), 7.80 (s, 1H), 7.62−7.50 (m, 10H), 6.83 (s, 1H), 2.70 (s, 2H), 2.21 (s, 3H), 1.28 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) 196.3, 146.9, 136.1, 132.5, 130.0, 129.7, 129.5, 129.0, 128.9, 128.7, 128.5, 128.0, 127.9, 127.8, 127.4, 127.1, 126.8, 126.5, 126.3, 120.9, 117.3, 111.9, 108.0, 56.6, 40.9, 35.5, 30.2, 13.8; HRMS (ESI-TOF) m/z calcd for $C_{42}H_{31}N_3NaO_2$ 632.2314 $[M + Na]^+$, found 632.2290.

6-(2-Naphthoyl)-3,3-dimethyl-2-(naphthalen-2-yl)-7,9-diphenyl-3,4-dihydropyrazolo[3,4-b]pyrrolo[3,2,1-ij]quinolin-5(9H)-one (**4u**). Yellow solid, 0.232 g, yield 69%; mp >300 °C; IR (KBr, ν, cm^{-1}) 2924, 2854, 1681, 1670, 1623, 1595, 1567, 1485, 1458, 1383, 1252, 1180, 1053, 821, 775, 752, 719; ^1H NMR (400 MHz, $CDCl_3$, δ, ppm) 8.12 (s, 1H), 7.90−7.69 (m, 10H), 7.59−7.46 (m, 8H), 7.18−7.11 (m, 3H), 7.00−6.96 (m, 2H), 6.87 (s, 1H), 2.73 (s, 2H), 1.29 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) 196.3, 195.0, 150.67, 130.9, 130.2, 129.7, 129.5, 129.3, 128.9, 128.7, 128.5, 128.4, 128.2, 127.9, 127.8, 127.7, 127.6, 127.4, 127.3, 126.5, 126.4, 126.3, 124.1, 121.3, 56.8, 35.5; HRMS (ESI-TOF) m/z calcd for $C_{47}H_{33}N_3NaO_2$ 694.2470 $[M + Na]^+$, found 694.2447.

6-(3-Chlorobenzoyl)-2-(3-chlorophenyl)-3,3,7-trimethyl-9-phenyl-3,4-dihydropyrazolo[3,4-b]pyrrolo[3,2,1-ij]quinolin-5(9H)-one (**4v**). Yellow solid, 0.202 g, 70%; mp 233−234 °C; IR (KBr, ν, cm^{-1}) 2924, 2853, 1668, 1634, 1568, 1495, 1466, 1383, 1290, 1227, 1113, 1077, 795, 785, 765, 744, 727; ^1H NMR (400 MHz, $CDCl_3$, δ, ppm)

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7.91 (s, 1H), 7.85 (d, J = 7.6 Hz, 1H), 7.58 (s, 5H), 7.56 (s, 1H), 7.45−7.41 (m, 1H), 7.35−7.28 (m, 3H), 7.24−7.22 (m, 1H), 6.71 (s, 1H), 2.69 (s, 2H), 2.19 (s, 3H), 1.26 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) 196.2, 194.9, 146.6, 138.7, 137.6, 135.2 133.8, 133.6, 130.2, 130.1, 130.0, 129.6, 128.8, 128.5, 127.6, 127.1, 120.8, 111.7, 106.6, 56.4, 35.4, 30.2, 13.7; HRMS (ESI-TOF) m/z calcd for $C_{34}H_{26}Cl_2N_3O_2$ 578.1402 $[M + H]^+$, found 578.1391.

*6-(3,4-Dimethoxybenzoyl)-2-(3,4-dimethoxyphenyl)-3,3,7-trimethyl-9-phenyl-3,4-dihydropyrazolo[3,4-b]pyrrolo[3,2,1-ij]quinolin-5(9H)-one (**4w**).* Brown solid, 0.220 g, yield 70%; mp 180−182 °C; IR (KBr, ν, cm^{-1}) 2924, 2864, 1679, 1665, 1609, 1572, 1502, 1458, 1377, 1311, 1256, 1109, 1037, 846, 778, 743, 717, 704; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm) 7.79 (s, 1H), 7.57 (s, 5H), 7.31 (d, J = 8.0 Hz, 1H), 6.91−6.86 (m, 3H), 6.80 (d, J = 8.4 Hz, 1H), 6.71 (s, 1H), 4.10 (s, 3H), 3.93 (s, 3H), 3.92 (s, 3H), 3.87 (s, 3H), 2.70 (s, 2H), 2.20 (s, 3H), 1.27 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) 196.3, 194.8, 153.9, 149.5, 148.5, 148.2, 146.9, 137.7, 135.9, 130.6, 130.1, 129.9, 129.5, 128.9, 128.1, 127.1, 126.0, 124.9, 122.4, 120.5, 116.9, 113.6, 111.4, 110.6, 110.1, 106.9, 56.7, 56.2, 56.1, 55.9, 35.3, 30.0, 13.7; HRMS (ESI-TOF) m/z calcd for $C_{38}H_{35}N_3NaO_6$ 652.2424 $[M + Na]^+$, found 652.2436.

*6-(4-Ethoxybenzoyl)-2-(4-ethoxyphenyl)-3,3,7-trimethyl-9-phenyl-3,4-dihydropyrazolo[3,4-b]pyrrolo[3,2,1-ij]quinolin-5(9H)-one (**4x**).* Yellow solid, 0.224 g, yield 75%; mp 242−243 °C; IR (KBr, ν, cm^{-1}) 2924, 2854, 2361, 1677, 1655, 1604, 1573, 1495, 1472, 1244, 1175, 1041, 984, 921, 831, 775, 752, 700; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm) 7.92 (d, J = 7.6 Hz, 2H), 7.56 (s, 5H), 7.24 (d, J = 8.8 Hz, 2H), 6.93−6.88 (m, 4H), 6.68 (s, 1H), 4.13−4.03 (m, 4H), 2.68 (s, 2H), 2.19 (s, 3H), 1.45−1.42 (m, 6H), 1.24 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) 197.9, 196.6, 147.0, 137.8, 136.1, 134.9, 134.8, 134.5, 134.0, 133.3, 132.2, 131.8, 130.1, 129.9, 129.6, 129.5, 128.5, 127.8, 127.6, 127.0, 120.5, 116.6, 111.3, 107.0, 56.4, 35.4, 21.4, 20.9, 20.8, 20.3, 13.8; HRMS (ESI-TOF) m/z calcd for $C_{38}H_{35}N_3NaO_4$ 620.2525 $[M + Na]^+$, found 620.2531.

*6-(4-Ethoxybenzoyl)-2-(4-ethoxyphenyl)-3,3-dimethyl-7,9-diphenyl-3,4-dihydropyrazolo[3,4-b]pyrrolo[3,2,1-ij]quinolin-5(9H)-one (**4y**).* Yellow solid, 0.237 g, yield 72%; mp 262−264 °C; IR (KBr, ν, cm^{-1}) 2924, 2852, 2360, 1680, 1657, 1599, 1566, 1492, 1463, 1383, 1242, 1163, 1049, 985, 847, 774, 720; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm) 7.64 (s, 2H), 7.59−7.57 (m, 5H), 7.24 (s, 2H), 7.20 (d, J = 7.2 Hz, 3H), 7.13−7.10 (m, 2H), 6.90 (d, J = 7.6 Hz, 2H), 6.74−6.73 (m, 3H), 4.07−4.05 (m, 4H), 2.72−2.68 (m, 2H), 1.46−1.40 (m, 6H), 1.25 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) 196.3, 193.6, 162.9, 158.4, 150.7, 137.8, 135.9, 131.3, 131.1, 130.5, 130.0, 129.7, 129.5, 129.0, 128.6, 127.7, 127.6, 127.2, 126.1, 117.9, 114.0, 113.8, 111.7, 106.5, 63.7, 63.5, 56.9, 35.4, 14.9, 14.7; HRMS (ESI-TOF) m/z calcd for $C_{43}H_{37}N_3NaO_4$ 682.2682 $[M + Na]^+$, found 682.2672.

*2-(Benzo[d][1,3]dioxol-5-yl)-6-(benzo[d][1,3]dioxole-5-carbonyl)-3,3,7-trimethyl-9-phenyl-3,4-dihydropyrazolo[3,4-b]pyrrolo[3,2,1-ij]quinolin-5(9H)-one (**4z**).* Yellow solid, 0.230 g, yield 77%; mp 279−281 °C; IR (KBr, ν, cm^{-1}) 2956, 2862, 1648, 1578, 1476, 1423, 1387, 1255, 1152, 1039, 930, 811, 704; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm) 7.56 (s, 6H), 7.46 (s, 1H), 6.80 (s, 4H), 6.68 (s, 1H), 6.05 (s, 2H), 5.98 (s, 2H), 2.69 (s, 2H), 2.21 (s, 3H), 1.27 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) 196.4, 194.2, 152.4, 148.5, 147.1, 147.0, 146.8, 137.7, 135.9, 132.2, 130.0, 129.9, 129.5, 129.2, 128.8, 127.1, 125.9, 123.6, 120.5, 116.9, 111.5, 110.7, 108.2, 107.8, 106.7, 102.1, 101.2, 56.7, 35.3, 30.1, 13.6; HRMS (ESI-TOF) m/z calcd for $C_{36}H_{27}N_3NaO_6$ 620.1798 $[M + Na]^+$, found 620.1794.

*6-(3,4-Dimethylbenzoyl)-2-(3,4-dimethylphenyl)-3,3,7-trimethyl-9-phenyl-3,4-dihydropyrazolo[3,4-b]pyrrolo[3,2,1-ij]quinolin-5(9H)-one (**4a′**).* Yellow solid, 0.207g, 73%; mp 269−271 °C; IR (KBr, ν, cm^{-1}) 2924, 2855, 1681, 1659, 1606, 1572, 1492, 1456, 1385, 1299, 1250, 1101, 1020, 825, 773, 723, 714; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm) 7.79 (s, 1H), 7.65−7.63 (m, 1H), 7.56−7.53 (m, 5H), 7.20 (d, J = 8.0 Hz, 1H), 7.14−7.08 (m, 3H), 6.71 (s, 1H), 2.67 (s, 2H), 2.32−2.28 (m, 12H), 2.20 (s, 3H), 1.25 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) 196.4, 196.2, 146.9, 143.5, 137.8, 137.3, 136.1, 136.0, 135.8, 135.2, 133.2, 131.5, 130.1, 129.8, 129.7, 129.5, 129.3, 129.2, 127.7, 127.1, 127.0, 126.2, 120.5, 116.9, 111.5, 106.8, 56.7, 35.4, 30.1, 20.2, 19.9, 19.8, 19.5, 13.7; HRMS (ESI-TOF) m/z calcd for $C_{38}H_{35}N_3NaO_2$ 588.2627 $[M + Na]^+$, found 588.2622.

*6-(2,5-Dimethylbenzoyl)-2-(2,5-dimethylphenyl)-3,3,7-trimethyl-9-phenyl-3,4-dihydropyrazolo[3,4-b]pyrrolo[3,2,1-ij]quinolin-5(9H)-one (**4b′**).* Yellow solid, 0.195 g, 69%; mp 236−238 °C; IR (KBr, ν, cm^{-1}) 2924, 2853, 1686, 1667, 1572, 1494, 1460, 1383, 1247, 1121, 1178, 1164, 1080, 1009, 827, 813, 769, 757, 724; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm) 7.57−7.53 (m, 5H), 7.32 (s, 1H), 7.24−7.22 (m, 2H), 7.14−7.07 (m, 2H), 7.03 (s, 1H), 6.65 (s, 1H), 2.85 (s, 3H), 2.64 (s, 2H), 2.31 (s, 3H), 2.26 (s, 3H), 2.24 (s, 3H), 2.08 (s, 3H), 1.14−1.07 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) 197.9, 196.6, 147.0, 137.8, 136.3, 136.1, 134.9, 134.8, 134.5, 134.0, 133.3, 132.2, 131.8, 131.1, 129.9, 129.6, 129.5, 128.5, 127.8, 127.6, 127.0, 120.5, 116.6, 111.3, 107.0, 56.4, 35.4, 21.4, 20.9, 20.8, 20.3, 13.8; HRMS (ESI-TOF) m/z calcd for $C_{38}H_{36}N_3O_2$ 566.2808 $[M + H]^+$, found 566.2799.

*6-(4-Ethylbenzoyl)-2-(4-ethylphenyl)-3,3,7-trimethyl-9-phenyl-3,4-dihydropyrazolo[3,4-b]pyrrolo[3,2,1-ij]quinolin-5(9H)-one (**4c′**).* Yellow solid, 0.215g, 76%; mp 227−228 °C; IR (KBr, ν, cm^{-1}) 2924, 2855, 1678, 1655, 1605, 1570, 1494, 1460, 1383, 1250, 1247, 987, 856, 834, 773, 748; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm) 7.88 (d, J = 7.6 Hz, 2H), 7.55 (s, 5H), 7.29−7.25 (m, 4H), 7.20 (d, J = 7.6 Hz, 2H), 6.72 (s, 1H), 2.74−2.68 (m, 6H), 2.19 (s, 3H), 1.29−1.25 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) 196.4, 196.0, 150.7, 146.8, 143.5, 137.8, 136.0, 135.0, 133.0, 130.1, 130.0, 129.9, 129.5, 129.2, 128.4, 127.4, 127.1, 126.1, 120.5, 117.0, 111.5, 106.7, 56.7, 35.4, 30.1, 29.1, 28.6, 15.5, 15.0, 13.7; HRMS (ESI-TOF) m/z calcd for $C_{38}H_{35}N_3NaO_2$ 588.2627 $[M + Na]^+$, found 588.2620.

*6-(4-Isopropylbenzoyl)-2-(4-isopropylphenyl)-3,3,7-trimethyl-9-phenyl-3,4-dihydropyrazolo[3,4-b]pyrrolo[3,2,1-ij]quinolin-5(9H)-one (**4d′**).* Yellow solid, 0.226 g, 76%; mp 288−290 °C; IR (KBr, ν, cm^{-1}) 2956, 2924, 2855, 1688, 1670, 1604, 1562, 1493, 1383, 1290, 1236, 1177, 1054, 984, 856, 841, 761, 714; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm) 7.90−7.88 (m, 2H), 7.56 (s, 5H), 7.31−7.29 (m, 3H), 7.26−7.24 (m, 3H), 6.73 (s, 1H), 2.96−2.95 (m, 2H), 2.69 (s, 2H), 2.18 (s, 3H), 1.28−1.26 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) 196.4, 196.0, 155.1, 148.1, 146.9, 137.8, 136.0, 135.0, 133.1, 130.1, 130.0, 129.9, 129.5, 129.3, 127.1, 127.0, 126.1, 126.0, 120.5, 116.9, 111.5, 106.7, 56.7, 35.4, 34.4, 33.8, 30.1, 24.0, 23.7, 13.7; HRMS (ESI-TOF) m/z calcd for $C_{40}H_{39}N_3NaO_2$ 616.2940 $[M + Na]^+$, found 616.2949.

*3,3,7-Trimethyl-9-phenyl-2-(thiophen-2-yl)-6-(thiophene-2-carbonyl)-3,4-dihydropyrazolo[3,4-b]pyrrolo[3,2,1-ij]quinolin-5(9H)-one (**4e′**).* Yellow solid, 0.167 g, 64%; mp 262−264 °C; IR (KBr, ν, cm^{-1}) 2924, 2854, 1681, 1645, 1572, 1496, 1460, 1416, 1382, 1300, 1272, 1246, 1234, 1167, 1068, 1047, 823, 763, 752, 714; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm) 7.77−7.75 (m, 1H), 7.64−7.57 (m, 5H), 7.54−7.53 (m, 1H), 7.36−7.34 (m, 1H), 7.13−7.11 (m, 1H), 7.09−7.07 (m, 1H), 7.05−7.04 (m, 1H), 6.83 (s, 1H), 2.75 (s, 2H), 2.29 (s, 3H), 1.36 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) 195.9, 187.8, 146.8, 144.4, 137.6, 136.0, 135.7, 134.9, 133.9, 130.0, 129.5, 128.3, 127.9, 127.1, 127.0, 125.9, 121.5, 120.9, 117.0, 112.8, 106.6, 56.7, 35.4, 29.6, 13.5; HRMS (ESI-TOF) m/z calcd for $C_{30}H_{23}N_3NaO_2S_2$ 544.1129 $[M + Na]^+$, found 544.1124.

*6-Benzoyl-7-methyl-2,9-diphenyl-3-propyl-3,4-dihydropyrazolo-[3,4-b]pyrrolo[3,2,1-ij]quinolin-5(9H)-one (**4f′**).* Brown solid, 0.175 g, 67%; mp 182−184 °C; IR (KBr, ν, cm^{-1}) 2964, 2930, 1676, 1666, 1588, 1557, 1491, 1305, 1249, 1177, 1018, 982, 854, 836, 771, 751; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm) 7.98−7.96 (m, 2H), 7.60−7.57 (m, 6H), 7.49−7.37 (m, 6H), 7.32−7.29 (m, 1H), 6.90 (s, 1H), 3.69−3.67 (m, 1H), 3.08−3.03 (m, 1H), 2.82−2.78 (m, 1H), 2.18 (s, 3H), 1.46−1.40 (m, 2H), 1.13−1.11 (m, 2H), 0.69−0.66 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) 196.4, 196.3, 146.9, 137.7, 136.1, 134.7, 133.7, 131.8, 130.0, 129.5, 129.0, 128.9, 128.8, 128.6, 128.0, 127.2, 127.1, 116.8, 115.4, 110.1, 106.8, 45.1, 39.5, 32.4, 19.6, 13.9, 13.7; HRMS (ESI-TOF) m/z calcd for $C_{35}H_{29}N_3NaO_2$ 546.2157 $[M + Na]^+$, found 546.2156.

*6-(4-Methoxybenzoyl)-2-(4-methoxyphenyl)-7-methyl-9-phenyl-3-propyl-3,4-dihydropyrazolo[3,4-b]pyrrolo[3,2,1-ij]quinolin-5(9H)-one (**4g′**).* Brown solid, 0.204 g, 70%; mp 184−185 °C; IR (KBr, ν, cm^{-1}) 2960, 2927, 1683, 1656, 1597, 1564, 1489, 1302, 1253, 1167, 1024, 987, 858, 826, 781, 751; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm)

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7.93 (s, 2H), 7.60 (s, 5H), 7.36−7.33 (m, 2H), 6.94−6.92 (m, 4H), 6.84 (s, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 3.65−3.63 (m, 1H), 3.08−3.01 (m, 1H), 2.82−2.78 (m, 1H), 2.22−2.16 (m, 3H), 1.44−1.42 (m, 2H), 1.15−1.13 (m, 2H), 0.70−0.69 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) 195.7, 194.4, 163.5, 158.3, 137.3, 135.6, 131.3, 130.7, 129.4, 129.0, 128.6, 127.8, 126.7, 126.6, 106.0, 114.6, 113.8, 113.6, 109.1, 106.3, 55.0, 54.8, 44.8, 38.8, 32.0, 19.1, 13.4, 13.1; HRMS (ESI-TOF) m/z calcd for $C_{37}H_{33}N_3NaO_4$ 606.2369 $[M + Na]^+$, found 606.2362.

*6-Benzoyl-3-isopropyl-7-methyl-2,9-diphenyl-3,4-dihydropyrazolo[3,4-b]pyrrolo[3,2,1-ij]quinolin-5(9H)-one (**4h**′).* Brown solid, 0.162 g, yield 62%; mp 149−151 °C; IR (KBr, ν, cm^{-1}) 2968, 2949, 1689, 1651, 1578, 1543, 1485, 1301, 1267, 1181, 1003, 996, 864, 839, 774, 747; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm) 7.95 (d, J = 6.8 Hz, 2H), 7.61 (s, 6H), 7.48−7.39 (m, 6H), 7.32−7.28 (m, 1H), 6.91 (s, 1H), 3.64 (s, 1H), 2.94−2.85 (m, 2H), 2.18 (s, 3H), 1.77 (s, 1H), 0.74 (s, 3H), 0.57−0.55 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) 196.1, 195.9, 146.4, 137.3, 135.6, 134.6, 133.1, 132.1, 129.5, 129.0, 128.6, 128.4, 128.3, 127.6, 126.6, 116.5, 113.3, 109.8, 106.2, 41.6, 38.4, 33.8, 19.9, 17.7, 13.2; HRMS (ESI-TOF) m/z calcd for $C_{35}H_{29}N_3NaO_2$ 546.2157 $[M + Na]^+$, found 546.2146.

*3-Isopropyl-7-methyl-6-(4-methylbenzoyl)-9-phenyl-2-(p-tolyl)-3,4-dihydropyrazolo[3,4-b]pyrrolo[3,2,1-ij]quinolin-5(9H)-one (**4i**′).* Brown solid, 0.177 g, yield 64%; mp 146−148 °C; IR (KBr, ν, cm^{-1}) 2968, 2946, 1682, 1652, 1563, 1549, 1498, 1311, 1257, 1164, 1005, 975, 876, 826, 786, 747, 706; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm) 7.85 (s, 2H), 7.59 (s, 5H), 7.32−7.30 (m, 2H), 7.26−7.24 (m, 2H), 7.20−7.18 (m, 2H), 6.87 (s, 1H), 3.62 (s, 1H), 2.88−2.84 (m, 2H), 2.41 (s, 3H), 2.37 (s, 3H), 2.21−2.17 (m, 3H), 1.78 (s, 1H), 0.75 (s, 3H), 0.57−0.55 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm) 196.0, 195.5, 146.4, 144.0, 137.3, 136.4, 135.6, 131.6, 129.4, 129.1, 129.0, 128.9, 128.5, 127.4, 126.6, 116.3, 113.2, 109.6, 106.2, 41.2, 38.3, 33.7, 21.3, 20.7, 19.9, 17.6, 13.2; HRMS (ESI-TOF) m/z calcd for $C_{37}H_{33}N_3NaO_2$ 574.2470 $[M + Na]^+$, found 574.2483.

■ ASSOCIATED CONTENT

Supporting Information

Additional text describing general methods; one figure and three tables with crystallographic data for product **4k**; ^{1}H and ^{13}C NMR spectra for all compounds (PDF). One crystallographic file (CIF). The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01314.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Michael, J. P. *Alkaloids* **2001**, *55*, 91. (b) Michael, J. P. *Nat. Prod. Rep.* **2002**, *19*, 742.
(2) (a) Kallay, K. R.; Doerge, R. F. *J. Pharm. Sci.* **1972**, *61*, 949. (b) Kitadokoro, K.; Hagishita, S.; Sato, T.; Ohtani, M.; Miki, K. *J. Biochem.* **1998**, *123*, 619. (c) Oslund, R. C.; Cermak, N.; Gelb, M. H. *J. Med. Chem.* **2008**, *51*, 4708.
(3) (a) Reddy, M. V.; Rao, M. R.; Rhodes, D.; Hansen, M. S.; Rubins, K.; Bushman, F. D.; Venkateswarlu, Y.; Faulkner, D. J. *J. Med. Chem.* **1999**, *42*, 1901. (b) Facompre, M.; Tardy, C.; Bal-Mahieu, C.; Colson, P.; Perez, C.; Manzanares, I.; Cuevas, C.; Bailly, C. *Cancer Res.* **2003**, *63*, 7392.
(4) (a) De, A. U.; Saha, B. P. *J. Pharm. Sci.* **1973**, *62*, 1897. (b) De, A. U.; Saha, B. P. *J. Pharm. Sci.* **1975**, *64*, 249.
(5) (a) Wani, M. C.; Nicholas, A. W.; Wall, M. E. *J. Med. Chem.* **1987**, *30*, 2317. (b) Bermudez, J.; Fake, C. S.; Joiner, G. F.; Joiner, K. A.; King, F. D.; Miner, W. D.; Sanger, G. J. *J. Med. Chem.* **1990**, *33*, 1924.
(6) (a) Chai, W.; Breitenbucher, J. G.; Kwok, A.; Li, X.; Wong, V.; Carruthers, N. I.; Lovenberg, T. W.; Mazur, C.; Wilson, S. J.; Axe, F. U.; Jones, T. K. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1767. (b) Gupta, S. P.; Mathur, A. N.; Nagappa, A. N.; Kumar, D.; Kumaran, S. *Eur. J. Med. Chem.* **2003**, *38*, 867.
(7) Antonini, I.; Claudi, F.; Gulini, U.; Micossi, L.; Venturi, F. *J. Pharm. Sci.* **1979**, *68*, 321.
(8) Harrell, W. B.; Doerge, R. F. *J. Pharm. Sci.* **1967**, *56*, 1200.
(9) Jørgensen, A. S.; Jacobsen, P.; Christiansen, L. B.; Bury, P. S.; Kanstrup, A.; Thorpe, S. M.; Nærum, L.; Wassermann, K. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2383.
(10) Gubin, J.; Lucchetti, J.; Mahaux, J.; Nisato, D.; Rosseels, G.; Clinet, M.; Polster, P.; Chatelain, P. *J. Med. Chem.* **1992**, *35*, 981.
(11) Hagishita, S.; Yamada, M.; Shirahase, K.; Okada, T.; Murakami, Y.; Ito, Y.; Matsuura, T.; Wada, M.; Kato, T.; Ueno, M.; Chikazawa, Y.; Yamada, K.; Ono, T.; Teshirogi, I.; Ohtani, M. *J. Med. Chem.* **1996**, *39*, 3636.
(12) La Pietra, V.; La Regina, G.; Coluccia, A.; Famiglini, V.; Pelliccia, S.; Plotkin, B.; Eldar-Finkelman, H.; Brancale, A.; Ballatore, C.; Crowe, A.; Brunden, K. R.; Marinelli, L.; Novellino, E.; Silvestri, R. *J. Med. Chem.* **2013**, *56*, 10066.
(13) (a) Kim, E.; Koh, M.; Ryu, J.; Park, S. B. *J. Am. Chem. Soc.* **2008**, *130*, 12206. (b) Liu, B.; Wang, Z.; Wu, N.; Li, M.; You, J.; Lan, J. *Chem. - Eur. J.* **2012**, *18*, 1599. (c) Amaral, M. F. Z. J.; Deliberto, L. A.; de Souza, C. R.; Naal, R. M. Z. G.; Naal, Z.; Clososki, G. C. *Tetrahedron* **2014**, *70*, 3249.
(14) (a) Miki, Y.; Hachiken, H.; Takemura, S.; Ikeda, M. *Heterocycles* **1984**, *22*, 701. (b) Tsuge, O.; Kanemasa, S.; Kuraoka, S.; Takenaka, S. *Chem. Lett.* **1984**, 279. (c) Wei, X.; Hu, Y.; Li, T.; Hu, H. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2487. (d) Padwa, A.; Austin, D. J.; Precedo, L.; Zhi, L. *J. Org. Chem.* **1993**, *58*, 1144. (e) De Bue, G.; Nasielski, J. *Bull. Soc. Chim. Belg.* **1997**, *106*, 97. (f) Poissonnet, G.; Theret-Bettiol, M. H.; Dodd, R. H. *J. Org. Chem.* **1996**, *61*, 2273. (g) Katritzky, A. R.; Qiu, G.; Yang, B.; He, H. Y. *J. Org. Chem.* **1999**, *64*, 7618. (h) Kucukdisli, M.; Opatz, T. *Eur. J. Org. Chem.* **2012**, *2012*, 4555.
(15) (a) Kel'in, A. V.; Sromek, A. W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 2074. (b) Seregin, I. V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2006**, *128*, 12050. (c) Liu, Y.; Song, Z.; Yan, B. *Org. Lett.* **2007**, *9*, 409. (d) Smith, C. R.; Bunnelle, E. M.; Rhodes, A. J.; Sarpong, R. *Org. Lett.* **2007**, *9*, 1169. (e) Seregin, I. V.; Schammel, A. W.; Gevorgyan, V. *Org. Lett.* **2007**, *9*, 3433. (f) Yan, B.; Liu, Y. *Org. Lett.* **2007**, *9*, 4323. (g) Hardin, A. R.; Sarpong, R. *Org. Lett.* **2007**, *9*, 4547. (h) Yan, B.; Zhou, Y.; Zhang, H.; Chen, J.; Liu, Y. *J. Org. Chem.* **2007**, *72*, 7783. (i) Chernyak, D.; Gadamsetty, S. B.; Gevorgyan, V. *Org. Lett.* **2008**, *10*, 2307. (j) Barluenga, J.; Lonzi, G.; Riesgo, L.; López, L. A.; Tomás, M. *J. Am. Chem. Soc.* **2010**, *132*, 13200. (k) Yang, Y.; Xie, C.; Xie, Y.; Zhang, Y. *Org. Lett.* **2012**, *14*, 957.
(16) (a) Ziyaadini, M.; Hazeri, N.; Maghsoodlou, M. T.; Habibi-Khorassani, S. M.; Willis, A. C. *Tetrahedron Lett.* **2011**, *52*, 5774. (b) Yang, Y.; Gao, M.; Zhang, D. X.; Wu, L. M.; Shu, W. M.; Wu, A. X. *Tetrahedron* **2012**, *68*, 7338. (c) Sun, J.; Hu, H.; Wang, F.; Wu, H.; Liu, Y. *RSC Adv.* **2014**, *4*, 36498.
(17) (a) Lee, J. H.; Kim, I. *J. Org. Chem.* **2013**, *78*, 1283. (b) Zhu, H.; Stöckigt, J.; Yu, Y.; Zou, H. *Org. Lett.* **2011**, *13*, 2792.

DOI: 10.1021/acs.joc.5b01314
J. Org. Chem. 2015, 80, 8435−8442

(18) (a) Jiang, B.; Tu, S. J.; Kaur, P.; Wever, W.; Li, G. *J. Am. Chem. Soc.* **2009**, *131*, 11660. (b) Han, X.; Li, H.; Hughes, R. P.; Wu, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 10390. (c) Knapp, J. M.; Zhu, J. S.; Tantillo, D. J.; Kurth, M. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 10588. (d) Roy, S.; Reiser, O. *Angew. Chem., Int. Ed.* **2012**, *51*, 4722. (e) Li, M.; Cao, H.; Wang, Y.; Lv, X. L.; Wen, L. R. *Org. Lett.* **2012**, *14*, 3470. (f) Wen, L. R.; Shi, Y. J.; Liu, G. Y.; Li, M. *J. Org. Chem.* **2012**, *77*, 4252.

(19) (a) Cao, C. P.; Lin, W.; Hu, M. H.; Huang, Z. B.; Shi, D. Q. *Chem. Commun.* **2013**, *49*, 6983. (b) Feng, X.; Wang, Q.; Lin, W.; Dou, G. L.; Huang, Z. B.; Shi, D. Q. *Org. Lett.* **2013**, *15*, 2542. (c) Wang, H. Y.; Liu, X. C.; Feng, X.; Huang, Z. B.; Shi, D. Q. *Green Chem.* **2013**, *15*, 3307. (d) Hu, J. D.; Cao, C. P.; Lin, W.; Hu, M. H.; Huang, Z. B.; Shi, D. Q. *J. Org. Chem.* **2014**, *79*, 7935. (e) Zhang, J. J.; Hu, J. D.; Cao, C. P.; Dou, G. L.; Fu, L.; Huang, Z. B.; Shi, D. Q. *RSC Adv.* **2014**, *4*, 62457. (f) Feng, X.; Wang, J. J.; Xun, Z.; Zhang, J. J.; Huang, Z. B.; Shi, D. Q. *Chem. Commun.* **2015**, *51*, 1528. (g) Feng, X.; Wang, J. J.; Xun, Z.; Huang, Z. B.; Shi, D. Q. *J. Org. Chem.* **2015**, *80*, 1025.

(20) (a) Kaur, P.; Pindi, S.; Wever, W.; Rajale, T.; Li, G. *Chem. Commun.* **2010**, *46*, 4330. (b) Kaur, P.; Pindi, S.; Wever, W.; Rajale, T.; Li, G. *J. Org. Chem.* **2010**, *75*, 5144. (c) Kaur, P.; Wever, W.; Pindi, S.; Milles, R.; Gu, P.; Shi, M.; Li, G. *Green Chem.* **2011**, *13*, 1288. (d) An, G.; Seifert, C.; Li, G. *Org. Biomol. Chem.* **2015**, *13*, 1600.

DOI: 10.1021/acs.joc.5b01314
J. Org. Chem. 2015, 80, 8435−8442