# Combinatorial Synthesis of Fused Tetracyclic Heterocycles Containing [1,6]Naphthyridine Derivatives under Catalyst Free Conditions

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Ⓢ *Supporting Information*
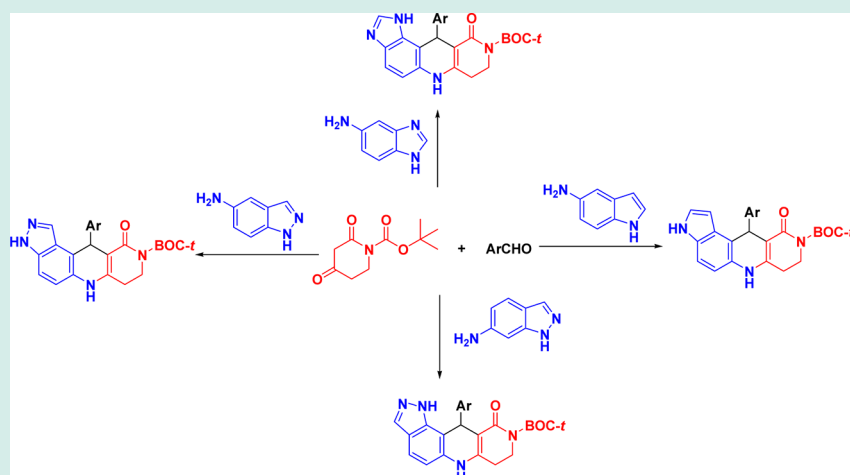
ABSTRACT: A three-component reaction between an aromatic aldehyde, an amine, and *tert*-butyl 2,4-dioxopiperidine-1-carboxylate in EtOH at refluxing temperature gave fused tetracyclic heterocycles in high yields. The amines include 1H-indazol-5-amine, 1H-indazol-6-amine, 1H-indol-5-amine, and 1H-benzo[d]imidazol-5-amine, giving 11-aryl-3H-indazolo[5,4-b][1,6] naphthyridine, 11-aryl-1H-indazolo[6,7-b][1,6]naphthyridine, 11-aryl-3H-indolo[5,4-b][1,6]naph-thyridine, and 11-aryl-3H-imidazo[4',5':3,4]benzo[1,2-b][1,6]naphthyridine derivatives, respectively.

KEYWORDS: [1,6]naphthyridine, 1H-indazol-5-amine, 1H-indazol-6-amine, 1H-indol-5-amine, 1H-benzo[d]imidazol-5-amine, tert-butyl 2,4-dioxopiperidine-1-carboxylate

■ INTRODUCTION

Naphthyridines are an important class of heterocycles found in a variety of biologically active molecules. It is reported that they are used for the prevention and treatment of angiogenic disorders and cancers.[1] They are also used as various kinds of inhibitors, such as the first clinical stage inhibitor of protein kinase CK2 for the treatment of cancer,[2] novel DNA ligase inhibitors with antistaphylococcal activity,[3] novel selective inhibitors of p38 mitogen activated protein kinase,[4] and the potent inhibitors of the protein kinase C isozymes.[5] In addition, there are many other remarkable applications reported in the literature.[6] Therefore, much attention has been devoted to the synthesis of these bioactive compounds.[7]

Indolonaphthyridine, indazolonaphthyridine and imidazo-benzonaphthyridine, which contain both indole (indazole, imidazole) and naphthyridine rings, are fused tetracyclic heterocycles. These heterocyclic motifs are found in numerous alkaloid natural products, such as indolo[1,7]naphthyridine,[8] which is also named *Incargranine B* (Figure 1, left). It was
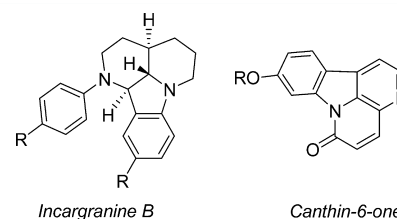
**Figure 1.** Interesting structures of natural products containing indolonaphthyridine.

isolated from the whole plant of *Incarvillea mairei var. grandiflora*. Another alkaloid of *Canthin-6-one* (Figure 1, right)[9] containing indolonaphthyridine nucleus was obtained and identified from the branches of *Picrolemma granatensis*.

Scheme 1. Optimization for the Synthesis of 4{1,1,1}
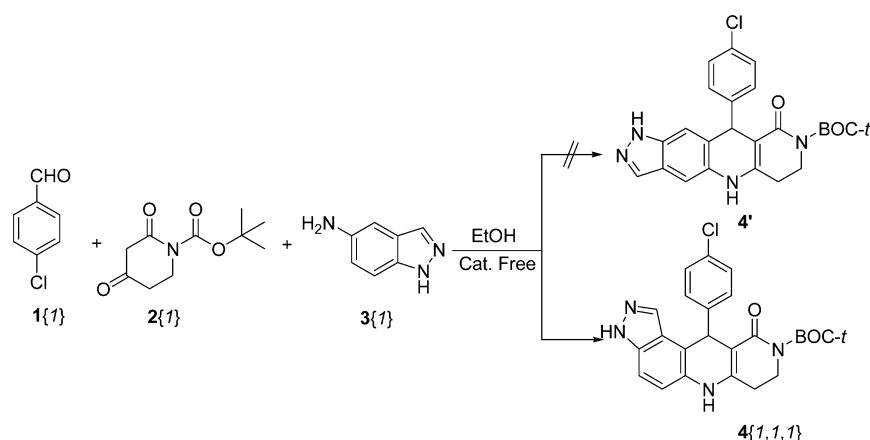
Some of them have been used as a selective 5-HT2C/2B receptor antagonist,[10] a 5-HT2C/2B receptor antagonist with low 5-HT2A receptor affinity,[11] and the cardiovascular agents.[12] They have also been used as a inhibitor of brain ischemia in rats for treating the brain disorder.[13]

To the best of our knowledge, only a few references exist concerning their synthesis.[14] Although these reported reactions have developed some useful synthetic procedures, still several limitations remained. For example, most of the procedures involve several steps, or low yields, or metal catalysts, or organic solvents. Thus, a simple, efficient, and green method to synthesize these fused tetracyclic heterocycles would be attractive.

Distinguished from classical sequential two-component synthetic procedures, multicomponent reactions (MCRs) use three or more chemical starting materials for product formation. They have attracted considerable attention in organic synthesis and medicinal chemistry because of their convergence and productivity.[15] As a continuation of our research devoted to the preparation of heterocycles by three-component reactions,[16] herein, we would like to report a convenient and efficient three-component synthesis of fused tetracyclic heterocycles. They include 3H-indazolo[5,4-b][1,6]-naphthyridine, 1H-indazolo[6,7-b][1,6]naphthyridine, 3H-indolo[5,4-b][1,6]naphthyridine, and 3H-imidazo[4',5':3,4]-benzo[1,2-b][1,6] naphthyridine derivatives, respectively.

■ RESULTS AND DISCUSSIONS

Treatment of 4-chlorobenzaldehyde 1{1}, tert-butyl 2,4-dioxopiperidine-1-carboxylate 2{1},[17] and 1H-indazol-5-amine 3{1} in refluxing EtOH under catalyst free conditions, gave tert-butyl 7,8-dihydro-10-oxo-11-aryl-3H-indazolo[5,4-b][1,6] naphthyridine-9(6H,10H,11H)-carboxylate 4{1,1,1} in high yield and regioselectivity, rather than tert-butyl 6,7-dihydro-9-oxo-10-aryl-1H-indazolo[5,6-b] [1,6]naphthyridine-8-(5H,9H,10H)-carboxylate 4' (Scheme 1).

Subsequently, the reaction of 4-chlorobenzaldehyde 1{1}, 2{1}, and 3{1} was used as a representative to optimize the experimental conditions. The reaction was first carried out in EtOH at room temperature for 10 h and only trace amount of product 4{1,1,1} was observed by TLC (Table 1, entry 1). The reaction temperature is key to product yields. At reflux, EtOH gives the best results. Furthermore, it should be noted that the products dissolved completely in refluxing EtOH, and crystallized in cold EtOH, therefore, the products of 4{1,1,1} were

Table 1. Synthetic Results of 4{1,1,1} under Different Reaction Conditions[a]

entry	temperature (°C)	time (h)	solvent	yields (%)[b]
1	r.t.	10	EtOH	Trace
2	50	16	EtOH	68
3	**reflux**	**10**	**EtOH**	**93**
4	80	8	toluene	87
5	reflux	14	CH₃CN	82
6	reflux	16	benzene	89
7	80	10	DMF	78
8	reflux	14	THF	85

[a]Reagents and conditions: 4-chlorobenzaldehyde 1{1} (0.140 g, 1.0 mmol), 2{1} (0.213 g, 1.0 mmol), 3{1} (0.133 g, 1.0 mmol), and solvent (10 mL). [b]Isolated yields.

obtained directly by filtration without further purification. In addition, the effects of different solvents, such as CH₃CN, benzene, DMF, and THF (Table 1, entries 5−8) were also compared, and EtOH gave the highest yield.

One the basis of the optimized reaction conditions, we next explored variations in the aldehyde 1 (Scheme 1), the diversity of aldehyde 1{1−20} was shown in Figure 2. Table 2 demonstrates that the reaction also tolerates significant functionalization of the aromatic aldehydes; both electron-donating (such as alkoxyl group) and electron-withdrawing (such as halide) groups can be accommodated, and substituents ortho, meta, or para to the aromatic group can all be generated. All aldehydes reacted well to provide a library of naphthyridine derivatives 4 (Table 2). Subsuquently, we investigated the applicability of amines, and found that 1H-indazol-5-amine 3{1}, 1H-indazol-6-amine 3{2}, 1H-indol-5-amine 3{3}, and 1H-benzo[d]imidazol-5-amine 3{4} (Figure 3) all gave satisfactory results (Table 2). It should be noted that 4{10,1,4} was tert-butyl 11-aryl-10-oxo-7,8,10,11-tetrahydro-1H-imidazo[4',5':3,4] benzo[1,2-b][1,6]naphthyridine-9(6H)-carboxylate rather than 3H-imidazo[4',5':3,4] benzo[1,2-b]-[1,6]naphthyridine (Scheme 3), when 1H-benzo[d]imidazol-5-amine 3{4} was used as a reactant. The crystal structure of 4{10,1,4} is shown in Figure 4. In order to prove this was not a special example; another single crystal of 4{12,1,4} was grown and determined. It gave the same result as shown in Figure 5. All the products of 4 were characterized by ^{1}H NMR, IR and HRMS, and the data were in good agreement with the preconceived structures.
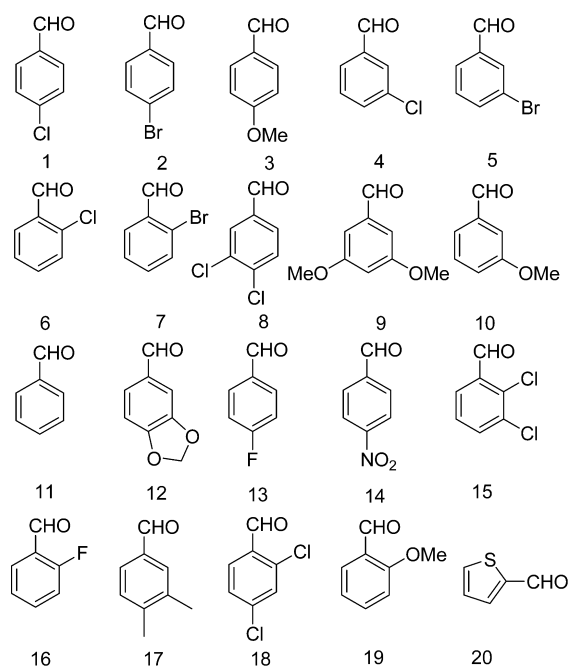
Figure 2. Diversity of aldehydes 1{*1−20*}.

X-ray diffraction analysis indicates that the 1,4-dihydropyridine rings in 4{*10,1,4*} and 4{*12,1,4*} are adopt a half-chair conformation. The atoms C1, C7, C9, C13, and N4 are coplanar, with C8 deviating from the defined planes by 0.297 (3) for 4{*10,1,4*} and 0.285 (4) Å for 4{*12,1,4*}, respectively. In 4{*10,1,4*}, the adjacent pyridine ring also adopts a half-chair conformation, the atom C11 deviates from the defined plane by 0.657 (3) Å. However, it adopts a skew boat conformation in 4{*12,1,4*}, with C11 and N3 deviating from the defined plane by 0.749 (6) and 0.197 (5) Å, respectively. The center 1,4-dihydropyridine ring is nearly parallel to the benzimidazole and pyridine rings, forming the dihedral angles of 6.2(1)° and 13.8(2)° (9.4(1)° and 9.0(1)° for 4{*10,1,4*}), respectively. Meanwhile, it is nearly perpendicular to the benzene ring, forming a dihedral angle of 88.3(1)° (87.5(1)° for 4{*10,1,4*}).

According to the structures of 4 and ref 18, we think the subsequent Knoevenagel condensation, Michael addition, intramolecular nucleophilic addition, and dehydration may take place in the formation of the observed products. The key step with high regioselectivity is the Michael addition reaction between 1H-indazol-6-amine and α,β-unsaturated ketone. The activity of the 7-position is higher than that of the 5-position in 1H-indazol-6-amine, because it is both the α-site of an amino group and the benzyl position of a pyrazole ring at the same time. The possible mechanism is outlined in Scheme 4 (using 1H-indazol-6-amine as an example).

■ CONCLUSION

In conclusion, we found a mild, efficient and highly regioselective method for the synthesis of fused tetracyclic heterocycles containing [1,6]naphthyridine derivatives via a three component reaction of an aromatic aldehyde, amine and tert-butyl 2,4-dioxopiperidine-1-carboxylate under catalyst free conditions. The procedure affords high regioselectivity while featuring mild reaction conditions, high yields and operational simplicity without catalysts.

Table 2. Reaction Time and Yields of the Products 4[a]

entry	Ar	product 4	time (h)	yields (%)[b]
1	4-ClC$_6$H$_4$	4{*1,1,1*}	10	93
2	4-BrC$_6$H$_4$	4{*2,1,1*}	14	90
3	4-MeOC$_6$H$_4$	4{*3,1,1*}	14	96
4	3-ClC$_6$H$_4$	4{*4,1,1*}	13	92
5	3-BrC$_6$H$_4$	4{*5,1,1*}	10	87
6	2-ClC$_6$H$_4$	4{*6,1,1*}	10	92
7	2-BrC$_6$H$_4$	4{*7,1,1*}	12	90
8	3,4-Cl$_2$C$_6$H$_3$	4{*8,1,1*}	8	90
9	3,5-(MeO)$_2$C$_6$H$_3$	4{*9,1,1*}	8	87
10	3-MeOC$_6$H$_4$	4{*10,1,1*}	10	95
11	C$_6$H$_5$	4{*11,1,1*}	12	90
12	piperonyl	4{*12,1,1*}	10	95
13	4-ClC$_6$H$_4$	4{*1,1,2*}	12	90
14	4-BrC$_6$H$_4$	4{*2,1,2*}	12	90
15	3-ClC$_6$H$_4$	4{*4,1,2*}	15	82
16	3-BrC$_6$H$_4$	4{*5,1,2*}	16	86
17	2-ClC$_6$H$_4$	4{*6,1,2*}	10	92
18	2-BrC$_6$H$_4$	4{*7,1,2*}	12	90
19	3,4-Cl$_2$C$_6$H$_3$	4{*8,1,2*}	14	93
20	piperonyl	4{*12,1,2*}	16	89
21	4-FC$_6$H$_4$	4{*13,1,2*}	12	85
22	4-NO$_2$C$_6$H$_4$	4{*14,1,2*}	10	86
23	2,3-Cl$_2$C$_6$H$_3$	4{*15,1,2*}	10	92
24	2-thienyl	4{*20,1,2*}	10	90
25	4-ClC$_6$H$_4$	4{*1,1,3*}	9	89
26	4-BrC$_6$H$_4$	4{*2,1,3*}	12	89
27	4-CH$_3$OC$_6$H$_4$	4{*3,1,3*}	10	90
28	3-ClC$_6$H$_4$	4{*4,1,3*}	10	85
29	3,4-Cl$_2$C$_6$H$_3$	4{*8,1,3*}	10	90
30	3,5-(MeO)$_2$C$_6$H$_3$	4{*9,1,3*}	12	87
31	3-CH$_3$OC$_6$H$_4$	4{*10,1,3*}	12	86
32	4-FC$_6$H$_4$	4{*13,1,3*}	10	90
33	2-FC$_6$H$_4$	4{*16,1,3*}	6	86
34	3,4-Me$_2$C$_6$H$_3$	4{*17,1,3*}	12	84
35	2,4-Cl$_2$C$_6$H$_3$	4{*18,1,3*}	8	92
36	2-thienyl	4{*20,1,3*}	9	85
37	4-ClC$_6$H$_4$	4{*1,1,4*}	12	86
38	4-BrC$_6$H$_4$	4{*2,1,4*}	10	79
39	4-CH$_3$OC$_6$H$_4$	4{*3,1,4*}	13	79
40	3-ClC$_6$H$_4$	4{*4,1,4*}	13	85
41	2-ClC$_6$H$_4$	4{*6,1,4*}	9	89
42	3,4-Cl$_2$C$_6$H$_3$	4{*8,1,4*}	10	86
43	3,5-(MeO)$_2$C$_6$H$_3$	4{*9,1,4*}	14	90
44	3-CH$_3$OC$_6$H$_4$	4{*10,1,4*}	12	90
45	piperonyl	4{*12,1,4*}	15	86
46	2,4-Cl$_2$C$_6$H$_3$	4{*18,1,4*}	9	83
47	2-CH$_3$OC$_6$H$_4$	4{*19,1,4*}	12	82

[a]Reaction condition: 1 (1.0 mmol), 2 (0.213 g, 1.0 mmol), 3 (1.0 mmol), EtOH (10.0 mL), 80 °C. [b]Isolated yields.
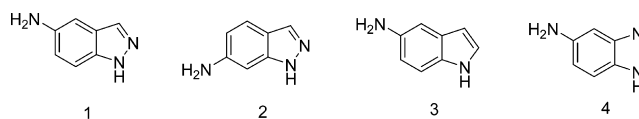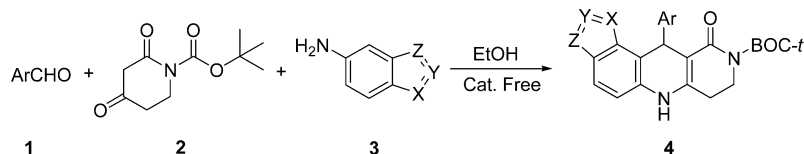

Figure 3. Diversity of amines 3{*1−4*}.

■ EXPERIMENTAL PROCEDURES

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a Tensor 27

Scheme 2. Regioselective Synthesis of Naphthyridines 4

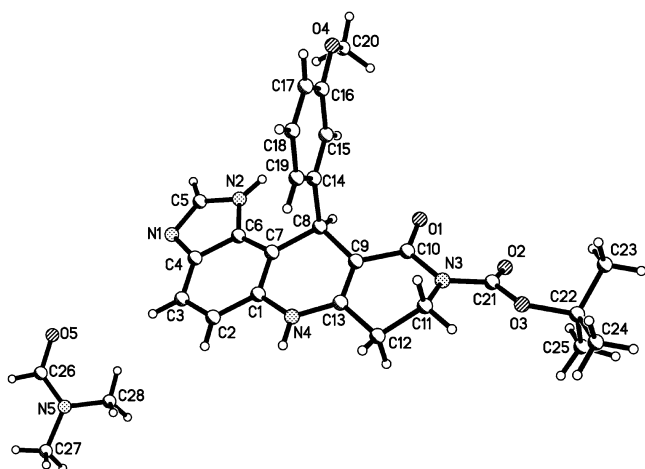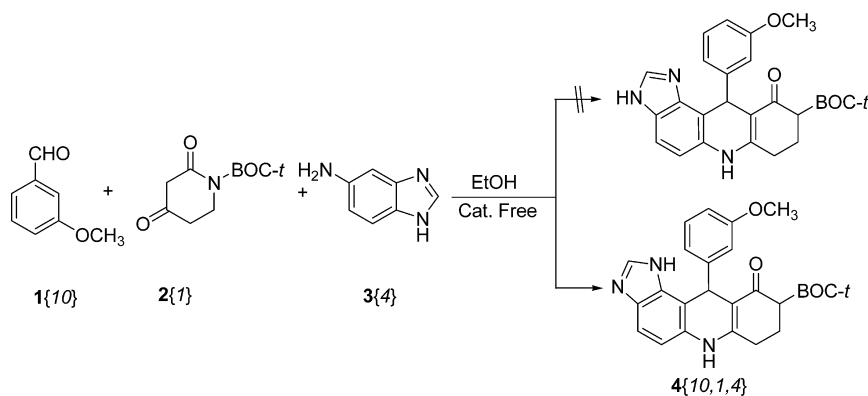**Scheme 3. Regioselective Synthesis of Product 4{10,1,4}**

Figure 4. Crystal structure of **4{10,1,4}** with DMF solvate.

spectrometer in KBr pellet. ^{1}H NMR spectra was obtained from a solution in DMSO-d_6 with Me$_4$Si as internal standard using a Bruker-400 spectrometer. HRMS analyses were carried out using a Bruker-micro-TOF-Q-MS analyzer.

General Procedure for the Synthesis of 4. A dry 25 mL flask was charged with aromatic aldehyde **1** (1.0 mmol), amine (1.0 mmol), *tert*-butyl 2,4-dioxopiperidine-1-carboxylate (0.213 g, 1.0 mmol), and EtOH (10.0 mL). The reaction mixture was stirred at refluxing temperature for 8−16 h until all the reactant amine was consumed (monitored by TLC). The products were obtained by filtration without further purification, after the reaction mixture was cooled to room temperature.

tert-Butyl 11-(4-chlorophenyl)-10-oxo-7,8,10,11-tetrahy-dro-3H-indazolo[5,4-b][1,6] naphthyridine-9(6H)-carboxy-late **4{1,1,1}**: mp 221−223 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 1.41 (s, 9H, 3CH$_3$), 2.59−2.64 (m, 1H, CH), 2.75−2.82 (m, 1H, CH), 3.50−3.60 (m, 1H, CH), 3.96−4.02 (m, 1H, CH), 5.52 (s, 1H, CH), 7.07 (d, J = 8.4 Hz, 1H, ArH), 7.23 (d, J = 8.4 Hz, 2H, ArH), 7.34−7.37 (m, 3H, ArH), 8.01 (s, 1H, ArH), 9.67 (s, 1H, NH), 13.01 (s, 1H, NH); ^{13}C NMR

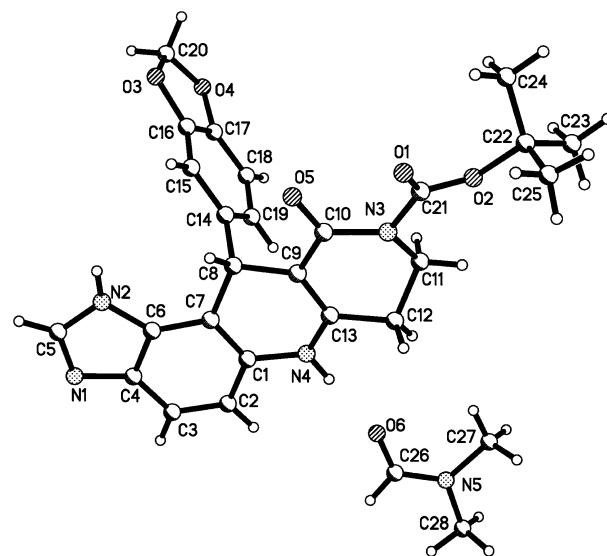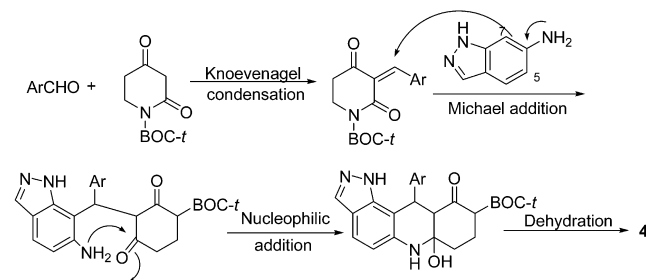**Figure 5.** Crystal structure of **4{12,1,4}** with DMF solvate.

Scheme 4. Possible Mechanism for the Formation of 4

(DMSO-d_6, 100 MHz) δ_C 27.8, 30.7, 35.7, 38.5, 80.8, 98.6, 109.5, 113.7, 116.7, 121.5, 127.9, 128.7, 129.5, 130.3, 146.7, 148.3, 148.4, 152.6, 162.3, 164.2; IR (KBr) ν 3297, 3079, 2977, 2933, 2885, 1719, 1681, 1605, 1543, 1492, 1401, 1369, 1331,

1253, 1213, 1142, 1092, 1049, 949, 846, 805, 775, 738, 703 cm^{-1}; HRMS (ESI, m/z) calcd for $C_{24}H_{22}N_4O_3Cl$ [M − H]$^-$ 449.1380, found 449.1384.

■ ASSOCIATED CONTENT

ⓈSupporting Information

Characterized data inclauding NMR, IR, and HRMS of **4** and copies of CIFs for **4**{10,1,4} and **4**{12,1,4}. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes
The authors declare no competing financial interest.

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