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FULL-LENGTH PAPER

Palladium-catalyzed regioselective synthesis of 2(2′-biphenyl)benzimidazoles through C–H activation

Li-Hsun Chen · Tz-Yi Wu · Vijaykumar Paike · Chung-Ming Sun

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Abstract An efficient palladium-catalyzed strategy through C–H bond activation for the synthesis of 2(2′-biphenyl)-benzimidazoles is reported herein. The regioselective C–C bond formation proceeds in a sealed tube *via* oxidative C–H activation of *ortho*-directed 2-aryl-benzimidazole to couple with various iodobenzene analogs in high yields. This arylation exhibited high regioselectivity which is able to increase molecular diversity in difficult functionalized positions of parent molecules. This strategy provides a convenient and simple synthesis of biphenyl heterocyclic compounds with high regioselectivity.

Keywords Palladium catalyst · C–H activation · C–C bond formation · Benzimidazole · Biphenyl heterocycles

Introduction

Transition metal catalyzed C–C bond formation has significant impact on the strategies used to simplify the synthesis of worthwhile bioactive scaffolds, building blocks, and relative complex molecules in organic and organometallic chemistry [1–3]. During the past several decades, development of palladium-catalyzed C–H activation and C–C bond forming reactions (e.g., Sonogashira, Negishi, Stille, Suzuki-Miyaura, Heck reaction) have received utmost attention [4–6]. The alkylation or arylation of aryl C–H bonds could be directly achieved by utilizing ruthenium, rhodium, palladium, iridium, and other metals with olefins or aryl organometallic fragments [1–10].

Enhancement in the regioselective activation of aromatic sp^2 and sp^3 C–H bonds with the help of directing effect of functional groups coordination is a predominant feature in the synthesis of many biological active compounds [11–14]. General methods construct biaryls by using transition-metal-catalyzed coupling reactions with the *ortho*-directing groups such as imine, pyridine, acetamine, carboxylic acid, oxazoline, and imidazole (Fig. 1) [15–18].

Benzimidazole containing molecules are fragment motifs in nature and have potential uses in medicinal chemistry as antitumor and antiparasitic agents [19,20]. Substituted biaryls imidazoles have important applications in pharmaceuticals such as farnesyl-protein transferase inhibitors [21,22] and sodium channel blockers in neuropathic pain [23]. Telmisartan and Candesartan are used for the treatment of hypertension an angiotensin II receptor antagonist (Fig. 2) [24–26]. Consequently, the synthesis of polysubstituted benzimidazoles and 2-biaryl benzimidazole *via* arylation of aromatic sp^2 C–H activation has received a lot of attention in recent years [27–33].

For example, Miura and co-workers [34] have reported the regioselective *ortho* arylation of 1-methyl-2-phenyl benzimidazole with sodium tetraphenylborate and [RhCl(cod)]$_2$/ClCH$_2$COEt/KF catalyst at 140 °C. The palladium-catalyzed synthesis of benzo4,5imidazo[2,1-*a*] isoquinolines *via* nucleophilic addition of 2-aryl benzimidazoles to alkynyl bromine followed by intermolecular C–H vinylation was reported by Li and co-workers [35].

These synthetic processes are usually complicated, have low efficiency and are accompanied with harmful by-products

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L.-H. Chen · T.-Y. Wu · V. Paike · C.-M. Sun (✉)
Laboratory of Combinatorial Drug Design,
Department of Applied Chemistry, National Chiao Tung University,
Hsin-chu 300-10, Taiwan
e-mail: cmsun@mail.nctu.edu.tw

Fig. 1 Arylation with *N* containing *o*-directing groups

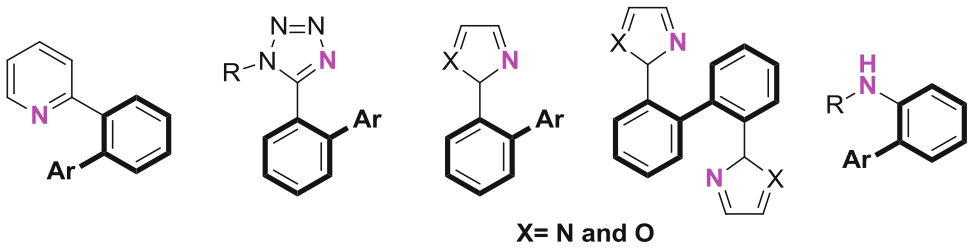
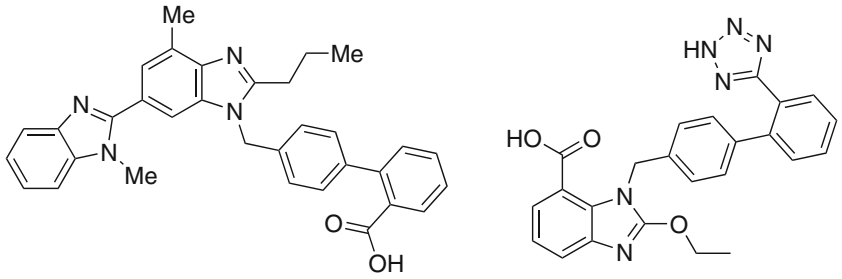


Fig. 2 Structurally related biologically active compounds



led to the search for improved methods to synthesize 2-biaryl benzimidazoles. Among the transition metals, palladium complexes are of utmost interest because of their cost-effectiveness and efficiency for direct sp^2 C–H activation and arylation to address the above mentioned problems.

As a part of our ongoing program to develop strategies for the synthesis of novel polyfunctionalized benzimidazole for medical scaffolds [36,37], we have investigated the reaction of substituted 2-aryl-benzimidazole **1** with iodobenzene **2** leading to the 2(2′-biphenyl)-benzimidazole framework through regioselective oxidative cleavage of C–H bond. The mechanistic pathway of this new process and its potential effectiveness in the synthesis of 2-biphenyl-1-benzimidazole directly from easily available starting components is presented.

Results and discussion

To understand the current protocol, we thoroughly studied the reaction between 2-aryl-benzimidazole **1** and iodobenzene **2** in different solvents using various metal catalysts and several additives (Scheme 1). We used the benzimidazole as an *ortho*-directing group in our current investigation due to direct coordination by palladium metal to functionalize the *ortho* C–H bond of 2-substituted aryl ring, and further elaboration through *ortho* C–H activation may proceed. When the model reaction was carried out in acetic acid in the presence of 5 mol.% $Pd(dba)_3$ and AgOAc (1.5 equiv.) at 120 °C for 120 h, product **3a** was isolated in only 29 % yield. Encouraged by this result, we decided to enhance the yield of desired product by examining various reaction parameters (Tables 1, 2). The reaction was performed with several metal catalysts in acetic acid with AgOAc as an additive and the results obtained are summarized in Table 1.

A significant drop in reactivity was observed when $Pd(dba)_3$ was replaced with other catalysts such as $[(cymene)RuCl_2]_2$ or $Rh_2(OAc)_4$ and the coupling reaction did not proceed even after prolonged heating at high temperature (Table 1, entries 2–5). A low yield of **3a** was obtained when the reaction was catalyzed by $Pd(dppf)Cl_2$ (Table 1, entry 9). Since a palladium catalyst is essential in this approach for sp^2 C–H activation, we have examined a number of palladium catalysts for this transformation (Table 1, entries 1, 6–9).

After several reactions, a catalytic amount of $Pd(OAc)_2$ with AgOAc in a sealed tube was found to be the most efficient system to the desired 2-(2′-biphenyl)-benzimidazole **3a** (Table 1, entry 8).

Next, we proceeded to optimize the reaction by varying solvents, additives, and temperature and the results obtained

Scheme 1 Synthesis of 2-biphenyl-benzimidazole

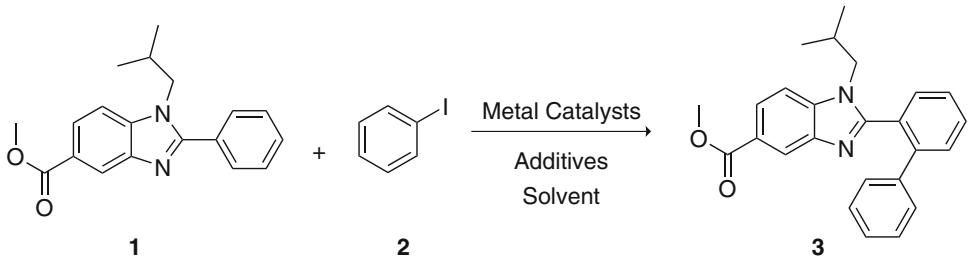


Table 1 Catalysts study for synthesis of 2-biphenyl-benzimidazole

Entries	Catalysts	T (°C)	*t* (h)	Yield[a] (%)
1	$Pd_2(dba)_3$	120	120	29
2	$Rh_2(OAc)_4$	120	120	NR
3[b]	$Rh_2(OAc)_4$	150	120	NR
4	$[(Cymene)RuCl_2]_2$	120	120	NR
5[b]	$[(Cymene)RuCl_2]_2$	150	120	NR
6	$Pd(OAc)_2$	120	120	43
7	$Pd(dppf)Cl_2$	120	120	45
8[b]	$Pd(OAc)_2$	150	72	56
9[b]	$Pd(dppf)Cl_2$	150	72	46

All reactions were performed in HOAc with 5 mol.% catalyst and AgOAc (1.5 equiv.)
NR no reaction
[a] Isolated yield after column chromatography
[b] Reaction was carried out in a sealed tube

Table 2 Reaction optimization for the synthesis of 2-biphenyl-benzimidazole

Entries[a]	Additives	Solvents	*t* (h)	Yield[b] (%)
1	AgOAc	HOAc	120	65
2	$Cu(OAc)_2$	HOAc	120	Trace
3	$Cu(OTf)_2$	HOAc	120	45
4	$K_2S_2O_8$	HOAc	120	Trace
5	Oxone	HOAc	120	Trace
6	$PhI(OAc)_2$	HOAc	120	Trace
7	AgOTf	HOAc	120	71
8	AgOTf	TFA	72	85
9	AgOTf	1,4-Dioxane	120	NR
10	AgOTf	IPA	120	NR
11	AgOTf	EDC	120	16
12	AgOTf	ACN	120	11

All reaction performed with $Pd(OAc)_2$ 5 mol.% in a sealed tube (150 °C)
NR no reaction
[a] Reaction carried out with 3 equiv. of additives
[b] Isolated yield after column purification

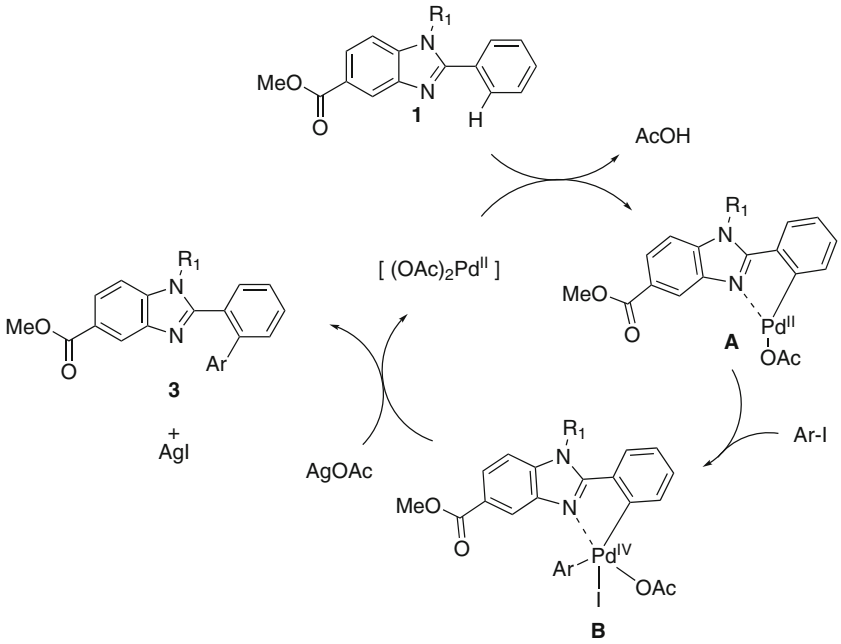
are summarized in Table 2. Initially, increasing the amount of additives to 3 equiv., the yield of **3a** increased to 65 % (Table 2, entry 1). When AgOAc additive was replaced by copper, this resulted in a lower yield of desired product because formation of biphenyl product was observed via Ullmann cross coupling reaction (Table 2, entries 2, 3). Potassium salts such as $K_2S_2O_8$, oxone, and $PhI(OAc)_2$ (Table 2, entries 4–6) failed to deliver the desired product. Addition of silver salt AgOTf in 1,4-dioxane or isopropyl alcohol did not deliver the desired product (Table 2, entries 9, 10). In contrast, when the reaction was performed in acetonitrile and ethylene dichloride the desired product obtained in lower yields (Table 2, entries 11, 12).

After several trials, the reaction carried out in trifluoroacetic acid (TFA) in the presence of $Pd(OAc)_2$ and AgOTf. This led to the formation of **3a** in 85 % yield (Table 2, entry 8). The use of TFA was found to be crucial for the success of this arylation strategy which could be attributed to the in situ replacement of (–OAc) group from palladium by trifluoromethanesulfonate (–OTf), a strong electron withdrawing group which helped to enhance reactivity and productivity [38]. Among the silver salt additives, AgOTf in TFA (Table 2, entry 8) was efficacious in palladium catalytic system and gave the high regioselectivity with best yields of 2-biarylated benzimidazoles.

Based on these results, a plausible mechanism for the reaction of 2-aryl-benzimidazoles **1** with iodobenzene **2**, through directed metalation involving palladacycle intermediate **A** and **B** is proposed in Scheme 2. In the first step, coordination of the nitrogen of benzimidazole in the 2-position of directing group on phenyl ring to Pd(II) species is the key for the regioselective C–H bond cleavage. The oxidative insertion of iodobenzene in palladacycle intermediate **A** to intermediate **B**, followed by reductive elimination to offer corresponding product **3** with regenerated palladium(II) by silver salt, and reuses in next catalytic cycles.

It was also observed that the C–C bond formation reaction between the aryl iodide and 2-phenyl-benzimidazoles can tolerate both electron-withdrawing groups and electron-donating groups (EDG) and the results are outlined in Table 3. 2-Aryl benzimidazoles containing EDG gave excellent isolated yields (68–85 %) in a short span of reaction time at 150 °C in TFA (Table 3, entries 3b, d–g, k, l). The absolute configuration and unambiguous structural elucidation of compound **3p** is accomplished by single crystal X-ray diffraction (CCDC-936241) illustrated in Fig. 3. The residue at N2 (benzyl group in **3p**) distinctly occupies the space perpendicular to the basic skeleton of benzimidazole. The crystallographic data reveal that the benzimidazole ring is perpendicular to the 2-phenyl group. Both N2 benzyl group and 2-biphenyl of benzimidazoles orient in a relative *anti*-position to each other. Such similar L-shaped benzimidazole nucleus with structural resemblance to the recently reported benzimidazole fluorophores may have interesting optical and electronic properties [39].

In summary, the present study has demonstrated that 2-phenyl benzimidazole and iodobenzene efficiently undergo regioselective arylation in a palladium catalytic system leading to 2-biaryl-benzimidazoles in high yields. Importantly, the challenging nature of this transformation is high regioselectivity for monoarylation to synthesize numerous 2-(2′-biphenyl)-benzimidazoles *via* C–H activation. These highly functionalized benzimidazoles are excellent building blocks



Scheme 2 Proposed mechanism pathway for 2-biphenyl-benzoimidazoles

for biological studies. Application of benzimidazole as a direction group constructs a C-heteroatom attachment and further exploration of the scope and utility is currently under investigation.

Experimental

Materials and methods

All reactions were carried out oven-dried glassware using standard sealed tube, syringe, cannula, septa, and other apparatus. Solvents were dried with calcium hydride or sodium/benzophenone and distilled before use. The ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker DRX-300 NMR in chloroform-d_1 ($CDCl_3$, $\delta = 7.24$ ppm [part per million] (as standard). Chemical shifts are reported in delta (δ) units, ppm. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, td = triplet of doublets, q = quartet, m = multiplet), coupling constants are reported in Hertz (Hz) and integration. The reactions were monitored by thin layer chromatography (TLC) using Merck TLC silica gel 60 F_{254}. High resolution ESI mass experiments were operated on a Thermo Finnigan Model: MAT 95 XL spectrometer. Infrared (IR) spectra were recorded (neat samples) on a HORIBA FT-720 Fourier Transform IR spectrophotometer and the characteristic IR absorption frequencies are reported in cm^{-1}. X-ray single crystal structure, relative and absolute configurations were assigned on a Bruker smart 1000 CCD single-crystal X-ray diffractometer. Unless otherwise noted, reagents were purchased from commercial sources and used without further purification.

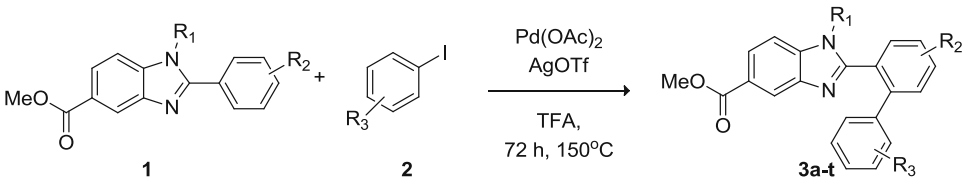
General procedures for methyl-2-(biphenyl-2-yl)-1-(2-methylpropyl)-1*H*-benzimidazole-5-carboxylate (3a)

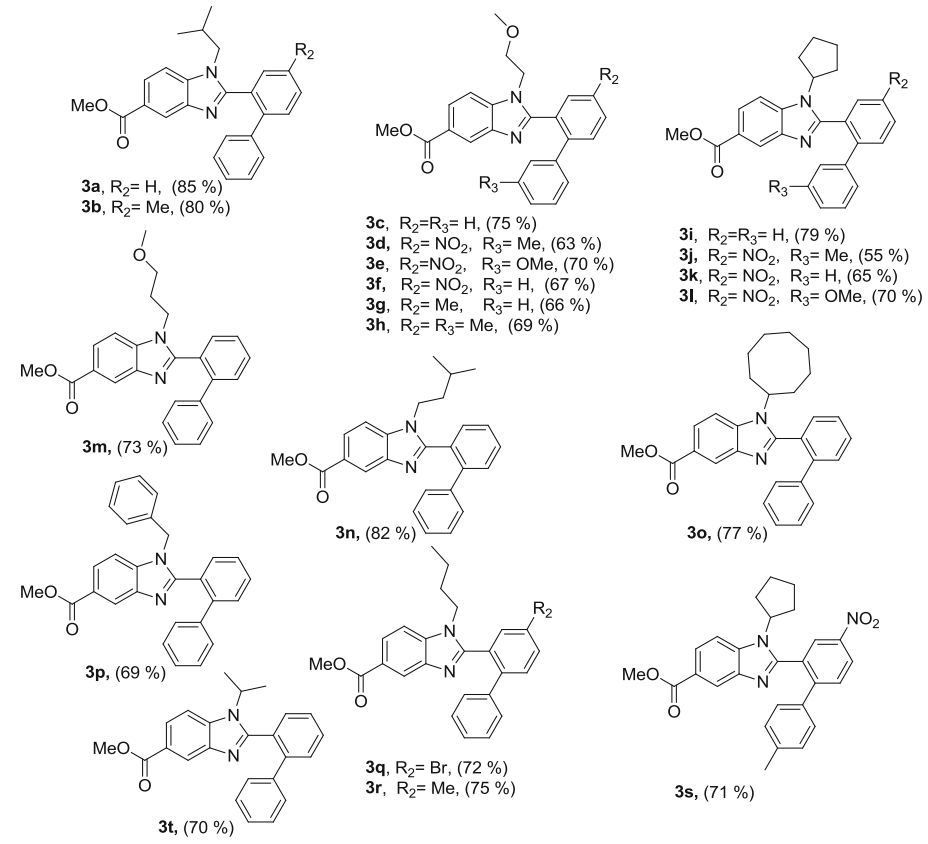
To a solution of the methyl 1-isobutyl-2-phenyl-1*H*-benzo[*d*] imidazole-5-carboxylate **1** (0.144 g, 0.47 mmol) in TFA (10 mL) were added iodobenzene **2** (0.381 g, 1.87 mmol), $Pd(OAc)_2$ (0.0132 g, 0.059 mmol) and AgOTf (0.1811 g, 0.705 mmol) at room temperature. The resulting reaction mixture was heated in a sealed tube for 72 h. The reaction progress was monitor by TLC, after the reaction was complete, mixture was cooled to room temperature and solvent was removed by extraction with water and ethyl acetate. The crude product was purified by column chromatography (eluent: 15 % EA in hexane) to afford the corresponding methyl-2-([1,1′-biphenyl]-2-*yl*)-1-isobutyl-1*H*-benzo[*d*]imidazole-5-carboxylate **3a** in 80 % yield. This general procedure was applied for the synthesis of all compound **3** analogs.

*Methyl-2-(biphenyl-2-yl)-1-(2-methylpropyl)-1H-benzimidazole-5-carboxylate (**3a**)*

^{1}H NMR (300 MHz, $CDCl_3$, $\delta = 7.24$ ppm as standard) δ 8.56 (d, $J = 1.2$ Hz, 1H), 7.95 (dd, $J = 8.7$, 1.2 Hz, 1H), 7.71 (dd, $J = 7.5$, 1.4 Hz, 1H), 7.64–7.47 (m, 3H), 7.18–7.15 (m, 6H), 3.94 (s, 3H), 3.20 (d, $J = 7.5$ Hz, 2H), 1.89 (m, 1H), 0.55 (d, $J = 6.6$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1,

Table 3 Substrate scope studies





All reaction preformed in TFA with 5 mol.% $Pd(OAc)_2$ and 3 equiv. Ag(OTf) in a sealed tube, aryl iodide (4 equiv.); in parenthesis isolated yield after column purification

156.0, 142.8, 141.7, 140.2, 138.4, 132.5, 131.0, 130.3, 129.2, 128.9, 128.9, 128.1, 127.9, 124.7, 124.4, 122.5, 110.4, 52.5, 51.6, 28.6, 20.2; IR (cm^{-1}, neat) 2958, 1716, 1616; MS (EI-MS) m/z 384 [M^+]; HRMS calculated for $C_{25}H_{24}N_2O_2$ m/z 384.1838; found 384.1836.

*Methyl-2-(4-methylbiphenyl-2-yl)-1-(2-methylpropyl)-1H-benzimidazole-5-carboxylate (**3b**)*

^{1}H NMR (300 MHz, $CDCl_3$, $\delta = 7.24$ ppm as standard) δ 8.56 (d, $J = 1.2$ Hz, 1H), 7.96 (dd, $J = 8.5$, 1.2 Hz, 1H), 7.54 (s, 1H), 7.46–7.41 (m, 2H), 7.18–7.13 (m, 6H), 3.95 (s, 3H), 3.19 (d, $J = 7.8$ Hz, 2H), 2.46 (s, 3H), 1.83 (m, 1H), 0.55 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 156.2, 142.6, 140.2, 138.7, 138.3, 138.1, 132.9, 131.8, 130.2, 128.9, 128.8, 128.8, 127.6, 124.7, 124.4, 122.4, 110.43, 52.5, 51.6, 28.5, 21.4, 20.2; IR (cm^{-1}, neat) 2958, 1716, 1616; MS (EI-MS) m/z 398 [M^+]; HRMS calculated for $C_{26}H_{26}N_2O_2$ m/z 398.1994; found 398.1995.

*Methyl-2-(biphenyl-2-yl)-1-(2-methoxyethyl)-1H-benzimidazole-5-carboxylate (**3c**)*

^{1}H NMR (300 MHz, $CDCl_3$, $\delta = 7.24$ ppm as standard) δ 8.54 (d, $J = 1.3$ Hz, 1H), 7.95 (dd, $J = 8.4$, 1.3 Hz, 1H), 7.66–7.46 (m, 4H), 7.30 (d, $J = 8.4$ Hz, 1H), 7.24–7.14 (m, 5H), 3.92 (s, 3H), 3.68 (t, $J = 5.6$ Hz, 2H), 3.07 (t, $J = 5.6$ Hz, 2H), 2.98 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 155.8, 142.7, 141.8, 140.2, 138.5, 132.5, 131.1, 130.3, 129.1, 129.0, 129.0, 128.9, 127.9, 124.8, 124.6, 122.4, 110.7, 69.0, 59.0, 52.4, 41.3; IR (cm^{-1}, neat) 2948, 1714, 1616; MS (EI-MS) m/z 386 [M^+]; HRMS calculated for $C_{24}H_{22}N_2O_3$ m/z 386.1630; found 386.1631.

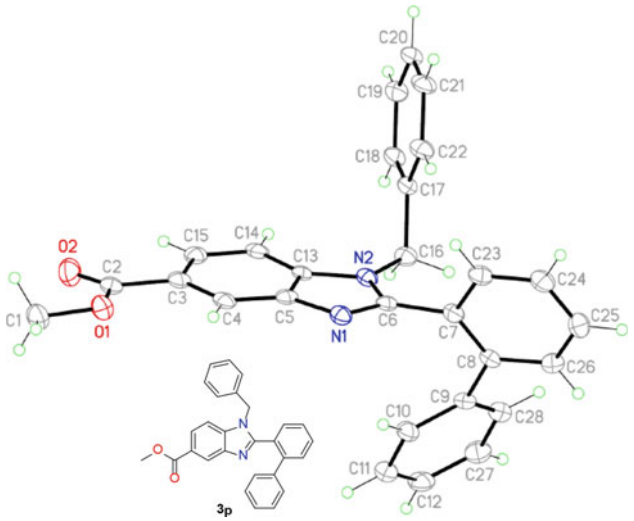


Fig. 3 ORTEP diagram of compound **3p**

*Methyl-1-(2-methoxyethyl)-2-(3′-methyl-4-nitrobiphenyl-2-yl)-1H-benzimidazole-5-carboxylate (**3d**)*

^{1}H NMR (300 MHz, $CDCl_3$, $\delta = 7.24$ ppm as standard) δ 8.56 (d, $J = 1.6$ Hz, 1H), 8.52 (d, $J = 1.7$ Hz, 1H), 8.41 (dd, $J = 8.6$, 1.6 Hz, 1H), 8.00 (dd, $J = 8.4$, 1.7 Hz, 1H), 7.72 (d, $J = 8.6$ Hz, 1H), 7.31 (d, $J = 8.4$ Hz, 1H), 7.07–7.06 (m, 3H), 6.99–6.95 (m, 1H), 3.93 (s, 3H), 3.70 (t, $J = 5.3$ Hz, 2H), 3.19 (t, $J = 5.2$ Hz, 2H), 3.01 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 153.6, 148.2, 147.1, 142.7, 139.1, 138.1, 137.9, 131.3, 130.5, 130.1, 129.6, 129.1, 128.0, 126.0, 125.6, 125.31, 125.1, 122.7, 110.6, 70.2, 59.1, 52.6, 44.6, 21.6; IR (cm^{-1}, neat) 2948, 1714, 1617; MS (EI-MS) m/z 445 [M^+]; HRMS calculated for $C_{25}H_{23}N_3O_5$ m/z 445.1638; found 445.1639.

*Methyl-1-(2-methoxyethyl)-2-(3′-methoxy-4-nitrobiphenyl-2-yl)-1H-benzimidazole-5-carboxylate (**3e**)*

^{1}H NMR (300 MHz, $CDCl_3$, $\delta = 7.24$ ppm as standard) δ 8.60 (d, $J = 1.9$ Hz, 1H), 8.57 (d, $J = 1.5$ Hz, 1H) 8.47 (dd, $J = 8.7$, 1.9 Hz, 1H), 8.05 (dd, $J = 8.7$, 1.5 Hz, 1H), 7.77 (d, $J = 8.7$ Hz, 1H), 7.36 (d, $J = 8.7$ Hz, 1H), 7.20 (t, $J = 8.0$ Hz, 1H), 6.89 (d, $J = 7.8$ Hz, 1H), 6.83 (dd, $J = 8.3$, 1.8 Hz, 1H), 6.76–6.75 (m, 1H), 3.98 (s, 3H), 3.76 (t, $J = 5.3$ Hz, 2H), 3.44 (s, 3H), 3.24 (t, $J = 5.3$ Hz, 2H), 3.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8, 160.1, 153.6, 147.8, 147.2, 142.6, 139.3, 138.1, 131.3, 130.5, 130.4, 128.0, 125.7, 125.4, 125.2, 122.6, 121.2, 115.9, 113.5, 110.6, 70.2, 59.1, 55.4, 52.6, 44.6; IR (cm^{-1}, neat) 2948, 1716, 1617; MS (ESI-MS) m/z 462 [M+1]$^+$; HRMS calculated for $C_{25}H_{23}N_3O_6$ m/z 461.1587; found 462.1666 (M+1)$^+$.

*Methyl-1-(2-methoxyethyl)-2-(4-nitrobiphenyl-2-yl)-1H-benzimidazole-5-carboxylate (**3f**)*

^{1}H NMR (300 MHz, $CDCl_3$, $\delta = 7.24$ ppm as standard) δ 8.61 (d, $J = 1.9$ Hz, 1H), 8.56 (d, $J = 1.4$ Hz, 1H), 8.48 (dd, $J = 8.4$, 1.9 Hz, 1H), 8.04 (dd, $J = 8.6$, 1.4 Hz, 1H), 7.76 (d, $J = 8.4$ Hz, 1H), 7.34 (d, $J = 8.7$ Hz, 1H), 7.32–7.25 (m, 5H), 3.98 (s, 3H), 3.74 (t, $J = 5.4$ Hz, 2H), 3.22 (t, $J = 5.4$ Hz, 2H), 3.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8, 153.4, 148.1, 147.2, 142.2, 138.0, 137.9, 131.5, 130.2, 129.4, 129.3, 128.9, 128.1, 125.8, 125.6, 125.3, 122.6, 110.7, 70.1, 59.2, 52.6, 44.7; IR (cm^{-1}, neat) 2948, 1716, 1617; MS (EI-MS) m/z 431 [M^+]; HRMS calculated for $C_{24}H_{21}N_3O_5$ m/z 431.1481; found 431.1479.

*Methyl-1-(2-methoxyethyl)-2-(4-methyl-[1,1′-biphenyl]-2-yl)-1H-benzo[d]imidazole-5-carboxylate (**3g**)*

^{1}H NMR (300 MHz, $CDCl_3$, $\delta = 7.24$ ppm as standard) δ 8.53 (d, $J = 1.4$ Hz, 1H), 7.98 (dd, $J = 8.6$, 1.4 Hz, 1H), 7.50–7.44 (m, 3H), 7.32 (m, 1H), 7.26–7.14 (m, 5H), 3.97 (s, 3H), 3.70 (t, $J = 5.8$ Hz, 2H), 3.07 (t, $J = 5.8$ Hz, 2H), 3.03 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7, 155.8, 142.6, 139.8, 138.3, 138.2, 137.6, 132.6, 131.4, 129.8, 129.8, 128.6, 128.4, 127.3, 124.3, 124.1, 122.1, 110.2, 70.0, 58.6, 52.1, 43.9, 20.9; IR (cm^{-1}, neat) 2925, 1714, 1616; MS (ESI-MS) m/z 401 [M+1]$^+$; HRMS calculated for $C_{25}H_{24}N_2O_3$ m/z 400.1787; found 401.1864 (M+1)$^+$.

*Methyl-2-(3′,4-dimethyl-[1,1′-biphenyl]-2-yl)-1-(2-methoxyethyl)-1H-benzo[d]imidazole-5-carboxylate (**3h**)*

^{1}H NMR (300 MHz, $CDCl_3$, $\delta = 7.24$ ppm as standard) δ 8.54 (s, 1H), 7.98 (dd, $J = 8.5$, 1.6 Hz, 1H), 7.49–7.41 (m, 3H), 7.33 (d, $J = 8.6$ Hz, 1H), 7.08–6.99 (m, 4H), 3.98 (s, 3H), 3.71 (m, 2H), 3.06 (m, 2H), 3.04 (s, 3H), 2.47 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7, 155.9, 142.4, 139.6, 138.5, 138.2, 138.2, 137.5, 132.5, 131.4, 129.8, 129.3, 128.4, 128.3, 128.0, 125.7, 124.3, 124.1, 122.0, 110.2, 70.1, 58.6, 52.1, 43.9, 21.3, 20.9; IR (cm^{-1}, neat) 2925, 1716, 1616; MS (ESI-MS) m/z 415 [M+1]$^+$; HRMS calculated for $C_{26}H_{26}N_2O_3$ m/z 414.1943; found 415.2025 [M+1]$^+$.

*Methyl-2-(biphenyl-2-yl)-1-cyclopentyl-1H-benzimidazole-5-carboxylate (**3i**)*

^{1}H NMR (300 MHz, $CDCl_3$, $\delta = 7.24$ ppm as standard) δ 8.54 (s, 1H), 7.91 (d, $J = 8.7$ Hz, 1H), 7.63–7.44 (m, 4H), 7.30 (d, $J = 8.7$ Hz, 1H), 7.18–7.17 (m, 5H), 4.16 (m, 1H), 3.92 (s, 3H), 1.88–1.40 (m, 8H), 0.68 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 156.3, 143.7, 141.7, 140.2, 135.9,

132.4, 130.9, 130.2, 129.4, 129.1, 129.0, 128.1, 128.0, 124.4, 123.9, 122.8, 111.7, 57.9, 52.4, 30.9, 28.4, 25.2. IR (cm^{-1}, neat) 2952, 2875, 1716, 1616; MS (EI-MS) m/z 396 [M^+]; HRMS calculated for $C_{26}H_{24}N_2O_2$ m/z 396.1838; found 396.1840.

*Methyl-1-cyclopentyl-2-(3′-methyl-4-nitrobiphenyl-2-yl)-1H-benzimidazole-5-carboxylate (**3j**)*

^{1}H NMR (300 MHz, $CDCl_3$, $\delta = 7.24$ ppm as standard) δ 8.56–8.54 (m, 2H), 8.45 (dd, $J = 8.5$, 2.4 Hz, 1H), 7.97 (dd, $J = 8.6$, 1.9 Hz, 1H), 7.75 (d, $J = 8.7$ Hz, 1H), 7.35 (d, $J = 8.7$ Hz, 1H), 7.15–6.98 (m, 4H), 4.09 (m, 1H), 3.96 (s, 3H), 2.17 (s, 3H), 1.95–1.80 (m, 4H), 1.65–1.47 (m, 3H), 0.65 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8, 153.6, 148.3, 147.3, 143.2, 139.3, 138.0, 135.7, 131.3, 130.6, 130.1, 129.7, 129.3, 127.7, 126.2, 125.7, 125.1, 124.6, 123.0, 111.9, 58.3, 52.6, 31.1, 28.6, 25.2, 21.6; IR (cm^{-1}, neat) 2952, 1714, 1616; MS (EI-MS) m/z 455 [M^+]; HRMS calculated for $C_{27}H_{25}N_3O_4$ m/z 455.1845; found 455.1845.

*Methyl-1-cyclopentyl-2-(4-nitrobiphenyl-2-yl)-1H-benzimidazole-5-carboxylate (**3k**)*

^{1}H NMR (300 MHz, $CDCl_3$, $\delta = 7.24$ ppm as standard) δ 8.57–8.55 (m, 2H), 8.46 (dd, $J = 8.7$, 2.3 Hz, 1H), 7.97 (dd, $J = 8.7$, 1.5 Hz, 1H), 7.76 (d, $J = 8.7$ Hz, 1H), 7.35 (d, $J = 8.7$ Hz, 1H), 7.30–7.25 (m, 5H), 4.08 (m, 1H), 3.96 (s, 3H), 1.90–1.79 (m, 4H), 1.62–1.46 (m, 3H), 0.62 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7, 153.4, 148.1, 147.3, 142.9, 138.0, 135.6, 131.5, 130.4, 129.5, 129.5, 129.1, 127.8, 125.9, 125.2, 124.8, 122.9, 112.1, 58.3, 52.6, 31.2, 28.5, 25.2; IR (cm^{-1}, neat) 2952, 1716, 1617; MS (EI-MS) m/z 441 [M+1]$^+$; HRMS calculated for $C_{26}H_{23}N_3O_4$ m/z 441.1689; found 441.1690.

*Methyl-1-cyclopentyl-2-(3′-methoxy-4-nitrobiphenyl-2-yl)-1H-benzimidazole-5-carboxylate (**3l**)*

^{1}H NMR (300 MHz, $CDCl_3$, $\delta = 7.24$ ppm as standard) δ 8.57 (s, 1H), 8.56 (s, 1H), 8.47 (dd, $J = 8.7$, 1.7 Hz, 1H), 7.99 (dd, $J = 8.6$, 1.7 Hz, 1H), 7.80 (d, $J = 8.7$ Hz, 1H), 7.38 (d, $J = 8.7$ Hz, 1H), 7.23 (t, $J = 8.0$ Hz, 1H), 6.92 (d, $J = 7.5$ Hz, 1H), 6.84 (dd, $J = 8.3$, 2.3 Hz, 1H), 6.70 (s, 1H), 4.11 (m, 1H), 3.99 (s, 3H), 3.37 (s, 3H), 1.97–1.48 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8, 160.3, 153.7, 147.9, 147.4, 143.8, 139.3, 135.8, 131.2, 131.1, 130.5, 127.6, 125.7, 124.9, 124.5, 123.1, 121.4, 116.2, 113.6, 111.9, 58.2, 55.5, 52.6, 31.2, 28.6, 25.3; IR (cm^{-1}, neat) 2954, 1716, 1616; MS (ESI-MS) m/z 472 [M+1]$^+$; HRMS calculated for $C_{27}H_{25}N_3O_5$ m/z 471.1794; found 472.1875 [M+1]$^+$.

*Methyl-2-(biphenyl-2-yl)-1-(3-methoxypropyl)-1H-benzimidazole-5-carboxylate (**3m**)*

^{1}H NMR (300 MHz, $CDCl_3$, $\delta = 7.24$ ppm as standard) δ 8.57 (d, $J = 1.4$ Hz, 1H), 7.99 (dd, $J = 8.4$, 1.4 Hz, 1H), 7.68 (d, $J = 8.3$ Hz, 1H), 7.64–7.49 (m, 3H), 7.28–7.17 (m, 6H), 3.96 (s, 3H), 3.61 (t, $J = 6.9$ Hz, 2H), 3.08 (s, 3H), 2.97 (t, $J = 5.7$ Hz, 2H), 1.48 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 155.8, 142.7, 141.7, 140.2, 138.3, 132.2, 131.1, 130.4, 129.0, 128.9, 128.9, 128.0, 127.9, 124.8, 124.5, 122.4, 110.2, 69.0, 58.8, 52.5, 41.3, 29.3; IR (cm^{-1}, neat) 2925, 1714, 1616; MS (EI-MS) m/z 400 [M^+]; HRMS calculated for $C_{25}H_{24}N_2O_3$ m/z 400.1787; found 400.1784.

*Methyl-2-(biphenyl-2-yl)-1-(3-methylbutyl)-1H-benzimidazole-5-carboxylate (**3n**)*

^{1}H NMR (300 MHz, $CDCl_3$, $\delta = 7.24$ ppm as standard) δ 8.54 (d, $J = 1.2$ Hz, 1H), 7.96 (dd, $J = 8.4$, 1.2 Hz, 1H), 7.64 (d, $J = 8.4$ Hz, 1H), 7.60–7.46 (m, 3H), 7.24–7.14 (m, 6H), 3.93 (s, 3H), 3.47 (t, $J = 7.6$ Hz, 2H), 1.29 (m, 1H), 1.12–1.11 (m, 2H), 0.63 (d, $J = 6.3$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 155.8, 142.9, 141.7, 140.2, 138.1, 132.4, 131.1, 130.3, 129.1, 128.9, 128.9, 128.1, 127.9, 124.7, 124.4, 122.5, 110.2, 52.4, 42.9, 37.6, 25.9, 22.4; IR (cm^{-1}, neat) 2954, 1716, 1616; MS (EI-MS) m/z 398 [M^+]; HRMS calculated for $C_{26}H_{26}N_2O_2$ m/z 398.1994; found 398.1993.

*Methyl-2-(biphenyl-2-yl)-1-cyclooctyl-1H-benzimidazole-5-carboxylate (**3o**)*

^{1}H NMR (300 MHz, $CDCl_3$, $\delta = 7.24$ ppm as standard) δ 8.55 (d, $J = 1.4$ Hz, 1H), 7.92 (dd, $J = 8.6$, 1.4 Hz, 1H), 7.66–7.46 (m, 4H), 7.38 (d, $J = 8.6$ Hz, 1H), 7.32–7.17 (m, 5H), 3.94 (s, 3H), 3.89 (m, 1H), 2.05–1.92 (m, 2H), 1.63–1.16 (m, 11H), 0.51–0.48 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 155.2, 143.2, 141.8, 139.9, 136.3, 132.2, 131.1, 130.1, 129.4, 129.2, 129.0, 128.0, 128.0, 124.4, 124.0, 122.5, 112.4, 58.4, 52.5, 33.6, 31.5, 26.6, 26.2, 26.0, 25.7, 25.0; IR (cm^{-1}, neat) 2923, 1716, 1616; MS (EI-MS) m/z 438 [M^+]; HRMS calculated for $C_{29}H_{30}N_2O_2$ m/z 438.2307; found 438.2310.

*Methyl-1-benzyl-2-(biphenyl-2-yl)-1H-benzimidazole-5-carboxylate (**3p**)*

^{1}H NMR (300 MHz, $CDCl_3$, $\delta = 7.24$ ppm as standard) δ 8.57 (s, 1H), 7.85 (d, $J = 7.9$ Hz, 1H), 7.64 (d, $J = 7.5$ Hz, 1H), 7.60–7.41 (m, 3H), 7.26–7.05 (m, 8H), 6.96 (d, $J = 8.7$ Hz, 1H), 6.63 (m, 2H), 4.68 (s, 2H), 3.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 156.2, 143.1, 142.0, 140.2, 138.2, 135.6, 132.3, 131.1, 130.4, 1292, 129.1, 129.1, 129.1, 128.9,

128.1, 128.0, 126.9, 124.9, 124.6, 122.6, 110.8, 52.4, 48.3; IR (cm^{-1}, neat) 2923, 1716, 1616; MS (EI-MS) m/z 418 [M^+]; HRMS calculated for $C_{28}H_{22}N_2O_2$ m/z 418.1681; found 418.1680.

*Methyl-2-(4-bromobiphenyl-2-yl)-1-butyl-1H-benzimidazole-5-carboxylate (**3q**)*

^{1}H NMR (300 MHz, $CDCl_3$, $\delta = 7.24$ ppm as standard) δ 8.53 (d, $J = 1.2$ Hz, 1H), 7.97 (dd, $J = 8.4$, 1.2 Hz, 1H), 7.83 (d, $J = 2.1$ Hz, 1H), 7.74 (dd, $J = 8.3$, 2.1 Hz, 1H), 7.43 (d, $J = 8.3$ Hz, 1H), 7.26–7.16 (m, 6H), 3.95 (s, 3H), 3.45 (t, $J = 7.2$ Hz, 2H), 1.26–1.16 (m, 2H), 1.04–0.92 (m, 2H), 0.67 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 154.1, 142.7, 140.7, 139.1, 138.0, 135.0, 134.2, 131.8, 130.8, 129.1, 128.8, 128.3, 125.0, 124.7, 122.6, 122.1, 110.4, 52.5, 44.4, 30.9, 20.1, 13.7; IR (cm^{-1}, neat) 2956, 1716, 1616; MS (EI-MS) m/z 462 [M^+]; HRMS calculated for $C_{25}H_{23}BrN_2O_2$ m/z 462.0943; found 462.0945.

*Methyl-1-butyl-2-(4-methylbiphenyl-2-yl)-1H-benzimidazole-5-carboxylate (**3r**)*

^{1}H NMR (300 MHz, $CDCl_3$, $\delta = 7.24$ ppm as standard) δ 8.53 (d, $J = 1.2$ Hz, 1H), 7.95 (dd, $J = 8.4$, 1.2 Hz, 1H), 7.47–7.38 (m, 3H), 7.21–7.13 (m, 6H), 3.93 (s, 3H), 3.44 (t, $J = 7.2$ Hz, 2H), 2.43 (s, 3H), 1.24–1.16 (m, 2H), 1.02–0.89 (m, 2H), 0.64 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 156.1, 142.8, 140.1, 138.8, 138.1, 138.1, 132.9, 131.9, 130.2, 128.9, 128.9, 128.6, 127.7, 124.7, 124.4, 122.4, 110.3, 52.4, 44.3, 30.8, 21.3, 20.1, 13.7; IR (cm^{-1}, neat) 2956, 1716, 161; MS (EI-MS) m/z 398 [M^+]; HRMS calculated for $C_{26}H_{26}N_2O_2$ m/z 398.1994; found 398.1995.

*Methyl-1-cyclopentyl-2-(4′-methyl-4-nitrobiphenyl-2-yl)-1H-benzimidazole-5-carboxylate (**3s**)*

^{1}H NMR (300 MHz, $CDCl_3$, $\delta = 7.24$ ppm as standard) δ 8.57 (d, $J = 1.5$ Hz, 1H), 8.55 (d, $J = 1.8$ Hz, 1H), 8.46 (dd, $J = 8.6$, 1.5 Hz, 1H), 7.99 (dd, $J = 8.6$, 1.8 Hz, 1H), 7.75 (d, $J = 8.4$ Hz, 1H), 7.37 (d, $J = 8.7$ Hz, 1H), 7.14 (d, $J = 8.4$ Hz, 2H), 7.08 (d, $J = 8.1$ Hz, 2H), 4.12 (m, 1H), 3.99 (s, 3H), 2.30 (s, 3H), 1.96–1.49 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 153.8, 148.2, 147.1, 143.7, 139.7, 135.9, 135.2, 131.2, 130.7, 130.1, 128.9, 127.7, 125.7, 124.9, 124.5, 123.2, 111.9, 58.2, 52.5, 31.1, 28.5, 25.2, 21.5; IR (cm^{-1}, neat) 2952, 1716, 1616; MS (ESI-MS) m/z 456 [M+1]$^+$; HRMS: calculated for $C_{27}H_{25}N_3O_4$ m/z 455.1845; found 456.1295 [M+1]$^+$.

*Methyl-2-([1,1′-biphenyl]-2-yl)-1-isopropyl-1H-benzo[d]imidazole-5-carboxylate (**3t**)*

^{1}H NMR (300 MHz, $CDCl_3$, $\delta = 7.24$ ppm as standard) δ 8.57 (d, $J = 1.3$ Hz, 1H), 7.95 (dd, $J = 8.6$, 1.3 Hz, 1H), 7.67–7.49 (m, 4H), 7.45 (d, $J = 8.7$ Hz, 1H), 7.28–7.19 (m, 5H), 4.10 (m, 1H), 3.97 (s, 3H), 1.27 (d, $J = 6.9$ Hz, 3H), 0.71 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 155.4, 141.9, 140.1, 136.1, 132.2, 131.1, 130.2, 129.3, 129.3, 129.1, 129.1, 128.2, 128.0, 124.6, 124.2, 122.5, 112.1, 52.5, 49.4, 21.7, 19.9; IR (cm^{-1}, neat) 2983, 1716, 1616; MS (ESI-MS) m/z 371 [M+1]$^+$; HRMS calculated for $C_{24}H_{22}N_2O_2$ m/z 370.1681; found 371.1750 [M+1]$^+$.

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