Development of a copper(II)-catalyzed three-component tandem synthesis of isoindolinone derivatives

Leon Xuetong Sun, Tieqiang Zeng, Dong Jiang, Li-Yi Dai, and Chao-Jun Li

Abstract: Isoindolinone derivatives are important pharmaceutical building blocks in medicinal chemistry. Isoindolo[2,1-*a*]quinolines are a class of interesting compounds that possess protective effects against N_2-induced hypoxia and inhibitory activities against human topoisomerase II and bacterial DNA-gyrase. The conventional methods for synthesizing these compounds are unsatisfactory because of their harsh reaction conditions, complex starting materials, and multistaged purification procedures. This synthesis of the propargyl-isoindolinone core features an aldehyde–alkyne–amine (A^3) coupling-based tandem strategy using methyl 2-formylbenzoate, primary aryl amine, and terminal alkyne under $Cu(OTf)_2$ catalysis.

Key words: aldehyde–alkyne–amine (A^3) coupling, propargyl-isoindolinone, isoindolo[2,1-*a*]quinoline, copper(II) catalysis, tandem reaction.

Résumé : Les dérivés de l'isoindolinone sont d'importants synthons en chimie médicinale. Les isoindolo[2,1-*a*]quinoléines font partie d'une classe intéressante de composés qui possèdent effets protecteurs contre l'hypoxie induite par N_2 et des activités inhibitrices contre la topoisomérase II humaine et la gyrase d'ADN bactérienne. Les méthodes de synthèse conventionnelles de ces composés ne sont pas satisfaisantes en raison de la sévérité de leurs conditions réactionnelles, de la nature complexes de leurs produits de départ et des méthodes de purification en plusieurs étapes. Cette synthèse du synthon propargyl-isoindolinone comporte un couplage d'aldéhyde, d'alcyne et d'amine (A^3) à base d'une stratégie en tandem impliquant du 2-formylbenzoate de méthyle, une amine aromatique primaire et un alcyne terminal sous l'influence d'un catalyseur de $Cu(OTf)_2$.

Mots-clés : couplage d'aldéhyde, d'alcyne et d'amine (A^3), propargyl-isoindolinone, isoindolo[2,1-*a*]quinoléine, catalyse par le cuivre(II), réaction en tandem.

[Traduit par la Rédaction]

Introduction

A tandem reaction, also called a cascade or domino reaction, is defined as a consecutive series of reactions that usually proceed via highly reactive intermediates; the product of each reaction acts as the substrate of subsequent reactions.[1] These reactions possess high synthetic value in the sense that they not only allow efficient construction of complex structures from simple precursors but also display overall reduced operations and better step economy, which translates into reduced labor time, energy input, and waste; therefore, they have been the subject of extensive investigations in recent years.[2]

Isoindoline derivatives are important pharmaceutical building blocks that possess unique medicinal properties. For instance, the diuretic activity of sulfonamide-functionalized isoindoline in Fig. 1 is 100 times more than for chlorothiazide.[3] Furthermore, isoindolylalkylphosphonium salts possess antitumour activities and have displayed substantial activity in the P-388 lymphocytic leukemia screen.[4] In some recent reports, these salts have been demonstrated to possess herbicidal activity[5] and to act as antagonists of the 5-hydroxytryptamine 2C ($5\text{-}HT_{2C}$) receptor,[6] as well as being candidates to treat various cancers.[7] There have also been some recent studies in applying isoindoline derivatives in pigments.[8]

One of the most common isoindoline derivatives is isoindolinone, which has also attracted much research interest owing to its substantial biological activities. N-Substituted isoindolinones of general structure **1** possess anxiolytic activity and are commonly applied as sedatives, hypnotics, and muscle relaxants.[9] Some examples, such as anxiolytics pazinaclone, pagoclone (Sanofi-Aventis and Pfizer, phase III

Received 27 April 2011. Accepted 14 June 2011. Published at www.nrcresearchpress.com/cjc on 10 November 2011.

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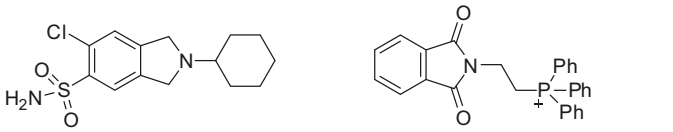
This article is part of a Special Issue dedicated to Professor Tak-Hang Chan.

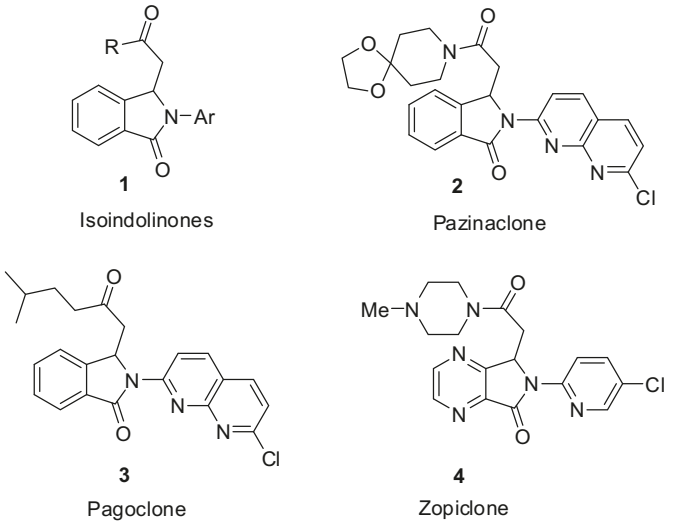
Fig. 1. Early discoveries of isoindoline and isoindolinone derivatives.[3,4]



Isoindoline synthesized in 1963 with high diuretic activity

Isoindolinone synthesized in 1977 with substantial activity in the P-388 lymphocytic leukemia screen

Fig. 2. Important N-substituted isoindolinone derivatives as pharmaceuticals.[9]



clinical trials), and the anticonvulsant zopiclone, are shown in Fig. 2.[10]

Conventional synthetic methods adopted in approaching polysubstituted isoindolinone derivatives are usually unsatisfactory because of their harsh reaction conditions, complex starting materials, and lengthy synthetic sequence.[11] In recent years, more and more cascade reactions have been devoted to the construction of the isoindolinone skeletons. For example, an elegant palladium(0)-catalyzed three-component carbonylation – amination – Michael addition was used by Grigg and et al.[9a] in 2005 in their synthesis of various isoindolinones. Nevertheless, the applications of cascade reactions are still quite limited.

While working on the aldehyde–alkyne–amine (A^3) methodology (A^3 coupling; Scheme 1) for the synthesis of monopropargyl amines,[12] we envisioned that the secondary amine formed in the product could also be utilized as a nucleophile to perform consecutive reactions. Under proper conditions, this nucleophilic nitrogen can be treated as the building block for a lactam ready to access various isoindolinone derivatives.

Results and discussion

Li and co-workers[13] developed the first copper-catalyzed addition as well as asymmetric addition of acetylenes to various imine and acylimines. This discovery has attracted much attention and also triggered intensive research in this area[14] because the final products are synthetically versatile building blocks for the preparation of many nitrogen-containing compounds that possess valuable biological activities. It has been proven that the A^3 coupling can be catalyzed by various types of transition-metal catalysts, including Cu(I), Cu(II), Ag(I), Au(I), and Au(III) salts and Cu/Ru bimetallic systems, etc.[12] Depending on the nature of the substrates, the reaction can proceed in organic solvent, water, or neat. We rationalized that from simple commercially available starting materials **5**, **6**, and **7**, under transition-metal catalysis, the A^3-coupling product **8** would quickly form in situ, and upon intramolecular cyclization, the isoindolinone core **9** would be constructed in one step (Scheme 2).

Our initial examination started by using 2-carboxybenzaldehyde, aniline, and phenyl acetylene as the starting materials, all of which are inexpensive readily available commercial substrates. Unfortunately, no desired product was obtained. ^{1}H NMR studies showed that 2-carboxybenzaldehyde mainly exists in its fused bicyclic form (Scheme 3). We believe that this form obstructs the formation of imine and thus prevents A^3 coupling from occurring. Another factor possibly responsible for the failure of the reaction is that the substrate does not contain a good leaving group to facilitate the cyclization of the amido ring.

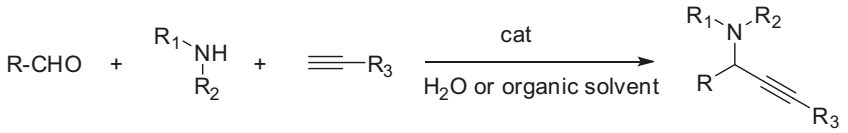
To render a good leaving group into the substrate as well as converting it into its "open" form, we decided to use its methyl ester, "methyl 2-formylbenzoate", and re-subject it to the same sets of conditions examined previously; in this case, all metal catalysts offered the desired product in different yields, among which $Cu(OTf)_2$ had the highest product:impurities ratio. Upon systematic screening, the optimized conditions were determined to be 15 mol % of $Cu(OTf)_2$ at 100 °C for 12 h in toluene. One noteworthy fact is that the solvent is an essential component of the reaction, without which the conditions provided would be too harsh for the substrates used, and in most cases the phenylacetylene would be converted into acetophenone.

Various types of aniline derivatives were examined. Experimental results (Table 1) indicated that any ortho substituent on the aniline ring (**9g–9m**) impedes the formation of the desired product with no reaction observed, most likely because of steric hindrance. The presence of electron-withdrawing groups on the meta or para position (**9b–9f**) can reduce the yield compared with electron-donating groups.

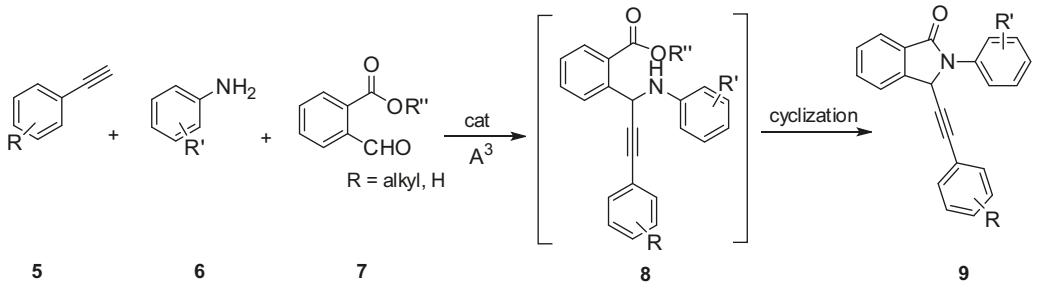
Screening of the acetylene substrates proved to be challenging using this methodology. The results for the reactions tend to vary upon repetitions; thus, each yield reported in Table 2 is the averaged isolated yield among a few trials. Similar to the results of anilines, ortho-substitution patterns in aryl acetylenes (**9u** and **9z**) do not favour formation of desired products; most importantly, electronic characters of the aryl cycles do not seem to play a crucial role in the yield, despite the fact that in the para-substituted cases, electron-donating groups seem to offer a better yield than electron-withdrawing groups. Alkyl acetylenes (**9v** and **9w**) always provide higher yields than aryl acetylenes (**9n–9t**).

Two special situations have been observed. Firstly, when the aryl acetylene contains a nitrogen heterocycle, the yield diminishes to nearly zero. Based on the colour of the catalyst and the amount of starting materials recovered, we can clearly conclude that the catalyst is not turning over. We suspect that this is caused by the strong coordination and

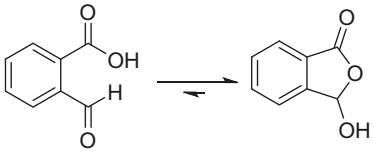
Scheme 1. Three-component coupling of aldehyde, alkyne, and amine (A^3 coupling).



Scheme 2. Proposed isoindoline synthesis via the A^3-coupling strategy.



Scheme 3. Equilibrium of 2-carboxybenzaldehyde.



complexation between the heterocyclic nitrogen and copper(II), which prevents the formation of copper acetylide. An elevated temperature or the addition of a catalytic amount of acid does not solve this problem. Secondly, when using propiolate as the alkyne, the desired isoindolinone core does not form; in this case, the mechanistic pathway is altered and the reaction exclusively yields the 1,4-dihydropyridine system (>90% isolated yield), as shown in Scheme 4. Initially, we were quite impressed by this outcome because previously known synthesis of 1,4-dihydropyridines either requires a microwave apparatus[15] or preformation of the imine with a rare earth metal catalyst (RE triflates, RE = Sc, Y, La, Ce, Pr, Nd, Sm, or Yb).[16] Unfortunately, upon careful review of the synthetic literature, we concluded that this methodology is not the greenest approach to date; as with our studies, Mai et al.[17] in 2009 used Brønsted acid as the catalyst and completed the same transformation in a one-pot tandem manner in the absence of any transition metal.

Conclusion

In summary, we have demonstrated a one-pot synthesis of the pharmaceutically interesting propargyl-isoindolinone core (**9**) based on the tandem A^3-coupling methodology, starting from methyl 2-formylbenzoate, aniline derivative, and alkynes as the precursors. Such methodology provides a simple and efficient access to a variety of isoindolinone building blocks from inexpensive starting materials readily. Within the scope of this reaction, two exceptions were observed: (*i*) using propiolates as the acetylene source provides 1,4-dihydropyridine as the only product and (*ii*) heterocyclic amines do not favour the formation of the desired product. For future work, chiral ligands shall be introduced into the reaction to generate enantio- or diastereo-selectivity. the isoindolinone core (**9**) can also be transformed into a series of biologically active compounds.

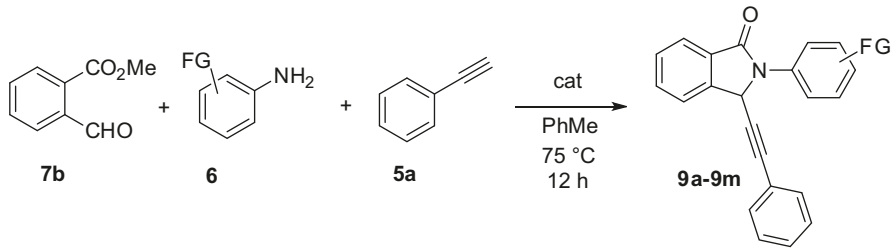
Experimental

All glassware used for moisture-sensitive reactions was flame-dried under vacuum and subsequently purged with nitrogen. All reagents were commercially available materials and were used without further purification unless specified. Standard column chromatography was performed on 20–60 μm silica gel (obtained from Silicycle Inc.) or on Sorbent silica gel (30–60 μm) using standard flash column chromatography techniques. Infrared analyses were recorded as a thin film on NaCl plates and solid compounds as KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded on a Varian 400 MHz or 300 MHz spectrometer. Chemical shifts for ^{1}H NMR spectra were reported in parts per million (ppm) from tetramethylsilane with the solvent resonance as the internal standard (deuterated chloroform: δ 7.26 ppm, DMSO: δ 2.50 ppm). Chemical shifts for ^{13}C NMR spectra were reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (deuterated chloroform: δ 77.0 ppm). Mass spectrometry (MS) data were obtained by using a Kratos MS25RFA mass spectrometer. High-resolution mass spectrometry electrospray ionization (HR-MS-ESI) measurements were performed at the McGill University MS Laboratory.

General procedure for the synthesis of isoindolinones

Under an argon atmosphere, acetylene (0.36 mmol), aniline (0.36 mmol), methyl 2-formylbenzoate (0.30 mmol), Cu $(OTf)_2$ (15 mol %), and anhydrous toluene (1 mL) were added into a tube and stirred at 75 °C for 12 h. After the reaction, 15 mL of ethyl acetate was added into the tube and the entire reaction mixture was filtered through a short plug of silica. The filtrate was concentrated in vacuo and then subjected to liquid column chromatography (hexane/EtOAc = 7:1 to 5:1 gradient elution). The solvent of the combined fractions was removed under reduced pressure to afford the desired isoindolinone compound as a viscous light yellow oil or semisolid.

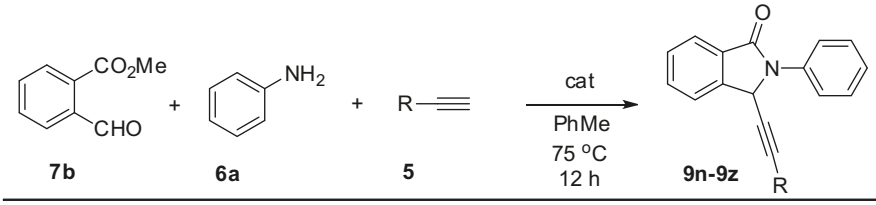
Table 1. The effect of various anilines on the reaction.



Entry	Aniline	Product	Isolated yield (%)
1	$C_6H_5NH_2$	**9a**	75
2	3-F-$C_6H_4NH_2$	**9b**	70
3	3-Cl-$C_6H_4NH_2$	**9c**	55
4	4-Cl-$C_6H_4NH_2$	**9d**	52
5	4-Br-$C_6H_4NH_2$	**9e**	66
6	4-NO_2-$C_6H_4NH_2$	**9f**	60
7	2-I-$C_6H_4NH_2$	**9g**	N.R.
8	2-NO_2-6-Me-$C_6H_3NH_2$	**9h**	N.R.
9	2-Cl-4-Cl-6-Cl-$C_6H_2NH_2$	**9i**	N.R.
10	2-OMe-5-OMe-$C_6H_3NH_2$	**9j**	N.R.
11	2-*i*-Pr-6-*i*-Pr-$C_6H_3NH_2$	**9k**	N.R.
12	2-Cl-4-Cl-$C_6H_3NH_2$	**9l**	<5
13	2-OMe-4-OMe-$C_6H_3NH_2$	**9m**	<5

Note: N.R. = no reaction. Conditions: phenylacetylene (0.36 mmol), aniline (0.36 mmol), methyl 2-formylbenzoate (0.30 mmol), and $Cu(OTf)_2$ (15 mol %) in 1 mL toluene, reacted for 12 h at 75 °C under argon.

Table 2. The effect of alkynes on the reaction.

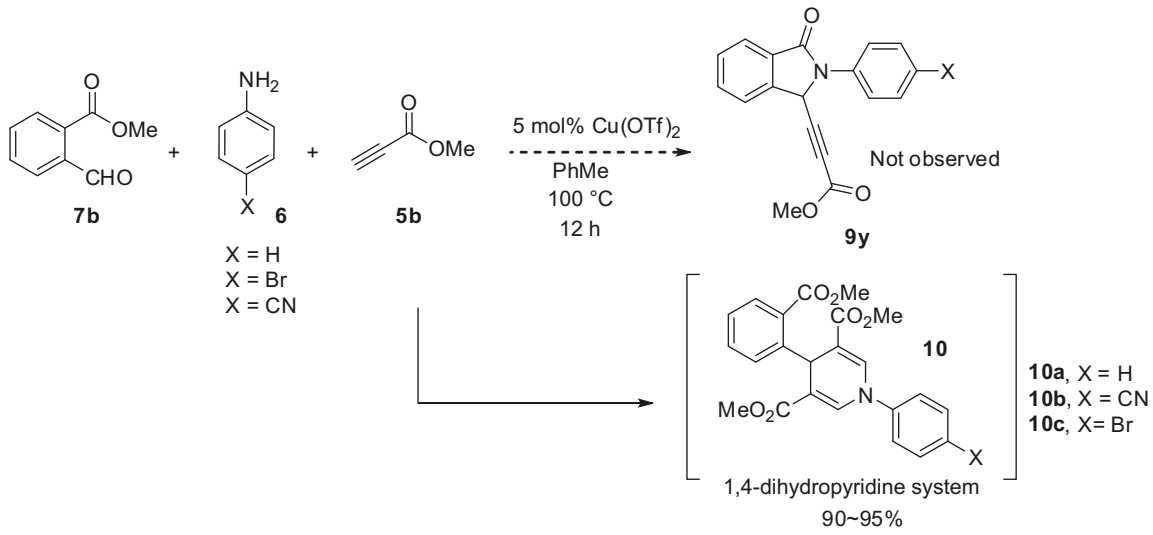


Entry	Acetylene	Product	Isolated yield (%)
1	4-Me-phenylacetylene	**9n**	31
2	4-OMe-phenylacetylene	**9o**	25
3	4-*t*-Bu-phenylacetylene	**9p**	35
4	4-*n*-Bu-phenylacetylene	**9q**	45
5	4-CF_3-phenylacetylene	**9r**	20
6	4-Ph-phenylacetylene	**9s**	20
7	3-F-phenylacetylene	**9t**	44
8	2-NO_2-phenylacetylene	**9u**	N.R.
9	Tetradec-1-yne	**9v**	55
10	5-Methylhex-1-yne	**9w**	60
11	Ethynyl-triisopropylsilane	**9x**	32
12	Methyl propiolate	**9y**[a]	0
13	2-Ethynylpyridine	**9z**	N.R

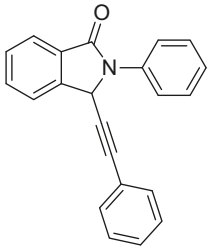
Note: N.R. = no reaction. Conditions: acetylene (0.36 mmol), aniline (0.36 mmol), methyl 2-formylbenzoate (0.30 mmol), and $Cu(OTf)_2$ (15 mol %) in 1 mL toluene, reacted for 12 h at 75 °C under argon.

[a]Product **9y** does not bear an isoindolinone structure, instead it is a 1,4-dihydropyridine structure, noted as compound **10**.

Scheme 4. Formation of 1,4-dihydropyridine structural scaffolds.

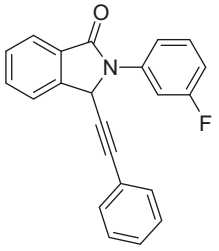


Characterization of products



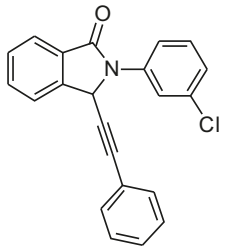
9a

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.96 (d, 1H, J = 7.6 Hz), 7.86 (dd, 2H, J = 7.8, 1.0 Hz), 7.72–7.68 (m, 2H), 7.58–7.45 (m, 3H), 7.32–7.26 (m, 6H), 6.04 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ: 166.7, 141.8, 137.7, 132.8, 131.8, 131.7, 129.3, 129.0, 128.9, 128.3, 125.3, 124.2, 123.0, 122.2, 121.7, 86.2, 83.5, 53.2. HR-MS (ESI) exact mass calcd. for $C_{22}H_{16}NO$ ([M + H]) m/z: 310.1237; found m/z: 310.1230.



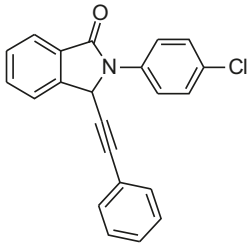
9b

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.96 (d, 1H, J = 7.6 Hz), 7.82–7.56 (m, 5H), 7.44–7.24 (m, 6H), 6.94 (td, 1H, J = 10.8, 2.6 Hz), 6.00 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ: 165.6 (d, J = 211.8 Hz), 161.3, 141.6, 139.3 (d, J = 13.9 Hz), 133.1, 131.8, 131.3, 130.1, 129.9, 129.4, 129.0, 128.3, 124.4, 123.1, 121.7, 116.6 (d, J = 4.3 Hz), 111.8 (d, J = 27.9 Hz), 108.9 (d, J = 35.2 Hz), 86.5, 83.0, 53.1. HR-MS (ESI) exact mass calcd. for $C_{22}H_{13}FNO$ ([M – H]) m/z: 326.0987; found m/z: 326.0988.



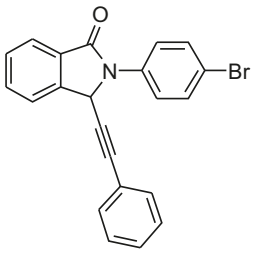
9c

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.94 (d, 1H, J = 7.6 Hz), 7.84 (d, 2H, J = 8.8 Hz), 7.71–7.69 (m, 2H), 7.59–7.57 (m, 1H), 7.43 (d, 2H, J = 8.8 Hz), 7.33–7.26 (m, 5H), 5.99 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ: 166.6, 141.6, 138.9, 134.6, 133.1, 131.8, 131.3, 129.9, 129.4, 129.0, 128.3, 125.1, 124.4, 123.1, 121.7, 121.5, 119.5, 86.6, 82.9, 53.0. HR-MS (ESI) exact mass calcd. for $C_{22}H_{15}ClNO$ ([M + H]) m/z: 344.0837; found m/z: 344.0842.



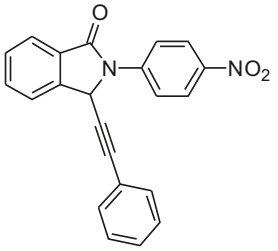
9d

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.94 (d, 1H, J = 7.6 Hz), 7.84 (d, 2H, J = 8.8 Hz), 7.72–7.69 (m, 2H), 7.57–7.56 (m, 1H), 7.43 (dd, 2H, J = 7.0, 2.0 Hz), 7.30–7.26 (m, 5H), 6.00 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ: 166.6, 141.6, 136.3, 132.9, 131.8, 131.3, 130.4, 129.4, 129.1, 128.8, 128.3, 124.3, 123.1, 122.9. HR-MS exact mass calcd. for $C_{22}H_{14}ClNONa$ ([M + Na]) m/z: 366.0656; found m/z: 366.0664.



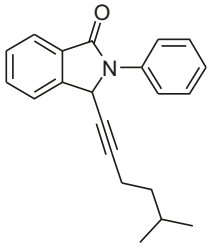
9e

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.94 (d, 1H, J = 7.2 Hz), 7.80 (d, 2H, J = 8.8 Hz), 7.79–7.67 (m, 2H), 7.59–7.56 (m, 3H), 7.33–7.25 (m, 5H), 5.99 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ: 166.6, 141.6, 136.8, 133.0, 131.9, 131.8, 131.3, 129.4, 129.0, 128.3, 124.3, 123.2, 123.1, 121.5, 118.2, 86.5, 82.9, 52.9. HR-MS (ESI) exact mass calcd. for $C_{22}H_{15}BrNO$ ([M + H]) m/z: 388.0332; found m/z: 388.0338.



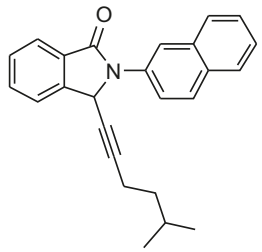
9f

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 8.34 (dd, 2H, J = 7.2, 2.0 Hz), 8.19 (dd, 2H, J = 9.6, 2.0 Hz), 7.90–7.50 (m, 4H), 7.34–7.29 (m, 5H), 6.09 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ: 166.9, 143.6, 143.5, 141.5, 133.8, 131.8, 130.7, 129.7, 129.3, 128.4, 124.8, 124.6, 123.2, 121.1, 119.9, 87.1, 82.4, 52.7. HR-MS (ESI) exact mass calcd. for $C_{22}H_{13}N_2O_3$ ([M – H]) m/z: 353.0932; found m/z: 353.0953.



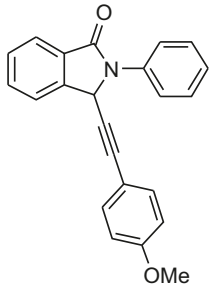
9w

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.91 (d, 1H, J = 7.6 Hz), 7.79 (d, 2H, J = 7.6 Hz), 7.67–7.62 (m, 2H), 7.58–7.51 (m, 1H), 7.46–7.42 (m, 2H), 7.26–7.21 (m, 1H), 5.79 (s, 1H), 2.13–2.09 (m, 2H), 1.51–1.43 (m, 1H), 1.28–1.23 (m, 2H), 0.86–0.76 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 166.6, 142.4, 137.7, 132.6, 131.6, 128.9, 128.8, 125.1, 124.1, 122.9, 122.2, 87.3, 74.4, 52.9, 36.9, 26.9, 22.0, 21.9, 16.6. HR-MS (ESI) exact mass calcd. for $C_{21}H_{22}NO$ ([M + H]) m/z: 304.1707; found m/z: 304.1698.



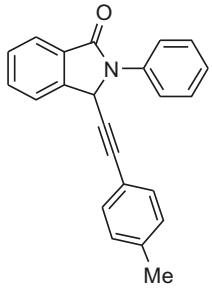
9w2

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 8.18 (d, 1H, J = 2 Hz), 8.02 (dd, 1H, J = 8.8, 2.4 Hz), 7.96–7.84 (m, 4H), 7.67 (dd, 1H, J = 2.8, 1.2 Hz), 7.58–7.44 (m, 3H), 5.94 (s, 1H), 2.10–2.06 (m, 2H), 1.38–1.33 (m, 1H), 1.25–1.18 (m, 2H), 0.68–0.64 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 166.6, 142.5, 135.3, 133.6, 132.6, 131.6, 131.1, 129.1, 128.6, 127.9, 127.5, 126.3, 125.5, 124.1, 122.9, 121.4, 119.8, 87.5, 74.5, 53.2, 36.9, 26.8, 21.8, 16.6. HR-MS (ESI) exact mass calcd. for $C_{25}H_{24}NO$ ([M + H]) m/z: 354.1852; found m/z: 354.1851.



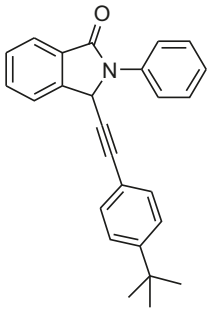
9o

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.95 (d, 1H, J = 7.2 Hz), 7.86 (d, 2H, J = 8 Hz), 7.73–7.65 (m, 2H), 7.59–7.45 (m, 3H), 7.26–7.22 (m, 3H), 6.77 (d, 2H, J = 7.6 Hz), 6.02 (s, 1H), 3.77 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 166.7, 159.9, 142.0, 137.7, 133.3, 132.7, 131.6, 129.2, 128.9, 125.3, 124.2, 123.0, 122.2, 113.9, 86.2, 82.0, 80.2, 55.3, 53.4. HR-MS (ESI) exact mass calcd. for $C_{23}H_{18}NO_2$ ([M + H]) m/z: 340.1332; found m/z: 340.1333.



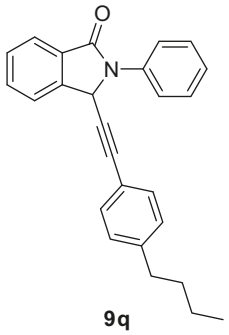
9n

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.95 (d, 1H, J = 7.6 Hz), 7.87 (d, 2H, J = 8 Hz), 7.73–7.65 (m, 2H), 7.59–7.44 (m, 4H), 7.26–7.19 (m, 2H), 7.06 (d, 2H, J = 7.6 Hz), 6.02 (s, 1H), 3.31 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 166.7, 141.9, 139.1, 137.7, 132.7, 131.7, 129.2, 129.1, 129.0, 128.9, 125.3, 124.2, 123.1, 122.2, 119.4, 118.7, 86.4, 82.8, 53.3. HR-MS (ESI) exact mass calcd. for $C_{23}H_{16}NO$ ([M – H]) m/z: 322.1237; found m/z: 322.1231.



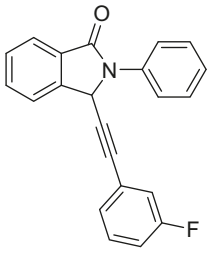
9p

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.95 (d, 1H, J = 7.6 Hz), 7.86 (d, 2H, J = 7.6 Hz), 7.73–7.65 (m, 2H), 7.57 (t, 1H, J = 7.6 Hz), 7.46 (t, 2H, J = 8.4 Hz), 7.30–7.22 (m, 5H), 6.03 (s, 1H), 1.27 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 166.7, 152.2, 141.9, 137.7, 132.7, 131.7, 131.6, 129.2, 128.9, 125.3, 125.2, 124.2, 123.0, 122.2, 118.7, 86.3, 82.8, 53.4, 34.8, 31.1. HR-MS (ESI) exact mass calcd. for $C_{26}H_{23}NONa$ ([M + Na]) *m*/*z*: 388.1672; found *m*/*z*: 388.1679.



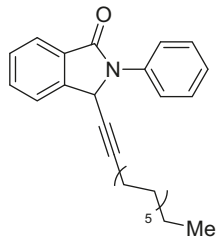
9q

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.95 (d, 1H, J = 7.6 Hz), 7.87 (d, 2H, J = 8 Hz), 7.73–7.65 (m, 2H), 7.59–7.55 (m, 1H), 7.49–7.45 (m, 2H), 7.26–7.22 (m, 3H), 7.07 (d, 2H, J = 8 Hz), 6.03 (s, 1H), 2.58–2.54 (m, 2H), 1.67–1.50 (m, 2H), 1.35–1.26 (m, 2H), 0.91–0.86 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 166.7, 144.1, 141.9, 137.7, 132.7, 131.7, 131.6, 129.2, 128.9, 128.4, 125.3, 124.2, 123.1, 122.2, 118.9, 86.4, 82.8, 53.3, 35.5, 33.3, 22.2, 13.9. HR-MS (ESI) exact mass calcd. for $C_{26}H_{23}NONa$ ([M + H]) *m*/*z*: 388.1672; found *m*/*z*: 388.1678.



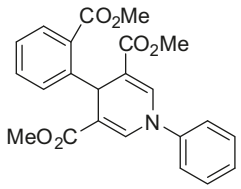
9t

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.97–7.83 (m, 3H), 7.71–7.66 (m, 1H), 7.60–7.41 (m, 4H), 7.27–7.20 (m, 2H), 7.07 (d, 1H, J = 8 Hz), 7.02–6.03 (m, 2H), 6.03 (s, 1H), 4.86 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 166.6, 141.5, 137.5, 132.8, 131.6, 129.9, 129.3, 129.2, 129.1, 129.0, 127.7, 127.6, 125.4, 124.3, 122.9, 122.1, 119.4, 118.6 (d, J = 22.5 Hz), 116.4, 116.3 (d, J = 21.9 Hz), 84.5 (d, J = 29 Hz), 53.1. HR-MS (ESI) exact mass calcd. for $C_{22}H_{13}FNO$ ([M – H]) *m*/*z*: 326.0987; found *m*/*z*: 326.0995.



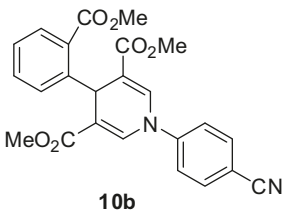
9v

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.91 (d, 1H, J = 7.6 Hz), 7.80 (d, 2H, J = 7.6 Hz), 7.64 (d, 2H, J = 2.4 Hz), 7.55–7.52 (m, 1H), 7.46–7.42 (m, 2H), 7.26–7.20 (m, 1H), 5.80 (s, 1H), 2.13–2.08 (m, 2H), 1.38–1.78 (m, 20H), 0.93–0.87 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 166.7, 142.4, 137.7, 134.4, 132.6, 131.5, 128.9, 128.8, 126.6, 125.1, 124.1, 123.7, 122.9, 122.1, 87.4, 74.5, 52.9, 31.9, 29.6, 29.4, 29.0, 28.6, 28.2, 22.7, 18.6, 14.1. HR-MS (ESI) exact mass calcd. for $C_{28}H_{36}NO$ ([M + H]) *m*/*z*: 402.2791; found *m*/*z*: 402.2801.



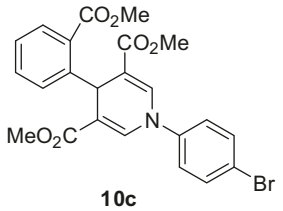
10a

^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ: 7.75 (dd, 1H, J = 8 Hz, 1.5 Hz), 7.68 (s, 2H), 7.48–7.40 (m, 5H), 7.32–7.28 (m, 2H), 7.21 (m, 1H), 6.10 (s, 1H), 3.99 (s, 3H), 3.60 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 168.5, 167.0, 146.8, 143.0, 136.1, 131.9, 130.2, 130.1, 129.9, 129.7, 126.4, 126.3, 120.6, 111.4, 51.9, 51.4, 32.9. HR-MS (ESI) exact mass calcd. for $C_{23}H_{22}NO_6$ ([M + H]) *m*/*z*: 408.1442; found *m*/*z*: 408.1439.



10b

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.78–7.73 (m, 5H), 7.43–7.36 (m, 3H), 7.25–7.21 (m, 2H), 6.14 (s, 1H), 3.98 (s, 3H), 3.62 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 168.3, 166.5, 145.8, 145.7, 134.1, 134.0, 131.9, 130.3, 130.2, 129.9, 126.6, 119.8, 118.1, 113.5, 109.1, 52.02, 51.66, 32.97, 31.58, 22.65, 14.12. HR-MS (ESI) exact mass calcd. for $C_{24}H_{20}N_2O_6Na$ ([M + Na]) *m*/*z*: 455.1214; found *m*/*z*: 455.1206.



10c

^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ: 7.75 (d, 1H, J = 8 Hz), 7.62 (s, 2H), 7.57 (dd, 2H, J = 6.8, 2 Hz), 7.42 (d, 2H, J = 4.4 Hz), 7.21–7.18 (m, 3H), 6.10 (s, 1H), 3.98 (s, 3H), 3.60 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 168.4, 166.9, 146.5, 142.0, 135.5, 133.0, 131.9, 130.2, 130.1, 129.7, 129.4, 126.4, 122.0, 111.9, 51.9, 51.5, 32.8. HR-MS (ESI) exact mass calcd. for $C_{23}H_{20}BrNO_6Na$ ([M + Na]) *m/z*: 508.0366; found *m/z*: 508.0371.

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