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Synthesis of Triazolo Isoquinolines and Isochromenes from 2-Alkynylbenzaldehyde via Domino Reactions under Transition-Metal-Free Conditions

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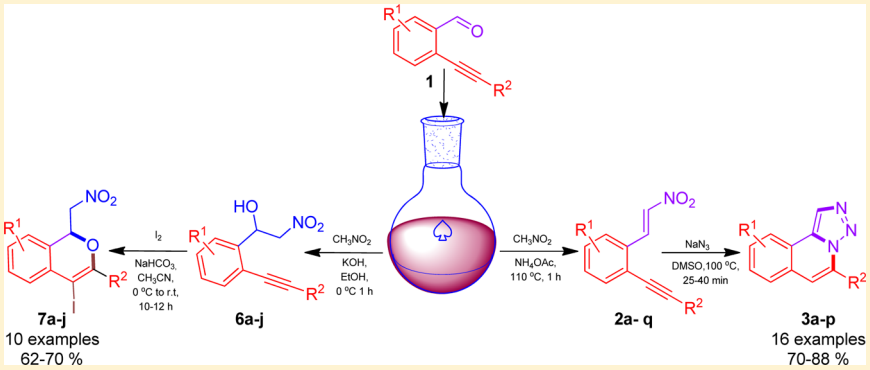
Supporting Information



ABSTRACT: We describe two simple straightforward syntheses of triazolo isoquinolines (**3**) and isochromenes (**7**) from 2-alkynylbenzaldehydes (**1**) as a common synthon. The synthetic strategy for **3** involves formation of the (*E*)-1-(2-nitrovinyl)-2-(alkynyl)benzene species **2** via condensation of synthon **1** with nitromethane followed by a [3 + 2] cycloaddition/extrusion of the nitro group/regioselective 6-endo cyclization domino sequence. In yet another strategy, the synthon **1** was condensed with nitromethane followed by electrophilic iodo cyclization of the resulting 2-nitro-1-(2-(alkynyl)phenyl)ethanol (**6**) to furnish iodo isochromene derivatives. The salient feature of the above two strategies involves formation of the corresponding heterocycles under metal-free conditions in good yields.

INTRODUCTION

An efficient and rapid construction of polyheterocyclic molecules from readily available reactants in a one-pot format via domino[1]/cascade[2] reactions remains a challenging task for synthetic organic chemists. In particular, one-pot synthesis of nitrogen-/oxygen-containing annulated polyheterocycles[3] has drawn much attention due to their ubiquitous core structure, present in a numerous biologically active natural products[4] and pharmaceutically important compounds.[5] Among variety of O/N-heterocycles, triazolo isoquinolines[6] and isochromenes[7] are important classes of heteroaromatic compounds present in many bioactive natural products,[8] pharmaceuticals,[9] and materials.[10] In addition, structurally fused isoquinolines[11] possess a broad spectrum of biological activities such as antifertility, anti-inflammatory, CNS antidepressant,[6] and antitumor activity.[12]

In our laboratory, we have been interested in the development of new synthetic strategies in a one-pot format for the construction of nitrogen-containing fused heterocycles from terminal/internal alkynes as one of the reactants.[13] In this continuation, we next directed our efforts toward a one-pot transformation of a suitably derivatized bifunctionalized internal alkyne such as 2-alkynylbenzaldehyde into the O/N-heterocycles triazolo isoquinolines and isochromenes (Figure 1). The 2-alkynylbenzaldehyde **1** has been extensively used as a synthon by us[13c,d] and others[14] for the synthesis of structurally diverse polyheterocycles in a one-pot format. In particular, Verma et al.[14g] demonstrated the potential of **1** by synthesizing several structurally diverse polyheterocycles in both nonaqueous and aqueous solvents.

The versatility of synthon **1** for the synthesis of **3** and **7** in a one-pot format can be envisaged by their retrosynthetic analysis (Figure 2). It suggests that triazolo isoquinolines **3** can be obtained in a domino fashion from (*E*)-1-(2-nitrovinyl)-2-(alkynyl)benzene **2**, which in turn can be derived from 2-alkynylbenzaldehyde and nitromethane. The strategy is likely to proceed via three new C−N bond formations, resulting in the formation of two annulated heterocyclic rings. Similarly, the isochromene derivatives **7** can be obtained via iodocyclization

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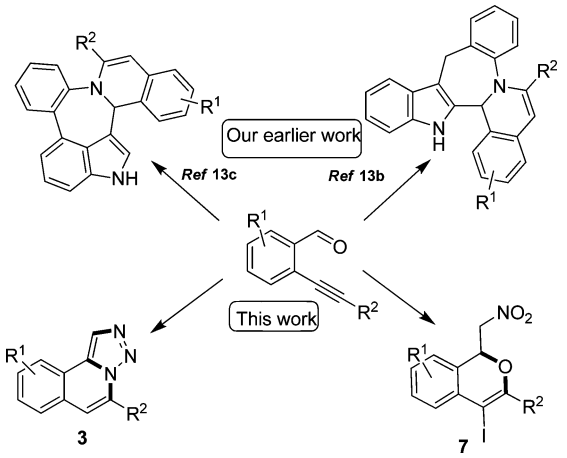


Figure 1. 2-Alkynylbenzaldehydes **1** as versatile synthons in a one-pot format.

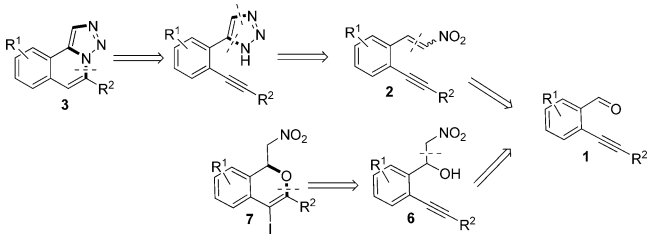


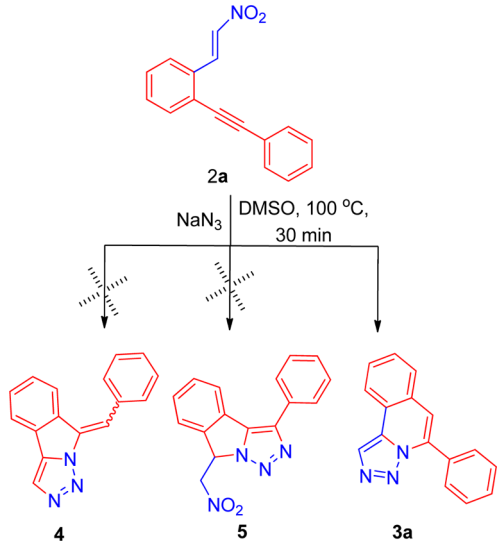
Figure 2. Retrosynthetic strategies for the synthesis of triazolo isoquinolines **3** and isochromenes **7** from 2-alkynylbenzaldehyde **1**.

of **6**, which again can be obtained by treating 2-alkynylbenzaldehyde with nitromethane. A careful survey of the literature revealed the synthesis of isochromene from synthon **1** employing Au as a catalyst;[15] however, the reaction suffered from a drawback involving poor regioselectivity, as it was accompanied by the formation of the additional byproducts 1,3-dihydroisobenzofurans (Figure 3).

RESULTS AND DISCUSSION

In the first instance, we investigated the reaction conditions for the condensation of the 2-alkynyl nitro olefin[16] **2** (obtained from 2-alkynylbenzaldehyde) and sodium azide. We envisaged that initially the nitro olefin may undergo aza-Michael addition to form triazoles, which could be then followed by the intramolecular hydroamination involving N−H of triazole and the internal alkyne present in close proximity to furnish thermodynamically stable annulated products. Accordingly, we treated **2a** with sodium azide in the presence of CuI at 100 °C in DMSO. The reaction was found to be complete within 30 min and after its workup furnished the new regioselective product **3a** in 85% isolated yield (Table 1, entry 1) with no detectable formation of regioisomers **4** and **5**. The structure of the resulting product was elucidated by various NMR studies that led to its identification as triazolo isoquinoline **3a** (entry

Table 1. Optimization of the Reaction Conditions[a] for the Synthesis of 3a



entry	catalyst	solvent	temp (°C)	time	yield (%)
1	CuI	DMSO	100	30 min	85
2		**DMSO**	**100**	**30** min	**85**
3		DMSO	80	40 min	78/*b*
4		DMSO	room temp	16 h	62/*b*
5		DMF	100	40 min	72
6		DCE	90	40 min	N.R.
7		H_2O	100	45 min	N.R.
8		CH_3CN/H_2O (9/1)	90	45 min	53
9		toluene/H_2O (9/1)	100	45 min	60

[a]Reaction conditions: **2a** (1.0 mmol), NaN_3 (2.0 mmol) in 5 mL of DMSO. N.R. = no reaction. [b]Starting material.

1). Next, we performed the same reaction without any catalyst and maintained the thermal condition (100 °C) constant and to our delight within 30 min we obtained **3a** (entry 2) in 85% isolated yield. Carrying out the reaction at reduced temperature (80 °C) or at room temperature not only made the reaction sluggish but also furnished products in reduced yields with recovery of unchanged **2a** (entries 3 and 4). Switching solvents from DMSO to DMF afforded **3a** in diminished yields with no reaction being observed in DCE and water (entries 5−7). On the other hand, carrying out the reaction in toluene/H_2O and CH_3CN/H_2O (9/1) mixtures in order to facilitate the solubility of NaN_3 produced **3a** in 53% (entry 8) and 60% (entry 9) isolated yields, respectively.

A plausible mechanism (Figure 4) for the formation of **3a** may involve an aza-Michael addition of sodium azide with **2a** to afford the azide-appended intermediate **I**, which may then transform into the triazole intermediate **II**. Next, **II** undergoes aromatization via extrusion of HNO_2 to afford the N−H triazole containing intermediate **III**.[17] The latter species upon tautomerization may give **IV** followed by intramolecular

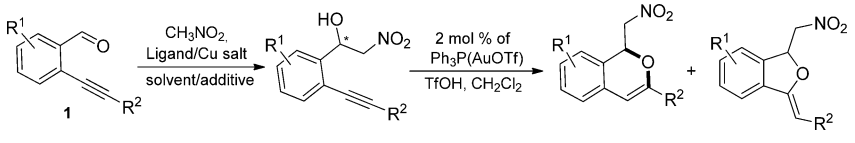


Figure 3. Nonregioselective synthesis of isochromene reported in the literature[15] from **1**.

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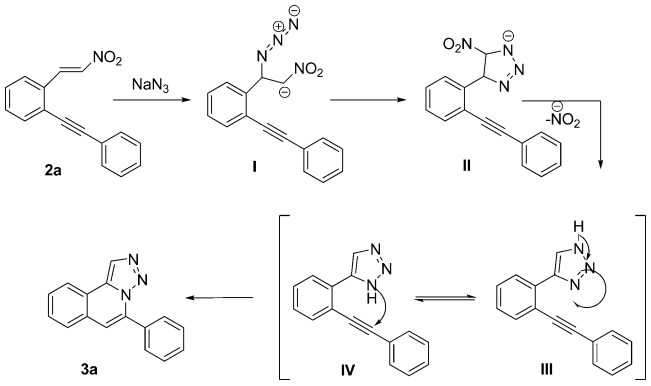


Figure 4. Plausible mechanism for the formation of **3a** from **2a**.

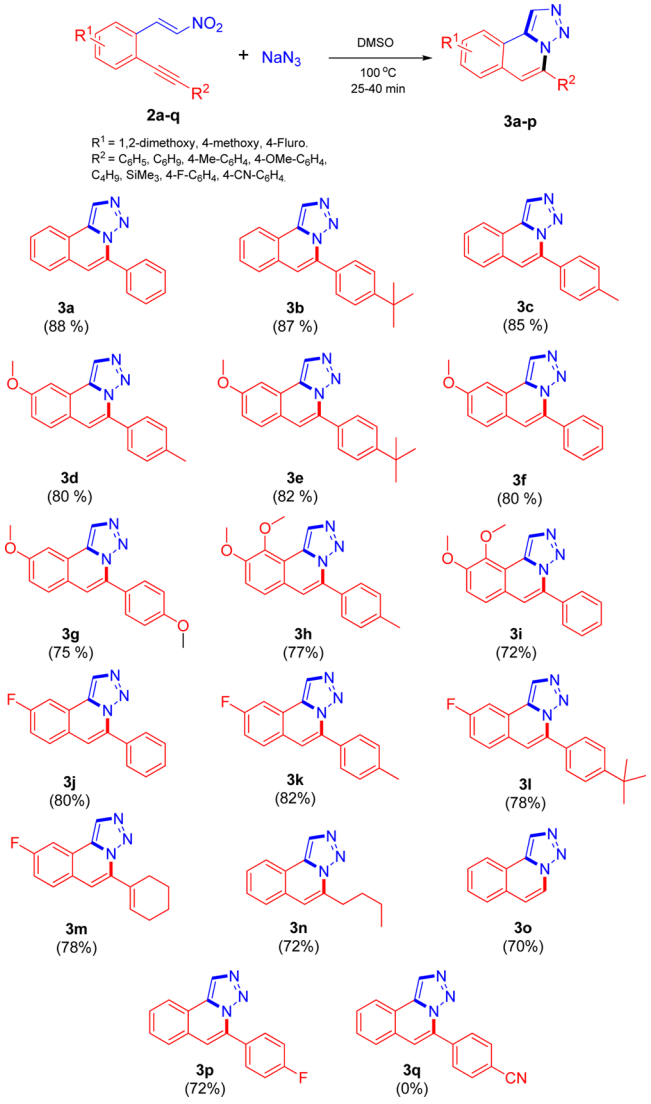
hydroamination via 6-endo-dig cyclization to furnish the final product **3a**. To the best of our knowledge, reports dealing with the formation of intramolecular C−N bond formation on the alkyne via in situ hydroamination under transition-metal-free conditions are scarce.[18]

Once we had the optimized reaction conditions in hand for the synthesis of **3a**, we then embarked on examining the scope and limitation of substrates. R^1 in the aromatic ring of the 2-alkynyl nitro olefin synthon **2** has been substituted with 5-methoxy, 4,5-dimethoxy, and 5-fluoro groups whereas R^2 in the alkyne included aliphatic, aromatic (with electron-donating groups), and trimethylsilyl moieties. It is interesting to note that in all cases products were obtained with minimal variation in isolated yields (Scheme 1; 70−88%). However, replacing R^2 in the alkyne with either an aliphatic moiety or H afforded **3m−o** in slightly reduced the isolated yields (70−78%). Further, it has been observed that when R^2 in the alkyne is replaced by an electron-withdrawing group such as 4-fluoro, formation of the corresponding product **3p** was obtained in 72% isolated yield. In contrast, when R^2 was replaced with a relatively strong electron-withdrawing group such as 4-cyano, formation of the corresponding desired product **3q** was not observed.

Encouraged by the potential of 2-alkynylbenzaldehyde **1** as a synthon to furnish annulated polyheterocycles, we next examined its versatility by converting it into yet another nitro derivative, 2-nitro-1-(2-(phenylethynyl)phenyl)ethanol **6**.[19] We envisioned that the hydroxyl group and the internal alkyne moiety present in **6** can be subjected to electrophilic O-cyclization to afford even more biologically demanding structure isochromenes. Although many groups have synthesized isochromes[7b] and analogous structures under either metal-catalyzed[20,15] or metal-free[7b,21] conditions with various substrates, we followed a alternative approach to obtain the isochromene via electophilic iodo cyclization. Over the past few years, molecular iodine has become a major tool for synthesizing various classes of heterocycles of biological significance via electrophilic cyclization,[22] C−H activation,[23] decarboxylation,[24] and cycloaddition reactions[25] and in multi-component reactions.[12c,26] Moreover, iodo cyclization generally leaves an iodine functionality attached to the product, which can be further modified using palladium-catalyzed coupling reactions.

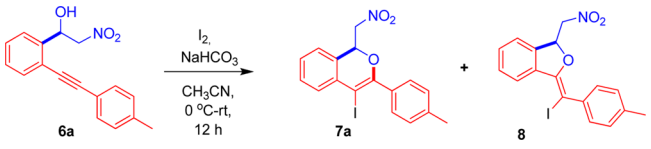
Accordingly, we commenced our reaction by treating 1.0 mmol of **6a** with 3.0 mmol of both I_2 and $NaHCO_3$, and after 12 h of stirring from 0 °C to room temperature, we were delighted to observe a new product in 68% isolated yield (Table 2, entry 1). The resulting product was characterized by various

Scheme 1. Synthesis of Triazolo Isoquinoline Derivatives 3a−p[a]



[a]Reaction conditions: **2a** (1.0 mmol), NaN_3 (1.5 mmol) in 5 mL of DMSO.

Table 2. Optimization of Reaction Conditions for the Synthesis of Isochromene Derivatives[a]



entry	catalyst	base	solvent	yield **7a**/**8a** (%)
1	**I_2**	**$NaHCO_3$**	**CH_3CN**	**68**/n.d.
2	I_2	$NaHCO_3$	DCM	62/n.d.
3	I_2	$NaHCO_3$	THF	58/n.d.
4	I_2	K_2CO_3	CH_3CN	60/n.d.
5	I_2	Na_2CO_3	CH_3CN	62/n.d.
6	ICl	$NaHCO_3$	CH_3CN	*b*

[a]Reaction conditions: **6** (1.0 mmol), I_2 (3.0 mmol), and $NaHCO_3$ (3.0 mmol) in acetonitrile under N_2. [b]Inseparable mixtures. n.d = not detected.

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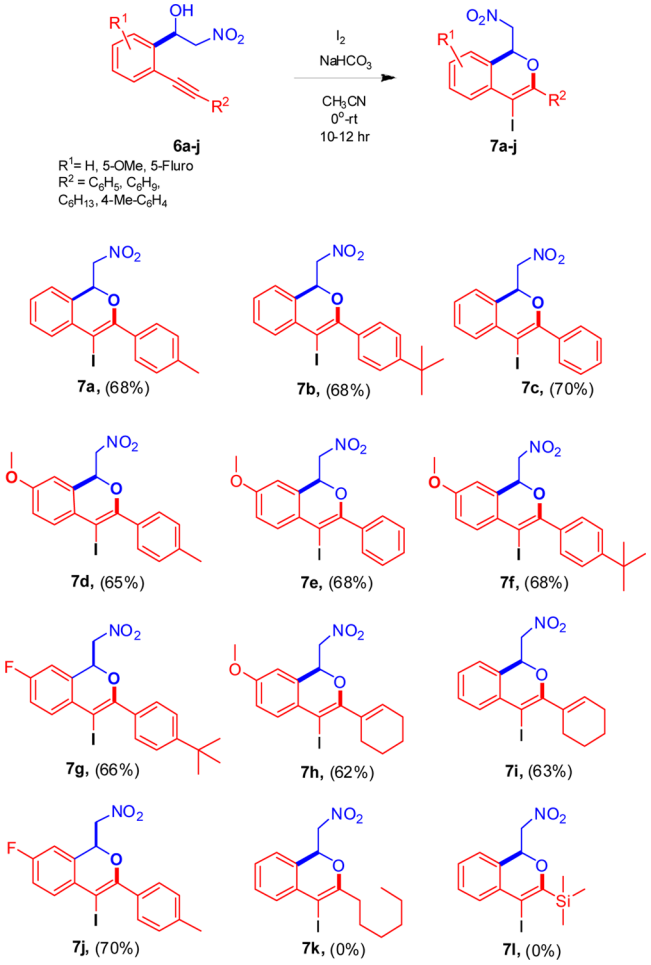
NMR techniques and found to be the regioselective iodo derivative of isochromene **7a**. Next, in an attempt to improve the yield, we screened various solvents such as DCM and THF and bases such as Na_2CO_3 and K_2CO_3. However, none of the changes could improve the yield of the final product (entries 2−5). Next, we changed the iodine source to ICl, which resulted in inseparable mixtures (entry 6). With the optimized conditions in hand, we then investigated the scope of the reaction with respect to substitution on the phenyl rings, and the results have been summarized in Scheme 2. As is evident,

Scheme 2. Synthesis of Isochromene Derivatives via Electrophilic Iodo Cyclization (7a−j)[a]



[a]Reaction conditions: **6a** (1.0 mmol), I_2 (3.0 mmol), $NaHCO_3$ (3.0 mmol) in 5 mL of CH_3CN under N_2.

R^1 in the aromatic ring of the synthon (**6**) has been substituted with 5-methoxy and 5-fluoro groups, whereas R^2 in the alkyne included both aliphatic (1-cyclohexene) and aromatic, furnishing the corresponding products with minimal variation in isolated yield (62−70%). It is noteworthy that the reaction was not fruitful with other aliphatic alkyl moieties such as hex-1-yne and trimethylsilyl. A plausible mechanism for the formation of **6a** may first involve the formation of iodonium complex **V** with the internal alkyne **6a** (Figure 5). This is then followed by the attack of the concomitant nucleophile at the complex to afford **7a**.

In conclusion, we have developed an efficient methodology to construct two biologically important scaffolds, i.e. triazolo

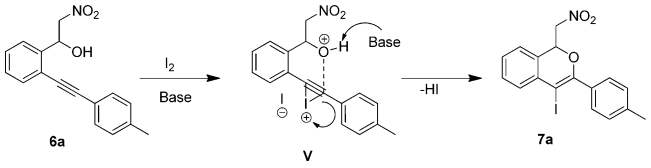


Figure 5. Plausible mechanism for the formation of isochromene from **6a**.

isoquinoline and isochromene derivatives, from the single readily available synthon 2-alkynylbenzaldehyde by a transition-metal-free domino process. Further studies are in progress to expand the potential application of the synthon to the synthesis of other annulated polyheterocycles, and the results will be published elsewhere.

EXPERIMENTAL SECTION

General Information and Methods. All reagents and solvents were purchased from commercial sources and used without purification. NMR spectra were recorded with 300 and 400 MHz spectrometers for ^1H NMR and 75 and 100 MHz for ^{13}C NMR. Chemical shifts δ are given in ppm relative to the residual signals of tetramethylsilane in $CDCl_3$ or deuterated solvent $CDCl_3$/DMSO-d_6 for ^1H and ^{13}C NMR. Multiplicities are reported as follows: singlet (s), doublet (d), doublet of doublets (dd), triplet (t), broad singlet (bs), multiplet (m). High-resolution mass spectra were taken with a mass spectrometer. Column chromatography was performed using silica gel (100−200 mesh) as the stationary phase. All reactions were monitored by thin-layer chromatography (TLC). The purity and characterization of these compounds were further established using HR/ESI mass spectroscopy and UV detection at 220/254 nm. Melting points were measured on a capillary melting point apparatus and are uncorrected.

General Procedure for Synthesis of (*E*)-1-(2-Nitrovinyl)-2-(phenylethynyl) (2a−o). The title compound **2a** was prepared according to the literature procedure.[16] A solution of **1a** (1 g, 4.85 mmol, 1 equiv) and ammonium acetate (373 mg, 5.82 mmol, 1.0 equiv) in dry nitromethane (5.0 mL) was stirred at 110 °C for 1 h. After completion of the reaction as determined by TLC analysis, the reaction mixture was warmed to room temperature followed by addition of 10 mL of water. The aqueous layer was extracted with EtOAc (3 × 20 mL), and the combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (10% EtOAc/90% hexanes) to afford the product **2a** (1.027 g, 85%).

In some cases we noticed formation of *E*/*Z* isomers (**2b**,**e**,**n**); we proceeded with the mixture for final product synthesis.

Compounds **2a**,**c**,**k**,**j**,**p** matched well with the reported data.[13]

*(E)-1-((4-tert-Butylphenyl)ethynyl)-2-(2-nitrovinyl)benzene (**2b**):* yellow solid; R_f = 0.5 (10% ethyl acetate/90% hexanes); yield 258 mg, 74% (isomers formed in 1:0.23 ratio on the basis of NMR analysis; mp 98−100 °C; FT-IR (KBr) 3402, 3021, 2965, 761 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.54 (d, J = 12.0 Hz, 1H), 7.82 (d, J = 16.0 Hz, 1H), 7.67−7.64 (m, 1H), 7.62−7.59 (m, 1H), 7.57−7.52 (m, 2H), 7.47−7.38 (m, 3H + 1H of isomer), 7.36−7.33 (m, 1H), 1.34 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.6, 138.2, 137.2, 133.3, 131.5, 131.2, 128.6, 128.0, 125.7, 125.5, 119.3, 97.4, 86.0, 34.9, 31.2 ppm; HRMS (ESI) calcd for $C_{20}H_{20}NO_2$ [M + H] 306.1494, found 306.1489.

*(E)-4-Methoxy-2-(2-nitrovinyl)-1-(p-tolylethynyl)benzene (**2d**):* yellow solid; R_f = 0.5 (10% ethyl acetate/90% hexanes); yield 228 mg, 78%; mp 75−77 °C; FT-IR (KBr) 3400, 3021, 2929, 2401, 1291 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.48 (d, J = 12.0 Hz, 1H), 7.78 (d, J = 12.0 Hz, 1H), 7.55−7.53 (m, 1H), 7.46−7.44 (m, 2H), 7.20−7.17 (m, 2H), 7.03−6.98 (m, 2H), 3.85 (s, 3H), 2.38 (s, 3H) ppm; ^{13}C NMR (100 MHz,$CDCl_3$) δ 159.5, 139.1, 138.4, 137.3, 134.6, 132.4, 131.4, 129.3, 119.6, 118.0, 112.6, 95.8, 85.9, 55.6, 21.6 ppm; HRMS (ESI) calcd for $C_{18}H_{16}NO_3$ [M + H] 294.1130, found 294.1126.

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*(E)-1-((4-tert-Butylphenyl)ethynyl)-4-methoxy-2-(2-nitrovinyl)-benzene (**2e**):* yellow solid; R_f = 0.40 (10% ethyl acetate/90% hexanes); yield 234 mg, 68% (isomers formed in 1:0.3 ratio on the basis of ^{1}H NMR analysis; mp 98−100 °C; FT-IR (KBr) 3970, 3778, 3401, 670 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.49 (d, J = 16.0 Hz, 1H), 7.79 (d, J = 20.0 Hz, 1H), 7.56−7.49 (m, 4H for both isomers), 7.41−7.39 (m, 2H), 7.04−7.00 (m, 2H), 3.86 (s, 3H), 3.83 (s, 1H of isomer), 1.33 (s, 9H) ppm; ^{13}C NMR (75 MHz,$CDCl_3$) δ 159.5, 152.2, 138.4, 137.3, 134.6, 132.5, 131.3, 125.6, 119.6, 119.2, 118.0, 112.6, 95.8, 85.9, 55.7, 55.6, 34.9, 31.2 ppm; HRMS (ESI) calcd for $C_{21}H_{22}NO_3$ [M + H] 336.1600, found 336.1591.

*(E)-4-Methoxy-2-(2-nitrovinyl)-1-(phenylethynyl)benzene (**2f**):* yellow solid; R_f = 0.50 (10% ethyl acetate/90% hexanes); yield 126 mg, 66%; mp 88−90 °C; FT-IR (KBr) 3776, 3407, 3019, 1293 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (d, J = 15.0 Hz, 1H), 7.78 (d, J = 15.0 Hz, 1H), 7.57−7.55 (m, 3H), 7.39−7.33 (m, 3H), 7.05−7.00 (m, 2H), 3.87 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 138.5, 137.2, 134.7, 132.6, 131.5, 128.8, 128.6, 122.7, 118.0, 117.7, 113.5, 112.6, 95.5, 86.5, 55.6 ppm; HRMS (ESI) calcd for $C_{17}H_{14}NO_3$ [M + H] 280.0974, found 280.0970.

*(E)-4-Methoxy-1-((4-methoxyphenyl)ethynyl)-2-(2-nitrovinyl)-benzene (**2g**):* yellow solid; R_f = 0.45 (10% ethyl acetate/90% hexanes); yield 203 mg 70%; mp 92−94 °C; FT-IR (KBr) 3402, 3021, 2401, 670 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.49 (d, J = 16.0 Hz, 1H), 7.79 (d, J = 20.0 Hz, 1H), 7.55−7.50 (m, 3H), 7.04−6.99 (m, 2H), 6.98−6.89 (m, 2H) 3.86 (s, 3H), 3.84 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 159.4, 138.4, 137.4, 134.5, 133.0, 132.3, 118.2, 118.0, 114.8, 114.3, 112.5, 95.7, 85.4, 55.6, 55.4 ppm; HRMS (ESI) calcd for $C_{18}H_{16}NO_4$ [M + H] 310.1079, found 310.1071.

*(E)-1,2-Dimethoxy-4-(2-nitrovinyl)-5-(p-tolylethynyl)benzene (**2h**):* yellow solid; R_f = 0.45 (10% ethyl acetate/90% hexanes); yield 263 mg, 76%; mp 96−98 °C; FT-IR (KBr) 3772, 3682, 3405, 2400, 1333 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (d, J = 12.0 Hz, 1H), 7.74 (d, J = 12.0 Hz, 1H), 7.50−7.48 (m, 2H), 7.21−7.19 (m, 2H), 7.07−6.98 (m, 2H) 3.97 (s, 3H), 3.95 (s, 3H), 2.39 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 149.6, 139.3, 137.4, 136.3, 131.5, 129.4, 124.4, 120.0, 119.4, 114.8, 109.2, 96.3, 85.9, 56.3, 56.1, 21.6 ppm; HRMS (ESI) calcd for $C_{19}H_{18}NO_4$ [M + H] 324.1236, found 324.1228.

*(E)-1,2-Dimethoxy-4-(2-nitrovinyl)-5-(phenylethynyl)benzene (**2i**):* yellow solid; R_f = 0.42 (10% ethyl acetate/90% hexanes); yield 220 mg, 76%; mp 94−96 °C; FT-IR (KBr) 3403, 3022, 2401, 1629, 759 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (d, J = 15.0 Hz, 1H), 7.72 (d, J = 15.0 Hz, 1H), 7.60−7.59 (m, 2H), 7.40 (m, 3H), 7.08−7.00 (m, 2H), 3.97 (s, 3H), 3.95 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.2, 149.7, 137.3, 136.4, 131.6, 129.0, 128.6, 124.5, 122.4, 119.8, 114.8, 109.0, 96.0, 86.4, 56.3, 56.2 ppm; HRMS (ESI) calcd for $C_{18}H_{16}NO_4$ [M + H] 310.1079, found 310.1068.

*(E)-1-((4-tert-Butylphenyl)ethynyl)-4-fluoro-2-(2-nitrovinyl)-benzene (**2l**):* yellow solid; R_f = 0.48 (10% ethyl acetate/90% hexanes); yield 242 mg, 78%; mp 93−95 °C; FT-IR (KBr) 3404, 3021, 2966, 1215 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48 (d, J = 15.0 Hz, 1H), 7.75 (d, J = 12.0 Hz, 1H), 7.64−7.60 (m, 1H), 7.53−7.50 (m, 2H), 7.43−7.40 (m, 2H), 7.28−7.25 (m, 1H), 7.24−7.14 (m, 1H), 1.34 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7, 160.4, 152.7, 139.1, 136.2, 135.2, 135.0, 133.2 (d, J = 16.5 Hz), 131.4, 125.7 (d, J = 9.0 Hz), 121.8 (d, J = 6.0 Hz), 119.2 (d, J = 22.5 Hz), 119.0, 114.3 (d, J = 46.5 Hz), 97.1, 84.9, 35.0, 31.2 ppm; HRMS (ESI) calcd for $C_{20}H_{19}FNO_2$ [M + H] 324.1400, found 324.1394.

*(E)-1-(Cyclohexenylethynyl)-4-fluoro-2-(2-nitrovinyl)benzene (**2m**):* yellow solid; R_f = 0.55 (10% ethyl acetate/90% hexanes); yield 222 mg, 75%; mp 78−80 °C; FT-IR (KBr) 3740, 2823, 1508, 1201, 638 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (d, J = 15.0 Hz, 1H), 7.56 (d, J = 6.0 Hz, 1H), 7.29−7.25 (m, 1H), 7.20−7.18 (m, 1H), 7.17−7.11 (m, 1H), 6.38−6.30 (m, 1H), 2.33−2.26 (m, 4H), 1.90−1.80 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.4, 160.1, 138.9, 136.7 (d, J = 132.0 Hz), 134.9 (d, J = 16.5 Hz), 132.9 (d, J = 15.0 Hz), 122.1, 120.1, 118.9 (d, J = 43.5 Hz), 114.3 (d, J = 46.5 Hz), 96.9, 83.1, 28.9, 25.9, 22.2, 21.4 ppm; HRMS (ESI) calcd for $C_{16}H_{15}FNO_2$ [M + H] 272.1087, found 272.1082.

*(E)-1-(Hex-1-ynyl)-2-(2-nitrovinyl)benzene (**2n**):* yellow oil; R_f = 0.58 (10% ethyl acetate/90% hexanes); yield 167 mg, 68% (compound formed in 1:0.3 ratio; FT-IR (neat) 3403, 3021, 2964, 2401, 760 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 (d, J = 16.0 Hz, 1H), 7.74 (d, J = 16.0 Hz, 1H), 7.55−7.49 (m, 3H for both isomers), 7.41−7.32 (m, 3H for both isomers), 2.54−2.50 (m, 2H), 1.68−1.50 (m, 4H), 1.00−0.96 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0, 137.5, 133.4, 131.4, 131.2, 128.1, 127.6, 126.3, 98.9, 30.6, 22.1, 19.4, 13.6 ppm; HRMS (ESI) calcd for $C_{14}H_{16}NO_2$ [M + H] 230.1181, found 230.1171.

*(E)-Trimethyl((2-(2-nitrovinyl)phenyl)ethynyl)silane (**2o**):* white solid; R_f = 0.6 (10% ethyl acetate/90% hexanes); yield 157 mg, 65%; mp 68−70 °C; FT-IR (KBr) 3404, 3021, 2401, 1634 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (d, J = 12.0 Hz, 1H), 7.82 (d, J = 12.0 Hz, 1H), 7.58−7.54 (m, 3H), 7.40−7.38 (m, 1H), 0.31 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 137.2, 133.8, 131.4, 129.1, 128.0, 125.0, 103.3, 102.0, −0.17 ppm; HRMS (ESI) calcd for $C_{13}H_{16}NO_2Si$ [M + H] 246.0950, found 246.0947.

*(E)-4-((2-(2-Nitrovinyl)phenyl)ethynyl)benzonitrile (**2q**):* yellow solid; R_f = 0.50 (10% ethyl acetate/90% hexanes); yield 231 mg, 65%; mp 88−90 °C; FT-IR (KBr) 3404, 3021, 2220, 1550 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (d, J = 6.8 Hz, 1H), 7.78 (d, J = 6.0 Hz, 1H), 7.71−7.65 (m, 6H), 7.55−7.46 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 136.8, 133.7, 132.4, 132.3, 131.8, 129.9, 127.8, 124.3, 118.4, 112.6, 94.9, 90.5 ppm; HRMS (ESI) calcd for $C_{17}H_{11}N_2O_2$ [M + H] 275.0821, found 275.0852.

: General Procedure for the Preparation of Intermediates[15] 6a−i. In a stir-bar-equipped flame-dried 50 mL round-bottom flask containing a stirred mixture of 2-alkynylbenzaldehyde **1** (1.00 g, 4.854 mmol), nitromethane (0.592 mL, 9.708 mmol, 2 equiv), and ethanol (10 mL) in an ice−water bath was added a solution of KOH (0.289 g, 5.365 mmol, 1.1 equiv) in anhydrous ethanol (10 mL), dropwise. After it was stirred for 1 h, the reaction mixture was quenched with AcOH (3.0 mL) and water (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to afford an oil. The crude product was taken up in a small amount of CH_2Cl_2 and added to silica gel, and the mixture was evaporated to dryness. The resulting powder was purified by column chromatography with elluent (20% EtOAc/80% hexanes) to give the product.

*1-{2-[2-(4-Methylphenyl)ethynyl]phenyl}-2-nitroethan-1-ol (**6a**):* yellow solid: R_f = 0.35 (1/5 ethyl acetate/hexanes); yield 530 mg, 83%; mp 125−127 °C; FT-IR (KBr) 3778, 3399, 3015, 2402, 1215 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54−7.53 (m, 1H), 7.52−7.44 (m, 1H), 7.42−7.40 (m, 2H) 7.35−7.33 (m, 1H), 7.32−7.31 (m, 1H), 7.19−7.17 (m, 2H), 6.02−6.00 (m, 1H), 4.83−4.80 (m, 1H), 4.55−4.50 (m, 1H), 3.04 (bs, 1H), 2.83 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.5, 139.3, 132.3, 131.6, 129.4, 129.0, 128.5, 128.5, 120.1, 119.3, 96.7, 85.0, 80.4, 69.7, 21.6 ppm; HRMS (ESI) calcd for $C_{17}H_{16}NO_3$ [M + H] 282.1130, found 282.1125.

*1-(2-{2-[4-(tert-Butyl)phenyl]ethynyl}phenyl)-2-nitroethan-1-ol (**6b**):* yellow oil; R_f = 0.35 (1/5 ethyl acetate/hexanes); yield 542 mg, 88%; FT-IR (neat) 3778, 3683, 3403, 3020, 2965, 1216 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65−7.63 (m, 1H), 7.55−7.53 (m, 1H), 7.50−7.48 (m, 2H) 7.41−7.33 (m, 3H), 7.25 (s, 1H), 6.02−6.00 (m, 1H), 4.83−4.80 (m, 1H), 4.55−4.52 (m, 1H), 2.98−2.97 (m, 1H), 1.32 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 139.6, 132.3, 131.4, 129.0, 128.5, 121.0, 119.3, 96.7, 85.0, 80.4, 69.7, 35.0, 31.2 ppm; HRMS (ESI) calcd for $C_{20}H_{22}NO_3$ [M + H] 324.1600, found 324.1597.

*2-Nitro-1-[2-(2-phenylethynyl)phenyl]ethan-1-ol (**6c**):* yellow oil; R_f = 0.41 (1/5 ethyl acetate/hexanes); yield 466 mg, 72%; FT-IR (neat) 3402, 3021, 1555, 1216 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66−7.56 (m, 1H), 7.55−7.54 (m, 3H), 7.43−7.39 (m, 1H), 7.39−7.31 (m, 4H), 6.03−6.00 (m, 1H), 4.88−4.83 (m, 1H), 4.55−4.49 (m, 1H), 2.87 (bs, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.6, 132.3, 131.6, 129.1, 129.0, 128.9, 128.6, 125.7, 122.3, 120.6, 96.4, 85.5, 80.4, 69.6 ppm; HRMS (ESI) calcd for $C_{16}H_{14}NO_3$ [M + H] 268.0974, found 268.0971.

*1-(5-Methoxy-2-((4-methylphenyl)ethynyl)phenyl)-2-nitroethanol (**6d**):* yellow solid; R_f = 0.35 (1/5 ethyl acetate/hexanes); yield 528 mg, 85%; mp 98−100 °C; FT-IR (KBr) 3710, 3548, 3403, 3020, 2965, 1216 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45−7.40 (m, 3H), 7.18−7.14 (m, 3H), 6.85−6.82 (m, 1H), 5.95−5.92 (m, 1H), 4.83−4.80 (m, 1H), 4.51−4.45 (m, 1H), 3.82 (s, 3H), 3.08 (bs, 1H), 2.35 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 141.5, 138.8, 133.7, 131.3, 129.3, 119.6, 114.4, 112.8, 111.2, 95.2, 85.2, 80.3, 69.7, 55.5, 21.6 ppm; HRMS (ESI) calcd for $C_{18}H_{18}NO_4$ [M + H] 312.1236, found 312.1225

*1-[5-Methoxy-2-(2-phenylethynyl)phenyl]-2-nitroethan-1-ol (**6e**):* yellow oil; R_f = 0.38 (1/5 ethyl acetate/hexanes); yield 503 mg, 80%; FT-IR (neat) 3402, 3021, 2965, 1500 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56−7.55 (m, 2H), 7.54−7.40 (m, 1H) 7.39−7.37 (m, 3H), 7.28−7.23 (m, 1H), 6.90−6.88 (m, 1H), 6.02−6.00 (m, 1H), 4.88−4.84 (m, 1H), 4.57−4.51 (m, 1H), 3.88 (s, 3H), 3.06 (bs, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 141.5, 133.8, 131.4, 128.6, 122.7, 114.4, 112.5, 111.2, 95.0, 85.6, 80.3, 69.6, 55.5 ppm; HRMS (ESI) calcd for $C_{17}H_{16}NO_4$ [M + H] 298.1079, found 298.1071.

*1-(2-{2-[4-(tert-Butyl)phenyl]ethynyl}-5-methoxyphenyl)-2-nitroethan-1-ol (**6f**):* colorless oil; R_f = 0.38 (1/5 ethyl acetate/hexanes); yield 471 mg, 78%; FT-IR (neat) 3777, 3403, 3020, 1216 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51−7.46 (m, 3H), 7.45−7.37 (m, 2H) 7.25−7.19 (m, 1H), 6.87−6.84 (m, 1H), 5.98−5.96 (m, 1H), 4.85−4.82 (m, 1H), 4.55−4.48 (m, 1H), 3.85 (s, 3H), 2.98 (bs, 1H), 1.32 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 152.0, 141.3, 139.7, 131.1, 125.5, 119.6, 114.3, 112.7, 111.2, 95.2, 84.9, 80.2, 69.6, 55.5, 34.8, 31.1 ppm; HRMS (ESI) calcd for $C_{21}H_{24}NO_4$ [M + H] 354.1705, found 354.1697.

*1-(2-{2-[4-(tert-Butyl)phenyl]ethynyl}-5-fluorophenyl)-2-nitroethan-1-ol (**6g**):* yellow oil; R_f = 0.40 (1/5 ethyl acetate/hexanes); yield 487 mg, 80%; FT-IR (neat) 3776, 3681, 3401, 1521, 1343 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54−7.53 (m, 1H), 7.52−7.50 (m, 2H), 7.48−7.38 (m, 3H), 7.06−7.01 (m, 1H), 6.00−5.97 (m, 1H), 4.87−4.84 (m, 1H), 4.51−4.45 (m, 1H), 3.01 (bs, 1H), 1.33 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 161.7, 152.5, 142.4 (d, J = 12.0 Hz), 134.2 (d, J = 12.0 Hz), 125.7, 119.2, 116.8, 115.8 (d, J = 33.0 Hz) 113.5 (d, J = 36.0 Hz), 96.4, 84.1, 80.1, 69.3, 35.0, 31.2 ppm; HRMS (ESI) calcd for $C_{20}H_{21}FNO_3$ [M + H] 342.1505, found 342.1526.

*1-[2-(2-Cyclohex-1-en-1-ylethynyl)-5-methoxyphenyl]-2-nitroethan-1-ol (**6h**):* colorless oil; R_f = 0.38 (1/5 ethyl acetate/hexanes); yield 476 mg, 76%; FT-IR (neat) 3776, 3656, 1560, 1047 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36−7.34 (m, 1H), 7.15−7.14 (m, 1H), 6.82−6.79 (m, 1H), 6.22−6.20 (m, 1H), 5.83−5.81 (m, 1H), 4.78−4.73 (m, 1H), 4.50−4.43 (m, 1H), 3.82 (s, 3H), 3.00 (bs, 1H), 2.20−2.14 (m, 4H), 1.70−1.60 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 141.1, 135.7, 133.6, 120.4, 114.3, 113.1, 111.2, 97.0, 83.0, 80.2, 69.6, 55.5, 29.1, 25.9, 22.3, 21.5 ppm; HRMS (ESI) calcd for $C_{17}H_{20}NO_4$ [M + H] 302.1392, found 302.1386.

*1-(2-(2-Cyclohex-1-en-1-ylethynyl)phenyl)-2-nitroethanol (**6i**):* colorless oil; R_f = 0.5 (1/5 ethyl acetate/hexanes); yield 465 mg, 72%; FT-IR (neat) 3763, 3562, 1260, 1043 cm^{-1}; ^1H NMR (3400 MHz, $CDCl_3$) δ 7.53−7.50 (m, 1H), 7.36−7.35 (m, 1H), 7.34−7.28 (m, 1H), 7.23−7.18 (m, 1H), 6.20−6.19 (m, 1H), 5.80−5.78 (m, 1H), 4.68−4.65 (m, 1H), 4.44−4.39 (m, 1H), 2.92 (bs, 1H), 2.15−2.20 (m, 4H), 1.62−1.54 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.3, 136.7, 132.2, 128.6, 125.7, 121.2, 120.3, 98.5, 83.1, 69.7, 29.1, 25.9, 22.3, 21.5 ppm; HRMS (ESI) calcd for $C_{16}H_{17}NO_3$ [M + H] 271.1208, found 271.1213.

*1-(5-Fluoro-2-(4-methylphenylethynyl)phenyl)-2-nitroethanol (**6j**):* yellow solid; R_f = 0.42 (1/5 ethyl acetate/hexanes); yield 500 mg, 80%); m.pt 108−110 °C; FT-IR (KBr) 3770, 3652, 1521, 1343 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45−7.43 (m, 1H), 7.42−7.36 (m, 2H), 7.33−7.30 (m, 2H), 7.10−7.09 (m, 1H), 7.00−6.93 (m, 1H),5.90−5.88 (m, 1H), 4.78−4.74 (m, 1H), 4.43−4.37 (m, 1H), 3.00 (bs, 1H), 2.30 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 161.6, 142.3 (d, J = 14.0 Hz), 139.4, 134.1 (d, J = 16 Hz), 129.4, 119.1, 116.7 (d, J = 6.0 Hz), 115.7 (d, J = 44.0 Hz), 113.4 (d, J = 48.0 Hz), 96.4, 84.1, 80.0, 69.2, 21.6 ppm; HRMS (ESI) calcd for $C_{17}H_{15}FNO_3$: 300.1036 [M + H], found 300.1045.

Typical Procedure for the Preparation of Final Products 3a−p. In a stir-bar-equipped flame-dried 50 mL round-bottom flask containing a stirred mixture of (*E*)-1-(2-nitrovinyl)-2-(phenylethynyl)-benzene (**2a**; 250 mg, 1.0 mmol) in DMSO (5 mL) was added sodium azide (97 mg, 1.5 mmol). After it was stirred for 0.5 h, the reaction mixture was brought to room temperature and diluted with water (10 mL) and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified on a 100−200 mesh column (30/70 EtOAc/hexanes) to give the product.

*5-Phenyl[1,2,3]triazolo[5,1-a]isoquinoline (**3a**):* white solid; R_f = 0.43 (1/5 ethyl acetate/hexanes); yield 216 mg, 88%; mp 166−168 °C; FT-IR (KBr) 3776, 3681, 3408, 2400, 1215 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1H), 8.10−8.08 (m, 1H), 7.91−7.90 (m, 2H), 7.75−7.73 (m, 1H) 7.58−7.56 (m, 2H), 7.55−7.17 (m, 3H), 7.16 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.1, 133.4, 132.2, 129.9, 129.7, 129.4, 129.2, 128.6, 127.5, 126.1, 123.9, 122.3, 115.6 ppm; HRMS (ESI) calcd for $C_{16}H_{12}N_3$ [M + H] 246.1031, found 246.1027.

*5-[4-(tert-Butyl)phenyl][1,2,3]triazolo[5,1-a]isoquinoline (**3b**):* brown solid; R_f = 0.40 (1/5 ethyl acetate/hexanes); yield 214 mg, 87%; mp 170−172 °C; FT-IR (KBr) 3779, 3403, 3016, 2926, 1216 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.53 (s, 1H), 8.20−8.17 (m, 1H), 7.95−7.92 (m, 2H), 7.84−7.81 (m, 1H), 7.68−7.64 (m, 2H), 7.63−7.57 (m, 2H), 7.24 (s, 1H), 1.40 (s, 9H) ppm;^{13}C NMR (75 MHz, $CDCl_3$) δ 153.3, 136.3, 133.5, 129.9, 129.4, 129.2, 128.4, 127.5, 126.2, 126.0, 125.7, 124.0, 122.3, 115.3, 35.0, 31.3 ppm; HRMS (ESI) calcd for $C_{20}H_{20}N_3$ [M + H] 302.1657, found 302.1649.

*5-(4-Methylphenyl)[1,2,3]triazolo[5,1-a]isoquinoline (**3c**):* brown solid; R_f = 0.41 (1/5 ethyl acetate/hexanes); yield 209 mg, 85%; mp 168−170 °C; FT-IR (KBr) 3787, 3681, 3401, 3019, 1481 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 8.04 −8.03 (m, 1H), 8.02−7.69 (m, 2H), 7.69−7.67 (m, 1H), 7.53−7.48 (m, 2H), 7.23−7.16 (m, 2H), 7.09 (s, 1H), 2.36 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.1, 136.1, 129.7, 129.3, 129.1, 128.3, 127.4, 123.8, 122.2, 115.2, 21.5 ppm; HRMS (ESI) calcd for $C_{17}H_{14}N_3$ [M + H] 260.1188, found 260.1182.

*9-Methoxy-5-(4-methylphenyl)[1,2,3]triazolo[5,1-a]isoquinoline (**3d**):* brown solid; R_f = 0.40 (1/5 ethyl acetate/hexanes); yield 197 mg, 80%; mp 166−168 °C; FT-IR (KBr) 3402, 3131, 3009, 2842, 1616 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.87−7.85 (m, 2H), 7.74−7.71 (m, 1H), 7.51 (s, 1H), 7.36−7.34 (m, 2H), 7.25 (s, 1H), 7.17 (s, 1H), 4.00 (s, 3H), 2.45 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.7, 139.8, 129.6, 129.3, 129.3, 129.1, 124.0, 123.7, 119.0, 115.0, 105.2, 55.8, 21.5 ppm; HRMS (ESI) calcd for $C_{18}H_{16}N_3O$ [M + H] 290.1293, found 290.1291.

*5-[4-(tert-Butyl)phenyl]-9-methoxy[1,2,3]triazolo[5,1-a]-isoquinoline (**3e**):* brown solid; R_f = 0.40 (1/5 ethyl acetate/hexanes); yield 202 mg, 82%; mp 172−174 °C; FT-IR (KBr) 3787, 3681, 3404, 2972, 1215 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.91 (d, J = 9.0 Hz, 2H), 7.74 (d, J = 9.0 Hz, 1H), 7.58−7.53 (m, 3H), 7.26 (s, 1H), 7.19 (s, 1H), 4.00 (s, 3H), 1.39 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.6, 152.8, 133.9, 133.1, 129.5, 129.0, 126.0, 125.5, 123.8, 118.9, 115.0, 105.1, 55.7, 34.8, 31.3 ppm; HRMS (ESI) calcd for $C_{21}H_{22}N_3O$ [M+ H] 332.1763, found 332.1764.

*9-Methoxy-5-phenyl[1,2,3]triazolo[5,1-a]isoquinoline (**3f**):* brown solid; R_f = 0.42 (1/5 ethyl acetate/hexanes); yield 197 mg, 80%; mp 176−178 °C; FT-IR (KBr) 3778, 2402, 1308, 670 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.51 (s, 1H), 7.99−7.96 (m, 2H), 7.77−7.45 (m, 1H), 7.53 (s, 4H), 7.26−7.21 (m, 2H), 4.00 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.6, 133.7, 133.0, 132.3, 129.6, 129.3, 129.0, 128.5, 126.0, 123.7, 123.6 118.9, 115.4, 105.0, 55.7 ppm; HRMS (ESI) calcd for $C_{17}H_{14}N_3O$ [M + H] 276.1137, found 276.1130.

*9-Methoxy-5-(4-methoxyphenyl)-[1,2,3]triazolo[5,1-a]-isoquinoline (**3g**):* white solid; R_f = 0.32 (1/5 ethyl acetate/hexanes); yield 185 mg, 75%; mp 184−186 °C; FT-IR (KBr) 3787, 3681, 3405, 2400, 1181 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.93 (d, J = 9.0 Hz, 2H), 7.74 (d, J = 6.0 Hz, 1H), 7.52 (d, J = 3.0 Hz, 1H),

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7.26 (s, 1H), 7.16 (s, 1H), 7.07 (d, J = 9.0 Hz, 2H), 4.00 (s, 3H), 3.90 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.7, 159.6, 130.8, 129.0, 124.8, 124.0, 123.5, 119.0, 114.7, 114.0, 105.2, 55.8, 55.5 ppm; HRMS (ESI) calcd for $C_{18}H_{16}N_3O_2$ [M + H] 306.1243, found 306.1235.

*8,9-Dimethoxy-5-(4-methylphenyl)[1,2,3]triazolo[5,1-a]-isoquinoline (**3h**):* brown solid; R_f = 0.40 (1/5 ethyl acetate/hexanes); yield 190 mg, 77%; mp 178−180 °C; FT-IR (KBr) 3787, 3405, 3019, 1216 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.87 (d, J = 6.0 Hz, 2H), 7.47 (s, 1H), 7.35 (d, J = 6.0 Hz, 2H), 7.16 (d, J = 12.0 Hz, 2H), 4.08 (s, 3H), 4.02 (s, 3H), 2.45 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.8, 150.4, 139.7, 134.5, 133.1, 129.5, 129.2, 129.1, 124.7, 124.6, 116.6, 114.6, 107.6, 104.3, 56.3, 56.1, 21.4 ppm; HRMS (ESI) calcd for $C_{19}H_{18}N_3O_2$ [M+ H] 320.1399, found 320.1394.

*8,9-Dimethoxy-5-phenyl[1,2,3]triazolo[5,1-a]isoquinoline (**3i**):* white solid; R_f = 0.45 (1/5 ethyl acetate/hexanes); yield 197 mg, 72%; mp 180−182 °C; FT-IR (KBr) 3777, 3683, 3614, 3020, 1506, 1216 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$):δ 8.41 (s, 1H), 8.00−7.97 (m, 2H), 7.55−7.48 (m, 4H), 7.20−7.17 (m, 2H), 4.09 (s, 3H), 4.03 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.6 (d, J = 26.2 Hz), 134.2, 132.4, 129.5, 128.5, 124.5, 116.6, 115.0, 107.6, 104.2, 56.3, 56.1 ppm; HRMS (ESI) calcd for $C_{18}H_{16}N_3O_2$ [M + H] 306.1243, found 306.1236.

*9-Fluoro-5-phenyl[1,2,3]triazolo[5,1-a]isoquinoline (**3j**):* brown solid; R_f = 0.44 (1/5 ethyl acetate/hexanes); yield 197 mg, 80%; mp 168−170 °C; FT-IR (KBr) 3776, 3681, 3400, 3019, 2400 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (s, 1H), 7.98−7.96 (m, 2H), 7.86−7.82 (m, 2H), 7.57−7.55 (m, 3H), 7.42−7.36 (m, 1H), 7.24 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.9, 160.5, 132.0, 130.1, 129.9, 129.4, 128.7, 126.4, 118.1 (d, J = 46.5 Hz) 115.0, 109.6 (d, J = 46.5 Hz) ppm; HRMS (ESI) calcd for $C_{16}H_{11}FN_3$ [M + H] 264.0937, found 264.0934.

*9-Fluoro-5-(4-methylphenyl)[1,2,3]triazolo[5,1-a]isoquinoline (**3k**):* brown solid; R_f= 0.40 (1/5 ethyl acetate/hexanes); yield 202 mg, 82%; mp 172−174 °C; FT-IR (KBr) 3776, 3679, 3019, 757 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.88−7.80 (m, 4H), 7.37−7.35 (m, 3H), 7.20 (s, 1H), 2.46 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.8, 160.4, 140.3, 135.7, 130.0, 129.8, 129.4, 129.3, 129.2, 126.5, 123.7 (d, J = 19.5 Hz), 123.6, 118.0 (d, J = 46.5 Hz), 114.5, 109.5 (d, J = 46.5 Hz), 21.5 ppm; HRMS (ESI) calcd for $C_{17}H_{13}FN_3$ [M + H] 278.1094, found 278.1088.

*5-[4-(tert-Butyl)phenyl]-9-fluoro[1,2,3]triazolo[5,1-a]isoquinoline (**3l**):* brown solid; R_f= 0.42 (1/5 ethyl acetate/hexanes); yield 192 mg, 78%; mp 176−178 °C; FT-IR (KBr) 3855, 3787, 3681, 3658, 1417 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.92−7.83 (m, 2H), 7.82−7.80 (m, 2H), 7.58 (d, J = 9.0 Hz, 2H), 7.40−7.35 (m, 1H), 7.22 (s, 1H), 1.39 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7, 160.4, 153.3, 135.7, 135.7, 132.9, 132.8, 130.0, 129.8, 129.1, 126.6, 126.5, 125.7, 123.7 (d, J = 19.5 Hz), 118.2 (d, J = 46.5 Hz), 114.6, 109.5 (d, J = 45 0 Hz), 34.9, 31.3 ppm; HRMS (ESI) calcd for $C_{20}H_{19}FN_3$ [M + H] 320.1563, found 320.1570.

*5-Cyclohex-1-en-1-yl-9-fluoro[1,2,3]triazolo[5,1-a]isoquinoline (**3m**):* brown solid; R_f = 0.38 (1/5 ethyl acetate/hexanes); yield 192 mg, 78%; mp 158−160 °C; FT-IR (KBr) 3775, 3681, 3401, 3019, 1215 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.87−7.73 (m, 2H), 7.38−7.30 (m, 1H), 7.04 (s, 1H), 6.60 (s, 1H), 2.67 (s, 2H), 2.34−2.33 (m, 2H), 1.89−1.79 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.0, 160.0, 137.9 (d, J = 3.0 Hz), 132.7, 131.4, 129.6 (d, J = 18.0 Hz), 126.4, 126.1, 123.4 (d, J = 19.5 Hz), 117.7 (d, J = 45.0 Hz), 112.6, 109.2 (d, J = 46.5 Hz), 27.4, 25.8, 22.5, 21.9 ppm; HRMS (ESI) calcd for $C_{16}H_{15}FN_3$ [M + H] 268.1250, found 268.1253.

*5-Butyl[1,2,3]triazolo[5,1-a]isoquinoline (**3n**):* brown solid; R_f = 0.45 (1/5 ethyl acetate/hexanes); yield 176 mg, 72%; mp 162−164 °C; FT-IR (KBr) 3776, 3680, 3400, 3019, 669 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1H), 8.15−8.13 (m, 1H), 7.77−7.45 (m, 1H), 7.62−7.60 (m, 2H), 7.00 (s, 1H), 3.34−3.30 (s, 2H), 1.97−1.90 (m, 2H), 1.58−1.49 (m, 2H), 1.03−1.01 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2, 132.8, 129.7, 129.0, 127.8, 126.9, 126.1, 123.8, 122.0, 113.0, 30.5, 28.9, 22.5, 13.9 ppm; HRMS (ESI) calcd for $C_{14}H_{16}N_3$ [M+ H] 226.1344, found 226.1338.

*5-Butyl[1,2,3]triazolo[5,1-a]isoquinoline (**3o**):* brown solid; R_f = 0.36 (1/5 ethyl acetate/hexanes); yield 120 mg, 70%; mp 154−156 °C; FT-IR (KBr) 3399, 3020, 2401, 760 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, J = 6.0 Hz, 1H), 8.43 (s, 1H), 8.16 (d, J = 6.0 Hz, 1H), 7.81 (d, J = 6.0 Hz, 1H), 7.70−7.62 (m, 2H), 7.21−7.20 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.5, 129.1, 129.1, 128.9, 127.6, 125.8, 124.0, 123.0, 122.6, 116.1 ppm; HRMS (ESI) calcd for $C_{10}H_8N_3$ [M + H] 170.0718, found 170.0710.

*5-(4-Fluorophenyl)-[1,2,3]triazolo[5,1-a]isoquinoline (**3p**):* brown solid; R_f = 0.36 (1/5 ethyl acetate/hexanes); yield 56 mg, 72%; mp 182−184 °C; FT-IR (KBr) 3818, 3756, 3692, 1417 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.90 (s, 1H), 8.46 (d, J = 0.8 Hz, 1H), 8.44−8.04 (m, 3H), 7.77−7.55 (m, 2H), 7.75−7.66 (m, 1H), 7.48−7.43 (m, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.0, 161.5, 133.9, 132.9, 131.7 (d, J = 4.0, Hz), 129.3 (d, J = 6.5, Hz), 128.5, 128.4, 127.8, 126.6, 124.0, 121.8, 115.8, 115.4 (d, J = 11.0, Hz) ppm; HRMS (ESI) calcd for $C_{16}H_{11}FN_3$ [M + H] 264.0937, found 264.0930.

Typical Procedure for the Preparation of Final Products 7a−i. In a stir-bar-equipped flame-dried 50 mL round-bottom flask was added stirred mixture of 2-nitro-1-(2-(*p*-tolylethynyl)phenyl)ethanol (**6a**; 300 mg, 1.0 mmol), I_2 (809 mg, 3.0 mmol), and $NaHCO_3$ (265 mg, 3.0 mmol) in CH_3CN (5 mL). After completion of the reaction as determined by TLC analysis the reaction mixture was quenched with $Na_2S_2O_3$ solution, diluted with water (10 mL), and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified on a 100−200 mesh column (1/9 EtOAc/hexanes).

*4-Iodo-3-(4-methylphenyl)-1-(nitromethyl)-1H-isochromene (**7a**):* green oil; R_f = 0.42 (1/9 ethyl acetate/hexanes); yield 283 mg, 65%; FT-IR (neat) 3785, 3420, 3120, 2970, 2401, 1216 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55−7.52 (m, 1H), 7.50−7.43 (m, 2H), 7.41−7.39 (m, 1H), 7.31−7.29 (m, 1H), 7.29−7.19 (m, 2H), 7.05−7.03 (m, 1H), 6.09−6.07 (m, 1H), 5.12−5.06 (m, 1H), 4.47−4.43 (m, 1H), 2.38 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.9, 140.4, 133.0, 132.7, 130.5, 130.3, 130.1, 128.8, 128.5, 125.8, 124.0, 76.8, 75.3, 72.0, 21.7 ppm; HRMS (ESI) calcd for $C_{17}H_{15}INO_3$ [M + H] 408.0097, found 408.0120.

*3-[4-(tert-Butyl)phenyl]-4-iodo-1-(nitromethyl)-1H-isochromene (**7b**):* green oil; R_f = 0.50 (1/9 ethyl acetate/hexanes); yield 283 mg, 68%; FT-IR (neat) 3775, 3404, 3019, 2967, 1215 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56−7.55 (m, 3H), 7.54−7.33 (m, 3H), 7.31−7.28 (m, 1H), 7.07−7.05 (m, 1H), 6.11−6.08 (m, 1H),5.14−5.08 (m, 1H) 4.49−4.45 (m, 1H), 1.34 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.3, 152.6, 132.7, 132.6, 130.2, 130.0, 128.4, 125.8, 124.9, 123.8, 76.6, 75.2, 34.9, 31.3 ppm; HRMS (ESI) calcd for $C_{20}H_{21}INO_3$ [M + H] 450.0566, found 450.0557.

*4-Iodo-1-(nitromethyl)-3-phenyl-1H-isochromene (**7c**):* green oil; R_f = 0.50 (1/9 ethyl acetate/hexanes); yield 308 mg, 70% (compound formed in 1:018 ratio **7c**:**8c**); FT-IR (neat) 3404, 3022, 2402, 1604, 921 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60−7.58 (m, 2H), 7.57−7.41 (m, 1H), 7.33−7.31 (m, 1H), 7.29−7.25 (m, 3H), 7.18−7.14 (m, 1H), 7.07−7.05 (m, 1H), 6.14−6.01 (m, 1H), 5.14−5.08 (m, 1H) 4.48−4.45 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.7, 135.8, 132.4, 130.5, 130.2, 130.1, 128.6, 128.0, 125.7, 123.9, 76.7, 75.2, 72.5 ppm; HRMS (ESI) calcd for $C_{16}H_{13}INO_3$ [M +H] 393.9940, found 393.9938.

*4-Iodo-7-methoxy-3-(4-methylphenyl)-1-(nitromethyl)-1H-isochromene (**7d**):* green oil; R_f = 0.40 (1/9 ethyl acetate/hexanes); yield 265 mg, 63%; FT-IR (neat) 3772, 3540, 3200, 2840, 2401, 1216 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52−7.48 (m, 3H), 7.28−7.22 (m, 2H), 6.97−6.94 (m, 1H), 6.66−6.65 (m, 1H), 6.07−6.03 (m, 1H), 5.14−5.08 (m, 1H), 4.50−4.46 (m, 1H), 3.87 (s, 3H), 2.38 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 150.5, 140.0, 132.9, 131.8, 130.4, 128.7, 127.0, 125.5, 114.7, 109.7, 75.2, 71.7, 55.7, 21.6 ppm; HRMS (ESI) calcd for $C_{18}H_{17}INO_4$ [M + H] 438.0202, found 438.0192.

*4-Iodo-7-methoxy-1-(nitromethyl)-3-phenyl-1H-isochromene (**7e**):* green oil; R_f = 0.50 (1/9 ethyl acetate/hexanes); yield 267 mg, 68%; FT-IR (neat) 3785, 3680, 3402, 3019, 2959, 1215 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60−7.58 (m, 2H), 7.57−7.50 (m, 1H),

7.47−7.39 (m, 3H), 6.95−6.93 (m, 1H), 6.63 (s, 1H), 6.05−6.02 (m, 1H), 5.12−5.07 (m, 1H), 4.48−4.45 (m, 1H), 3.84 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.0, 150.5, 135.9, 131.8, 130.5, 129.8, 128.0, 127.0, 125.3, 114.8, 109.7, 75.2, 72.2, 55.7 ppm; HRMS (ESI) calcd for $C_{17}H_{15}INO_4$ [M + H] 424.0046, found 424.0034.

*3-[4-(tert-Butyl)phenyl]-4-iodo-7-methoxy-1-(nitromethyl)-1H-isochromene (**7f**):* green oil; R_f = 0.50 (1/9 ethyl acetate/hexanes); yield 276 mg, 68%; FT-IR (neat) 3776, 3681, 3401, 3019, 1215 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54−7.53 (m, 2H), 7.48−7.46 (m, 1H), 7.41−7.40 (m, 2H), 6.93−6.91 (m, 1H), 6.62 (s, 1H), 6.03−6.00 (m, 1H), 5.10−5.04 (m, 1H) 4.46−4.43 (m, 1H), 3.83 (s, 3H), 1.33 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 153.0, 132.7, 131.8, 130.1, 127.0, 125.4, 124.7, 114.7, 109.6, 76.5, 75.1, 71.5, 55.6, 34.8, 31.2 ppm; HRMS (ESI) calcd for $C_{21}H_{23}INO_4$ [M + H] 480.0672, found 480.0691.

*3-[4-(tert-Butyl)phenyl]-7-fluoro-4-iodo-1-(nitromethyl)-1H-isochromene (**7g**):* green oil; R_f = 0.50 (1/9 ethyl acetate/hexanes); yield 271 mg, 66%; FT-IR (neat) 3787, 3681, 3403, 3019, 1215 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55−7.52 (m, 3H), 7.43−7.40 (m, 2H), 7.14−7.08 (m, 1H), 6.85−6.82 (m, 1H), 6.06−6.02 (m, 1H), 5.13−5.05 (m, 1H), 4.50−4.45 (m, 1H), 1.33 (s, 9H) ppm; ^{13}C NMR (100 MHz,$CDCl_3$) δ 163.7, 161.2, 153.5, 152.1, 132.4, 129.8 (d, J = 154.0 Hz), 127.3 (d, J = 26.0 Hz), 125.0, 116.7 (d, J = 44.0 Hz), 111.0 (d, J = 48.0 Hz), 76.2, 74.7, 70.5, 35.0, 31.3 ppm; HRMS (ESI) calcd for $C_{20}H_{20}FINO_3$ [M + H] 468.0472, found 468.0454.

*3-Cyclohex-1-en-1-yl-4-iodo-7-methoxy-1-(nitromethyl)-1H-isochromene (**7h**):* green oil; R_f = 0.50 (1/9 ethyl acetate/hexanes); yield 263 mg, 62%; FT-IR (neat) 3778, 3399, 2967, 760 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.36 (m, 1H), 6.90−6.86 (m, 1H), 6.57 (s, 1H), 6.04 (s, 1H), 5.91−5.88 (m, 1H), 4.96−4.90 (m, 1H), 4.36−4.31 (m, 1H), 3.83 (s, 3H), 2.26−2.06 (m, 4H), 1.7−1.60 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 152.9, 134.3, 134.2, 131.5, 126.9, 125.2, 114.5, 109.7, 76.3, 74.5, 70.7, 55.6, 26.3, 25.2, 22.4, 21.7 ppm; HRMS (ESI) calcd for $C_{17}H_{19}INO_4$ [M + H] 428.0359, found 428.0345.

*3-Cyclohex-1-en-1-yl-4-iodo-1-(nitromethyl)-1H-isochromene (**7i**):* green oil; R_f = 0.60 (1/9 ethyl acetate/hexanes); yield 276 mg, 63%; FT-IR (neat); 3390, 2956, 760 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−7.44 (m, 1H), 7.37−7.36 (m, 1H), 7.24−7.23 (m, 1H), 7.00−7.98 (m, 1H), 6.07−6.06 (m, 1H), 5.97−5.95 (m, 1H), 4.97−4.92 (m, 1H), 4.36−4.32 (m, 1H), 2.18−2.15 (m, 4H), 1.7−1.60 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 134.5, 134.2, 132.3, 129.9, 129.8, 125.0, 123.9, 76.4, 74.5, 71.0, 26.3, 25.2, 22.4, 21.6 ppm; HRMS (ESI) calcd for $C_{16}H_{17}INO_3$ [M + H] 398.0253, found 398.0255.

*7-Fluoro-4-iodo-1-(nitromethyl)-3−4-methylphenyl-1H-isochromene (**7j**):* green oil; R_f = 0.53 (1/9 ethyl acetate/hexanes); yield 297 mg, 70%; FT-IR (neat) 3785, 3665, 3403, 1215 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54−7.53 (m, 1H), 7.49−7.47 (m, 2H), 7.22−7.20 (m, 2H), 7.13−7.09 (m, 1H), 6.84−6.82 (m, 1H), 6.05−6.02 (m, 1H), 5.11−5.06 (m, 1H), 4.50−4.45 (m, 1H), 2.39 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 161.2, 152.3, 140.4, 132.4 (d, J = 60.0 Hz), 130.4, 128.9 (d, J = 40.0 Hz), 127.2 (d, J = 14.0 Hz), 116.7 (d, J = 44.0 Hz), 111.0 (d, J = 58.0 Hz), 110.9, 76.3, 74.7, 70.6, 21.6 ppm; HRMS (ESI) calcd for $C_{17}H_{14}FINO_3$ [M + H] 426.0002, found 426.0016.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Figures giving NMR spectra. 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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