

Article

Passerini–Smiles Pathways to Spirooxindoles: Isatin-Based Scaffolds in Anticancer Drug Design

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Abstract

The underexplored Passerini–Smiles reaction (PSR), a variant of the 3-component Passerini reaction (3CPR), was successfully employed to create a tailored library of phenoxy-indoline carboxamide derivatives based on a fragment-based hybrid drug design strategy. Under mild conditions, inexpensive and commercially available isatin was utilized as a privileged carbonyl core, combined with electron-deficient phenols to establish a highly functionalized framework. Post-Passerini–Smiles transformations leveraged this strategic layout to provide a step-economical route to a complementary library of three-dimensional spirooxindole hybrids derived from the PS adducts. This study reinforces the relevance of combining structural hybridization with multicomponent reaction strategies in the discovery of potential anticancer active pharmaceutical ingredients (APIs). Both libraries were evaluated against six human solid-tumor cell lines, including non-small cell lung carcinoma, cervical and colon adenocarcinoma, and breast and pancreatic cancers. The most active compound **4gaa** exhibited GI_{50} values below 10 μ M for most of the tested cancer cell lines.

Keywords: Passerini–Smiles; cancer; isatin; drug design; spirooxindole; GI_{50}

1. Introduction

The development of new medicines is a costly, lengthy, and complex process. In its early phase, the drug design process begins with the identification and synthesis of new molecules capable of interacting with a specific biological target to produce a therapeutic effect. The demands of the modern world, both in terms of health and socio-economic factors, are prompting the scientific community to work on the basis of sustainability and innovation in all areas of knowledge. Medicinal chemistry, and particularly the synthesis of new active pharmaceutical ingredients (APIs), is no exception. Detailed analysis of the literature over recent decades demonstrated that multicomponent reactions (MCRs) are indeed a powerful tool to access complex libraries of new bioactive molecules in a straightforward and fashion way and are imperative for structure-activity studies in drug design and development pipelines [1,2]. Our group has been actively working over the past decade on the use of MCRs to synthesize novel oxindole hybrid scaffolds with potential as new drug candidates for complex diseases, such as central nervous system (CNS) disorders and cancer. Special focus has been placed on the Petasis [3,4], Ugi [5,6], and Passerini [7] reactions, which have yielded encouraging results, particularly regarding antiproliferative activities in human cancer cell lines (Figure 1) [8].



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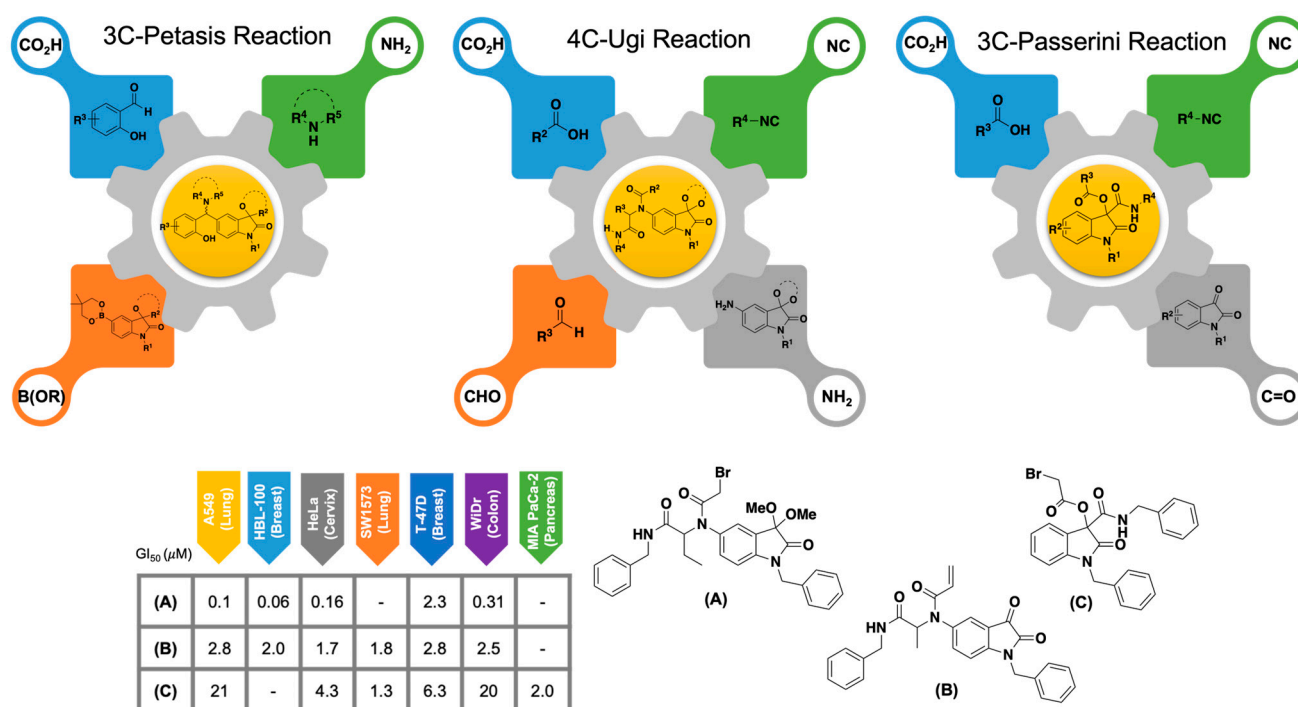
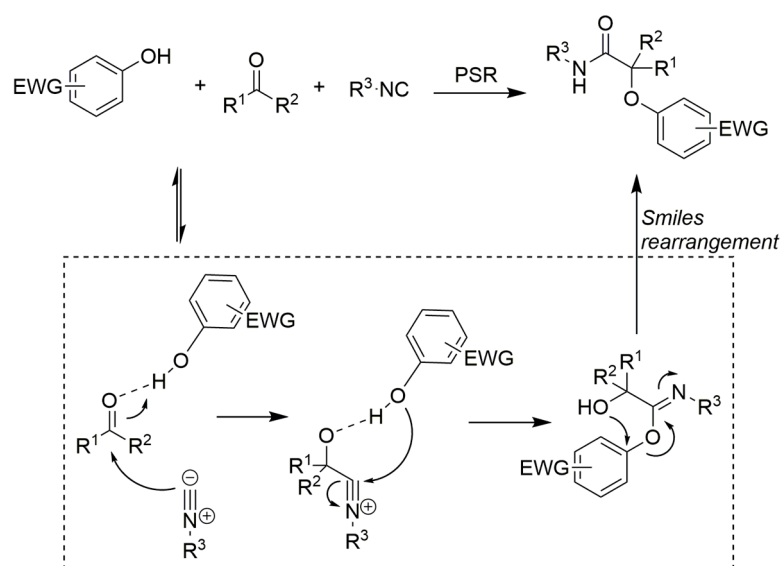


Figure 1. Application of MCRs to generate diverse libraries of oxindole hybrid compounds with promising antiproliferative activity (GI_{50}) against human cancer cell lines.

Cancer remains a major global health concern and will continue to pose significant challenges in the near future. Due to the disease's complex nature and the persistent issue of drug resistance, the search for new and effective therapeutic molecules remains an urgent and ongoing need [9]. Very recently we established a mild and straightforward process to easily access a fine-tuned library of α -acyloxyamide-oxindole hybrids using the 3-component Passnerini reaction (3CPR), and after antiproliferative assays on six human solid-tumor cell lines (lung, cervical, colon, breast and pancreas) we find out GI_{50} values in the range of 1.3–21 μ M for the most potent compound (Figure 1, (C)) [7].

In an effort to enhance the potency of α -acyloxyamide-oxindole hybrids, we decided to make slight modifications to the scaffold and explore the poorly reported Passnerini–Smiles reaction (PSR) [10] using a fragment-based hybrid design strategy. The choice of substrates was guided by two distinct medicinal chemistry rationales. First, isatin was selected as the central carbonyl source due to its status as a privileged core in oncology, capable of providing rigid setups that mimic natural bioactive compounds. Second, the introduction of electron-deficient phenols as carboxylic acid surrogates was envisioned not only to access highly functionalized O-aryl carboxamide adducts, but also to strategically place an electrophilic aryl ring ideal for subsequent transformations. This architectural layout was specifically designed to trigger a post-condensation intramolecular cyclization, leading to complementary libraries of spirooxindole hybrids. Thus, the PSR is a variant of the 3CPR where acidic phenols (electron-deficient) were used instead of carboxylic acids, giving access to O-aryl carboxamide adducts through a subsequent irreversible Smiles rearrangement (Scheme 1) [11]. Spirooxindoles possess a rigid, three-dimensional spatial orientation that improves metabolic stability and target selectivity in solid-tumor models. This approach therefore bridges fragment-based drug design with step-economical multicomponent chemistry.

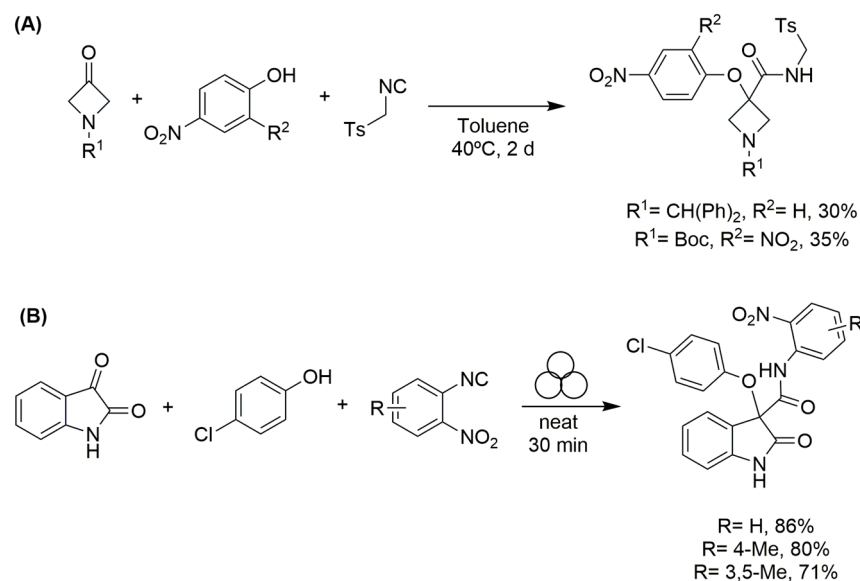


Scheme 1. The PSR and the postulated mechanism.

El Kaim's group reported pioneering studies regarding this reaction approach, having established as optimal conditions the use of methanol as solvent and 40 °C as reaction temperature [12,13]. Despite great reaction scope and moderate to high yields (26–80%) using several heteroaromatic phenols, aldehydes and isocyanides, the reaction was still very slow (up to 3 days). To solve this problem, the same group, several years later, developed new experimental conditions where the use of a tertiary nucleophilic amine like 1,4-diazabicyclo[2.2.2]octane (DABCO) as an additive, together with solvent-free conditions, significantly reduced the reaction time to 12 h [14,15].

Parallel work conducted by Dai and Li proposed the activation of the aldehyde component using a Lewis base catalyst, such as diisopropylethylamine (DIPEA), in acetonitrile as the solvent [16]. Although the exact role of DIPEA in the reaction mechanism remains unclear, these conditions have proven to be compatible with a wide range of aldehydes, including α,β -unsaturated derivatives. Using the same reaction conditions, the group of Luesse [17] extended the reaction scope to furfuraldehyde-derived compounds, in a tandem process involving the PSR, and Krishna and co-workers [18] developed a diastereoselective version of the PSR using chiral aldehydes.

Although the number of studies on the PSR is relatively limited, the use of ketones as carbonyl components is even less common. This is largely due to their reduced electrophilicity and greater steric hindrance compared to aldehydes. Very recently, the group of Soós [19] reported an interesting methodology that incorporates four-membered heterocycles into highly functionalized scaffolds using 3-oxoazetidine derivatives in Passerini and Ugi MCRs. The process extension toward PSR afforded only two examples of the desired adducts in poor yields (Scheme 2A). Krause's group [20] investigated the 3CPR under mechanochemical conditions, successfully synthesizing a range of α -acyloxycarboxamide derivatives in high to excellent yields within just 15 min of milling. This environmentally friendly method was also applied using 4-chlorophenol as the acid surrogate and isatin as the carbonyl component, yielding three examples of the corresponding PS adducts in good yields (Scheme 2B). Biju and co-workers, while investigating the 3CPR on isatin scaffolds, also reported preliminary results concerning the PSR on the same substrates. However, only three products were obtained, each in moderate yields [21]. To the best of our knowledge, these were the only reported examples in the literature of isatin being used in the PSR.



Scheme 2. The PSR using ketones as carbonyl component. (A) Access to four-membered heterocycle adducts using 3-oxoazetidine derivatives; (B) Access to α -acyloxycarboxamide derivatives using isatin.

Despite the synthetic potential of the PSR, the use of isatin derivatives as carbonyl components remains underexplored, and a systematic evaluation of their scope and limitations is still lacking. To address this limitation, we report a detailed investigation of a ZnF_2 -catalyzed PSR involving isatin derivatives, electron-deficient phenols, and isocyanides. This MCR approach provides direct access to structurally diverse phenoxy-indoline carboxamides under mild reaction conditions, expanding the application of the PSR to oxindole-based scaffolds relevant to API synthesis [22,23].

2. Materials and Methods

2.1. General Information

All reagents were obtained from Sigma-Aldrich (St. Louis, MO, USA), Acros Organics (Geel, Belgium), BLDPharm (Shanghai, China) and TCI (Zwijndrecht, Belgium) and were used as received. Solvents were used as received. Reactions were conducted in round-bottom flasks, glass vials with plastic caps, or in a Radley's® 12-position carousel reactor (Carousel 12 Plus™ Reaction Station, Radleys, Saffron Walden, UK). Column chromatography was carried out on silica gel (Carlo Erba, 40–63 μm , 60 Å, CARLO ERBA Reagents, Cornaredo, Italy). Thin-layer chromatography (TLC) was carried out on aluminum-backed Kieselgel 60 F254 plates (Merck, Darmstadt, Germany) and Macherey–Nagel, (Düren, Germany). Plates were visualized either by UV light or with phosphomolybdic acid in ethanol. Melting points (m.p.) were determined with a Barnstead Electrothermal 9100 apparatus (Barnstead International, Dubuque, IA, USA) and are uncorrected. NMR spectra were recorded with a Bruker Avance III instrument (400 MHz, Bruker BioSpin GmbH, Rheinstetten, Germany). Chemical shifts (δ) are given in parts per million (ppm) with respect to the solvent (CDCl_3 , ^1H : $\delta = 7.26$ ppm, ^{13}C : $\delta = 77.2$ ppm). Coupling constants (J) are reported in Hz and refer to apparent peak multiplicities. Splitting patterns are reported as s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet), br (broad), dd (double of doublets), dt (double of triplets), dq (double of quadruplets). Mass spectra (MS) were recorded with a quadrupole mass spectrometer Waters ZQ4000 (Chemistry Department, University of Salamanca, Waters Corporation, Milford, MA, USA). The ionization was performed by ESI, and the samples were infused in methanol.

Isatin derivatives **1d** and **1e** were commercially available and used as received. The other isatin derivatives were synthesized using our previously reported procedures [7].

2.2. General Procedure for the Synthesis of Phenoxy-Indoline Carboxamide Derivatives **4** Using the PSR

In a round-bottom flask, or glass vial with plastic cap or glass reactor tube with a magnetic stirrer, the corresponding isatin derivative **1a–k** (0.6 mmol), the phenol derivative **2a–f** (0.6 mmol), the isocyanide **3a–e** (1.8 mmol), ZnF₂ (0.06 mmol, 10 mol%), and CH₂Cl₂ (2 mL) were added. The reaction mixture was left stirred at room temperature for 48 h. The solvent was evaporated under reduced pressure, and the crude reaction mixture was purified in a short chromatographic glass column with SiO₂ flash using CH₂Cl₂ and AcOEt mixtures as the eluents.

N-Cyclohexyl-3-(2,4-dinitrophenoxy)-1-methyl-2-oxoindoline-3-carboxamide (**4aaa**): **1a** (105.9 mg, 0.66 mmol), **2a** (114 mg, 0.6 mmol, 1 equivalent), **3a** (230 µL, 1.8 mmol, 3 equivalents), ZnF₂ (6.4 mg, 0.06 mmol, 10 mol%), and CH₂Cl₂ (2 mL) were used to obtain the corresponding **4aaa** as a pale yellow foam type solid (276.7 mg, 93% yield), m.p. = 136.2–137.5 °C. ¹H NMR (CDCl₃, 400 MHz) δ: 1.35–1.40 (m, 4H, CH₂), 1.60–1.68 (m, 2H, CH₂), 1.76–1.78 (m, 2H, CH₂), 1.95–1.99 (m, 2H, CH₂), 3.35 (s, 3H, CH₃), 3.76–3.78 (m, 1H, CH), 6.54 (d, *J* = 8 Hz, 1H, Ar), 7.01 (d, *J* = 8 Hz, 1H, Ar), 7.08 (t, *J* = 8 Hz, 1H, Ar), 7.22 (d, *J* = 4 Hz, 1H, Ar), 7.45 (t, *J* = 8 Hz, 1H, Ar), 7.59–7.61 (s br, 1H, NH), 8.15–8.18 (m, 1H, Ar), 8.90 (s, 1H, Ar). ¹³C APT NMR (CDCl₃, 100 MHz) δ: 24.66, 24.68, 27.23, 32.57, 32.73, 49.14, 85.53, 109.95, 118.29, 122.99, 123.36, 124.06, 124.29, 129.70, 132.28, 139.67, 141.83, 144.72, 152.98, 163.44, 169.71. HRMS (ESI) *m/z*: calculated for C₂₂H₂₂O₇N₄Na [M] + Na 477.13807, found 477.1375.

N-Cyclohexyl-3-(2,4-dinitrophenoxy)-1,5-dimethyl-2-oxoindoline-3-carboxamide (**4baa**): **1b** (108.6 mg, 0.60 mmol), **2a** (114 mg, 0.6 mmol, 1 equivalent), **3a** (230 µL, 1.8 mmol, 3 equivalents), ZnF₂ (6.4 mg, 0.06 mmol, 10 mol%), and CH₂Cl₂ (2 mL) were used to obtain the corresponding **4baa** as a pale yellow foam type solid (134.1 mg, 48% yield), m.p. = 150.6–151.0 °C. ¹H NMR (CDCl₃, 400 MHz) δ: 1.25–1.41 (m, 5H, CH₂), 1.61–1.64 (m, 1H, CH₂), 1.79 (s br, 2H, CH₂), 1.97–2.00 (m, 2H, CH₂), 2.27 (s, 3H, CH₃), 3.33 (s, 3H, CH₃), 3.77–3.79 (m, 1H, CH), 6.53 (d, *J* = 8 Hz, 1H, Ar), 6.90 (d, *J* = 8 Hz, 1H, Ar), 7.03 (s, 1H, Ar), 7.24 (s br, 1H, NH), 7.60 (d, *J* = 8 Hz, 1H, Ar), 8.17–8.20 (m, 1H, Ar), 8.92 (s, 1H, Ar). HRMS (ESI) *m/z*: calculated for C₂₃H₂₄O₇N₄Na [M] + Na 491.15372, found 491.1525.

5-Bromo-N-cyclohexyl-3-(2,4-dinitrophenoxy)-1-methyl-2-oxoindoline-3-carboxamide (**4caa**): **1c** (142 mg, 0.59 mmol), **2a** (114 mg, 0.6 mmol, 1 equivalent), **3a** (230 µL, 1.8 mmol, 3 equivalents), ZnF₂ (6.4 mg, 0.06 mmol, 10 mol%), and CH₂Cl₂ (2 mL) were used to obtain the corresponding **4caa** as a pale yellow foam type solid (243.9 mg, 78% yield), m.p. = 179.3–180.6 °C. ¹H NMR (CDCl₃, 400 MHz) δ: 1.26–1.43 (m, 5H, CH₂), 1.62–1.65 (m, 1H, CH₂), 1.78–1.80 (m, 2H, CH₂), 1.98–2.00 (m, 2H, CH₂), 3.33 (s, 3H, CH₃), 3.76–3.78 (m, 1H, CH), 6.52 (d, *J* = 8 Hz, 1H, Ar), 6.89–6.91 (d, *J* = 8 Hz, 1H, Ar), 7.37 (d, 1H, Ar), 7.55–7.60 (m, 2H, Ar + NH), 8.21 (dd, *J* = 4 Hz, 1H, Ar), 8.92 (d, *J* = 4 Hz, 1H, Ar). ¹³C APT NMR (CDCl₃, 100 MHz) δ: 24.65, 24.69, 25.46, 27.36, 32.57, 32.70, 49.35, 85.00, 111.38, 116.97, 117.89, 123.21, 125.39, 127.25, 129.86, 135.11, 139.61, 142.03, 143.68, 152.71, 162.80, 169.04. HRMS (ESI) *m/z*: calculated for C₂₂H₂₁O₇N₄BrNa [M] + Na 555.04858, found 555.0479.

N-Cyclohexyl-3-(2,4-dinitrophenoxy)-2-oxoindoline-3-carboxamide (**4daa**): **1d** (96.7 mg, 0.66 mmol), **2a** (114 mg, 0.66 mmol, 1 equivalent), **3a** (230 µL, 1.8 mmol, 3 equivalents), ZnF₂ (6.4 mg, 0.06 mmol, 10 mol%), and CH₂Cl₂ (2 mL) were used to obtain the corresponding **4daa** as a white foam type solid (81.7 mg, 29% yield), m.p. = 197.8–199.0 °C. ¹H NMR (CDCl₃, 400 MHz) δ: 1.40–1.47 (m, 5H, CH₂), 1.67 (m, 1H, CH₂), 1.81–1.84 (m, 2H, CH₂), 1.99–2.07 (m, 2H, CH₂), 3.84–3.86 (m, 1H, CH), 6.75–6.78 (m, 1H, Ar), 6.87 (d, *J* = 8 Hz, 1H, Ar), 7.02 (t, *J* = 8 Hz, 1H, Ar), 7.17 (d, *J* = 8 Hz, 1H, Ar), 7.28–7.33 (m, 1H, Ar), 7.74 (d, 1H, Ar).

NH), 8.17–8.20 (m, 1H, Ar), 8.91 (d, $J = 4$ Hz, 1H, Ar), 9.20 (s br, 1H, NH). ^{13}C APT NMR (CDCl_3 , 100 MHz) δ : 24.72, 25.51, 32.61, 32.76, 49.35, 85.58, 112.32, 118.59, 123.03, 123.25, 124.05, 124.10, 129.95, 132.33, 139.57, 141.96, 142.30, 152.80, 164.48, 170.79. HRMS (ESI) m/z : calculated for $\text{C}_{21}\text{H}_{20}\text{O}_7\text{N}_4\text{Na}$ [M] + Na 463.12242, found 463.1217.

N-Cyclohexyl-3-(2,4-dinitrophenoxy)-5-methyl-2-oxoindoline-3-carboxamide (**4eaa**): **1e** (97.2 mg, 0.60 mmol), **2a** (114 mg, 0.6 mmol, 1 equivalent), **3a** (230 μL , 1.8 mmol, 3 equivalents), ZnF_2 (6.4 mg, 0.06 mmol, 10 mol%), and CH_2Cl_2 (2 mL) were used to obtain the corresponding **4eaa** as a pale yellow foam type solid (134.1 mg, 50% yield), m.p. = 184.2–185.8 $^\circ\text{C}$. ^1H NMR (CDCl_3 , 400 MHz) δ : 1.26–1.44 (m, 5H, CH_2), 1.64–1.68 (m, 1H, CH_2), 1.81–1.83 (m, 2H, CH_2), 2.00–2.08 (m, 2H, CH_2), 2.24 (s, 3H, CH_3), 3.83–3.85 (m, 1H, CH), 6.77 (t, $J = 8$ Hz, 2H, Ar), 6.96 (s, 1H, Ar), 7.11 (d, $J = 8$ Hz, 1H, Ar), 7.73 (d br, 1H, NH), 8.17 (dd, $J = 4$ Hz, 1H, Ar), 8.91 (d, $J = 4$ Hz, 1H, Ar), 9.21 (s br, 1H, NH). ^{13}C APT NMR (CDCl_3 , 100 MHz) δ : 21.17, 24.74, 25.55, 32.67, 32.78, 49.37, 85.77, 112.10, 118.59, 122.98, 123.33, 124.57, 129.99, 132.77, 134.00, 139.58, 139.81, 141.95, 152.55, 164.55, 170.86. HRMS (ESI) m/z : calculated for $\text{C}_{22}\text{H}_{22}\text{O}_7\text{N}_4\text{Na}$ [M] + Na 477.13807, found 477.1372.

1-((1-Benzyl-1H-1,2,3-triazol-4-yl)methyl)-N-cyclohexyl-3-(2,4-dinitrophenoxy)-2-oxoindoline-3-carboxamide (**4faa**): **1f** (146.1 mg, 0.46 mmol), **2a** (114 mg, 0.6 mmol, 1 equivalent), **3a** (230 μL , 1.8 mmol, 3 equivalents), ZnF_2 (6.4 mg, 0.06 mmol, 10 mol%), and CH_2Cl_2 (2 mL) were used to obtain the corresponding **4faa** as a white solid (51.5 mg, 18% yield), m.p. = 121.5–123.0 $^\circ\text{C}$. ^1H NMR (CDCl_3 , 400 MHz) δ : 1.31–1.42 (m, 5H, CH_2), 1.59–1.65 (m, 1H, CH_2), 1.79 (m, 2H, CH_2), 1.96–1.99 (m, 2H, CH_2), 3.78 (m, 1H, CH), 5.04 (d, $J = 16$ Hz, 1H, CH_2), 5.16 (d, $J = 16$ Hz, 1H, CH_2), 5.45–5.53 (m, 2H, CH_2), 6.74 (d, $J = 12$ Hz, 1H, Ar), 7.03–7.09 (m, 2H, Ar), 7.19–7.24 (m, 3H, Ar), 7.32–7.39 (m, 4H, Ar), 7.61–7.63 (m, 2H, Ar + NH), 8.04 (dd, $J = 4$ Hz, 1H, Ar), 8.86 (d, $J = 4$ Hz, 1H, Ar). ^{13}C APT NMR (CDCl_3 , 100 MHz) δ : 24.72, 25.56, 32.61, 32.79, 36.34, 49.19, 54.48, 85.28, 111.17, 119.26, 122.68, 122.78, 123.29, 123.91, 124.35, 128.16, 128.99, 129.29, 129.83, 132.21, 134.43, 139.46, 141.93, 142.11, 143.71, 152.68, 163.72, 169.82. HRMS (ESI) m/z : calculated for $\text{C}_{31}\text{H}_{29}\text{O}_7\text{N}_7\text{Na}$ [M] + Na 634.20207, found 634.2007.

1-Benzyl-N-cyclohexyl-3-(2,4-dinitrophenoxy)-2-oxoindoline-3-carboxamide (**4gaa**): **1g** (142.7 mg, 0.60 mmol), **2a** (114 mg, 0.6 mmol, 1 equivalent), **3a** (230 μL , 1.8 mmol, 3 equivalents), ZnF_2 (6.4 mg, 0.06 mmol, 10 mol%), and CH_2Cl_2 (2 mL) were used to obtain the corresponding **4gaa** as a pale yellow solid (213.0 mg, 67% yield), m.p. = 188.9–190.0 $^\circ\text{C}$. ^1H NMR (CDCl_3 , 400 MHz) δ : 1.33–1.44 (m, 5H, CH_2), 1.62–1.65 (m, 1H, CH_2), 1.78–1.81 (m, 2H, CH_2), 1.97–2.03 (m, 2H, CH_2), 3.82–3.84 (m, 1H, CH), 4.96–5.06 (q, $J = 16$ Hz, 2H, CH_2), 6.32–6.34 (d, $J = 8$ Hz, 1H, Ar), 6.96–6.98 (d, $J = 8$ Hz, 1H, Ar), 7.03–7.07 (t, $J = 8$ Hz, 1H, Ar), 7.22–7.24 (d, $J = 8$ Hz, 1H, Ar), 7.34–7.40 (m, 4H, Ar), 7.43–7.45 (m, 2H, Ar), 7.62–7.64 (d br, 1H, NH), 7.83–7.85 (d, $J = 8$ Hz, 1H, Ar), 8.89–8.90 (d, $J = 4$ Hz, 1H, Ar). ^{13}C APT NMR (CDCl_3 , 100 MHz) δ : 24.71, 25.53, 32.65, 32.86, 44.83, 49.11, 85.50, 110.98, 118.61, 122.99, 123.58, 124.20, 124.30, 128.22, 128.52, 129.21, 129.53, 132.14, 134.59, 139.61, 141.80, 143.88, 152.87, 163.52, 169.78. HRMS (ESI) m/z : calculated for $\text{C}_{28}\text{H}_{26}\text{O}_7\text{N}_4\text{Na}$ [M] + Na 553.16937, found 553.1685.

5-Bromo-N-cyclohexyl-3-(2,4-dinitrophenoxy)-1-(3-methoxybenzyl)-2-oxoindoline-3-carboxamide (**4haa**): **1h** (212.4 mg, 0.61 mmol), **2a** (114 mg, 0.6 mmol, 1 equivalent), **3a** (230 μL , 1.8 mmol, 3 equivalents), ZnF_2 (6.4 mg, 0.06 mmol, 10 mol%), and CH_2Cl_2 (2 mL) were used to obtain the corresponding **4haa** as a pale yellow solid (226.1 mg, 65% yield), m.p. = 211.7–213.2 $^\circ\text{C}$. ^1H NMR (CDCl_3 , 400 MHz) δ : 1.32–1.43 (m, 5H, CH_2), 1.62–1.65 (m, 1H, CH_2), 1.79–1.80 (m, 2H, CH_2), 1.97–2.04 (m, 2H, CH_2), 3.73 (s, 3H, OCH_3), 3.81–3.83 (m, 1H, CH), 4.96 (d, $J = 16$ Hz, 1H, CH_2), 5.20–5.25 (m, 1H, CH_2), 6.66 (d, $J = 8$ Hz, 1H, Ar), 6.74 (dd, $J = 4$ Hz, 1H, Ar), 6.86 (d, $J = 8$ Hz, 1H, Ar), 7.01 (d, 1H, Ar), 7.08 (t, $J = 8$ Hz, 1H, Ar), 7.28 (s, 1H, Ar), 7.36 (t, $J = 8$ Hz, 1H, Ar), 7.49 (d, $J = 12$ Hz, 1H, Ar), 7.62 (d br,

1H, NH), 8.21 (dd, $J = 4$ Hz, 1H, Ar), 8.93 (d, 1H, Ar). ^{13}C APT NMR (CDCl_3 , 100 MHz) δ : 24.70, 24.73, 25.59, 32.66, 32.85, 44.65, 49.18, 55.91, 85.95, 110.99, 112.82, 114.14, 115.61, 118.83, 123.05, 123.68, 124.08, 124.52, 129.95, 132.32, 133.70, 134.45, 139.88, 142.12, 143.67, 153.00, 159.86, 163.50, 170.08. HRMS (ESI) m/z : calculated for $\text{C}_{29}\text{H}_{27}\text{O}_8\text{N}_4\text{BrNa}$ [M] + Na 661.09045, found 661.0897.

N-Cyclohexyl-3-(2,4-dinitrophenoxy)-2-oxo-1-(prop-2-yn-1-yl)indoline-3-carboxamide (**4iaa**): **1i** (123.9 mg, 0.67 mmol), **2a** (114 mg, 0.6 mmol, 1 equivalent), **3a** (230 μL , 1.8 mmol, 3 equivalents), ZnF_2 (6.4 mg, 0.06 mmol, 10 mol%), and CH_2Cl_2 (2 mL) were used to obtain the corresponding **4iaa** as a white solid (154.4 mg, 48% yield), m.p. = 177.8–179.0 $^\circ\text{C}$. ^1H NMR (CDCl_3 , 400 MHz) δ : 1.30–1.41 (m, 5H, CH_2), 1.62–1.65 (m, 2H, CH_2), 1.78–1.80 (m, 2H, CH_2), 1.96–2.02 (m, 2H, CH_2), 2.38–2.39 (m, 1H, CH), 3.79–3.81 (m, 1H, CH), 4.29–4.34 (m, 1H, CH_2), 4.94–4.99 (m, 1H, CH_2), 6.59 (d, $J = 8$ Hz, 1H, Ar), 7.12 (t, $J = 8$ Hz, 1H, Ar), 7.17 (d, $J = 8$ Hz, 1H, Ar), 7.26 (d, $J = 8$ Hz, 1H, Ar), 7.48 (t, $J = 8$ Hz, 1H, Ar), 7.60 (d br, 1H, NH), 8.11 (d, $J = 8$ Hz, 1H, Ar), 8.91 (d, $J = 4$ Hz, 1H, Ar). ^{13}C APT NMR (CDCl_3 , 100 MHz) δ : 24.70, 25.53, 30.17, 32.61, 32.79, 49.16, 73.25, 75.89, 85.13, 111.12, 118.74, 123.04, 123.42, 124.22, 124.74, 129.65, 132.27, 139.65, 141.92, 142.87, 152.78, 163.27, 169.17. HRMS (ESI) m/z : calculated for $\text{C}_{24}\text{H}_{22}\text{O}_7\text{N}_4\text{Na}$ [M] + Na 501.13807, found 501.1372.

(E)-1-(But-2-en-1-yl)-N-cyclohexyl-3-(2,4-dinitrophenoxy)-2-oxoindoline-3-carboxamide (**4jaa**): **1j** (123.0 mg, 0.61 mmol), **2a** (114 mg, 0.6 mmol, 1 equivalent), **3a** (230 μL , 1.8 mmol, 3 equivalents), ZnF_2 (6.4 mg, 0.06 mmol, 10 mol%), and CH_2Cl_2 (2 mL) were used to obtain the corresponding **4jaa** as a white solid (113.7 mg, 38% yield), m.p. = 108.3–109.8 $^\circ\text{C}$. ^1H NMR (CDCl_3 , 400 MHz) δ : 1.33–1.38 (m, 5H, CH_2), 1.61–1.64 (m, 1H, CH_2), 1.73–1.79 (m, 5H, CH_3 + CH_2), 1.96–2.02 (m, 2H, CH_2), 3.78–3.80 (m, 1H, CH), 4.31–4.44 (m, 2H, CH_2), 5.48–5.55 (m, 1H, CH_2), 5.88–5.94 (m, 1H, CH_2), 6.57 (d, $J = 8$ Hz, 1H, Ar), 7.00 (d, $J = 8$ Hz, 1H, Ar), 7.06 (t, $J = 8$ Hz, 1H, Ar), 7.22 (d, $J = 8$ Hz, 1H, Ar), 7.39–7.44 (m, 1H, Ar), 7.59 (d br, 1H, NH), 8.13 (dd, $J = 4$ Hz, 1H, Ar), 8.91 (d, $J = 4$ Hz, 1H, Ar). ^{13}C NMR (CDCl_3 , 100 MHz) δ : 18.01, 24.72, 25.53, 32.62, 32.84, 42.63, 49.12, 85.54, 110.86, 118.59, 122.65, 123.02, 123.51, 124.09, 124.12, 129.50, 131.33, 132.14, 139.69, 141.84, 144.12, 153.03, 163.52, 169.40. HRMS (ESI) m/z : calculated for $\text{C}_{25}\text{H}_{26}\text{O}_7\text{N}_4\text{Na}$ [M] + Na 517.16937, found 517.1688.

1-Allyl-N-cyclohexyl-3-(2,4-dinitrophenoxy)-2-oxoindoline-3-carboxamide (**4kaa**): **1k** (99.3 mg, 0.53 mmol), **2a** (114 mg, 0.6 mmol, 1 equivalent), **3a** (230 μL , 1.8 mmol, 3 equivalents), ZnF_2 (6.4 mg, 0.06 mmol, 10 mol%), and CH_2Cl_2 (2 mL) were used to obtain the corresponding **4kaa** as a pale yellow foam type solid (197.3 mg, 77% yield), m.p. = 129.2–131.0 $^\circ\text{C}$. ^1H NMR (CDCl_3 , 400 MHz) δ : 1.33–1.42 (m, 5H, CH_2), 1.61–1.64 (m, 1H, CH_2), 1.77–1.79 (m, 2H, CH_2), 1.95–2.02 (m, 2H, CH_2), 3.78–3.80 (m, 1H, CH), 4.35 (dd, $J = 8$ Hz, 1H, CH_2), 4.52–4.57 (m, 1H, CH_2), 5.33 (d, $J = 12$ Hz, 1H, CH_2), 5.49 (d, $J = 16$ Hz, 1H, CH_2), 5.83–5.93 (m, 1H, CH), 6.59 (d, $J = 8$ Hz, 1H, Ar), 6.99 (d, $J = 8$ Hz, 1H, Ar), 7.07 (t, $J = 8$ Hz, 1H, Ar), 7.23 (d, $J = 8$ Hz, 1H, Ar), 7.42 (t, $J = 8$ Hz, 1H, Ar), 7.60 (d br, 1H, NH), 8.17 (dd, $J = 4$ Hz, 1H, Ar), 8.91 (d, $J = 4$ Hz, 1H, Ar). ^{13}C APT NMR (CDCl_3 , 100 MHz) δ : 24.72, 25.52, 32.62, 32.82, 43.08, 49.16, 85.56, 110.81, 118.48, 119.32, 123.06, 123.44, 124.06, 124.24, 129.61, 129.68, 132.17, 139.67, 141.87, 143.94, 152.99, 163.51, 169.53. HRMS (ESI) m/z : calculated for $\text{C}_{24}\text{H}_{24}\text{O}_7\text{N}_4\text{Na}$ [M] + Na 503.15372, found 503.1530.

N-(tert-Butyl)-3-(2,4-dinitrophenoxy)-1-methyl-2-oxoindoline-3-carboxamide (**4aab**): **1a** (98.4 mg, 0.61 mmol), **2a** (114 mg, 0.6 mmol, 1 equivalent) **3b** (210 μL , 1.8 mmol, 3 equivalents), ZnF_2 (6.4 mg, 0.06 mmol, 10 mol%), and CH_2Cl_2 (2 mL) were used to obtain the corresponding **4aab** as a pale yellow solid (204.5 mg, 79% yield), m.p. = 171.2–173.0 $^\circ\text{C}$. ^1H NMR (CDCl_3 , 400 MHz) δ : 1.44 (s, 9H, CH_3), 3.35 (s, 3H, CH_3), 6.50–6.53 (m, 1H, Ar), 7.01 (d, $J = 8$ Hz, 1H, Ar), 7.09 (t, $J = 8$ Hz, 1H, Ar), 7.23 (d, $J = 8$ Hz, 1H, Ar), 7.45 (t, $J = 8$ Hz, 1H, Ar), 7.60 (s br, 1H, NH), 8.17 (dd, $J = 4$ Hz, 1H, Ar), 8.90 (s, 1H, Ar). ^{13}C APT NMR (CDCl_3 , 100 MHz) δ : 27.22, 28.59, 52.52, 85.59, 109.95, 118.17, 123.01, 123.49, 123.93, 124.33,

129.71, 132.26, 139.61, 141.79, 144.77, 152.96, 163.41, 169.86. HRMS (ESI) m/z : calculated for $C_{20}H_{20}O_7N_4Na$ [M] + Na 451.12242, found 451.1218.

Ethyl (3-(2,4-dinitrophenoxy)-1-methyl-2-oxoindoline-3-carbonyl)glycinate (**4aac**): **1a** (103.1 mg, 0.64 mmol), **2a** (114 mg, 0.6 mmol, 1 equivalent), **3c** (200 μ L, 1.8 mmol, 3 equivalents), ZnF_2 (6.4 mg, 0.06 mmol, 10 mol%), and CH_2Cl_2 (2 mL) were used to obtain the corresponding **4aac** as a pale yellow foam type solid (105.0 mg, 36% yield), m.p. = 82.6–83.0 °C. 1H NMR ($CDCl_3$, 400 MHz) δ : 1.29–1.32 (m, 3H, CH_3), 3.36 (s, 3H, CH_3), 4.04 (dd, J = 4 Hz, 1H, CH_2), 4.24–4.30 (m, 3H, CH_2), 6.62–6.64 (m, 1H, Ar), 7.01 (d, J = 8 Hz, 1H, Ar), 7.11 (t, J = 8 Hz, 1H, Ar), 7.32–7.34 (d, J = 8 Hz, 1H, Ar), 7.45–7.49 (t, J = 8 Hz, 1H, Ar), 8.06–8.09 (m br, 1H, NH), 8.20 (dd, J = 4 Hz, 1H, Ar), 8.90 (s, 1H, Ar). ^{13}C NMR ($CDCl_3$, 100 MHz) δ : 14.28, 27.31, 41.94, 61.95, 85.57, 109.99, 118.57, 122.95, 123.02, 124.49, 124.66, 129.58, 132.54, 140.03, 142.09, 144.68, 152.82, 164.98, 168.73, 169.39. HRMS (ESI) m/z : calculated for $C_{20}H_{18}O_9N_4Na$ [M] + Na 481.0966, found 481.0960.

N-Benzyl-3-(2,4-dinitrophenoxy)-1-methyl-2-oxoindoline-3-carboxamide (**4aad**): **1a** (112.3 mg, 0.70 mmol), **2a** (114 mg, 0.6 mmol, 1 equivalent), **3d** (230 μ L, 1.8 mmol, 3 equivalents), ZnF_2 (6.4 mg, 0.06 mmol, 10 mol%), and CH_2Cl_2 (2 mL) were used to obtain the corresponding **4aad** as a pale yellow foam type solid (72.8 mg, 23% yield), m.p. = 80.6–81.7 °C. 1H NMR ($CDCl_3$, 400 MHz) δ : 3.34 (s, 3H, CH_3), 4.50–4.61 (m, 2H, CH_2), 6.58–6.61 (m, 1H, Ar), 7.01 (d, J = 8 Hz, 1H, Ar), 7.09 (t, J = 8 Hz, 1H, Ar), 7.24–7.31 (m, 2H, Ar), 7.33–7.36 (m, 4H, Ar), 7.46 (t, J = 8 Hz, 1H, Ar), 8.00 (t br, 1H, NH), 8.13 (dd, J = 4 Hz, 1H, Ar), 8.83 (d, J = 4 Hz, 1H, Ar). ^{13}C APT NMR ($CDCl_3$, 100 MHz) δ : 27.20, 44.03, 85.64, 109.99, 118.48, 122.83, 123.14, 124.29, 124.31, 127.22, 127.78, 128.88, 129.59, 132.38, 137.16, 139.75, 141.90, 144.66, 152.80, 164.50, 169.54. HRMS (ESI) m/z : calculated for $C_{23}H_{18}O_7N_4Na$ [M] + Na 485.10677, found 485.1063.

Ethyl 4-(3-(2,4-dinitrophenoxy)-1-methyl-2-oxoindoline-3-carboxamido)benzoate (**4aae**): **1a** (99.0 mg, 0.61 mmol), **2a** (114 mg, 0.6 mmol, 1 equivalent), **3e** (326 mg, 1.8 mmol, 3 equivalents), ZnF_2 (6.4 mg, 0.06 mmol, 10 mol%), and CH_2Cl_2 (2 mL) were used to obtain the corresponding **4aae** as a pale orange solid (24.7 mg, 8% yield), m.p. = 162.3–163.9 °C. 1H NMR ($CDCl_3$, 400 MHz) δ : 1.40 (t, J = 8 Hz, 3H, CH_3), 3.39 (s, 3H, CH_3), 4.37 (q, J = 8 Hz, 2H, CH_2), 6.55–6.58 (m, 1H, Ar), 7.07 (d, J = 8 Hz, 1H, Ar), 7.14 (t, J = 8 Hz, 1H, Ar), 7.34 (d, J = 8 Hz, 1H, Ar), 7.52 (t, J = 8 Hz, 1H, Ar), 7.81 (d, 2H, Ar), 8.05 (d, 2H, Ar), 8.22 (dd, J = 4 Hz, 1H, Ar), 8.99 (m, 1H, Ar), 9.80 (s br, 1H, NH). ^{13}C APT NMR ($CDCl_3$, 100 MHz) δ : 14.46, 27.39, 61.11, 85.89, 110.24, 118.26, 119.28, 122.87, 123.55, 124.58, 124.64, 127.14, 130.07, 130.98, 132.81, 139.56, 141.02, 142.18, 144.73, 152.74, 162.64, 166.09, 169.06. HRMS (ESI) m/z : calculated for $C_{25}H_{20}O_9N_4Na$ [M] + Na 543.11225, found 543.1118.

3-(2-Bromo-6-nitrophenoxy)-N-cyclohexyl-1-methyl-2-oxoindoline-3-carboxamide (**4aba**): **1a** (99.1 mg, 0.61 mmol), **2b** (135 mg, 0.6 mmol, 1 equivalent), **3a** (230 μ L, 1.8 mmol, 3 equivalents), ZnF_2 (6.4 mg, 0.06 mmol, 10 mol%), and CH_2Cl_2 (2 mL) were used to obtain the corresponding **4aba** as a pale yellow solid (14.4 mg, 5% yield), m.p. = 130.9–132.0 °C. 1H NMR ($CDCl_3$, 400 MHz) δ : 1.21–1.41 (m, 5H, CH_2), 1.64 (m, 1H, CH_2), 1.71–1.79 (m, 2H, CH_2), 1.99–2.07 (m, 2H, CH_2), 3.20 (s, 3H, CH_3), 3.78–3.85 (m, 1H, CH), 6.79 (d, J = 8 Hz, 1H, Ar), 6.83 (t, J = 8 Hz, 1H, Ar), 6.95 (d, J = 8 Hz, 1H, Ar), 7.07 (t, J = 8 Hz, 1H, Ar), 7.24 (s br, 1H, NH), 7.29 (dt, J = 8 Hz, 1H, Ar), 7.58 (dd, J = 8 Hz, 1H, Ar), 7.66 (dd, J = 8 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$, 100 MHz) δ : 24.92, 25.00, 25.64, 26.88, 32.74, 32.80, 49.34, 86.10, 109.22, 121.39, 121.88, 122.95, 124.05, 124.17, 126.49, 126.57, 126.95, 131.86, 131.74, 137.60, 137.70, 145.97, 146.07, 146.60, 164.08, 171.38. HRMS (ESI) m/z : calculated for $C_{22}H_{22}O_5N_3BrNa$ [M] + Na 510.0635, found 510.0633.

N-Cyclohexyl-1-methyl-3-(2-nitrophenoxy)-2-oxoindoline-3-carboxamide [21] (**4aca**): **1a** (107.0 mg, 0.66 mmol), **2c** (86 mg, 0.6 mmol, 1 equivalent), **3a** (230 μ L, 1.8 mmol, 3 equivalents), ZnF_2 (6.4 mg, 0.06 mmol, 10 mol%), and CH_2Cl_2 (2 mL) were used to obtain

the corresponding **4aca** as a pale yellow solid (6.0 mg, 2% yield), m.p. = 122.4–123.8 °C. ^1H NMR (CDCl_3 , 400 MHz) δ : 1.35–1.42 (m, 5H, CH_2), 1.63 (s br, 1H, CH_2), 1.77–1.79 (m, 2H, CH_2), 1.95–2.02 (m, 2H, CH_2), 3.32 (s, 3H, CH_3), 3.74–3.81 (m, 1H, CH), 6.47 (d, J = 8 Hz, 1H, Ar), 6.92 (d, J = 8 Hz, 1H, Ar), 7.00–7.08 (m, 2H, Ar), 7.20 (d, J = 8 Hz, 1H, Ar), 7.25–7.29 (m, 1H, Ar), 7.38 (dt, J = 8 Hz, 1H, Ar), 7.79 (d br, 1H, NH), 7.97–8.00 (m, 1H, Ar). ^{13}C APT NMR (CDCl_3 , 100 MHz) δ : 24.76, 25.59, 27.07, 32.64, 32.79, 48.95, 85.09, 109.49, 118.53, 123.30, 123.89, 124.08, 124.37, 126.85, 131.61, 135.03, 140.78, 144.94, 148.61, 164.54, 171.03. HRMS (ESI) m/z : calculated for $\text{C}_{22}\text{H}_{23}\text{O}_5\text{N}_3\text{Na}$ [M] + Na 432.15299, found 432.1525.

N-Cyclohexyl-3-(2-fluoro-4-nitrophenoxy)-1-methyl-2-oxoindoline-3-carboxamide (**4ada**): **1a** (99.0 mg, 0.60 mmol), **2d** (94 mg, 0.6 mmol, 1 equivalent) **3a** (230 μL , 1.8 mmol, 3 equivalents), ZnF_2 (6.4 mg, 0.06 mmol, 10 mol%), and CH_2Cl_2 (2 mL) were used to obtain the corresponding **4ada** as a white solid (151.3 mg, 59% yield), m.p. = 150.4–151.8 °C. ^1H NMR (CDCl_3 , 400 MHz) δ : 1.32–1.41 (m, 5H, CH_2), 1.60–1.65 (m, 1H, CH_2), 1.74–1.77 (m, 2H, CH_2), 1.94–2.00 (m, 2H, CH_2), 3.28 (s, 3H, CH_3), 3.79–3.86 (m, 1H, CH), 6.64–6.69 (m, 1H, Ar), 6.90 (d, J = 8 Hz, 1H, Ar), 7.03–7.07 (m, 2H, Ar + NH), 7.25 (d, J = 8 Hz, 1H, Ar), 7.38 (dt, J = 8 Hz, 1H, Ar), 7.76–7.79 (m, 1H, Ar), 7.94 (dd, J = 8 Hz, 1H, Ar). ^{13}C APT NMR (CDCl_3 , 100 MHz) δ : 24.64, 24.67, 25.55, 27.03, 32.64, 32.83, 48.86, 85.28, 109.54, 112.82 (d, $^2J_{\text{C-F}}$ = 23 Hz), 119.34, 120.43, 120.47, 123.79, 123.88, 124.54, 131.93, 143.45, 144.89, 147.96 (d, $^2J_{\text{C-F}}$ = 11 Hz), 153.25 (d, $^1J_{\text{C-F}}$ = 251 Hz), 163.98, 170.57. HRMS (ESI) m/z : calculated for $\text{C}_{22}\text{H}_{22}\text{O}_5\text{N}_3\text{FNa}$ [M] + Na 450.14357, found 450.1429.

5-Bromo-N-(tert-butyl)-1-methyl-3-(2-nitrophenoxy)-2-oxoindoline-3-carboxamide [**21**] (**4ccb**): **1c** (129.6 mg, 0.54 mmol), **2c** (86 mg, 0.6 mmol, 1 equivalent), **3b** (210 μL , 1.8 mmol, 3 equivalents), ZnF_2 (6.4 mg, 0.06 mmol, 10 mol%), and CH_2Cl_2 (2 mL) were used to obtain the corresponding **4ccb** as a pale orange solid (19.2 mg, 8% yield), m.p. = 137.2–138.0 °C. ^1H NMR (CDCl_3 , 400 MHz) δ : 1.45 (s, 9H, CH_3), 3.29 (s, 3H, CH_3), 6.38 (d, J = 8 Hz, 1H, Ar), 6.82 (d, J = 8 Hz, 1H, Ar), 7.10 (t, J = 8 Hz, 1H, Ar), 7.30 (t, J = 8 Hz, 1H, Ar), 7.34 (s, 1H, Ar), 7.52 (t, J = 8 Hz, 1H, Ar), 7.77 (s br, 1H, NH), 8.02 (d, J = 8 Hz, 1H, Ar). ^{13}C APT NMR (CDCl_3 , 100 MHz) δ : 27.16, 28.62, 52.42, 84.66, 110.93, 116.59, 117.84, 123.49, 126.60, 127.08, 127.10, 134.44, 135.16, 143.96, 148.33, 163.88, 170.40. HRMS (ESI) m/z : calculated for $\text{C}_{20}\text{H}_{20}\text{O}_5\text{N}_3\text{BrNa}$ [M] + Na 484.04785, found 484.0473.

N-(tert-Butyl)-1-methyl-3-(2-nitrophenoxy)-2-oxoindoline-3-carboxamide [**21**] (**4acb**): **1a** (101.0 mg, 0.63 mmol), **2c** (86 mg, 0.6 mmol, 1 equivalent), **3b** (210 μL , 1.8 mmol, 3 equivalents), ZnF_2 (6.4 mg, 0.06 mmol, 10 mol%), and CH_2Cl_2 (2 mL) were used to obtain the corresponding **4acb** as a pale yellow solid (150.0 mg, 62% yield), m.p. = 145.4–146.9 °C. ^1H NMR (CDCl_3 , 400 MHz) δ : 1.44 (s, 9H, CH_3), 3.31 (s, 3H, CH_3), 6.46 (d, J = 8 Hz, 1H, Ar), 6.92 (d, J = 8 Hz, 1H, Ar), 7.01–7.07 (m, 2H, Ar), 7.20 (d, J = 8 Hz, 1H, Ar), 7.24–7.26 (m, 1H, Ar), 7.37 (t, J = 8 Hz, 1H, Ar), 7.78 (s br, 1H, NH), 7.96–7.99 (m, 1H, Ar). ^{13}C APT NMR (CDCl_3 , 100 MHz) δ : 27.00, 28.62, 52.18, 85.17, 109.47, 118.41, 123.25, 123.87, 123.89, 124.45, 126.77, 131.56, 134.98, 140.73, 144.97, 148.54, 164.55, 171.17. HRMS (ESI) m/z : calculated for $\text{C}_{20}\text{H}_{21}\text{O}_5\text{N}_3\text{Na}$ [M] + Na 406.13734, found 406.1368.

N-(tert-Butyl)-1-methyl-3-(4-nitrophenoxy)-2-oxoindoline-3-carboxamide (**4aeb**): **1a** (94.6 mg, 0.59 mmol), **2e** (86 mg, 0.6 mmol, 1 equivalent), **3b** (210 μL , 1.8 mmol, 3 equivalents), ZnF_2 (6.4 mg, 0.06 mmol, 10 mol%), and CH_2Cl_2 (2 mL) were used to obtain the corresponding **4aeb** as a pale yellow solid (69.0 mg, 31% yield), m.p. = 163.2–164.5 °C. ^1H NMR (CDCl_3 , 400 MHz) δ : 1.43 (s, 9H, CH_3), 3.27 (s, 3H, CH_3), 6.81–6.84 (m, 1H, Ar), 6.91–6.94 (m, 2H, Ar + NH), 7.10 (t, J = 8 Hz, 1H, Ar), 7.28 (d, J = 8 Hz, 1H, Ar), 7.38–7.43 (m, 1H, Ar), 8.02–8.05 (m, 2H, Ar). ^{13}C APT NMR (CDCl_3 , 100 MHz) δ : 27.00, 28.70, 52.34, 85.05, 109.60, 119.19, 123.91, 124.52, 125.67, 131.63, 143.61, 144.76, 159.36, 164.19, 170.91. HRMS (ESI) m/z : calculated for $\text{C}_{20}\text{H}_{21}\text{O}_5\text{N}_3\text{Na}$ [M] + Na 406.13734, found 406.1366.

N-(tert-Butyl)-3-(2-fluoro-4-nitrophenoxy)-1-methyl-2-oxoindoline-3-carboxamide (**4adb**): **1a** (98.0 mg, 0.61 mmol), **2d** (98 mg, 0.6 mmol, 1 equivalent) **3b** (210 μ L, 1.8 mmol, 3 equivalents), ZnF_2 (6.4 mg, 0.06 mmol, 10 mol%), and CH_2Cl_2 (2 mL) were used to obtain the corresponding **4adb** as a pale orange foam type solid (83.2 mg, 34% yield), m.p. = 95.6–97.0 $^\circ\text{C}$. ^1H NMR (CDCl_3 , 400 MHz) δ : 1.44 (s, 9H, CH_3), 3.27 (s, 3H, CH_3), 6.61–6.66 (m, 1H, Ar), 6.89 (d, J = 8 Hz, 1H, Ar), 7.06 (t, J = 8 Hz, 1H, Ar), 7.14 (s br, 1H, NH), 7.25–7.26 (m, 1H, Ar), 7.38 (t, J = 8 Hz, 1H, Ar), 7.76–7.79 (m, 1H, Ar), 7.93–7.96 (m, 1H, Ar). ^{13}C APT NMR (CDCl_3 , 100 MHz) δ : 27.04, 28.67, 52.31, 85.37, 109.55, 112.82 (d, $^2J_{\text{C-F}}$ = 24 Hz), 119.14, 120.50, 123.95, 124.42, 131.92, 143.48, 144.95, 147.95 (d, $^2J_{\text{C-F}}$ = 11 Hz), 153.18 (d, $^1J_{\text{C-F}}$ = 251 Hz), 164.00, 170.71. HRMS (ESI) m/z : calculated for $\text{C}_{20}\text{H}_{20}\text{O}_5\text{N}_3\text{FNa}$ [M] + Na 424.12792, found 424.1274.

Ethyl (3-(2-fluoro-4-nitrophenoxy)-1-methyl-2-oxoindoline-3-carbonyl)glycinate (**4adc**): **1a** (108.5 mg, 0.67 mmol), **2d** (98 mg, 0.6 mmol, 1 equivalent), **3c** (200 μ L, 1.8 mmol, 3 equivalents), ZnF_2 (6.4 mg, 0.06 mmol, 10 mol%), and CH_2Cl_2 (2 mL) were used to obtain the corresponding **4adc** as a pale yellow foam type solid (21.3 mg, 7% yield), m.p. = 147.7–148.3 $^\circ\text{C}$. ^1H NMR (CDCl_3 , 400 MHz) δ : 1.31 (t, J = 8 Hz, 3H, CH_3), 3.28 (s, 3H, CH_3), 4.01–4.07 (m, 1H, CH_2), 4.23–4.29 (m, 3H, CH_2), 6.69–6.74 (m, 1H, Ar), 6.90 (d, J = 8 Hz, 1H, Ar), 7.07 (t, J = 8 Hz, 1H, Ar), 7.33 (d, J = 8 Hz, 1H, Ar), 7.40 (t, J = 8 Hz, 1H, Ar), 7.75–7.80 (m, 2H, Ar + NH), 7.95 (dd, J = 4 Hz, 1H, Ar). ^{13}C APT NMR (CDCl_3 , 100 MHz) δ : 14.24, 27.06, 41.74, 61.99, 85.39, 109.60, 112.90 (d, $^2J_{\text{C-F}}$ = 24 Hz), 119.56, 120.40, 120.44, 123.37, 124.01, 124.91, 132.17, 143.67 (d, $^3J_{\text{C-F}}$ = 7 Hz), 144.84, 147.77 (d, $^2J_{\text{C-F}}$ = 11 Hz), 153.33 (d, $^1J_{\text{C-F}}$ = 252 Hz), 165.40, 169.07, 170.15. HRMS (ESI) m/z : calculated for $\text{C}_{20}\text{H}_{18}\text{O}_7\text{N}_3\text{FNa}$ [M] + Na 454.1021, found 454.1016.

N-Benzyl-3-(2-fluoro-4-nitrophenoxy)-1-methyl-2-oxoindoline-3-carboxamide (**4add**): **1a** (111.8 mg, 0.69 mmol), **2d** (98 mg, 0.6 mmol, 1 equivalent), **3d** (230 μ L, 1.8 mmol, 3 equivalents), ZnF_2 (6.4 mg, 0.06 mmol, 10 mol%), and CH_2Cl_2 (2 mL) were used to obtain the corresponding **4add** as a pale yellow foam type solid (180.6 mg, 59% yield), m.p. = 154.8–156.1 $^\circ\text{C}$. ^1H NMR (CDCl_3 , 400 MHz) δ : 3.30 (s, 3H, CH_3), 4.59 (dq, J = 4 Hz, 2H, CH_2), 6.67–6.72 (m, 1H, Ar), 6.92 (d, J = 8 Hz, 1H, Ar), 7.08 (t, J = 8 Hz, 1H, Ar), 7.29–7.43 (m, 7H, Ar), 7.53 (s br, 1H, NH), 7.76–7.79 (m, 1H, Ar), 7.91 (dd, J = 4 Hz, 1H, Ar). ^{13}C APT NMR (CDCl_3 , 100 MHz) δ : 27.09, 43.94, 85.54, 109.64, 112.88 (d, $^2J_{\text{C-F}}$ = 23 Hz), 119.57, 120.42, 120.46, 123.58, 124.01, 124.78, 124.79, 127.73, 127.93, 129.02, 132.12, 137.33, 143.64 (d, $^3J_{\text{C-F}}$ = 7 Hz), 144.89, 147.82 (d, $^2J_{\text{C-F}}$ = 11 Hz), 154.28 (d, $^1J_{\text{C-F}}$ = 251 Hz), 165.12, 170.44. HRMS (ESI) m/z : calculated for $\text{C}_{23}\text{H}_{18}\text{O}_5\text{N}_3\text{FNa}$ [M] + Na 458.11227, found 458.1120.

N-(tert-Butyl)-3-(2-fluoro-4-nitrophenoxy)-1,5-dimethyl-2-oxoindoline-3-carboxamide (**4bdb**): **1b** (113.5 mg, 0.65 mmol), **2d** (98 mg, 0.6 mmol, 1 equivalent), **3b** (210 μ L, 1.8 mmol, 3 equivalents), ZnF_2 (6.4 mg, 0.06 mmol, 10 mol%), and CH_2Cl_2 (2 mL) were used to obtain the corresponding **4bdb** as a pale orange solid (118.7 mg, 45% yield), m.p. = 132.1–133.8 $^\circ\text{C}$. ^1H NMR (CDCl_3 , 400 MHz) δ : 1.44 (s, 9H, CH_3), 2.28 (s, 3H, CH_3), 3.26 (s, 3H, CH_3), 6.56–6.60 (m, 1H, Ar), 6.80 (d, J = 8 Hz, 1H, Ar), 7.07–7.09 (m, 2H, Ar + NH), 7.19 (d, J = 8 Hz, 1H, Ar), 7.76–7.79 (m, 1H, Ar), 7.96 (dd, J = 4 Hz, 1H, Ar). ^{13}C APT NMR (CDCl_3 , 100 MHz) δ : 21.21, 27.08, 28.68, 52.30, 85.34, 109.33, 112.78 (d, $^2J_{\text{C-F}}$ = 23 Hz), 118.58, 120.50, 120.54, 123.84, 125.10, 132.26, 133.82, 142.49, 143.24 (d, $^3J_{\text{C-F}}$ = 7 Hz), 148.05 (d, $^2J_{\text{C-F}}$ = 12 Hz), 153.00 (d, $^1J_{\text{C-F}}$ = 250 Hz), 164.11, 170.50. HRMS (ESI) m/z : calculated for $\text{C}_{21}\text{H}_{22}\text{O}_5\text{N}_3\text{FNa}$ [M] + Na 438.14357, found 438.1433.

5-Bromo-N-(tert-butyl)-3-(2-fluoro-4-nitrophenoxy)-1-methyl-2-oxoindoline-3-carboxamide (**4cdb**): **1c** (152.8 mg, 0.64 mmol), **2d** (98 mg, 0.6 mmol, 1 equivalent) **3b** (210 μ L, 1.8 mmol, 3 equivalents), ZnF_2 (6.4 mg, 0.06 mmol, 10 mol%), and CH_2Cl_2 (2 mL) were used to obtain the corresponding **4cdb** as a pale yellow foam type solid (207.0 mg, 68% yield), m.p. = 183.3–184.9 $^\circ\text{C}$. ^1H NMR (CDCl_3 , 400 MHz) δ : 1.43 (s, 9H, CH_3), 3.25 (s, 3H, CH_3),

6.60–6.64 (m, 1H, Ar), 6.80 (d, $J = 8$ Hz, 1H, Ar), 7.05 (s br, 1H, NH), 7.40 (s, 1H, Ar), 7.52 (dd, $J = 4$ Hz, 1H, Ar), 7.79–7.82 (m, 1H, Ar), 7.97 (dd, $J = 4$ Hz, 1H, Ar). ^{13}C APT NMR (CDCl_3 , 100 MHz) δ : 27.15, 28.64, 52.49, 84.93, 110.96, 113.01 (d, $^2J_{\text{C-F}} = 23$ Hz), 116.61, 118.91, 120.54, 120.58, 125.90, 127.63, 134.74, 143.92, 147.64 (d, $^2J_{\text{C-F}} = 11$ Hz), 153.09 (d, $^1J_{\text{C-F}} = 251$ Hz), 163.33, 170.04. HRMS (ESI) m/z : calculated for $\text{C}_{20}\text{H}_{19}\text{O}_5\text{N}_3\text{BrFNa}$ [M] + Na 502.03843, found 502.0380.

5-Bromo-N-(tert-butyl)-3-(2-fluoro-4-nitrophenoxy)-1-(3-methoxybenzyl)-2-oxoindoline-3-carboxamide (**4hdb**): **1h** (224.0 mg, 0.65 mmol), **2d** (98 mg, 0.6 mmol, 1 equivalent), **3b** (210 μL , 1.8 mmol, 3 equivalents), ZnF_2 (6.4 mg, 0.06 mmol, 10 mol%), and CH_2Cl_2 (2 mL) were used to obtain the corresponding **4hdb** as a pale yellow foam type solid (61.1 mg, 15% yield), m.p. = 147.4–148.7 $^\circ\text{C}$. ^1H NMR (CDCl_3 , 400 MHz) δ : 1.45 (s, 9H, CH_3), 3.70 (s, 3H, OCH_3), 4.93 (d, $J = 16$ Hz, 1H, CH_2), 5.11 (d, $J = 16$ Hz, 1H, CH_2), 6.68–6.79 (m, 4H, Ar), 7.05–7.09 (m, 2H, Ar + NH), 7.28–7.32 (m, 2H, Ar), 7.45 (d, $J = 8$ Hz, 1H, Ar), 7.81–7.84 (m, 1H, Ar), 7.97 (dd, $J = 4$ Hz, 1H, Ar). ^{13}C APT NMR (CDCl_3 , 100 MHz) δ : 28.70, 44.41, 52.33, 55.78, 85.89, 110.54, 112.68, 112.93 (d, $^2J_{\text{C-F}} = 23$ Hz), 113.47, 115.64, 119.79, 120.76, 120.80, 124.10, 124.17, 124.31, 131.95, 133.58, 134.48, 143.79, 147.79 (d, $^2J_{\text{C-F}} = 11$ Hz), 153.25 (d, $^1J_{\text{C-F}} = 251$ Hz), 159.72, 164.06, 170.99. HRMS (ESI) m/z : calculated for $\text{C}_{27}\text{H}_{15}\text{O}_6\text{N}_3\text{BrFNa}$ [M] + Na 608.0803, found 608.0797.

N-(tert-Butyl)-3-(2-fluoro-4-nitrophenoxy)-2-oxo-1-(prop-2-yn-1-yl)indoline-3-carboxamide (**4idb**): **1i** (115.0 mg, 0.62 mmol), **2d** (98 mg, 0.6 mmol, 1 equivalent), **3b** (210 μL , 1.8 mmol, 3 equivalents), ZnF_2 (6.4 mg, 0.06 mmol, 10 mol%), and CH_2Cl_2 (2 mL) were used to obtain the corresponding **4idb** as a white solid (105.2 mg, 63% yield), m.p. = 168.8–169.6 $^\circ\text{C}$. ^1H NMR (CDCl_3 , 400 MHz) δ : 1.44 (s, 9H, CH_3), 2.31–2.32 (m, 1H, CH), 4.24 (d, $J = 16$ Hz, 1H, CH_2), 4.90 (d, $J = 16$ Hz, 1H, CH_2), 6.61–6.65 (m, 1H, Ar), 7.07–7.12 (m, 3H, Ar + NH), 7.26–7.28 (m, 1H, Ar), 7.40–7.44 (m, 1H, Ar), 7.71–7.74 (m, 1H, Ar), 7.95 (dd, $J = 4$ Hz, 1H, Ar). ^{13}C APT NMR (CDCl_3 , 100 MHz) δ : 28.69, 29.98, 52.39, 73.10, 75.87, 84.86, 110.70, 112.77 (d, $^2J_{\text{C-F}} = 24$ Hz), 119.02, 120.44, 120.48, 123.86, 124.37, 131.91, 143.07, 147.71 (d, $^2J_{\text{C-F}} = 11$ Hz), 152.99 (d, $^1J_{\text{C-F}} = 251$ Hz), 163.80, 170.06. HRMS (ESI) m/z : calculated for $\text{C}_{22}\text{H}_{20}\text{O}_5\text{N}_3\text{FNa}$ [M] + Na 448.12792, found 448.1274.

(E)-1-(But-2-en-1-yl)-N-(tert-butyl)-3-(2-fluoro-4-nitrophenoxy)-2-oxoindoline-3-carboxamide (**4jdb**): **1j** (127.4 mg, 0.63 mmol), **2d** (98 mg, 0.6 mmol, 1 equivalent), **3b** (210 μL , 1.8 mmol, 3 equivalents), ZnF_2 (6.4 mg, 0.06 mmol, 10 mol%) and CH_2Cl_2 (2 mL) were used to obtain the corresponding **4jdb** as a pale yellow solid (102.9 mg, 36% yield), m.p. = 104.1–105.9 $^\circ\text{C}$. ^1H NMR (CDCl_3 , 400 MHz) δ : 1.44 (s, 9H, CH_3), 1.68–1.70 (m, 3H, CH_3), 4.22–4.39 (m, 2H, CH_2), 5.40–5.47 (m, 1H, CH), 5.75–5.81 (m, 1H, CH), 6.65–6.69 (m, 1H, Ar), 6.89 (d, $J = 8$ Hz, 1H, Ar), 7.04 (t, $J = 8$ Hz, 1H, Ar), 7.08 (s br, 1H, NH), 7.25–7.27 (m, 1H, Ar), 7.33–7.37 (m, 1H, Ar), 7.73–7.76 (m, 1H, Ar), 7.94 (dd, $J = 4$ Hz, 1H, Ar). ^{13}C APT NMR (CDCl_3 , 100 MHz) δ : 17.88, 28.69, 42.45, 52.26, 85.35, 110.45, 112.79 (d, $^2J_{\text{C-F}} = 23$ Hz), 119.53, 120.23, 120.27, 122.98, 123.74, 123.99, 124.46, 130.88, 131.76, 143.47 (d, $^3J_{\text{C-F}} = 8$ Hz), 144.17, 144.33, 147.91 (d, $^2J_{\text{C-F}} = 11$ Hz), 153.24 (d, $^1J_{\text{C-F}} = 251$ Hz), 164.01, 170.35. HRMS (ESI) m/z : calculated for $\text{C}_{23}\text{H}_{24}\text{O}_5\text{N}_3\text{FNa}$ [M] + Na 464.15922, found 464.1588.

1-Allyl-N-(tert-butyl)-3-(2-fluoro-4-nitrophenoxy)-2-oxoindoline-3-carboxamide (**4kdb**): **1k** (116.4 mg, 0.62 mmol), **2d** (98 mg, 0.6 mmol, 1 equivalent), **3b** (210 μL , 1.8 mmol, 3 equivalents), ZnF_2 (6.4 mg, 0.06 mmol, 10 mol%), and CH_2Cl_2 (2 mL) were used to obtain the corresponding **4kdb** as a pale yellow foam type solid (211.9 mg, 80% yield), m.p. = 134.0–135.8 $^\circ\text{C}$. ^1H NMR (CDCl_3 , 400 MHz) δ : 1.44 (s, 9H, CH_3), 4.37–4.39 (m, 2H, CH_2), 5.25–5.35 (m, 2H, CH_2), 5.77–5.84 (m, 1H, CH), 6.68–6.72 (m, 1H, Ar), 6.87 (d, $J = 8$ Hz, 1H, Ar), 7.05 (t, $J = 8$ Hz, 1H, Ar), 7.09 (s br, 1H, NH), 7.26–7.28 (m, 1H, Ar), 7.34 (t, $J = 8$ Hz, 1H, Ar), 7.75–7.78 (m, 1H, Ar), 7.94 (dd, $J = 4$ Hz, 1H, Ar). ^{13}C APT NMR (CDCl_3 , 100 MHz) δ : 28.68, 42.95, 52.31, 85.44, 110.44, 112.84 (d, $^2J_{\text{C-F}} = 23$ Hz), 118.98,

119.57, 120.33, 120.37, 123.86, 123.89, 124.41, 124.42, 130.06, 131.80, 143.59, 144.16, 147.85 (d, $^2J_{C-F}$ = 11 Hz), 153.25 (d, $^1J_{C-F}$ = 250 Hz), 164.05, 170.49. HRMS (ESI) m/z : calculated for $C_{22}H_{22}O_5N_3FNa$ [M] + Na 450.14467, found 450.1434.

N-((3-((3-Hydroxy-1-methyl-2-oxoindolin-3-yl)oxy)-1-methyl-2-oxoindolin-3-yl)methylidene)cyclohexanaminium (**5a**): **1a** (100 mg, 0.62 mmol), **2g** or **2h** (136 mg or 100 μ L, 0.6 mmol, 1 equivalent), **3a** (230 μ L, 1.8 mmol, 3 equivalents), ZnF_2 (6.4 mg, 0.06 mmol, 10 mol%), and CH_2Cl_2 (2 mL) were used to obtain the corresponding **5a** as a white solid (29.9 mg or 81.3 mg, 11% or 29% yield), m.p. = 256.9 °C decomposition. 1H NMR ($CDCl_3$, 400 MHz) δ : 1.06–1.34 (m, 5H, CH_2), 1.51–1.54 (m, 1H, CH_2), 1.62–1.68 (m, 3H, CH_2), 1.82–1.83 (m, 1H, CH_2), 3.19 (s, 3H, CH_3), 3.21 (s, 3H, CH_3), 3.54–3.59 (m, 1H, CH), 6.81–6.87 (m, 2H, Ar), 7.11–7.19 (m, 2H, Ar), 7.37 (dt, J = 8 Hz, 1H, Ar), 7.42–7.46 (m, 2H, Ar), 7.55 (d, J = 8 Hz, 1H, Ar). ^{13}C APT NMR ($CDCl_3$, 100 MHz) δ : 24.78, 24.89, 25.65, 26.55, 26.89, 33.19, 33.35, 57.31, 80.93, 102.95, 109.23, 123.07, 123.34, 123.47, 123.81, 124.74, 127.56, 131.34, 132.94, 144.96, 145.08, 151.85, 169.51, 170.51. HRMS (ESI) m/z : calculated for $C_{25}H_{26}O_4N_3$ [M]+ 432.19178, found 432.1913.

N-((3-((3-Hydroxy-1-methyl-2-oxoindolin-3-yl)oxy)-1-methyl-2-oxoindolin-3-yl)methylidene)-2-methylpropan-2-aminium (**5b**): **1a** (100 mg, 0.62 mmol), **2g** or **2h** (136 mg or 100 μ L, 0.6 mmol, 1 equivalent), **3b** (210 μ L, 1.8 mmol, 3 equivalents), ZnF_2 (6.4 mg, 0.06 mmol, 10 mol%), and CH_2Cl_2 (2 mL) were used to obtain the corresponding **5b** as a white solid (40.1 mg or 25.8 mg, 17% or 10% yield), m.p. = 257.0 °C decomposition. 1H NMR ($CDCl_3$, 400 MHz) δ : 1.22 (s, 9H, CH_3), 3.18 (s, 3H, CH_3), 3.20 (s, 3H, CH_3), 6.84 (dd, J = 8 Hz, 2H, Ar), 7.12–7.19 (m, 2H, Ar), 7.37 (dt, J = 8 Hz, 1H, Ar), 7.41–7.47 (m, 2H, Ar), 7.53–7.56 (m, 1H, Ar). ^{13}C APT NMR ($CDCl_3$, 100 MHz) δ : 26.53, 26.79, 29.67, 55.00, 81.25, 103.01, 109.02, 109.19, 123.23, 123.41, 123.55, 124.68, 128.17, 131.11, 132.84, 144.98, 145.05, 149.11, 169.57, 170.79. HRMS (ESI) m/z : calculated for $C_{23}H_{23}O_4N_3Na$ [M] + Na 428.15808, found 428.1572.

2.3. General Procedure for the Synthesis of Spirooxindole Derivatives **6**

In a round-bottom flask, the corresponding phenoxy-indoline carboxamide derivatives **4** (1 equivalent), $KOtBu$ (1.5 equivalents) and DMF (1–2 mL) were added. The reaction mixture was left stirred at 100 °C for 1 h. The reaction was quenched with 1M HCl aq. (10 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 $\times$ 10 mL). The combined organic phases were dried with anhydrous Na_2SO_4 and filtrated, and the solvent was evaporated under reduced pressure. The crude reaction mixture was purified in a short chromatographic glass column with SiO_2 flash using CH_2Cl_2 and AcOEt mixtures as the eluents.

4-Cyclohexyl-1'-methyl-6-nitrospiro[benzo[b][1,4]oxazine-2,3'-indoline]-2',3(4H)-dione (**6aa**): **4ada** (110.1 mg, 0.26 mmol), $KOtBu$ (43 mg, 0.39 mmol, 1.5 equivalents), and DMF (1 mL) were used to obtain the corresponding **6aa** as a pale yellow solid (45.1 mg, 43% yield), m.p. = 125.7–126.3 °C. 1H NMR ($CDCl_3$, 400 MHz) δ : 1.27–1.42 (m, 3H, CH_2), 1.70–1.73 (m, 1H, CH_2), 1.82–1.91 (m, 4H, CH_2), 2.32–2.40 (m, 2H, CH_2), 3.23 (s, 3H, CH_3), 4.28–4.34 (m, 1H, CH), 6.89–6.94 (m, 2H, Ar), 6.98–7.05 (m, 1H, Ar), 7.36–7.43 (m, 2H, Ar), 7.85 (d, J = 4 Hz, 1H, Ar), 8.03 (dd, J = 4 Hz, 1H, Ar). ^{13}C APT NMR ($CDCl_3$, 100 MHz) δ : 25.28, 26.35, 26.37, 26.72, 29.04, 29.29, 29.77, 58.27, 80.96, 109.48, 114.01, 115.58, 119.28, 123.65, 124.26, 124.96, 131.98, 135.14, 143.47, 144.05, 144.80, 163.72, 169.84. HRMS (ESI) m/z : calculated for $C_{22}H_{21}O_5N_3Na$ [M] + Na 430.13734, found 430.1370.

4-(tert-Butyl)-1'-methyl-6-nitrospiro[benzo[b][1,4]oxazine-2,3'-indoline]-2',3(4H)-dione (**6ab**): **4adb** (166.8 mg, 0.42 mmol), $KOtBu$ (70 mg, 0.62 mmol, 1.5 equivalents), and DMF (2 mL) were used to obtain the corresponding **6ab** as a pale yellow solid (69.3 mg, 43% yield), m.p. = 223.0–224.8 °C. 1H NMR ($CDCl_3$, 400 MHz) δ : 1.71 (s, 9H, CH_3), 3.22 (s,

3H, CH₃), 6.67 (dd, *J* = 8 Hz, 1H, Ar), 6.89 (d, *J* = 8 Hz, 1H, Ar), 6.95 (t, *J* = 8 Hz, 1H, Ar), 7.37–7.43 (m, 2H, Ar), 7.88 (d, *J* = 4 Hz, 1H, Ar), 8.04 (dd, *J* = 4 Hz, 1H, Ar). ¹³C APT NMR (CDCl₃, 100 MHz) δ: 26.77, 29.83, 61.01, 84.40, 109.49, 114.49, 118.70, 120.99, 123.58, 123.84, 125.32, 131.88, 135.97, 143.83, 145.02, 147.01, 169.47, 169.96. HRMS (ESI) *m/z*: calculated for C₂₀H₁₉O₅N₃Na [M] + Na 404.12169, found 404.1210.

Ethyl 2-(1'-methyl-6-nitro-2',3-dioxospiro[benzo[b][1,4]oxazine-2,3'-indolin]-4(3H)-yl)acetate (**6ac**): **4adc** (158.6 mg, 0.37 mmol), KO^tBu (62 mg, 0.55 mmol, 1.5 equivalents), and DMF (2 mL) were used to obtain the corresponding **6ac** as a pale orange solid (27.5 mg, 18% yield), m.p. = 149.8–151.0 °C. ¹H NMR (CDCl₃, 400 MHz) δ: 1.27 (t, 3H, CH₃), 3.26 (s, 3H, CH₃), 4.23 (q, *J* = 4 Hz, 2H, CH₂), 4.43 (d, *J* = 16 Hz, 1H, CH₂), 5.09–5.14 (m, 1H, CH₂), 6.91 (d, *J* = 8 Hz, 1H, Ar), 6.93–6.96 (m, 1H, Ar), 7.02 (t, *J* = 8 Hz, 1H, Ar), 7.09–7.11 (m, 1H, Ar), 7.43 (t, *J* = 8 Hz, 1H, Ar), 7.89 (d, *J* = 4 Hz, 1H, Ar), 8.02 (dd, *J* = 4 Hz, 1H, Ar). ¹³C APT NMR (CDCl₃, 100 MHz) δ: 14.20, 26.89, 43.57, 62.45, 80.35, 109.55, 113.94, 114.31, 119.50, 123.76, 124.52, 124.92, 132.30, 133.95, 142.99, 144.04, 144.69, 162.60, 166.82, 169.29. HRMS (ESI) *m/z*: calculated for C₂₀H₁₈O₇N₃ [M] + H 412.11393, found 412.1134.

4-Benzyl-1'-methyl-6-nitrospiro[benzo[b][1,4]oxazine-2,3'-indoline]-2',3(4H)-dione (**6ad**): **4add** (161.1 mg, 0.37 mmol), KO^tBu (62 mg, 0.55 mmol, 1.5 equivalents), and DMF (2 mL) were used to obtain the corresponding **6ad** as a pale yellow solid (57.9 mg, 38% yield), m.p. = 224.5–225.8 °C. ¹H NMR (CDCl₃, 400 MHz) δ: 3.26 (s, 3H, CH₃), 5.27 (q, *J* = 16 Hz, 2H, CH₂), 6.95 (d, *J* = 8 Hz, 1H, Ar), 7.04 (d, *J* = 8 Hz, 1H, Ar), 7.09 (t, *J* = 8 Hz, 1H, Ar), 7.17 (d, *J* = 8 Hz, 1H, Ar), 7.28–7.37 (m, 5H, Ar), 7.47 (dt, *J* = 8 Hz, 1H, Ar), 7.87–7.90 (m, 2H, Ar). ¹³C APT NMR (CDCl₃, 100 MHz) δ: 26.86, 46.14, 80.61, 109.62, 113.37, 115.47, 119.28, 123.86, 124.86, 124.90, 126.45, 128.11, 129.34, 132.21, 134.18, 134.61, 143.25, 143.85, 144.95, 162.55, 169.92. HRMS (ESI) *m/z*: calculated for C₂₃H₁₇O₅N₃Na [M] + Na 438.10604, found 438.1054.

4-(tert-Butyl)-1',5'-dimethyl-6-nitrospiro[benzo[b][1,4]oxazine-2,3'-indoline]-2',3(4H)-dione (**6bb**): **4bdb** (82.6 mg, 0.20 mmol), KO^tBu (35 mg, 0.30 mmol, 1.5 equivalents), and DMF (1 mL) were used to obtain the corresponding **6bb** as a pale yellow solid (19.8 mg, 25% yield), m.p. = 235.0–236.4 °C. ¹H NMR (CDCl₃, 400 MHz) δ: 1.71 (s, 9H, CH₃), 2.22 (s, 3H, CH₃), 3.19 (s, 3H, CH₃), 6.55 (s, 1H, Ar), 6.78 (d, *J* = 8 Hz, 1H, Ar), 7.19 (d, *J* = 8 Hz, 1H, Ar), 7.41 (d, *J* = 8 Hz, 1H, Ar), 7.88 (m, 1H, Ar), 8.05 (dd, *J* = 4 Hz, 1H, Ar). ¹³C APT NMR (CDCl₃, 100 MHz) δ: 21.18, 26.76, 29.85, 60.97, 84.59, 109.24, 114.36, 118.62, 120.92, 124.58, 125.38, 132.15, 133.37, 135.93, 142.60, 143.78, 147.00, 169.61, 169.97. HRMS (ESI) *m/z*: calculated for C₂₁H₂₁O₅N₃Na [M] + Na 418.13734, found 418.1369.

5'-Bromo-4-(tert-butyl)-1'-methyl-6-nitrospiro[benzo[b][1,4]oxazine-2,3'-indoline]-2',3(4H)-dione (**6cb**): **4cdb** (168.6 mg, 0.35 mmol), KO^tBu (60 mg, 0.53 mmol, 1.5 equivalents), and DMF (2 mL) were used to obtain the corresponding **6cb** as a white solid (22.7 mg, 14% yield), m.p. = 233.5–234.0 °C. ¹H NMR (CDCl₃, 400 MHz) δ: 1.71 (s, 9H, CH₃), 3.19 (s, 3H, CH₃), 6.78 (d, *J* = 8 Hz, 1H, Ar), 6.86 (d, *J* = 4 Hz, 1H, Ar), 7.42 (d, *J* = 8 Hz, 1H, Ar), 7.53 (dd, *J* = 4 Hz, 1H, Ar), 7.88 (d, *J* = 4 Hz, 1H, Ar), 8.05 (dd, *J* = 4 Hz, 1H, Ar). ¹³C APT NMR (CDCl₃, 100 MHz) δ: 26.85, 29.83, 61.22, 84.03, 110.88, 114.32, 116.07, 118.86, 121.09, 127.18, 127.22, 134.67, 135.58, 143.90, 144.13, 146.55, 168.87, 169.54. HRMS (ESI) *m/z*: calculated for C₂₀H₁₈O₅N₃BrNa [M] + Na 482.0322, found 482.0319.

5'-Bromo-4-(tert-butyl)-1'-(3-methoxybenzyl)-6-nitrospiro[benzo[b][1,4]oxazine-2,3'-indoline]-2',3(4H)-dione (**6hb**): **4hdb** (46.7 mg, 0.08 mmol), KO^tBu (13.4 mg, 0.12 mmol, 1.5 equivalents), and DMF (1 mL) were used to obtain the corresponding **6hb** as a pale yellow solid (12.6 mg, 28% yield), m.p. = 222.2–224.0 °C. ¹H NMR (CDCl₃, 400 MHz) δ: 1.72 (s, 9H, CH₃), 3.73 (s, 3H, OCH₃), 4.81 (d, *J* = 16 Hz, 1H, CH₂), 5.15 (d, *J* = 16 Hz, 1H, CH₂), 6.63 (d, *J* = 4 Hz, 1H, Ar), 6.70–6.73 (m, 2H, Ar), 6.90–6.95 (m, 2H, Ar), 7.27–7.31 (m, 1H, Ar), 7.44 (t, *J* = 8 Hz, 2H, Ar), 7.93 (d, *J* = 4 Hz, 1H, Ar), 8.07 (dd, *J* = 4 Hz, 1H, Ar).

^{13}C APT NMR (CDCl_3 , 100 MHz) δ : 29.86, 44.17, 55.72, 61.07, 84.78, 110.47, 112.60, 112.76, 114.61, 116.35, 118.78, 121.05, 123.82, 123.83, 125.42, 131.93, 133.61, 134.44, 135.90, 143.70, 143.97, 147.02, 159.79, 169.53, 170.45. HRMS (ESI) m/z : calculated for $\text{C}_{27}\text{H}_{24}\text{O}_6\text{N}_3\text{BrNa}$ [M] + Na 588.07407, found 588.0737.

4-(tert-Butyl)-6-nitro-1'-(prop-2-yn-1-yl)spiro[benzo[b][1,4]oxazine-2,3'-indoline]-2',3(4H)-dione (**6ib**): **4idb** (90.8 mg, 0.21 mmol), KO t Bu (35.0 mg, 0.32 mmol, 1.5 equivalents), and DMF (2 mL) were used to obtain the corresponding **6ib** as a pale yellow solid (20.7 mg, 24% yield), m.p. = 196.8–198.0 °C. ^1H NMR (CDCl_3 , 400 MHz) δ : 1.71 (s, 9H, CH_3), 2.29–2.30 (m, 1H, CH), 4.43 (dd, J = 20 Hz, 1H, CH_2), 4.55 (dd, J = 20 Hz, 1H, CH_2), 6.70 (d, J = 8 Hz, 1H, Ar), 6.99 (dt, J = 8 Hz, 1H, Ar), 7.12 (d, J = 8 Hz, 1H, Ar), 7.40–7.44 (m, 2H, Ar), 7.90 (s br, 1H, Ar), 8.04 (dd, J = 4 Hz, 1H, Ar). ^{13}C APT NMR (CDCl_3 , 100 MHz) δ : 29.83, 61.09, 73.41, 75.90, 84.31, 110.60, 114.57, 118.74, 121.03, 123.94, 125.26, 131.82, 135.87, 143.14, 143.91, 146.88, 169.06, 169.18. HRMS (ESI) m/z : calculated for $\text{C}_{22}\text{H}_{19}\text{O}_5\text{N}_3\text{Na}$ [M] + Na 428.12169, found 428.1209.

(E)-1'-(But-2-en-1-yl)-4-(tert-butyl)-6-nitrospiro[benzo[b][1,4]oxazine-2,3'-indoline]-2',3(4H)-dione (**6jb**): **4jdb** (76.9 mg, 0.17 mmol), KO t Bu (30.0 mg, 0.26 mmol, 1.5 equivalents), and DMF (2 mL) were used to obtain the corresponding **6jb** as a pale yellow solid (16.2 mg, 23% yield), m.p. = 160.9–161.3 °C. ^1H NMR (CDCl_3 , 400 MHz) δ : 1.69–1.71 (m, 12H, CH_3), 4.18–4.33 (m, 2H, CH_2), 5.42–5.51 (m, 1H, CH), 5.75–5.81 (m, 1H, CH), 6.67 (d, J = 8 Hz, 1H, Ar), 6.88 (d, J = 8 Hz, 1H, Ar), 6.94 (dt, J = 8 Hz, 1H, Ar), 7.35 (dt, J = 8 Hz, 2H, Ar), 7.41 (d, J = 8 Hz, 1H, Ar), 7.89 (d, J = 4 Hz, 1H, Ar), 8.04 (dd, J = 4 Hz, 1H, Ar). ^{13}C APT NMR (CDCl_3 , 100 MHz) δ : 17.86, 29.85, 42.27, 60.96, 84.44, 110.44, 114.52, 118.67, 120.97, 123.20, 123.40, 123.84, 125.46, 130.01, 131.71, 136.00, 143.83, 144.41, 147.06, 169.50, 160.68. HRMS (ESI) m/z : calculated for $\text{C}_{23}\text{H}_{23}\text{O}_5\text{N}_3\text{Na}$ [M] + Na 444.15299, found 444.1524.

1'-Allyl-4-(tert-butyl)-6-nitrospiro[benzo[b][1,4]oxazine-2,3'-indoline]-2',3(4H)-dione (**6kb**): **4kdb** (178.2 mg, 0.42 mmol), KO t Bu (70.0 mg, 0.63 mmol, 1.5 equivalents), and DMF (2 mL) were used to obtain the corresponding **6kb** as a pale yellow solid (26.7 mg, 16% yield), m.p. = 212.6–213.2 °C. ^1H NMR (CDCl_3 , 400 MHz) δ : 1.71 (s, 9H, CH_3), 4.23–4.44 (m, 2H, CH_2), 5.31 (dd, J = 16 Hz, 2H, CH_2), 5.80–5.88 (m, 1H, CH), 6.68 (d, J = 8 Hz, 1H, Ar), 6.87 (d, J = 8 Hz, 1H, Ar), 6.94 (t, J = 8 Hz, 1H, Ar), 7.35 (dt, J = 8 Hz, 2H, Ar), 7.41 (d, J = 12 Hz, 1H, Ar), 7.89 (d, J = 4 Hz, 1H, Ar), 8.04 (dd, J = 4 Hz, 1H, Ar). ^{13}C APT NMR (CDCl_3 , 100 MHz) δ : 29.83, 42.70, 60.98, 84.46, 110.36, 114.50, 118.23, 118.68, 120.99, 123.51, 123.87, 125.43, 130.18, 131.72, 135.96, 143.86, 144.22, 147.02, 169.46, 169.79. HRMS (ESI) m/z : calculated for $\text{C}_{22}\text{H}_{21}\text{O}_5\text{N}_3\text{Na}$ [M] + Na 430.13734, found 430.1367.

2.4. Antiproliferative Bioassays

The human mammalian cell lines used in this study were obtained and authenticated as follows: A-549 (Human lung adenocarcinoma; ATCC Cat# CCL-185, RRID:CVCL_0023); HeLa (Human cervical adenocarcinoma; ATCC Cat# CCL-2, RRID:CVCL_0030); MIA PaCa-2 (Human pancreatic undifferentiated carcinoma; ATCC Cat# CRL-1420, RRID:CVCL_0428); SW1573 [also known as SW-1573] (Human alveolar exocrine lung carcinoma; ATCC Cat# CRL-2170, RRID:CVCL_1720); T-47D (Human mammary ductal carcinoma; ATCC Cat# HTB-133, RRID:CVCL_0553); and WiDr (Human colon adenocarcinoma; ATCC Cat# CCL-218 or ECACC Cat# 85111501, RRID:CVCL_2760). All cell lines were kindly provided by Prof. Godefridus J. Peters (VUmc, Amsterdam, NL). The cell lines were tested for their authentication by PCR profiling using short tandem repeats, which was performed by BaseClear (Leiden, NL), and regularly checked for mycoplasma infection.

Culturing was performed in 60 mm Petri dishes at 37 °C within a humidified incubator set to 5% CO_2 . The growth medium consisted of RPMI 1640 enriched with 5% heat-inactivated fetal calf serum (FCS), 2 mM L-glutamine, 100 U/mL penicillin, and 0.1 mg/mL

streptomycin. To ensure viability and maintain a low passage number, cell lines were passaged twice per week via detachment with 0.05% trypsin. Cell density assessments were routinely executed utilizing an automated Moxi Z cell counter.

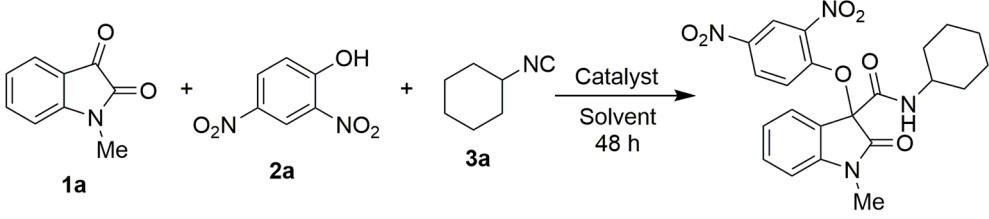
The antiproliferative tests were conducted using our implementation of the NCI protocol [24]. The cell-seeding densities were 2500 (A549, HeLa, MIA PaCa-2, and SW1573) or 5000 (T-47D and WiDr) cells/well. Stock solutions of isatin-based Passerini adducts were prepared in DMSO at 40 mM. The maximum test concentration was 100 μ M. The exposure time was set at 48 h. Cisplatin and 5-fluoruracil were used as positive controls, whereas control cells received the corresponding concentration of DMSO (0.25% *v/v*) as negative control. Treatments were applied 24 h after seeding, and cells were incubated with the compounds for 48 h. Subsequently, the NCI sulforhodamine B (SRB) colorimetric assay was performed. Optical density (OD) values were recorded in dual mode (530 and 620 nm) using a Absorbance Microplate Reader (BioTek PowerWave XS, Agilent, Santa Clara, CA, USA). Background OD values obtained from wells containing only culture medium were subtracted from all measurements. The antiproliferative activity of the tested compounds, expressed as GI₅₀ values, was determined according to the NCI calculation method.

3. Results and Discussion

3.1. Tuning the Passerini–Smiles Reaction with Isatin as the Carbonyl Component

Inspired by the research developed by Dai and Li [16] and our previous work considering the Ugi-4 component reaction using isatin derivatives [5], we began the optimization of the PSR using *N*-methyl isatin **1a**, electron-deficient 2,4-dinitrophenol **2a** and cyclohexyl isocyanide **3a** as components. The results can be seen in Table 1.

Table 1. Optimization of the PSR using *N*-methyl isatin **1a**, 2,4-dinitrophenol **2a** and cyclohexyl isocyanide **3a**.



Entry ^a	(3a) (eq)	Catalyst	Solvent	T/°C	(4aaa) ^b /%
1	1	-	EtOH	60	<10
2	1	-	MeOH	60	<10
3	1.5	-	EtOH	60	46
4	1.5	-	CH ₃ CN	80	40
5	1.5	-	CH ₂ Cl ₂	rt	59
6	3	-	CH ₂ Cl ₂	rt	85
7 ^c	3	-	CH ₂ Cl ₂	rt	83
8	3	Ti(O <i>i</i> Pr) ₄	CH ₂ Cl ₂	rt	64
9	3	In(OTf) ₂	CH ₂ Cl ₂	rt	74
10	3	ZnBr ₂	CH ₂ Cl ₂	rt	70
11	3	TfOH	CH ₂ Cl ₂	rt	87
12	3	ZnF ₂	CH ₂ Cl ₂	rt	93
13	3	DIPEA	CH ₂ Cl ₂	rt	90
14 ^d	3	ZnF ₂	CH ₂ Cl ₂	rt	89

^a Reaction conditions: **1a** (0.62 mmol), **2a** (0.62 mmol), **3a**, catalyst (10 mol%) and the solvent (2 mL) were added to a Radley's® 12-position carousel reactor tube and stirred at the indicated temperature for 48 h. ^b Isolated yield.

^c The reaction was stirred for 160 h. ^d 100 mg of MS 4Å were added to the reaction tube.

We start our study by using a stoichiometric amount of each component in the PSR with EtOH and MeOH as solvents at 60 °C for 2 days (Table 1, entries 1 and 2, respectively). Only a vestigial amount of the desired aryl ether derivative **4aaa** was obtained in both reaction tests, as expected by using a polar and protic solvent [25]. We decided to increase the amount of **3a** to 1.5 equivalents, and the yield of **4aaa** increased considerably (46% using EtOH as solvent, Table 1, entry 3). Similar reactions were performed using CH₃CN and CH₂Cl₂ as solvents, at 80 °C and room temperature, respectively (Table 1, entries 4 and 5), and the best yield of **4aaa** so far (59%) was obtained using the latter mild reaction conditions (Table 1, entry 5). Establishing CH₂Cl₂ as the best solvent to get **4aaa** at room temperature, we tested the effect of using an excess of isocyanide **3a** on the reaction outcome, and a dramatic increase in the yield of **4aaa** was noted (85%, Table 1, entry 6).

It is well established that the classical PSR typically requires a longer reaction time than its related Ugi reaction, primarily due to the lower electrophilicity of the aldehyde or ketone involved in the mechanism [26]. In light of this, we extended the reaction time to 160 h (Table 1, entry 7). However, this modification did not result in a significant improvement in the yield of **4aaa** (Table 1, compare entries 6 and 7).

At this stage, we proceeded to evaluate a series of Lewis acids (10 mol%) as catalysts under the optimized reaction conditions previously established (Table 1, entry 6). Given the anticipated activation of ketone **1a** by the Lewis acids, an increase in the yield of the PS adduct was expected. Among the catalysts tested, ZnF₂ proved to be the most effective, affording **4aaa** in 93% yield (Table 1, entry 12; compare entries 8 to 12). As previously reported for the Ugi reaction [5], the superior performance of ZnF₂ may arise from a favorable balance between Lewis acidity and functional-group compatibility. Its coordination to the isatin carbonyl could increase its electrophilicity and facilitate nucleophilic attack by the isocyanide, promoting formation of the proposed nitrilium intermediate. In contrast, stronger Lewis acids may coordinate too strongly to the carbonyl or other reaction components, promote competing pathways, or inhibit subsequent reaction steps.

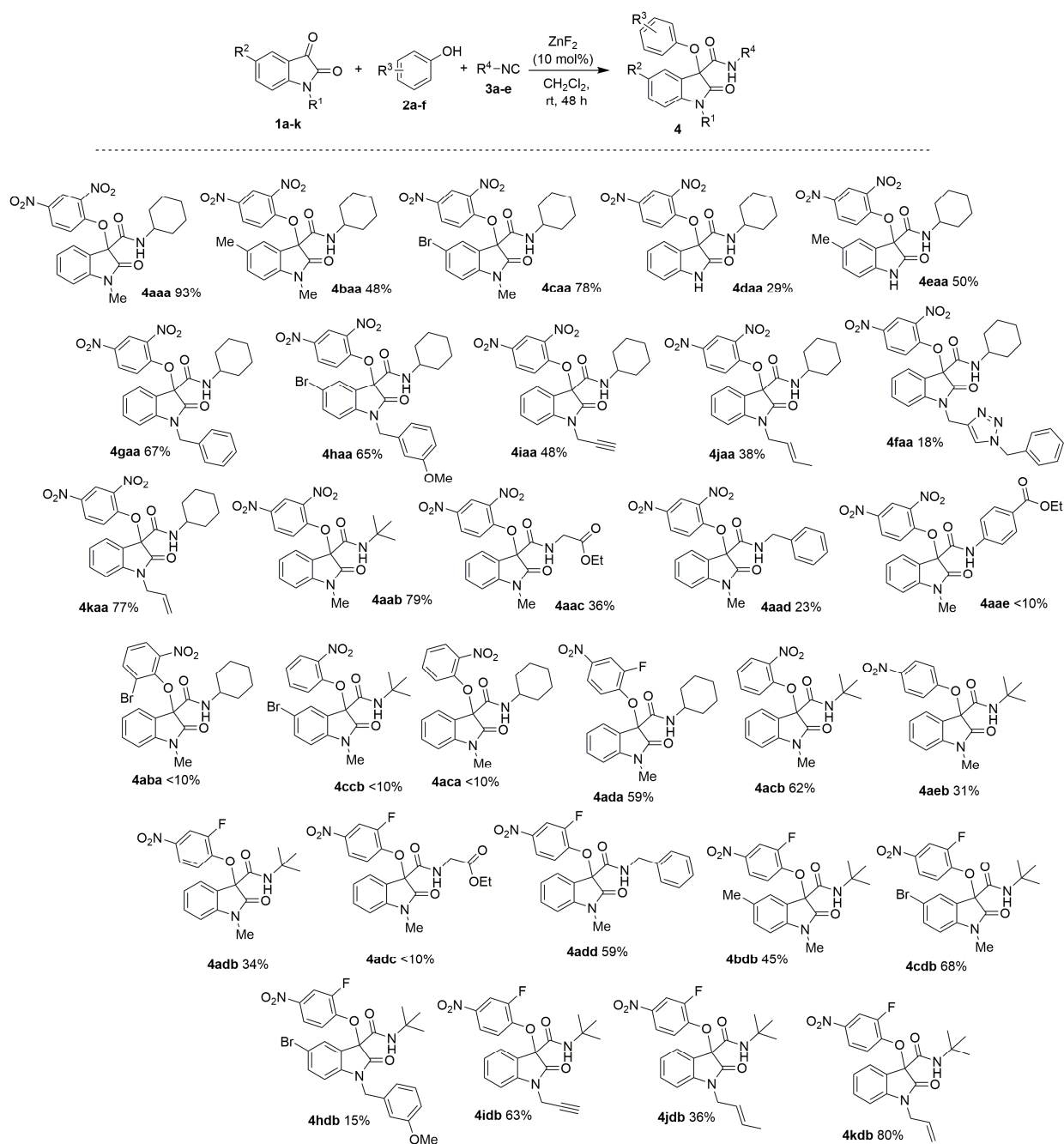
Additionally, the use of a Brønsted base such as DIPEA also resulted in a high yield of **4aaa** (90%, Table 1, entry 13), consistent with the findings previously reported by Dai and Lu [16], as well as by El Kaim and co-workers [10,12,13].

Although the use of molecular sieves (MS) plays a significant role in the 3CPR [7], their addition in this PSR protocol did not lead to any improvement in the yield of PS adduct **4aaa** (Table 1, compare entries 12 and 14).

Having established that the optimal reaction conditions for accessing the PS adducts **4** comprise the use of three equivalents of isocyanide **3**, 10 mol% of ZnF₂ as catalyst, CH₂Cl₂ as the solvent, and a reaction time of 48 h at room temperature, the scope of the reaction was subsequently evaluated by varying each of the reaction components (Scheme 3). A variety of *N*- and C5-substituted isatins **1a–k** was evaluated under the established PSR conditions, generally affording the corresponding PS adducts in moderate to good yields (18–93%; Table 1, entry 12, and Scheme 3). The highest yields were observed when *N*-methyl **1a**, C5-Br-*N*-methyl **1c** and *N*-allyl **1k** isatin derivatives were used, providing the corresponding adducts **4aaa**, **4caa** and **4kaa** in 93%, 78% and 77% yield, respectively (Table 1, entry 12 and Scheme 3). These results indicate that the reaction tolerates several substituents at both the isatin nitrogen and the C5 position.

The nature of the isocyanide had a pronounced effect on the reaction efficiency. *tert*-Butyl isocyanide **3b** performed well, affording **4aab** in 79% yield (Scheme 3). In contrast, isocyanides comprising electron-withdrawing substituents gave substantially lower yields: compounds **4aac** and **4aae** were obtained in 36% and <10% yield, respectively (Scheme 3). This trend may reflect a reduction in the nucleophilicity of the isocyanide carbon caused by the electron-withdrawing ester group, thereby disfavoring its addition to the activated

carbonyl group and the subsequent formation of the proposed nitrilium intermediate (Scheme 1). Benzyl isocyanide **3d** also gave lower yields, with **4aad** being isolated in 23% yield (Scheme 3). Although this result cannot be explained solely by electronic effects, it suggests that the steric and electronic properties of the isocyanide influence the efficiency of the reaction. Accordingly, the present methodology appears to be most effective with relatively nucleophilic aliphatic isocyanides that do not contain strongly electron-withdrawing substituents.



Scheme 3. Scope of the PSR to access a library of phenoxy-indoline carboxamide derivatives **4**.

Although quite efficient with disubstituted-nitrophenol **2a**, we found some difficulties using other phenol derivatives bearing electro-withdrawing substituents. The reaction was tested with monosubstituted nitrophenols (nitro group in positions *ortho*, *meta* and *para*), and the yields of the corresponding PS adducts were very low, with the exception of compound **4acb**, obtained in 62% yield using 2-nitrophenol **2c** (Scheme 3). This PSR

approach failed in accessing the corresponding PS adduct **4** when 3-nitrophenol was used. This behavior is consistent with the electronic requirements of the Smiles rearrangement: a nitro group located *ortho* or *para* to the phenolic oxygen can facilitate the proposed intramolecular nucleophilic aromatic substitution by stabilizing the negatively charged transition state or Meisenheimer-type intermediate [10,11]. In contrast, a *meta*-nitro group cannot provide comparable resonance stabilization, which may account for the failure of 3-nitrophenol under the conditions examined.

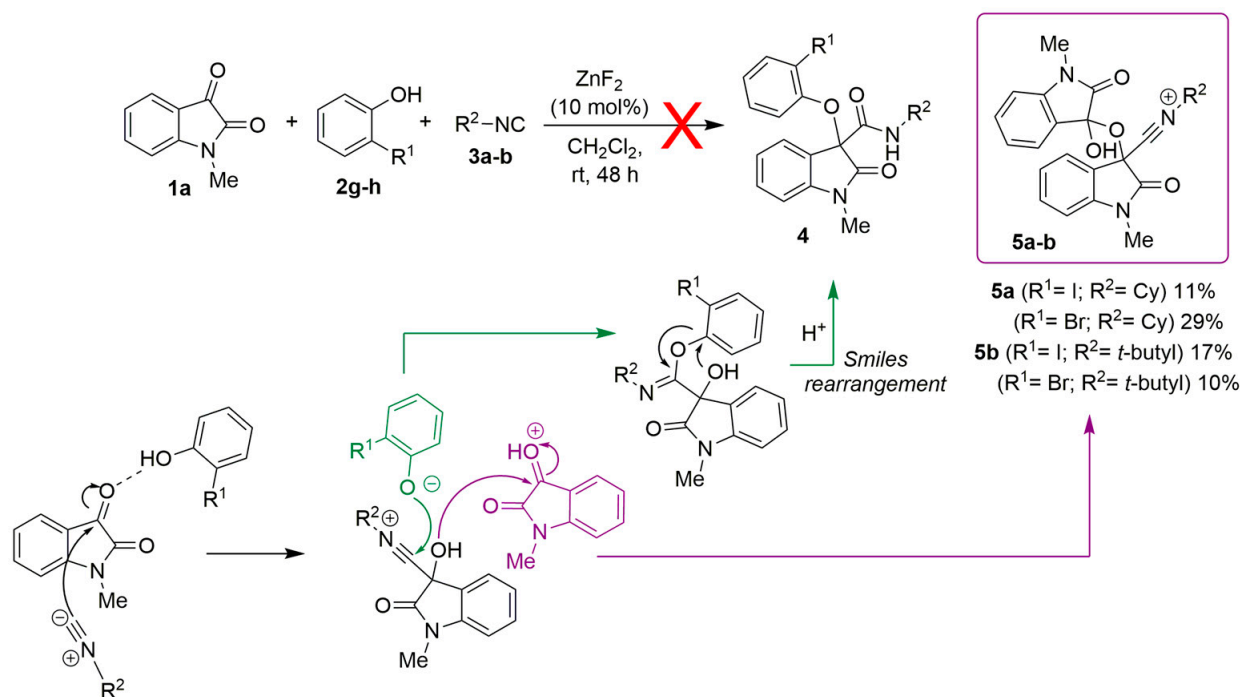
Despite some lack of reproducibility, apparently nitrophenols bearing two electron-withdrawing groups are more efficient in the formation of the three-component adducts **4**. 2-Fluoro-4-nitrophenol **2d** generates the corresponding phenoxy-indoline carboxamide derivatives **4** in moderate to very good yields (see, for instance, products **4ada**, **4add**, **4bdb**, **4cdb**, **4idb** and **4kdb** were obtained in 59%, 59%, 45%, 68%, 63% and 80% yields, respectively, Scheme 3). The combined inductive effects of fluorine and the nitro group may increase the acidity of the phenol and facilitate both the initial incorporation of the phenolic component and the subsequent rearrangement.

Nevertheless, electronic activation alone was not sufficient to ensure efficient product formation. Interestingly, 2-bromo-5-nitrophenol failed to produce the corresponding PS adduct, while 2-bromo-6-nitrophenol **2b** afforded compound **4aba** in only vestigial yield (<10%, Scheme 3). For 2-bromo-5-nitrophenol, the position of the nitro group may provide insufficient resonance stabilization for the proposed Smiles rearrangement. In the case of 2-bromo-6-nitrophenol, the simultaneous presence of two *ortho* substituents may introduce substantial steric blockage around the phenolic oxygen and the aromatic carbon involved in the rearrangement. The smaller fluorine substituent in 2-fluoro-4-nitrophenol appears to provide a more favorable balance between electronic activation and steric accessibility. These interpretations are consistent with the observed substrate scope, although further mechanistic studies would be required to establish the precise origin of these effects.

To further investigate the scope of the PSR, we extended our study to include additional phenol derivatives, namely 2-iodophenol **2g** and 2-bromophenol **2h** (Scheme 4), which, to the best of our knowledge, have not been successfully employed in this type of reaction. Under the established reaction conditions, the formation of the expected PS adducts **4** was not observed. Instead, a by-product (**5a–b**, Scheme 4), identified as a nitrilium acetal intermediate (**5**), was isolated via liquid chromatography and characterized by NMR and HRMS analyses. These findings suggest a preferential formation of the acetal intermediate, which appears to hinder the Smiles rearrangement necessary to access adduct **4** (Scheme 4). Previous work by Ramozzi and Morokuma [27], based on high-level DFT calculations, supported the existence of the nitrilium species as a stable intermediate in solution during the 3CPR. Furthermore, the groups of Eberlin and Neto [28], as well as Angelis [29], experimentally confirmed the presence of this type of nitrilium intermediate in the Ugi reaction using ESI-MS(/MS).

Although similar evidence has not been reported for the PSR, the reaction is proposed to proceed through a nitrilium acetal intermediate (not directly detected or isolated in the present study), consistent with previously reported mechanisms for the PS reaction, rationalizing the formation of intermediate **5**, isolated under our conditions (Scheme 4).

Based on the general mechanism previously described for the PSR [11], and in line with the observations of Ramozzi and Morokuma [27], we postulate that the initial nitrilium ion (formed from the reaction between the isocyanide and the isatin) subsequently reacts with a second molecule of activated isatin, leading to the formation of the nitrilium acetal derivative **5** (Scheme 4).



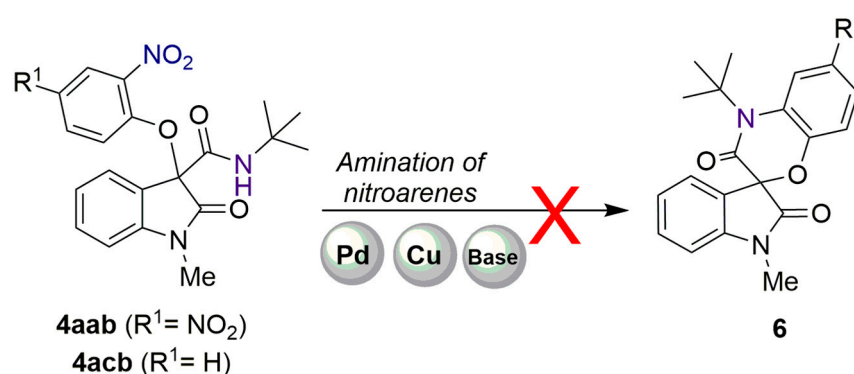
Scheme 4. The PSR using 2-iodo and 2-bromophenol (**2g** and **2h**, respectively) derivatives and the postulated mechanism to access the PS adducts **4** and the nitrilium acetal intermediate **5**.

In general, low yields (10–29%) were obtained when halogenated phenols (**2g–h**) were used in combination with either of the tested isocyanides (**3a–b**), with partial recovery of the starting materials also observed. Interestingly, the formation of by-products **5a** and **5b** did not occur in the absence of halogenated phenols, highlighting the crucial role of these reagents in promoting the formation of intermediate **5**. To further explore this observation, the reaction was repeated using 3-nitrophenol (a component that previously failed to yield the desired product in the component scope study), and the nitrilium acetal intermediate **5b** was isolated, albeit in vestigial yield (<10%).

The nitrilium acetal intermediate **5** was not detected across the broader substrate scope (Scheme 3), suggesting that its formation may depend on the electronic and/or steric properties of the phenol component and may reflect a deviation from the proposed Smiles rearrangement pathway.

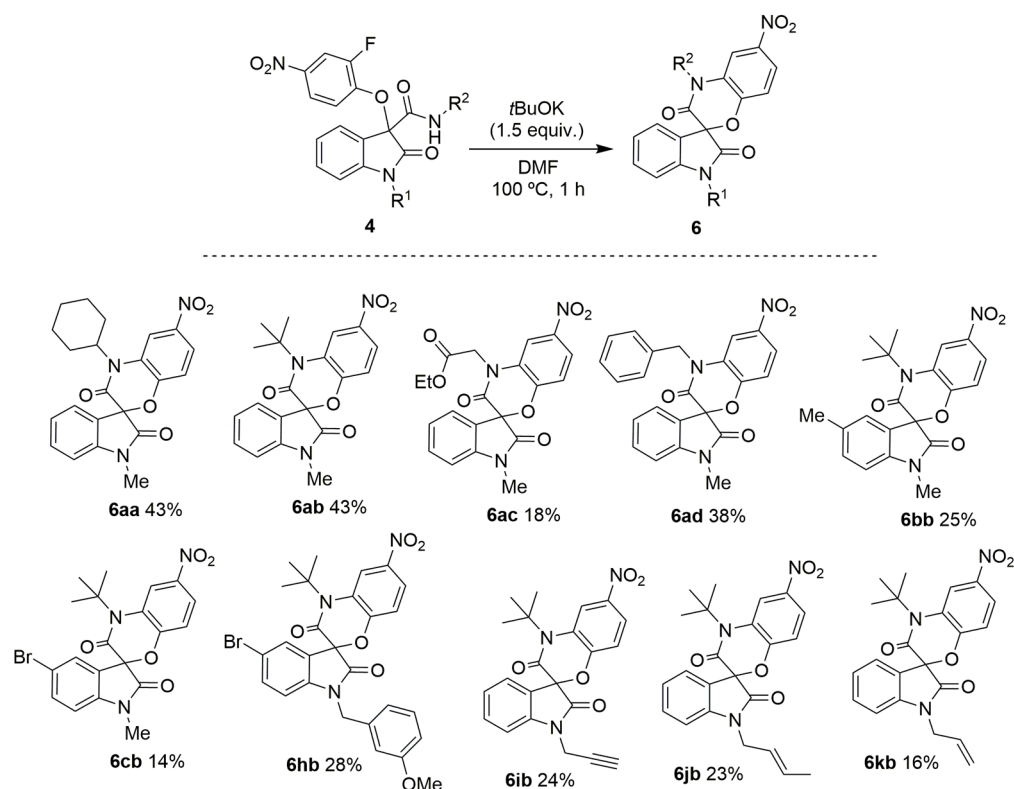
3.2. Synthetic Divergence via Post-Passerini–Smiles Modifications

Nitroarenes, which are among the most readily accessible electrophilic precursors [30], serve as valuable building blocks for the synthesis of novel molecular scaffolds. Among the various synthetic transformations available, cross-coupling reactions represent particularly attractive strategies [31,32]. Building on this and utilizing our previously obtained PS adducts **4aab** and **4acb**, we applied literature-reported methodologies to access the corresponding spiro-oxindole derivatives **6** (Scheme 5), which are considered promising candidates for cancer research [33]. The reaction was unsuccessful when Buchwald–Hartwig amination protocols employing palladium catalysts were applied, in accordance with the procedures reported by Nakao [34] and Liu [35]. Similarly, the copper-catalyzed direct amination method developed by Seko [36] was tested; however, it resulted only in the formation of unidentified decomposition by-products in the crude reaction mixture.



Scheme 5. Attempts to access spirooxindole derivatives via nitroarene reactions.

In their exploration of post-condensation transformations of PS adducts, El Kaim and co-workers reported the synthesis of benzoxazinone derivatives via a second Smiles rearrangement, employing basic conditions in polar aprotic solvents [14,15]. When these conditions were applied to our PS adducts **4a** and **4b** (Scheme 5), no spirocyclic ring formation was observed. However, when 2-fluoro-4-nitrophenol (**2d**) was used as the phenolic component in the PSR, the reaction proceeded efficiently, resulting in the release of a fluoride ion and the formation of the corresponding spirooxindole derivative **6**, under the action of *t*BuOK in DMF at 100 °C (Scheme 6). Under these conditions, a series of spirooxindole derivatives **6** was synthesized in moderate yields within just one hour of reaction time (Scheme 6).



Scheme 6. A family of spirooxindole hybrids **6** from PS adducts **4**.

Although the exact mechanism remains unclear, it is likely that a second Smiles rearrangement [11] contributes to the cyclization step through the migration of the electrophilic aryl ring, as proposed by El Kaim and co-workers [14,15]. An attempt to carry out the transformation in a one-pot sequence was made but proved unsuccessful. A possible explanation can likely be attributed to the markedly different conditions required

for the two transformations. The PSR proceeds with ZnF_2 in CH_2Cl_2 at room temperature (Scheme 3), whereas the subsequent cyclization requires $t\text{-BuOK}$ in DMF at 100°C (Scheme 6). Residual ZnF_2 , unreacted starting materials, and reaction by-products may consume or deactivate the base and interfere with the intramolecular nucleophilic aromatic substitution. In addition, the incompatibility between the solvents required for the two transformations may have contributed to the failure of this approach.

3.3. Antiproliferative Activity

Next, we performed a preliminary biological evaluation of the PS adducts **4**, the nitrilium acetal intermediates **5** and the spirooxindole hybrids **6** to assess their antiproliferative activity. A panel of six representative human solid-tumor cell lines, including lung (A549 and SW1573), cervix (HeLa), pancreas (MIA PaCa-2), breast (T-47D), and colon (WiDr) cancer cells, was used following our implementation of the NCI screening protocol [24]. Among the synthesized compounds, a total of forty-one compounds were screened, while compounds **5a**, **5b**, **6ad** and **6bb** were excluded due to poor solubility under the experimental conditions. Overall, most of the synthesized compounds displayed weak ($\text{GI}_{50} = 10\text{--}100\ \mu\text{M}$) or no activity ($\text{GI}_{50} \geq 100\ \mu\text{M}$), indicating that only specific structural features are compatible with antiproliferative activity (Figure 2, Table S1).

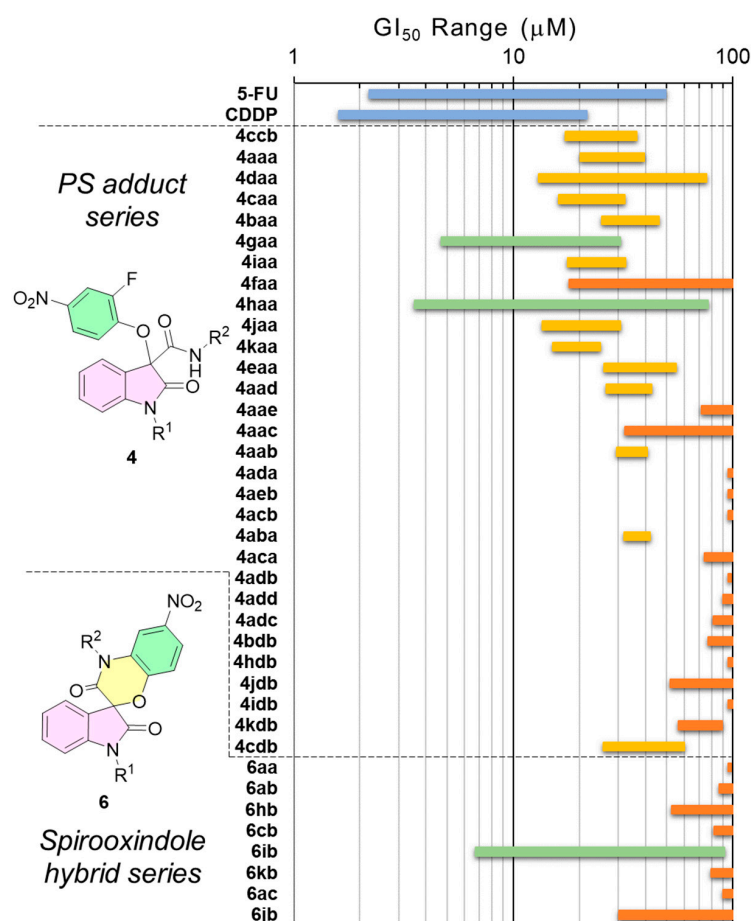


Figure 2. GI_{50} range plot of investigated PS adducts **4** and spirooxindole hybrids **6** against human solid tumor cell lines. Bars represent standard anticancer drugs 5-fluorouracil (5-FU) and cisplatin (CDDP) (blue), the most relevant active compounds (green), compounds with modest activity (yellow), and compounds with negligible activity (orange). The horizontal log-scale represents values ranging from 1 to 100 μM ; compounds with a calculated GI_{50} value exceeding the maximum tested concentration are capped and plotted at the 100 μM threshold line.

Derivatives **4gaa**, **4haa**, and **6ib** provided the most notable screening results. The primary interest of these three derivatives lies in how minor structural variations appear to influence the spectrum of biological activity, modulating the profile from a broader antiproliferative effect to a narrower cell line distribution. Compound **4gaa** showed the highest overall potency within this specific series, displaying low micromolar values against most tested cell lines, particularly against SW1573 lung cancer cells ($GI_{50} = 4.7 \mu\text{M}$; Table S1). These preliminary data suggest that this specific substitution pattern might be favorable for maintaining an extended antiproliferative profile. In contrast, **4haa** and **6ib** exhibited a more limited activity profile. Compound **4haa** disclosed moderate inhibitory values, particularly against HeLa, MIA PaCa-2, and SW1573 cells, highlighting the potential interest of the benzyl unit attached to the nitrogen of isatin.

Regarding the spirooxindole derivatives, compound **6ib** demonstrated preferential activity for the SW1573 lung line ($GI_{50} = 6.7 \mu\text{M}$, Table S1) while remaining mostly inactive ($GI_{50} > 100 \mu\text{M}$) against the other solid tumor models in the panel. Interestingly, SW1573 cells (harboring a $KRAS^{G12C}$ mutation) consistently proved to be more sensitive to the PS adducts than A549 cells (harboring a $KRAS^{G12S}$ mutation), despite both sharing a lung tissue origin. This observation aligns with our historical data on corresponding Ugi [5,6] and Passerini adducts [7]. However, because these two cell lines differ in numerous other molecular and genetic features beyond their oncogenic mutations, this differential response cannot be definitively assigned to a specific $KRAS$ variant. At this stage, this correlation remains a preliminary hypothesis that explicitly requires validation using a broader, dedicated isogenic cell line panel.

4. Conclusions

A library of 30 phenoxy-indoline carboxamide hybrids was efficiently synthesized via the underexplored PSR. Optimization of temperature, reaction time, solvent, and additives demonstrated the versatility of this approach, enabling broad functionalization of isatin scaffolds. The method exhibited tolerance toward isatin derivatives, electron-deficient phenols, and various isocyanides, affording the desired hybrid compounds in yields ranging from low to excellent depending on the specific electronic features of the substrates. Overall, non-activated aliphatic isocyanides, particularly *tert*-butyl and cyclohexyl isocyanides, showed the highest performance, whereas benzyl isocyanide displayed moderate performance and isocyanides bearing electron-withdrawing ester groups generally showed low performance. Regarding the phenol component, 2,4-dinitrophenol and 2-fluoro-4-nitrophenol generally exhibited high-to-moderate performance, while mono-nitrophenols showed moderate-to-low performance depending on the nitro-group position. Brominated nitrophenols and 3-nitrophenol displayed low performance or failed to afford the desired products.

Both libraries were assessed in a preliminary screening for antiproliferative activity against six human solid-tumor cell lines. While most compounds showed modest to negligible activity, derivative **4gaa** emerged as a promising starting point, displaying GI_{50} values in the low micromolar range ($< 10 \mu\text{M}$). Further mechanistic studies are required to validate these early observations, clarify the mode of action, and advance lead compound optimization.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/chemistry8080106/s1>.

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