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Diversity-Oriented Synthesis of Highly Fluorescent Fused-isoquinolines for Specific Subcellular Localization.

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ABSTRACT: A multicomponent Diversity-Oriented Synthesis of new highly emissive tetracyclic isoquinolines that target specific organelles is described. The title compounds were prepared via a three-step protocol starting with an Ugi four-component reaction, followed by either an intramolecular alkyne hydro-arylation and subsequent alkene isomerization, or through a Pomeranz–Fritsch type cyclization with a final intramolecular Heck reaction. Subcellular localization studies of these compounds using green-channel confocal microscopy revealed remarkable and distinctive distribution patterns in live cells, showing an unprecedent high selectivity and imaging contrast. The differentiated organelle visualization –including localizers for mitochondria, lysosomes, Golgi apparatus, endoplasmic reticulum and plasma membrane– was achieved by varying the nature of the tetracyclic system and substituent pattern, changing the original four-component set in the starting Ugi reaction.

INTRODUCTION.

Small-molecule fluorescent probes with different organelle localization abilities have remarkable interest in biological applications.[1] Numerous biological assays and new experimental techniques have been developed to monitor the output profiles of these fluorescent probes. They span from single-channel fluorescence intensity recordings to single-molecule localization methods.[2] Ideally, those molecular probes should be of low molecular weight, high photostability and high brightness, so that good signal-to-noise ratios and short acquisition times can be achieved. Importantly, the probes should lack of fluorescence intensity fluctuations due to spectral diffusion or triplet and rotational jumps.[3] These properties acquire significant relevance in the rational design of subcellular fluorescent probes where highly heterogeneous environments can influence the probe response profile, as well as its spatial distribution within the cell. Although some strategies to achieve specific subcellular localizations have been demonstrated,[4] the synthetic methods to obtain single organelle-targeted probes are still very scarce. Diversified fluorogenic probes with distinctive molecular structures are highly needed to monitor different subcellular membranes and the dynamics of local biomolecular events thus understanding the cell status in health and disease. Most of the recent molecular fluorescent probes are based on the same relatively small set of sometimes expensive fluorophores such as Mitotracker® dyes (cyanines) Lysotracker® dyes (BODIPY's), AlexaFluor™ dyes (xanthenes) and Atto® dyes (carbopyronines) (Figure 1).[5] Thanks to the new technologies to study the different subcellular organelles based on optical microscopy techniques, the synthesis of novel fluorescent markers suitable for site-specific intracellular labeling remains an unmet need.[6] Considering that the structure and function of the cell organelles is highly diverse in nature, developing a single synthetic route that can afford structurally fine-tuned probes with distinct optical responses, cytotoxicity and lifetimes is a very challenging task. Designing such a family of subcellular probes that share a skeleton and at the same time are able to show structural variations for different organelle localizations requires innovative synthetic approaches. In this regard, the *Diversity-Oriented Synthesis* (*DOS*)[7] has emerged as a powerful approach for the construction of compound libraries with diverse molecular architectures.

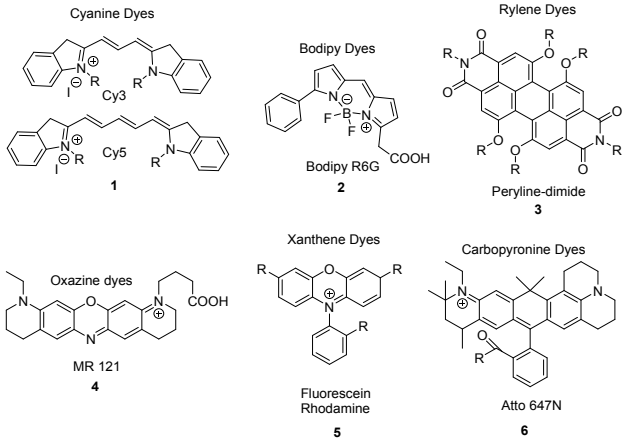
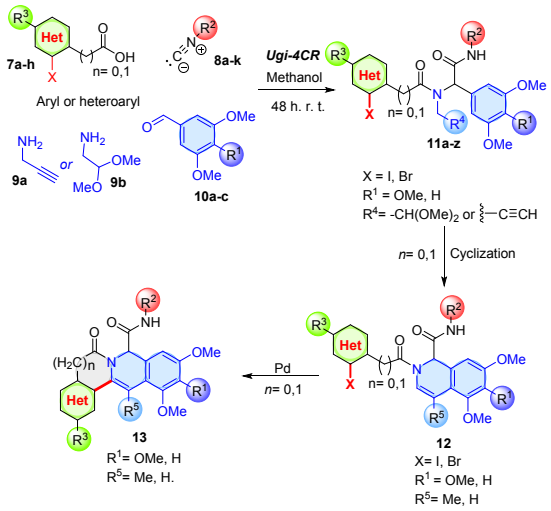


Figure 1. Different fluorophore families (top labels) with commercially available fluorescent probes (bottom labels) used in optical microscopy techniques.

Using this strategy, the molecular structure can be significantly modified, either by varying the peripheral functional groups or by producing large skeletal changes, and is a very promising platform for the efficient exploration of the chemical space.[8] Indeed, these approaches produce a range of compounds that allow to investigate their influence in different biological systems, mainly for the discovery of new medicinal leads.[9] However, *DOS*-strategies for the discovery of novel molecular materials for other applications have been explored to a much lesser extent. Recently, as a part of our ongoing program in the Diversity-Oriented Synthesis of different heterocyclic scaffolds,[10] we envisioned that the modular nature of the Ugi four component reaction (Ugi-4CR) might offer the unique opportunity to design novel and expedient methods for the synthesis of complex fluorescent scaffolds. In principle by the judicious choice of the starting four-component input set, the photophysical properties of the

final structure might be rapidly fine-tuned for different applications. It is important to note that the chemical complexity increased when the Ugi-4CR adducts engage in further bond forming processes.[11] Based on this, we became interested in the synthesis of a small library of the conjugated tetracyclic fused isoquinolines **13** (Scheme 1).

Scheme 1. General synthetic approach for the scaffold diversity generation of highly fluorescent fused-isoquinolines.

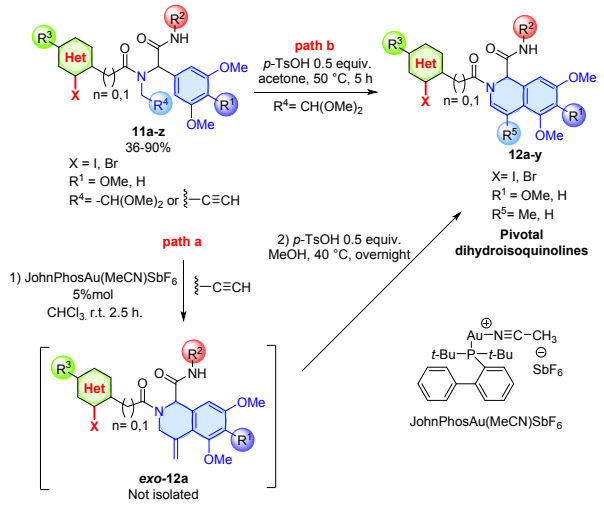


Consequently, a three-step protocol was devised starting with an Ugi-4CR (component input set: 2-halobenzoic or phenylacetic acids, substituted benzaldehydes, different isocyanides and **9a** or **9b** as amine input). With these frameworks in hand, either an intramolecular alkyne hydro-arylation followed by an alkene isomerization (*exo*→*endo*), or a Pomeranz–Fritsch type cyclization were carried out to assemble isoquinolines **12**. The final event relied on the intramolecular Heck reaction to afford the fused-isoquinolines **13** (Scheme 1). Gratifyingly, we discovered that the all final compounds were highly fluorescent and decide to investigate further. Thus, a wide array of molecular candidates was rapidly obtained to ascertain their fluorescent properties and their potential as selective biological localizers for the various cell organelles. As the ultimate success of any molecule library is determined by the biological relevance of the compounds,[12] it is crucial that the implemented synthetic sequence warrants an optimal functionalization strategy. In this regard, our synthetic protocol subsequently provided access to molecules with chemical vectors to target a desired cellular organelle, therefore combining the goals of DOS with the advantages of organelle-targeting functionalization, which aims to access a precise structural unit for a specific organelle. The fluorescence response efficiency, partition coefficient and subcellular localization for each compound was also correlated, finding excellent fluorescent localizers for mitochondria, lysosomes, Golgi apparatus, endoplasmic reticulum and plasma membrane.

RESULTS AND DISCUSSION

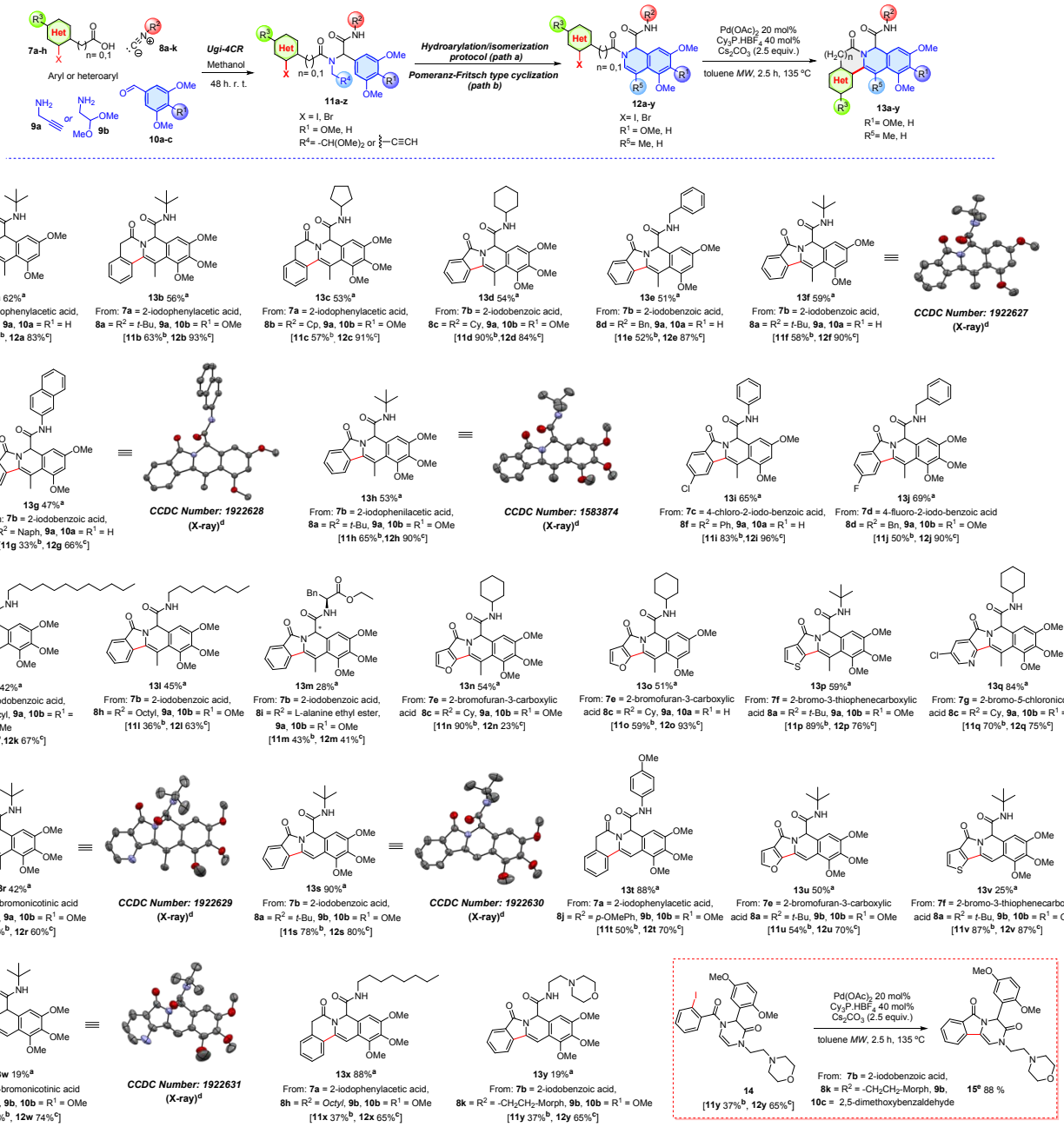
Diversity-Oriented Synthesis of highly emissive fluorophores. The synthesis of the multicomponent Ugi-adducts **11** was carried out through an equimolar mixture of the corresponding carboxylic halo-(hetero)arene (**7a-h**), one of the two key amines (**9a** or **9b**), an electron rich benzaldehyde (**10a-b**) and isocyanides with various electronic and steric demands (**8a-k**) reacted in methanol at room temperature in an open flask to give the

Scheme 2. Synthesis of isoquinolines **12a-y** through hydroarylation/isomerization protocol (*path a*), or Pomeranz-Fritsch type cyclization (*path b*).



corresponding Ugi propargylic or acetamido adducts **11a-z** (36-90%, Scheme 2). Several diversification vectors were secured in the protocol. In principle, not only the peripheric functional groups can be varied, the nature and size of the (hetero)aromatic systems, might be modulated in the final scaffolds by the simple variation of the carboxylic acid, isocyanide and aldehyde. Once the propargyl- and dimethylacetamido-adducts **11a-z** were obtained, the intramolecular alkyne hydro-arylation/isomerization or Pomeranz–Fritsch condensation were conducted. In the case of the propargyl-Ugi adducts **11a-r**, we found that the catalytic use of the JohnPhosAu(MeCN)SbF_6 (5 mol%) in chloroform resulted in the complete transformation to the corresponding tetrahydroisoquinoline ***exo*-12a**. It is worth mentioning that the use of an electron rich benzaldehyde is mandatory for the cycloisomerization to have an acceptable reaction rate. We found that the reaction of the crude ***exo*-12a-r** products with 0.5 equiv. of *p*-toluenesulfonic acid in methanol completely equilibrated the product to the *endo* isomers; which gave the targeted isoquinolines (***endo*-12a-r**) (yields 33-96%, Scheme 2, *path a*). In the case of the dimethylacetamido-Ugi adducts **11s-z**, the treatment with 0.5 equiv. of *p*-TsOH in acetone enabled the cyclization to the desired isoquinolines **12s-y** in good reaction yields ranging from 70% to 80% (Scheme 2, *path b*). Interestingly, we observed that the compound **11z** (from 2,5-dimethoxybenzaldehyde as the starting aldehyde) exclusively afforded the ketopirazinone **14** which was formed by the acetal deprotection reaction of **11z** in acid media followed by the intramolecular nucleophilic attack of the primary amide moiety. At this point, the dihydroisoquinolines **12a-y** were directly submitted to Heck ring closing conditions,[13] to afford the densely functionalized fused-isoquinoline fluorophores **13** in good yields (Table 1). Starting from 2-iodophenylacetic acid (**7b**) in this approach, it was possible to obtain fused isoquinolinone-isoquinolines (**13a-c**, **13t** and **13x**)

Table 1. Multicomponent sequence and Pd-catalyzed ring closing for the Diversity-Oriented Synthesis of isoquinolines **13a-y**. *Inset:* obtained tricyclic compound **15** *via* Heck reaction of compound **14**.



[a] Isolated yield of the Heck ring closing event. [b] Isolated yield of the Ugi-4CR, [c] Isolated yield of the cyclization reactions, [d] Thermal ellipsoids are drawn at 50% probability, all hydrogen atoms are omitted for clarity purposes.[15e] The tricyclic compound **15** was obtained from the ketopirazinone **14**. All Heck reactions were carried out by microwave assistance.

in isolated yields ranging from 53 % to 88 %. Fused isoindolone-isoquinolines (**13d-m**, **13s**, **13y**) were also obtained in comparable isolated yields (28 - 90 %) using 2-iodobenzoic acids (**7a**, **c** and **d**). The use of 2-bromofuran-3-carboxylic acid **7e** afforded the corresponding furo-pyrrolone-isoquinolines **13n**, **13o** and **13u** in good isolated yields (50 - 54%). Additionally, the use of 2-bromothiophene-3-carboxylic acid **7f** gave the corresponding thieno-pyrrolone-isoquinolines **13p** and **13v** in moderate isolated yields (59 and 25% respectively). Finally, when 2-bromonicotinic acids (**7g-h**) were used, we found that the pyrido-pyrrolone-isoquinolines **13q**, **13r** and **13w** were obtained in moderate to excellent isolated yields. Importantly, that halogens such as chloride (**13i**) and fluoride (**13j**) were well tolerated under the Heck conditions. A range of isocyanides with different electronic and steric demands such as *tert*-butyl **8a**, cyclopentyl **8b**, cyclohexyl **8c**, benzyl **8d,** naphthyl **8e** and the lipidic isocyanides **8g-h** were also successfully implemented in the protocol. Finally, the Heck cyclization of ketopirazinone **14** gave the pyrido-pyrrolo-pyperazinone fused tricycle **15** in excellent yield.

Fluorescence and partition coefficient studies. As mentioned before, the relevance of a molecular library obtained by DOS is dictated by the visualized application, which implies that most of the molecules could be unsuccessful no matter how structurally diverse they are or how efficiently this diversity has been achieved. Here we present a new fluorophore architecture having a different chemical composition. To verify the optical performance of the molecules, their photophysical properties were evaluated by spectrophotometric means. Notably, all the compounds exhibited moderate to high fluorescence quantum yields (Φ_{fl}), ranging from 0.19 to 0.99 (*see supporting information*). This indicates that the compounds can be considered as an efficient fluorophore library, avoiding auto-fluorescence problems under cell conditions as demonstrated by spectrally resolved confocal microscopy experiments (Figure S33). Real-time spectrally resolved confocal images provided structural information through the emission spectra of the fluorophore and blank samples under subcellular environments.

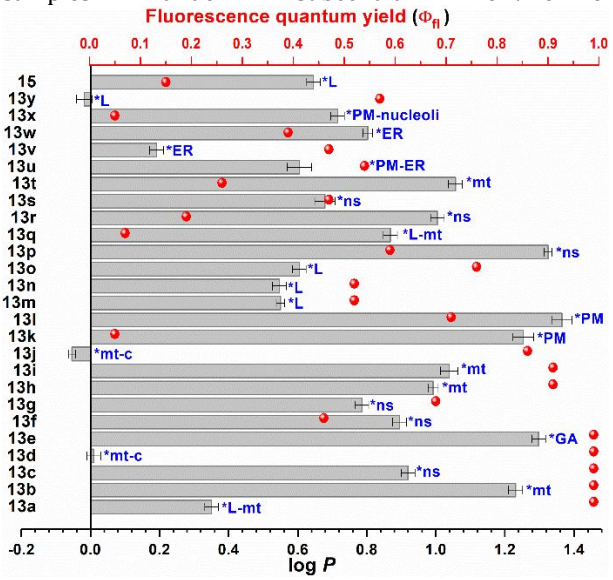


Figure 2. Representation of the experimental partition coefficients (log P, grey bars) and fluorescence quantum yields (Φfl, red points) for the fluorophore library. L: lysosome; PM: plasma membrane; mt: mitochondria; ER: endoplasmic reticulum; GA: Golgi apparatus and ns: non-specific localization.

However, to evaluate the performance of these fluorophores as subcellular fluorescent labels for bioimaging applications, the partition coefficient in terms of log *P* were obtained (Table S2). Due to the structural diversity presented in this collection, highly diverse partition coefficients were found, as shown in Figure 2. Nevertheless, interesting correlations between the degree of lipophilicity and the membrane localization were observed. The measured log *P* values suggest that while most of the molecules are highly lipophilic, important differences in their localization pattern can be found, for example, the most lipophilic fluorophores with log $P > 0.8$ exhibited a high membrane distribution (**13b**, **13e**, **13i**, **13k**, **13l**, **13p** and **13t**), and molecules with less lipophilic character were found to be equilibrated between the lipid membranes and cytosol as non-organelle specific. Moreover, the more hydrophilic fluorophores **13d** and **13j** were found to be specific for two organelles while **13y**, hydrophilic as well, were derivatized to target lysosomes using a morpholine-derived group, thus finding a highly lysosomal distribution (Pearson's correlation coefficient, PCC = 0.91). In addition to the log *P* values, the high fluorescence quantum yields (Φ_{fl}) together with the high absorption cross-section of the fluorophores indicates excellent photostability (Figure S34). As shown in Figure 2 (red points) most of the fluorophores presented a highly efficient radiative deactivation in terms of Φ_{fl} thus avoiding photobleaching. This is an excellent photophysical feature that provides high signal-to-noise ratio images for large time-course experiments useful for high-resolution confocal microscopy techniques.

Confocal fluorescence imaging studies for organelle distribution. These experiments were performed in HeLa cells using the fluorescence profile of the synthetized fluorophore library. Gratifyingly, compounds **13a-y** showed specific organelle distribution. Among the most interesting results, fluorophores **13i** and **13t** were highly specific for mitochondria, an unexpected finding since both fluorophores are not cationic (non-Nernstian lipophilic cations),[14] compared to the well-known MitoTrackers, TMRM, JC-1 or oxonols in general. Although non-cationic mitochondrial localizers have rarely been described,[15] it is interesting to note that **13i** and **13t** presented the larger log *P* values, and it is possible that such lipophilicity can assist the mitochondrial targeting, Figure 3 (see Fig. S35) for the co-localization study). Thus, **13i** and **13t** fluorophores can be used for large time-course experiments of mitochondria when membrane polarization variations can affect the fluorescence profiles of common Nernstian probes such as MitoTrackers. Mitochondrial membrane potential depolarization experiments using the common CCCP uncoupler were carried out to confirm that **13i** and **13t** are not of the Nernstian features (Fig. S36).

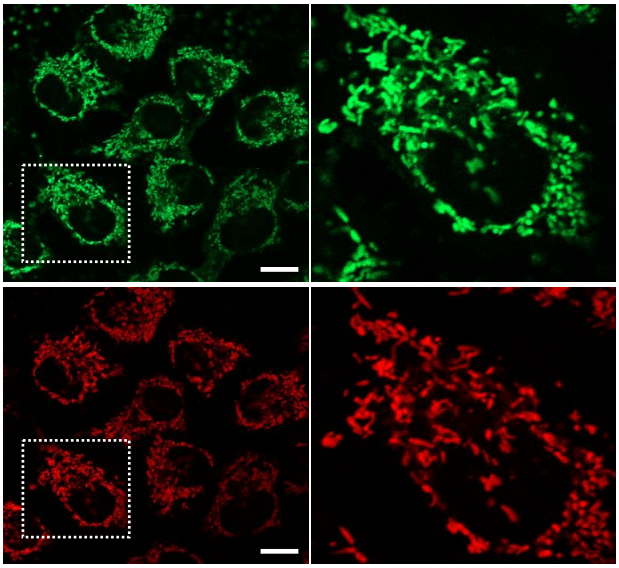


Figure 3. Intracellular localization redistribution of 5 μM **13t** probe in live HeLa cells. Panel (A) shows 30 minutes **13t** incubation observed in the confocal green channel (λ_{exc} = 405 nm, λ_{em} = 450 nm), indicating a clean mitochondrial localization, while panel (B) shows the distribution in the

red channel (λ_{exc} = 561 nm, λ_{em} = 613 nm). Scale bars represent 20 μm.

The low-dose experiments confirmed this hypothesis as no fluorophore release was observed under *in vitro* imaging analysis, however, large exposure to CCCP promoted cell death and thus fluorophore release, indicating that the mitochondrial distribution of **13i** and **13t** is not governed by the membrane potential but a specific interaction possibly with lipid domains is taking place.[16] Further screening of the library evidenced the localization breadth of the synthesized fluorescent dyes. Fluorophores **13k**, and **13l** underwent plasma membrane targeting with PCC of 0.83 and 0.91, respectively (Figure 4). Conversely, Golgi apparatus (GA) targeting was only observed for **13e**. This is relevant because GA labels are scarcely reported in literature since it has been considered a "low-concern" organelle,[4] thus such commercially available fluorophores are very uncommon. On the other hand, lysosome targeting was observed for **13m**, **13n**, **13o** and **13y** where a varied degree of co-localization was found for these compounds. Endoplasmic reticulum (ER) was efficiently localized by **13v** and **13w**, while **13d** and **13j** equilibrate mitochondria and cytosol having low specificity for one of them. Fluorophores localizing two organelles were found to be **13a**, **13q**, **13u** and **13x**. Finally, co-localization studies for the rest of the fluorophores indicated non-specific organelle localization, although membrane distribution was observed for all of them. Figure 2 summarizes the *in vivo* subcellular distribution of the fluorophore library. Two representative examples of plasma

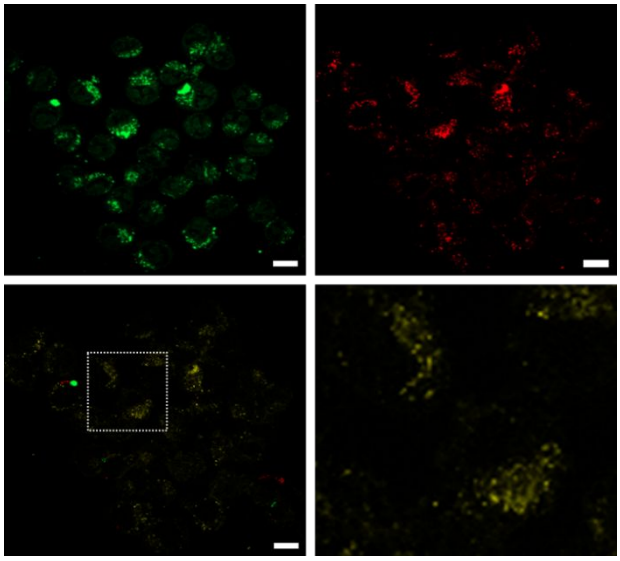


Figure 4. Intracellular localization redistribution of 5 μM **13e** probe in live HeLa cells under 30 minutes incubation indicating a high Golgi Apparatus (GA) distribution when observed in the confocal green (λ_{exc} = 405 nm, λ_{em} = 450 nm) red (λ_{exc} = 561 nm, λ_{em} = 613 nm) channels. The high degree of overlap in yellow when using CellLight® Golgi-RFP co-localizer indicates that **13e** is GA specific. Scale bars represent 20 μm.

membrane (PM) localizers are shown in Figure 5. Panel A shows 30 minutes 5 μM **13l** incubation observed in the green channel indicating a clean PM localization, while **13x** (panel B) equilibrates PM and nucleoli. CellMask co-localization for PM indicated a PCC of 0.87 for **13l** and 0.81 for **13x**, Figure S37. Importantly, no significant crosstalk of the green emission of these fluorophores with the red channel was observed by using CellMask with excitation wavelength above 560 nm. Then, the nucleoli distribution present in the **13x** fluorescence profile can be explained not only by its lower lipophilicity compared to **13l** or **13k**, but by structural differences. Although **13x** also contains a hydrocarbon chain and similar polyaromatic composition, the 6-membered heteroaromatic ring seems to promote intercalation in the nucleoli probably through RNA grove interactions. Importantly, no significant crosstalk of the green emission of these fluorophores with the red channel was observed by using CellMask with excitation wavelength above 560 nm. Considering these results, the nucleoli distribution present in the **13x** fluorescence profile can be explained not only by its lower lipophilicity compared to **13l** or **13k**, but also by important structural differences.[17] Although **13x** also contains a hydrocarbon chain and similar polyaromatic composition, the 6-membered heteroaromatic ring seems to promote intercalation in the nucleoli probably through RNA grove interactions.

Refining the structures by organelle-targeting functionalization. Given the interesting results obtained with the DOS strategy, the organelle-targeting functionalization approach was subsequently employed to develop fluorophores **13y** and **15** as presented in Figure 6.

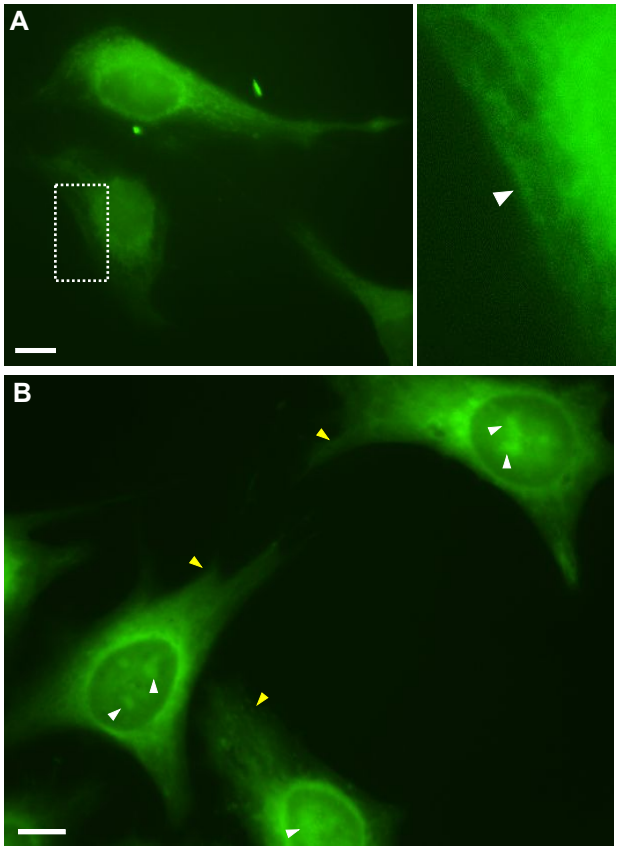


Figure 5. Intracellular localization redistribution in live HeLa cells. Panel (A) shows 30 minutes 5 μM **13l** incubation observed in the confocal green channel (λ_{exc} = 405 nm, λ_{em} = 450 nm, indicating a clean plasma membrane (PM) localization; while panel (B) shows equilibration between PM and nucleolar distribution observed by 5 μM **13x**. Scale

bars represent 20 μm. CellMask co-localization for PM is presented in Figure S37.

This strategy, helped us tune the localization properties of those fluorophores by functionalization with a lipophilic morpholine derivative, which has been used as targeting group for lysosomes.[4] It is important to note the difference in the fluorophore structure, while **13y** is highly fluorescent (Φ_{fl} = 0.57), the low fluorescence response of **15** gives only low-contrast with poor signal-to-noise ratio images (Φ_{fl} = 0.01). Interestingly, the organelle-targeting functionalization approach could be applied to all the fluorophore library if deemed necessary, not only targeting lysosome but also other organelles could be visualized using the appropriate targeting group, *i.e.* tetraphenylphosphonium ion for mitochondria or specific cell-penetrating peptides for other organelles.

CONCLUSIONS

We have successfully implemented a diversity-oriented synthesis for the efficient development of twenty-six small-molecule fluorophores as specific subcellular localizers. Starting with DOS, we obtained not only new fluorescent structures with high fluorescent quantum yields but also new specific organelle-targeted molecules. Through a complementary organelle-targeting functionalization strategy, the library was further refined to increase the specificity for cell organelles. The readily access to tailored fluorophore libraries makes the reported strategy far superior over classical synthesis of fluorescent molecules and commercial co-localizers.

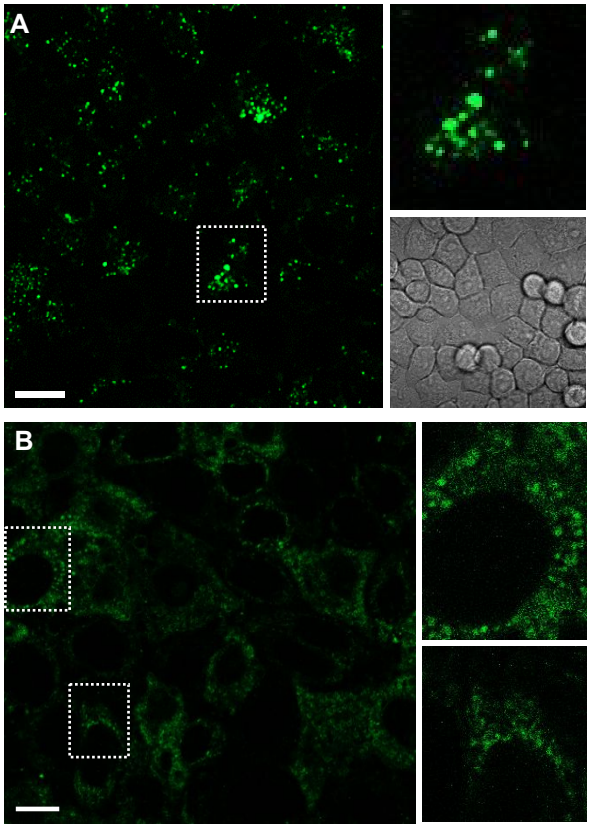


Figure 6. Intracellular localization redistribution in live HeLa cells. Panel (A) shows 30 minutes 5 μM **13y** incubation observed in the confocal green channel (λ_{exc} = 405 nm, λ_{em} = 450 nm), indicating a clean lysosome localization, while panel (B) shows 5 μM 15 distribution giving low signal-to-noise ratio imaging. Scale bars represent 20 μm. Co-localization imaging is shown in Figure S37

EXPERIMENTAL SECTION

Experimental Methods

All reagents and solvents including the compounds **7a-h** and **10a-c** were obtained from Aldrich and Fluka. Toluene was freshly distilled from sodium/benzophenone, methanol was dried over magnesium/iodide and stored over 4 Å molecular sieves. The reaction progress was monitored by TLC using silica gel 60 (ALUGRAM® SIL G/UV); the spots were visualized under UV light (254 nm), or with phosphomolybdic acid, *p*-isoaldehyde and vanillin. Melting points were determined on a Fisher apparatus and are uncorrected. All reactions were performed under a dry argon atmosphere unless otherwise specified. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AV400 MHz, JEOL Eclipse-300 MHz and Varian Unity Inova-500 MHz model spectrometers using $CDCl_3$ and DMSO-d_6 as solvents. Chemical shifts (δ) are reported in ppm relative to $Si(CH_3)_4$ for ^{1}H and ^{13}C NMR experiments were carried out in $CDCl_3$. Coupling constants (J) are reported in hertz (Hz), peak multiplicity is indicated as follows: s= singlet, d= doublet, t= triplet, m= multiplet, bs: broad signal for proton spectra. Microwave-assisted reactions were performed using a Biotage® microwave reactor. IR spectra were obtained with a Bruker Tensor 27 FT-IR spectrometer. High-resolution mass spectra were recorded with an AccuTOFLC equipped with an ionSense DART controller ionization source. X-Ray diffraction: X-ray diffraction studies were realized on a Bruker Smart APEX II CCD diffractometer with graphite-monochromatic Mo Kα irradiation. Solution and refinement have been carried out by Simon Hernández-Ortega and Ruben A. Toscano.

Protocol for octanol/water partitioning (log P) measurements

The log *P* values were measured by octanol partitioning using the shake-flask method.[18] An aliquot of each fluorophore (100 mL, 50–300 mm) in Tris buffer (10 mm, pH 7.4) and 1-octanol (100 mL; Aldrich) were added to a microtube (0.5 mL). The tubes were vortexed for 2 min and centrifuged for 2 min; 25 mL of each layer was removed and diluted either in 100 mL 3:1 methanol/Tris or methanol/octanol for a final composition of 3:1:1 methanol/octanol/Tris. The aqueous layer was diluted an additional fourfold. Three dilutions were prepared per layer, each dilution (100 mL) was pipetted into a 384-well plate, and the absorbance was read at 500 nm with a reference wavelength at 625 nm. The mean A_{500} of three dilutions was calculated for each layer. The log (A_{500} of the organic layer/A_{500} of the aqueous layer) yielded log *P*. This procedure was repeated a minimum of four times per fluorophore to calculate the mean log *P* and standard error. All absorbance measurements used were within the linear range of the instrument.

Protocol for the synthesis of lipidic isocyanides **8g-h**

lipidic isocyanides (**8g-h**) were prepared according to the described procedure in the literature:[19] The corresponding

lipidic amine (Octyl or Dodecylamine, 1 mmol) was dissolved in ethylformate (10 mL). the resulting solution was stirred at reflux for 20 h, After that, the volatiles were removed under reduced pressure furnishing the corresponding formamide in quantitative yield. Finally, the formamides were dehydrated using Et_3N (2 mL) and phosphorus oxychloride (1 mmol) in dry dichloromethane (0.5 mL). The lipidic compounds was yielded **8g-h** in excellent yields after two steps. All spectroscopic data agree directly with the data reported in the literature.

Protocol for the synthesis of the isocyanoacetate **8i**.

The isocyanoacetate (**8i**) was prepared using a slightly modified procedure found in the literature.[20] Therefore, compound **8i** was synthesized from the L-phenylalanine ethyl ester hydrochloride (634 mg, 2.76 mmol). In a first step, the ethyl ester was formylated using formic acid (0.136 mL, 3.58 mmol), dicyclohexylcarbodiimide (DCC 738 mg, 3.58 mmol) and dimethylaminopyridine (DMAP 67 mg, 0.552 mmol) at 0° C in dichloromethane (12 mL), after 16 hours, the ethyl formyl-L-phenylalaninate was yielded in 98% yield (600 mg). With the formamide in hand, dehydration was carried out using triphosgene (916 mg, 1 mmol) in dichloromethane (12 mL) at -78 ° C, obtaining the desired compound **8i** as a yellow oil in 86% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.41 – 7.17 (m, 5H), 4.44 (dd, *J* = 8.3, 5.0 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.35 – 3.04 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ: 166.2, 160.8, 134.5, 129.4, 128.9, 127.9, 62.8, 58.2, 39.0, 14.0. HRMS (DART, $[M+H]^+$) *m/z* calcd for $C_{12}H_{14}N_1O_2$ 204.1024, found 204.1026.

Ugi-4CR/alkyne hydro-arylation/isomerization/ Heck cyclization process experimental methods

General procedure for the synthesis of the Ugi adducts **11a-11z**

Method A. To a 25 mL round bottom flask equipped with a magnetic stirring bar were added propargylamine (Compounds **11a-r**), or aminoacetaldehyde dimethyl acetal (Compounds **11s-z**) (1.8 mmol, 1.0 eq) and the corresponding aldehyde (1.8 mmol, 1.0 eq.) in methanol (10 mL). The mixture was stirred for 30 min at room temperature under argon atmosphere. Then the corresponding carboxylic acid (1.8 mmol, 1.0 eq.) was added. After stirring the mixture for further 5 min at room temperature, the corresponding isocyanide (1.8 mmol, 1.0 eq.) was added. The reaction was stirred at room temperature for 48 h. After that, the solvent was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate (20 mL), washed with 10% aqueous $NaHCO_3$ (2 × 10 mL portions), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (SiO_2).

Method B. To a 10 mL vial equipped with a magnetic stirring bar were added propargylamine (Compounds **11a-r**) or aminoacetaldehyde dimethyl acetal (Compounds **11s-z**) (1.8 mmol, 1.0 eq.), the corresponding aldehyde (1.8 mmol, 1.0 eq.) in anhydrous methanol (10 mL). The mixture was stirred for 30 min at room temperature under argon atmosphere. The carboxylic acid (1.8 mmol, 1.0 eq.) was added; and after 15 min, the isocyanide (1.8 mmol, 1.0 eq.) was added. The vial was capped and placed in the microwave cavity. The reaction was irradiated for 2.5 h at 85 °C (the temperature was monitored using an internal IR probe) under microwave irradiation (100 W) using a sealed vessel. After the vial was cooled to room temperature, the solvent was evaporated under reduced pressure and the residue was dissolved in ethyl acetate (20 mL), washed with 10% aqueous $NaHCO_3$ (2 × 10 mL portions), dried with Na_2SO_4, and evaporated. The crude product was purified by flash chromatography (SiO_2).

N-(*tert*-butyl)-2-(3,5-dimethoxyphenyl)-2-(2-(2-iodophenyl)-*N*-(prop-2-yn-1-yl)acetamido)acetamide (**11a**)

Using the general procedure, this compound was obtained as a pale-yellow solid in 60% (591 mg) yield after purification by flash column chromatography (4/6 EtOAc–hexanes) *Rf.* 0.6 (4/6 EtOAc–hexanes). m. p. 94-97 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.85 (d, *J* = 8.2 Hz, 1H), 7.43–7.17 (m, 2H), 7.06–6.86 (m, 1H), 6.58 (s, 2H), 6.44 (s, 1H), 6.08 (s, 1H), 5.75 (s, 1H), 4.21 (s, 2H), 4.06 (s, 2H), 3.78 (s, 6H), 2.18 (s, 1H), 1.37 (s, 9H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ: 171.4, 168.5, 161.1, 139.5, 138.9, 137.1, 130.8, 128.8, 128.6, 107.4, 101.4, 101.0, 79.8, 72.5, 61.4, 55.6, 52.0, 46.2, 35.8, 28.8. IR (ν_{max}/cm^{-1}): 3331, 3292, 2962, 1644, 1594, 747. HRMS (DART, $[M+H]^+$) *m/z* calcd for $C_{25}H_{30}I_1N_2O_4$ 549.1250, found 549.1235.

N-(*tert*-butyl)-2-(2-(2-iodophenyl)-*N*-(prop-2-yn-1-yl)acetamido)-2-(3,4,5-trimethoxyphenyl)acetamide (**11b**)

Using the general procedure, this compound was obtained as a white solid in 63% (656 mg) yield after purification by flash column chromatography (4/6 EtOAc–hexanes), *Rf*. 0.72 (4/6 EtOAc–hexanes), m. p. 62-65 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.81 (d, *J* = 7.8 Hz, 1H), 7.39–7.17 (m, 2H), 7.01–6.87 (m, 1H), 6.65 (s, 2H), 6.14 (d, *J* = 5.5 Hz, 2H), 4.20 (s, 2H), 4.04 (d, J = 3.7 Hz, 2H), 3.86 (s, 3H), 3.83 (s, 6H), 2.20 (s, 1H), 1.34 (s, 9H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ: 171.2, 168.6, 153.2, 139.2, 138.7, 137.9, 130.6, 130.2, 128.6, 128.3, 106.5, 101.2, 79.7, 72.2, 61.0, 60.8, 56.1, 51.6, 46.0, 35.5, 28.5. IR (ν_{max}/cm^{-1}): 3328, 3247, 2963, 2934, 1643, 1179, 1123, 1007, 746, 531. HRMS (DART, $[M+H]^+$) *m/z* calcd for $C_{26}H_{31}I_1N_2O_5$ 579.1355, found 579.1334.

N-cyclopentyl-2-(2-(2-iodophenyl)-*N*-(prop-2-yn-1-yl)acetamido)-2-(3,4,5-trimethoxyphenyl)acetamide (**11c**)

Using the general procedure, this compound was obtained as a white solid in 57% (605 mg) yield after purification by flash column chromatography (4/6 EtOAc–hexanes) *Rf*. 0.4 (4/6 EtOAc–hexanes), m. p. 151-154 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.82 (d, *J* = 7.9 Hz, 1H), 7.37–7.22 (m, 2H), 7.02–6.89 (m, 1H), 6.63 (s, 2H), 6.16 (s, 1H), 6.08 (d, *J* = 7.2 Hz, 1H), 4.29–4.12 (m, 2H), 4.03 (d, *J* = 4.5 Hz, 2H), 3.84 (s, 3H), 3.82 (s, 6H), 2.18 (t, *J* = 1.9 Hz, 1H), 2.05–1.91 (m, 2H), 1.80 (s, 1H), 1.63–1.55 (m, 4H), 1.45–1.18 (m, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ: 171.4, 168.7, 153.4, 139.4, 138.7, 138.2, 130.7, 130.1, 128.9, 128.6, 106.6, 101.3, 79.6, 72.5, 61.0, 60.8, 56.3, 51.5, 46.2, 35.7, 33.0, 32.8, 23.8, 23.8. IR (ν_{max}/cm^{-1}): 3253, 2952, 2867, 1636, 1589, 730. HRMS (DART, $[M+H]^+$) *m/z* calcd for $C_{27}H_{32}I_1N_2O_5$ 591.1355, found 591.1364.

N-(2-(cyclohexylamino)-2-oxo-1-(3,4,5-trimethoxyphenyl)ethyl)-2-iodo-*N*-(prop-2-yn-1-yl)benzamide (**11d**)

Using the general procedure, this compound was obtained as a white solid in 90% (956 mg) yield after purification by flash column chromatography (4/6 EtOAc–hexanes) *Rf.* 0.4 (4/6 EtOAc–hexanes), m. p. 79-82 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.85 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.43 – 7.34 (m, 2H), 7.15 – 7.08 (m, 1H), 6.82 (s, 2H), 6.70 (s, 1H), 6.17 – 5.96 (m, 1H), 3.86 (s, 8H), 3.84 (s, 4H), 2.04 (d, *J* = 0.9 Hz, 1H), 1.96 (s, 2H), 1.73 – 1.57 (m, 4H), 1.36 – 1.16 (m, 4H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ: (major rotamer) 171.3, 167.9, 153.4, 141.2, 139.7, 139.3, 138.4, 130.8, 128.3, 127.8, 127.4, 107.4, 78.9, 72.5, 67.1, 61.0, 56.3, 48.8, 33.1, 33.0, 32.9, 25.6, 24.9. IR (ν=$_{max}$/cm^{-1}): 3293, 2930, 2851, 1637, 1589, 1328, 1246, 1125, 1007, 771. HRMS (DART, [M+H]$^+$) *m/z* calcd $C_{27}H_{32}I_1N_2O_5$ 591.1359, found 591.1355.

N-(2-(benzylamino)-1-(3,5-dimethoxyphenyl)-2-oxoethyl)-2-iodo-*N*-(prop-2-yn-1-yl)benzamide (**11e**)

Using the general procedure, this compound was obtained as a pale yellow solid in 52% (532 mg) yield after purification by flash column chromatography (4/6 EtOAc–hexanes) *Rf.* 0.5 (4/6 EtOAc–hexanes), m. p. 60-63 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: (major rotamer) 7.93 – 7.74 (m, 1H), 7.49 – 7.28 (m, 7H), 7.10 (t, *J* = 6.6 Hz, 1H), 6.72 (s, 2H), 6.61 (s, 1H), 6.45 (s, 2H), 4.54 (s, 2H), 4.48 – 3.93 (m, 2H), 3.76 (s, 7H), 2.00 (s, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ: (major rotamer) 171.4, 168.8, 161.2, 141.2, 139.4, 138.0, 136.0, 130.8, 128.8, 128.5, 128.2, 127.9, 127.7, 127.5, 108.1, 101.3, 92.7, 78.7, 73.0, 62.5, 55.6, 44.0, 37.6. IR (ν=$_{max}$/cm^{-1}): 3288, 2932, 2837, 1637, 2598, 1153, 748. HRMS (DART, [M+H]$^+$) *m/z* calcd for $C_{27}H_{26}I_1N_2O_4$ 569.0937, found 569.0909.

N-(2-(tert-butylamino)-1-(3,5-dimethoxyphenyl)-2-oxoethyl)-2-iodo-*N*-(prop-2-yn-1-yl)benzamide (**11f**)

Using the general procedure, this compound was obtained as a white solid in 58% (557 mg) yield after purification by flash column chromatography (4/6 EtOAc–hexanes) *Rf.* 0.6 (4/6 EtOAc–hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.91 – 7.81 (m, 1H), 7.43 – 7.35 (m, 2H), 7.16 – 7.06 (m, 1H), 6.73 (d, *J* = 1.8 Hz, 2H), 6.66 (d, *J* = 2.1 Hz, 1H), 6.46 (q, *J* = 2.1 Hz, 1H), 5.95 (s, 1H), 3.79 (d, *J* = 4.2 Hz, 8H), 2.12 (t, *J* = 2.3 Hz, 1H), 1.39 (d, *J* = 10.2 Hz, 9H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ: 171.39, 161.09, 141.39, 139.40, 130.95, 130.74, 128.36, 128.25, 127.92, 127.65, 108.25, 101.06, 79.00, 71.35, 55.58, 51.99, 37.53, 33.49, 28.82. IR (ν=$_{max}$/cm^{-1}): 3300, 2964, 2837, 1677, 1635, 1597, 1152, 1050, 769. HRMS (DART, [M+H]$^+$) *m/z* calcd for $C_{24}H_{28}I_1N_2O_4$ 535.1093, found 535.1085.

N-(1-(3,5-dimethoxyphenyl)-2-(naphthalen-2-ylamino)-2-oxoethyl)-2-iodo-*N*-(prop-2-yn-1-yl)benzamide (**11g**)

Using the general procedure, this compound was obtained as a white solid in 33% (359 mg) yield after purification by flash column chromatography (3/7 EtOAc–hexanes) *Rf.* 0.5 (3/7 EtOAc–hexanes), m. p. 92-95 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.20 (s, 1H), 7.82 (s, 1H), 7.72 – 7.65 (m, 4H), 7.40 (dd, *J* = 8.9, 2.2 Hz, 5H), 7.13 – 7.08 (m, 1H), 6.82 (s, 2H), 6.46 (s, 1H), 4.14 – 4.00 (m, 2H), 3.80 (s, 1H), 3.72 (s, 6H), 2.09 (s, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ: 171.9, 161.2, 141.0, 139.4, 136.0, 133.8, 130.9, 130.8, 128.6, 128.3, 127.8, 127.7, 127.6, 126.4, 125.0, 120.2, 116.9, 101.0, 78.7, 72.9, 55.6, 37.8. IR (ν=$_{max}$/cm^{-1}): 3289, 3247, 3956, 2956, 2926, 1691, 1627, 766. HRMS (DART, [M+H]$^+$) *m/z* calcd for $C_{30}H_{26}I_1N_2O_4$ 605.0937, found 605.0913.

N-(2-(*tert*-butylamino)-2-oxo-1-(3,4,5-trimethoxyphenyl)ethyl)-2-iodo-*N*-(prop-2-yn-1-yl)benzamide (**11h**)

Using the general procedure, this compound was obtained as an orange solid in 65% (367 mg) yield after purification by flash column chromatography (5/5 EtOAc–hexanes) *Rf.* 0.5 (5/5 EtOAc–hexanes), m. p. 202-205 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: (mixture of rotamers) 7.92 – 7.78 (m, 2H), 7.40 (dt, *J* = 12.4, 6.6 Hz, 3H), 7.18 – 7.05 (m, 2H), 6.82 (s, 2H), 6.73 (s, 1H), 3.86 (s, 9H), 3.84 (s, 6H), 2.10 (s, 1H), 2.04 (s, 1H), 1.42 (s, 9H), 1.38 (s, 4H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ: (mixture of rotamers) 171.4, 170.4, 153.4, 141.3, 139.7, 139.4, 138.4, 130.9, 130.7, 129.8, 128.7, 128.2, 127.8, 127.6, 107.4, 107.2, 92.5, 79.9, 79.1, 72.3, 71.1, 67.1, 61.0, 56.3, 52.2, 51.9, 37.3, 33.5, 28.8, 28.7. IR (ν=$_{max}$/cm^{-1}): 3296, 2962, 2929, 2832, 2120, 1665, 1592, 761. HRMS (DART+) *m/z* calcd for $C_{25}H_{30}I_1N_2O_5$ [M + H]$^+$ 565.1199, found 565.1203.

4-chloro-*N*-(1-(3,5-dimethoxyphenyl)-2-oxo-2-(phenylamino)ethyl)-2-iodo-*N*-(prop-2-yn-1-yl)benzamide (**11i**)

Using the general procedure, this compound was obtained as a pale yellow solid in 83% (878mg) yield after purification by flash column chromatography (3/7 EtOAc–hexanes) *Rf.* 0.3 (3/7 EtOAc–hexanes), m.p. 79-82 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.84 (d, *J* = 1.9 Hz, 1H), 7.48 (d, *J* = 7.6 Hz, 2H), 7.44 – 7.22 (m, 4H), 7.20 – 6.99 (m, 2H), 6.76 (s, 2H), 6.47 (t, *J* = 1.9 Hz, 1H), 6.28 (s, 1H), 4.14 – 3.80 (m, 2H), 3.78 (s, 6H), 2.05 (d, *J* = 16.2 Hz, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ: 171.0, 161.3, 139.5, 138.9, 137.7, 135.9, 135.7, 129.0, 128.6, 128.3, 124.6, 120.3, 108.5, 108.0, 101.1, 78.5, 73.0, 55.6, 55.5, 37.7. IR (ν=$_{max}$/cm^{-1}): 3329, 3063, 2835, 1631, 1598, 1153, 1099, 829, 747. HRMS (DART, [M+H]$^+$) *m/z* calcd for $C_{26}H_{23}Cl_1I_1N_2O_4$ 589.0391, found 589.0383.

N-(2-(benzylamino)-2-oxo-1-(3,4,5-trimethoxyphenyl)ethyl)-4-fluoro-2-iodo-*N*-(prop-2-yn-1-yl)benzamide (**11j**)

Using the general procedure, this compound was obtained as a white solid in 50% (554 mg) yield after purification by flash column chromatography (3/7 EtOAc–hexanes) *Rf.* 0.2 (3/7 EtOAc–hexanes), m. p. 175-178 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.56 (dd, *J* = 8.0, 2.3 Hz, 1H), 7.36 – 7.27 (m, 7H), 7.16 – 7.06 (m, 1H), 6.77 (s, 2H), 6.62 (s, 1H), 6.09 (s, 1H), 4.63 – 4.41 (m, 3H), 3.84 (s, 3H), 3.79 (s, 8H), 1.99 (s, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ: 170.7, 168.6, 168.3, 162.05 (d, J = 255.6 Hz), 153.4, 138.6, 137.9, 137.38 (d, J = 3.4 Hz), 129.1, 128.7, 128.0, 127.6, 126.49 (d, *J* = 23.8 Hz), 115.63 (d, *J* = 20.9 Hz), 107.3, 78.6, 72.6, 62.0, 60.9, 56.3, 43.8, 37.4. IR (ν=$_{max}$/cm^{-1}): 3116, 2922, 2833, 1671, 1638, 1591, 1123, 997, 752. HRMS (DART, [M+H]$^+$) *m/z* calcd for $C_{28}H_{27}F_1I_1N_2O_5$ 617.0948, found 617.0972.

N-(2-(dodecylamino)-2-oxo-1-(3,4,5-trimethoxyphenyl)ethyl)-2-iodo-*N*-(prop-2-yn-1-yl)benzamide (**11k**)

Using the general procedure, this compound was obtained as a pale yellow oil in 43% (350 mg) yield after purification by flash column chromatography (3/7 EtOAc–hexanes) *Rf.*

0.2 (3/7 EtOAc–hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.87 – 7.76 (m, 1H), 7.42 – 7.31 (m, 2H), 7.09 (td, *J* = 7.9, 2.0 Hz, 2H), 6.79 (s, 2H), 6.64 (s, 1H), 3.82 (s, 9H), 3.80 (d, *J* = 3.5 Hz, 2H), 3.26 (ddd, *J* = 22.6, 12.2, 5.6 Hz, 2H), 1.53 – 1.43 (m, 2H), 1.22 (s, 18H), 0.83 (d, *J* = 6.9 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ: (mixture of rotamers) 171.4, 170.6, 168.8, 153.4, 141.2, 139.7, 139.3, 131.0, 130.8, 129.7, 128.5, 128.3, 127.8, 127.4, 107.5, 107.2, 92.5, 79.7, 78.8, 72.4, 71.2, 67.1, 61.7, 60.9, 56.4, 56.3, 39.9, 37.2, 31.9, 29.7, 29.7, 29.6, 29.5, 29.4, 27.1, 22.7, 14.2. IR (ν=$_{max}$/cm^{-1}): 3309, 2925, 2853, 1678, 1642, 1463, 1127, 771, 727. HRMS (DART, [M+H]$^+$) *m/z* calcd for $C_{33}H_{46}I_1N_2O_5$ 677.2451, found 677.2448.

2-iodo-*N*-(2-(octylamino)-2-oxo-1-(3,4,5-trimethoxyphenyl)ethyl)-*N*-(prop-2-yn-1-yl)benzamide (**11l**)

Using the general procedure, this compound was obtained as a pale yellow oil in 36% (401 mg) yield after purification by flash column chromatography (3/7 EtOAc–hexanes) *Rf*. 0.3 (3/7 EtOAc–hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.82 (d, *J* = 8.0 Hz, 1H), 7.44 – 7.33 (m, 2H), 7.14 – 7.08 (m, 1H), 6.79 (s, 2H), 6.19 (s, 1H), 3.85 – 3.83 (m, 6H), 3.81 (d, *J* = 2.7 Hz, 5H), 3.28 (ddq, *J* = 18.9, 12.9, 6.1 Hz, 2H), 2.01 (s, 1H), 1.49 (d, *J* = 6.5 Hz, 2H), 1.23 (s, 10H), 0.92 – 0.82 (m, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ: 171.4, 168.9, 153.4, 141.2, 139.8, 139.4, 131.0, 130.8, 128.5, 128.3, 127.8, 127.4, 107.5, 107.1, 78.8, 72.5, 67.1, 61.8, 61.0, 56.4, 39.9, 33.4, 29.6, 29.3, 27.1, 22.7, 14.2. IR (ν=$_{max}$/cm^{-1}): 3307, 2928, 2854, 1640, 1540, 1463, 1128, 773, 747. HRMS (DART, [M+H]$^+$) *m/z* calcd for $C_{29}H_{38}I_1N_2O_5$ 621.1825, found 621.1825.

Ethyl (2-(2-iodo-*N*-(prop-2-yn-1-yl)benzamido)-2-(3,4,5-trimethoxyphenyl)acetyl)-L-phenylalaninate (**11m**)

Using the general procedure, this compound was obtained as a pale yellow oil in 43% (264 mg) yield after purification by flash column chromatography (4/6 EtOAc–hexanes) *Rf*. 0.3 (4/6 EtOAc–hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: (diasteromeric mixture) 7.90 – 7.76 (m, 3H), 7.37 (dd, *J* = 16.5, 6.9 Hz, 8H), 7.21 – 6.97 (m, 13H), 6.82 (s, 1H), 6.80 (s, 1H), 6.77 (s, 3H), 6.66 (s, 1H), 4.31 – 4.07 (m, 7H), 3.86 (s, 3H), 3.85 (s, 9H), 3.83 (s, 10H), 3.80 (s, 4H), 3.28 – 3.08 (m, 6H), 2.33 (dd, *J* = 5.0, 2.5 Hz, 1H), 2.09 – 1.99 (m, 1H), 1.92 (t, *J* = 2.2 Hz, 1H), 1.70 (s, 2H), 1.25 (dt, *J* = 14.1, 6.9 Hz, 10H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ: (diasteromeric mixture) 171.3, 171.2, 153.6, 153.5, 144.2, 141.2, 139.3, 135.8, 130.9, 129.4, 129.2, 128.7, 128.4, 128.0, 127.3, 107.6, 107.4, 78.7, 61.9, 61.6, 61.0, 56.4, 53.8, 53.5, 37.9, 37.6, 14.2. IR (ν=$_{max}$/cm^{-1}): 3293, 3260, 2935, 2835, 1737, 1677, 1643, 1589, 1505, 1183, 1122, 1008, 771, 744, 699, 636. HRMS (DART, [M+H]$^+$) *m/z* calcd for $C_{32}H_{34}I_1N_2O_7$ 685.1410, found 685.1410.

2-bromo-*N*-(2-(cyclohexylamino)-2-oxo-1-(3,4,5-trimethoxyphenyl)ethyl)-*N*-(prop-2-yn-1-yl)furan-3-carboxamide (**11n**)

Using the general procedure, this compound was obtained as a white solid in 90% (861 mg) yield after purification by flash column chromatography (5/5 EtOAc–Hexanes) *Rf*. 0.2 (5/5 EtOAc–Hexanes). m. p. 166-168 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.45 (d, *J* = 2.1 Hz, 1H), 6.65 (s, 3H), 6.07 (d, *J* = 8.0 Hz, 1H), 5.87 (s, 1H), 4.25 – 3.94 (m, 2H), 3.86 – 3.84 (m, 1H), 3.82 (s, 3H), 3.81 (s, 6H), 2.10 (s, 1H), 1.93 (d, *J* = 11.5 Hz, 2H), 1.71 – 1.55 (m, 3H), 1.36 – 1.12 (m, 5H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ: 167.8, 165.0, 153.5, 144.6, 138.4, 129.6, 120.0, 111.9, 106.8, 79.6, 72.4, 60.9, 56.3, 48.8, 32.9, 25.5, 24.9. IR (ν=$_{max}$/cm^{-1}): 3259, 3090, 2998, 2932, 2853, 2117, 1741, 1641, 1590, 1497, 1451, 1423, 1330, 1249, 1176, 1129, 1007, 943, 845, 757. HRMS (DART, [M+H]$^+$) *m/z* calcd for $C_{25}H_{30}{}^{79}Br_1N_2O_6$ 533.1287, found 533.1287.

2-bromo-*N*-(2-(cyclohexylamino)-1-(3,5-dimethoxyphenyl)-2-oxoethyl)-*N*-(prop-2-yn-1-yl)furan-3-carboxamide (**11o**)

Using the general procedure, this compound was obtained as a beige solid in 59% (533 mg) yield after purification by flash column chromatography (3/7 EtOAc–Hexanes) *Rf*. 0.2 (3/7 EtOAc–Hexanes). m. p. 140-143 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.43 (d, *J* = 2.1 Hz, 1H), 6.68 (s, 1H), 6.54 (s, 2H), 6.40 (t, *J* = 2.2 Hz, 1H), 6.16 (s, 1H), 5.85 (s, 1H), 4.28 – 3.96 (m, 2H), 3.82 (ddt, *J* = 14.4, 7.7, 3.8 Hz, 1H), 3.74 (s, 6H), 2.11 (s, 1H), 1.91 (d, *J* = 12.2 Hz, 2H), 1.62 (ddd, *J* = 29.0, 8.6, 3.3 Hz, 3H), 1.38 – 1.06 (m, 5H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ: 167.7, 165.0, 161.1, 144.5, 136.4, 120.0, 111.9, 107.5, 100.8, 79.6, 72.4, 55.5, 48.8, 32.9, 25.5, 24.9, 24.8. HRMS (DART, [M+H]$^+$) *m/z* calcd for $C_{24}H_{28}{}^{79}Br_1N_2O_5$ 503.1181, found 503.1171.

2-bromo-*N*-(2-(tert-butylamino)-2-oxo-1-(3,4,5-trimethoxyphenyl)ethyl)-*N*-(prop-2-yn-1-yl)thiophene-3-carboxamide (**11p**)

Using the general procedure, this compound was obtained as a white solid in 89% (835 mg) yield after purification by flash column chromatography (4/6 EtOAc–Hexanes) *Rf.* 0.2 (4/6 EtOAc–Hexanes). m. p. 204-206 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.30 (d, *J* = 5.6 Hz, 1H), 7.05 (s, 1H), 6.73 (s, 1H), 6.53 (s, 1H), 5.99 (d, *J* = 22.7 Hz, 1H), 4.18 – 3.93 (m, 2H), 3.82 (s, 9H), 2.03 (s, 1H), 1.38 (s, 9H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ: 168.0, 153.5, 138.4, 136.5, 129.9, 127.6, 126.8, 112.3, 106.8, 79.4, 72.2, 62.4, 61.0, 56.2, 52.0, 37.1, 28.7. IR (ν=$_{max}$/cm^{-1}): 3302, 3113, 3067, 3008, 2966, 2932, 2834, 1677, 1658, 1595, 1545, 1438, 1330, 1236, 1174, 1130, 1045, 998, 917, 849, 743. HRMS (DART, [M+H]$^+$) *m/z* calcd for $C_{23}H_{28}{}^{79}Br_1N_2O_5S_1$ 523.0902, found 523.0888.

2-bromo-5-chloro-*N*-(2-(cyclohexylamino)-2-oxo-1-(3,4,5-trimethoxyphenyl)ethyl)-*N*-(prop-2-yn-1-yl)nicotinamide (**11q**)

Using the general procedure, this compound was obtained as a beige solid in 70% (726 mg) yield after purification by flash column chromatography (3/7 EtOAc–Hexanes) *Rf*. 0.1 3/7 EtOAc–Hexanes). m. p. 149-152 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.37 (d, *J* = 2.6 Hz, 1H), 7.73 (s, 1H), 6.71 (s, 2H), 6.62 (s, 1H), 3.84 (s, 9H), 3.81 (d, *J* = 3.3 Hz, 3H), 2.11 (s, 1H), 1.94 (t, *J* = 14.4 Hz, 2H), 1.73 – 1.57 (m, 3H), 1.34 (t, *J* = 11.0 Hz, 2H), 1.13 (q, *J* = 10.7, 9.9 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ: 167.4, 166.9, 153.6, 149.5, 138.7, 136.8, 135.9, 135.1, 131.7, 106.8, 78.6, 72.8, 71.4, 66.7, 61.0, 56.3, 49.0, 32.9, 25.4, 24.8. IR (ν=$_{max}$/cm^{-1}): 3228, 3282, 3079, 2931, 2853, 1678, 1634, 1592, 1509, 1451, 1404, 1330, 1245, 1125, 1007, 904, 754. HRMS (DART, [M+H]$^+$) *m/z* calcd for $C_{26}H_{30}{}^{79}Br_1Cl_1N_3O_5$ 578.1057, found 578.1055.

2-bromo-*N*-(2-(tert-butylamino)-2-oxo-1-(3,4,5-trimethoxyphenyl)ethyl)-*N*-(prop-2-yn-1-yl)nicotinamide (**11r**)

Using the general procedure, this compound was obtained as a white solid in 79% (736 mg) yield after purification by flash column chromatography (5/5 EtOAc–Hexanes) *Rf*. 0.2 (5/5 EtOAc–Hexanes). m. p. 83-85 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: (major rotamer) 8.40 (dd, *J* = 4.8, 2.0 Hz, 1H), 7.69 (d, *J* = 25.0 Hz, 1H), 7.32 (dtd, *J* = 8.9, 6.5, 5.7, 3.0 Hz, 2H), 6.74 (s, 2H), 6.66 (s, 1H), 3.83 (s, 9H), 3.81 (s, 2H), 2.01 (s, 1H), 1.38 (s, 9H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ: (mixture of rotamers) 168.24, 167.86, 153.54, 150.92, 150.78, 138.70, 138.52, 136.94, 134.52, 129.43, 128.02, 122.92, 122.68, 107.30, 106.92, 78.76, 72.48, 71.24, 66.96, 61.91, 61.00, 56.22, 52.06, 36.85, 33.35, 28.71. IR (ν_{max}/cm^{-1}): 3404, 3110, 2966, 2936, 2936, 1682, 1646, 1592, 1550, 1508, 1457, 1391, 1330, 1243, 1127, 1004, 813, 510, 534. HRMS (DART, [M+H]$^+$) *m/z* calcd for $C_{24}H_{29}{}^{79}Br_1N_3O_5$ 518.1290, found 518.1291.

N-(2-(tert-butylamino)-2-oxo-1-(3,4,5-trimethoxyphenyl)ethyl)-*N*-(2,2-dimethoxyethyl)-2-iodobenzamide (**11s**)

Using the general procedure, this compound was obtained as a pale yellow oil in 78% (861 mg) yield after purification by flash column chromatography (3/7 EtOAc–hexanes) *Rf*. 0.4 (3/7 EtOAc–hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: (major rotamer) 7.91 (d, *J* = 7.9 Hz, 1H), 7.81 (d, *J* = 7.9 Hz, 1H), 7.44 – 7.24 (m, 5H), 7.17 – 7.02 (m, 2H), 6.93 (s, 1H), 6.86 (s, 1H), 6.62 (s, 2H), 3.86 (s, 6H), 3.83 (s, 12H), 3.50 (s, 3H), 3.40 (s, 3H), 1.45 (s, 9H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ: (mixture of rotamers) 168.2, 168.0, 153.2, 139.9, 139.0, 131.0, 130.2, 128.7, 128.5, 128.3, 128.0, 127.2, 107.3, 103.6, 103.1, 102.5, 68.1, 65.2, 63.9, 60.8, 56.2, 55.8, 55.5, 54.8, 54.6, 51.7, 51.4, 50.8, 49.1, 47.2, 28.6. IR (ν_{max}/cm^{-1}): 3325, 2963, 2937, 2834, 1681, 1646, 1589, 1506, 1459, 1387, 1234, 1127, 1074, 1009, 751, 565, 525. HRMS (DART, [M+H]$^+$) *m/z* calcd for $C_{26}H_{36}I_1N_2O_7$ 615.1567, found 615.1578.

N-(2,2-dimethoxyethyl)-2-(2-iodophenyl)-*N*-(2-((4-methoxyphenyl)amino)-2-oxo-1-(3,4,5-trimethoxyphenyl)ethyl)acetamide (**11t**)

Using the general procedure, this compound was obtained as a pale yellow solid in 50% (610 mg) yield after purification by flash column chromatography (5/5 EtOAc–hexanes) *Rf*. 0.3 (5/5 EtOAc–hexanes). m. p.76-79 °C ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.35 (s, 1H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.54 (d, *J* = 11.1 Hz, 1H), 7.38 – 7.25 (m, 4H), 6.95 – 6.88 (m, 2H), 6.79 (s, 2H), 6.48 (s, 1H), 6.06 (s, 1H), 4.06 (s, 2H), 3.86 (s, 3H), 3.82 (s, 6H), 3.79 (s, 1H), 3.76 (s, 3H), 3.49 (s, 2H), 3.31 (s, 3H), 3.29 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ: (mixture of rotamers) 172.8, 167.7, 167.4, 156.4, 153.4, 139.5, 139.3, 139.2, 138.3, 130.9, 130.7, 130.6, 130.3, 129.7, 129.0, 128.8, 128.6, 128.5, 128.4, 122.3, 122.0, 114.3, 114.0, 107.1, 106.6, 104.2, 102.5, 101.3, 67.2, 63.3, 60.9, 56.3, 55.9, 55.9, 55.5, 49.0, 47.6, 46.7, 45.9. IR (ν_{max}/cm^{-1}): 3313, 3062, 2936, 2834, 1686, 1650, 1591, 1461, 1126, 1008, 830, 749. HRMS (FAB+, [M+H]$^+$) *m/z* calcd for $C_{30}H_{36}I_1N_2O_8$ 679.1516, found 679.1517.

2-bromo-*N*-(2-(tert-butylamino)-2-oxo-1-(3,4,5-trimethoxyphenyl)ethyl)-*N*-(2,2-dimethoxyethyl)furan-3-carboxamide (**11u**)

Using the general procedure, this compound was obtained as a colorless oil in 54% (540 mg) yield after purification by flash column chromatography (6/4 EtOAc–Hexanes) *Rf*. 0.4 (6/4 EtOAc–Hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.49 (d, *J* = 2.1 Hz, 1H), 6.64 (d, *J* = 1.9 Hz, 1H), 6.59 (s, 2H), 6.09 (s, 1H), 6.00 (d, *J* = 6.0 Hz, 1H), 3.92 – 3.83 (m, 6H), 3.81 (s, 9H), 1.54 (s, 9H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ: 167.7, 153.5, 153.2, 144.9, 137.9, 130.6, 130.0, 112.2, 111.6, 106.6, 106.3, 106.1, 105.8, 102.6, 65.8, 60.8, 56.1, 53.5, 51.7, 28.5, 28.5. IR (ν_{max}/cm^{-1}): 3330, 3118, 2966, 2938, 2837, 1732, 1681, 1641, 1591, 1458, 1237, 1127, 1006, 743. HRMS (DART, [M+H]$^+$) *m/z* calcd for $C_{24}H_{34}{}^{79}Br_1N_2O_8$ 557.1498, found 557.1498.

2-bromo-*N*-(2-(tert-butylamino)-2-oxo-1-(3,4,5-trimethoxyphenyl)ethyl)-*N*-(2,2-dimethoxyethyl)thiophene-3-carboxamide (**11v**)

Using the general procedure, this compound was obtained as a yellow oil in 87% (895 mg) yield after purification by flash column chromatography (6/4 EtOAc–Hexanes) *Rf*. 0.4 (6/4 EtOAc–Hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: (mixture of rotamers) 7.50 (s, 1H), 7.30 (d, *J* = 4.3 Hz, 1H), 7.21 (d, *J* = 5.3 Hz, 1H), 6.88 (d, *J* = 16.9 Hz, 2H), 6.71 (s, 2H), 6.31 (s, 3H), 5.61 (s, 1H), 5.19 (s, 1H), 4.95 (s, 1H), 3.74 (d, *J* = 9.4 Hz, 16H), 3.44 – 3.33 (m, 6H), 3.05 (d, *J* = 6.6 Hz, 6H), 1.37 (s, 9H), 1.31 (s, 9H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ: (mixture of rotamers) 167.7, 153.5, 153.2, 144.9, 137.9, 130.6, 130.0, 112.2, 111.6, 106.6, 106.3, 106.1, 105.8, 102.6, 65.8, 60.8, 56.1, 53.5, 51.7, 28.5. IR (ν_{max}/cm^{-1}): 3334, 3082, 2964, 2937, 2835, 1682, 1638, 1591, 1507, 1456, 1237, 1127, 1076, 727. HRMS (FAB+, [M+H]$^+$) *m/z* calcd for $C_{24}H_{34}{}^{79}Br_1N_2O_7S_1$ 573.1270, found 573.1288.

2-bromo-*N*-(2-(tert-butylamino)-2-oxo-1-(3,4,5-trimethoxyphenyl)ethyl)-*N*-(2,2-dimethoxyethyl)nicotinamide (**11w**)

Using the general procedure, this compound was obtained as a colorless oil in 64% (683 mg) yield after purification by flash column chromatography (7/3 EtOAc–Hexanes) *Rf*. 0.4 (7/3 EtOAc–Hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: (major rotamer) 8.35 (d, *J* = 4.5 Hz, 1H), 7.70 – 7.62 (m, 1H), 7.36 – 7.30 (m, 1H), 6.85 (s, 1H), 6.78 (s, 1H), 6.61 (s, 1H), 4.79 (dd, *J* = 6.5, 3.8 Hz, 1H), 3.85 (d, *J* = 3.9 Hz, 6H), 3.80 (s, 3H), 3.38 (d, *J* = 23.7 Hz, 4H), 3.21 (s, 2H), 3.07 (s, 3H), 1.36 (s, 9H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ: (mixture of rotamers) 169.1, 168.1, 167.8, 167.4, 153.5, 150.9, 150.3, 150.2, 138.2, 138.0, 136.5, 135.1, 130.7, 129.5, 129.0, 122.9, 122.6, 107.6, 107.1, 107.0, 103.4, 102.7, 67.9, 64.1, 63.4, 61.0, 56.2, 56.1, 55.5, 55.3, 55.1, 55.0, 51.9, 51.7, 50.5, 48.8, 46.6, 28.7. IR (ν_{max}/cm^{-1}): 3341, 3062, 2964, 2937, 1683, 1642, 1591, 1507, 1458, 1237, 1126, 1082, 751, 710. HRMS (DART, [M+H]$^+$) *m/z* calcd for $C_{25}H_{35}{}^{79}Br_1N_3O_7$ 568.1658, found 568.1655.

N-(2,2-dimethoxyethyl)-2-(2-iodophenyl)-*N*-(2-(octylamino)-2-oxo-1-(3,4,5-trimethoxyphenyl)ethyl)acetamide (**11x**)

Using the general procedure, this compound was obtained as a white solid in 48% (590 mg) yield after purification by flash column chromatography (3/7 EtOAc–Hexanes) *Rf*. 0.2 (3/7 EtOAc–Hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.80 (d, *J* = 7.7 Hz, 1H), 7.37 – 7.19 (m, 2H), 6.99 – 6.88 (m, 1H), 6.73 (s, 2H), 6.38 (s, 1H), 6.18 (t, *J* = 5.6 Hz, 1H), 5.85 (s, 1H), 4.02 (s, 2H), 3.83 (s, 3H), 3.81 (s, 5H), 3.77 (s, 2H), 3.27 (d, *J* = 1.2 Hz, 6H), 1.43 (q, *J* = 7.0 Hz, 2H), 1.22 (s, 10H), 0.84 (t, *J* = 6.4

Hz, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ: (mixture of rotamers) 172.4, 169.4, 153.5, 139.5, 139.3, 138.3, 130.7, 128.6, 128.4, 107.1, 106.6, 104.3, 102.6, 101.3, 66.9, 62.5, 60.9, 56.3, 55.9, 55.7, 49.0, 45.9, 39.8, 31.8, 29.5, 29.3, 29.2, 27.0, 22.7, 14.1. IR ($\nu=_{max}/cm^{-1}$): 3297, 3092, 2928, 2855, 1650, 1587, 1466, 1425, 1458, 1328, 1243, 1185, 1125, 1076, 1010, 821, 747, 727, 599, 532. HRMS (FAB+, $[M+H]^+$) *m/z* calcd for $C_{31}H_{46}I_1N_2O_7$ 685.2350, found 685.2343.

N-(2,2-dimethoxyethyl)-2-iodo-*N*-(2-((2-morpholinoethyl)amino)-2-oxo-1-(3,4,5-trimethoxyphenyl)-ethyl)benzamide (**11y**)

Using the general procedure, this compound was obtained as a colorless solid in 37% (456 mg) yield after purification by flash column chromatography (9/1 EtOAc–MeOH) *Rf*. 0.2 (9/1 EtOAc–MeOH). m. p. 62-63°C. ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.81 (d, *J* = 8.0 Hz, 2H), 7.62 (d, *J* = 7.0 Hz, 1H), 7.39 (d, *J* = 5.9 Hz, 2H), 7.14 – 7.05 (m, 2H), 6.93 (t, *J* = 7.2 Hz, 1H), 6.80 (s, 2H), 3.91 – 3.74 (m, 14H), 3.67 (d, *J* = 14.6 Hz, 5H), 3.57 – 3.42 (m, 3H), 2.69 – 2.41 (m, 9H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ: 171.3, 169.1, 153.4, 141.2, 140.1, 139.3, 138.5, 130.8, 128.3, 127.9, 127.7, 107.5, 72.5, 66.2, 61.0, 56.9, 56.4, 53.3, 35.8. IR ($\nu=_{max}/cm^{-1}$): 3410, 3296, 2937, 2836, 1676, 1642, 1590, 1508, 1461, 1424, 1330, 1246, 1125, 1010, 914, 749, 638. HRMS (DART, $[M+H]^+$) *m/z* calcd for $C_{28}H_{39}I_1N_3O_8$ 672.1781, found 672.1800.

N-(2,2-dimethoxyethyl)-*N*-(1-(2,5-dimethoxyphenyl)-2-((2-morpholinoethyl)amino)-2-oxoethyl)-2-iodobenzamide (**11z**)

Using the general procedure, this compound was obtained as a colorless oil in 65% (749 mg) yield after purification by flash column chromatography (2/8 EtOAc–hexanes) *Rf*. 0.5 (2/8 EtOAc–hexanes). ^1H NMR ($CDCl_3$, 300 MHz) δ: (mixture of rotamers) 7.75 (d, *J* = 8.1 Hz, 2H), 7.51 (s, 1H), 7.39 – 7.25 (m, 6H), 7.07 – 6.96 (m, 3H), 6.83 (d, *J* = 1.8 Hz, 4H), 6.76 (s, 3H), 6.06 (s, 1H), 5.78 (s, 1H), 4.20 (t, *J* = 5.0 Hz, 2H), 3.77 (s, 5H), 3.74 (s, 4H), 3.68 (s, 4H), 3.45 (s, 6H), 3.02 (s, 3H), 2.97 (s, 3H), 2.58 – 2.35 (m, 17H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ: (mixture of rotamers) 171.5, 169.8, 168.8, 153.7, 153.4, 152.2, 151.8, 141.8, 140.4, 140.0, 139.7, 139.1, 130.8, 130.6, 130.3, 130.1, 128.9, 128.4, 128.0, 127.9, 127.8, 124.7, 123.4, 118.2, 117.7, 117.0, 114.7, 114.3, 111.4, 111.3, 103.7, 103.5, 102.7, 102.2, 92.6, 66.7, 63.2, 60.0, 59.5, 57.4, 57.1, 56.8, 56.2, 55.9, 55.7, 54.9, 54.8, 54.7, 54.5, 53.5, 53.3, 53.2, 51.9, 49.8, 49.3, 46.9, 36.4, 36.2, 36.1. IR ($\nu=_{max}/cm^{-1}$): 3333, 3070, 2953, 2832, 1676, 1647, 1501, 1461, 1118, 1073, 772, 749. HRMS (DART, $[M+H]^+$) *m/z* calcd for $C_{27}H_{37}I_1N_3O_7$ 642.1676, found 642.1688.

General procedure for the synthesis of dihydroisoquinolines **12a-12r**

In a round-bottom flask equipped with a magnetic stirring bar, the corresponding Ugi adduct **11a-r** (0.2 mmol, 1 equiv.) was added to a solution of JohnPhosAu(MeCN)SbF_6 (5 mol%, 0.05 equiv) and $CHCl_3$ (1 mL/0.1 mmol of Ugi adduct **11a-r**). The mixture was stirred for 2.5 h at room temperature under argon atmosphere. After that, the crude of the hydro-arylation reaction was treated with *p*-toluenesulfonic acid (0.1 mmol, 0.5 equiv.) in MeOH (0.1 M for the Ugi adduct) for 12 hours at 40 °C in an oil bath. Finally, after removal of volatiles the crude was extracted with ethyl acetate (sat. NaCl), washed with sodium bicarbonate (sat. solution) and the organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2).

N-(*tert*-butyl)-2-(2-(2-iodophenyl)acetyl)-5,7-dimethoxy-4-methyl-1,2-dihydroisoquinoline-1-carboxamide (**12a**)

Using the general procedure, this compound was obtained as a brown solid in 83% (90 mg) yield after purification by flash column chromatography (4/6 EtOAc–hexanes), *Rf.* 0.4 (4/6 EtOAc–hexanes), m. p. 70-73 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.87 (d, *J* = 7.5 Hz, 1H), 7.35 – 7.29 (m, 2H), 6.99 (ddd, *J* = 7.9, 6.2, 2.8 Hz, 1H), 6.44 – 6.40 (m, 2H), 6.35 (s, 1H), 6.00 (s, 1H), 5.95 (s, 1H), 4.06 (d, *J* = 16.3 Hz, 2H), 3.82 (s, 3H), 3.80 (s, 3H), 2.24 (s, 3H), 1.28 (s, 9H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ: 168.6, 167.8, 160.0, 157.8, 139.5, 138.0, 133.6, 130.3, 129.0, 128.7, 121.1, 118.7, 114.3, 105.0, 101.3, 99.3, 58.2, 55.5, 51.5, 45.5, 28.8, 28.6, 20.1. IR ($\nu=_{max}/cm^{-1}$): 3395, 3332, 2963, 2837, 1686, 1652, 742. HRMS (DART, $[M+H]^+$) *m/z* calcd for $C_{25}H_{30}I_1N_2O_4$ 549.1244, found 549.1250.

N-(*tert*-butyl)-2-(2-(2-iodophenyl)acetyl)-5,6,7-trimethoxy-4-methyl-1,2-dihydroisoquinoline-1-carboxamide (**12b**)

Using the general procedure, this compound was obtained as a pale yellow solid in 93% (107 mg) yield after purification by flash column chromatography (4/6 EtOAc–hexanes), *Rf*. 0.5, (4/6 EtOAc–hexanes) m. p. 66-69 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.88 (d, *J* = 7.8 Hz, 1H), 7.38 – 7.27 (m, 2H), 7.05 – 6.95 (m, 1H), 6.57 (s, 1H), 6.40 (s, 1H), 6.04 (s, 1H), 5.92 (s, 1H), 4.12 – 3.92 (m, 2H), 3.88 (s, 3H), 3.86 (s, 6H), 2.24 (s, 3H), 1.28 (s, 9H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ: 168.8, 168.1, 153.0, 151.3, 142.8, 139.6, 138.0, 130.4, 129.2, 128.8, 127.0, 120.9, 119.6, 118.8, 107.8, 101.4, 61.3, 60.9, 58.0, 56.2, 51.7, 45.7, 29.0, 19.4. IR ($\nu=_{max}/cm^{-1}$): 3325, 3059, 2962, 2839, 1737, 1663, 739. HRMS (DART, $[M+H]^+$) *m/z* calcd for $C_{26}H_{32}I_1N_2O_5$ 579.1355, found 579.1337.

N-cyclopentyl-2-(2-(2-iodophenyl)acetyl)-5,6,7-trimethoxy-4-methyl-1,2-dihydroisoquinoline-1-carboxamide (**12c**)

Using the general procedure, this compound was obtained as a brown solid in 91% (107 mg) yield after purification by flash column chromatography (4/6 EtOAc–hexanes) *Rf.* 0.4 (4/6 EtOAc–hexanes), m. p. 164-167 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.81 (d, *J* = 7.9 Hz, 1H), 7.25 (qd, *J* = 7.7, 1.7 Hz, 2H), 6.93 (td, *J* = 7.5, 2.2 Hz, 1H), 6.53 (s, 1H), 6.33 (s, 1H), 6.03 (d, *J* = 7.1 Hz, 1H), 5.91 (s, 1H), 4.13 – 3.91 (m, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 3.79 (s, 3H), 3.75 (s, 1H), 2.17 (s, 3H), 1.96 – 1.74 (m, 2H), 1.54 – 1.48 (m, 4H), 1.24 (dd, *J* = 11.2, 6.2 Hz, 1H), 0.92 – 0.71 (m, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ: 168.8, 168.4, 153.0, 151.2, 142.8, 139.6, 137.9, 130.3, 129.1, 128.8, 126.7, 120.6, 119.6, 118.7, 107.7, 101.3, 61.3, 60.8, 57.3, 56.2, 51.5, 45.6, 33.3, 33.2, 23.9, 19.4. IR ($\nu=_{max}/cm^{-1}$): 3327, 2921, 2853, 1649, 1099, 727. HRMS (DART, $[M+H]^+$) *m/z* calcd for $C_{27}H_{32}I_1N_2O_5$ 591.1355, found 591.1346.

N-cyclohexyl-2-(2-iodobenzoyl)-5,6,7-trimethoxy-4-methyl-1,2-dihydroisoquinoline-1-carboxamide (**12d**)

Using the general procedure, this compound was obtained as a beige solid in 84% (99 mg) yield after purification by flash column chromatography (3/7 EtOAc–hexanes), *Rf*. 0.5 (3/7 EtOAc–hexanes), m. p. 152-155 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.89 (d, *J* = 9.3 Hz, 1H), 7.41 (t, *J* = 7.1 Hz, 2H), 7.15 (td, *J* = 7.9, 1.7 Hz, 2H), 6.70 (s, 1H), 6.08 (s, 1H), 5.85 – 5.78 (m, 1H), 3.90 (s, 3H), 3.87 (s, 4H), 3.83 (s, 4H), 3.77 – 3.68 (m, 1H), 2.06 (s, 3H), 1.96 – 1.81 (m, 2H), 1.64 (d, *J* = 6.5 Hz, 2H), 1.36 – 1.13 (m, 6H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ: 168.6, 167.5, 152.9, 151.1, 142.8, 140.4, 139.5, 131.1, 128.7, 128.4, 126.1, 120.4, 119.6, 107.9, 92.9, 61.1, 60.7, 57.6, 56.1, 48.9, 33.1, 33.0, 25.5, 24.7, 19.1. IR (cm^{-1}): 3319, 2926, 2851, 1635, 1596, 1101, 772. HRMS (DART, [M+H]$^+$) *m/z* calcd for $C_{27}H_{32}I_1N_2O_5$ 591.1355, found 591.1369.

N-benzyl-2-(2-iodobenzoyl)-5,7-dimethoxy-4-methyl-1,2-dihydroisoquinoline-1-carboxamide (**12e**)

Using the general procedure, this compound was obtained as a pale yellow solid in 87% (99 mg) yield after purification by flash column chromatography (4/6 EtOAc–hexanes) *Rf.* 0.4 (4/6 EtOAc–hexanes), m. p. 171-174 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.82 (d, *J* = 7.9 Hz, 1H), 7.44 – 7.20 (m, 7H), 7.18 – 6.98 (m, 2H), 6.55 (s, 1H), 6.45 (d, *J* = 2.0 Hz, 1H), 6.21 (s, 1H), 5.76 (s, 1H), 4.45 (d, *J* = 5.5 Hz, 2H), 3.84 (s, 3H), 3.79 (s, 3H), 2.07 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ: 168.8, 168.5, 160.2, 157.9, 140.6, 139.5, 138.0, 132.5, 131.2, 128.8, 128.7, 128.4, 128.1, 127.6, 127.1, 119.5, 114.4, 105.3, 99.8, 92.9, 57.9, 55.6, 55.6, 44.0, 20.1. IR (ν=$_{max}$/cm^{-1}): 3223, 2924, 2847, 1652, 1631, 1577, 1206, 1096, 745, 696. HRMS (DART, [M+H]$^+$) *m/z* calcd for $C_{27}H_{26}I_1N_2O_4$ 569.0937, found 569.0915.

N-(*tert*-butyl)-2-(2-iodobenzoyl)-5,7-dimethoxy-4-methyl-1,2-dihydroisoquinoline-1-carboxamide (**12f**)

Using the general procedure, this compound was obtained as a pale yellow solid in 90% (96 mg) yield after purification by flash column chromatography (4/6 EtOAc–hexanes), *Rf.* 0.4 (4/6 EtOAc–hexanes), m. p. 79-82 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.88 (d, *J* = 7.9 Hz, 1H), 7.40 (t, *J* = 7.2 Hz, 1H), 7.14 (t, *J* = 7.7 Hz, 2H), 6.45 (d, *J* = 7.1 Hz, 3H), 6.04 (s, 1H), 5.76 (s, 1H), 3.84 (s, 3H), 3.78 (s, 3H), 2.06 (s, 3H), 1.33 (s, 9H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ: 168.7, 167.5, 160.0, 157.9, 139.6, 133.0, 131.2, 128.9, 128.4, 119.4, 114.4, 105.2, 99.5, 93.2, 58.5, 55.6, 55.5, 51.8, 29.0, 20.1. IR (ν=$_{max}$/cm^{-1}): 3393, 2966, 2927, 2837, 1686, 1626, 747. HRMS (DART, [M+H]$^+$) *m/z* calcd for $C_{24}H_{28}I_1N_2O_4$ 535.1093, found 535.1086.

2-(2-iodobenzoyl)-5,7-dimethoxy-4-methyl-*N*-(naphthalen-2-yl)-1,2-dihydroisoquinoline-1-carboxamide (**12g**)

Using the general procedure, this compound was obtained as a brown solid in 66% (80 mg) yield after purification by flash column chromatography (3/7 EtOAc–hexanes), *Rf.* 0.5 (3/7 EtOAc–hexanes), m. p. 100-103 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.81 (s, 1H), 8.32 (s, 1H), 7.90 (d, *J* = 7.9 Hz, 1H), 7.73 (t, *J* = 8.1 Hz, 3H), 7.42 (tt, *J* = 15.2, 8.6 Hz, 5H), 7.17 (t, *J* = 7.7 Hz, 1H), 6.52 (d, *J* = 11.8 Hz, 2H), 6.39 (s, 1H), 5.81 (s, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 2.10 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ: 169.4, 167.0, 160.2, 158.0, 139.6, 135.3, 133.8, 131.3, 130.6, 128.7, 128.6, 128.4, 127.7, 127.5, 126.4, 124.9, 120.6, 120.0, 118.9, 116.7, 114.6, 104.9, 100.0, 99.8, 93.0, 58.6, 55.5, 55.4, 20.2. IR (ν=$_{max}$/cm^{-1}): 3289, 2933, 2837, 1694, 1629, 1595, 1142, 830, 754. HRMS (DART, [M+H]$^+$) *m/z* calcd for $C_{30}H_{26}I_1N_2O_4$ 605.0937, found 605.0963.

N-(*tert*-butyl)-2-(2-iodobenzoyl)-5,6,7-trimethoxy-4-methyl-1,2 dihydroisoquinoline-1-carboxamide (**12h**)

Using the general procedure, this compound was obtained as a pale yellow solid in 90% (101 mg) yield after purification by flash column chromatography (4/6 EtOAc–hexanes), *Rf.* 0.4 (4/6 EtOAc–hexanes), m. p. 79-82 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.88 (d, *J* = 7.9 Hz, 1H), 7.46 – 7.34 (m, 2H), 7.14 (td, *J* = 7.9, 1.7 Hz, 2H), 6.64 (s, 1H), 6.01 (s, 1H), 5.84 – 5.77 (m, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.83 (s, 3H), 2.07 (s, 3H), 1.33 (s, 9H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ: 168.0, 166.8, 153.4, 152.9, 143.2, 135.8, 132.2, 129.5, 129.1, 128.3, 126.2, 123.9, 123.8, 120.5, 117.2, 107.5, 61.4, 61.0, 58.1, 56.3, 51.8, 29.8, 28.8, 17.0. IR (ν=$_{max}$/cm^{-1}): 3405, 2924, 2853, 1692, 1653, 1385, 1102, 1015, 813, 766. HRMS (DART, [M+H]$^+$) *m/z* calcd for $C_{25}H_{30}I_1N_2O_5$ 565.1199, found 565.1188.

2-(4-chloro-2-iodobenzoyl)-5,7-dimethoxy-4-methyl-*N*-phenyl-1,2dihydroisoquinoline-1 carboxamide (**12i**)

Using the general procedure, this compound was obtained as a beige solid in 96% (113 mg) yield after purification by flash column chromatography (3/7 EtOAc–hexanes), *Rf.* 0.4 (3/7 EtOAc–hexanes), m. p. 70-73 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.47 (s, 1H), 7.90 (s, 1H), 7.52 (d, *J* = 7.9 Hz, 2H), 7.40 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.32 – 7.20 (m, 3H), 7.12 – 7.00 (m, 1H), 6.52 (d, *J* = 2.2 Hz, 1H), 6.48 (d, *J* = 2.4 Hz, 1H), 6.29 (s, 1H), 5.80 – 5.74 (m, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 2.09 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ: 168.5, 166.5, 160.3, 158.1, 139.2, 137.8, 136.5, 131.7, 129.6, 129.0, 128.8, 124.4, 119.9, 118.9, 114.5, 105.0, 99.8, 93.4, 58.7, 55.6, 55.5, 20.2. IR (ν=$_{max}$/cm^{-1}): 3331, 2965, 2931, 2832, 1667, 1631, 1599, 1089, 830, 748. HRMS (DART, [M+H]$^+$) *m/z* calcd for $C_{26}H_{23}Cl_1I_1N_2O_4$ 589.0391, found 589.0381.

N-benzyl-2-(4-fluoro-2-iodobenzoyl)-5,6,7-trimethoxy-4-methyl-1,2-dihydroisoquinoline-1-carboxamide (**12j**)

Using the general procedure, this compound was obtained as a white solid in 90% (111 mg) yield after purification by flash column chromatography (5/5 EtOAc–hexanes) *Rf.* 0.5 (5/5 EtOAc–hexanes), m. p. 187-190 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.56 (d, *J* = 7.8 Hz, 2H), 7.30 – 7.21 (m, 5H), 7.12 (d, *J* = 8.0 Hz, 2H), 6.75 (s, 1H), 6.18 (s, 1H), 5.80 (s, 1H), 4.45 (dq, *J* = 16.0, 9.1, 7.4 Hz, 2H), 3.89 (s, 3H), 3.88 (s, 3H), 3.85 (s, 3H), 2.10 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ: 168.3, 168.0, 162.35 (d, J = 255.6 Hz), 153.1, 151.2, 143.0, 137.8, 129.94 (d, J = 8.2 Hz), 128.7, 127.9, 127.6, 126.8, 126.5, 125.7, 120.10 (d, J = 27.6 Hz), 118.5, 115.85 (d, J = 21.6 Hz), 107.9, 92.9, 61.2, 60.7, 57.7, 56.1, 43.9, 19.2. IR (ν=$_{max}$/cm^{-1}): 3322, 3075, 2922, 2834, 1652, 1629, 1404, 1013, 758. HRMS (DART, [M+H]$^+$) *m/z* calcd for $C_{28}H_{27}F_1I_1N_2O_5$ 617.0948, found 617.0945.

N-dodecyl-2-(2-iodobenzoyl)-5,6,7-trimethoxy-4-methyl-1,2-dihydroisoquinoline-1-carboxamide (**12k**)

Using the general procedure, this compound was obtained as a pale yellow solid in 67% (90 mg) yield after purification by flash column chromatography (3/7 EtOAc–hexanes) *Rf.* 0.4 (3/7 EtOAc–hexanes) m. p. 177-181 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.88 (d, *J* = 7.8 Hz, 1H), 7.41 (t, *J* = 7.4 Hz, 2H), 7.24 – 7.06 (m, 2H), 6.72 (s, 1H), 6.11 (s, 1H), 5.82 (s, 1H),

3.88 (s, 3H), 3.86 (s, 3H), 3.82 (s, 3H), 3.22 (q, *J* = 6.5 Hz, 2H), 2.05 (s, 3H), 1.51 – 1.41 (m, 2H), 1.22 (s, 16H), 0.85 (d, *J* = 6.9 Hz, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ: 168.7, 168.4, 152.9, 151.2, 142.8, 140.4, 139.6, 131.3, 129.8, 128.7, 128.5, 126.0, 120.4, 119.7, 118.6, 107.9, 92.9, 61.2, 60.8, 57.5, 56.1, 39.9, 31.9, 29.7, 29.7, 29.6, 29.6, 29.5, 29.4, 29.3, 26.9, 22.7, 19.2, 14.2. IR (ν_{max}/cm^{-1}): 3330, 3067, 2926, 2853, 1652, 1596, 1462, 1108, 768, 749. HRMS (DART, $[M+H]^+$) *m/z* calcd for $C_{33}H_{46}I_1N_2O_5$ 677.2451, found 677.2438.

2-(2-iodobenzoyl)-5,6,7-trimethoxy-4-methyl-*N*-octyl-1,2-dihydroisoquinoline-1-carboxamide (**12l**)

Using the general procedure, this compound was obtained as a yellow solid in 63% (78 mg) yield after purification by flash column chromatography (3/7 EtOAc–hexanes) *Rf*. 0.3 (3/7 EtOAc–hexanes). m. p. 78-81 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.88 (d, *J* = 7.8 Hz, 1H), 7.41 (t, *J* = 7.3 Hz, 1H), 7.23 – 7.11 (m, 1H), 6.71 (s, 1H), 6.10 (s, 1H), 5.82 (s, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.82 (s, 3H), 3.23 (q, *J* = 6.5 Hz, 2H), 2.05 (s, 3H), 1.47 (dq, *J* = 10.8, 6.4, 4.9 Hz, 2H), 1.23 (s, 10H), 0.88 – 0.81 (m, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ: 168.8, 168.5, 153.0, 151.2, 142.9, 139.6, 131.3, 128.7, 126.0, 120.4, 119.8, 108.0, 92.9, 61.3, 60.8, 57.5, 56.2, 39.9, 31.9, 29.6, 29.3, 27.0, 22.7, 19.3, 14.2. IR (ν_{max}/cm^{-1}): 3330, 2926, 2853, 1652, 1596, 1462, 1108, 768, 749. HRMS (DART, $[M+H]^+$) *m/z* calcd for $C_{29}H_{38}I_1N_2O_5$ 621.1825, found 621.1802.

ethyl (2-(2-iodobenzoyl)-5,6,7-trimethoxy-4-methyl-1,2-dihydroisoquinoline-1-carbonyl)-L-phenylalaninate (**12m**)

Using the general procedure, this compound was obtained as a pale yellow oil in 41% (68 mg) yield after purification by flash column chromatography (3/7 EtOAc–hexanes) *Rf*. 0.3 (3/7 EtOAc–hexanes). ^1H NMR ($CDCl_3$, 300 MHz) δ: (diastereomeric mixture) 7.83 (d, *J* = 7.6 Hz, 2H), 7.39 (t, *J* = 6.9 Hz, 2H), 7.26 – 7.10 (m, 11H), 7.05 – 6.91 (m, 4H), 6.67 (d, *J* = 9.8 Hz, 3H), 6.14 (d, *J* = 13.9 Hz, 1H), 5.82 (d, *J* = 29.3 Hz, 1H), 4.80 (t, *J* = 6.1 Hz, 2H), 4.14 (q, *J* = 5.6, 4.5 Hz, 4H), 3.86 (s, 12H), 3.81 (s, 7H), 3.10 (dd, *J* = 12.7, 5.2 Hz, 4H), 2.04 (d, *J* = 6.4 Hz, 6H), 1.29 – 1.18 (m, 8H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ: (diastereomeric mixture) 170.9, 168.7, 168.4, 167.9, 152.9, 151.2, 143.0, 140.5, 139.4, 135.8, 131.2, 129.5, 128.8, 128.7, 128.6, 128.5, 127.1, 125.4, 121.2, 120.6, 119.1, 118.5, 107.8, 93.0, 61.6, 61.3, 60.8, 57.6, 57.2, 56.1, 53.5, 37.8, 37.5, 29.7, 19.2, 19.1, 14.2. IR (ν_{max}/cm^{-1}): 3329, 3061, 2933, 2851, 1737, 1622, 1633, 1598, 1492, 1405, 1375, 1328, 1196, 1106, 1022, 772, 740, 702. HRMS (DART, $[M+H]^+$) *m/z* calcd for $C_{32}H_{34}I_1N_2O_7$ 685.1410, found 685.1386.

2-(2-bromofuran-3-carbonyl)-*N*-cyclohexyl-5,6,7-trimethoxy-4-methyl-1,2-dihydroisoquinoline-1-carboxamide (**12n**)

Using the general procedure, this compound was obtained as a pale yellow solid in 23% (26 mg) yield after purification by flash column chromatography (4/6 EtOAc–Hexanes) *Rf.* 0.2 (4/6 EtOAc–Hexanes). m. p. 148-149 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.48 (d, *J* = 2.1 Hz, 1H), 6.64 (s, 1H), 6.60 (s, 1H), 6.37 (d, *J* = 7.1 Hz, 1H), 6.20 (s, 1H), 5.93 (s, 1H), 3.86 (s, 6H), 3.85 (s, 3H), 3.76 – 3.60 (m, 1H), 2.17 (s, 3H), 1.86 – 1.73 (m, 2H), 1.65 – 1.50 (m, 3H), 1.34 – 1.14 (m, 5H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ: 167.8, 162.0, 153.0, 151.3, 144.5, 142.9, 126.4, 121.1, 119.5, 119.2, 119.1, 113.1, 107.5, 61.3, 60.9, 58.1, 56.2, 48.4, 32.8, 25.6, 24.5, 19.2. IR (ν_{max}/cm^{-1}): 3312, 2930, 2854, 1648, 1597, 1494, 1457, 1409, 1329, 1253, 1161, 1110, 1026, 942, 887, 754. HRMS (DART, $[M+H]^+$) *m/z* calcd for $C_{25}H_{30}{}^{79}Br_1N_2O_6$ 533.1287, found 533.1305.

2-(2-bromofuran-3-carbonyl)-*N*-cyclohexyl-5,7-dimethoxy-4-methyl-1,2-dihydroisoquinoline-1-carboxamide (**12o**)

Using the general procedure, this compound was obtained as a beige solid in 93% (94 mg) yield after purification by flash column chromatography (4/6 EtOAc–Hexanes) *Rf*. 0.5 (4/6 EtOAc–Hexanes). m. p. 208-209 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.46 (d, *J* = 2.1 Hz, 1H), 6.60 (d, *J* = 1.9 Hz, 1H), 6.44 (s, 2H), 6.29 (d, *J* = 7.8 Hz, 1H), 6.14 (s, 1H), 5.94 (s, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 2.14 (s, 3H), 1.79 (t, *J* = 10.8 Hz, 2H), 1.70 – 1.46 (m, 3H), 1.35 – 1.11 (m, 5H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ: 167.7, 161.9, 160.1, 157.9, 144.3, 132.9, 126.3, 120.2, 120.0, 119.3, 114.7, 113.1, 104.7, 99.4, 60.5, 58.4, 55.6, 55.5, 48.3, 32.8, 25.6, 24.5, 19.9, 14.3. IR (ν_{max}/cm^{-1}): 3293, 3089, 2924, 2853, 1648, 1604, 1574, 1493, 1464, 1402, 1334, 1210, 1166, 1103, 1040, 889, 810, 735. HRMS (DART, $[M+H]^+$) *m/z* calcd for $C_{24}H_{28}{}^{79}Br_1N_2O_5$ 503.1181, found 503.1181.

2-(2-bromothiophene-3-carbonyl)-*N*-(*tert*-butyl)-5,6,7-trimethoxy-4-methyl-1,2-dihydroisoquinoline-1-carboxamide (**12p**)

Using the general procedure, this compound was obtained as a white solid solid in 76% (80 mg) yield after purification by flash column chromatography (3/7 EtOAc–Hexanes) *Rf*. 0.2 (3/7 EtOAc–Hexanes). m. p. 152-154 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.31 (d, *J* = 5.6 Hz, 1H), 6.97 (d, *J* = 5.7 Hz, 1H), 6.62 (s, 1H), 6.35 (s, 1H), 6.02 (s, 1H), 5.95 (s, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 2.13 (s, 3H), 1.31 (s, 9H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ: 167.9, 163.6, 152.9, 151.2, 142.8, 135.1, 128.0, 127.3, 126.4, 120.4, 119.9, 118.9, 114.8, 107.7, 61.3, 60.8, 58.4, 56.1, 51.7, 28.8, 19.2. IR (ν_{max}/cm^{-1}): 3378, 3077, 2966, 2937, 2849, 1689, 1652, 1627, 1522, 1491, 1417, 1327, 1268, 1184, 1108, 1024, 877, 825, 707. HRMS (DART, $[M+H]^+$) *m/z* calcd for $C_{23}H_{28}{}^{79}Br_1N_2O_5S_1$ 523.0902, found 523.0893.

2-(2-bromo-5-chloronicotinoyl)-*N*-cyclohexyl-5,6,7-trimethoxy-4-methyl-1,2-dihydroisoquinoline-1-carboxamide (**12q**)

Using the general procedure, this compound was obtained as a pale yellow solid in 75% (87 mg) yield after purification by flash column chromatography (3/7 EtOAc–Hexanes) *Rf*. 0.2 (3/7 EtOAc–Hexanes). m. p. 238-239 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ: (major rotamer) 8.44 (d, *J* = 2.6 Hz, 1H), 7.54 (s, 1H), 6.70 (s, 1H), 6.05 (s, 1H), 5.86 (s, 1H), 3.91 (s, 3H), 3.87 (s, 3H), 3.84 (s, 3H), 3.78 – 3.65 (m, 1H), 2.10 (s, 3H), 1.73 – 1.50 (m, 5H), 1.22 – 0.85 (m, 5H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ: (mixture of rotamers) 167.4, 166.9, 153.3, 153.1, 151.5, 150.0, 149.6, 139.7, 137.0, 136.2, 135.1, 132.2, 120.6, 120.3, 107.1, 61.3, 60.9, 57.7, 56.3, 49.1, 33.1, 32.6, 29.8, 25.5, 25.3, 24.8, 24.3, 19.3. IR (ν_{max}/cm^{-1}): 3305, 3078, 2924, 2851, 1645, 1597, 1550, 1495, 1454, 1401, 1332, 1278, 1112, 1024, 898, 772. HRMS (DART, $[M+H]^+$) *m/z* calcd for $C_{26}H_{30}{}^{79}Br_1Cl_1N_3O_5$ 578.1057, found 578.1055.

2-(2-bromonicotinoyl)-*N*-(tert-butyl)-5,6,7-trimethoxy-4-methyl-1,2-dihydroisoquinoline-1-carboxamide (**12r**)

Using the general procedure, this compound was obtained as a white solid in 60% (558 mg) yield after purification by flash column chromatography (5/5 EtOAc–Hexanes) *Rf*. 0.3 (5/5 EtOAc–Hexanes). m. p. 74-77 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.48 (dd, *J* = 4.8, 2.0 Hz, 1H), 7.57 (s, 1H), 7.37 (dd, *J* = 7.4, 4.9 Hz, 1H), 6.66 (s, 1H), 6.02 (s, 1H), 5.88 – 5.79 (m, 1H), 3.91 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 2.08 (s, 3H), 1.32 (s, 9H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ: 167.2, 165.5, 153.2, 151.3, 142.9, 138.9, 137.6, 133.9, 126.2, 123.1, 120.9, 119.3, 107.8, 61.3, 60.8, 58.1, 56.2, 51.9, 28.9, 19.2. IR (ν=$_{max}$/cm^{-1}): 3444, 2924, 2856, 1684, 1631, 1600, 1458, 1405, 1326, 1276, 1110, 1023, 846, 812, 756, 525. HRMS (DART, [M+H]$^+$) *m/z* calcd for $C_{24}H_{29}{}^{79}Br_1N_3O_5$ 518.1290, found 518.1287.

General procedure for the synthesis of dihydroisoquinolines **12s-y** and **14**

In a round-bottom flask equipped with a magnetic stirring bar the corresponding Ugi adduct **11s-z** (0.5 mmol) was added to a solution of *p*-toluenesulfonic acid (0.5 equiv; in the case of morpholine derivates 1.5 equiv) and acetone (100 mg of the Ugi Adduct/1 mL of Acetone). The mixture was stirred for 5 h at 50°C (for 12 h at 50°C in the case of the morpholine derivates) in an oil bath. After that, the volatiles were removed under reduced pressure and the crude was extracted with ethyl acetate and sodium bicarbonate (sat. solution) and the organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2).

N-(*tert*-butyl)-2-(2-iodobenzoyl)-5,6,7-trimethoxy-1,2-dihydroisoquinoline-1-carboxamide (**12s**)

Using the general procedure, this compound was obtained as a pale yellow solid in 80% (220 mg) yield after purification by flash column chromatography (5/5 EtOAc–hexanes) *Rf.* 0.5 (5/5 EtOAc–hexanes). m. p. 136-139 °C ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.86 (s, 1H), 7.39 (s, 2H), 7.13 (t, *J* = 8.4 Hz, 2H), 6.64 (s, 1H), 6.09 (s, 2H), 6.06 (s, 1H), 3.84 (s, 9H), 1.32 (s, 9H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ: 169.3, 167.5, 153.2, 148.8, 141.9, 139.6, 131.3, 128.4, 122.5, 107.1, 106.8, 92.9, 61.5, 60.9, 57.9, 56.2, 28.9, 28.5. IR (ν=$_{max}$/cm^{-1}): 3400, 3054, 2969, 2937, 1687, 1652, 1463, 1366, 1119, 1092, 769, 742. HRMS (DART, [M+H]$^+$) *m/z* calcd for $C_{24}H_{28}I_1N_2O_5$ 551.1042, found 551.1049.

2-(2-(2-iodophenyl)acetyl)-5,6,7-trimethoxy-*N*-(4-methoxyphenyl)-1,2-dihydroisoquinoline-1-carboxamide (**12t**)

Using the general procedure, this compound was obtained as a pale yellow solid in 70% (214 mg) yield after purification by flash column chromatography (5/5 EtOAc–hexanes) *Rf*. 0.6 (5/5 EtOAc–hexanes). m. p. 99-102 °C ^{1}H NMR ($CDCl_3$, 300 MHz) (mixture of rotamers) δ: 7.86 (d, *J* = 7.8 Hz, 1H), 7.39 – 7.13 (m, 5H), 7.05 – 6.89 (m, 3H), 6.80 – 6.72 (m, 1H), 6.67 (s, 1H), 6.35 (s, 1H), 5.92 (d, *J* = 5.6 Hz, 1H), 3.92 (s, 1H), 3.88 (s, 1H), 3.86 – 3.74 (m, 12H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) (mixture of rotamers) δ: 169.7, 168.3, 163.6, 158.9, 156.3, 153.7, 153.4, 148.9, 139.6, 137.5, 137.4, 130.3, 130.2, 129.2, 128.7, 128.5, 127.0, 121.5, 121.3, 116.3, 115.1, 114.6, 114.5, 114.0, 107.1, 107.1, 104.0, 103.2, 62.7, 61.5, 60.9, 60.8, 58.6, 57.7, 56.3, 56.2, 55.6, 55.5, 45.6, 45.5, 45.1. IR (ν=$_{max}$/cm^{-1}): 3297, 3056, 2936, 2834, 1682, 1661, 1590, 1462, 1125, 1011, 832, 746. HRMS (DART, [M+H]$^+$) *m/z* calcd for $C_{28}H_{28}I_1N_2O_6$ 615.0992, found 615.0992.

2-(2-bromofuran-3-carbonyl)-*N*-(tert-butyl)-5,6,7-trimethoxy-1,2-dihydroisoquinoline-1-carboxamide (**12u**)

Using the general procedure, this compound was obtained as a pale brown solid in 70% (172 mg) yield after purification by flash column chromatography (5/5 EtOAc–Hexanes) *Rf.* 0.4 (5/5 EtOAc–Hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.49 (d, *J* = 2.1 Hz, 1H), 6.60 (s, 2H), 6.49 (d, *J* = 10.9 Hz, 1H), 6.35 (s, 1H), 6.25 (d, *J* = 9.6 Hz, 1H), 5.93 (s, 1H), 3.91 (s, 3H), 3.87 (s, 6H), 1.29 (s, 9H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ: 182.5, 179.3, 167.7, 162.6, 153.3, 144.5, 124.4, 122.8, 119.0, 112.9, 106.9, 106.8, 61.5, 60.9, 58.2, 56.2, 56.3, 51.6, 28.7. IR (ν=$_{max}$/cm^{-1}): 3368, 3113, 2967, 2937, 1690, 1654, 1625, 1569, 1461, 1259, 1121, 1038, 745. HRMS (DART, [M+H]$^+$) *m/z* calcd for $C_{22}H_{26}{}^{79}Br_1N_2O_6$ 493.0974, found 493.0984.

2-(2-bromothiophene-3-carbonyl)-*N*-(tert-butyl)-5,6,7-trimethoxy-1,2-dihydroisoquinoline-1-carboxamide (**12v**)

Using the general procedure, this compound was obtained as a yellow solid in 87% (221 mg) yield after purification by flash column chromatography (6/4 EtOAc–Hexanes) *Rf.* 0.4 (6/4 EtOAc–Hexanes). m. p. 73-76 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) 7.33 (d, *J* = 5.7 Hz, 1H), 6.98 (d, *J* = 5.6 Hz, 1H), 6.63 (s, 1H), 6.32 (d, *J* = 7.6 Hz, 2H), 6.20 (d, *J* = 7.8 Hz, 1H), 6.02 (s, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.87 (s, 3H), 1.32 (s, 9H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ: 167.3, 164.0, 152.9, 148.5, 141.6, 134.6, 127.4, 127.2, 123.9, 122.2, 117.0, 114.1, 106.8, 106.5, 61.2, 60.6, 57.8, 55.8, 51.3, 28.4. IR (ν=$_{max}$/cm^{-1}): 3334, 3082, 2964, 2937, 2835, 1682, 1638, 1591, 1507, 1456, 1237, 1127, 1076, 727. HRMS (DART, [M+H]$^+$) *m/z* calcd for $C_{22}H_{26}{}^{79}Br_1N_2O_5S_1$ 509.0746, found 509.0744

2-(2-bromonicotinoyl)-*N*-(tert-butyl)-5,6,7-trimethoxy-1,2-dihydroisoquinoline-1-carboxamide (**12w**)

Using the general procedure, this compound was obtained as a yellow solid in 74% (186 mg) yield after purification by flash column chromatography (7/3 EtOAc–Hexanes) *Rf*. 0.5 (7/3 EtOAc–Hexanes). m. p.152-155 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.46 (dd, *J* = 4.8, 2.0 Hz, 1H), 7.53 (s, 1H), 7.44 – 7.27 (m, 2H), 6.66 (s, 1H), 6.17 (s, 1H), 6.12 (s, 1H), 6.07 (s, 1H), 3.86 (s, 3H), 3.86 (s, 3H), 3.85 (s, 3H), 1.30 (s, 9H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ: 167.0, 166.2, 153.4, 151.3, 150.8, 139.9, 138.7, 137.4, 123.0, 122.2, 121.4, 108.1, 107.3, 106.9, 106.6, 61.4, 60.9, 57.9, 56.2, 51.8, 28.8. IR (ν=$_{max}$/cm^{-1}): 3403, 3365, 3065, 2968, 2937, 2842, 1688, 1631, 1575, 1496, 1462, 1395, 1363, 1249, 1120, 1092, 889, 813, 753, 677, 631, 469. HRMS (DART, [M+H]$^+$) *m/z* calcd for $C_{23}H_{27}{}^{79}Br_1N_3O_5$ 504.1134, found 504.1134.

2-(2-(2-iodophenyl)acetyl)-5,6,7-trimethoxy-*N*-octyl-1,2-dihydroisoquinoline-1-carboxamide (**12x**)

Using the general procedure, this compound was obtained as a pale yellow oil in 92% (285 mg) yield after purification by flash column chromatography (3/7 EtOAc–Hexanes) *Rf*. 0.3 (3/7 EtOAc–Hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.89 – 7.74 (m, 1H), 7.34 – 7.11 (m, 2H), 7.04 – 6.89 (m, 1H), 6.55 (s, 1H), 6.25 (dd, *J* = 5.8, 1.4 Hz, 1H), 6.18 (s, 1H), 5.71 – 5.64 (m, 1H), 3.97 – 3.87 (m, 2H), 3.84 – 3.74 (m, 9H), 3.55 (q, *J* = 7.0 Hz, 2H), 1.65 – 1.50 (m, 2H), 1.34 – 1.16 (m, 10H), 0.86 (t, *J* = 6.5 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ: (major rotamer) 168.2, 163.9, 153.4, 139.6, 137.5, 131.8, 130.2,

129.2, 128.8, 128.5, 115.0, 113.7, 108.5, 104.1, 103.2, 101.1, 60.9, 58.4, 56.2, 46.7, 46.4, 45.6, 45.2, 31.8, 29.2, 28.5, 26.7, 22.7, 14.2. IR (ν_{max}/cm^{-1}): 3450, 2928, 2854, 1675, 1589, 1505, 1459, 1420, 1367, 1327, 1240, 1127, 1010, 845, 746, 593, 490. HRMS (DART, $[M+H]^+$) *m/z* calcd for $C_{29}H_{38}I_1N_2O_5$ 621.1825, found 621.1810.

2-(2-iodobenzoyl)-5,6,7-trimethoxy-*N*-(2-morpholinoethyl)-1,2-dihydroisoquinoline-1-carboxamide (**12y**)

Using the general procedure, this compound was obtained as a white solid in 65% (197 mg) yield after purification by flash column chromatography (9/1 EtOAc–MeOH) *Rf*. 0.3 (9/1 EtOAc–MeOH). m. p. 95-98 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.79 (dd, *J* = 28.8, 7.9 Hz, 2H), 7.46 – 7.33 (m, 2H), 7.20 – 6.98 (m, 2H), 6.74 (s, 1H), 6.47 – 6.33 (m, 1H), 6.22 – 6.03 (m, 1H), 3.84 – 3.77 (m, 9H), 3.67 – 3.64 (m, 2H), 3.40 – 3.20 (m, 2H), 2.68 – 2.34 (m, 8H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ: (mixture of rotamers) 169.5, 166.2, 166.0, 153.3, 153.2, 140.3, 139.1, 131.6, 131.3, 131.2, 130.7, 130.6, 129.2, 128.6, 128.5, 128.4, 128.2, 106.8, 86.7, 67.0, 66.3, 61.5, 61.0, 57.8, 57.3, 57.2, 56.6, 56.3, 55.9, 54.0, 53.3, 42.1, 41.8. IR (ν_{max}/cm^{-1}): 3432, 3292, 2939, 2855, 1678, 1643, 1591, 1461, 1332, 1187, 1125, 1035, 1010, 815, 774, 749, 683, 568. HRMS (DART, $[M+H]^+$) *m/z* calcd for $C_{26}H_{31}I_1N_3O_6$ 608.1257, found 608.1245.

2-(2-iodobenzoyl)-5,8-dimethoxy-*N*-(2-morpholinoethyl)-1,2-dihydroisoquinoline-1-carboxamide (**14**)

Using the general procedure, this compound was obtained as a white solid in 67% (193 mg) yield after purification by flash column chromatography (9/1 EtOAc–MeOH) *Rf*. 0.6 (9/1 EtOAc–MeOH). m. p. 71-74 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.81 (d, *J* = 7.8 Hz, 1H), 7.46 – 7.34 (m, 1H), 7.16 – 6.99 (m, 3H), 6.89 – 6.71 (m, 2H), 6.58 (s, 1H), 5.91 (d, *J* = 6.4 Hz, 1H), 5.74 (d, *J* = 6.0 Hz, 1H), 5.59 (s, 1H), 3.87 (s, 2H), 3.73 (s, 3H), 3.65 – 3.57 (m, 4H), 3.30 (s, 1H), 2.58 – 2.48 (m, 2H), 2.47 – 2.39 (m, 4H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ: 168.9, 164.0, 153.6, 151.6, 139.4, 138.7, 130.9, 130.5, 128.4, 127.7, 115.1, 113.9, 112.8, 111.2, 66.9, 66.3, 56.9, 56.5, 55.9, 55.7, 54.2, 53.7, 43.2. IR (ν_{max}/cm^{-1}): 3463, 2953, 2832, 2810, 1656, 1585, 1500, 1459, 1246, 1115, 1017, 771, 763. HRMS (DART, $[M+H]^+$) *m/z* calcd for $C_{25}H_{29}I_1N_3O_5$ 578.1151, found 578.1153.

General Procedure for the synthesis of fused-isoquinolines **13a-y** and **15**

A deoxygenated solution (Argon-1 h) of the corresponding dihydroisoquinoline **12a–y** (0.15 mmol, 1.0 equiv.), palladium(II) acetate (20 mol%), tricyclohexylphosphine tetrafluoroborate (40 mol %), and cesium carbonate (2.5 equiv.) in anhydrous toluene (0.1 M) was heated at 135 °C (the temperature was monitored using an internal IR probe) under microwave irradiation (100 W) for 2.5 hours using a sealed vessel. After removal of volatiles the crude was partitioned between ethyl acetate and sat. NaCl, and the organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude was purified by flash column chromatography (SiO_2).

N-(*tert*-butyl)-10,12-dimethoxy-13-methyl-6-oxo-5,8-dihydro-6H-isoquinolino[3,2-*a*]isoquinoline-8-carboxamide (**13a**)

Using the general procedure, this compound was obtained as an pale brown solid in 62% (39 mg) yield after purification by flash column chromatography (2/8 EtOAc–hexanes) *Rf.* 0.3 (2/8 EtOAc–hexanes), m. p. 199-201 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.64 (dd, *J* = 6.3, 2.1 Hz, 1H), 7.38–7.27 (m, 3H), 6.59 (d, *J* = 2.4 Hz, 1H), 6.47 (d, *J* = 2.5 Hz, 1H), 5.95 (s, 1H), 5.32 (s, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 3.65 (s, 2H), 2.62 (s, 3H), 1.04 (s, 9H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ: 168.7, 167.6, 160.3, 158.6, 135.7, 133.1, 132.2, 128.0, 127.8, 127.2, 126.9, 126.4, 121.7, 114.4, 105.9, 100.2, 56.5, 55.7, 55.6, 51.4, 40.0, 28.4, 16.6. IR (ν_{max}/cm^{-1}): 3321, 2970, 2923, 1691, 1641, 1600, 1324, 1161, 761. HRMS (DART, $[M+H]^+$) *m/z* calcd for $C_{25}H_{29}N_2O_4$ 421.2127, found 421.2129.

N-(*tert*-butyl)-10,11,12-trimethoxy-13-methyl-6-oxo-5,8-dihydro-6*H*-isoquinolino[3,2-*a*]isoquinoline-8-carboxamide (**13b**)

Using the general procedure, this compound was obtained as an orange solid in 56% (38 mg) yield after purification by flash column chromatography (3/7 EtOAc–hexanes) *Rf*. 0.4 (3/7 EtOAc–hexanes), m. p. 79-82 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.72 – 7.57 (m, 1H), 7.33 (dq, *J* = 11.1, 6.3, 4.8 Hz, 4H), 6.77 (s, 1H), 5.93 (s, 1H), 3.93 (s, 3H), 3.87 (s, 3H), 3.84 (s, 3H), 3.62 (d, *J* = 27.7 Hz, 2H), 2.65 (s, 3H), 1.04 (s, 9H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ: 168.6, 167.7, 153.3, 152.4, 143.0, 132.9, 132.3, 129.1, 128.3, 127.9, 127.6, 127.3, 126.5, 121.2, 118.5, 108.7, 61.3, 60.9, 56.2, 51.5, 40.0, 29.8, 28.4, 15.9. IR (ν_{max}/cm^{-1}): 3420, 3345, 2923, 2852, 1735, 1674, 1100. HRMS (DART, $[M+H]^+$) *m/z* calcd for $C_{26}H_{31}N_2O_5$ 451.2233, found 451.2233.

N-cyclopentyl-10,11,12-trimethoxy-13-methyl-6-oxo-5,8-dihydro-6*H*-isoquinolino[3,2-*a*]isoquinoline-8-carboxamide (**13c**)

Using the general procedure, this compound was obtained as an orange solid in 53% (37 mg) yield after purification by flash column chromatography (4/6 EtOAc–hexanes) *Rf.* 0.4 (4/6 EtOAc–hexanes), m. p. 72-75 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.67 – 7.59 (m, 1H), 7.39 – 7.28 (m, 3H), 6.80 (s, 1H), 6.00 (s, 1H), 5.41 (d, *J* = 7.1 Hz, 1H), 4.08 – 3.96 (m, 1H), 3.93 (s, 3H), 3.87 (s, 3H), 3.84 (s, 3H), 3.67 (s, 2H), 2.64 (s, 3H), 1.79 – 1.67 (m, 2H), 1.42 – 1.34 (m, 2H), 1.06 – 0.84 (m, 4H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ: 168.7, 167.9, 153.3, 152.4, 143.1, 132.7, 132.3, 128.8, 128.3, 127.9, 127.5, 127.3, 126.5, 121.0, 118.5, 108.7, 61.3, 60.9, 56.2, 55.6, 51.5, 40.0, 33.1, 32.8, 29.8, 23.6, 23.5, 16.0. IR (ν_{max}/cm^{-1}): 3411, 3327, 2921, 2853, 1649, 1596, 1099. 761. HRMS (DART, $[M+H]^+$) *m/z* calcd for $C_{27}H_{31}N_2O_5$ 463.2233, found 463.2217.

N-cyclohexyl-1,2,3-trimethoxy-12-methyl-7-oxo-5,7-dihydroisoindolo[2,1-*b*]isoquinoline-5-carboxamide (**13d**)

Using the general procedure, this compound was obtained as an yellow solid in 54% (37 mg) yield after purification by flash column chromatography (3/7 EtOAc–hexanes) *Rf.* 0.4 (3/7 EtOAc–hexanes), m. p. 232-235 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.03 (d, *J* = 8.0 Hz, 1H), 7.90 (d, *J* = 7.5 Hz, 1H), 7.65 (t, *J* = 7.6 Hz, 1H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.03 (s, 1H), 6.78 (d, *J* = 7.8 Hz, 1H), 5.98 (s, 1H), 3.95 (s, 3H), 3.89 (s, 6H), 3.63 (tt, *J* = 13.7, 6.7 Hz, 1H), 2.79 (s, 3H), 1.83 – 1.68 (m, 2H), 1.54 (d, *J* = 15.3 Hz, 2H), 1.27 – 1.03 (m, 5H), 0.92 – 0.78 (m, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ: 168.1, 166.9, 153.4,

152.8, 143.1, 135.8, 132.2, 129.8, 129.1, 128.2, 126.3, 124.0, 123.6, 120.3, 117.2, 107.6, 61.4, 60.9, 57.6, 56.2, 48.7, 32.6, 32.6, 25.5, 24.6, 17.0. IR (ν_{max}/cm^{-1}): 3301, 2928, 2852, 1705, 1651, 1102, 1019, 726. HRMS (DART, [M+H]$^+$) *m/z* calcd for $C_{27}H_{31}N_2O_5$ 463.2233, found 463.2240.

N-benzyl-1,3-dimethoxy-12-methyl-7-oxo-5,7-dihydroisoindolo[2,1-*b*]isoquinoline-5-carboxamide (**13e**)

Using the general procedure, this compound was obtained as an yellow solid in 46% (30 mg) yield after purification by flash column chromatography (4/6 EtOAc–hexanes) *Rf.* 0.3 (4/6 EtOAc–hexanes), m. p. 237-240 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.96 (d, *J* = 8.0 Hz, 1H), 7.90 (d, *J* = 7.5 Hz, 1H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.26 (d, *J* = 2.6 Hz, 1H), 7.17 (dq, *J* = 5.2, 2.7 Hz, 3H), 7.08 (dt, *J* = 4.8, 2.6 Hz, 2H), 6.65 (s, 1H), 6.48 (s, 1H), 5.93 (s, 1H), 4.40 – 4.30 (m, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 2.73 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ: 168.9, 166.8, 160.6, 159.3, 132.1, 128.6, 128.0, 127.3, 123.9, 123.6, 105.2, 99.9, 57.7, 43.7, 29.8, 18.0. IR (ν_{max}/cm^{-1}): 3296, 2920, 2850, 1720, 1690, 1652, 1455, 1396, 1158, 1028, 753, 694. HRMS (DART, [M+H]$^+$) *m/z* calcd for $C_{27}H_{25}N_2O_4$ 441.1814, found 441.1801.

N-(*tert*-butyl)-1,3-dimethoxy-12-methyl-7-oxo-5,7-dihydroisoindolo[2,1-*b*]isoquinoline-5-carboxamide (**13f**)

Using the general procedure, this compound was obtained as an yellow solid in 59% (36 mg) yield after purification by flash column chromatography (3/7 EtOAc–hexanes) *Rf.* 0.4 (3/7 EtOAc–hexanes), m. p. 245-248 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.96 (d, *J* = 8.0 Hz, 1H), 7.90 (dt, *J* = 7.5, 0.9 Hz, 1H), 7.75 – 7.39 (m, 3H), 6.65 (d, *J* = 2.5 Hz, 1H), 6.45 (d, *J* = 2.4 Hz, 1H), 6.37 (s, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 2.73 (s, 3H), 1.20 (s, 9H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ: 167.9, 166.8, 160.4, 159.3, 135.9, 134.1, 132.9, 132.0, 129.1, 128.9, 128.6, 127.8, 123.7, 118.0, 105.1, 99.6, 60.5, 58.4, 55.7, 51.7, 28.7, 18.0. IR (ν_{max}/cm^{-1}): 3293, 3054, 2967, 2930, 2838, 1660, 1602, 1207, 1157. HRMS (DART, [M+H]$^+$) *m/z* calcd for $C_{24}H_{27}N_2O_4$ 407. 1970, found 407.1966.

1,3-dimethoxy-12-methyl-*N*-(naphthalen-2-yl)-7-oxo-5,7-dihydroisoindolo[2,1-*b*]isoquinoline-5-carboxamide (**13g**)

Using the general procedure, this compound was obtained as an yellow solid in 47% (34 mg) yield after purification by flash column chromatography (2/8 EtOAc–hexanes) *Rf.* 0.3 (2/8 EtOAc–hexanes), m. p. decomposition at > 200 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 10.76 (s, 1H), 8.21 (s, 1H), 8.12 (d, *J* = 7.9 Hz, 1H), 7.88 – 7.73 (m, 4H), 7.58 (t, *J* = 7.5 Hz, 2H), 7.41 (dt, *J* = 14.8, 6.8 Hz, 2H), 7.18 (d, *J* = 1.9 Hz, 1H), 6.65 (d, *J* = 2.0 Hz, 1H), 6.02 (s, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 2.68 (s, 3H). ^{13}C{^{1}H} NMR (DMSO-d_6, 75 MHz) δ: 167.6, 165.7, 160.2, 159.0, 135.96, 135.4, 133.3, 132.3, 132.2, 129.9, 129.4, 128.7, 128.5, 128.1, 127.4, 127.3, 126.5, 124.8, 123.8, 123.0, 119.6, 115.5, 115.1, 114.8, 105.8, 99.2, 57.4, 56.0, 55.5, 17.6. HRMS (DART, [M+H]$^+$) *m/z* calcd for $C_{30}H_{25}N_2O_4$ 477. 1814, found 477.1820.

N-(*tert*-butyl)-1,2,3-trimethoxy-12-methyl-7-oxo-5,7-dihydroisoindolo[2,1-*b*]isoquinoline-5-carboxamide (**13h**)

Using the general procedure, this compound was obtained as a yellow solid in 53% (34 mg) yield after purification by flash column chromatography (3/7 EtOAc–hexanes) *Rf.* 0.4 (3/7 EtOAc–hexanes), m. p. 89-92 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.01 (d, *J* = 7.9 Hz, 1H), 7.93 (d, *J* = 7.6 Hz, 1H), 7.67–7.60 (m, 1H), 7.53–7.46 (m, 1H), 6.77 (s, 1H), 6.27 (s, 1H), 5.79 (s, 1H), 3.93 (s, 3H), 3.90 (s, 6H), 2.78 (s, 3H), 1.23 (s, 9H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ: 168.0, 166.8, 153.4, 152.9, 143.2, 135.8, 132.2, 129.5, 129.1, 128.3, 126.2, 123.9, 123.8, 120.5, 117.2, 107.5, 61.5, 61.0, 58.1, 56.3, 51.8, 28.8, 17.0. IR (ν_{max}/cm^{-1}): 3326, 3063, 3031, 2924, 2852, 1738, 1644, 1111. HRMS (DART+) *m/z* calcd for $C_{25}H_{29}N_2O_5$ [M+H]$^+$ 437.2076, found 437.2069.

10-chloro-1,3-dimethoxy-12-methyl-7-oxo-*N*-phenyl-5,7-dihydroisoindolo[2,1-*b*]isoquinoline-5-carboxamide (**13i**)

Using the general procedure, this compound was obtained as an yellow solid in 65% (45 mg) yield after purification by flash column chromatography (5/5 EtOAc–hexanes) *Rf.* 0.4 (5/5 EtOAc–hexanes), m. p. 280-283 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.66 (s, 1H), 7.96 (d, *J* = 1.8 Hz, 1H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.44 (dd, *J* = 8.1, 1.7 Hz, 2H), 7.42–7.36 (m, 2H), 7.23–7.13 (m, 1H), 7.07–6.95 (m, 1H), 6.71 (d, *J* = 2.5 Hz, 1H), 6.50 (d, *J* = 2.5 Hz, 1H), 6.14 (s, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 2.74 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ: 166.7, 166.4, 161.1, 159.7, 138.6, 137.8, 137.2, 132.0, 128.9, 128.3, 127.7, 127.2, 125.0, 124.4, 123.8, 120.3, 119.9, 116.0, 105.5, 99.9, 58.4, 55.7, 29.9, 18.2. IR (ν_{max}/cm^{-1}): 3284, 3079, 2924, 2839, 1693, 1662, 1598, 1201, 946, 751. HRMS (DART, [M+H]$^+$) *m/z* calcd for $C_{26}H_{22}Cl_1N_2O_4$ 461.1268, found 461.1258.

N-benzyl-10-fluoro-1,2,3-trimethoxy-12-methyl-7-oxo-5,7-dihydroisoindolo[2,1-*b*]isoquinoline-5-carboxamide (**13j**)

Using the general procedure, this compound was obtained as an yellow pale solid in 49% (36 mg) yield after purification by flash column chromatography (3/7 EtOAc–hexanes) *Rf.* 0.3 (3/7 EtOAc–hexanes), m. p. 254-257 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.86 (dd, *J* = 8.4, 5.3 Hz, 1H), 7.65 (dd, *J* = 9.6, 1.9 Hz, 1H), 7.23 – 7.14 (m, 4H), 7.07 (dd, *J* = 6.8, 2.5 Hz, 2H), 6.86 (s, 1H), 6.62 (t, *J* = 5.4 Hz, 1H), 5.88 (s, 1H), 4.41 – 4.28 (m, 2H), 3.91 (s, 6H), 3.90 (s, 3H), 2.73 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ: 168.9, 166.7, 165.06 (d, J = 178.8 Hz), 153.8, 153.1, 143.4, 137.9, 128.7, 127.5, 127.4, 125.89 (d, J = 8.1 Hz), 120.1, 118.4, 116.11 (d, J = 24.2 Hz), 111.01 (d, J = 26.4 Hz), 107.6, 61.5, 61.0, 57.6, 56.3, 43.8, 29.9, 16.9. HRMS (DART, [M+H]$^+$) *m/z* calcd for $C_{28}H_{26}F_1N_2O_5$ 489. 1825, found 489.1851.

N-dodecyl-2-(2-iodobenzoyl)-5,6,7-trimethoxy-4-methyl-1,2-dihydroisoquinoline-1-carboxamide (**13k**).

Using the general procedure, this compound was obtained as a pale yellow solid in 67% (90 mg) yield after purification by flash column chromatography (3/7 EtOAc–hexanes) *Rf.* 0.4 (3/7 EtOAc–hexanes) m. p. 177-181 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (mixture of rotamers) 7.61 (d, *J* = 8.3 Hz, 2H), 7.45 (d, *J* = 7.4 Hz, 3H), 6.71 (s, 1H), 6.53 (t, *J* = 5.5 Hz, 1H), 6.19 (s, 1H), 6.02 (s, 1H), 3.87 (d, *J* = 2.9 Hz, 9H), 3.19 (q, *J* = 6.6 Hz, 2H), 2.12 (s, 3H), 1.44 (s, 2H), 1.24 (s, 32H), 0.87 (t, *J* = 6.7 Hz, 6H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ 169.2, 169.1, 152.9, 151.2, 142.9, 133.7, 131.5, 129.4, 128.5, 126.4, 123.8, 122.6, 120.3, 119.2, 117.8, 107.4, 61.3, 60.8, 58.4, 56.2, 39.7, 32.0, 29.7, 29.4, 29.3, 26.9, 22.8, 19.1, 14.2. IR (ν_{max}/cm^{-1}): 3330, 3067, 2926, 2853, 1652, 1596, 1462, 1108, 768, 749. HRMS (DART, [M+H]$^+$) *m/z* calcd for $C_{33}H_{45}N_2O_5$ 549.3328, found 549.3327.

1,2,3-trimethoxy-12-methyl-*N*-octyl-7-oxo-5,7-dihydroisoindolo[2,1-*b*]isoquinoline-5-carboxamide (**13l**)

Using the general procedure, this compound was obtained as a yellow solid in 45% (33 mg) yield after purification by flash column chromatography (3/7 EtOAc–hexanes) *Rf*. 0.3 (3/7 EtOAc–hexanes). m. p. 184-187 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.02 (d, *J* = 8.0 Hz, 1H), 7.87 (d, *J* = 7.4 Hz, 1H), 7.64 (td, *J* = 7.7, 1.2 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.05 (s, 1H), 6.87 (t, *J* = 5.5 Hz, 1H), 5.99 (s, 1H), 3.95 (s, 3H), 3.88 (s, 3H), 3.88 (s, 3H), 3.11 (dtq, *J* = 27.3, 14.0, 7.1 Hz, 2H), 2.78 (s, 3H), 1.34 – 1.11 (m, 10H), 0.83 (t, *J* = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ: 169.0, 166.9, 153.4, 152.7, 143.1, 135.8, 132.2, 129.7, 129.1, 128.2, 126.2, 123.9, 123.6, 120.2, 117.3, 107.6, 61.4, 60.9, 57.4, 56.2, 39.8, 31.8, 29.3, 29.2, 29.2, 26.8, 22.7, 16.9, 14.1. IR (ν_{max}/cm^{-1}): 3307, 2926, 2853, 1706, 1654, 1464, 1106, 759, 720. HRMS (DART, [M+H]$^+$) *m/z* calcd for $C_{29}H_{37}N_2O_5$ 493.2702, found 493.2696.

ethyl (2*S*)-2-phenyl-2-(1,2,3-trimethoxy-12-methyl-7-oxo-5,7-dihydroisoindolo[2,1-*b*]isoquinoline-5-carboxamido)acetate (**13m**)

Using the general procedure, this compound was obtained as a yellow solid in 28% (23 mg) yield after purification by flash column chromatography (4/6 EtOAc–hexanes) *Rf*. 0.3 (4/6 EtOAc–hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.95 (dd, *J* = 13.7, 7.7 Hz, 2H), 7.71 – 7.59 (m, 1H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.11 – 6.99 (m, 3H), 6.86 – 6.79 (m, 2H), 6.75 (s, 1H), 6.54 (d, *J* = 7.6 Hz, 1H), 5.85 (s, 1H), 4.70 (dt, *J* = 7.5, 5.5 Hz, 1H), 4.06 (q, *J* = 7.1 Hz, 2H), 3.93 (d, *J* = 8.8 Hz, 1H), 3.90 – 3.89 (m, 5H), 3.88 (s, 3H), 3.14 – 2.89 (m, 2H), 2.71 (s, 3H), 1.12 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ: 170.4, 168.2, 166.2, 153.4, 153.0, 152.4, 142.9, 135.2, 135.2, 131.8, 128.9, 128.7, 128.0, 127.9, 126.5, 124.9, 123.7, 123.5, 119.8, 116.1, 107.2, 101.5, 61.2, 60.6, 56.9, 55.9, 53.0, 37.1, 29.4, 16.4, 13.7. IR (ν_{max}/cm^{-1}): 3299, 2927, 2852, 1691, 1658, 1597, 1457, 1329, 1199, 1104, 1026, 744, 699. HRMS (DART, [M+H]$^+$) *m/z* calcd for $C_{32}H_{33}N_2O_7$ 557.2287, found 557.2287.

N-cyclohexyl-8,9,10-trimethoxy-11-methyl-4-oxo-4,6-dihydrofuro[2',3':3,4]pyrrolo[1,2-*b*]isoquinoline-6-carboxamide (**13n**)

Using the general procedure, this compound was obtained as a beige solid in 51% (35 mg) yield after purification by flash column chromatography (4/6 EtOAc–Hexanes) *Rf*. 0.2 (4/6 EtOAc–Hexanes). m. p. 167-170 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.59 (d, *J* = 1.9 Hz, 1H), 6.82 (s, 1H), 6.68 (d, *J* = 1.9 Hz, 1H), 6.04 (d, *J* = 8.4 Hz, 1H), 5.66 (s, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 3.87 (s, 3H), 3.71 – 3.57 (m, 1H), 2.66 (s, 3H), 1.84 – 1.72 (m, 3H), 1.57 – 1.45 (m, 3H), 1.13 – 1.03 (m, 3H), 0.84 (dd, *J* = 10.6, 5.3 Hz, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ: 168.5, 161.5, 153.8, 153.5, 148.9, 143.0, 127.1, 122.0, 120.2, 118.3, 116.1, 107.8, 106.2, 61.5, 60.9, 57.8, 56.3, 48.7, 32.8, 29.8, 25.5, 24.6, 17.3. IR (ν_{max}/cm^{-1}): 3294, 2928, 2853, 1677, 1649, 1596, 1554, 1465, 1106, 1027, 988 HRMS (DART, [M+H]$^+$) *m/z* calcd for $C_{25}H_{29}N_2O_6$ 453.2025, found 453.2032.

N-cyclohexyl-8,10-dimethoxy-11-methyl-4-oxo-4,6-dihydrofuro[2',3':3,4]pyrrolo[1,2-*b*]isoquinoline-6-carboxamide (**13o**)

Using the general procedure, this compound was obtained as a yellow solid in 74% (47 mg) yield after purification by flash column chromatography (4/6 EtOAc–Hexanes) *Rf*. 0.2 (4/6 EtOAc–Hexanes). m. p. 270-272 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.55 (d, *J* = 1.9 Hz, 1H), 6.67 (d, *J* = 1.9 Hz, 1H), 6.61 (d, *J* = 2.2 Hz, 1H), 6.41 (d, *J* = 2.4 Hz, 1H), 6.06 (d, *J* = 8.0 Hz, 1H), 5.66 (s, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.71 – 3.51 (m, 1H), 2.63 (s, 3H), 1.74 (d, *J* = 12.9 Hz, 4H), 1.55 (d, *J* = 10.0 Hz, 2H), 1.05 (d, *J* = 11.8 Hz, 2H), 0.83 (d, *J* = 7.5 Hz, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ: 168.3, 161.6, 160.9, 160.1, 148.5, 133.8, 121.0, 119.8, 117.0, 113.9, 106.1, 105.5, 99.3, 58.0, 55.6, 48.6, 32.8, 29.8, 27.8, 26.7, 25.5, 24.6, 18.4. IR (ν_{max}/cm^{-1}): 3299, 2924, 2855, 1695, 1648, 1602, 1548, 1455, 1360, 1323, 1204, 1162, 1093, 1047, 892, 846, 727. HRMS (DART, [M+H]$^+$) *m/z* calcd for $C_{24}H_{27}N_2O_5$ 423.1920, found 423.1910.

N-(*tert*-butyl)-8,9,10-trimethoxy-11-methyl-4-oxo-4,6-dihydrothieno[2',3':3,4]pyrrolo[1,2-*b*]isoquinoline-6-carboxamide (**13p**)

Using the general procedure, this compound was obtained as a pale yellow solid in 16% (11 mg) yield after purification by flash column chromatography (4/6 EtOAc–Hexanes) *Rf*. 0.1 (4/6 EtOAc–Hexanes). m. p. 222-225 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.42 (d, *J* = 5.0 Hz, 1H), 7.27 (d, *J* = 5.7 Hz, 1H), 6.90 (s, 1H), 6.61 (s, 1H), 5.74 (s, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 3.86 (s, 3H), 2.56 (s, 3H), 1.24 (s, 9H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ: 168.4, 163.2, 153.6, 153.1, 143.5, 142.9, 136.6, 130.9, 127.8, 127.0, 120.1, 118.9, 115.9, 107.6, 61.4, 60.9, 58.6, 56.2, 51.8, 28.7, 18.1. IR (ν_{max}/cm^{-1}): 3409, 3305, 3077, 2967, 2856, 1662, 1594, 1550, 1457, 1363, 1325, 1250, 1152, 1102, 1018, 1018, 981, 883, 732, 518. HRMS (DART, [M+H]$^+$) *m/z* calcd for $C_{23}H_{27}N_2O_5S_1$ 443.1640, found 443.1629.

3-chloro-*N*-cyclohexyl-9,10,11-trimethoxy-12-methyl-5-oxo-5,7-dihydropyrido[2',3':3,4]pyrrolo[1,2-*b*]isoquinoline-7-carboxamide (**13q**)

Using the general procedure, this compound was obtained as a pale yellow solid in 84% (62 mg) yield after purification by flash column chromatography (3/7 EtOAc–Hexanes) *Rf*. 0.2 (3/7 EtOAc–Hexanes). m. p. 258-260 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.76 (d, *J* = 2.4 Hz, 1H), 8.11 (d, *J* = 2.4 Hz, 1H), 6.80 (s, 1H), 6.11 (d, *J* = 8.1 Hz, 1H), 5.83 (s, 1H), 3.92 (s, 3H), 3.91 (s, 3H), 3.88 (s, 3H), 3.67 – 3.56 (m, 1H), 3.06 (s, 3H), 1.74 (dd, *J* = 13.9, 3.7 Hz, 4H), 1.61 – 1.56 (m, 2H), 1.05 (dd, *J* = 10.4, 2.3 Hz, 2H), 0.90 – 0.79 (m, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ: 167.5, 165.0, 162.7, 154.2, 153.6, 151.8, 143.4, 130.8, 126.1, 123.8, 122.2, 119.3, 109.5, 107.2, 61.4, 60.9, 57.6, 56.3, 48.9, 32.8, 32.7, 29.8, 25.4, 24.6, 15.9. IR (ν_{max}/cm^{-1}): 3311, 3292, 2928, 2854, 1704, 1646, 1593, 1461, 1329, 1112, 1034, 799. HRMS (DART, [M+H]$^+$) *m/z* calcd for $C_{26}H_{29}ClN_3O_5$ 498.1795, found 498.1788.

N-(*tert*-butyl)-9,10,11-trimethoxy-12-methyl-5-oxo-5,7-dihydropyrido[2',3':3,4]pyrrolo[1,2-*b*]isoquinoline-7-carboxamide (**13r**)

Using the general procedure, this compound was obtained as a yellow solid in 42% (33 mg) yield after purification by flash column chromatography (5/5 EtOAc–Hexanes) *Rf*. 0.2 (5/5 EtOAc–Hexanes). m. p. decomposition at > 205 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.84 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.12 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.35 (ddd, *J* = 7.7, 4.9, 2.4 Hz, 1H), 6.91 (s, 1H), 6.49 (s, 1H), 5.88 (s, 1H), 3.93 (s, 3H), 3.90 (s, 3H), 3.87 (s, 3H), 3.11 (s, 3H), 1.22 (s, 9H). ^{13}C{^{1}H} NMR

($CDCl_3$, 75 MHz) δ: 167.9, 164.2, 156.1, 154.0, 152.8, 143.2, 131.1, 127.2, 126.5, 123.1, 122.2, 121.5, 119.6, 107.2, 61.4, 60.9, 58.1, 56.2, 51.8, 28.7, 15.9. IR (ν=$_{max}$/cm^{-1}): 3310, 2966, 2931, 2851, 1699, 1667, 1592, 1546, 1456, 1403, 1368, 1322, 1194, 1108, 1022, 1194, 1108, 1022, 950, 787, 553, 512. HRMS (DART, $[M+H]^+$) *m/z* calcd for $C_{24}H_{28}N_3O_5$ 438.2029, found 438.2033.

N-(*tert*-butyl)-1,2,3-trimethoxy-7-oxo-5,7-dihydroisoindolo[2,1-*b*]isoquinoline-5-carboxamide (**13s**)

Using the general procedure, this compound was obtained as a brown solid in 62% (40 mg) yield after purification by flash column chromatography (5/5 EtOAc–hexanes) *Rf*. 0.4 (5/5 EtOAc–hexanes). m. p. 185-188 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.76 (t, *J* = 6.8 Hz, 2H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 1H), 6.91 (s, 1H), 6.80 (s, 1H), 6.69 (s, 1H), 5.84 (s, 1H), 3.91 (s, 3H), 3.84 (s, 3H), 3.81 (s, 3H), 1.19 (s, 9H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ: 168.2, 166.8, 153.6, 150.0, 141.9, 135.2, 132.0, 131.6, 128.9, 128.4, 125.0, 123.1, 120.5, 117.6, 106.9, 99.2, 61.7, 60.9, 58.1, 56.2, 51.7, 28.6. IR (ν=$_{max}$/cm^{-1}): 3306, 3062, 2966, 2843, 1671, 1599, 1494, 1464, 1120, 1090, 761, 727. HRMS (DART, $[M+H]^+$) *m/z* calcd for $C_{24}H_{27}N_2O_5$ 423.1920, found 423.1915.

10,11,12-trimethoxy-*N*-(4-methoxyphenyl)-6-oxo-5,8-dihydro-6*H*-isoquinolino[3,2-*a*]isoquinoline-8-carboxamide (**13t**)

Using the general procedure, this compound was obtained as a pale brown solid in 35% (26 mg) yield after purification by flash column chromatography (5/5 EtOAc–hexanes) *Rf*. 0.4 (5/5 EtOAc–hexanes). m. p. 95-98 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.41 (d, *J* = 6.3 Hz, 1H), 7.33 – 7.21 (m, 5H), 6.99 – 6.92 (m, 2H), 6.56 (s, 2H), 6.47 (s, 1H), 6.42 (s, 1H), 3.90 (d, *J* = 6.6 Hz, 2H), 3.82 (s, 3H), 3.78 (s, 3H), 3.66 (s, 6H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ: 167.1, 163.2, 159.0, 153.5, 132.0, 130.2, 129.3, 128.6, 128.1, 127.4, 127.2, 122.0, 120.6, 114.6, 111.9, 103.1, 60.8, 57.8, 55.9, 55.6, 38.0. IR (ν=$_{max}$/cm^{-1}): 3351, 3072, 2936, 2836, 1687, 1590, 1509, 1245, 1125, 1001, 833, 760. HRMS (DART, $[M+H]^+$) *m/z* calcd for $C_{28}H_{27}N_2O_6$ 487.1869, found 487.1878.

N-(*tert*-butyl)-8,9,10-trimethoxy-4-oxo-4,6-dihydrofuro[2',3':3,4]pyrrolo[1,2-*b*]isoquinoline-6-carboxamide (**13u**)

Using the general procedure, this compound was obtained as a brown solid in 50% (31 mg) yield after purification by flash column chromatography (5/5 EtOAc–Hexanes) *Rf*. 0.5 (5/5 EtOAc–Hexanes). m. p. 191-194 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.56 (d, *J* = 1.9 Hz, 1H), 6.94 (s, 1H), 6.74 (s, 1H), 6.64 (d, *J* = 1.9 Hz, 1H), 6.57 (s, 1H), 5.71 (s, 1H), 3.94 (s, 3H), 3.89 (s, 3H), 3.86 (s, 3H), 1.26 (s, 9H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ: 168.6, 161.9, 160.3, 154.1, 150.5, 149.0, 141.8, 125.7, 123.6, 120.3, 116.7, 106.9, 106.0, 103.5, 100.2, 61.7, 60.9, 58.0, 56.2, 51.7, 28.6. IR (ν=$_{max}$/cm^{-1}): 3431, 3314, 2970, 2940, 1694, 1667, 1596, 1548, 1495, 1468, 1330, 1302, 1128, 987, 737, 565. HRMS (DART, $[M+H]^+$) *m/z* calcd for $C_{22}H_{25}N_2O_6$ 413.1712, found 413.1728.

N-(*tert*-butyl)-8,9,10-trimethoxy-4-oxo-4,6-dihydrothieno[2',3':3,4]pyrrolo[1,2-*b*]isoquinoline-6-carboxamide (**13v**)

Using the general procedure, this compound was obtained as a yellow solid in 34% (21 mg) yield after purification by flash column chromatography (6/4 EtOAc–Hexanes) *Rf*. 0.5 (6/4 EtOAc–Hexanes). m. p. 100-103 °C: ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.42 (d, J = 4.9 Hz, 1H), 7.30 (d, J = 2.9 Hz, 2H), 6.80 (s, 1H), 6.71 (s, 1H), 6.08 (s, 1H), 5.64 (s, 1H), 3.99 (s, 3H), 3.91 (s, 3H), 3.90 (s, 3H), 1.30 (s, 9H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ: 168.2, 153.9, 137.7, 130.5, 128.5, 127.6, 126.1, 125.1, 120.3, 106.9, 105.9, 101.0, 70.3, 60.9, 58.6, 57.2, 56.2, 45.6, 28.6. IR (ν=$_{max}$/cm^{-1}): 3311, 3068, 1665, 1600, 1458, 1359, 1232, 1119, 1086, 1029, 730, 618, 482. HRMS (DART, $[M+H]^+$) *m/z* calcd for $C_{22}H_{25}N_2O_5S_1$ 429.1484, found 429.1487.

N-(*tert*-butyl)-9,10,11-trimethoxy-5-oxo-5,7-dihydropyrido[2',3':3,4]pyrrolo[1,2-*b*]isoquinoline-7-carboxamide (**13w**)

Using the general procedure, this compound was obtained as a yellow solid in 19% (15 mg) yield after purification by flash column chromatography (7/3 EtOAc–Hexanes) *Rf*. 0.4 (7/3 EtOAc–Hexanes). m. p. 182-185 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ: (major rotamer) 8.75 (dd, *J* = 4.9, 1.5 Hz, 1H), 8.06 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.34 (dd, *J* = 7.8, 4.9 Hz, 2H), 6.87 (s, 1H), 6.59 (s, 1H), 5.82 (s, 1H), 3.90 (s, 3H), 3.85 (s, 3H), 3.82 (s, 3H), 1.20 (s, 9H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ: (mixture of rotamers) 169.3, 167.9, 164.4, 154.3, 153.4, 152.8, 142.0, 140.9, 131.8, 131.7, 131.3, 125.4, 124.5, 123.3, 122.7, 117.2, 106.6, 105.4, 101.5, 61.7, 60.9, 58.2, 55.9, 55.9, 55.2, 51.8, 28.7, 28.6. IR (ν=$_{max}$/cm^{-1}): 3312, 3064, 2970, 2939, 1672, 1594, 1549, 1462, 1366, 1324, 1226, 1179, 1119, 1083, 1028, 991, 781. HRMS (DART, $[M+H]^+$) *m/z* calcd for $C_{23}H_{26}N_3O_5$ 424.1872, found 424.1882.

10,11,12-trimethoxy-*N*-octyl-6-oxo-5,8-dihydro-6*H*-isoquinolino[3,2-*a*]isoquinoline-8-carboxamide (**13x**)

Using the general procedure, this compound was obtained as a brown oil in 48% (35 mg) yield after purification by flash column chromatography (4/6 EtOAc–Hexanes) *Rf*. 0.3 (4/6 EtOAc–Hexanes). m. p. 182-185 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ:7.45 – 7.38 (m, 1H), 7.30 – 7.25 (m, 2H), 7.23 – 7.17 (m, 1H), 6.45 (s, 1H), 6.30 (s, 1H), 6.20 (s, 1H), 3.82 (s, 2H), 3.74 (s, 3H), 3.62 (s, 6H), 1.67 – 1.59 (m, 2H), 1.26 (dd, *J* = 9.3, 4.5 Hz, 12H), 0.84 (d, *J* = 7.0 Hz, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ: 167.1, 163.5, 153.4, 130.6, 129.3, 128.5, 128.1, 127.9, 127.5, 122.0, 120.5, 110.7, 103.2, 60.8, 57.5, 55.9, 47.0, 38.0, 31.8, 29.2, 28.6, 26.7, 22.7, 14.1. IR (ν=$_{max}$/cm^{-1}): 3431, 2928, 2855, 1677, 1591, 1461, 1418, 1327, 1127, 1007, 760, 525. HRMS (DART, $[M+H]^+$) *m/z* calcd for $C_{29}H_{37}N_2O_5$ 493.2702, found 493.2684.

1,2,3-trimethoxy-*N*-(2-morpholinoethyl)-7-oxo-5,7-dihydroisoindolo[2,1-*b*]isoquinoline-5-carboxamide (**13y**)

Using the general procedure, this compound was obtained as a yellow solid in 72% (51 mg) yield after purification by flash column chromatography (9/1 EtOAc–MeOH) *Rf*. 0.3 (9/1 EtOAc–MeOH). m. p. 79-82 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ: (major rotamer) 7.87 – 7.79 (m, 2H), 7.68 – 7.61 (m, 1H), 7.52 (d, *J* = 7.5 Hz, 1H), 7.12 (s, 1H), 6.90 (s, 1H), 6.69 (d, *J* = 7.1 Hz, 1H), 6.04 (s, 1H), 3.97 (s, 3H), 3.95 (s, 3H), 3.87 (s, 4H), 3.84 (s, 2H), 3.73 (s, 2H), 2.95 – 2.84 (m, 4H), 2.76 – 2.68 (m, 2H), 2.64 – 2.56 (m, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ: (major rotamer) 169.9, 166.9, 154.2, 153.6, 150.2, 142.1, 135.2, 132.3, 131.0, 129.2, 128.3, 123.3, 120.7, 116.9, 107.3, 105.4, 99.6, 65.0, 61.8, 61.0, 57.7, 56.9, 56.5, 53.2, 34.4. IR (ν=$_{max}$/cm^{-1}): 3386, 2929, 2852, 2246, 1652, 1592, 1506, 1460, 1422, 1329, 1237, 1188, 1126, 1012, 915, 814,

731, 694, 567. HRMS (DART, $[M+H]^+$) m/z calcd for $C_{26}H_{30}N_3O_6$ 480.2134, found 480.2138.

1,4-dimethoxy-*N*-(2-morpholinoethyl)-7-oxo-5,7-dihydroisoindolo[2,1-b]isoquinoline-5-carboxamide (**15**)

Using the general procedure, this compound was obtained as a brown solid in 88% (60 mg) yield after purification by flash column chromatography (9/1 EtOAc–MeOH) *Rf*. 0.5 (9/1 EtOAc–MeOH). m. p. 75-78 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.74 (d, *J* = 7.7 Hz, 1H), 7.62 – 7.48 (m, 2H), 7.41 – 7.34 (m, 1H), 6.87 (d, *J* = 2.8 Hz, 1H), 6.78 (s, 1H), 6.75 (d, *J* = 2.8 Hz, 1H), 6.51 (s, 1H), 6.12 (s, 1H), 3.74 (s, 3H), 3.68 (s, 3H), 3.66 – 3.53 (m, 2H), 2.60 (t, *J* = 6.5 Hz, 1H), 2.52 – 2.45 (m, 3H), 1.92 – 1.78 (m, 3H), 1.46 – 1.36 (m, 1H), 1.28 – 1.18 (m, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ: 165.1, 164.7, 153.6, 151.3, 133.7, 131.7, 128.8, 128.1, 123.7, 118.9, 116.2, 113.9, 112.9, 107.9, 67.0, 56.7, 55.2, 53.7, 44.6, 35.7, 34.9, 27.0, 26.9, 26.3, 26.2. IR (ν_{max}/cm^{-1}): 3388, 3080, 2930, 2852, 1676, 1616, 1502, 1449, 1248, 1115, 1045, 759, 718. HRMS (DART, $[M+H]^+$) m/z calcd for $C_{25}H_{28}N_3O_5$ 450.2029, found 450.2030.

Supporting Information. Spectroscopic ^{1}H and ^{13}C NMR data, UV-Vis emission spectrophotometry, confocal microscopy figures, X-ray crystallography data and CIF files are provided in the supporting information file. This material is available free of charge via the Internet at http://pubs.acs.org.

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