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Exploiting polycyclic aromatic isonitriles in GBB strategy for the design of functional scaffolds

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Dedicated to our friend and colleague Prof. Thomas J. J. Müller in recognition of his support and scientific guidance

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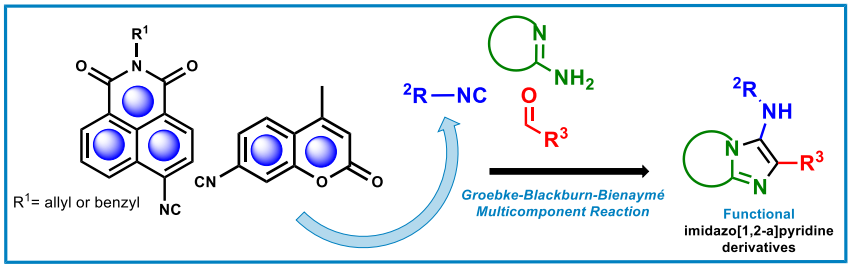
Abstract

In this work, we describe an exploratory study on the use of polycyclic aromatic isocyanides, based on the naphthalimide and coumarin cores, for the synthesis of novel and valuable imidazo[1,2-*a*]pyridine derivatives. By exploiting the Groebke-Blackburn-Bienaymé (GBB) multicomponent reaction, we successfully incorporated two functional aromatic isonitriles into the heterocyclic core in a single step. As a proof-of-concept, we combined this strategy with starting materials exhibiting distinct fluorescent and bioactive characteristics (naphthalimide and coumarin-based cores) to evaluate the feasibility of generating new functionalized scaffolds. The synthesis of the isocyanides was evaluated considering both synthetic strategies and fluorescent properties, with preliminary insights into the photophysical behavior depending on the functional groups present (i.e. amine, formamide, isocyanide) in these specific systems.



Keywords: Heteroaromatic Isocyanide, Multicomponent reaction, Groebke-Blackburn-Bienaymé, Fluorescence

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Introduction

Isocyanides, discovered nearly two centuries ago,[1,2] have gained significant importance in organic synthesis,[3] particularly since the development of the Passerini multicomponent reaction (P-3CR) in 1921,[4,5] and today they represent a milestone in modern synthetic chemistry. Contemporary research has elevated the isocyanide functional group far beyond its synthetic origins, establishing its strategic importance across diverse frontiers including medicine,[6] material science[7] and photochemistry.[8] Despite their early discovery and potential, isocyanide research remained underdeveloped for nearly a century, largely due to the notoriously repulsive odor and the absence of reliable synthetic protocols. A significant turning point that opened the doors for the isocyanide-based chemistry field, occurred in 1958 with the development of an efficient synthesis via the dehydration of the corresponding formamides.[9] Simple, volatile, liquid isocyanides suffer from drawbacks such as their unappealing odor and intrinsic toxicity, but they are easily available commercially. As reported by Dömling,[10] although over 26,000 isocyanides have been identified (with more than 3,000 commercially available), research in this field is heavily focused on a small subset, such as the well-known tert-butyl and cyclohexyl derivatives. Despite this, functionalized isocyanides have long been recognized as important tools in organic synthesis and, fascinated by their unique electronic properties, we report in this communication the introduction of this functional group in well-known fluorescent cores to exploit polycyclic aromatic isocyanides as starting material in isocyanide-based multicomponent reactions (I-MCRs).[11]

Among I-MCRs, the Groebke-Blackburn-Bienaymé (GBB) reaction[12,13] stands out for its ability to produce imidazo-fused nitrogen heterocycles, which are considered privileged scaffolds in both medicinal chemistry and materials science. Discovered in 1998, the Groebke-Blackburn-Bienaymé (GBB) reaction has matured into the third most significant isocyanide-based multicomponent reaction, right after the Ugi and Passerini processes. Unlike its linear-structure-producing counterparts, the GBB reaction is prized for generating cyclic and heteroaromatic, drug-like scaffolds, highly valuable for diversity-oriented synthesis.

Since its discovery, the GBB reaction has matured significantly, with recent research focusing on broadening its scope using novel building blocks to impart specific physical or biological properties to the final products. While many studies have focused on varying the aldehyde[14-16] or the amidine[17-19] components, the use of polycyclic aromatic isonitriles remains largely underinvastigated, yet it may constitute a promising avenue for creating new functional substrates. As previously mentioned, the adducts thus synthesized have different properties, among which the photophysical ones stand out. There are several published examples in this field, including the seminal work by some of us,[20] and others.[21-23] A breakthrough in the field would involve introducing the functional moiety directly from the isocyanide, thereby extending the complexity (and conjugation) of the imidazo-azine GBB core and opening new avenues for its convenient access.[24,25]

This report details the synthesis of coumarin- and naphthalimide-based isonitriles (well-known cores in medicinal chemistry[26,27] that also exhibit valuable photophysical properties[28,29]), investigating the influence of the isocyano group on their photophysical properties. Furthermore, these derivatives are employed in the preparation of GBB adducts to evaluate the potential extension of conjugation between the imidazopyridine scaffold and the isonitrile-derived moiety.

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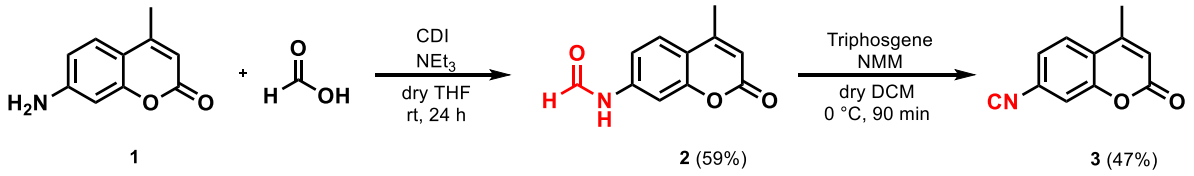
Results and Discussion

Recently, our research has focused on the synthesis of polycyclic heteroaromatic isonitriles to exploit their unique electronic properties, starting from an evaluation of their potential as photoredox catalysts.[30-32] Between the selected scaffold, we identified two isocyanides relating to particularly well-known fluorescent structures: the first is characterized by a coumarin-based core, while the second features a naphthalimide scaffold.

Our initial focus was on exploring the synthesis of these compounds and investigating their fluorescent properties in comparison with those of their corresponding precursors to define the relationship between the modification of the fluorescence emission and the functional groups present in the structure (i.e. amine, formamide, isocyanide).

Isonitriles were synthesized following a classical multistep procedure starting from the corresponding amines, via a formylation step and a subsequent dehydration.

Regarding the coumarin scaffold, commercially available 7-amino-4-methylcoumarin [**1**] was formylated using carbonyldiimidazole (CDI) and formic acid to afford the intermediate formamide [**2**] in 59% yield. At this stage, purification was unnecessary; a simple work-up via vacuum filtration provided the crude formamide, which was directly dehydrated with triphosgene in the presence of *N*-methylmorpholine (NMM) to yield the desired isocyanide [**3**] (47% yield, Scheme 1), albeit in low yield due to partial degradation of the product during work-up.



Scheme 1. Synthesis of the coumarin-based isocyanide **3**.

In contrast, the synthesis of naphthalimide-based isocyanides was slightly more elaborated, as it required the prior assembly of the naphthalimide core. Nevertheless, the route remained straightforward and allowed for the preparation of two derivatives, [**8**] and [**12**], featuring different *N*-alkyl functionalities (benzyl and allyl, respectively). Neither modification was expected to significantly alter the electronic properties of the core structure (Scheme 2). For the *N*-benzyl derivative, the synthesis commenced from 4-nitro-1,8-naphthalic anhydride [**4**], which was reacted with benzylamine in acetic acid, followed by $SnCl_2$-mediated reduction of the nitro group to give the amino-naphthalimide [**6**]. The *N*-allyl derivative [**10**] was synthesized starting from 4-amino-1,8-naphthalic anhydride [**9**] (either purchased or prepared by hydrogenation of [**4**] over 10% Pd/C in acetonitrile) by reaction with allylamine under the same conditions used for [**5**]. Once intermediates [**6**] and [**10**] were obtained, both underwent a common sequence: formylation with a mixture of formic acid and acetic anhydride, followed by dehydration with triphosgene and NMM. To further optimize the process, an alternative dehydration protocol inspired by Dömling and co-workers[9] was also employed to avoid aqueous work-up. In this procedure, following treatment with $POCl_3$, the crude mixture was directly loaded onto a dry silica column and eluted with hexane/dichloromethane. This method proved significantly faster, provided higher yields, and minimized waste compared to conventional protocols. Applying this approach to [**7**] afforded the desired isocyanide [**8**] in an improved yield of 83%.

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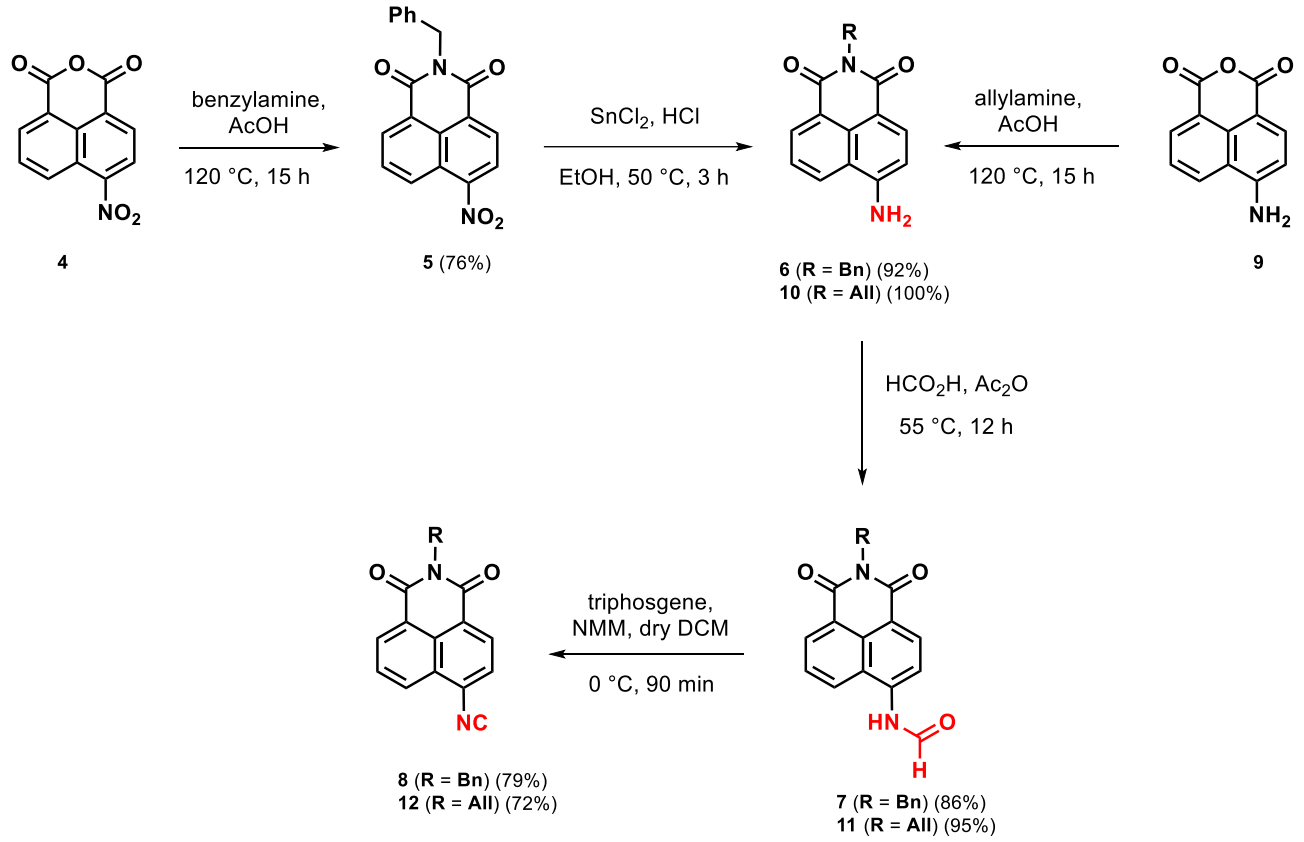

Scheme 2. Synthesis of the N-alkyl naphthalimide-based isocyanides.

Following the synthesis of the isonitriles, we turned our attention to their application in Groebke–Blackburn–Bienaymé (GBB) reactions. Initially, we focused on the naphthalimide-based isocyanide [**8**], which was reacted with 2-aminopyridine [**13**] and 4-chlorobenzaldehyde [**14**]. Given the inherently low reactivity of aromatic isonitriles, careful screening of reaction conditions was required to achieve satisfactory yields of the aminopyrazole adduct [**15**]. Specifically, matching established literature conditions with the pre-formation of the imine in the presence of a Lewis acid, followed by the subsequent addition of the isonitrile to the reaction mixture, proved to be crucial for obtaining the product. The use of methanol as a solvent facilitated the solubilization of the substrates, while rapid microwave-assisted heating at 80 °C (75 minutes) limited product decomposition, allowing adduct [**15**] to be isolated in 33% yield. No substantial differences were observed between the use of $Yb(OTf)_3$ and $Sc(OTf)_3$, whereas p-toluenesulfonic acid resulted in lower yields. Using this adapted methodology, compounds [**16**-**18**] (Scheme 3) were also synthesized with low to moderate yields (33-79%), reflecting the exploratory nature of these substrates. Notably, the alkyl group on the naphthalimide core appears to have no significant influence on the outcome, whereas the electronic nature of the aldehyde seems to play a more critical role.

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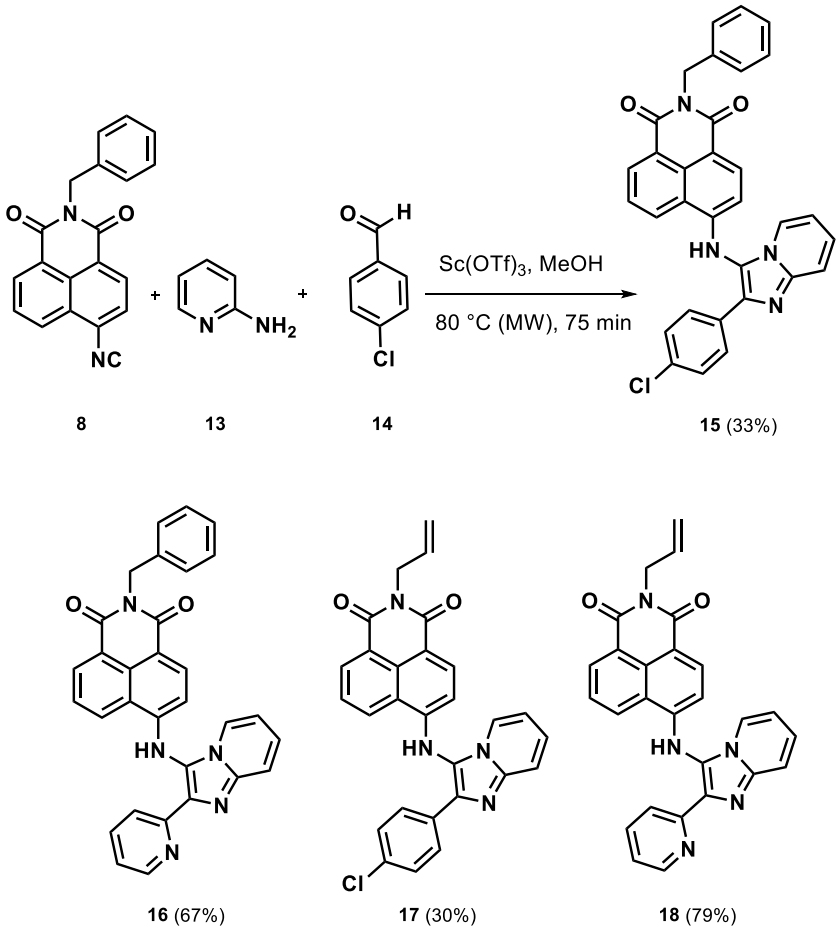

Scheme 3. Conditions for the GBB reaction with isocyanide [**8**] and naphthalimide-based GBB adducts.

Similarly, the coumarin isocyanide [**3**] was reacted with 2-aminopyridine and a range of aromatic aldehydes under the same conditions, providing adducts [**19**-**21**] in fair yields (Figure 1).

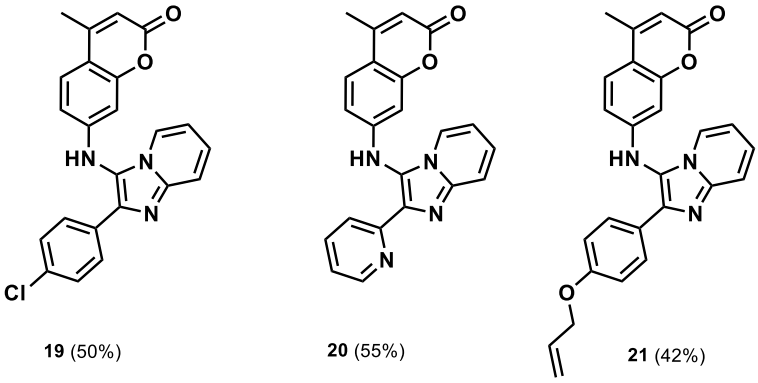

Figure 1. Coumarin-based GBB adducts.

The fluorescent properties of isocyanides **3** and **11**, as well as those of their precursors, were investigated in water, ethanol, and dioxane (from left to right), and they are shown in Figure 2.

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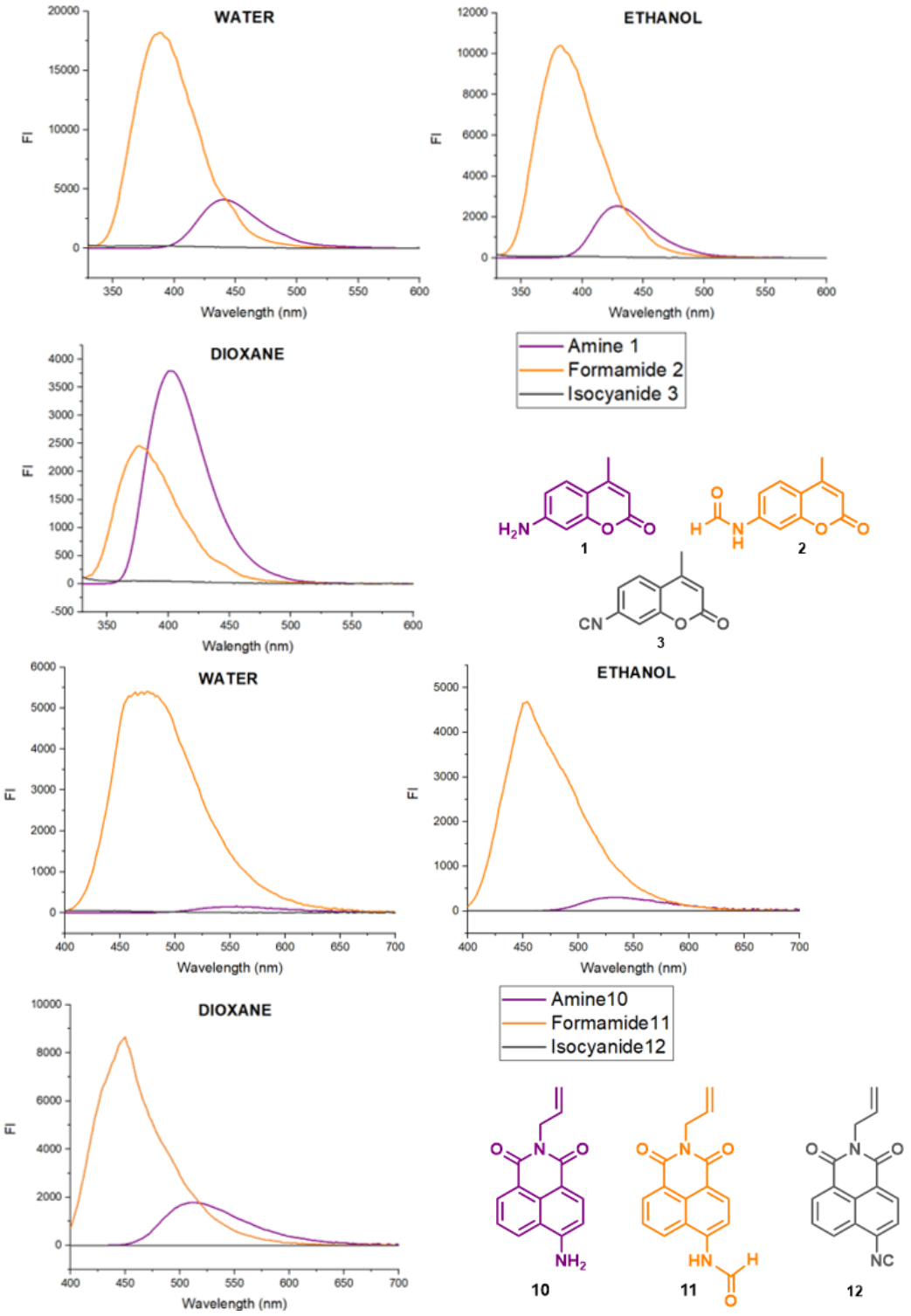

Figure 2. Fluorescence emission spectra of a) coumarin-based derivatives (amine **1**, formamide **2**, isocyanide **3**) in water, ethanol and dioxane; upon excitation at 300 nm (gain = 60) and b) naphtalimide -based derivatives (amine **10**, formamide **11**, isocyanide **12**) in water, ethanol and dioxane; upon excitation at 370 nm (gain = 60).

Interestingly, both isonitriles exhibited very weak fluorescence emission when excited respectively at 300 nm and 370 nm. In contrast, a remarkably strong emission was observed for their precursors—specifically the formamide precursor (orange line). The influence of the solvent was observed for the corresponding amines, for which the solvent polarity strongly influenced the emission, showing higher emission intensity in dioxane

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in both cases. At the same time, dioxane was found to be the least favorable solvent for the emission of formamide **2** (naphthalimide derivative), suggesting that in this case, the amine form is the more fluorescent species. The significant fluorescence quenching observed upon the introduction of the isocyanide group is consistent with the change of electronic properties in the functional group.

Within the GBB multicomponent framework, it was therefore of great interest to investigate whether the fluorescence could be restored or even enhanced by the conjugation with the imidazopyridine system. However, the photophysical data gathered remain strictly qualitative.

To this end, a first comparison between the naphtalimide derivatives was made and the relative GBB adduct **17** was found to be poorly fluorescent, in a trend consistent with the complete lack of fluorescence emission of their precursor isonitriles, even in dioxane as shown in Figure 3.

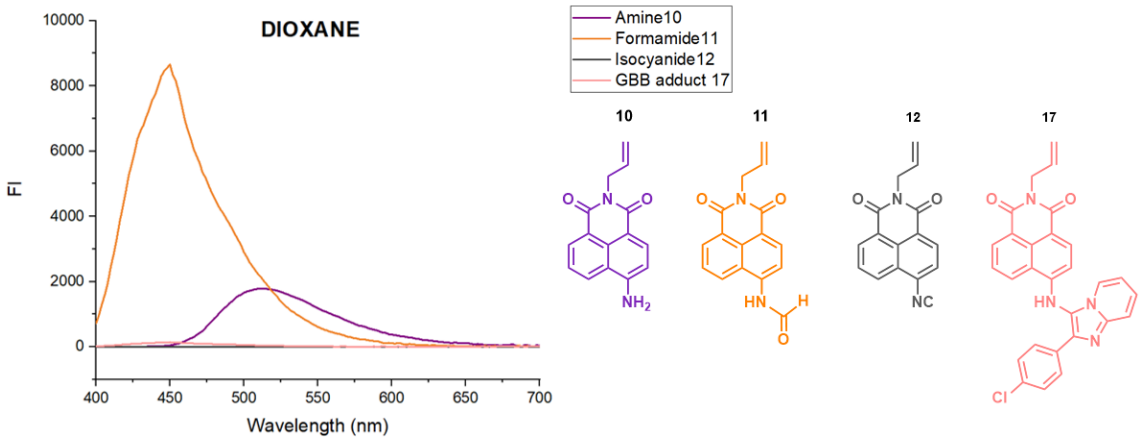

Figure 3. Fluorescence emission spectra of naphtalimide -based derivatives (Amine **10**, formamide **11**, isocyanide **12** and GBB adduct **17**) in dioxane, upon excitation at 370 nm (gain = 60).

Then the coumarin-based scaffold was explored. However, only the *p*-Cl-derivative **19** displayed a modest fluorescence readout which is most intense in water (about 4 times fold increase compared to the precursor isonitrile), while compounds **20** and **21** were found to be non-fluorescent irrespectively of the solvent system. (Figure 4). This general lack of fluorescence restoration highlights the current structural and electronic limitations of this specific scaffold combination.

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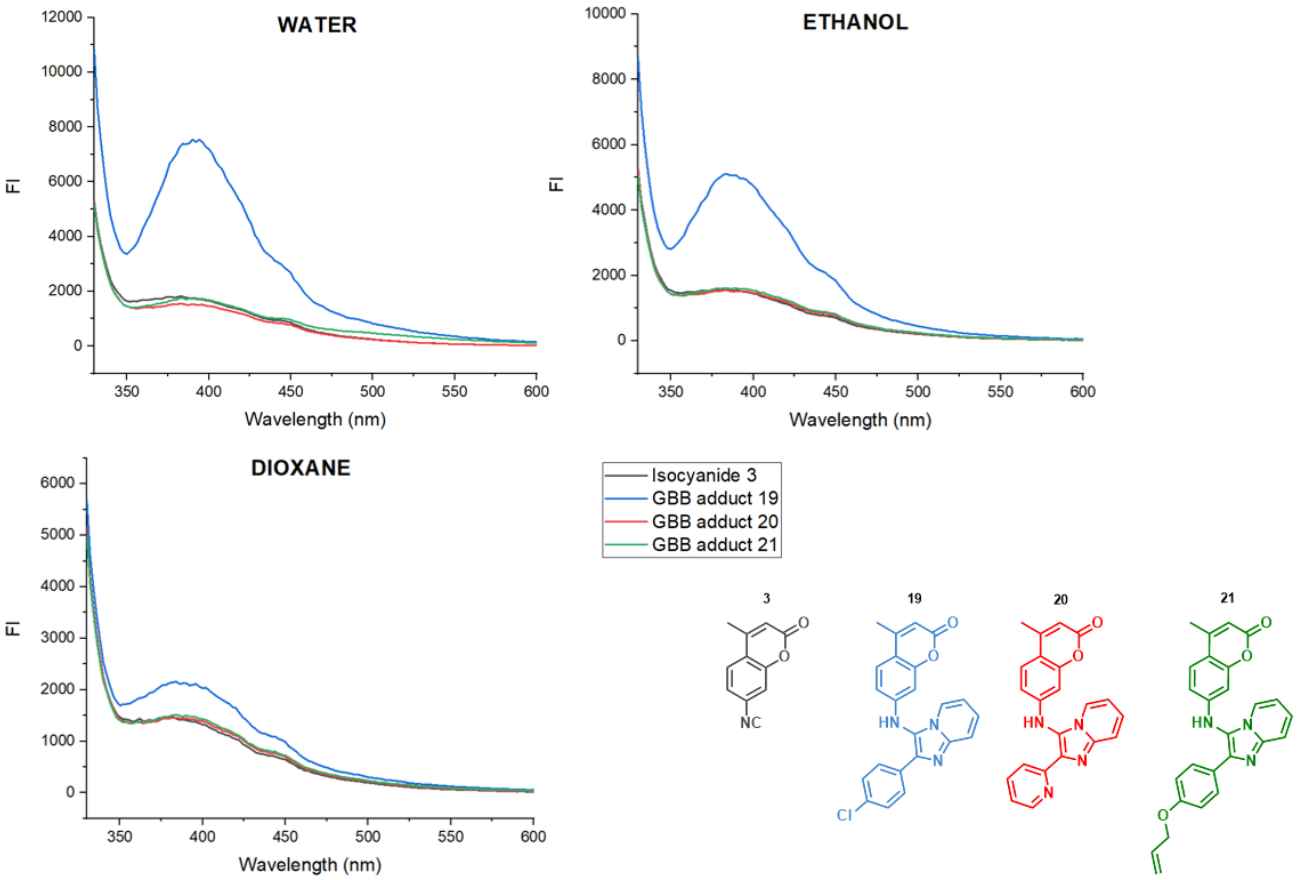

Figure 4. Fluorescence emission spectra of coumarin-based derivatives (Isocyanide **3** and GBB adducts **19**–**21**) in water, ethanol, and dioxane, respectively, upon excitation at 300 nm (gain = 90).

Conclusions

In summary, we have demonstrated as a proof-of-concept that polycyclic heteroaromatic isonitriles based on coumarin and naphthalimide cores can undergo GBB multicomponent reactions under specific conditions to afford seven new derivatives. Although the GBB transformation does not restore fluorescence to the levels of the starting substrates—likely due to conformational twisting hindering π-conjugation—this exploratory study outlines the current scope and limitations of introducing such complex polycyclic cores via MCRs. Moreover, these results establish a preliminary basis for exploring the boundaries of these molecular architectures in chemical biology and drug discovery: specifically, the incorporation of a pyridine-2-carbaldehyde moiety enables the synthesis of highly fluorescent BODIPY derivatives,[33] as demonstrated by Lavilla;[20] preliminary trials on *N*-benzylnaphthalimide-based adducts have already shown promising results, that will be reported in due course. Furthermore, the inclusion of functional groups like the allyl moiety facilitates rapid post-synthetic modifications, such as thiol-ene click reactions[34-36] for anchoring to biomolecules.

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Experimental Section

General Aspects.

Solvents and reagents. Commercial solvents and reagents were used directly without any other purification. All non-aqueous reactions were performed under an inert atmosphere of argon or nitrogen. Inert gases were passed over a U-tube of silica and activated 3 Å molecular sieves. When inert atmosphere was used, commercially available dry solvents were employed, and every possible precaution was taken.

Routine procedure. Every piece of glassware was dried and stored in oven at 100°C. Analytical TLC was performed on Merck silica gel 60 F254 0.25 mm TLC glass plates and visualized by UV (254 nm). TLC plates were also stained by dipping and heating with Hanessian stain (CAM, 21 g $(NH_4)_4MoO_4{\cdot}4H_2O$ and 1g $Ce(SO_4)_2{\cdot}4H_2O$ in 31 mL of H_2SO_4 and 469 mL of H_2O), $KMnO_4$ (1,5 g of $KMnO_4$, 10 g of K_2CO_3, 1 mL of 10% aq. NaOH in 200 mL of deionized water). After extractions, the aqueous phases were always reextracted three times with the appropriate organic solvent, and the organic extracts were always dried over Na_2SO_4 and filtered before evaporation to dryness. Concentration under reduced pressure was performed by rotavapor at 40 °C. Chromatographic purification was performed as flash chromatography (FC) on MERCK Geduran® Si 60 Å (40–63 µm, 230–400 mesh) under positive pressure and the crude mixtures were loaded as solid absorbed on silica or as solution in the eluent. Petroleum ether (PE) is 40–60 °C. Purified compounds were dried further under high vacuum (~10–2 torr).

All products were characterized by ^{1}H,^{13}C.

Microwave equipment. Microwave-assisted reactions were performed in a CEM Discover single-mode microwave reactor, operating in closed-vessel (sealed tube) mode under continuous pressure and temperature monitoring. The reactions were carried out using a dynamic temperature control program, where the microwave power was automatically modulated (up to a maximum of 150 W) to maintain the target temperature. The internal pressure was safely maintained below the reactor upper limit (typically 15 bar) throughout the duration of the process.

Nuclear magnetic resonance spectroscopic analysis (NMR). ^{1}H and ^{13}C NMR spectra were recorded on a JEOL 400 (at 400 MHz and 101 MHz respectively) or Varian Mercury Plus 300 (300 MHz and 75 MHz respectively). NMR spectra were recorded using residual solvent and TMS as the internal standard ^{1}H NMR: TMS = 0.00, $CDCl_3$ at 7.26 ppm for ^{1}H and 77.16 ppm for ^{13}C, DMSO-d_6 at 2.50 ppm for ^{1}H and 39.52 for ^{13}C and CD_3OD at 3.31 ppm for ^{1}H and 49.00 for ^{13}C. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, integration, and coupling constants (Hz). Data for ^{13}C NMR spectra are reported in terms of chemical shift (δ ppm). Interpretation of spectra has been made also with the aid of COSY, HSQC and HMBC experiments. The following abbreviations are used to indicate the multiplicity in NMR spectra: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet and their combinations; the b in front of the multiplicity stands for a broad signal. For some compounds the extra peaks are due to residual undefined impurities (<5%) due to difficulties in the purification. All the NMR spectrums were analysed using the software MestReNova (Mestrelab Research® v. 14.2).

HPLC-MS and elemental analyses. HPLC analysis was performed on Agilent 1100 or Agilent 1260 Infinity II equipped with a DAD detector (220 nm) and column Gemini C18 150 x 3 mm, 5 µm. Mobile phases were (A) H_2O + 0.1% TFA and (B) CH3CN + 0.1% TFA, gradient from 10% to 100% of B in 15 min, flow 0.34 mL/min, and 25 °C. Mass analysis was performed on Microsaic 4000 MiD® mass spectrometer (mass range 100-800 *m/z*). Elemental analyses were determined by an EA1110 Analyzer, Fison Instruments.

Photophysical characterization. Absorbance and fluorescence emission spectra were measured using a Synergy HT spectrophotometer (Biotek) in 96-well clear bottom polystyrene microplates on 10 µM substrate

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solutions, measured in triplicate and corrected by solvent blank subtraction. For each substrate, a 1 mM stock solution was prepared in DMSO and subsequently diluted to 10 µM in the solvent used for optical measurements (water, ethanol, or dioxane), depending on the experiment.

Procedure for the synthesis of compounds 3, 8 and 12. Isocyanides **3**, **8** and **12** were synthesized from the corresponding amines via a two-step sequence: formylation followed by dehydration. For substrate **3**, the aniline was formylated according to Procedure **A**. For substrates **8** and **12** the aniline was formylated according to Procedure **B**. After work-up, the resulting formamides were dehydrated, without further purification, to afford the corresponding isocyanides (General Procedure **C**).

General Procedure A. The formic acid (1.2 equiv) and the dry THF (0.12 M) were added in a flame-dried round-bottom flask and flushed with nitrogen. N,N'-Carbonyldiimidazole (CDI, 1.6 equiv). was added portion wise to facilitate dissolution, and the reaction mixture was stirred at room temperature for 5 h. Subsequently, triethylamine (2.0 equiv) and the amine (1 equiv) were added. The reaction was stirred overnight at room temperature. After completion of the reaction, AcOEt was added to induce precipitation of the product. The resulting solid was collected by vacuum filtration, washed with a small amount of AcOEt, and concentrated under reduced pressure to afford the corresponding formamide. The resulting crude formamide was used directly in the subsequent dehydration step without further purification.

General Procedure B. The amine (1.0 equiv) was suspended in formic acid (0.3 M), and acetic anhydride (3.7 equiv) was added. The reaction mixture was stirred at 55 °C overnight. After cooling to room temperature, the mixture was diluted with dichloromethane and washed sequentially with aqueous saturated Na_2CO_3, water, and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude formamide was used directly in the subsequent dehydration step without further purification.

General Procedure C. The crude formamide was transferred to a flame-dried round-bottom flask and flushed with nitrogen. The substrate was dissolved in dry DCM (0.1 M), and *N*-methylmorpholine (3.2 equiv) was added. The reaction mixture was cooled to 0 °C using an ice bath, and triphosgene (0.5 equiv) was added dropwise. The reaction was stirred at 0 °C for 1 h and at room temperature until the full conversion of the starting material (1.5-4 h) The reaction mixture was diluted with DCM and washed with saturated aqueous $NaHCO_3$. The organic layer was separated, treated with brine and then dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude material was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate) to afford the corresponding isocyanide as a solid.

7-Isocyano-4-methylcoumarin (3) Starting from 7-amino-4-methylcoumarin **1** (3 mmol), the corresponding formamide **2** was synthesized according to General Procedure **A**. Yield: 59%. The NMR data were fully consistent with those reported in the literature.[37] Starting from the crude 7-formamido-4-methylcoumarin **2** (1.5 mmol), isocyanide **3** was synthesized according to General Procedure **C.** Yield: 47%; white foam. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.62 (d, *J* = 8.4 Hz, 1H), 7.36 – 7.26 (m, 2H), 6.34 (q, *J* = 1.3 Hz, 1H), 2.44 (d, *J* = 1.3 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 167.8, 159.6, 153.7, 151.3, 128.6, 126.0, 122.4, 121.0, 116.6, 115.3, 18.8. HPLC-MS (ESI+)-UV. Rt: 14.08 min, 478.0 [M + H]+. Anal calcd for $C_{11}H_7NO_2$: C: 71.35; H: 3.81; N: 7.56. Found: C: 71.79; H: 3.71; N: 7.55.

4-Isocyano-*N*-benzyl-1,8-naphthalimide (8) The 4-nitronaphthalic-1,8-anhydride **4** (4.0 mmol, 1.0 equiv) and benzylamine (1.0 equiv) were dissolved in acetic acid (0.3 M), and the reaction mixture was heated at reflux overnight. After complete consumption of the starting material, the reaction mixture was cooled to room temperature, resulting in the formation of a solid. The precipitate was collected by vacuum filtration and washed sequentially with 2 M HCl, 10% aqueous Na_2CO_3, H_2O, and EtOH. No further purification was carried

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out. Yield: 85%; orange foam. The data were consistent with those reported in the literature.[38] The 4-nitro-N-phenyl-1,8-naphthalimide **5** (3.5 mmol, 1.0 equiv) was dissolved in ethanol (0.16 M), and $SnCl_2$ (8.2 equiv) was added. The reaction mixture was heated to 50 °C, and concentrated HCl (0.05 equiv) was added dropwise. The mixture was maintained at 50 °C for 3 h. After complete consumption of the starting material, the reaction mixture was poured into ice-cold deionized water, resulting in the formation of a precipitate. The solid was collected by vacuum filtration and washed sequentially with water, 1 M NaOH, and a few drops of ethanol. No further purification was carried out. Yield: 83%; orange foam. The NMR data were fully consistent with those reported in the literature.[39]

Starting from the crude 4-amino-N-phenyl-1,8-naphthalimide **6** (3.0 mmol), the corresponding formamide **7** was synthesized according to General Procedure **B**. No further purification was carried out. Yield: 59%; orange foam. ^{1}H NMR (300 MHz, DMSO-*d*6) δ 10.70 (s, 1H), 8.74 – 8.65 (m, 2H), 8.60 – 8.45 (m, 2H), 8.31 (s, 1H), 7.89 (dd, J = 8.5, 7.3 Hz, 1H), 7.46 – 7.16 (m, 5H), 5.27 (s, 2H).

^{13}C NMR (75 MHz, DMSO-*d*6) δ 163.1, 162.5, 161.0, 139.4, 137.1, 131.5, 130.7, 128.3, 127.8 (2C), 127.2 (2C), 126.5, 126.2, 123.2, 122.0, 117.3, 117.2, 42.5.

Starting from the crude 4-formamido-N-phenyl-1,8-naphthalimide 7 (1.5 mmol), isocyanide **8** was synthesized according to General Procedure **C.** Yield: 64%; white foam. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.72 (dd, J = 7.3, 1.1 Hz, 1H), 8.60 (d, J = 7.8 Hz, 1H), 8.53 (dd, J = 8.5, 1.2 Hz, 1H), 7.94 (dd, J = 8.5, 7.3 Hz, 1H), 7.83 (d, J = 7.8 Hz, 1H), 7.58 – 7.50 (m, 2H), 7.36 – 7.22 (m, 3H), 5.37 (s, 2H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 172.4, 163.6, 163.0, 136.9, 132.9, 130.9, 129.2, 129.2 (2C), 129.0, 128.7 (2C), 128.6, 127.9, 126.7, 125.5, 123.7, 123.3, 43.9. HPLC-MS (ESI+)-UV. Rt: 9.4 min, 311.2 [M + H]+. Anal calcd for $C_{20}H_{12}N_2O_2$: C: 76.91, H: 3.87, N: 8.97. Found: C: 77.1, H: 3.76 N: 8.99.

4-Isocyano-*N*-allyl-1,8-naphthalimide (12) 4-Aminonaphthalic-1,8-anhydride **9** (1.5 mmol, 1.0 equiv) was transferred in a flame-dried round-bottom flask under a nitrogen atmosphere and dissolved in ethanol (0.1 M). Allylamine (2.0 equiv) was then added, and the reaction mixture was heated at 90 °C overnight. After cooling to room temperature, a solid precipitated. The resulting solid was collected, washed with diethyl ether, and concentrated under reduced pressure. No further purification was carried out. Yield = 98%; orange foam. The NMR data were fully consistent with those reported in the literature.[40]

Starting from the crude 4-amino-N-allyl-1,8-naphthalimide **10** (1.5 mmol), the corresponding formamide **11** was synthesized according to General Procedure **B**. No further purification was carried out. Yield: 95%; yellow foam. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.92 (s, 1H), 8.78 – 8.31 (m, 5H), 7.88 (t, J = 8.0 Hz, 1H), 5.93 (ddt, J = 17.3, 10.4, 5.2 Hz, 1H), 5.20 – 5.05 (m, 2H), 4.63 (dt, J = 5.2, 1.7 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 163.1, 162.5, 160.9, 139.3, 132.8, 131.9, 131.0, 128.3, 128.2, 126.8, 122.9, 122.2, 117.6, 117.3, 116.3, 41.7.

Starting from the crude 4-formamido-N-allyl-1,8-naphthalimide **11** (1.2 mmol), the corresponding isocyanide **12** was synthesized according to General Procedure **C**. Yield: 72%; white foam. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.72 (dd, *J* = 7.3, 1.1 Hz, 1H), 8.60 (d, *J* = 7.8 Hz, 1H), 8.55 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.96 (dd, *J* = 8.5, 7.3 Hz, 1H), 7.84 (d, *J* = 7.8 Hz, 1H), 5.98 (ddt, *J* = 17.2, 10.2, 5.8 Hz, 1H), 5.34 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.23 (dq, *J* = 10.2, 1.3 Hz, 1H), 4.80 (dt, *J* = 5.9, 1.4 Hz, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 172.5, 163.3, 162.7, 132.8, 131.9, 130.8, 129.2, 129.1, 128.6, 126.8, 125.5, 123.3, 118.3, 42.8. HPLC-MS (ESI+)-UV. Rt: 12.34 min, 263.0 [M + H]+. Anal calcd for $C_{16}H_{10}N_2O_2$: C: 73.27, H: 3.84, N: 10.68. Found: C: 73.34, H: 3.97, N: 10.76.

Procedure for the synthesis of compounds 15-21

General Procedure D. A solution of aminopyridine (1.0 equiv) and the aldehyde (1.0 equiv) in methanol (0.25 M) was transferred into a microwave reactor tube, and a Lewis acid (LA; $Sc(OTf)_3$ or $Yb(OTf)_3$, 0.2 equiv) was added at room temperature. After 45 min, the isocyanide was introduced to the stirring mixture. The vessel was sealed and irradiated in a microwave reactor at 80 °C for 75 min. Upon completion, as confirmed by TLC

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and HPLC, methanol was removed under reduced pressure, and the residue was dissolved in dichloromethane (DCM). The organic solution was washed with saturated aqueous $NaHCO_3$ to pH 8. The layers were separated, and the aqueous phase was extracted with DCM. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography using DCM/MeOH or AcOEt/ ETP as eluent to afford the pure compound.

***N*-Benzyl naphthalimide-based GBB adduct (15)** 4-isocyano-*N*-benzyl-1,8-naphthalimide **8** (0.2 mmol) and the p-chlorobenzaldehyde (1 equiv), as the aldehyde partner, were used. The purification through silica gel flash chromatography (DCM/MeOH) led to the final product which appears as an orange foam. Yield: 67%. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.83 (s, 1H, NH), 9.04 (dd, *J* = 8.5, 1.1 Hz, 1H), 8.61 (dd, *J* = 7.4, 1.0 Hz, 1H), 8.21 (d, *J* = 8.3 Hz, 1H), 8.08 (dt, *J* = 6.8, 1.2 Hz, 1H), 8.03 – 7.98 (m, 2H), 7.95 (dd, *J* = 8.4, 7.4 Hz, 1H), 7.72 (dt, *J* = 9.1, 1.1 Hz, 1H), 7.49 – 7.42 (m, 2H), 7.40 (ddd, *J* = 9.1, 6.7, 1.3 Hz, 1H), 7.34 – 7.25 (m, 4H), 7.25 – 7.18 (m, 1H), 6.94 (td, *J* = 6.7, 1.1 Hz, 1H), 6.27 (d, *J* = 8.4 Hz, 1H), 5.24 (s, 2H, CH_2).
^{13}C NMR (75 MHz, DMSO-d_6) δ 163.7, 162.9, 148.1, 142.5, 137.7, 137.1, 134.1, 132.5, 132.1, 131.5, 129.5, 129.1, 128.8 (2C), 128.3 (2C), 128.0 (2C), 127.4 (2C), 127.0, 126.1, 125.8, 123.4, 122.2, 120.9, 117.4, 116.4, 112.9, 111.8, 106.7, 42.6. Anal calcd for $C_{32}H_{21}ClN_4O_2$: C: 72.66, H: 4.00, N: 10.59. Found: C: 73.22, H: 4.08, N: 10.48.

***N*-Benzyl naphthalimide-based GBB adduct (16)** 4-isocyano-*N*-benzyl-1,8-naphthalimide **8** (0.2 mmol) and ~~As~~ the pyridine-2-carbaldehyde (1 equiv), as the aldehyde partner, were used. The purification through silica gel flash chromatography (DCM/MeOH) led to the final product which appears as a yellow chartreuse foam. Yield: 33%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.70 (s, 1H), 8.76 – 8.61 (m, 2H), 8.50 (s, 1H), 8.40 (d, *J* = 8.1 Hz, 1H), 8.26 (d, *J* = 8.0 Hz, 1H), 7.87 (dd, *J* = 8.4, 7.4 Hz, 1H), 7.80 (td, *J* = 7.8, 1.7 Hz, 1H), 7.74 (dt, *J* = 9.1, 1.1 Hz, 1H), 7.57 – 7.49 (m, 3H), 7.34 – 7.26 (m, 4H), 7.25 – 7.12 (m, 2H), 6.84 (td, *J* = 6.8, 1.1 Hz, 1H), 6.28 (d, *J* = 8.2 Hz, 1H), 5.37 (s, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 164.5, 163.9, 154.0, 148.8, 144.8, 142.1, 137.6, 137.2, 133.6, 133.0, 131.8, 129.9, 128.9 (2C), 128.5 (2C), 127.7, 127.4, 126.4, 124.7, 123.8, 123.3, 123.2, 123.0, 122.2, 121.2, 118.5, 114.8, 112.8, 110.6, 43.5. Anal calcd for $C_{31}H_{21}N_5O_2$: C: 75.14, H: 4.27, N: 14.13. Found: C: 75.18, H: 4.35, N: 14.05.

***N*-Allyl naphthalimide-based GBB adduct (17)**. 4-isocyano-*N*-allyl-1,8-naphthalimide **12** (0.3 mmol) and the p-chlorobenzaldehyde (1 equiv), as the aldehyde partner, were used The purification through silica gel flash chromatography (AcOEt/ETP) led to the final product which appears as a yellow foam. Yield: 30%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.80 (s, 1H), 9.03 (dd, *J* = 8.5, 1.1 Hz, 1H), 8.58 (dd, *J* = 7.3, 1.0 Hz, 1H), 8.18 (d, *J* = 8.3 Hz, 1H), 8.09 (dt, *J* = 6.8, 1.2 Hz, 1H), 8.04 – 7.98 (m, 2H), 7.94 (dd, *J* = 8.5, 7.3 Hz, 1H), 7.72 (dt, *J* = 9.1, 1.1 Hz, 1H), 7.47 – 7.36 (m, 3H), 6.94 (td, *J* = 6.8, 1.1 Hz, 1H), 6.26 (d, *J* = 8.4 Hz, 1H), 5.92 (ddt, *J* = 17.3, 10.1, 5.1 Hz, 1H), 5.07 (dq, *J* = 5.9, 1.6 Hz, 1H), 4.63 (dt, *J* = 5.4, 1.7 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 163.3, 162.6, 148.0, 142.5, 137.1, 133.9, 133.1, 132.5, 132.1, 131.3, 129.5, 129.0, 128.8 (2C), 128.0 (2C), 126.1, 125.8, 123.4, 122.3, 120.9, 117.4, 116.6, 116.0, 112.9, 111.9, 106.6, 41.4. HPLC-MS (ESI+)-UV. Rt: 12.75 min, 479.2 [M + H]+. Anal calcd for $C_{28}H_{19}ClN_4O_2$: C: 70.22, H: 4.00, N: 11.70. Found: C: 70.34, H: 4.12, N: 11.65.

***N*-Allyl naphthalimide-based GBB adduct (18).** 4-isocyano-*N*-allyl-1,8-naphthalimide **12** (0.2 mmol) and the pyridine-2-carbaldehyde (1 equiv), as the aldehyde partner, were used. . The purification through silica gel flash chromatography (DCM/MeOH) led to the final product which appears as a dark orange foam. Y: 79%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.72 (s, 1H), 8.77 – 8.63 (m, 2H), 8.51 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1H), 8.39 (d, *J* = 8.2 Hz, 1H), 8.27 (dt, *J* = 8.1, 1.1 Hz, 1H), 7.88 (dd, *J* = 8.4, 7.3 Hz, 1H), 7.81 (td, *J* = 7.8, 1.8 Hz, 1H), 7.74 (dt, *J* = 9.2, 1.1 Hz, 1H), 7.55 (dt, *J* = 6.9, 1.2 Hz, 1H), 7.28 (ddd, *J* = 7.5, 4.9, 1.2 Hz, 1H), 7.17 (ddd, *J* = 7.5, 4.9, 1.2 Hz, 1H), 6.84 (td, *J* = 6.8, 1.1 Hz, 1H), 6.29 (d, *J* = 8.1 Hz, 1H), 5.99 (ddt, *J* = 17.2, 10.2, 5.6 Hz, 1H), 5.29 (dq, *J* = 10.2, 1.4 Hz, 1H), 5.19 (dq, *J* = 10.2, 1.4 Hz, 1H), 4.80 (dt, *J* = 5.8, 1.5 Hz, 2H).^{13}C NMR (101 MHz, Chloroform-*d*) δ

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164.3, 163.7, 154.1, 148.8, 144.7, 142.1, 137.2, 133.5, 133.0, 132.5, 131.7, 129.9, 127.7, 126.4, 124.7, 123.8, 123.3, 123.2, 123.1, 122.2, 121.2, 118.5, 117.3, 114.8, 112.8, 110.6, 42.4. HPLC-MS (ESI+)-UV. Rt: 7.14 min, 445.8 [M + H]+. Anal calcd for $C_{27}H_{19}N_5O_2$: C: 72.80, H: 4.30, N: 15.72. Found: C: 72.90, H: 4.25, N: 15.82.

Coumarin-based GBB adduct (19). 7-isocyano-4-methylcoumarin **3** (0.4 mmol) and the p-chlorobenzaldehyde (1 equiv), as the aldehyde partner, were used. The purification through silica gel flash chromatography (AcOEt/ETP) led to the final product which appears as a yellow foam. Yield: 50%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.92 – 7.85 (m, 2H), 7.81 (dt, *J* = 6.8, 1.2 Hz, 1H), 7.64 (dt, *J* = 9.1, 1.1 Hz, 1H), 7.41 (d, *J* = 8.6 Hz, 1H), 7.33 – 7.23 (m, 3H), 6.82 (td, *J* = 6.8, 1.1 Hz, 1H), 6.62 (d, *J* = 2.4 Hz, 1H), 6.55 – 6.43 (m, 2H), 6.05 (q, *J* = 1.2 Hz, 1H), 2.34 (d, *J* = 1.2 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 161.5, 155.8, 152.9, 148.6, 143.2, 138.9, 134.1, 131.6, 129.0 (2C), 128.4 (2C), 126.7, 125.9, 122.6, 118.0, 116.7, 113.4, 113.0, 111.4, 110.1, 101.0, 18.7. HPLC-MS (ESI+)-UV. Rt: 10.47 min, 369.0 [M + H]+. Anal calcd for $C_{23}H_{16}ClN_3O_2$: C: 68.75, H: 4.01, N: 10.46. Found: C: 68.73, H: 4.09, N: 10.67.

Coumarin-based GBB adduct (20). 7-isocyano-4-methylcoumarin **3** (0.3 mmol) and the pyridine-2-carbaldehyde (1 equiv), as the aldehyde partner, were used. The purification through silica gel flash chromatography (DCM/MeOH) led to the final product which appears as a dark orange foam. Yield: 55%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.57 (ddd, J = 4.9, 1.8, 0.9 Hz, 1H), 8.31 (s, 1H), 8.22 (dt, J = 8.0, 1.1 Hz, 1H), 7.78 (ddd, J = 8.0, 7.5, 1.8 Hz, 1H), 7.71 – 7.65 (m, 2H), 7.45 (d, J = 8.6 Hz, 1H), 7.26 (m, 1H), 7.17 (ddd, J = 7.5, 4.9, 1.2 Hz, 1H), 6.87 – 6.79 (m, 1H), 6.66 (dd, J = 8.6, 2.3 Hz, 1H), 6.41 (d, J = 2.3 Hz, 1H), 6.07 (q, J = 1.2 Hz, 1H), 2.36 (d, J = 1.2 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 161.2, 155.3, 153.9, 152.5, 148.9, 147.6, 141.9, 136.8, 133.4, 125.8, 124.7, 123.4, 122.9, 122.0, 121.1, 118.2, 113.4, 112.7, 112.7, 111.6, 102.8, 18.6. HPLC-MS (ESI+)-UV. Rt: 5.22 min, 402.2 [M + H]+. Anal calcd for $C_{22}H_{16}N_4O_2$: C: 71.73, H: 4.38, N: 15.21. Found: C, 71.97, H: 4.06, N: 15.05.

Coumarin-based GBB adduct (21). 7-isocyano-4-methylcoumarin **3** (0.3 mmol) and the 4-allyloxybenzaldehyde (1 equiv), as the aldehyde partner, were used. The purification through silica gel flash chromatography (AcOEt/ETP) led to the final product which appears as a yellow foam. Yield: 42%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.92 – 7.82 (m, 2H), 7.77 (dt, *J* = 6.8, 1.2 Hz, 1H), 7.61 (dt, *J* = 9.0, 1.1 Hz, 1H), 7.39 (d, *J* = 8.6 Hz, 1H), 7.23 (ddd, *J* = 9.1, 6.7, 1.3 Hz, 1H), 6.93 – 6.82 (m, 2H), 6.77 (td, *J* = 6.7, 1.1 Hz, 1H), 6.64 – 6.40 (m, 3H), 6.13 – 5.92 (m, 2H), 5.39 (dq, *J* = 17.3, 1.7 Hz, 1H), 5.27 (dq, *J* = 10.5, 1.4 Hz, 1H), 4.51 (dt, *J* = 5.3, 1.6 Hz, 2H), 2.33 (d, *J* = 1.2 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 161.5, 158.7, 155.8, 152.9, 148.9, 143.0, 139.8, 133.2, 128.4 (2C), 126.5, 125.8, 125.4, 122.4, 117.9, 117.6, 115.7, 114.9 (2C), 113.1, 112.5, 111.1, 110.1, 100.8, 68.8, 18,7. HPLC-MS (ESI+)-UV. Rt: 13.12 min, 424.2 [M + H]+. Anal calcd for $C_{26}H_{21}N_3O_3$: C: 73.74, H: 5.00, N: 9.92. Found: C: 73.25, H: 5.45, N: 10.02.

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Supplementary Material

The supplementary information (SI) contains copies of the original ^{1}H, ^{13}C and 2D NMR spectra, alongside HPLC-MS chromatograms and both absorption and fluorescence emission spectra.

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