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Three-Component, One-Pot Sequential Synthesis of Functionalized Cyclazines: 3*H*-1,2a[1],3-Triazaacenaphthylenes

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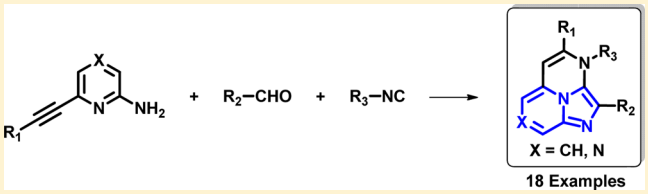
Supporting Information

ABSTRACT: An efficient tandem route to the synthesis of 3*H*-1,2a[1],3-triazaacenaphthylene derivatives of the cyclazine family has been developed. Target compounds were obtained in moderate to good yields by a $Yb(OTf)_3/Ag_2CO_3$-catalyzed, three-component domino reaction. This in turn will set the stage for a wide application of this useful reaction for the synthesis of structurally diverse polyheterocyclic skeletons containing the imidazo[1,2-*a*]pyridine privileged structure.



INTRODUCTION

Cyclazines are tricyclic fused N-heterocyclic systems with a central nitrogen atom and an unsaturated periphery.[1] A representative [3.3.3]cyclazine is shown in Figure 1A. We herein report a synthesis of a functionalized cyclazine, 3*H*-1,2a[1],3-triazaacenaphthylene (Figure 1B), via a one-pot multicomponent reaction (Scheme 1). Multicomponent reactions (MCRs) are of increasing importance in organic and medicinal chemistry.[2] By generating several new covalent bonds with high efficiency and atom economy in a single-step process from three or more reactants, MCRs provide an attractive way for the generation of molecules having diverse structures, especially unusual heterocyclic scaffolds. The latter are particularly useful for the creation of diverse chemical libraries of druglike molecules for biological screening.[3] Furthermore, there has been a growing interest in combinations of MCRs with subsequent post-MCR modifications (mainly intramolecular cyclizations) to produce novel compounds possessing increased molecular complexity and diversity.[4]

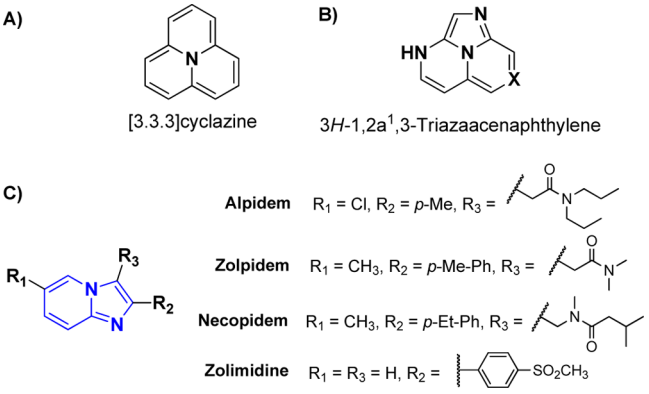
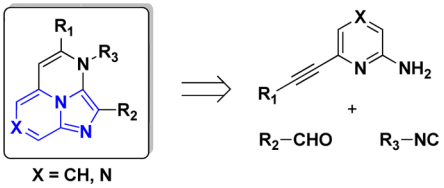


Figure 1. (A) A classic cyclazine. (B) The heterocycle synthesized in this work (X = N, CH). (C) Therapeutic agents based on imidazo[1,2-*a*]pyridine (blue).

Scheme 1. Proposed MCR Approach to New Cyclazines



Nitrogen bridgehead-fused heterocycles containing an imidazole ring are common structural motifs in pharmacologically important molecules, with activities spanning a diverse range of targets.[5] Among the numerous N-heterocycles, imidazo[1,2-*a*]pyridine moieties (Figure 1C), which may be regarded as privileged structures, have been shown to possess diverse therapeutic activities.[6] Imidazo[1,2-*a*]pyridine is also found in marketed drugs such as alpidem (a nonsedative anxiolytic),[7] zolpidem (a hypnotic drug),[8] necopidem (a nonsedative anxiolytic), and zolimidine (an antiulcer drug)[9] (Figure 1C), as well as other therapeutic molecules still in development.[10] To access such medicinally important N-fused imidazoles, several isocyanide-based multicomponent reaction (IMCR) approaches have been developed.[11] Therefore, it would be of particular interest to design and synthesize a series

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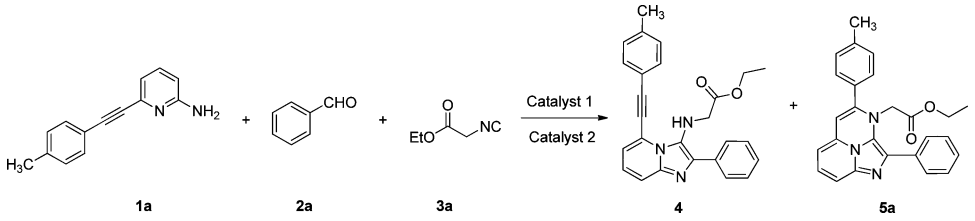
Table 1. Optimization of the Cyclization Conditions[a]



1a 2a 3a 4 5a

entry	catalyst 1 (mol %)	catalyst 2 (mol %)	solvent	**4**, yield (%)[b]	**5a**, yield (%)[b]
1	–	–	EtOH	0	0
2	$Yb(OTf)_3$ (10)	–	EtOH	71	trace
3	AgOTf (10)	–	EtOH	0	0
4	$Yb(OTf)_3$ (10)	AgOTf (10)	EtOH	0	61
5	$Yb(OTf)_3$ (10)	$AgNO_3$ (10)	EtOH	0	62
6	$Yb(OTf)_3$ (10)	$AuCl_3$ (10)	EtOH	trace	47
7	$Yb(OTf)_3$ (10)	$AgBF_4$ (10)	EtOH	0	56
8	$Yb(OTf)_3$ (10)	Ag_2CO_3 (10)	EtOH	0	81
9	$Yb(OTf)_3$ (10)	Ag_2CO_3 (10)	DCM	11	16
10	$Yb(OTf)_3$ (10)	Ag_2CO_3 (10)	DMF	trace	13

[a]Reaction conditions: **1a** (1.0 mmol, 1.0 equiv), **2a** (1.05 equiv), **3a** (1.20 equiv), catalyst 1 (10 mol %), catalyst 2 (10 mol %), solvent (5 mL), 65 °C, 4 h. Tf = triflate. [b]Isolated yields.

of tricyclic fused imidazo[1,2-*a*]pyridines bridged between the C(3) and C(5) positions (Scheme 1), which also belong to the cyclazine family.[12] To the best of our knowledge, this series of compounds has never been reported.

Recent studies in our group have focused on the development of new synthetic pathways for the preparation of fused imidazo[1,2-*a*]pyridine scaffolds, which rely on the use of cascade or one-pot reactions based on the Groebke–Blackburn–Bienaymé reaction.[13] As part of this effort, we envisioned that 6-alkynyl-2-aminopyridines would participate with aldehydes and isocyanides in a Groebke-like condensation followed by a transition metal-catalyzed intramolecular cyclization sequence that would result in the one-pot synthesis of a 3*H*-1,2a[1],3-triazaacenaphthylene scaffold (Scheme 1). The attractiveness of the one-pot preparation of these structurally unique molecules is a fundamental goal in organic synthesis, as it avoids the tedious purification that follows the step-by-step synthesis.[14]

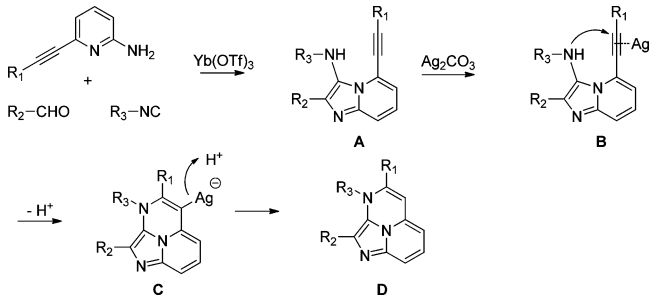
RESULTS AND DISCUSSION

The investigation was initiated with substituted 6-alkynyl-2-aminopyridines, which can be readily prepared from the corresponding alkynes and 2-amino-6-bromopyridine by Sonogashira coupling with satisfactory yields according to the literature protocol.[15] Subsequently, 6-(*p*-tolylethynyl)-2-aminopyridine, benzaldehyde, and ethyl isocyanoacetate were used as the model substrates to optimize reaction conditions including different catalysts and various solvents, and the results are summarized in Table 1. No reaction occurred in the absence of catalysts (Table 1, entry 1), and using $Yb(OTf)_3$ alone afforded the GBB product **4** in 71% yield, as well as a trace amount of cyclized product **5a** (Table 1, entry 2). Because silver(I) forms a complex with isocyanide,[16] therefore inhibiting the initial step (Table, entry 3), it is crucial that AgOTf is added to the reaction mixture after the $Yb(OTf)_3$-catalyzed GBB-3CR transformation has completed. The reaction mixture was then stirred at 65 °C for 3 h, and the cyclized product **5a** was obtained in 61% yield (Table 1, entry 4). The structure of **5a** was unambiguously established by X-ray crystallographic analysis (see Supporting Information).

Encouraged by this result, we continued to optimize reaction conditions to further improve the chemical yield. Screening of catalysts indicated that Ag_2CO_3 displayed the highest catalytic activity toward the formation of **5a** with an 81% yield (Table 1, entry 8). Furthermore, changing the solvents from EtOH to CH_2Cl_2 or DMF dramatically decreased the yields of **4** and **5a** (Table 1, entries 9 and 10).

On the basis of the results obtained above, a plausible mechanism of this reaction is illustrated in Scheme 2. The

Scheme 2. Proposed Mechanism for the Silver-Catalyzed Cyclization



reaction is expected to proceed via the in situ formation of **A**. The next step involves alkyne activation by the silver carbonate, followed by intramolecular nucleophilic attack of the amine at the triple bond via a 6-endo-dig fashion to give the six-membered intermediate **C**. Finally, protonation of **C** affords the final product **D**.

With the optimal conditions established, we then investigated the scope of this method. The simplicity of a one-pot procedure is perfectly amenable to automation for combinatorial synthesis. Likewise, all the syntheses were performed on a 15-reaction setup in a parallel synthesizer (Radleys Discovery Technology, Carousel 12 Place Reaction Station) to give corresponding products **5b–r** in yields ranging from 28% to 85% (Table 2). First, we examined the reactions of various aldehydes **2a–d** and

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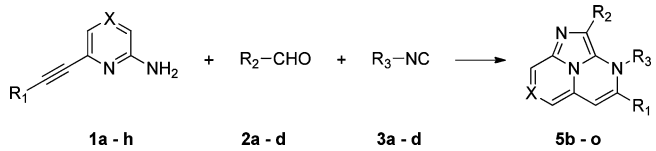
Table 2. Synthesis of 5b−o under Optimized Conditions[a]



1a - h 2a - d 3a - d 5b - o

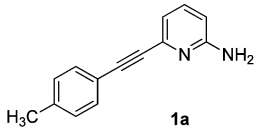
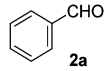
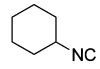
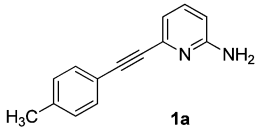
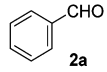
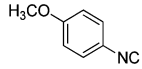
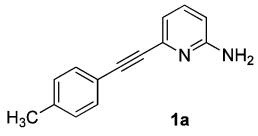
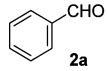
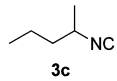
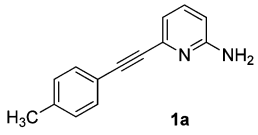
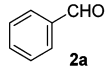
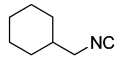
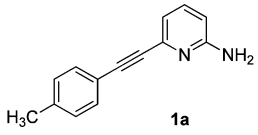
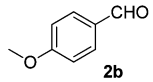
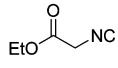
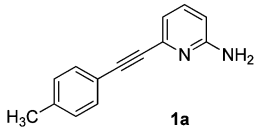
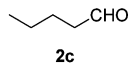
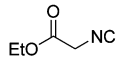
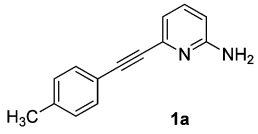
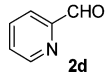
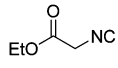
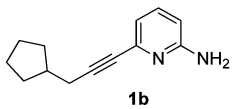
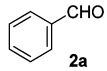
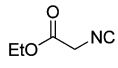
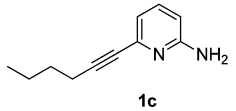
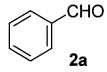
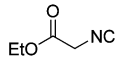
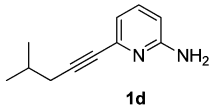
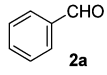
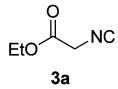
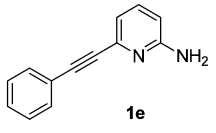
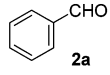
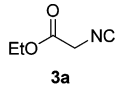
entry	Substrate 1	Aldehyde 2	Isocyanide 3	Product, Yield (%)[b]
1	 1a	 2a	 3b	**5b**, 77
2	 1a	 2a	 3b	**5c**, 28
3	 1a	 2a	 3c	**5d**, 85
4	 1a	 2a	 3d	**5e**, 65
5	 1a	 2b	 3a	**5f**, 83
6	 1a	 2c	 3a	**5g**, 75
7	 1a	 2d	 3a	**5h**, 51
8	 1b	 2a	 3a	**5i**, 40
9	 1c	 2a	 3a	**5j**, 46
10	 1d	 2a	 3a	**5k**, 43
11	 1e	 2a	 3a	**5l**, 70

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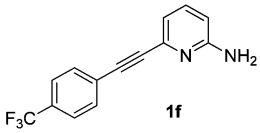
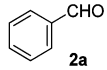
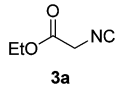
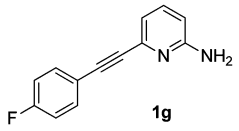
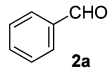
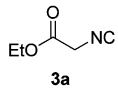
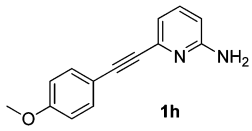
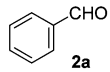
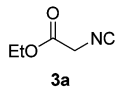
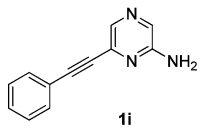
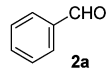
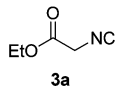
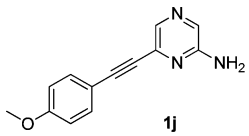
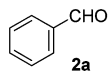
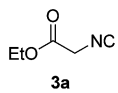
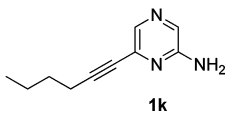
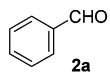
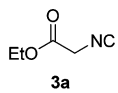
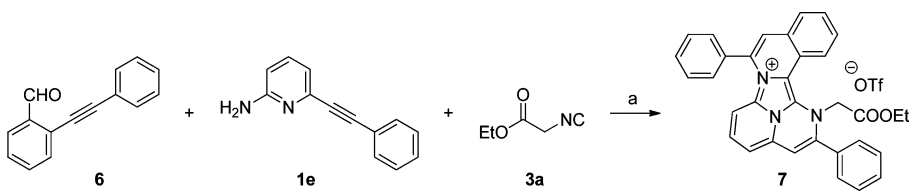
Table 2. continued

entry	Substrate 1	Aldehyde 2	Isocyanide 3	Product, Yield (%)[b]
12	 **1f**	 **2a**	 **3a**	**5m**, 78
13	 **1g**	 **2a**	 **3a**	**5n**, 75
14	 **1h**	 **2a**	 **3a**	**5o**, 70
15	 **1i**	 **2a**	 **3a**	**5p**, 47
16	 **1j**	 **2a**	 **3a**	**5q**, 42
17	 **1k**	 **2a**	 **3a**	**5r**, 31

[a]Reaction conditions: **1a**−**k** (1.0 mmol, 1.0 equiv), **2a**−**d** (1.05 equiv), **3a**−**d** (1.20 equiv), $Yb(OTf)_3$ (10 mol %), Ag_2CO_3 (10 mol %), EtOH (5 mL), 65 °C, 16 h. Tf = triflate. [b]Isolated yields.

Scheme 3. Synthesis of Compound 7[a]



[a]Reagents and conditions: (a) $Yb(OTf)_3$, 65 °C, 4 h, then AgOTf, 65 °C, 12 h.

isocyanides **3a**−**e** with 6-(*p*-tolylethynyl)-2-aminopyridine, which proceeded smoothly and efficiently to produce the corresponding products (**5b**−**h**) in moderate to good yields. The low yield observed for the aromatic isocyanide (**3c**, Table 2, entry 2) was probably due to the low nucleophilicity of the aniline in the cyclization step. Subsequently, to extend the scope of this transformation, reactions of various 6-alknyl-2-aminopyridines (**1b**−**h**) with benzaldehyde (**2a**) and ethyl isocyanoacetate (**3a**) were investigated (Table 2, entries 8−13). All reactions worked well to produce the expected products **5i**−**o** in 40−78% yields. As can be seen, the aromatic groups attached to the triple bond worked better than aliphatic groups (Table 2, entries 8−10 vs 11−14). Moreover, we were pleased to find that the pyridine core could be successfully extended to pyrazine. For example, 6-alknyl-2-aminopyrazines (**1i**−**k**) smoothly reacted with benzaldehyde and ethyl isocyanoacetate to give the corresponding products **5p**−**r** in 31−47% yields (Table 2, entries 15−17).

We have recently described the one-pot synthesis of substituted pyrido[2′,1′:2,3]imidazo[5,1-*a*]isoquinoliniums, catalyzed by ytterbium triflate and silver triflate.[17] Herein, we envisioned that by using 2-alknylbenzaldehyde (**6**) as the substrate the reaction may also furnish the polyheterocyclic compound **7** (Scheme 3). According to our previous study, an equimolar amount of triflate was required as the counterion for the quaternary ammonium products formation.[17] Thus, using $Yb(OTf)_3$/AgOTf conditions, this unique polycyclic compound **7** could be obtained in 66% yield.

■ CONCLUSION

In summary, we have developed an efficient and convenient method for the one-pot construction of novel functionalized

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cyclazines containing imidazo[1,2-*a*]pyridine and imidazo[1,2-*a*]pyrazine. Conversion is achieved by treatment of 6-alknyl-2-aminopyridines/pyrazines, aldehydes, and isocyanides with ytterbium triflate and silver carbonate. To the best of our knowledge, this type of scaffold has never been reported. This approach could be easily applied to the synthesis of more privileged structure-based analogues that are of interest in drug discovery. Meanwhile, biological properties of this rarely described class of compounds are currently under investigation.

EXPERIMENTAL SECTION

General Comments. The ^{1}H NMR (400 MHz) spectra were recorded using high performance digital FT-NMR with TMS as internal standard, and the ^{13}C NMR (100 MHz) spectra were recorded using high performance digital FT-NMR. LR-MS and HR-MS were obtained by EI on a double-focusing mass analyzer, ESI (positive ion mode) on TOF mass analyzer. Purity was recorded with high-performance liquid chromatography (HPLC); conditions were as follows: ACN/H_2O eluent at 2 mL/min flow (containing 0.05% TFA) at 40 °C, 5 min, gradient 5% ACN to 95% ACN, monitored by UV absorption at both 214 and 254 nm. TLC was carried out with glass precoated silica gel plates. TLC spots were visualized under UV light. All the solvents and reagents were used directly as obtained commercially unless otherwise noted.

Typical Procedure for the Synthesis of Ethyl 2-[2-Phenyl-4-(*p*-tolyl)-3*H*-1,2a^1,3-triazaacenaphthylen-3-yl]acetate (5a). To a solution of 6-(*p*-tolylethynyl)pyridin-2-amine (**1a**, 50 mg, 0.24 mmol) in EtOH (5 mL) was added benzaldehyde (**2a**, 26 μL, 0.25 mmol) . After the mixture was stirred at rt for 10 min, $Yb(OTf)_3$ (15 mg, 0.024 mmol) and ethyl 2-isocyanoacetate (**3a**, 31 μL, 0.29 mmol) were added. The mixture was stirred at 65 °C for about 4 h. Then Ag_2CO_3 (6.6 mg, 0.024 mmol) was added to the reaction mixture, and the mixture was stirred at 65 °C for 12 h. The reaction mixture was cooled to room temperature and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, petroleum ether:ethyl acetate = 2:1) giving a dark brown oil, which was crystallized from a mixture of petroleum ether and ethyl acetate to give 80 mg (81% yield) of **5a** as a dark red solid. HPLC purity 100%. mp 152−153 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69−7.67 (m, 2H), 7.41 (t, *J* = 7.7 Hz, 2H), 7.37−7.33 (m, 2H), 7.29−7.24 (m, 1H), 7.21 (d, *J* = 7.8 Hz, 2H), 6.60 (d, *J* = 9.2 Hz, 1H), 6.52−6.47 (m, 1H), 5.56 (d, *J* = 6.7 Hz, 1H), 5.46 (s, 1H), 4.03 (q, *J* = 7.1 Hz, 2H), 3.77 (s, 2H), 2.39 (s, 3H), 1.08 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 151.1, 141.1, 140.4, 136.3, 133.9, 132.1, 129.8 (2 × C), 128.5 (2 × C), 127.5, 127.0, 126.7 (2 × C), 126.6, 126.5 (2 × C), 126.2, 115.1, 106.6, 103.1, 61.1, 52.8, 21.4, 13.8. HRMS(EI) *m*/*z* calcd for $C_{26}H_{23}O_2N_3$: 409.1790, found 409.1796.

3-Cyclohexyl-2-phenyl-4-(*p*-tolyl)-3*H*-1,2a^1,3-triazaacenaphthylene (5b). Orange solid (77% yield). HPLC purity 95%. mp 168−169 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02−8.00 (m, 2H), 7.58−7.56 (m, 2H), 7.44−7.40 (m, 2H), 7.28−7.21 (m, 3H), 6.86 (d, *J* = 9.0 Hz, 1H), 6.72−6.68 (m, 1H), 6.01 (s, 1H), 5.87 (d, *J* = 6.8 Hz, 1H), 2.87 (m, 1H), 2.42 (s, 3H), 2.03 −1.95 (m, 2H), 1.52 (d, *J* = 14.7 Hz, 2H), 1.33 (d, *J* = 13.5 Hz, 1H), 1.04 (ddd, *J* = 15.8, 11.9, 3.0 Hz, 2H), 0.94−0.82 (m, 2H), 0.79−0.69 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.3, 140.8, 139.8, 135.7, 135.4, 134.6, 131.6, 129.3 (2 × C), 128.3 (2 × C), 126.9, 126.7 (2 × C), 126.6, 126.4 (2 × C), 124.9, 114.9, 110.9, 104.8, 71.1, 32.0 (2 × C), 26.1 (2 × C), 25.2, 21.4. HRMS(EI) *m*/*z* calcd for $C_{28}H_{27}N_3$: 405.2205, found 405.2201.

3-(4-Methoxyphenyl)-2-phenyl-4-(*p*-tolyl)-3*H*-1,2a^1,3-triazaacenaphthylene (5c). Dark red solid (28% yield). HPLC purity 100%. mp 71−73 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.40(m, 2H), 7.29−7.25 (m, 2H), 7.18−7.10 (m, 3H), 7.04−7.01 (m, 4H), 6.61 (d, *J* = 9.2 Hz, 1H), 6.53−6.48 (m, 1H), 6.45−6.41 (m, 2H), 5.56 (d, *J* = 6.8 Hz, 1H), 5.41 (s, 1H), 3.58 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 151.7, 140.6, 139.3, 138.7, 136.4, 133.6, 133.1, 129.3 (2 × C), 129.0 (2 × C), 128.3, 127.7 (2 × C), 127.6 (2 × C), 127.3 (2 × C), 127.2, 127.0, 126.6, 115.1, 113.8 (2 × C), 104.6, 102.9, 55.2, 21.3. HRMS(EI) *m*/*z* calcd for $C_{29}H_{23}N_3O$: 429.1841, found 429.1841.

3-(Pentan-2-yl)-2-phenyl-4-(*p*-tolyl)-3*H*-1,2a^1,3-triazaacenaphthylene (5d). Dark red amorphous solid (85% yield). HPLC purity 98%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94−7.88 (m, 2H), 7.52 (d, *J* = 8.1 Hz, 2H), 7.46−7.35 (m, 3H), 7.24−7.17 (m, 2H), 6.82 (d, *J* = 8.7 Hz, 1H), 6.66 (m, 1H), 5.89 (s, 1H), 5.81 (d, *J* = 6.7 Hz, 1H), 3.05 (dd, *J* = 14.4, 6.3 Hz, 1H), 2.40 (s, 3H), 1.08−1.02 (m, 2H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.91−0.83 (m, 2H), 0.58 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0, 140.8, 139.7, 135.6, 135.5, 134.6, 131.1, 129.2 (2 × C), 128.3 (2 × C), 127.0 (2 × C), 126.9, 126.8 (2 × C), 126.7, 125.3, 114.9, 110.7, 104.4, 67.0, 37.8, 21.4, 20.2, 19.2, 13.7. HRMS(EI) *m*/*z* calcd for $C_{27}H_{27}N_3$: 393.2205, found 393.2205.

3-(Cyclohexylmethyl)-2-phenyl-4-(*p*-tolyl)-3*H*-1,2a^1,3-triazaacenaphthylene (5e). Dark red solid (65% yield). HPLC purity 98%. mp 92−93 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59−7.56 (m, 2H), 7.39−7.35 (m, 2H), 7.29−7.18 (m, 5H), 6.45−6.38 (m, 1H), 6.34 (dd, *J* = 9.4, 6.6 Hz, 1H), 5.26 (d, *J* = 6.4 Hz, 1H), 5.04 (s, 1H), 2.82 (d, *J* = 6.3 Hz, 2H), 2.39 (s, 3H), 1.64−1.57 (m, 3H), 1.51−1.47 (m, 3H), 1.14−1.03 (m, 2 H), 0.96−0.86 (m, 1H), 0.62−0.52 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6, 141.3, 139.9, 137.7, 134.1, 133.0, 129.5 (2 × C), 128.1 (2 × C), 128.0, 127.1 (2 × C), 126.8 (2 × C), 126.7, 126.6, 125.6, 114.4, 103.9, 101.4, 56.3, 36.5, 30.4 (2 × C), 26.1, 25.7 (2 × C), 21.4. HRMS(EI) *m*/*z* calcd for $C_{29}H_{29}N_3$: 419.2361, found 419.2354.

Ethyl 2-[2-(4-Methoxyphenyl)-4-(*p*-tolyl)-3*H*-1,2a^1,3-triazaacenaphthylen-3-yl]acetate (5f). Dark red solid (83% yield). HPLC purity 100%. mp 136−138 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62−7.58 (m, 2H), 7.36−7.32 (m, 2H), 7.23−7.19 (m, 2H), 6.98−6.94 (m, 2H), 6.60−6.56 (m, 1H), 6.48 (dd, *J* = 9.3, 6.7 Hz, 1H), 5.54 (d, *J* = 6.5 Hz, 1H), 5.43 (s, 1H), 4.03 (q, *J* = 6.8 Hz, 2H), 3.85 (s, 3H), 3.75 (s, 2H), 2.39 (s, 3H), 1.09 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 158.6, 151.1, 140.9, 140.3, 136.2, 132.2, 129.7 (2 × C), 127.7 (2 × C), 127.3, 126.6, 126.5, 126.4, 125.3, 115.0, 113.9 (2 × C), 106.5, 103.0, 61.1, 55.3, 52.5, 21.4, 13.8. HRMS(EI) *m*/*z* calcd for $C_{27}H_{25}N_3O_3$: 439.1896, found 439.1895.

Ethyl 2-[2-Butyl-4-(*p*-tolyl)-3*H*-1,2a^1,3-triazaacenaphthylen-3-yl]acetate (5g). Dark red amorphous solid (75% yield). HPLC purity 98%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.26 (m, 2H), 7.19−7.15 (m, 2H), 6.39−6.36 (m, 1H), 6.31 (dd, *J* = 9.3, 6.5 Hz, 1H), 5.30 (dd, *J* = 6.5, 0.5 Hz, 1H), 5.07 (s, 1H), 4.18−4.13 (q, *J* = 7.2 Hz, 2H), 3.77 (s, 2H), 2.42−2.35 (m, 5H), 1.65−1.56 (m, 2H), 1.27−1.22 (m, 2H), 1.19 (t, *J* = 7.1 Hz, 3H), 0.95 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 151.5, 140.4, 140.1, 136.6, 132.2, 129.6 (2 × C), 127.1, 126.7 (2 × C), 126.3, 125.6, 114.4, 104.2, 102.0, 61.2, 53.2, 31.4, 27.4, 22.6, 21.3, 14.0, 13.9. HRMS(EI) *m*/*z* calcd for $C_{24}H_{27}N_3O_2$: 389.2103, found 389.2101.

Ethyl 2-[2-(Pyridin-2-yl)-4-(*p*-tolyl)-3*H*-1,2a^1,3-triazaacenaphthylen-3-yl]acetate (5h). Dark red solid (51% yield). HPLC purity 98%. mp 147−150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59−8.56 (m, 1H), 8.05−8.01 (m, 1H), 7.71−7.65 (m, 1H), 7.40−7.35 (m, 2H), 7.23−7.18 (m, 2H), 7.10−7.06 (m, 1H), 6.53−6.44 (m, 2H), 5.46−5.42 (m, 1H), 5.33 (s, 1H), 4.56 (s, 2H), 4.02 (q, *J* = 7.2 Hz, 2H), 2.38 (s, 3H), 1.08 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 153.4, 151.9, 148.3, 141.2, 140.2, 137.2, 136.2, 132.1, 129.6 (2 × C), 129.4, 128.4, 126.9 (2 × C), 125.3, 121.5, 120.4, 114.6, 105.5, 102.0, 60.9, 53.1, 21.4, 13.9. HRMS(EI) *m*/*z* calcd for $C_{25}H_{22}N_4O_2$: 410.1743, found 410.1746.

Ethyl 2-[4-(Cyclopentylmethyl)-2-phenyl-3*H*-1,2a^1,3-triazaacenaphthylen-3-yl]acetate (5i). Dark red amorphous solid (40% yield). HPLC purity 98%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49−7.52 (m, 2H), 7.34−7.43 (m, 2H), 7.23−7.27 (m, 1H), 6.51 (d, *J* = 9.3 Hz, 1H), 6.40 (dd, *J* = 9.4, 6.7 Hz, 1H), 5.31 (d, *J* = 6.6 Hz, 1H), 5.01 (s, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.82(s, 2H), 2.03−1.87 (m, 4H), 1.68−1.57 (m, 4H), 1.29−1.20 (m, 3H), 1.15 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 150.6, 140.9, 136.5, 133.6, 128.3 (2 × C), 128.1, 127.2 (2 × C), 127.1, 126.4, 124.4, 114.0, 103.0, 101.1, 61.3, 50.2, 38.0, 36.9, 32.2 (2 × C), 24.9 (2 × C), 13.8. HRMS(EI) *m*/*z* calcd for $C_{25}H_{27}O_2N_3$: 401.2103, found 401.2095.

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Ethyl 2-(4-Butyl-2-phenyl-3*H*-1,2a^1,3-triazaacenaphthylen-3-yl)acetate (5j). Dark red amorphous solid (46% yield). HPLC purity 97%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51−7.48 (m, 2H), 7.44−7.34 (m, 2H), 7.28−7.23 (m, 1H), 6.49 (d, J = 9.3 Hz, 1H), 6.39 (dd, J = 9.4, 6.7 Hz, 1H), 5.29 (d, J = 6.6 Hz, 1H), 4.99 (s, 1H), 4.11 (q, J = 7.1 Hz, 2H), 3.80 (s, 2H), 1.92 (t, J = 7.2 Hz, 2H), 1.49−1.39 (m, 4H), 1.15 (t, J = 7.1 Hz, 3H), 0.96 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 150.9, 140.9, 136.6, 133.6, 128.3 (2 × C), 128.2, 127.3 (2 × C), 127.1, 126.4, 124.1, 113.9, 102.0, 100.9, 61.3, 49.9, 31.3, 28.7, 22.0, 13.9, 13.8. HRMS(EI) m/z calcd for $C_{23}H_{25}O_2N_3$: 375.1947, found 375.1949.

Ethyl 2-(4-Isobutyl-2-phenyl-3*H*-1,2a^1,3-triazaacenaphthylen-3-yl)acetate (5k). Dark red amorphous solid (43% yield). HPLC purity 97%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53−7.49 (m, 2H), 7.44−7.35 (m, 2H), 7.27−7.24 (m, 1H), 6.53 (d, J = 9.3 Hz, 1H), 6.41 (dd, J = 9.4, 6.7 Hz, 1H), 5.33 (d, J = 6.7 Hz, 1H), 5.02 (s, 1H), 4.11 (q, J = 6.8 Hz, 2H), 3.81 (s, 2H), 1.84−1.76 (m, 3H), 1.16 (t, J = 7.1 Hz, 3H), 1.04 (d, J = 6.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 149.9, 140.9, 136.3, 133.5, 128.3 (2 × C), 128.0, 127.9, 127.1 (2 × C), 126.3, 124.5, 114.1, 103.9, 101.1, 61.3, 50.2, 41.0, 25.8, 22.1 (2 × C), 13.81. HRMS(EI) m/z calcd for $C_{23}H_{25}O_2N_3$: 375.1947, found 375.1940.

Ethyl 2-(2,4-Diphenyl-3*H*-1,2a^1,3-triazaacenaphthylen-3-yl)-acetate (5l). Dark red solid (70% yield). HPLC purity 100%. mp 143−144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.66 (m, 2H), 7.48−7.39 (m, 7H), 7.30−7.24 (m, 1H), 6.64−6.59 (m, 1H), 6.50 (dd, J = 9.3, 6.7 Hz, 1H), 5.58 (d, J = 6.6 Hz, 1H), 5.49 (s, 1H), 4.03 (q, J = 7.2 Hz, 2H), 3.76 (s, 2H), 1.08 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 150.9, 141.1, 136.1, 135.1, 133.8, 130.1, 129.1 (2 × C), 128.5 (2 × C), 127.5, 127.0, 126.7 (2 × C), 126.6, 126.4 (2 × C), 126.1, 115.3, 107.2, 103.3, 61.1, 52.7, 13.8. HRMS(EI) m/z calcd for $C_{25}H_{21}N_3O_2$: 395.1634, found 395.1649.

Ethyl 2-{2-Phenyl-4-[4-(trifluoromethyl)phenyl]-3*H*-1,2a^1,3-triazaacenaphthylen-3-yl}acetate (5m). Dark red solid (78% yield). HPLC purity 96%. mp 150−152 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.66 (m, 4H), 7.62−7.58 (m, 2H), 7.45−7.40 (m, 2H), 7.32−7.26 (m, 1H), 6.66 (d, J = 9.3 Hz, 1H), 6.53 (dd, J = 9.4, 6.7 Hz, 1H), 5.65 (d, J = 6.6 Hz, 1H), 5.57 (s, 1H), 4.04 (q, J = 7.2 Hz, 2H), 3.71 (s, 2H), 1.08 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1, 139.1, 135.4, 133.5, 131.8, 128.6 (2 × C), 128.4, 127.4, 127.3, 127.1 (2 × C), 126.4 (2 × C), 126.2, 126.1, 125.8, 125.7, 125.0, 122.3, 116.0, 109.1, 104.3, 61.3, 52.8, 13.8. HRMS(EI) m/z calcd for $C_{26}H_{20}N_3O_2F_3$: 463.1508, found 463.1508.

Ethyl 2-[4-(4-Fluorophenyl)-2-phenyl-3*H*-1,2a^1,3-triazaacenaphthylen-3-yl]acetate (5n). Dark red solid (75% yield). HPLC purity 96%. mp 146−148 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69−7.65 (m, 2H), 7.48−7.39 (m, 4H), 7.30−7.25 (m, 1H), 7.14−7.08 (m, 2H), 6.64−6.60 (m, 1H), 6.51 (dd, J = 9.4, 6.7 Hz, 1H), 5.58 (d, J = 6.6 Hz, 1H), 5.45 (s, 1H), 4.03 (q, J = 7.1 Hz, 2H), 3.73 (s, 2H), 1.08 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 164.9, 162.4, 149.8, 141.1, 135.9, 133.7, 131.1, 131.0, 128.7, 128.6, 128.5 (2 × C), 127.5, 127.1, 126.4 (2 × C), 116.4, 116.1, 115.4, 107.3, 103.5, 61.2, 52.7, 13.8. HRMS(EI) m/z calcd for $C_{25}H_{20}N_3O_2F$: 413.1540, found 413.1542.

Ethyl 2-(4-(4-Methoxyphenyl)-2-phenyl-3*H*-1,2a^1,3-triazaacenaphthylen-3-yl)acetate (5o). Dark red solid (70% yield). HPLC purity 100%. mp 156−159 °C;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72−7.66 (m, 2H), 7.45−7.36 (m, 4H), 7.30−7.24 (m, 1H), 6.96−6.90 (m, 2H), 6.60 (dd, J = 9.3, 0.6 Hz, 1H), 6.50 (dd, J = 9.3, 6.7 Hz, 1H), 5.56 (d, J = 6.6 Hz, 1H), 5.44 (s, 1H), 4.03 (q, J = 7.2 Hz, 2H), 3.84 (s, 3H), 3.78 (s, 2H), 1.08 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 161.1, 150.8, 141.2, 136.4, 133.9, 128.6 (2 × C), 128.2 (2 × C), 127.6, 127.0, 127.2, 126.2, 126.4 (2 × C), 126.6, 114.9, 114.5 (2 × C), 106.1, 103.0, 61.1, 55.4, 52.9, 13.9. HRMS(EI) m/z calcd for $C_{26}H_{23}N_3O_3$: 425.1739, found 425.1743.

Ethyl 2-(2,4-Diphenyl-3*H*-1,2a^1,3,7-tetraazaacenaphthylen-3-yl)acetate (5p). Dark red amorphous solid (47% yield). HPLC purity 97%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.71−7.24 (m, 10H), 6.61 (s, 1H), 5.40 (s, 1H), 4.04 (q, J = 7.1 Hz, 2H), 3.74 (s, 2H), 1.08 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 152.6, 142.3, 135.7, 134.5, 132.8, 130.5, 130.1, 129.2 (2 × C), 128.9, 128.7 (2 × C), 128.0, 127.2, 126.7 (2 × C), 126.6 (2 × C), 119.4, 104.3, 61.3, 52.1, 13.8. HRMS(EI) m/z calcd for $C_{24}H_{20}N_4O_2$: 396.1586, found 396.1581.

Ethyl 2-(4-(4-Methoxyphenyl)-2-phenyl-3*H*-1,2a^1,3,7-tetraazaacenaphthylen-3-yl)acetate (5q). Dark red amorphous solid (42% yield). HPLC purity 95%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.66 (d, J = 7.9 Hz, 2H), 7.50−7.29 (m, 5H), 6.94 (d, J = 7.2 Hz, 2H), 6.63 (s, 1H), 5.36 (s, 1H), 4.04 (q, J = 6.5 Hz, 2H), 3.85 (s, 3H), 3.77 (s, 2H), 1.09 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, CDCl3) δ 168.5, 160.9, 152.1, 141.5, 135.3, 132.4, 130.0, 128.5, 128.3 (2 × C), 127.7 (2 × C), 127.4, 126.9, 126.3 (2 × C), 125.9, 118.7, 114.2 (2 × C), 102.8, 60.9, 55.0, 51.8, 13.4. HRMS(ESI) m/z calcd for $C_{25}H_{23}N_4O_3$ (M + H): 427.1770, found 427.1749.

Ethyl 2-(4-Butyl-2-phenyl-3*H*-1,2a^1,3,7-tetraazaacenaphthylen-3-yl)acetate (5r). Dark red amorphous solid (31% yield). HPLC purity 95%; ^{1}H NMR (400 MHz, CDCl3) δ 7.85 (s, 1H), 7.45 (m, 2H), 7.41−7.35 (m, 2H), 7.35−7.29 (m, 2H), 6.31 (s, 1H), 4.11 (q, J = 7.1 Hz, 2H), 3.78 (s, 2H), 1.89 (t, J = 7.1 Hz, 2H), 1.49−1.39 (m, 4H), 1.16 (t, J = 7.1 Hz, 3H), 0.96 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, CDCl3) δ 168.8, 152.6, 141.8, 135.4, 133.1, 130.7, 128.4 (2 × C), 127.9, 127.7 (2 × C), 127.5, 126.8, 117.1, 98.9, 61.5, 49.2, 31.4, 28.7, 22.0, 13.9, 13.7. HRMS(EI) m/z calcd for $C_{22}H_{24}N_4O_2$: 376.1899, found 376.1897.

Procedure for the Synthesis of 6-(2-Ethoxy-2-oxoethyl)-12-phenyl-5-(*p*-tolyl)-6*H*-3a^1,6,12a-triazabenzo[*j*]fluoranthen-12a-ium triflate (7). To a solution of 6-(*p*-tolylethynyl)pyridin-2-amine (**1a**, 50 mg, 0.24 mmol) in EtOH (5 mL) was added 2-(phenylethynyl)benzaldehyde (**6**, 52 mg, 0.25 mmol). After the mixture was stirred at rt for 10 min, $Yb(OTf)_3$ (15 mg, 0.024 mmol) and ethyl 2-isocyanoacetate (**3a**, 31 μL, 0.29 mmol) were added. The mixture was stirred at 65 °C for about 4 h. Then AgOTf (6 mg, 0.024 mmol) was added to the reaction mixture, and the mixture was stirred at 65 °C for 12 h. The reaction mixture was cooled to room temperature and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, petroleum ether:ethyl acetate = 2:1) to give **7** (81 mg, 66% yield) as a dark brown solid, HPLC purity 95%. mp 188−190 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00−7.98 (m, 1H), 7.88−7.83 (m, 1H), 7.74−7.62 (m, 6H), 7.59−7.52 (m, 4H), 7.36−7.32 (m, 2H), 7.19(dd, J = 9.46, 7.32 Hz, 1H), 6.89 (s, 1H), 6.82 (d, J = 7.4 Hz, 1H), 6.30 (s, 1H), 5.69 (d, J = 9.1 Hz, 1H), 4.18 (s, 2H), 4.08 (q, J = 7.0 Hz, 2H), 2.43 (s, 3H), 1.10 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 152.2, 142.5, 137.1, 135.3, 133.9, 131.7, 131.4, 131.3, 130.5 (2 × C), 130.4, 130.1, 130.0 (2 × C), 129.5 (2 × C), 129.4, 128.8, 128.0, 127.0 (2 × C), 124.1, 123.4, 121.0, 118.0, 116.8, 112.1, 109.9, 108.3, 62.1, 53.9, 21.6, 13.8. HRMS(ESI) m/z calcd for $C_{34}H_{28}N_3O_2^+$: 510.2182, found 510.2165.

Ethyl 2-{[2-Phenyl-5-(*p*-tolylethynyl)imidazo[1,2-*a*]pyridin-3-yl]amino}acetate (4). To a solution of 6-(*p*-tolylethynyl)pyridin-2-amine (**1a**, 50 mg, 0.24 mmol) in EtOH (5 mL) was added benzaldehyde (**2a**, 26 μL, 0.25 mmol). After the mixture was stirred at rt for 10 min, $Yb(OTf)_3$ (15 mg, 0.024 mmol) and ethyl 2-isocyanoacetate (**3a**, 31 μL, 0.29 mmol) were added. The mixture was stirred at 65 °C for about 4 h. The reaction mixture was cooled to room temperature and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, petroleum ether: ethyl acetate = 2:1) to give **4** as a yellow oil (70 mg, 71% yield). HPLC purity 100%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, J = 7.2 Hz, 2H), 7.56 (dd, J = 7.7, 2.4 Hz, 1H), 7.45 (dd, J = 15.1, 7.9 Hz, 4H), 7.31 (t, J = 7.4 Hz, 1H), 7.19 (d, J = 8.0 Hz, 2H), 7.09−7.02 (m, 2H), 4.65 (t, J = 6.2 Hz, 1H), 4.03 (q, J = 7.1 Hz, 2H), 3.87 (d, J = 6.2 Hz, 2H), 2.38 (s, 3H), 1.11 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 141.6, 139.5, 135.1, 133.3, 131.1 (2 × C), 128.9 (2 × C), 128.1 (2 × C), 127.0, 127.1, 126.8 (2 × C), 122.9, 119.9, 118.5, 117.9, 117.7, 97.8, 81.1, 60.6, 50.4, 21.2, 13.5. HRMS(ESI) m/z calcd for $C_{26}H_{24}N_3O_2$ (M + H): 410.1869, found 410.1861.

■ ASSOCIATED CONTENT

Supporting Information

Copies of spectra for all the compounds, and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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