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Intramolecular Inverse Electron Demand Diels–Alder Reactions of Tryptamine with Tethered Heteroaromatic Azadienes[1]

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Abstract—1,2,4,5-Tetrazines and 1,2,4-triazines tethered to tryptamine via the ethylamine side chain undergo intramolecular inverse electron demand cycloadditions to produce adducts with the [ABazaCE]-ring skeleton of the Aspidosperma alkaloids.

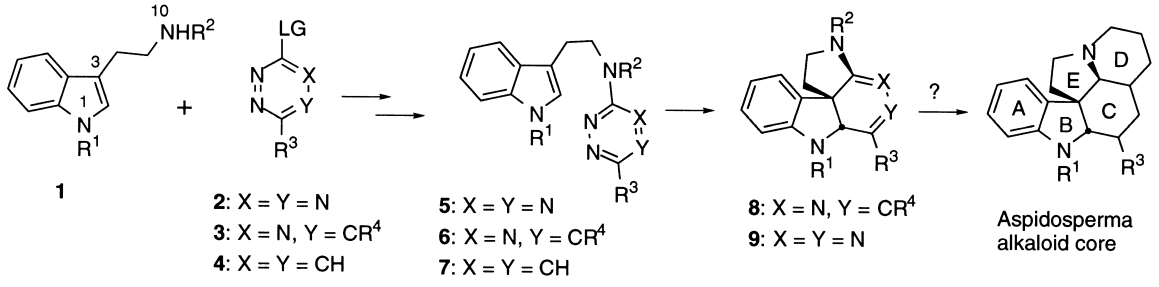
Introduction

The inverse electron demand Diels–Alder cycloadditions of heteroaromatic azadienes have proven to be valuable, fundamental reactions for the construction of various heterocyclic compounds.[2] Indole and its derivatives have been established as suitable dienophiles in this chemistry,[3] with intramolecular cycloadditions onto the indole 2,3-double bond allowing for the formation of a variety of polycyclic compounds.[4] We recently communicated preliminary results exploring the dienophilicity of 3-substituted indoles, including tryptamine, with 1,2,4-triazines and 1,2,4,5-tetrazines in both intermolecular and intramolecular reactions.[5] Upon acylation of the tethering tryptamine nitrogen, the intramolecular reactions proceeded smoothly to provide the desired cycloadducts in good to excellent yields (Scheme 1). Our interest in pursuing this chemistry stemmed from the recognition that adducts **8** and **9** incorporated four of the five rings of the Aspidosperma alkaloids with the azadiene C-ring poised for a second intramolecular cycloaddition to complete the pentacyclic core structure. We now report the full details and scope of this chemistry, including the limitations.

Results and Discussion

Preparation of tethered heteroaromatic azadienes 5–7

Heteroaromatic azadienes such as pyridazines, 1,2,4-triazines, and 1,2,4,5-tetrazines bearing suitable leaving groups



Scheme 1.

Table 1. Tethering of 1,2,4,5-tetrazines to tryptamine and derivatives

Item	Indole	R^1	R^2	Tetrazine	R^3	LG	Conditions[a]	Product[b]
1	**1a**	H	H	**2a**	SCH_3	SCH_3	A	**5a** (94)
2	**1b**	Bn	H	**2a**	SCH_3	SCH_3	A	**5b** (95)
3	**1c**	Bn	Ac	**2a**	SCH_3	SCH_3	B	**5c** (60)
4	**1a**	H	H	**2b**	H	SCH_3	A	**5d** (86)
5	**1b**	Bn	H	**2b**	H	SCH_3	A	**5e** (85)
6	**1b**	Bn	H	**2c**	CH_3	SCH_3	A	**5f** (85)
7	**1b**	Bn	H	**2d**	Cl	Cl	C	**5h** (83)

[a] Conditions: A=reflux in MeOH; B=*n*-BuLi in THF, −30°C; C=reflux in CH_2Cl_2.
[b] % Isolated yield in parentheses.

Keywords: cycloaddition; indoles; tetrazines; triazines.
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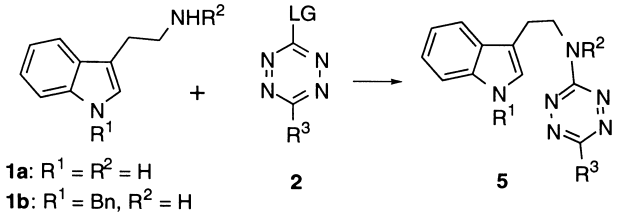
Table 2. Tethering of 1,2,4-triazines and 3,6-dichloropyridazine to tryptamine and derivatives

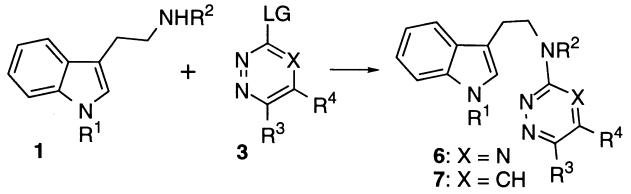
Item	Indole	R^1	R^2	Azadiene	X	LG	R^3	R^4	Conditions[a]	Product[b]
1	**1a**	H	H	**3a**	N	SCH_3	CO_2Me	CO_2Me	A	**6a** (99)
2	**1b**	Bn	H	**3a**	N	SCH_3	CO_2Me	CO_2Me	A	**6b** (99)
3	**1c**	Bn	Ac	**3a**	N	SCH_3	CO_2Me	CO_2Me	B	**6c** (52)
4	**1d**	Bn	Me	**3a**	N	SCH_3	CO_2Me	CO_2Me	A	**6d** (89)
5	**1a**	H	H	**3b**	N	SCH_3	H	H	D	**6e** (55)
6	**1a**	H	H	**3c**	N	OCH_3	H	H	A	**6e** (49)
7	**1a**	H	H	**3d**	N	SCH_3	CH_3	CH_3	D	**6f** (58)
8	**1a**	H	H	**3e**	N	OCH_3	CH_3	CH_3	A	**6f** (54)
9	**1b**	Bn	H	**3f**	N	SCH_3	Ph	Ph	A	**6g** (89)
10	**1a**	H	H	**4**	CH	Cl	Cl	H	E	**7a** (35)

[a] Conditions: A=reflux in MeOH; B=*n*-BuLi in THF, −30°C; D=reflux in MeOH in presence of NaOMe (2 equiv.); E=reflux in DMF.
[b] % Isolated yield in parentheses.

as substituents are well known to undergo S_NAr displacement reactions with appropriate nucleophiles.[6] Heteroaromatic azadienes, prepared from literature procedures, were tethered to the primary amino group of tryptamine (**1a**) and N^1-benzyltryptamine (**1b**) through simple S_NAr displacements (Tables 1 and 2). Thus, tryptamine-tethered tetrazines were prepared by the displacements of methylthiolate from tetrazines in excellent yields (Scheme 2, LG=SMe) by refluxing **1a** and **1b** with 3,6-bis-(methylthio)-1,2,4,5-tetrazine (**2a**)[7] and 3-methylthio-1,2,4,5-tetrazine (**2b**)[8] in methanol to give **5a** and **5b** (94 and 95%, Table 1, Items 1 and 2, respectively) and **5d** and **5e** (86 and 85%, Items 4 and 5, respectively).[9] Similar displacement of methylthiolate from 3-methyl-6-methylthio-1,2,4,5-tetrazine (**2c**)[8] by **1b** (85%, Item 6) was equally successful. Dichlorotetrazine **2d**[10] was very sensitive toward displacement, and the tethering reaction had to be performed in CH_2Cl_2 (Item 7, Scheme 2, LG=R^3=Cl); in MeOH, displacement of chloride by the solvent occurred.



Scheme 2.

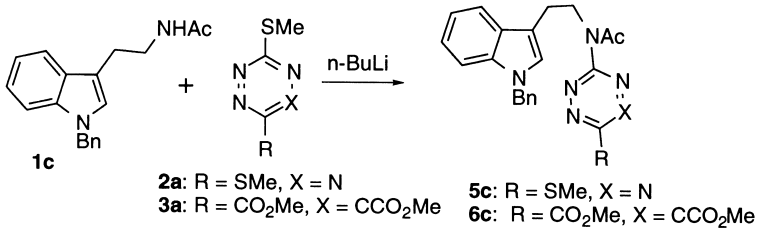


Scheme 3.

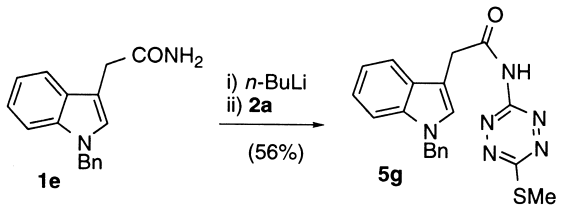
Displacements of methylthiolate from triazines were also straightforward (Scheme 3, LG=SMe, X=N; Table 2).[11] Refluxing dimethyl 3-methylthio-1,2,4-triazine-5,6-dicarboxylate (**3a**)[12] in methanol with **1a** and **1b** gave the tethered triazines **6a** and **6b** (each 99%, Table 2, Items 1 and 2, respectively), while similar reactions of **3a** with N^1-benzyl-N^{10}-methyltryptamine (**1d**, 89%, Item 4) and 5,6-diphenyl-3-methylthio-1,2,4-triazine (**3f**)[11a] with **1b** (89%, Item 9) were also successful.

Displacement of methyl thiolate from the more electron rich triazines **3b**[11a] and **3d**[11a] required the presence of added base; NaOMe (2 equiv.) was used (Table 2, Items 5 and 7), which also gave rise to small amounts of the 3-methoxytriazines **3c** (8%) and **3e** (10%), respectively. On the assumption that the tethering of these triazines proceeded through initial production of the methoxy triazines followed by methoxide displacement,[11a] **3c** and **3e** were prepared from **3b** and **3d** (86 and 81%, respectively)[11a] and resubjected to the tethering reaction. The methoxyl groups were displaced, but the yields of the tethered tryptamines **6e** and **6f** remained approximately the same (Table 1, Items 5–8). Chloride displacement from 3,6-dichloropyridazine (**4**) by **1a**, however, required more vigorous conditions (refluxing DMF), and the yield of the tethered pyridazine **7a** (35%, Item 10) was considerably less than that of the tethered triazines and tetrazines.[13] Thus as expected, the ease of displacements followed the series tetrazines>triazines >pyridazines, matching the decrease in electron deficiency.

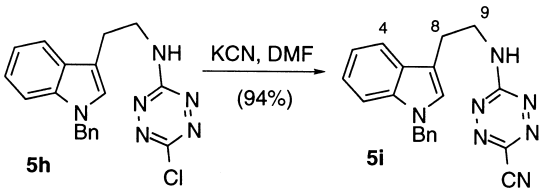
Since preliminary results had indicated that acylation of the nitrogen linker was necessary for the cycloaddition to proceed,[5] tetrazine **2a** and triazine **3a** were also tethered to N^1-benzyl-N^{10}-acetyltryptamine **1c** following deprotonation of the amide with *n*-BuLi (60 and 52%, Table 1, Item 3, and Table 2, Item 3, respectively; Scheme 4).[14] Attempts to apply the same tethering reaction of **1c** to tetrazines **2b**, **2c**, and **2d** (see Table 1 for tetrazine



Scheme 4.



Scheme 5.



Scheme 6.

structures), triazines **3b** and **3d** (see Table 2 for triazine structures), as well as pyridazine **4** were all unsuccessful. The tetrazines **2b**–**2d** decomposed under the strongly basic conditions,[15] while only starting materials were recovered from the reactions of the triazines **3b** and **3d** and pyridazine **4**. In order to discern whether the location of the carbonyl group would impact upon the cycloaddition of the tethered azadienes, N^1-benzylindoleacetamide (**1e**) was also prepared and linked to **2a** to give **5g** (Scheme 5). Finally, tethered tetrazine **5i** was prepared from **5h** by cyanide displacement (KCN, DMF, rt) of the remaining chloro substituent (Scheme 6).

In general, the tethered products were evidenced in the ^{1}H NMR spectrum by an approximate 1 ppm downfield shift of the H9 methylene protons of the tryptamine side chain (now appearing near δ 4.0), comparable to the deshielding observed upon *N*-acylation. The ^{1}H NMR spectrum of tethered triazine **6a** recorded at room temperature indicated the presence of two distinct rotamers (Fig. 1) about the tethering, amino nitrogen–triazine bond in a 2:1 ratio. Thus, three singlets for the methyl ester protons appeared at δ 4.02, 3.98, and 3.95 in a 2:3:1 ratio, while the tethering amino proton, both pairs of methylene protons (H8/8′ and H9/9′), and the indole H4 all appeared as two separate resonances in 2:1 ratios. Upon warming to 40°C, the methyl ester resonances collapsed to a single, sharp singlet (δ 3.97, 6H), and the indole H4 also appeared as a single resonance (δ 7.59, d, J=8 Hz). At this temperature, severe broadening, but not coalescence, was observed in the tethering amino NH and the tryptamine side chain methylene resonances. Further warming of the sample was not pursued since the coalescence observed at 40°C and the broadening of the other resonances confirmed the existence of NMR-distinct rotamers at room temperature. Slowly interconverting rotamers were not observed in the proton spectrum at ambient temperature (270 MHz) of the corresponding acetylated tethered triazine **6c**, nor in the spectra of tethered triazines **6e**–**6g** which do not bear electron withdrawing substituents at the triazinyl 4-, and 5-positions. Similar rotamers were observed, however, in the proton and carbon spectra of **6b** and **6d**.

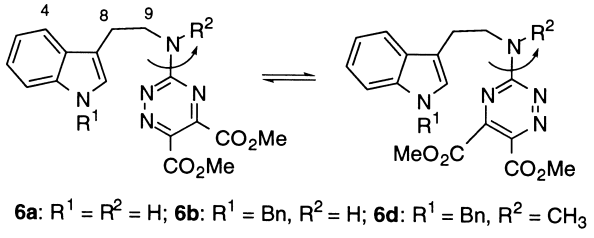
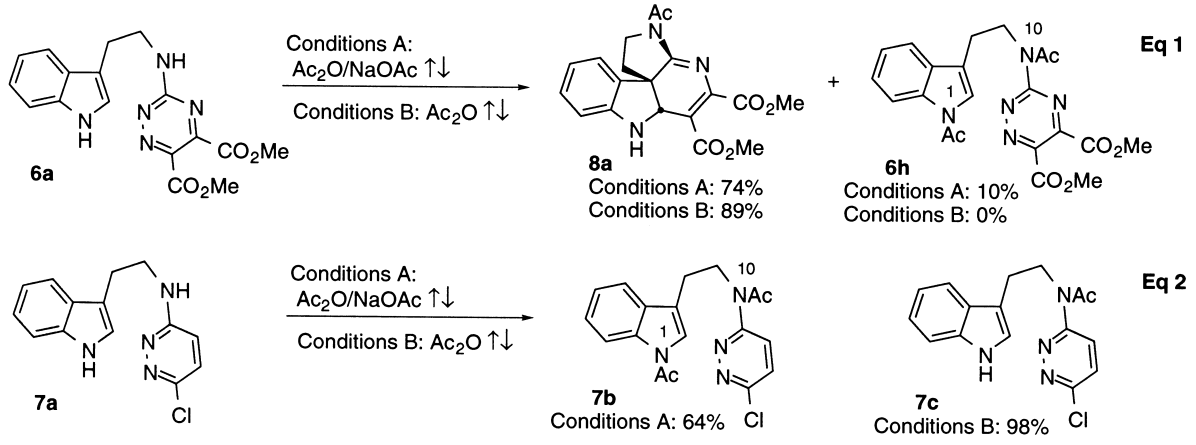


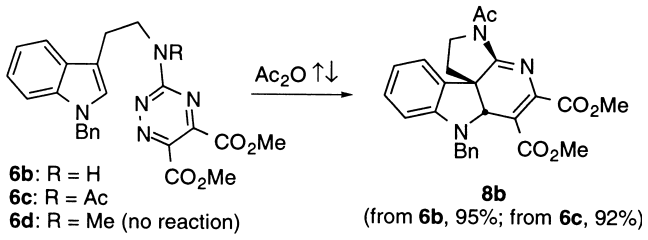
Figure 1. Rotamers observed in the NMR spectra of **6a**, **6b**, and **6d**.

Cycloadditions of the tethered triazines

Tethered tetrazines **5** and triazines **6** without N^{10}-acylation did not produce cycloadducts upon heating in 1,3,5-triisopropylbenzene (TIPB, bp 232°C); prolonged heating at reflux led only to decomposition. With the assumption that electron donation from the tethering nitrogen lone pair of electrons was inhibiting the cycloaddition due to the relatively high LUMO level of the azadiene, **5a**, **6a**, and **7a** were each submitted to the in situ acetylation procedure employed by Boger for inducing intramolecular cycloadditions between pyridazines and tethered alkynes.[16] Under these conditions, **6a** produced cycloadduct **8a** in 74% yield, along with a 10% yield of N^1,N^{10}-diacetylated tethered triazine **6h** (Scheme 7, Eq. 1). Upon refluxing in Ac_2O in the absence of added NaOAc, cycloadduct **8a** was obtained in 89% yield with no **6h** detected. The *cis*-fused



Scheme 7.



Scheme 8.

1,2-dihydro tautomeric form of the dihydropyridine ring in **8a** was readily assigned by NOE's as described later. In contrast, no cycloadducts were obtained from **5a** or **7a** under these conditions (with and without NaOAc). Acetate addition to the tetrazine ring with multiple *N*-acetylations resulted in unidentified products from the reaction of **5a**, while **7a** only yielded the N^1,N^{10}-diacetylated and N^{10}-acetylated tethered pyridazines **7b** and **7c**, respectively (Scheme 7, Eq. 2).

It was concluded that initial acetylation of the tethering nitrogen was essential to allow the cycloaddition of tethered triazine **6a** to proceed. If competing acetylation of the indole nitrogen (N^1), which apparently requires base (acetate) promotion, occurs first, no cycloaddition would result presumably due to the lowering of the HOMO of the indole 2,3-double bond upon acetylation,[17] and subsequent N^{10}-acetylation would give only **6h**. In support of this conclusion, heating **6h** to 150°C in diglyme (well above the reflux temperature of Ac_2O: 138°C) produced no reaction; **6h** was recovered unchanged. Subjecting **6h** to refluxing Ac_2O also did not produce any cycloadduct. Higher temperatures led only to decomposition.

In order to prevent detrimental acylation at the indole N^1-position, N^1-benzyl derivatives **6b** and **6c** were prepared (Table 2, Items 2 and 3). Refluxing **6b** in Ac_2O produced an excellent yield (95%) of cycloadduct **8b** (Scheme 8). Based on this result, and the presumed necessity of N^{10}-acylation prior to the intramolecular cycloaddition, it was anticipated that **6c** would undergo a facile cycloaddition under thermal conditions. Surprisingly, only starting material was recovered when **6c** was heated in TIPB (160–200°C), while decomposition resulted in refluxing TIPB (232°C). However, refluxing **6c** in Ac_2O produced **8b** in excellent yield (92%). The requirement of Ac_2O to produce **8b** from **6c**, while no reaction ensued at much higher temperatures but without an acylating agent present, suggested that acetylation of both the tethering nitrogen and a triazine ring nitrogen may be necessary for the cycloaddition to proceed. The importance of the acetylation of the tethering nitrogen for the cycloaddition was emphasized by the failure of N^{10}-methylated tethered triazine **6d**, which cannot be acylated on the tethering nitrogen, to react under the same conditions (refluxing Ac_2O).

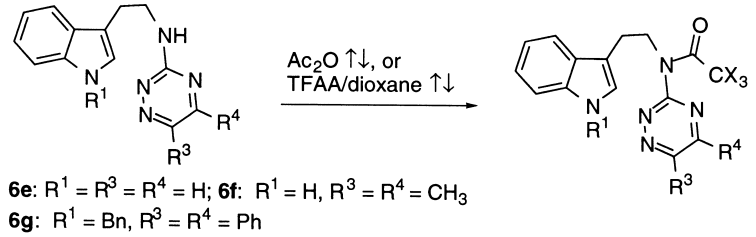
None of the other tethered triazines **6e**–**g** (see Table 2, Items 5–9, Scheme 9), which do not have strongly electron withdrawing triazine substituents, participated in intramolecular cycloadditions under any of the conditions that were successful with **6a**–**6c**. In refluxing Ac_2O, only the N^{10}-acetylated tethered triazines were produced (96–97%), while trifluoroacetic anhydride (TFAA, 8 equiv.) in refluxing dioxane (100°C) yielded only the N^{10}-trifluoro-acetylated derivatives (92–94%). Addition of NaOAc resulted only in further acylation of the indole nitrogen, yielding N^1,N^{10}-bis-acylated tethered triazines. Thus, the requisite N^{10}-acylation, acylating reaction medium, and electron withdrawing triazine substituents indicated that the intramolecular cycloadditions of tryptamine-tethered azadienes required very electron-deficient diene systems to react with the indole 2,3-double bond.

With the successful cycloadditions of tethered diester triazines **6a**–**6c**, the corresponding tethered (*S*)-tryptophan **6i** was prepared (Scheme 10) to determine whether the amino acid chirality could control the facial selectivity of the cycloaddition. As with **6a**, **6b**, and **6d**, distinct rotamers (1:1 ratio) about the tethering nitrogen–triazinyl bond of **6i** were observed in the proton and carbon spectra at ambient temperature. Refluxing **6i** with TFAA (8 equiv.) in dioxane produced adduct **8c** as the sole product (>99% de), the loss of the trifluoro-acetate group occurring during chromatographic purification. Key to the assignment of the stereochemistry of **8c** was an NOE between H5 and H12 observed in the 2D-NOE spectrum; NOE's between H9a and H11 protons confirmed the *cis* ring fusion as well as the 1,2-dihydro tautomeric form of the dihydropyridine subunit.

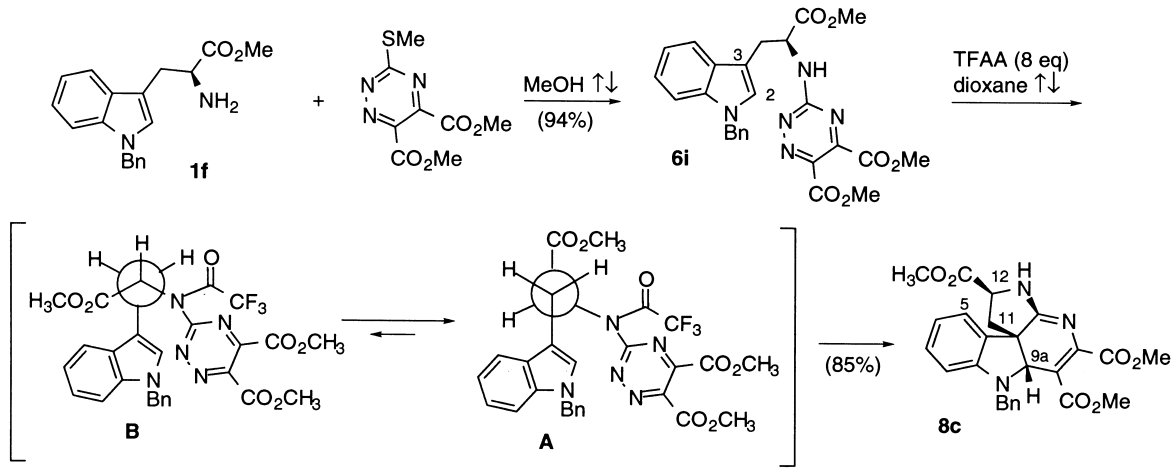
Exclusive diastereoselectivity in the cycloaddition to give **8c** can be hypothesized to originate from preferred conformation **A**, which would result in *si*-face approach of the triazine subunit to the indole ring 2,3-double bond. The alternative conformation **B**, which would lead to cycloaddition across the *re*-face, suffers an additional *gauche* interaction.

Cycloadditions of the tethered tetrazines

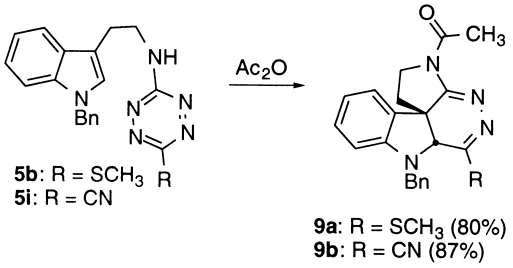
As noted, **5a** did not produce a cycloadduct upon refluxing in Ac_2O, giving only complex product mixtures. When **5a** and **5d** were treated with TFAA (8 equiv.) in dioxane at rt,



Scheme 9.



Scheme 10.

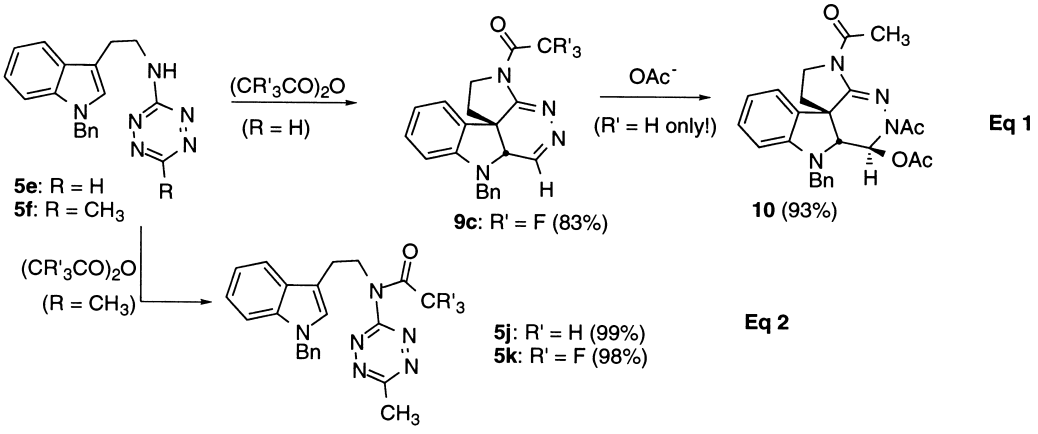


Scheme 11.

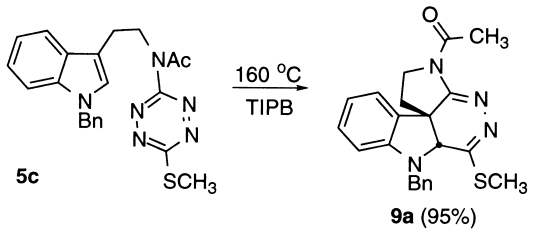
however, a single product was formed in each reaction in near quantitative crude yields. Both products appeared to be cycloadducts, but were unstable to chromatography on both silica gel and alumina, though the presence of multiple trifluoroacetyl groups was apparent from the ^{13}C NMR spectra. Since the instability was thought to be due to these trifluoro-acetyl groups, one of which was assumed to be on the indole nitrogen, N^1-benzylated tryptamine derivatives **5b** and **5i** were prepared and subjected to the cycloaddition conditions.

Refluxing N^1-benzyl protected tethered tetrazines **5b** and **5i** in Ac_2O produced the 1,2-dihydrotautomeric cycloadducts **9a** and **9b**, respectively, in good yields (Scheme 11). Tetrazine **5e** also underwent a cycloaddition under these conditions, but nucleophilic addition of acetate to the cycloadduct followed by a second acetylation, led to **10** (93%, Scheme 12, Eq. 1). Similar products resulting from nucleophilic addition to dihydropyridazine and dihydropyridine cycloadducts had been previously observed in the intermolecular reactions of indole with both tetrazines[17] and triazines.[12] When **5e** was refluxed in dioxane with TFAA (8 equiv.), the desired cycloadduct **9c** was obtained (83%). Presumably, the considerably less nucleophilic trifluoroacetate anion was unable to add to this adduct. Tethered tetrazine **5f** produced only the acylated derivatives **5j** and **5k** upon treatment with refluxing Ac_2O and TFAA/dioxane, respectively (Scheme 12, Eq. 2); no cycloadducts were detected.

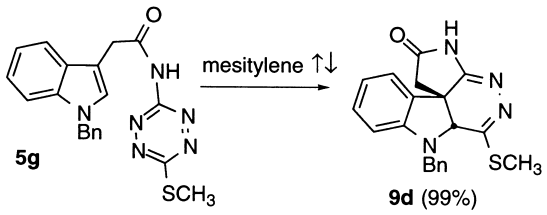
In contrast to the N^{10}-acetylated tethered triazine **6c**, the cycloaddition of the *N*-acetylated tethered tetrazine **5c** proceeded in good yield simply by heating (160°C, 45 min in TIPB) to produce **9a** in excellent yield (95%, Scheme 13). Thus, further activation of the tetrazine nucleus by refluxing in an acylating medium was not necessary. Reinforcing this point, indoleacetamide **5g** also underwent a thermally



Scheme 12.



Scheme 13.



Scheme 14.

promoted cycloaddition in refluxing mesitylene (bp 162–164°C) to produce **9d** (99%, Scheme 14).

Catalysis of the intramolecular cycloaddition

Reports of Lewis acid catalysis of inverse electron Diels–Alder reactions are extremely rare. Conceptually, this is understandable since Lewis acids seek electrons, and the electron-rich dienophiles of the inverse electron demand Diels–Alder reactions are likely to function as Lewis bases. This acid–base interaction would lower the dienophile HOMO and thereby retard the cycloaddition (and often induce dienophile polymerization or decomposition!). Indole itself is well known to oligomerize in the presence of both Lewis and Bronsted acids.[18] Lewis acid catalysis of such cycloadditions is feasible, however, if the Lewis acid would preferentially coordinate with the electron deficient diene. Mariano, for example, has reported that cycloadditions of 2-azadienes with enamines and vinyl ethers can be catalyzed by BF_3 Et_2O, though the yields of cycloadducts were rather modest.[19] Boger and Panek had also sought Lewis acid catalysis in the cycloadditions between enamines and 1,2,4-triazines, but without success.[20] We had previously noted a very mild catalysis of the intramolecular cycloaddition between indole and the tethered diethyl 1,2,4-triazine-5,6-dicarboxylate **11** by the NMR shift reagent $Eu(fod)_3$ to produce the canthine **12** (Fig. 2),[21] a Lewis acid used extensively by Danishefsky in catalyzing hetero Diels–Alder reactions of aldehydes.[22] Thus in refluxing diglyme, the cycloaddition of **11** was sluggish and required 8 h for completion. Addition of $Eu(fod)_3$ enabled completion of the reaction under the otherwise same conditions in only 2 h.[21b] Catalysis of the cycloaddition of any other tethered triazines in that series, however, was not realized using $Eu(fod)_3$ or any other Lewis acid, and it was speculated that the presence of a chelation site offered by the triazine ester substituents made the catalysis possible.

The tryptamine-tethered tetrazines and triazines **5** and **6** present several nitrogen lone pairs on the azadiene subunit which could function as basic sites and allow for Lewis acid catalysis of the cycloaddition. Thus, the possibility of catalysis in the intramolecular cycloaddition of tethered tetrazine **5c** (see Scheme 13), which also contains a sulfur as a potential site for Lewis acid coordination, was examined (Table 3), with attention paid to azaphilic Lewis acids. While some did catalyze the cycloaddition in low yields at 60°C or lower temperatures (in control experiments, no reaction occurred at 60°C in TIPB or DMF after 24 h), the best yield obtained [with $Ni(CN)_2$, 62%, Item 2] was considerably lower than that achieved by heating **5c** to 160°C in TIPB (95%, Scheme 13). Nevertheless, this catalysis did enable the cycloaddition to proceed at a considerably lower temperature. The NMR shift reagent $Eu(hfc)_3$ also promoted the cycloaddition to a very limited extent at lower temperature, but the yields of cycloadduct **9a** were poor (Items 7 and 8). Attempts to apply $Ni(CN)_2$ catalysis to the cycloaddition of triazine **6c** were unsuccessful: no reaction was observed.

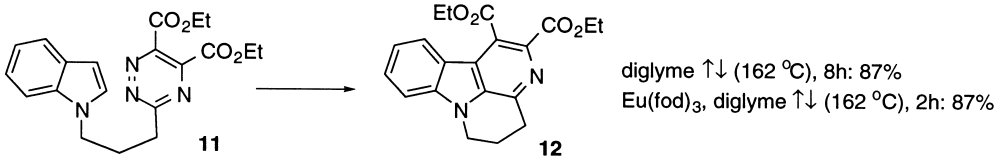


Figure 2. Mild catalysis of the cycloaddition of **11** by the NMR shift reagent $Eu(fod)_3$.[21b]

Table 3. Lewis acid catalyzed cycloadditions of **5c** to **9a**

Item	Catalyst (eqiv.)	Conditions	Yield (%) **9a**	Recovered (%) **5c**
1	None	TIPB or DMF, 60°C, 24 h	0	100
2	$Ni(CN)_2$ (1.5)	DMF, 60°C, 3 h	62	27
3	$Ni(acac)_2$ (1)	DMF, 60°C, 3 h	40	44
4	$AlCl_3$ (1)	CH_2Cl_2, rt, 14 h	12	71
5	$MeAlCl_2$ (1 equiv.)	TIPB, rt, 12 h	<2	98
6	$MeAlCl_2$ (1 equiv.)	TIPB, 80°C, 4 h	0	0
7	$Eu(hfc)_3$ (0.05)	CH_2Cl_2, reflux, 8 h	10	82
8	$Eu(hfc)_3$ (0.05)	TIPB, 70°C, 8 h	24	68
9	CuI(1)	DMF, 60°C, 3 h	10	23
10	$BF_3{\cdot}OEt_2$	CH_2Cl_2, rt, 10 h	22	53

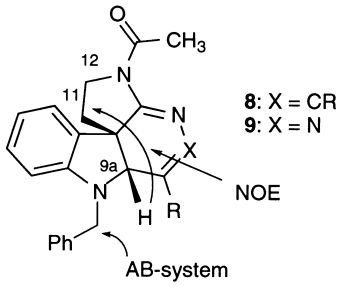


Figure 3. Cycloadduct NMR characteristics.

Structure of the cycloadducts

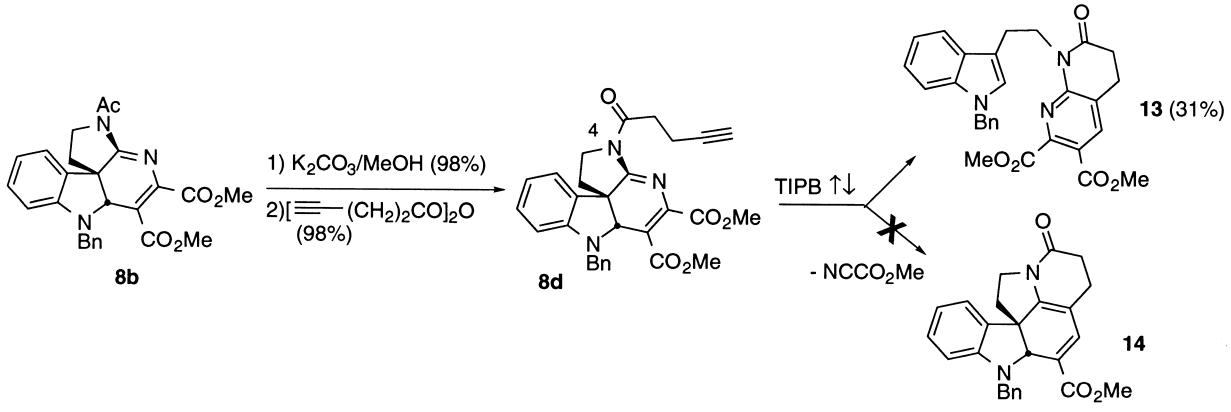
The formation of cycloadducts **8** and **9** was indicated in the NMR spectra by several key features (Fig. 3). In the N^1-benzylated derivatives, the benzylic methylene protons, a singlet (s, 2H) near δ 5.2–5.3 in the tethered precursors **5** and **6**, became an AB-system ($J_{AB}\approx$15 Hz) in the cycloadducts with the two resonances appearing between 4.9 and 4.3, indicating the formation of a nearby stereogenic center. The methylene resonances of the tryptamine side chain, originally simple multiplets (2H each) in **5** and **6**, became distinct one proton mutliplets suggesting the formation of a cyclic structure (H11/11′, H12/12′). Furthermore, the disappearance of the indole H2 resonance near δ 6.9 in the spectra of the starting materials coincided with the appearance of a broad singlet of a methine near δ 4.6–5.6 for H9a with the corresponding carbon C9a appearing near δ 65 in the triazine adducts **8**, and near δ 3.9–4.6 (^{13}C near δ 50) in the tetrazines adducts **9**. The structures were further supported by ^{13}C and HMQC spectra, with the *cis* fusion of the newly formed C-ring confirmed by NOE's between H9a and the H11 protons in DNOE or NOESY experiments.

Preliminary attempts to complete the Aspidosperma alkaloidal pentacyclic skeleton

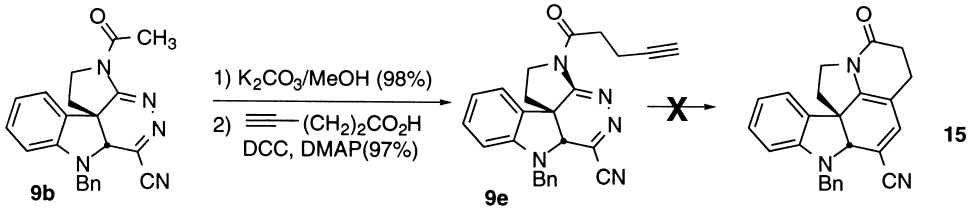
A second cycloaddition across the aza C-ring of adducts **8** and **9** with a dienophile tethered to N4 (Aspidosperma alkaloid numbering) would complete the pentacyclic skeleton of the Aspidosperma alkaloids. Deacetylation of **8b** followed by reacylation with pentynoyl anhydride produced **8d** (96%, 2 steps, Scheme 15). Refluxing **8d** in TIPB gave rise to **13** (31%) with none of the desired adduct **14** detected. Formation of **13** arises from the desired cycloaddition, but a subsequent retro Diels–Alder reaction to free the indole subunit and generate the aromatic pyridine ring of **13** dominates over a release of methyl cyanoformate.[23]

Similar to **8b**, tethered tetrazine adduct **9b** was deacetylated, then reacylated with the pentynoic acid and DCC to give **9e** (Scheme 16). However, **9e** did not undergo a cycloaddition under any conditions examined, including refluxing in TIPB (232°C), which only led to decomposition.

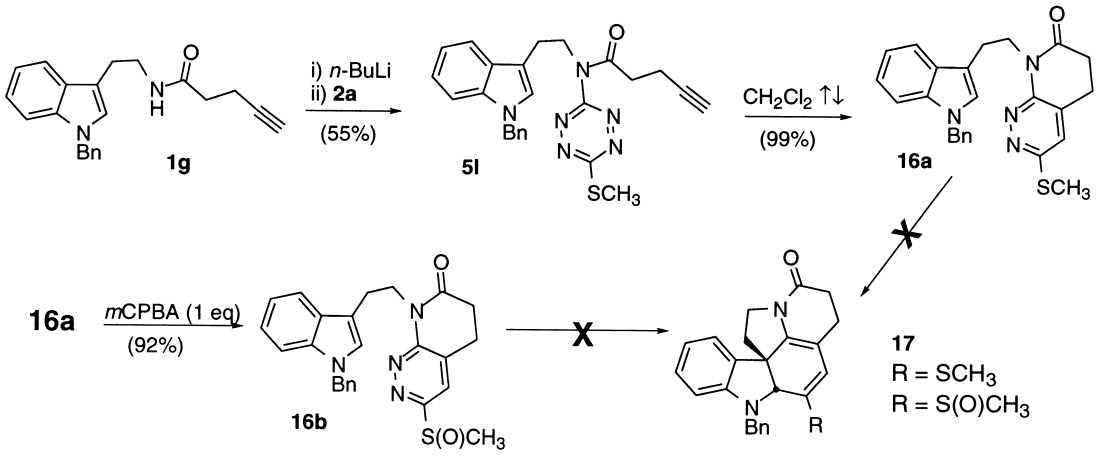
An alternative approach to complete the pentacyclic core of the Aspidosperma alkaloids with the second cycloaddition of the tandem strategy forming the C- and E-rings was also briefly investigated (Scheme 17). Tetrazine **2a** was tethered to tryptamine derivative **1g** to produce **5l**, which underwent a very facile cycloaddition in refluxing CH_2Cl_2 to produce adduct **16a**, confirming the better dienophilicity of the alkyne in comparison to the indole double bond. No conditions were found which could induce **16a** to undergo an intramolecular cycloaddition to produce **17** (R=SCH_3). Refluxing **16a** in Ac_2O or dioxane with TFAA (8 equiv.), with or without Ni(II), conditions which had been successful in promoting the cycloadditions of other tethered azadienes, all returned only starting material, similar to the results observed with the other tethered pyridazine **7a** (Scheme 7,



Scheme 15.



Scheme 16.



Scheme 17.

Eq. 2). Refluxing **16a** in TIPB (232°C) led only to decomposition. Oxidation of **16a** to the corresponding sulfoxide **16b** proceeded smoothly, but again, **16b** would not participate in the desired intramolecular cycloaddition. Attempts to oxidize **16b** to the sulfone were unsuccessful, resulting in oxidation of the indole 2,3-double bond.

Conclusions

The intramolecular inverse electron demand cycloadditions of heteroaromatic azadienes tethered to the primary amine of tryptamine proceed in excellent yields as long as the tethered triazines or tetrazines are very electron deficient, and the tethering nitrogen is acylated. In the case of the triazines, further activation by reaction in an acylating medium is also required. Catalysis of the reaction by $Ni(CN)_2$ was successful with tetrazine **5c** bearing the thiol substituent, but not with triazine **6c**. Attempts to convert the cycloadducts produced in the intramolecular reactions of tethered triazines and tetrazines to the pentacyclic core of the Aspidosperma alkaloids have to-date been unsuccessful. We are continuing to explore methods to achieve this final cycloaddition.

Experimental

General

Melting points were determined in capillaries and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Varian UNITY PLUS 400 (93.94 kG, ^1H 400 MHz, ^{13}C 100 MHz), a Varian Gemini 300 (70.5 kG, ^1H 300 MHz, ^{13}C 75 MHz) and a JEOL GSX-270 (63.41 kG, ^1H 270 MHz, ^{13}C 67.5 MHz) in $CDCl_3$ (0.5 mL). The δ 7.24 resonance of residual $CHCl_3$, and the center line of the $^{13}CDCl_3$ triplet (δ 77.0) were used as internal references for the ^1H and ^{13}C spectra, respectively. All exchangeable protons resonances (NH) were identified by the addition of D_2O. Relative intensities of carbon resonance were determined by integration of spectra recorded under inverse gated decoupling. Carbon chemical shifts are reported to a single decimal place with the exception of resolved resonances which can be distinguished numerically only to the second decimal position. Infrared spectra were recorded on a Perkin–Elmer 1800 spectrometer on NaCl plates unless otherwise noted. Solid samples were deposited on the NaCl plate as a solution in an appropriate, volatile solvent (typically CH_2Cl_2) followed by evaporation of the solvent. Only diagnostic bands, such as carbonyl and triple bond stretching bands, are reported. Mass spectra were measured on a Finnigan MAT-90 spectrometer as indicated.

Tryptamine (**1a**), *l*-(*S*)-tryptophan, 3-indolylacetic acid, 3,6-dichloropyridazine (**4**) and pentynoic acid were purchased from Aldrich or Lancaster and used without further purification. Tetrazines **2a**,[7] **2b**,[8] **2c**,[8] **2d**,[10] and triazines **3a**,[12] **3b**,[11a] **3c**,[11a] **3d**,[11a] **3e**,[11a] and **3f**[11a] were prepared according to literature procedures. All solvents were anhydrous, dried and distilled according to standard procedures[24] immediately before use.

***N*^{1}-Benzyltryptamine (1b).** Di-*tert*-butyl dicarbonate [$(BOC)_2O$, 1.5 g, 6.86 mmol] was added to a solution of tryptamine (1.0 g, 6.24 mmol) in dioxane (10 mL) containing triethylamine (1.7 mL, 12.48 mmol), and the reaction mixture was stirred at rt for 3 h. The solvent was removed in vacuo, and the product purified by flash chromatography (10% EtOAc/CH_2Cl_2) to give *N*^{10}-BOC-tryptamine as a white solid (1.59 g, 6.12 mmol, 98%). Mp 94–95°C; IR (NaCl) 1692 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 8.47 (bs, NH), 7.48 (d, *J*=7.8 Hz, 1H), 7.21 (d, *J*=7.8 Hz, 1H), 7.07 (ddd, *J*=7.8, 7.8, 1.0 Hz, 1H), 7.00 (ddd, *J*=7.8, 7.8, 1.0 Hz, 1H), 6.79 (bs, 1H), 4.56 (bs, NH), 3.32 (dt, *J*=6.8, 5.9 Hz, 2H), 2.81 (t, *J*=6.8 Hz, 2H), 1.35 (s, 9H); (270 MHz, DMSO-d_6) δ 10.6 (bs, NH), 7.53 (d, *J*=7.8 Hz, 1H), 7.35 (d, *J*=7.8 Hz, 1H), 7.11 (bs, 1H), 7.10–6.97 (m, 2H), 6.55 (bs, NH), 3.24 (dt, *J*=7.5, 5.9 Hz, 2H), 2.84 (t, *J*=7.5, 2H), 1.40 (s, 9H); ^{13}C NMR (67.5 MHz, DMSO-d_6, 70°C)[25] δ 155.2, 136.1, 127.1, 122.2, 120.5, 117.89, 117.84, 111.7, 111.0, 77.2, 40.8, 28.0 (3C), 25.3; HRMS (EI, 70 eV) *m/z* 260.1534 ($[M]^+$ calcd for $C_{15}H_{20}O_2N_2$, 260.1525).

A solution of *N*^{10}-BOC-tryptamine (1.59 g, 6.12 mmol) in THF (10 mL) was added with stirring to a suspension of KH (0.7 g, 6.12 mmol, 35% in mineral oil) slurried in THF (0.5 mL) and cooled to −50°C. After 30 min, benzylbromide

(1.2 g, 6.73 mmol) was added, then the reaction was allowed to warm to rt and stirring continued for an additional 3 h. After quenching by the addition of water (10 mL), EtOAc (20 mL) was added and the organic phase was separated, dried over Na_2SO_4, and the solvent removed in vacuo. The product was purified by flash chromatography (2% EtOAc/CH_2Cl_2) to give N^1-benzyl-N^{10}-BOC-tryptamine as a pale yellow oil (2.05 g, 5.87 mmol, 96%). IR (NaCl) 1695 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.60 (dd, J=6.8, 1.0 Hz, 1H), 7.29–7.06 (m, 8H), 6.92 (s, 1H), 5.22 (s, 2H), 4.63 (bs, NH), 3.42 (bm, 2H), 2.93 (t, J=6.8, 2H), 1.42 (s, 9H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 155.9, 137.5, 136.7, 128.7 (2C), 128.0, 127.5, 126.7 (2C), 126.1, 121.8, 119.1, 119.0, 112.3, 109.6, 79.0, 49.8, 40.9, 28.4 (3C), 25.7; HRMS (EI 70 eV) m/z 350.1975 ($[M]^+$ calcd for $C_{22}H_{26}O_2N_2$, 350.1994). Gram quantities of N^1-benzyl-N^{10}-BOC-tryptamine were stored due to its greater stability and appropriate amounts deprotected to **1b** immediately before use in the S_NAr reactions.

A solution of N^1-benzyl-N^{10}-BOC-tryptamine (2.0 g, 5.71 mmol) in CH_2Cl_2 (16 mL) at rt was treated with trifluoroacetic acid (4 mL). After 1 h, the reaction was quenched by extraction with saturated aqueous $NaHCO_3$ solution (3×15 mL), the organic phase was separated, dried over Na_2SO_4, and the solvent removed in vacuo to afford **1b** as a colorless oil (1.4 g, 5.71 mmol, 99+%) which was used without further purification. ^1H NMR (270 MHz, $CDCl_3$) δ 7.63 (d, J=7.8 Hz, 1H), 7.27–7.07 (m, 8H), 6.93 (s, 1H), 5.21 (s, 2H), 3.00 (m, 2H), 2.91 (m, 2H), 1.4 (bs, NH_2); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 137.5, 136.6, 128.5, (2C) 128.0, 127.3, 126.62, 126.55 (2C), 121.6, 118.9, 118.8, 112.7, 109.5, 49.6, 42.2, 29.2; HRMS (EI, 70 eV) m/z 250.1485 ($[M]^+$ calcd for $C_{17}H_{18}N_2$, 250.1470).

N^1-Benzyl-N^{10}-acetyltryptamine (1c). A solution of tryptamine (**1a**, 1.0 g, 6.24 mmol) in acetic anhydride (5 mL) containing triethylamine (1.7 mL, 12.48 mmol) was stirred at rt for 2 h. The solvent was then concentrated in vacuo and the residue loaded onto a pad of silica gel in a Büchner funnel and eluted with 5% EtOAc/CH_2Cl_2 to afford N^{10}-acetyltryptamine (1.26 g, 6.24 mmol, 99+%) which was used in the next step without further purification. ^1H NMR (270 MHz, $CDCl_3$) δ 8.36 (bs, NH), 7.58 (d, J=7.7 Hz, 1H), 7.36 (d, J=7.9 Hz, 1H), 7.19 (dd, J=7.9, 7.1 Hz, 1H), 7.11 (dd, 7.7, 7.1 Hz, 1H), 7.00 (d, J=1.8 Hz, 1H), 5.62 (bs, NH), 3.58 (dt, J=6.6, 6.8 Hz, 2H), 2.95 (t, J=6.8 Hz, 1H), 1.90 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 170.0, 136.6, 127.9, 127.5, 122.2, 119.5, 118.7, 113.1, 111.3, 39.9, 25.3, 23.3. The same benzylation procedure used to prepare **1b** was followed with N^{10}-acetyltryptamine (1.26 g, 6.24 mmol) to afford **1c**, purified by flash chromatography (2% EtOAc/CH_2Cl_2), as a white solid (1.8 g, 6.16 mmol, 99%). Mp 93–94°C; IR (NaCl) 1651 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.58 (d, J=7.8 Hz, 1H), 7.27–7.06 (m, 8H), 6.92 (s, 1H), 5.60 (bs, NH), 5.23 (s, 2H), 3.54 (dt, J=6.8, 5.9 Hz, 2H), 2.93 (t, J=6.8 Hz, 1H), 1.86 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 170.0, 137.4, 136.7, 128.7 (2C), 127.9, 127.6, 126.8 (2C), 126.0, 121.9, 119.2, 118.9, 112.2, 109.7, 49.8, 39.8, 25.2, 23.3; HRMS (EI, 70 eV) m/z 292.1588 ($[M]^+$ calcd for $C_{19}H_{20}N_2O$, 292.1576).

N^1-Benzyl-N^{10}-methyltryptamine (1d). To a solution of tryptamine (**1a**, 1.0 g, 6.24 mmol) and triethylamine (5 mL) in CH_2Cl_2 (30 mL) cooled to 0°C, ethyl chloroformate (0.75 mL, 7.8 mmol) was added dropwise over 10 min with stirring. The reaction mixture was stirred for an additional 30 min at 0°C, then allowed to warm to rt and stirred for an additional 1.5 h. The solvent was removed in vacuo, and the residue purified by flash chromatography (CH_2Cl_2/EtOAc, 5:1) to give N^{10}-carboethoxytryptamine as a pale yellow oil (1.20 g, 84%). ^1H NMR 400 MHz, $CDCl_3$) δ 8.00 (bs, NH), 7.60 (d, J=8.0 Hz, 1H), 7.35 (d, J=8.0 Hz, 1H), 7.19 (ddd, J=8.0, 8.0, 1.0 Hz, 1H), 7.11 (ddd, J=8.0, 8.0, 1.0 Hz, 1H), 7.03 (bs, 1H), 4.68 (bs, NH), 4.09 q, J=6.8 Hz, 2H), 3.50 (dt, J=6.8, 5.9 Hz, 2H), 2.95 (t, J=6.8 Hz, 1H), 1.20 (t, J=6.8 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 156.7, 136.6, 127.5, 122.3, 122.0, 119.6, 118.8, 113.2, 111.2, 77.2, 60.7, 41.4, 25.9, 14.7; HRMS (EI, 70 eV) m/z 232.1201 ($[M]^+$ calcd for $C_{13}H_{16}N_2O_2$, 232.1197).

To a suspension of $LiAlH_4$ (1.75 g, 46.1 mmol) in THF (30 mL) cooled to 0°C under argon, a solution of N^{10}-carboethoxytryptamine (1.0 g, 4.2 mmol) in THF (10 mL) was slowly added with stirring via syringe. After the addition was complete, the reaction mixture was allowed to warm to rt, then refluxed for 3 h. After allowing to cool to rt, the reaction was quenched by the addition of water (5 mL) and 15% aqueous KOH (w/v, 1 mL). The precipitate was removed by filtration and washed with ether (100 mL), then with MeOH (20 mL). The combined filtrates were dried over Na_2SO_4, then the solvent removed in vacuo and the residues purified by flash chromatography (EtOAc/CH_2Cl_2, 1:1) to give N^{10}-methyltryptamine (0.37 g, 2.1 mmol, 50%) as a pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 8.11 (bs, NH), 7.62 (d, J=8.0 Hz, 1H), 7.353 (d, J=8.0 Hz, 1H), 7.18 (ddd, J=8.0, 8.0, 1.0 Hz, 1H), 7.10 (ddd, J=8.0, 8.0, 1.0 Hz, 1H), 7.03 (bs, 1H), 3.00–2.89 (A_2B_2, J_{AB}=6.8 Hz, 4H), 2.20 (s, 3H), 2.20 (bs, NH); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 136.3, 127.6, 121.9 (2C), 119.2, 118.8, 113.7, 111.0, 51.7, 36.0, 25.3; HRMS (EI, 70 eV) m/z 174.1157 ($[M]^+$ calcd for $C_{11}H_{14}N_2$, 174.1157).

To a solution of N^{10}-methyltryptamine (0.35 g, 2.0 mmol) and triethylamine (2 mL) in dioxane (10 mL) at rt was added BOC-ON (0.54 g, 2.2 mmol). The solution was stirred overnight (15 h), then the solvent was removed in vacuo, and the residue purified by flash chromatography (CH_2Cl_2/EtOAc, 5:1) to give N^{10}-BOC-N^{10}-methyltryptamine (0.38 g, 1.4 mmol, 70%) as a pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, ex, NH), 7.61 (d, J=8.0 Hz, 1H), 7.34 (d, J=8.0 Hz, 1H), 7.17 (ddd, J=8.0, 7.6, 1.0 Hz, 1H), 7.10 (ddd, J=8.0, 7.6, 1.0 Hz, 1H), 6.99 (bs, 1H), 3.49 (t, J=6.9 Hz, 2H), 2.95 (t, J=6.9 Hz, 1H), 2.84 (s, 3H), 1.37 (s, 9H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 155.8, 136.3, 127.5, 122.0, 121.9, 119.3, 118.7, 113.4, 111.1, 79.1, 49.5, 34.4, 28.4 (3C), 23.8; HRMS (EI, 70 eV) m/z 274.1664 ($[M]^+$ calcd for $C_{16}H_{22}N_2O_2$, 274.1681).

The same benzylation procedure which produced **1b** was then followed with N^{10}-BOC-N^{10}-methyltryptamine (0.23 g, 0.84 mmol) to afford N^1-benzyl-N^{10}-BOC-N^{10}-methyltryptamine after flash chromatography (CH_2Cl_2) as

a pale yellow oil (0.21 g, 0.59 mmol, 70%). Resonances in both the ^{1}H and ^{13}C NMR spectra were broadened due to the presence of slowly interconverting rotamers. ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.63 (d, J=7.5 Hz, 1H), 7.40–7.10 (m, 8H), 6.92 (bs, 1H), 5.25 (s, 2H), 3.50 (bt, J=7.0 Hz, 2H), 2.94 (bt, J=7.0 Hz, 1H), 2.84 (s, 3H), 1.37 (bs, 9H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 155.8, 137.6, 136.7, 128.7 (2C), 128.3, 127.5, 126.8 (2C), 126.0, 121.8 119.05, 118.99, 112.5, 109.6, 79.1, 49.9, 49.8, 34.5, 28.4 (3C), 24.0; HRMS (EI, 70 eV) m/z 364.2156 ([M]$^+$ calcd for $C_{23}H_{28}N_2O_2$, 364.2151).

The same deprotection procedure as described above for **1b** was applied to N^1-benzyl-N^{10}-BOC-N^{10}-methyltryptamine (0.10 g, 0.27 mmol) to afford **1d** after flash chromatography (CH_2Cl_2/MeOH, 10:1) as a pale yellow oil (63 mg, 0.24 mmol, 88%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (d, J=7.9 Hz, 1H), 7.40–7.06 (m, 8H), 6.98 (s, 1H), 5.24 (s, 2H), 3.09–3.01 (m, 4H), 2.851 (s, 3H) (NH not observed); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 137.5, 136.7, 128.7 (2C), 127.8, 127.6, 126.8 (2C), 126.3, 121.9, 119.2, 118.9, 111.6, 109.8, 51.1, 49.9, 34.9, 24.2; HRMS (EI, 70 eV) m/z 264.1638 ([M]$^+$ calcd for $C_{18}H_{20}N_2$, 264.1626).

(N^1-Benzyl-3-indolyl)acetamide (1e). Thionyl chloride (1.4 g, 11.4 mmol) was added dropwise to methanol (10 mL) cooled to −30°C and stirred for 0.5 h. (3-Indolyl)-acetic acid (1.0 g, 5.7 mmol) was added in one portion and the reaction mixture was allowed to warm to rt and stirred for 4 h. The reaction was quenched with water (10 mL) and partitioned with EtOAc (20 mL). The organic phase was separated, then dried over Na_2SO_4. After removal of the solvent in vacuo, the residue was purified by flash chromatography (2% EtOAc/CH_2Cl_2) to afford methyl (3-indolyl)-acetate as a colorless oil (1.1 g, 5.6 mmol, 98%). IR (NaCl) 1737 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.10 (bs, NH), 7.62 (d, J=7.9 Hz, 1H), 7.32 (d, J=7.9 Hz, 1H), 7.20–7.10 (m, 2H), 7.09 (s, 1H), 3.79 (s, 2H), 3.70 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 172.6, 136.0, 127.1, 123.1, 122.1, 119.6, 118.8, 111.2, 108.3, 51.9, 31.1; HRMS (EI, 70 eV) m/z 189.0802 ([M]$^+$ calcd for $C_{11}H_{11}NO_2$, 189.0790).

The same benzylation procedure used to prepare **1b** was followed with methyl (3-indolyl)acetate (2.0 g, 10.58 mmol) to afford methyl (N^1-benzyl-3-indolyl)acetate after flash chromatography (CH_2Cl_2) as a colorless oil (2.8 g, 10.16 mmol, 96% yield). IR (NaCl) 1731 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.59 (d, J=7.3 Hz, 1H), 7.26–7.08 (m, 9H), 5.24 (s, 2H), 3.75 (s, 2H), 3.66 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 172.4, 137.4, 136.5, 128.7 (2C), 127.9, 127.6, 127.1, 126.8 (2C), 121.9, 119.4, 119.0, 109.7, 107.5, 51.9, 50.0, 31.1; HRMS (EI, 70 eV) m/z 279.1254 ([M]$^+$ calcd for $C_{18}H_{17}NO_2$, 279.1259).

A mixture of $NH_4OH_{(aq)}$ and MeOH (10 mL each) was added to methyl (N^1-benzyl-3-indolyl)acetate (4.0 g, 14.34 mmol) at rt. After stirring for 12 h, additional $NH_4OH_{(aq)}$ (10 mL) was added and stirring continued for an additional 12 h. After extraction with EtOAc (20 mL) the organic phase was dried over Na_2SO_4 and the solvent removed in vacuo. Purification of the residue by flash chromatography (25% EtOAc/CH_2Cl_2) afforded **1e** as a white solid (2.87 g, 10.90 mmol, 76%). Mp 149–150°C; IR (NaCl) 1652 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.55 (d, J=7.3 Hz, 1H), 7.28–7.07 (m, 8H), 7.03 (s, 1H), 5.60 (bs, NH), 5.57 (bs, NH), 5.25 (s, 2H), 3.68 (s, 2H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 174.4, 137.0, 136.7, 128.7 (2C), 127.7, 127.5, 127.4, 126.8 (2C), 122.3, 119.8, 118.9, 109.9, 108.3, 49.9, 32.9; HRMS (EI, 70 ev) m/z 264.1255 ([M]$^+$ calcd for $C_{17}H_{16}N_2O$, 264.1263).

***N*^{1}-Benzyl-(L)-tryptophan methyl ester (1f).** The same benzylation and deprotection (removal of BOC group) procedures used to prepare **1b** were followed beginning with BOC-L-tryptophan methyl ester[26] (1.42 g, 4.61 mmol) to afford **1f** as a colorless oil (1.32 g, 4.29 mmol, 93% yield) which was used without further purification. $[\alpha]_D^{24}$=+6.0 (c 2 g/100 mL, $CDCl_3$); IR (NaCl) 1737 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.62 (d, J=7.8 Hz, 1H), 7.26–7.04 (m, 8H), 6.96 (s, 1H), 5.23 (s, 2H), 3.81 (m, 1H), 3.64 (s, 3H), 3.26 (m, 1H), 3.05 (m, 1H), 1.6 (bs, NH_2); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 175.4, 137.2, 136.3, 128.4 (2C), 127.9, 127.2, 126.7, 126.4 (2C), 121.6, 119.0, 118.7, 110.0, 109.4, 54.8, 51.5, 49.4, 30.5; HRMS (EI, 70 eV) m/z 308.1516 ([M]$^+$ calcd for $C_{19}H_{20}N_2O_2$, 308.1525).

***N*^{1}-Benzyl-*N*^{10}-(pent-4-ynoyl)tryptamine (1g).** To a solution of **1b** (1.0 g, 4 mmol) and 4-pentynoic acid (0.39 g, 4 mmol) in CH_2Cl_2 (10 mL) were added DCC (1.65 g, 8 mmol) and DMAP (25 mg, 0.20 mmol). After stirring for 3 h at rt, the reaction was cooled to 0°C to precipitate the N,N'-dicyclohexylurea, and the mixture filtered through a pad of Celite. The solvent was removed from the filtrate in vacuo, and the residue purified by flash chromatography (10% EtOAc/CH_2Cl_2) to afford 1 g as a white solid (1.28 g, 3.88 mmol, 97%). Mp 89–90°C; IR (NaCl) 2115, 1641 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.61 (d, J=7.8 Hz, 1H), 7.27–7.07 (m, 8H), 6.92 (s, 1H), 6.07 (bt, J=6.3 Hz, NH), 5.19 (s, 2H), 3.56 (dt, J=6.8, 6.3 Hz, 2H), 2.95 (t, J=6.8 Hz, 2H), 2.44 (dt, J=7.3, 1.5 Hz, 2H), 2.27 (t, J=7.3 Hz, 2H), 1.87 (t, J=1.5 Hz, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 170.7, 137.3, 136.5, 128.5 (2C), 127.8, 127.4, 126.6 (2C), 125.9, 121.7, 119.0, 118.8, 112.0, 109.5, 82.9, 69.1, 49.6, 39.7, 35.0, 25.0, 14.6; HRMS (EI, 70 eV) m/z 330.1762 ([M]$^+$ calcd for $C_{22}H_{22}N_2O$, 330.1732).

General procedure for tethering azadienes to tryptamines. A solution of the tryptamine derivative 1 with the azadiene (1 equiv.) in the appropriate solvent as listed in Tables 1 and 2, 5 mL/g azadiene, (conditions A: MeOH, C: CH_2Cl_2 and E: DMF) was refluxed for the time indicated below for each compound. In the case of condition D, Table 2, NaOMe (2 equiv.) was also added to the MeOH solution. After cooling to rt, the solvent was removed in vacuo and the residue purified by flash chromatography. For condition B, see below.

***N*^{10}-[6-Methylthio-3-(1,2,4,5-tetrazinyl)]-tryptamine (5a).** Prepared from tryptamine (**1a**, 1.0 g, 6.24 mmol) and tetrazine **2a** (1.09 g, 6.24 mmol) according to the general procedure, condition A (2 h) to afford **5a** after flash chromatography (3% EtOAc in CH_2Cl_2), as an orange solid (1.70 g, 5.92 mmol, 95%). Mp 184–186°C; ^{1}H NMR (270 MHz, DMSO-d_6) δ 10.1 (bd, J=1.5 Hz, NH), 7.64 (dd,

J=7.8, 1.0 Hz, 1H), 7.46 (bs, NH), 7.39 (dd, J=7.8, 1.0 Hz, 1H), 7.23 (d, J=1.5 Hz, 1H), 7.10 (ddd, J=7.8, 6.8, 1.0 Hz, 1H), 7.02 (ddd, J=7.8, 6.8, 1.0 Hz, 1H), 3.85 (dt, J=6.8, 5.8 Hz, 2H), 3.17 (t, J=6.8 Hz, 2H), 2.63 (s, 3H); ^{13}C NMR (270 MHz, DMSO-d_6) δ 164.9, 161.0, 136.3, 127.2, 123.0, 121.0, 118.3, 118.2, 111.4 (2C), 41.4, 24.4, 13.2; ^{13}C NMR (67.5 MHz, acetone-d_6) δ 167.0, 162.6, 137.8, 128.6, 123.7, 122.2, 119.6, 119.4, 113.0, 112.2, 42.5, 25.5, 13.5; HRMS (CI, 140 eV, ammonia) m/z 287.1061 ([M+1]$^+$ calcd for $C_{13}H_{15}N_6S$, 287.1079).

N^{10}-[6-Methylthio-3-(1,2,4,5-tetrazinyl)]-N^1-benzyltryptamine (5b). Prepared from N^1-benzyltryptamine (**1b**, 1.50 g, 6.0 mmol) and tetrazine **2a** (1.04 g, 6.0 mmol) according to the general procedure, condition A (3 h) to give **5b** after flash chromatography (CH_2Cl_2) as a red oil (2.1 g, 5.59 mmol, 93%). ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.61 (d, J=7.3 Hz, 1H), 7.27–7.06 (m, 8H), 6.96 (s, 1H), 5.66 (bt, J=5.9 Hz, NH), 5.24 (s, 2H), 3.85 (dt, J=6.9, 5.9 Hz, 2H), 3.12 (t, J=6.9 Hz, 2H), 2.62 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 166.9, 160.8, 137.3, 136.8, 128.7 (2C), 127.8, 127.6, 126.7 (2C), 126.3, 122.0, 119.3, 118.8, 111.4, 109.8, 49.8, 41.5, 24.8, 13.6; HRMS (EI, 70 eV) m/z 376.1466 ([M]$^+$ calcd for $C_{20}H_{20}N_6S$, 376.1470).

N^{10}-Acetyl-N^{10}-[6-methylthio-3-(1,2,4,5-tetrazinyl)]-N^1-benzyltryptamine (5c). A solution of n-BuLi (3.0 mL, 1.0 M in hexanes) was added dropwise with stirring to a solution of N^{10}-acetyl-N^1-benzyltryptamine (**1c**, 888 mg, 3.04 mmol) dissolved in THF (10 mL) and cooled to −30°C. After 20 min, a solution of tetrazine **2a** (529 mg, 3.04 mmol) in THF (2 mL) was added via cannula and the reaction continued for 30 min. The reaction was then quenched at −30°C with water (10 mL) and after warming to rt, the mixture extracted with EtOAc (3×15 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent removed in vacuo. Flash chromatography (CH_2Cl_2) of the residue provided **15c** as a red oil (709 mg, 1.76 mmol, 58%). IR (NaCl) 1678 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.56 (dd, J=6.8, 1.5 Hz, 1H), 7.29–7.24 (m, 3H), 7.18–7.06 (m, 5H), 6.86 (s, 1H), 5.20 (s, 2H), 4.50 (t, J=6.8 Hz, 2H), 3.13 (t, J=6.8 Hz, 2H), 2.60 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 171.6, 170.7, 162.5, 137.2, 136.4, 128.7 (2C), 127.6, 127.4, 127.0, 126.9 (2C), 121.8, 119.3, 119.1, 111.4, 109.6, 49.8, 47.5, 24.7, 24.5, 13.5; HRMS (CI, 140 eV, NH_3) m/z 403.1720 ([M+1]$^+$ calcd for $C_{22}H_{22}N_6S$, 403.1705).

N^{10}-[3-(1,2,4,5-Tetrazinyl)]-tryptamine (5d). Prepared from tryptamine (**1a**, 1.0 g, 6.24 mmol) and tetrazine **2b** (0.80 g, 6.25 mmol) according to the general procedure, condition A (2 h) to give **5d** after flash chromatography (5% EtOAc/CH_2Cl_2) as a red solid (1.3 g, 5.37 mmol, 86% yield). Mp 187–188°C; ^{1}H NMR (270 MHz, DMSO-d_6) δ 10.05 (bs, NH), 9.63 (s, 1H), 7.64 (d, J=7.8 Hz, 1H), 7.38 (d, J=7.8 Hz, 1H), 7.23 (s, 1H), 7.10 (dd, J=7.8, 7.3 Hz, 1H), 7.01 (dd, J=7.8, 7.3 Hz, 1H), 3.88 (dt, J=7.8, 5.9 Hz, 2H), 3.17 (t, J=7.8 Hz, 2H); ^{13}C NMR (67.5 MHz, DMSO-d_6) δ 162.7, 152.6, 136.2, 127.2, 122.9, 120.9, 118.3, 118.2, 111.4, 111.3, 41.1, 24.3; HRMS (CI, 140 eV, NH_3) m/z 241.1201 ([M+1]$^+$ calcd for $C_{12}H_{13}N_6$, 241.1202).

N^{10}-[3-(1,2,4,5-Tetrazinyl)]-N^1-benzyltryptamine (5e). Prepared from N^1-benzyltryptamine (**1b**, 1.5 g, 6 mmol) and tetrazine **2b** (0.77 g, 6 mmol) according to the general procedure, condition A (3 h) to give **5e** after flash chromatography (CH_2Cl_2) as a red solid (1.70 g, 5.16 mmol, 85%). Mp 146–148°C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 9.55 (s, 1H), 7.61 (d, J=7.3 Hz, 1H), 7.26–7.08 (m, 8H), 6.97 (s, 1H), 6.05 (bs, NH), 5.23 (s, 2H), 3.89 (dt, J=5.6, 5.4 Hz, 2H), 3.13 (t, J=5.6 Hz, 2H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 162.8, 153.2, 137.3, 136.8, 128.7 (2C), 127.7, 127.6, 126.7 (2C), 126.4, 122.1, 119.3, 118.8, 111.3. 109.8, 49.9, 41.2, 24.8; HRMS (CI, 140 eV, NH_3) m/z 330.1570 ([M]$^+$ calcd for $C_{19}H_{18}N_6$, 330.1593).

N^{10}-[6-Methyl-3-(1,2,4,5-tetrazinyl)]-N^1-benzyltryptamine (5f). Prepared from N^1-benzyltryptamine (**1b**, 1.0 g, 4.0 mmol) and tetrazine **2c** (0.57 g, 4 mmol) according to the general procedure, condition A (3 h) to give **5f** after flash chromatography (5% EtOAc/CH_2Cl_2) as a red solid (1.2 g, 3.4 mmol, 85%). Mp 148–150°C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.63 (d, J=7.3 Hz, 1H), 7.27–7.06 (m, 8H), 6.97 (s, 1H), 5.87 (bs, NH), 5.23 (s, 2H), 3.88 (dt, J=6.9, 6.6 Hz, 2H), 3.13 (t, J=6.9 Hz, 2H), 2.79 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 161.6, 137.4, 136.9, 128.9, 128.8 (2C), 127.8, 127.6, 126.8 (2C), 126.4, 122.1, 119.3, 118.9, 111.5, 109.9, 49.9, 41.4, 25.0, 20.0; HRMS (CI, 140 eV, NH_3) m/z 344.1734 ([M+1]$^+$ calcd for $C_{20}H_{20}N_6$, 344.1744).

{N^1-Benzyl-N^{10}-[6-methylthio-3-(1,2,4,5-tetrazinyl)]-3-indolyl}acetamide (5g). A solution of **1e** (0.1 g, 0.38 mmol) in THF (2 mL) cooled to −60°C was treated with n-BuLi (2.4 mL, 1.6 M solution in hexanes) with stirring. After 20 min, a solution of tetrazine **2a** (0.07 g, 0.38 mmol) in THF (2 mL) was added via cannula. The reaction was allowed to warm to rt, stirred for 4 h, then quenched by the addition of water (5 mL). The mixture was partitioned with EtOAc (10 mL), and the organic extracts dried over Na_2SO_4. The solvent was removed in vacuo, and the residue purified by flash chromatography (20% EtOAc/CH_2Cl_2) to give **5g** as a red solid (0.08 g, 0.21 mmol, 56%). Mp 148–150°C; IR (NaCl) 1700 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.60 (bs, ex, NH), 7.68 (d, J=7.9 Hz, 1H), 7.40–7.18 (m, 9H), 5.38 (s, 2H), 4.14 (s, 2H), 2.73 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 173.0, 169.1, 158.2, 137.0, 136.8, 128.9 (2C), 128.0, 127.9, 127.4, 126.9 (2C), 122.8, 120.4, 118.7, 110.2, 106.4, 50.1, 34.6, 13.5; HRMS (EI, 70 eV) m/z 390.1228 ([M]$^+$ calcd for $C_{20}H_{18}N_6OS$, 390.1263).

N^{10}-[6-Chloro-3-(1,2,4,5-tetrazinyl)]-N^1-benzyltryptamine (5h). Prepared from N^1-benzyltryptamine (**1b**, 1.5 g, 6 mmol) and tetrazine **2d** (0.90 g, 6 mmol) according to the general procedure, condition C (2 h) to give **5h** after flash chromatography (CH_2Cl_2) as a dark red solid (1.8 g, 4.95 mmol, 83%). Mp 147–149°C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.59 (d, J=7.3 Hz, 1H), 7.30–7.06 (m, 8H), 6.96 (s, 1H), 5.86 (bs, NH), 5.24 (s, 2H), 3.88 (dt, J=6.9, 6.6 Hz, 2H), 3.12 (t, J=6.9 Hz, 2H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 161.4, 160.4, 137.3, 136.9, 128.8 (2C), 127.7 (2C), 126.8 (2C), 126.4, 122.2, 119.5, 118.8, 111.0, 109.9, 49.9, 41.7, 24.8; HRMS (EI, 70 eV) m/z 364.1203 ([M]$^+$ calcd for $C_{19}H_{17}N_6Cl$, 364.1203).

N^{10}-[6-Cyano-3-(1,2,4,5-tetrazinyl)]-N^1-benzyltryptamine (5i). To a solution of **5h** (0.72 g, 1.98 mmol) in DMF (8 mL) at rt was added KCN (1.98 mmol), and the reaction was

stirred under argon for 4 h. The solvent was removed by vacuum distillation at room temperature, and the residue purified by flash chromatography (CH_2Cl_2) to give **5i** red solid (0.66 g, 1.86 mmol, 94%). Mp 170–172°C; IR (NaCl) 2243 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.58 (dd, J=7.6, 1.0 Hz, 1H), 7.32–7.07 (m, 8H), 6.99 (s, 1H), 6.31 (bs, ex, NH), 5.28 (s, 2H), 4.03 (dt, J=6.6, 6.4 Hz, 2H), 3.18 (t, J=6.6 Hz, 2H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 158.7, 145.0, 137.1, 136.9, 128.8 (2C), 127.8, 127.5, 126.8 (2C), 126.6, 122.4, 119.7, 118.6, 113.7, 110.4, 110.1, 40.0, 41.8, 24.7, a better quality ^{13}C spectrum was obtained in DMSO-d_6 due to improved solubility: ^{13}C NMR (67.5 MHz, DMSO-d_6) δ 158.5, 143.5, 138.3, 136.0, 128.5 (2C), 127.7, 127.3, 127.03, 126.95 (2C), 121.3, 118.7, 118.6, 115.1, 110.9, 110.1, 48.9, 41.4, 23.9; HRMS (CI, 140 eV, isobutane) m/z 355.1516 ($[M]^+$ calcd for $C_{20}H_{17}N_7$, 355.1546).

N^1-Benzyl-N^{10}-[6-methylthio-3-(1,2,4,5-tetrazinyl)]-N^{10}-pent-4-ynoyltryptamine (5l). To a solution of **1g** (700 mg, 2.1 mmol) in THF (15 ml) cooled to −60°C was added dropwise with stirring *n*-BuLi (2.1 mL, 1.0 M in hexanes). After 20 min, tetrazine **2a** (0.37 g, 2.1 mmol) in THF (2 mL) was added via cannula, and stirring continued for 30 min, then the reaction mixture allowed to warm to rt. The reaction was quenched with water (5 mL), extracted with EtOAc (3×10 mL), and the organic extracts were dried over Na_2SO_4. The solvent was removed in vacuo and the residue purified by flash chromatography (CH_2Cl_2) to give **5l** as a red oil (530 mg, 1.16 mmol, 55%). IR (NaCl) 2120, 1684 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.54 (dd, J=6.8, 1.4 Hz, 1H), 7.28–7.23 (m, 3H), 7.14–7.05 (m, 5H), 6.84 (s, 1H), 5.18 (s, 2H), 4.49 (t, J=7.3 Hz, 2H), 3.13 (t, J=7.3 Hz, 2H), 2.87 (t, J=6.8 Hz, 2H), 2.60 (s, 3H), 2.57 (td, J=6.8, 2.7 Hz, 2H), 1.90 (t, J=2.7 Hz, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 171.7, 171.6, 162.1, 137.1, 136.3, 128.7 (2C), 127.6, 127.3, 127.0, 126.90 (2C), 121.8, 119.3, 119.1, 111.3, 109.6, 82.8, 68.9, 49.8, 47.7, 35.6, 24.5, 14.7, 13.5; HRMS (EI, 70 eV) m/z 456 1778 ($[M]^+$ calcd for $C_{25}H_{24}N_6OS$, 456.1735).

N^{10}-[5,6-Dicarbomethoxy-3-(1,2,4-triazinyl)]tryptamine (6a). Prepared from tryptamine (**1a**, 1.0 g, 6.24 mmol) and triazine **3a** (1.0 g, 4.16 mmol) according to the general procedure, condition A (3 h) to give **6a** after flash chromatography (10% EtOAc/CH_2Cl_2) as a yellow solid (1.45 g, 4.1 mmol, 99% yield based on **3a**). Mp 149–151°C; IR (KBr) 1750, 1715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (bs, ex, NH), 7.62 (d, J=8.0 Hz, 0.33H), 7.60 (d, J=8.0 Hz, 0.67H), 7.36 (d, J=8.0 Hz, 1H), 7.20 (dd, J=8.0, 6.8 Hz, 1H), 7.12 (dd, J=8.0, 6.8 Hz 1H), 7.03 (bs, 1H), 6.63 (bs, ex, 0.67NH), 5.87 (bs, ex, 0.33NH), 4.05 (dt, J=6.4, 6.4 Hz, 0.66H), 4.01 (s, 2H), 3.98 (s, 3H), 3.96 (s, 1H), 3.82 (dt, J=6.4, 6.4 Hz, 1.34H), 3.14 (t, J=6.4 Hz, 0.66H), 3.06 (t, J=6.4 Hz, 1.34H); ^{13}C NMR (100 MHz, $CDCl_3$, *=resonances from minor rotamer) δ 164.4, 164.1,* 163.2, 161.2, 159.5,* 152.8, 152.4,* 138.0,* 136.4, 136.3, 127.0, 122.4, 122.1, 119.4,* 119.3, 118.5, 111.8, 111.3, 53.4, 52.9, 42.0,* 41.3, 24.8; HRMS (EI, 70 eV) m/z 355.1285 ($[M]^+$ calcd for $C_{17}H_{17}N_5O_4$, 355.1281).

N^{10}-[5,6-Dicarbomethoxy-3-(1,2,4-triazinyl)]-N^1-benzyltryptamine (6b). Prepared from N^1-benzyltryptamine (**1b**, 1.50 g, 6 mmol) and triazine **3a** (1.46 g, 6 mmol) according to the general procedure, condition A (4 h) to give **6b** after flash chromatography (3% EtOAc/CH_2Cl_2) as a yellow solid (2.64 g, 5.94 mmol, 99%). Mp 128–130°C; IR (NaCl) 1748, 1721 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, 50°C)[27] δ 7.60 (bd, J=6.9 Hz, 1H), 7.27–7.06 (m, 8H), 6.96 (s, 1H), 6.5 (bs, 0.67NH), 5.8 (bs, 0.33NH), 5.26 (s, 2H), 3.96 (bs, 6H), 3.85 (bm, 2H), 3.13 (bm, 2H); ^{13}C NMR (67.5 MHz, $CDCl_3$, three sp^2 hybridized carbons were not observed at ambient temperature presumably due to slow exchange; *=resonance due to minor rotamer) δ 163.3, 161.3, 137.4, 136.8, 128.7 (2C), 127.7, 127.6, 126.8 (2C), 126.4, 122.1, 119.3, 118.8, 111.2, 109.9, 53.3, 53.0, 49.9, 42.1,* 41.5, 24.9; HRMS (EI, 70 eV) m/z 445.1756 ($[M]^+$ calcd for $C_{24}H_{23}N_5O_4$, 445.1750).

N^{10}-Acetyl-N^{10}-[5,6-dicarbomethoxy-3-(1,2,4-triazinyl)]-N^1-benzyltryptamine (6c). A solution of **1c** (888 mg, 3.04 mmol) in THF (10 mL) cooled to −30°C was treated with *n*-BuLi (3.0 mL of 1.6 M solution in hexanes) with stirring. After 20 min, a solution of triazine **3a** (739 mg, 3.04 mmol) in THF (2 mL) was added via cannula. The reaction was stirred for 30 min at −30°C, then quenched by the addition of water (5 mL). After warming to rt, the mixture was partitioned with EtOAc (3×15 mL), and the combined organic extracts dried over Na_2SO_4. The solvent was removed in vacuo, and the residue purified by flash chromatography (CH_2Cl_2) to give **6c** as a yellow oil (770 mg, 1.58 mmol, 52%). IR (NaCl) 1752, 1732, 1694 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.67 (d, J=6.8 Hz, 1H), 7.29–7.05 (m, 8H), 6.92 (s, 1H), 5.22 (s, 2H), 4.50 (t, J=7.5 Hz, 2H), 4.05 (s, 3H), 4.01 (s, 3H), 3.12 (t, J=7.5 Hz, 2H), 2.55 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 172.0, 163.0, 162.6, 137.5, 136.4, 128.7 (2C), 127.8, 127.5, 126.9, 126.81 (2C), 126.76, 126.73, 121.8, 119.3, 119.2, 111.8, 109.6, 53.8, 53.6, 49.8, 47.1, 26.9, 24.1; HRMS (EI, 70 eV) m/z 487.1814 ($[M]^+$ calcd for $C_{26}H_{25}N_5O_5$, 487.1856).

N^{10}-[5,6-Dicarbomethoxy-3-(1,2,4-triazinyl)]-N^{10}-methyl-N^1-benzyltryptamine (6d). Prepared from N^1-benzyl-N^{10}-methyltryptamine (**1d**, 50 mg, 0.19 mmol) and triazine **3a** (46 mg, 0.19 mmol) according to the general procedure, condition A (4 h) to give **6d** after flash chromatography (3% EtOAc/CH_2Cl_2) as a yellow oil (0.08 g, 0.17 mmol, 89%). IR (NaCl) 1747, 1720 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.70 (m, 1H), 7.30–7.04 (m, 8H), 6.96 (s, 0.5H), 6.91 (s, 0.5H), 5.24 (s, 2H), 4.19 (t, J=7.8 Hz, 1H), 3.99 (bs, 6H), 3.94 (t, J=7.8 Hz, 1H), 3.39 (s, 1.5H), 3.16 (s, 1.5H), 3.16 (m, 1H), 3.04 (t, J=7.8 Hz, 1H) (doubled and broadened resonances were observed for many protons due to the presence of slowly equilibrating rotamers); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 164.6, 163.5, 159.4, 159.2, 137.5, 136.6, 135.5, 128.8, 128.7, 127.9, 127.6, 126.8, 126.7, 126.3, 126.2, 121.9, 119.3, 119.2, 119.1, 119.0, 118.9, 111.5, 111.4, 109.7, 53.3, 52.9, 51.1, 50.4, 49.87, 49.83, 36.2, 36.0, 22.84, 22.75 (doubled resonances were observed for many carbons due to the presence of slowly equilibrating rotamers); HRMS (CI, 140 eV, NH_3) m/z 460.1980 ($[M+1]^+$ calcd for $C_{26}H_{26}N_5O_4$, 460.1985).

N^1-Benzyl-N^{10}-[5,6-dicarbomethoxy-3-(1,2,4-triazinyl)]-L-tryptophan methyl ester (6i). Prepared from *N*-benzyltryptophan methyl ester (**1e**, 0.05 g, 0.16 mmol) and triazine

3a (0.04 g, 0.16 mmol) according to the general procedure, condition A (3 h) to give **6i** after flash chromatography (3% EtOAc/CH_2Cl_2) as a yellow solid (0.08 g, 0.15 mmol, 94%). Mp 56–58°C; $[\alpha]_D^{24}$=+35.7 (*c* 3 g/100 mL, $CDCl_3$); IR (NaCl) 1748, 1721 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, two rotamers observed, 1:1 ratio) δ 7.50 (d, *J*=7.3 Hz, 1H), 7.28–7.02 (m, 8H), 6.93 (s, 1H), 6.87 (bd, *J*=8.8 Hz, 0.5NH), 6.23 (bd, *J*=7.3, 0.5NH), 5.28 (m, 0.5H), 5.25 (s, 2H), 5.02 (m, 0.5H), 3.98 (s, 3H), 3.97 (s, 3H), 3.64 (s, 3H), 3.48 (m, 1H), 3.40 (m, 1H); ^{13}C NMR (67.5 MHz, DMSO-d_6, 75°C, three sp^2 hybridized carbons were not observed presumably due to slow exchange) δ 171.0, 163.2, 162.5, 137.8, 135.8, 128.0 (2C), 127.4, 127.3, 126.8, 126.5 (2C), 121.0, 118.5, 118.0, 109.7, 109.1, 54.8, 52.8, 52.3, 51.6, 48.7, 26.4; HRMS (CI, 140 eV, ammonia) *m/z* 503.1835 ($[M+1]^+$ calcd for $C_{26}H_{25}N_5O_6$, 503.1805).

Cycloaddition of 6a; cycloadduct 8a. A suspension of **6a** (0.3 g, 0.85 mmol) and NaOAc (0.69 g, 8.4 mmol) in freshly distilled Ac_2O (4 mL) was refluxed until TLC indicated no starting material remained (5 h). After evaporating the mixture to dryness in vacuo, the residue was purified by flash chromatography (5% MeOH/CH_2Cl_2) to give **8a** as a white solid (0.231 g, 0.63 mmol, 74%), and **6h** as a yellow solid (0.037 g, 0.085 mmol, 10%). The same reaction in the absence of NaOAc gave only **6a** (89%). **Cycloadduct 8a:** Mp 270–272°C; IR (KBr) 1710, 1668 cm^{-1}; ^1H NMR (400 MHz, DMSO–d_6, 50°C) δ 9.36 (bs, ex, NH), 7.77 (bs), 7.27 (ddd, *J*=7.6, 6.4, 2.8 Hz), 7.11–7.06 (m, 2H), 5.63 (s, 1H), 3.59 (s, 3H), 3.52 (s, 3H), 3.60–3.50 (m, 2H), 2.59 (ddd, 12.0, 9.0, 9.0 Hz), 2.35 (s, 3H), 1.94 (dd, 12.0, 3.2 Hz); ^{13}C NMR (100 MHz, DMSO–d_6) δ 170.9, 169.5, 167.3, 166.1, 152.9, 140.9, 133.8, 128.7, 124.5, 121.8, 118.7, 102.2, 65.9, 52.1, 51.8, 51.2, 41.9, 36.1, 23.4; HRMS (EI, 70 eV) *m/z* 369.1319 ($[M]^+$ calcd for $C_{19}H_{19}N_3O_5$, 369.1325). ***N*^{1},*N*^{10}-Diacetyl-*N*^{10}-[5,6-dicarbomethoxy-3-(1,2,4-triazinyl)]tryptamine (6h).** Mp 165–166°C; IR (KBr) 1740, 1718, 1682 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J*=7.2 Hz), 7.68 (d, *J*=7.2 Hz), 7.35–7.26 (m, 3H), 4.51 (t, *J*=7.6 Hz), 4.07 (s, 3H), 4.03 (s, 3H), 3.10 (t, *J*=7.6 Hz), 2.62 (s, 3H), 2.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 168.4, 163.0, 162.4, 160.9, 150.2, 142.2, 135.8, 130.1, 125.4, 123.6, 123.2, 119.1, 118.9, 116.6, 53.9, 53.8, 46.2, 27.0, 24.0 (2C); HRMS (EI, 70 eV) *m/z* 439.1498 ($[M]^+$ calcd for $C_{21}H_{21}N_5O_6$, 439.1491).

Cycloadditions of 6b and 6c; cycloadduct 8b. A solution of **6b** (0.05 g, 0.11 mmol) or **6c** (0.07 g, 0.15 mmol) was refluxed in freshly distilled Ac_2O (2 mL) for 1 h. After evaporating the mixture to dryness in vacuo, the residue was purified by flash chromatography (3% EtOAc/CH_2Cl_2) to give **8b** as a yellow oil (0.047 g, 0.105 mmol, 95% from **6b**). IR (NaCl) 1740, 1718, 1700 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.27–7.15 (m, 6H), 6.75–6.65 (m, 3H), 4.82 (s, 1H), 4.63 (d, J_{AB}=15.4 Hz, 1H), 4.39 (d, J_{AB}=15.4 Hz, 1H), 3.86 (m, 1H), 3.75 (s, 3H), 3.71 (s, 3H), 3.62 (m, 1H), 2.63 (s, 3H), 1.60 (m, 1H), 1.46 (m, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 171.3, 167.6, 166.8, 164.5, 148.2, 142.4, 137.8, 131.7, 129.8, 128.5 (2C), 127.9 (2C), 127.7, 121.9, 119.3, 115.9, 111.6, 67.1, 53.55, 53.48, 52.4, 52.1, 43.1, 34.4, 26.1; HRMS (EI, 70 eV) *m/z* 459.1797 ($[M]^+$ calcd for $C_{26}H_{25}N_3O_5$, 459.1794).

Cycloaddition of 6i; cycloadduct 8c. A solution of **6i** (0.10 g, 0.20 mmol) and trifluoroacetic anhydride (TFAA, 0.25 mL, 1.8 mmol) in dioxane (3 mL) was refluxed for 1 h. The reaction mixture was evaporated to dryness and the residue purified by flash chromatography (2% MeOH/CH_2Cl_2) to give **8c** as a yellow oil (0.80 g, 0.17 mmol, 85%). $[\alpha]_D^{24}$=+94.0 (*c* 0.2g/100mL, $CDCl_3$); IR (NaCl) 1741, 1718 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27–7.17 (m, 5H), 7.16 (ddd, *J*=7.8, 7.3, 1.0 Hz, 1H), 6.85 (dd, *J*=7.3, 1.0 Hz, 1H), 6.70 (dd, *J*=7.3, 7.3 Hz, 1H), 6.58 (d, *J*=7.8 Hz, 1H), 4.67 (s, 1H), 4.57 (d, J_{AB}=15.6 Hz, 1H), 4.51 (dd, *J*=10.3, 6.2 Hz, 1H), 4.35 (d, J_{AB}=15.6 Hz, 1H), 3.72 (s, 3H), 3.70 (s, 3H), 3.69 (s, 3H), 2.01 (dd, J_{AB}=12.2, *J*=6.2 Hz, 1H), 1.94 (dd, J_{AB}=12.2, *J*=10.3 Hz, 1H) (NH not observed); ^{13}C NMR (270 MHz, $CDCl_3$) δ 172.4, 167.9, 166.5, 164.4, 148.3, 138.0, 130.9, 129.8, 128.6 (2C), 127.7 (2C), 127.5, 121.9, 119.2, 112.8, 111.0, 67.3, 61.4, 56.0, 53.0, 52.8, 52.5, 52.1, 43.4; HRMS (CI, 140 eV, NH_3) *m/z* 475.1757 ($[M]^+$ calcd for $C_{26}H_{25}O_6N_3$, 475.1743).

Cycloaddition of 5b and of 5c; cycloadduct 9a. A solution of **5b** (0.05 g, 0.133 mmol) was refluxed in Ac_2O (2 mL) for 2 h. After evaporating the mixture to dryness in vacuo, the residue was purified by flash chromatography (5% pet ether/CH_2Cl_2) to give **9a** (0.041 g, 0.106 mmol, 80%) as a colorless oil. Alternatively, a solution of **5c** (0.05 g, 0.13 mmol) was heated in TIPB (2 mL) to 160°C for 45 min. After evaporating the mixture to dryness in vacuo, the residue was purified as described above to give **9a** (0.048 g, 0.124 mmol, 95%). IR (NaCl) 1677 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.28 (m, 5H), 7.18 (ddd, *J*=7.8, 7.3, 1.0 Hz, 1H), 6.84 (dd, *J*=7.8, 1.0 Hz, 1H), 6.74 (ddd, *J*=7.3, 7.8, 1.0 Hz, 1H), 6.71 (d, *J*=7.8 Hz, 1H), 4.80 (d, J_{AB}=14.9 Hz, 1H), 4.54 (d, J_{AB}=14.9 Hz, 1H), 3.99 (s, 1H), 3.91 (m, 1H), 3.61 (m, 1H), 2.67 (s, 3H), 2.40 (s, 3H), 1.76–1.70 (m, 2H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 171.0, 164.1, 156.5, 147.3, 137.2, 130.5, 129.9, 128.8 (2C), 128.2 (2C), 128.1, 122.2, 119.8, 110.6, 66.8, 53.5, 50.4, 42.7, 35.4, 26.2, 13.6; HRMS (CI, 140 eV, NH_3) *m/z* 391.1610 ($[M+1]^+$ calcd for $C_{22}H_{23}N_4OS$, 391.1593).

Cycloaddition of 5i; cycloadduct 9b. A solution of **5i** (1.0 g, 2.8 mmol) was refluxed in Ac_2O (2 mL) for 3 h. After evaporating the mixture to dryness, the residue was purified by flash chromatography (3% EtOAc/CH_2Cl_2) to give **9b** (0.90 g, 2.45 mmol, 87%) as a yellow solid. Mp >230°C (dec); IR (NaCl) 2225, 1690 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.33–7.21 (m, 6H), 6.83–6.75 (m, 3H), 4.87 (d, J_{AB}=15.4 Hz, 1H), 4.65 (d, J_{AB}=15.4 Hz, 1H), 4.11 (s, 1H), 4.00 (ddd, *J*=12.0, 8.3, 1.5 Hz, 1H), 3.68 (ddd, *J*=12.0, 11.2, 6.3 Hz, 1H), 2.69 (s, 3H), 1.86–1.81 (m, 2H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 170.9, 157.2, 147.3, 139.6, 136.3, 130.6, 129.0 (3C), 128.3, 128.1 (2C), 122.1, 120.2, 115.7, 110.7, 64.0, 51.7, 49.5, 43.2, 35.1, 26.6; HRMS (CI, 140 eV, isobutane) *m/z* 370.1639 ($[M+1]^+$ calcd for $C_{22}H_{19}N_5O$, 370.1663).

Cycloaddition of 5e; cycloadduct 9c. A solution of **5e** (0.05 g, 0.15 mmol) and TFAA (0.17, 1.2 mmol, 8 equiv.) in dioxane (2.3 mL) was refluxed for 45 min. After evaporating the mixture to dryness, the residue was purified by flash chromatography (2% MeOH/CH_2Cl_2) to give **9c** as a

colorless oil (0.05 g, 0.13 mmol, 83%). IR (NaCl) 1728 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.34–7.22 (m, 5H), 7.03 (dd, J=7.3, 7.3 Hz, 1H), 6.92 (d, J=7.3 Hz, 1H), 6.58 (dd, J=7.3 Hz, 1H), 6.35 (d, J=7.3 Hz, 1H), 6.01 (s, 1H), 4.60 (d, J_{AB}=16.1 Hz, 1H), 4.34 (d, J_{AB}=16.1 Hz, 1H), 3.91 (s, 1H), 3.65 (m, 1H), 3.44 (m, 1H), 2.27 (m, 1H), 2.16 (m, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 170.4, 154.6 (q, $^2J_{C,F}$=36.8 Hz), 149.5, 137.1, 129.7, 128.9, 128.8, 128.7 (2C), 127.43, 127.3 (2C), 122.5, 117.8, 116.2 (q, $^1J_{C,F}$=287.2 Hz) 106.8, 76.5, 49.9, 49.2, 42.6, 39.3; HRMS (EI, 70 eV) m/z 397.1260 ($[M]^+$ calcd for $C_{21}H_{16}N_4OF_3$, 397.1276).

Cycloaddition of 5e; cycloadduct 10. A solution of **5e** (0.05 g, 0.15 mmol) in Ac_2O (2 mL) was refluxed for 1 h. After evaporating the mixture to dryness, the residue was purified by flash chromatography (5% EtOAc/CH_2Cl_2) to give **10** as a colorless oil (0.06 g, 0.14 mmol, 93%). IR (NaCl) 1740, 1680 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.32–7.23 (m, 5H), 7.09 (dd, J=6.8, 6.8 Hz, 1H), 7.02 (s, 1H), 6.87 (d, J=6.8 Hz, 1H), 6.64 (dd, J=7.8, 6.8 Hz, 1H), 6.45 (d, J=7.8 Hz, 1H), 4.74 (d, J_{AB}=16.1 Hz, 1H), 4.51 (d, J_{AB}=16.1 Hz, 1H), 4.12 (s, 1H), 4.02–3.96 (m, 2H), 2.53 (s, 3H), 2.25 (m, 1H), 2.15 (s, 3H), 2.04 (s, 3H), 1.92 (m, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 172.6, 170.2, 169.7, 157.5, 149.9, 137.1, 130.1, 129.2, 128.7 (2C), 127.45, 127.38 (2C), 122.5, 118.1, 107.6, 71.8, 70.8, 49.4, 48.6, 44.3, 35.5, 25.4, 21.8, 20.9; HRMS (EI, 70 eV), m/z 447.2002 ($[M+1]^+$ calcd for $C_{25}H_{27}N_4O_4$, 447.2032).

Cycloaddition of 5g; cycloadduct 9d. A solution of **5g** (0.5 g, 1.28 mmol) was refluxed in mesitylene (3 mL) for 10 min. After cooling, the mixture was purified by passing through a short SiO_2 column (4% MeOH/CH_2Cl_2), affording **9d** as a yellow solid (0.46 g, 1.28 mmol, 99%). Mp 126–128°C; IR (NaCl) 1737 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.30–7.19 (m, 6H), 6.97 (d, J=6.8 Hz, 1H), 6.79 (m, 2H), 4.77 (d, J_{AB}=14.6 Hz, 1H), 4.46 (d, J_{AB}=14.6 Hz, 1H), 4.04 (s, 1H), 2.33 (s, 3H), 2.30 (d, J_{AB}=16.6 Hz, 1H), 2.12 (d, J_{AB}=16.6 Hz, 1H) (NH was not observed); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 179.3, 166.4, 164.2, 147.2, 137.0, 131.1, 130.0, 128.7 (2C), 128.2, 128.1 (2C), 121.8, 120.9, 111.0, 65.7, 54.0, 49.6, 46.4, 13.4; HRMS (EI, 70 eV) m/z 362.1223 ($[M]^+$ calcd for $C_{20}H_{18}N_4OS$, 362.1201).

Cycloadduct 8d. A solution of **8b** (0.50 g, 1.09 mmol) in MeOH (3 mL) was stirred with K_2CO_3 (0.30 g, 2.2 mmol) for 4 h. The mixture was filtered, and the filtrate concentrated in vacuo to afford dimethyl *N*-benzylindolino[2,3-*d*]pyrrolidino[2,3-*e*]-4,5-dihydropyridine-2,3-dicarboxylate as a pale yellow oil (0.45 g, 1.08 mmol, 98% yield, 99% pure by ^1H NMR), which was used in the next step without further purification. IR (neat) 1734, 1692 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.26–7.19 (m, 5H), 7.11 (ddd, J=7.8, 7.3, 1.0 Hz, 1H), 6.89 (dd, J=7.3, 1.0 Hz, 1H), 6.67 (ddd, J=7.8, 7.3, 1.0 1H), 6.62 (dd, J=7.8, 1.0 Hz, 1H), 4.70 (s, 1H), 4.65 (d, J_{AB}=15.4 Hz, 1H), 4.49 (d, J_{AB}=15.4 Hz, 1H), 3.72 (s, 3H), 3.63 (s, 3H), 3.46 (m, 1H), 3.34 (m, 1H), 1.77 (m, 1H), 1.51 (m, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 171.8, 168.0, 148.6, 147.1, 138.6, 131.9, 129.4, 128.4 (2C), 128.0, 127.9 (2C), 127.3, 122.0, 118.8, 111.3, 108.6, 67.0, 53.7, 53.5, 52.3, 51.6, 42.2, 38.7; HRMS (CI, 140 eV, NH_3) m/z 418.1717 ($[M+1]^+$ calcd for $C_{24}H_{24}N_3O_4$, 418.1767).

A solution of dimethyl *N*-benzylindolino[2,3-*d*]pyrrolidino[2,3-*e*]-4,5-dihydropyridine-2,3-dicarboxylate (0.05 g, 0.12 mmol) was treated with pentynoyl anhydride[28] (0.5 mL) at rt for 18 h. The anhydride was removed in vacuo and the residue purified by flash chromatography (2% EtOAc/CH_2Cl_2) to afford **8d** as a yellow oil (0.058 g, 0.12 mmol, 98%). IR (NaCl) 1743, 1720, 1692 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.28–7.12 (m, 5H), 6.76–6.65 (m, 4H), 4.82 (s, 1H), 4.63 (d, J_{AB}=15.6 Hz, 1H), 4.38 (d, J_{AB}=15.6 Hz, 1H), 3.88 (m, 1H), 3.76 (s, 3H), 3.72 (s, 3H), 3.65 (m, 1H), 3.28 (t, J=6.8 Hz, 2H), 2.57 (td, J=6.8, 2.0 Hz, 2H), 1.95 (t, J=2.0 Hz, 1H), 1.60 (m, 1H), 1.45 (m, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 172.2, 167.6, 166.6, 164.2, 148.3, 142.1, 137.8, 131.6, 129.9, 128.6 (2C), 128.0 (2C), 127.7, 121.9, 119.4, 116.3, 111.6, 83.1, 68.6, 67.1, 53.53, 53.48, 52.5, 52.2, 43.3, 37.1, 34.4, 13.7; HRMS (EI, 70 eV) m/z 497.1985 ($[M]^+$ calcd for $C_{29}H_{27}N_3O_5$, 497.1951).

Cycloaddition of 8d; cycloadduct 13. A solution of **8d** (0.05 g, 0.10 mmol) in TIPB (2 mL) was refluxed for 12 h. The reaction mixture was transferred directly to a silica gel column and purified by flash chromatography (5% EtOAc/CH_2Cl_2) to afford **13** as a colorless oil (16 mg, 0.03 mmol, 31%). IR (NaCl) 1744, 1724, 1693 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.79 (d, J=8.8 Hz, 1H), 7.29–7.07 (m, 7H), 6.99 (s, 1H), 5.24 (s, 2H), 4.40 (m, 2H), 4.00 (s, 3H), 3.90 (s, 3H), 3.08 (m, 2H), 2.86 (t, J=7.3 Hz, 2H), 2.68 (t, J=7.3 Hz, 2H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 170.0, 167.0, 164.9, 154.1, 150.0, 137.7, 137.0, 136.6, 128.7 (2C), 128.4, 127.5, 126.8 (2C), 126.4, 121.7, 121.5, 119.5, 119.0, 118.4, 112.2, 109.5, 53.0, 52.7, 49.9, 42.0, 30.8, 23.51, 23.45; HRMS (EI, 70 eV) m/z 497.1973 ($[M]^+$ calcd for $C_{29}H_{27}N_3O_5$, 497.1951).

Deacetylation and reacylation of 9b; cycloadduct 9e. A solution of **9b** (0.50 g, 1.36 mmol) in MeOH (3 mL) was stirred with K_2CO_3 (0.38 g, 2.72 mmol) for 4 h. The mixture was filtered, and the filtrate partitioned between EtOAc (10 mL) and H_2O (5 mL). The organic phase was separated, dried over Na_2SO_4, then the solvent removed in vacuo to afford *N*-benzylindolino[2,3-*d*]pyrrolidino[2,3-*e*]-3-cyano-4,5-dihydropyridine as a yellow solid (0.43 g, 1.33 mmol, 98% yield, 99% pure by ^1H NMR), which was used in the next step without further purification. Mp >250°C (dec); IR (neat) 2223 cm^{-1}; ^1H NMR (270 MHz, CD_3OD) δ 7.32–7.25 (m, 5H), 7.13 (dd, J=7.3, 7.3 Hz, 1H), 6.79–6.75 (m, 2H), 6.68 (dd, J=7.3, 7.3 1H), 4.81 (d, J_{AB}=15.1 Hz, 1H), 4.67 (s, 1H), 4.55 (d, J_{AB}=15.1 Hz, 1H), 3.58 (m, 2H), 2.08 (m, 1H), 1.61 (bdd, J=12.5, 4.6 Hz, 1H); ^{13}C NMR (67.5 MHz, CD_3OD) δ 158.8, 147.6, 137.7, 131.1, 129.4, 128.5 (2C), 127.9 (2C), 127.8, 127.5, 122.1, 119.3, 117.2, 110.8, 66.2, 54.3, 51.5, 51.1, 40.0; HRMS (CI, 140 eV, NH_3) m/z 327.1515 ($[M+1]^+$ calcd for $C_{20}H_{17}N_5$, 327.1484).

To a solution of (0.05 g, 0.12 mmol) *N*-benzylindolino-[2,3-*d*]pyrrolidino[2,3-*e*]-3-cyano-4,5-dihydropyridine (0.1 g, 0.30 mmol) and 4-pentynoic acid (0.03g, 0.30 mmol) in CH_2Cl_2 (2 mL) was added DCC (0.07g, 0.33 mmol) and DMAP (15 mg, 0.13 mmol), and the mixture was stirred at rt for 3 h. The reaction mixture then was cooled to 0°C to precipitate the *N*,*N*′-dicyclohexylurea, and the mixture

filtered through a pad of Celite. The solvent was removed from the filtrate in vacuo and the residue purified by flash chromatography (3% EtOAc/CH_2Cl_2) to afford **9e** as a yellow solid (0.12 g, 0.29 mmol, 99%). Mp 76–78°C; IR (NaCl) 2230, 2120, 1693 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.33–7.21 (m, 5H), 6.83–6.75 (m, 4H), 4.87 (d, J_{AB}=15.1 Hz, 1H), 4.65 (d, J_{AB}=15.1 Hz, 1H), 4.21 (s, 1H), 4.03 (ddd, J=9.8, 7.8, 2.0 Hz, 1H), 3.71 (m, 1H), 3.36 (t, J=7.3 Hz, 1H), 2.59 (td, J=7.3, 2.9 Hz, 1H), 1.96 (t, J=2.9 Hz, 2H), 1.83 (m, 2H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 171.9, 157.1, 147.3, 139.7, 136.3, 130.7, 129.0 (2C), 128.9 128.3, 128.1 (2C), 122.2, 120.2, 115.7, 110.8, 82.7, 69.0, 64.0, 51.7, 49.5, 43.3, 37.6, 35.2, 13.8; HRMS (EI, 70 eV) m/z 407.1747 ($[M]^+$ calcd for $C_{25}H_{21}N_5O$, 407.1746).

Cycloaddition of 5l; cycloadduct 16a. A solution of **5l** (0.50 g, 1.10 mmol) in CH_2Cl_2 (5 mL) was refluxed for 1 h. The solvent was removed in vacuo and the residue purified by flash chromatography (3% EtOAc/CH_2Cl_2) to afford **16a** as a white solid (0.47 g, 1.10 mmol, 99%). Mp 179–180°C; IR (NaCl) 1682 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.74 (dd, J=6.9, 1.0 Hz, 1H), 7.30–7.05 (m, 8H), 7.01 (s, 1H), 7.00 (s, 1H), 5.22 (s, 2H), 4.54 (t, J=7.8 Hz, 2H), 3.17 (t, J=7.8 Hz, 2H), 2.67 (s, 3H), 2.63 (m, 2H), 2.59 (m, 2H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 169.1, 157.5, 152.9, 137.7, 136.4, 128.7 (2C), 128.4, 127.5, 126.9, 126.8 (2C), 126.3, 124.5, 121.6, 119.4, 119.0, 112.1, 109.4, 49.8, 41.7, 30.2, 23.4, 23.1, 13.4; HRMS (EI, 70 eV) m/z 428.1628 ($[M]^+$ calcd for $C_{25}H_{24}N_4OS$, 428.1671).

Oxidation of 16a; sulfoxide 16b. To a solution of **16a** (0.25 g, 0.58 mmol) in CH_2Cl_2 (2 mL) cooled to −78°C was added with stirring *m*-CPBA (0.20 g, 0.58 mmol). After 3 h the reaction was quenched by the addition of Na_2SO_3 (0.10 g) and the solid residue filtered after allowing to warm to rt. The filtrate was evaporated in vacuo and the residue purified by flash chromatography to afford **16b** as a white solid (0.24 g, 0.54 mmol, 92%). Mp 193–194°C; IR (NaCl) 1700, 1056 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.70 (d, J=7.3 Hz, 1H), 7.30–7.06 (m, 8H), 6.99 (s, 1H), 5.21 (s, 2H), 4.58 (t, J=7.3 Hz, 2H), 3.16 (t, J=7.3 Hz, 2H), 2.96 (s, 3H), 2.87 (t, J=8.3 Hz, 2H), 2.66 (t, J=8.3 Hz, 2H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 169.0, 164.6, 155.8, 137.5, 136.4, 128.96, 128.7 (2C), 128.2, 127.5, 126.8 (2C), 126.3, 121.7, 121.4, 119.2, 119.0, 111.8, 109.5, 49.8, 42.3, 41.9, 29.8, 23.6, 23.1; HRMS (EI, 70 eV) m/z 443.9765 ($[M]^+$ calcd for $C_{25}H_{24}N_4O_2S$, 443.9949).

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