Facile Synthesis of [1,2,3]-Triazole-Fused Isoindolines, Tetrahydroisoquinolines, Benzoazepines and Benzoazocines by Palladium-Copper Catalysed Heterocyclisation

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Abstract: An elegant method for the synthesis of 1,2,3-triazoles fused with five-, six-, seven- and eight-membered benzoheterocycles, including isoindoline, tetrahydroisoquinoline, benzoazepine and benzoazocine, has been developed via palladium-copper catalysed reactions in one-pot. The broad scope of this reaction was illustrated by effecting bis-heteroannulations, synthesis of uracil derivatives of biological interest, and employment of acetylene gas as an inexpensive substrate. The reactions are experimentally simple and utilise easily accessible substrates of different types.

Key words: 1,2,3-triazoles, nitrogen heterocycles, intramolecular reactions, azide-alkyne cycloaddition, bis-heteroannulations

In recent years, novel nitrogen-containing heterocycles have found widespread applications in drug development. Notable among them are 1,2,3-triazoles, which have attracted enormous interest due to their wide range of biological activities such as antiviral,[1a] antifungal,[1b] antiparasitic,[1c] antimicrobial,[1d] immunostimulant[1e] and others.[1f] Additionally, these heterocycles have remarkable metabolic stability and have proven to be important as amide surrogates in various bioactive agents.[2] Historically, the first straightforward synthesis of 1,4- and 1,5-substituted 1,2,3-triazoles as a regioisomeric mixture was achieved by Huisgen[3] during the 1960s. Later, regioselective synthesis of 1,4-substituted 1,2,3-triazoles was established[4] through copper-catalysed azide–alkyne cycloaddition (CuAAC) under mild reaction conditions. In the recent past, synthesis of 1,5-substituted 1,2,3-triazoles, the other regioisomer, was achieved by Fokin, who employed a catalytic amount of tetramethylammonium hydroxide[5a] or [Cp*RuCl(PPh_3)$_2$].[5b,c] These catalysed cycloadditions, popularly known as 'click reactions', have found widespread applications in areas ranging from medicinal chemistry[6a,b,1f] to materials science.[6c–f] Mostly terminal alkynes have been used in these reactions, resulting in 1,4- or 1,5-substituted 1,2,3-triazoles. But an elegant synthesis of fully 1,4,5-substituted 1,2,3-triazoles in one pot[7] employing azide and internal alkyne as substrates is more challenging and remains to be developed. The employment of unsymmetrical internal alkynes in these reactions often results in diminished reaction rates and poor regioselectivity. However, intramolecular azide–alkyne cycloaddition[8] (IAAC), in which regioselectivity is usually determined by the initial positions of the azide and alkyne groups present in the starting compounds, has emerged as a possible solution to this problem.

On the other hand, benzo-fused aza-heterocycles (e.g., isoindoline,[9] tetrahydroisoquinoline,[10] benzoazepine,[11] benzoazocine[12]) are considered as important scaffolds because of their presence as key structural units in various drugs, bioactive compounds, and natural products. Notably, benzo-heterocycles fused with 1,2,3-triazoles have been shown[13] to mimic benzolactams that are difficult to access, but which are known for effectively mimicking teleocidines.[14] Therefore, fusion of the aforesaid heterocycles with 1,2,3-triazole, resulting in the formation of compounds **1**–**4** (Figure 1), could perhaps lead to potent pharmacophores and/or important building blocks in pharmaceutical research. Indeed, triazoles fused with other heterocycles have already proven to be important in drug discovery programs due to their broad spectrum of activities such as anxiolytic[15a] (e.g., alprazolam and estazolam drugs), antidepressant (e.g., triazolam drug),[15b] anti-allergic,[15c] glycosidase inhibitor,[15d] and 5-$HT_{1A/B/D}$ receptor antagonist.[15e] In addition, compounds **5**[16a] and **6**[16b] are being considered as potent chemotherapeutic agents (Figure 1). In view of the immense biological importance of this class of compounds, interest in this area has been growing in recent times.

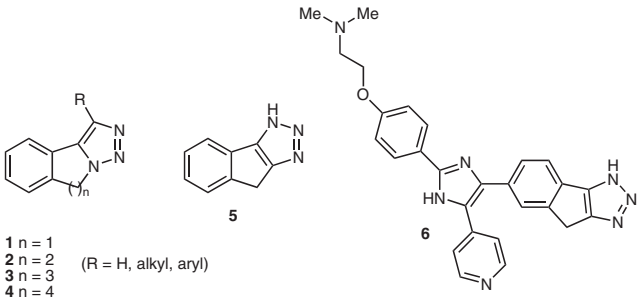

Figure 1 Important fused 1,2,3-triazoles

Literature reports indicate that fully 1,4,5-substituted 1,2,3-triazoles including fused derivatives can be synthesised primarily by two strategic approaches. One involves intermolecular regioselective dipolar cycloaddition between azide and terminal alkyne followed by metal-catalysed arylation of the resulting 1,2,3-triazole.[17] The

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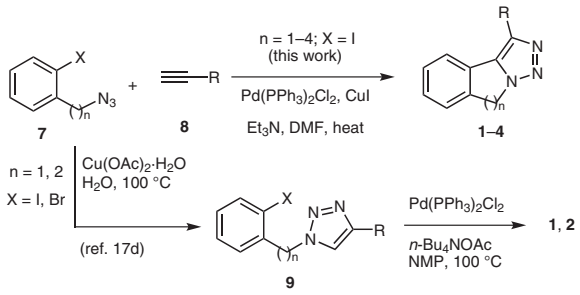
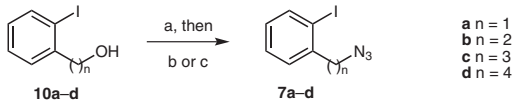
alternative approach[18] involves thermal or metal-catalysed regioselective IAAC of the azido-alkyne substrates in which the acetylenic group is disubstituted. In a continuation of our work on palladium-catalysed reactions, we followed the latter approach in which substrates having azide functionality tethered to acetylene underwent metal-catalysed C-arylation at the terminal acetylene and subsequent intramolecular cycloaddition affording 1,2,3-triazoles fused with morpholine,[19a] 1,4-benzoxazine,[19b] 1,4-benzodiazepin-5-one,[19c] 1,4-benzodiazocin-6-one,[19c] and piperazine.[19d] We speculated that replacement of these substrates by *ortho*-iodo-azides **7a–d** and subsequent reaction with terminal acetylenes **8** in the presence of a palladium catalyst could allow access to 1,2,3-triazole-fused five-, six-, seven- and eight-membered benzo-heterocycles **1–4** in one pot. In this paper, we describe in detail the results achieved (Scheme 1).[20] This straightforward synthesis of tricyclic nitrogen-containing heterocycles constitutes an important alternative strategy to the reported two-step route,[17d] as shown in Scheme 1.



Scheme 1 Synthesis of 1,2,3-triazole-fused heterocycles **1–4**

The starting *ortho*-iodo-azides **7a–d** (X = I, n = 1–4) required for this study were synthesised from their corresponding precursor alcohols **10a–d**. For this, the latter, which were prepared in a few steps using reported procedures,[21] were subjected to mesylation followed by azidation as shown in Scheme 2.

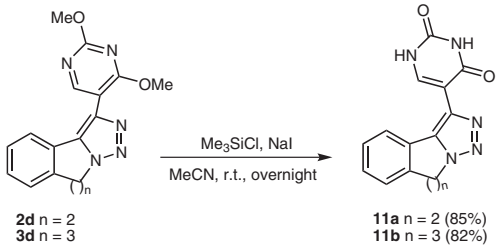


Scheme 2 Synthesis of starting substrates **7a–d**. *Reagents and conditions*: (a) MsCl, Et_3N, CH_2Cl_2, 0–5 °C, 2 h; (b) NaN_3, DMF, r.t., 2 h, 94% (for **7a**); (c) NaN_3, DMF, 90 °C, 1 h, 90–92% (for **7b–d**).

With substrates **7a–d** in hand, we investigated the influence of catalyst, solvent, base and temperature on the formation of the target products. These studies revealed that bis(triphenylphosphine)palladium(II) chloride and copper(I) iodide constitute the best catalytic system, whereas DMF and Et_3N prove to be the optimal solvent and base, respectively. We also observed that carrying out the reactions by immediate heating (115 °C for **7a–c**, 150 °C for **7d**) instead of initial stirring at r.t. (for 12 h) followed by heating (at 115 °C for a few hours) as reported earlier[20] provided comparable yields of the products. Therefore, we modified the previous reaction conditions and elaborated the scope of this present reaction procedure by using substrates **7a–d** as shown in Table 1. For substrates **7a–b**, the reactions were found to be complete within a few hours (0.5–6 h) upon heating at 115 °C, but the reactions with substrate **7c** to afford the seven-membered ring-fused product **3** required 7–17 hours heating (Table 1, entries 11–15). More significantly, the reaction did not proceed at all when compound **7d** was employed as a reactant. Therefore, we were forced to increase the reaction temperature to 150 °C (for 13–19 h) to achieve formation of the desired eight-membered-ring analogues **4** (Table 1, entries 16–18), albeit with moderate yields. Both aryl and alkyl acetylenes having different functional groups successfully participated in the reactions. Typically, aryl acetylenes having electron-withdrawing groups (EWGs) provided better yields than those with electron-donating groups (EDGs) as seen from Table 1 (entry 2 vs. 3, entry 7 vs. 6, entry 13 vs. 12, and entry 17 vs. 18). A sugar moiety with acetylene pendant was found to be compatible in this reaction, affording the products **2e** and **3e**, respectively (Table 1, entries 9 and 15). However, use of tosylated acetylene **8h** led to the isolation of the unexpected product **2f** (Table 1, entry 10), which is possibly formed through elimination of *p*-TsOH from the initially formed tosylated product under the reaction conditions.

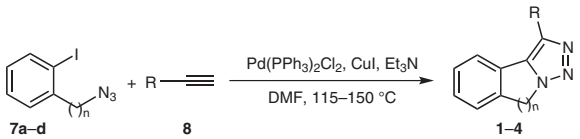
In view of the immense importance of 5-substituted uracils,[22] and in continuation of our work on the synthesis of biologically active compounds,[23] we became interested in the demethylation of 2,4-dimethoxypyrimidine derivatives **2d** and **3d** (Table 1, entries 8 and 14). Accordingly, when compounds **2d** and **3d** were successively treated with chlorotrimethylsilane and sodium iodide in anhydrous acetonitrile at room temperature overnight, the expected uracil derivatives **11a**,**b**[24] were produced smoothly in excellent yields (Scheme 3).

We then studied the applicability of the regioselective IAAC reaction for bis-heteroannulations, employing 1,3-diethynyl benzene **12** as reactant (Table 2). To our satisfaction, bis-heteroannulated products (**13a–d**) were formed readily when *o*-iodo-azides **7a–d** were employed as coupling partners (Table 2, entries 1–4). Thus, this method is amenable to the synthesis of polyheteroannulated frameworks in one pot and under operationally simple palladium-catalysed reaction conditions.



Scheme 3 Synthesis of uracil derivatives **11a** and **11b**

Table 1 Synthesis of Fused 1,2,3-Triazoles **1**–**4**[a]



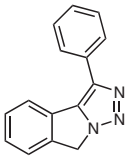
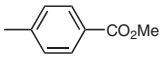
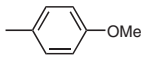
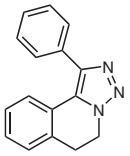
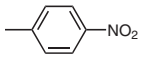
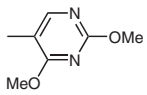
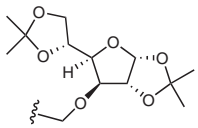
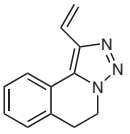
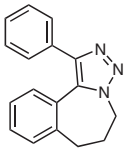
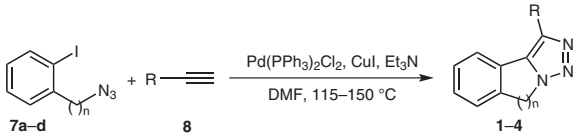
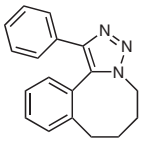
Entry	Azide **7**	n	Alkyne **8**	R	Temp (°C)	Time (h)	Product	Yield (%)[b]
1	**7a**	1	**8a**		115	2.0	 **1a**	70
2	**7a**	1	**8b**		115	0.5	**1b**	72
3	**7a**	1	**8c**		115	2.5	**1c**	65
4	**7a**	1	**8d**	*n*-Bu	115	5.5	**1d**	62
5	**7b**	2	**8a**		115	2.5	 **2a**	76
6	**7b**	2	**8c**		115	2.0	**2b**	47
7	**7b**	2	**8e**		115	0.5	**2c**	79
8	**7b**	2	**8f**		115	0.75	**2d**	68
9	**7b**	2	**8g**		115	1.0	**2e**	54
10[c]	**7b**	2	**8h**	CH_2CH_2OTs	115	2.5	 **2f**	40
11[d]	**7c**	3	**8a**		115	12.0	 **3a**	55
12[d]	**7c**	3	**8c**		115	17.0	**3b**	40
13	**7c**	3	**8e**		115	7.0	**3c**	50
14[d]	**7c**	3	**8f**		115	15.0	**3d**	32
15[d]	**7c**	3	**8g**		115	12.0	**3e**	38

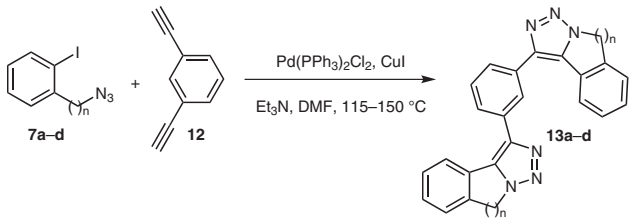
Table 1 Synthesis of Fused 1,2,3-Triazoles **1**–**4**[a] (continued)



Entry	Azide **7**	n	Alkyne **8**	R	Temp (°C)	Time (h)	Product	Yield (%)[b]
16[d]	**7d**	4	**8a**		150	13.0	 **4a**	40
17[d]	**7d**	4	**8b**		150	13.0	**4b**	43
18[d]	**7d**	4	**8c**		150	19.0	**4c**	38

[a] Reaction conditions: azide **7** (1.0 mmol), alkyne **8** (1.25 mmol), $[Pd(PPh_3)_2Cl_2]$ (0.035 mmol), CuI (0.07 mmol), Et_3N (5.0 mmol), anhydrous DMF (5 mL), 115–150 °C, 0.5–19 h.
[b] Yield of chromatographically isolated pure products based on azide **7**.
[c] Elimination of *p*-TsOH from the tosylated product under the reaction conditions leading to the formation of **2f**.
[d] In addition to the expected product **3**/**4**, the corresponding acyclic intermediate (internal alkyne), formed through coupling between terminal alkyne and *o*-iodo-azide **7c**/**7d** through the Sonogashira pathway, was also isolated (12–18%).

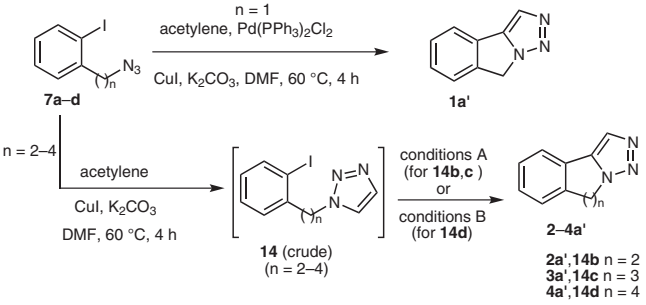
Table 2 Synthesis of Bis-heteroannulated Products **13a**–**d**[a]



Entry	Azide **7**	n	Temp (°C)	Time (h)	Yield (%)[b]
1	**7a**	1	115	2	**13a** (54)
2	**7b**	2	115	2	**13b** (50)
3	**7c**	3	130	12	**13c** (47)
4	**7d**	4	130	15	**13d** (27)

[a] Reaction conditions: azide **7** (1.0 mmol), alkyne **12** (0.6 mmol), $[Pd(PPh_3)_2Cl_2]$ (0.035 mmol), CuI (0.07 mmol), Et_3N (5.0 mmol), anhydrous DMF (6 mL), 115–150 °C, 2–15 h.
[b] Yield of chromatographically isolated pure product based on azide **7**.

We also tested the feasibility of using acetylene gas as an inexpensive substrate in place of substituted acetylenes **8** to gain access to fused triazoles **1**–**4** (R = H, see Figure 1) in which 1,2,3-triazoles are 1,5-disubstituted rather than fully substituted. Toward this objective, we first employed *o*-iodo-azide **7a** as a synthon and heated the reaction at 60 °C (4 h) under balloon pressure of acetylene in the presence of $[Pd(PPh_3)_2Cl_2]$ (1.5 mol%), CuI (3 mol%) and K_2CO_3 (2 equiv) in anhydrous DMF. Pleasingly, the desired product **1a′** was formed with 60% yield along with the acyclic 1,2,3-triazole derivative **14a** (where n = 1) with 24% yield (Scheme 4). With substrate **7b**, on the other hand, heating the reaction at 60 °C (4 h) under these conditions did not furnish any desired product **2a′**; instead, triazole **14b** (where n = 2) was isolated with 70% yield. However, carrying out this reaction at higher temperature (110 °C) succeeded in delivering the desired product **2a′**, albeit in only 23% yield. We then changed this one-pot strategy and used two-step reactions as shown in Scheme 4 (results in Table 3). Accordingly, cycloaddition of acetylene (gas) with the azido group of substrates **7b**–**d** was first carried out at 60 °C in the presence of CuI (3 mol%) and K_2CO_3 (2 equiv), affording the intermediate 1,2,3-triazoles **14b**–**d**. These crude intermediates were then directly submitted to palladium-catalysed cyclocondensation reaction, furnishing the target products **2a′**–**4a′** with moderate to good yields (Table 3, entries 2–4).



Scheme 4 Synthesis of fused 1,2,3-triazoles **1a′**, **2a′**, **3a′** and **4a′** by employing acetylene (gas). Conditions A: $[Pd(PPh_3)_2Cl_2]$, K_2CO_3, TBAB, DMF, 110–130 °C; Conditions B: $Pd(OAc)_2$, $NaHCO_3$, TBAB, DMF, 130 °C.

The structures of products **1**–**4** were determined on the basis of their spectral (^1H and ^{13}C NMR, IR and mass) and analytical data. In the ^1H NMR spectra, signals for the N-CH_2 protons appeared at δ = 5.39 ppm as a singlet for **1a**.

Table 3 Synthesis of Fused 1,2,3-Triazoles **1a′–4a′**

Entry	Substrate	Reaction temp. of the crude intermediate **14b–d** (heating time)	Yield **1–4a′** (%)[e]
1	**7a**[a]	–	**1a′** (60)
2	**7b**[b]	110 °C (4 h for **14b**)[c]	**2a′** (82)
3	**7c**[b]	130 °C (4 h for **14c**)[c]	**3a′** (52)
4	**7d**[b]	130 °C (2.5 h for **14d**)[d]	**4a′** (42)

[a] Azide **7a** was directly converted into product **1a′** as depicted in Scheme 4.
[b] Reaction conditions: azide **7b–d** (1.0 mmol), CuI (0.03 mmol), K_2CO_3 (2.0 mmol), anhydrous DMF (5 mL), 60 °C, 4 h under balloon pressure of acetylene; the resulting crude product **14b–d** obtained through standard work-up was then used for next step of the reaction.
[c] Heating was carried out under reaction conditions A (as described in Scheme 4).
[d] Heating was carried out under reaction conditions B (as described in Scheme 4).
[e] Chromatographically isolated, pure product.

As expected, these signals shifted upfield in the products with larger rings [XX′ part of AA′XX′ and AA′BB′XX′ systems at δ = 4.61 and 4.36 ppm, respectively, for **2a** and **3a**, and double doublets at δ = 4.81 (*J* = 14.1, 6.3 Hz) and 3.61 ppm (*J* = 14.1, 11.7 Hz) for **4a**] as the protons are no longer benzylic. The signals of the benzylic protons of **2a** and **3a** also appeared as components of subspectra of type AA′XX′ and AA′BB′XX′ at δ = 3.27 and 2.76 ppm, respectively, whereas in **4a**, one of the signals appeared as a double doublet at δ = 2.95 ppm (dd, *J* = 13.8, 8.4 Hz) and the second at around δ = 2.15 ppm, overlapped by peaks for other protons. Additionally, unambiguous structural confirmation also came from X-ray diffraction analysis of the representative eight-membered-ring product **4a** (Figure 2).

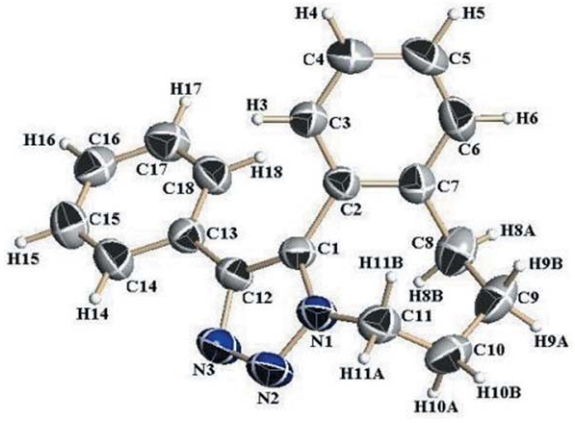


Figure 2 ORTEP representation of **4a**

In conclusion, we have described a straightforward palladium-copper catalysed method for the synthesis of 1,2,3-triazoles fused with five-, six-, seven- and eight-membered benzoheterocycles, featuring isoindoline, tetrahydroisoquinoline, benzoazepine and benzo-azocine, respectively.[25] A variety of *o*-iodo-azides and acetylenic substrates were found to react under the reaction conditions, affording a diverse array of products with moderate to good yields. The reaction protocol was successfully utilised for the formation of one C–C and two C–N bonds in a one-pot reaction. The broad scope of this reaction was illustrated by effecting bis-heteroannulations, synthesis of uracil derivatives of biological interest, and employment of acetylene gas as an inexpensive substrate. We believe that the reaction protocol can be used in library generation based on diversity oriented synthesis for lead development and, thus, would be of interest to the practitioners of organic and medicinal chemistry.

Melting points were determined in open capillaries and are uncorrected. IR spectra were obtained with a JASCO FT/IR-4200 infrared spectrometer either neat or as KBr plates. ^{1}H and ^{13}C NMR spectra were recorded with Bruker-300, 500 or 600 MHz NMR spectrometers and chemical shifts are reported relative to tetramethylsilane (TMS) as internal reference. Mass spectra were recorded in ESI-TOF, EI or FAB ionization mode. HRMS were recorded with a Q-Tof Micro or JEOL JMS-700 mass spectrometer. Crystallographic data were obtained with a Bruker Kappa Apex 2 instrument. Column chromatography was performed using silica gel (60–120 or 100–200 mesh) [Merck, India]. Thin-layer chromatography (TLC) was performed on silica gel 60 F_{254} aluminum sheets [Merck, Germany] and visualization of the developed chromatogram was achieved by UV absorbance. Petroleum ether (PE) refers to the fraction boiling in the range 60–80 °C.

Preparations of starting materials **7a–d** and their spectral data are provided in the Supporting Information.

[1,2,3]-Triazole-Fused Products 1–4; General Procedure

The reagents $[Pd(PPh_3)_2Cl_2]$ (24.6 mg, 0.035 mmol), CuI (13.3 mg, 0.07 mmol) and Et_3N (0.71 mL, 5.0 mmol) were sequentially added to a solution of *o*-iodo-azide **7a–c** (1.0 mmol) in anhydrous DMF (8 mL) and the mixture was stirred at r.t. under an argon atmosphere for 20 min. Acetylenic compound **8** (1.25 mmol) dissolved in anhydrous DMF (1 mL) was added dropwise under argon. The reaction mixture was then heated at 115 °C for the requisite time (0.5–17 h, see Table 1). After completion of the reaction (TLC), the solvent was removed in vacuo; the residue was mixed with H_2O (30 mL) and extracted with EtOAc (2 × 25 mL). The combined organic extracts were dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified through silica gel (100–200 mesh) column chromatography (EtOAc–PE, 15–20% v/v) to afford the corresponding product **1–3**.

The same procedure was adopted for the synthesis of products **4** (employing *o*-iodo-azide **7d** and acetylenic compound **8**, see Table 1), the only difference being that the reaction mixture was heated at 150 °C instead of 115 °C and for 13–19 h.

3-Phenyl-8*H*-[1,2,3]triazolo[5,1-*a*]isoindole (1a)

Yield: 0.163 g (70%); light-brown solid; mp 152–154 °C (lit.[17d] 153–155 °C).

IR (KBr): 3056, 2963, 1607, 1444, 1362, 1172, 982, 762, 699 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.39 (s, 2 H), 7.39–7.56 (m, 6 H), 7.90–7.97 (m, 3 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 50.9, 121.2, 124.1, 126.9, 128.0, 128.1, 128.3, 128.7, 128.9, 131.2, 138.9, 139.2, 141.1.

MS (ESI): *m*/*z* = 234.04 $[M + H]^+$.

HRMS (EI, 70 eV): *m*/*z* $[M]^+$ calcd for $C_{15}H_{11}N_3$: 233.0953; found: 233.0960.

Methyl 4-(8*H*-[1,2,3]Triazolo[5,1-*a*]isoindol-3-yl)benzoate (1b)
Yield: 0.210 g (72%); white solid; mp 196–198 °C.

IR (KBr): 2951, 1710, 1609, 1437, 1283, 1110, 766, 703 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 3.97 (s, 3 H), 5.42 (s, 2 H), 7.44–7.59 (m, 3 H), 7.93 (br d, *J* = 7.5 Hz, 1 H), 8.04 (d, *J* = 8.1 Hz, 2 H), 8.21 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 51.0, 52.2, 121.4, 124.3, 126.7, 127.7, 128.8, 128.9, 129.5, 130.2, 135.7, 138.3, 139.8, 141.3, 166.7.

MS (ESI): *m*/*z* = 314.14 $[M + Na]^+$.

HRMS (EI, 70 eV): *m*/*z* $[M]^+$ calcd for $C_{17}H_{13}N_3O_2$: 291.1008; found: 291.0999.

3-(4-Methoxyphenyl)-8*H*-[1,2,3]triazolo[5,1-*a*]isoindole (1c)
Yield: 0.171 g (65%); white solid; mp 146–148 °C (lit.[17d] 154–156 °C).

IR (KBr): 3069, 2838, 1614, 1576, 1507, 1451, 1419, 1358, 1301, 1250, 1174, 1029, 982, 828, 773 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 3.89 (s, 3 H), 5.38 (s, 2 H), 7.07 (d, *J* = 8.4 Hz, 2 H), 7.39–7.56 (m, 3 H), 7.88 (app d, *J* = 8.1 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 50.9, 55.3, 114.3, 120.9, 123.8, 124.1, 128.1, 128.2, 128.7, 138.3, 139.1, 140.9, 159.5.

MS (ESI): *m*/*z* = 264.05 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{13}N_3NaO$: 286.0956; found: 286.0950.

3-Butyl-8*H*-[1,2,3]triazolo[5,1-*a*]isoindole (1d)
Yield: 0.132 g (62%); colourless solid; mp 76–78 °C.

IR (KBr): 3067, 2926, 2860, 1448, 1302, 1163, 1006, 767, 724 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 0.97 (t, *J* = 7.2 Hz, 3 H), 1.38–1.51 (m, 2 H), 1.75–1.85 (m, 2 H, overlapped by H_2O signal), 2.95 (t, *J* = 7.5 Hz, 2 H), 5.30 (s, 2 H), 7.34–7.40 (m, 1 H), 7.44–7.51 (m, 2 H), 7.61 (d, *J* = 7.5 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 13.7, 22.2, 25.5, 31.5, 50.8, 120.7, 124.0, 127.6, 128.4, 128.6, 139.1, 139.3, 140.5.

MS (ESI): *m*/*z* = 236.05 $[M + Na]^+$.

1-Phenyl-5,6-dihydro[1,2,3]triazolo[5,1-*a*]isoquinoline (2a)
Yield: 0.188 g (76%); yellow solid; mp 150–151 °C (lit.[17d] 154–156 °C).

IR (KBr): 3049, 1496, 1440, 1360, 1195, 1153, 994, 759, 698 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 3.27, 4.61 (2 H each, comprising AA′XX′ system), 7.19 (td, *J* = 1.1, 7.4 Hz, 1 H), 7.26–7.36 (m, 2 H), 7.39–7.50 (m, 3 H), 7.60 (d, *J* = 7.5 Hz, 1 H), 7.71–7.75 (m, 2 H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 29.3, 45.0, 124.5, 125.1, 127.5, 128.42, 128.48, 128.5, 128.7, 129.1, 129.3, 131.7, 132.8, 143.0.

MS (ESI): *m*/*z* = 248.24 $[M + H]^+$.

HRMS (EI, 70 eV): *m*/*z* $[M]^+$ calcd for $C_{16}H_{13}N_3$: 247.1109; found: 247.1108.

1-(4-Methoxyphenyl)-5,6-dihydro[1,2,3]triazolo[5,1-*a*]isoquinoline (2b)
Yield: 0.130 g (47%); brown gum.

IR (neat): 2934, 2839, 1614, 1513, 1465, 1364, 1297, 1250, 1180, 1031, 838 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 3.26, 4.59 (2 H each, comprising AA′XX′ system), 3.88 (s, 3 H), 7.00 (d, *J* = 8.7 Hz, 2 H), 7.18–7.23 (m, 1 H), 7.29–7.35 (m, 2 H), 7.59–7.66 (m, 3 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 29.1, 44.9, 55.2, 113.9, 123.9, 124.1, 125.0, 127.3, 128.3, 128.7, 128.8, 129.6, 132.6, 142.7, 159.6.

MS (ESI): *m*/*z* = 300.20 $[M + Na]^+$.

HRMS (EI, 70 eV): *m*/*z* $[M]^+$ calcd for $C_{17}H_{15}N_3O$: 277.1215; found: 277.1212.

1-(4-Nitrophenyl)-5,6-dihydro[1,2,3]triazolo[5,1-*a*]isoquinoline (2c)
Yield: 0.231 g (79%); yellow solid; mp 192–193 °C.

IR (KBr): 3064, 2949, 1601, 1508, 1340, 1184, 1104, 858, 768, 689 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 3.30, 4.63 (2 H each, comprising AA′XX′ system), 7.24–7.29 (m, 1 H), 7.34–7.42 (m, 2 H), 7.56 (d, *J* = 7.8 Hz, 1 H), 7.97 (d, *J* = 8.7 Hz, 2 H), 8.34 (d, *J* = 8.7 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 29.2, 44.9, 124.0, 124.3, 124.4, 127.7, 128.8, 128.9, 129.9, 130.4, 133.2, 138.3, 140.6, 147.5.

MS (ESI): *m*/*z* = 315.02 $[M + Na]^+$.

HRMS (EI, 70 eV): *m*/*z* $[M]^+$ calcd for $C_{16}H_{12}N_4O_2$: 292.0960; found: 292.0962.

1-(2,4-Dimethoxypyrimidin-5-yl)-5,6-dihydro[1,2,3]triazolo[5,1-*a*]isoquinoline (2d)
Yield: 0.210 g (68%); white solid; mp 134–136 °C.

IR (KBr): 2953, 1619, 1563, 1490, 1468, 1399, 1358, 1282, 1191, 1078, 1013, 739 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 3.30, 4.65 (2 H each, comprising AA′XX′ system), 3.89 (s, 3 H), 4.09 (s, 3 H), 7.14–7.24 (m, 2 H), 7.27–7.35 (m, 2 H), 8.49 (s, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 28.9, 44.9, 53.9, 54.9, 107.1, 124.5, 124.6, 127.3, 128.2, 129.1, 131.1, 132.3, 134.8, 159.4, 165.5, 168.4.

MS (ESI): *m*/*z* = 332.06 $[M + Na]^+$.

HRMS (EI, 70 eV): *m*/*z* $[M]^+$ calcd for $C_{16}H_{15}N_5O_2$: 309.1226; found: 309.1222.

1-({(3a*R*,5*R*,6*S*,6a*R*)-5-[(*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-2,2-dimethyltetrahydrofuro[3,2-*d*][1,3]dioxol-6-yloxy}methyl)-5,6-dihydro[1,2,3]triazolo[5,1-*a*]isoquinoline (2e)
Yield: 0.240 g (54%); brown gum.

IR (neat): 2986, 2935, 2099, 1639, 1377, 1215, 1162, 1074, 1022, 849, 758 cm^{-1}.

^1H NMR ($CDCl_3$, 600 MHz): δ = 1.23 (s, 3 H), 1.32 (s, 3 H), 1.39 (s, 3 H), 1.50 (s, 3 H), 3.22–3.25 (m, 2 H), 3.97–4.03 (m, 2 H), 4.11–4.13 (m, 1 H), 4.17 (d, *J* = 3.0 Hz, 1 H), 4.29–4.31 (m, 1 H), 4.54–4.58 (m, 1 H), 4.61–4.66 (m, 1 H), 4.71 (d, *J* = 4.2 Hz, 1 H), 4.91 (d, *J* = 12 Hz, 1 H), 5.01 (d, *J* = 12 Hz, 1 H), 5.88 (d, *J* = 3.6 Hz, 1 H), 7.33–7.39 (m, 3 H), 7.84–7.86 (m, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 25.0, 26.0, 26.6, 26.7, 28.8, 44.6, 63.3, 67.1, 72.1, 80.9, 81.0, 82.1, 105.1, 108.8, 111.6, 124.3, 125.6, 127.7, 128.2, 129.2, 132.1, 132.3, 138.6.

MS (ESI): *m*/*z* = 465.97 $[M + Na]^+$.

HRMS (EI, 70 eV): *m*/*z* $[M]^+$ calcd for $C_{23}H_{29}N_3O_6$: 443.2056; found: 443.2049.

1-Vinyl-5,6-dihydro[1,2,3]triazolo[5,1-*a*]isoquinoline (2f)
Yield: 0.079 g (40%); yellow solid; mp 110–112 °C.

IR (KBr): 3062, 2930, 2836, 1450, 1300, 1158, 1002, 753 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 3.20, 4.56 (2 H each, comprising AA′XX′ system), 5.49 (dd, *J* = 1.5, 11.1 Hz, 1 H), 6.31 (dd, *J* = 1.8, 17.4 Hz, 1 H), 6.98 (dd, *J* = 11.1, 17.4 Hz, 1 H), 7.33–7.41 (m, 3 H), 7.71 (d, *J* = 6.9 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 29.2, 44.6, 117.6, 124.7, 124.8, 125.1, 127.7, 128.5, 128.9, 132.9, 140.5.

HRMS (EI, 70 eV): *m*/*z* $[M]^+$ calcd for $C_{12}H_{11}N_3$: 197.0953; found: 197.0944.

1-(Phenyl)-6,7-dihydro-5*H*-benzo[*c*][1,2,3]triazolo[1,5-*a*]azepine (3a)
Yield: 0.144 g (55%); yellow solid; mp 101–103 °C.

IR (KBr): 3059, 2926, 2856, 1605, 1448, 1361, 991, 768 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 2.44, 2.76, 4.36 (2 H each, forming AA′BB′XX′ system), 7.24–7.40 (m, 7 H), 7.71 (dd, *J* = 1.5, 7.8 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 30.2, 30.9, 45.8, 127.1, 127.8, 127.9, 128.5, 128.9, 129.7, 129.8, 131.0, 132.9, 138.9, 143.6.

MS (ESI): *m*/*z* = 284.12 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{15}N_3Na$: 284.1164; found: 284.1156.

1-(4-Methoxyphenyl)-6,7-dihydro-5*H*-benzo[*c*]-[1,2,3]triazolo[1,5-*a*]azepine (3b)
Yield: 0.117 g (40%); brown solid; mp 108–110 °C.

IR (KBr): 2935, 1610, 1512, 1465, 1359, 1296, 1248, 1180, 1025, 837, 771 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 2.42, 2.75, 4.34 (2 H each, forming AA′BB′XX′ system), 3.82 (s, 3 H), 6.89 (app d, *J* = 9.0 Hz, 2 H), 7.25–7.28 (m, 1 H), 7.33 (d, *J* = 7.2 Hz, 1 H), 7.37–7.39 (m, 2 H), 7.64 (app d, *J* = 9.0 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 30.3, 30.9, 45.9, 55.2, 113.9, 123.6, 127.2, 128.0, 128.5, 128.9, 129.6, 129.8, 132.3, 138.9, 143.5, 159.4.

MS (ESI): *m*/*z* = 292.23 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{17}N_3NaO$: 314.1269; found: 314.1261.

1-(4-Nitrophenyl)-6,7-dihydro-5*H*-benzo[*c*][1,2,3]triazolo[1,5-*a*]azepine (3c)
Yield: 0.153 g (50%); yellow solid; mp 178–180 °C.

IR (KBr): 2939, 2860, 1601, 1512, 1349, 1251, 1112, 989, 858, 759 cm^{-1}.

^1H NMR ($CDCl_3$, 600 MHz): δ = 2.47, 2.77, 4.38 (2 H each, forming AA′BB′XX′ system), 7.31–7.35 (m, 2 H), 7.44–7.47 (m, 2 H), 7.94 (d, *J* = 8.4 Hz, 2 H), 8.21 (d, *J* = 9.0 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 30.1, 31.0, 46.0, 123.9, 126.9, 127.4, 127.5, 128.8, 130.2, 130.5, 134.6, 137.6, 139.1, 141.3, 147.1.

MS (ESI): *m*/*z* = 328.97 $[M + Na]^+$.

HRMS (EI, 70 eV): *m*/*z* $[M]^+$ calcd for $C_{17}H_{14}N_4O_2$: 306.1117; found: 306.1121.

1-(2,4-Dimethoxypyrimidin-5-yl)-6,7-dihydro-5*H*-benzo[*c*][1,2,3]triazolo[1,5-*a*]azepine (3d)
Yield: 0.104 g (32%); brown liquid.

IR (neat): 2949, 2867, 2097, 1693, 1616, 1559, 1484, 1393, 1354, 1281, 1196, 1075, 1020, 753 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 2.47, 2.74, 4.41 (2 H each, forming AA′BB′XX′ system), 3.61 (s, 3 H), 4.03 (s, 3 H), 7.03 (d, *J* = 7.5 Hz, 1 H), 7.19–7.28 (m, 1 H), 7.32–7.36 (m, 2 H), 8.53 (s, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 30.1, 31.1, 46.1, 53.6, 54.9, 106.7, 126.9, 127.9, 128.1, 129.5, 135.3, 136.8, 138.1, 158.8, 165.2, 167.9.

MS (ESI): *m*/*z* = 346.23 $[M + Na]^+$.

Anal. Calcd for $C_{17}H_{17}N_5O_2$: C, 63.15; H, 5.30; N, 21.66. Found: C, 63.19; H, 5.27; N, 21.72.

1-({(3a*R*,5*R*,6*S*,6a*R*)-5-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,2-dimethyltetrahydrofuro[3,2-*d*][1,3]dioxol-6-yl-oxy}methyl)-6,7-dihydro-5*H*-benzo[*c*][1,2,3]triazolo[1,5-*a*]azepine (3e)
Yield: 0.174 g (38%); yellow liquid.

IR (neat): 2985, 2936, 2097, 1641, 1454, 1377, 1216, 1162, 1075, 1022, 849, 756 cm^{-1}.

^1H NMR ($CDCl_3$, 600 MHz): δ = 1.29 (s, 3 H), 1.31 (s, 3 H), 1.40 (s, 3 H), 1.50 (s, 3 H), 2.41–2.48 (m, 2 H), 2.62–2.68 (m, 2 H), 3.95–4.01 (m, 2 H), 4.12–4.15 (m, 2 H), 4.28–4.34 (m, 2 H), 4.41–4.46 (m, 1 H), 4.67 (d, *J* = 3.6 Hz, 1 H), 4.72 (d, *J* = 11.4 Hz, 1 H), 4.83 (d, *J* = 11.4 Hz, 1 H), 5.87 (d, *J* = 3.6 Hz, 1 H), 7.35–7.43 (m, 3 H), 7.62 (dd, *J* = 1.5, 7.5 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 25.3, 26.2, 26.8, 26.81, 30.3, 31.1, 46.0, 62.9, 67.2, 72.4, 81.2, 81.5, 82.3, 105.2, 108.9, 111.8, 126.9, 127.4, 129.1, 129.9, 129.91, 136.6, 138.7, 140.6.

MS (ESI): *m*/*z* = 458.25 $[M + H]^+$.

HRMS (EI, 70 eV): *m*/*z* $[M]^+$ calcd for $C_{24}H_{31}N_3O_6$: 457.2213; found: 457.2221.

Phenyl-5,6,7,8-tetrahydrobenzo[*c*][1,2,3]triazolo[1,5-*a*]azocine (4a)
Yield: 0.110 g (40%); white solid; mp 154–156 °C.

IR (KBr): 3059, 2933, 2859, 1603, 1445, 1353, 1253, 1218, 982, 768, 698 cm^{-1}.

^1H NMR ($CDCl_3$, 600 MHz): δ = 1.53–1.61 (m, 1 H), 1.81–1.92 (m, 1 H), 2.13–2.17 (m, 2 H), 2.23–2.26 (m, 1 H), 2.95 (dd, *J* = 8.4, 13.8 Hz, 1 H), 3.61 (dd, *J* = 11.7, 14.1 Hz, 1 H), 4.81 (dd, *J* = 6.3, 14.1 Hz, 1 H), 7.21 (dd, *J* = 1.2, 7.8 Hz, 1 H), 7.23–7.29 (m, 4 H), 7.43 (br d, *J* = 7.2 Hz, 1 H), 7.47 (td, *J* = 1.6, 7.4 Hz, 1 H), 7.59–7.62 (m, 2 H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 29.1, 29.3, 32.6, 48.1, 126.60, 126.65, 126.7, 127.6, 128.4, 130.1, 130.4, 130.6, 131.1, 133.3, 143.6, 143.7.

MS (ESI): *m*/*z* = 298.16 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M+ H]^+$ calcd for $C_{18}H_{18}N_3$: 276.1501; found: 276.1504.

1-(4-Carbomethoxyphenyl)-5,6,7,8-tetrahydrobenzo[*c*][1,2,3]triazolo[1,5-*a*]azocine (4b)
Yield: 0.143 g (43%); white solid; mp 180–182 °C.

IR (KBr): 3061, 2944, 2858, 1717, 1609, 1437, 1278, 1109, 978, 862, 775 cm^{-1}.

^1H NMR ($CDCl_3$, 600 MHz): δ = 1.54–1.61 (m, 1 H), 1.81–1.89 (m, 1 H), 2.12–2.19 (m, 2 H), 2.23–2.27 (m, 1 H), 2.98 (dd, *J* = 8.4, 13.8 Hz, 1 H), 3.62 (dd, *J* = 11.7, 14.1 Hz, 1 H), 3.89 (s, 3 H), 4.82 (dd, *J* = 6.3, 14.1 Hz, 1 H), 7.19 (dd, *J* = 0.6, 7.8 Hz, 1 H), 7.27 (td, *J* = 1.2, 8.4 Hz, 1 H, overlapped by solvent peak), 7.45 (br d, *J* = 7.2 Hz, 1 H), 7.50 (td, *J* = 1.2, 7.5 Hz, 1 H), 7.69 (app d, *J* = 8.4 Hz, 2 H), 7.95 (app d, *J* = 9.0 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 29.0, 29.2, 32.7, 48.2, 52.1, 126.2, 126.4, 126.8, 129.0, 129.8, 129.9, 130.5, 130.9, 134.3, 135.6, 142.7, 143.6, 166.9.

MS (ESI): *m*/*z* = 356.23 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{20}H_{19}N_3NaO_2$: 356.1375; found: 356.1382.

1-(4-Methoxyphenyl)-5,6,7,8-tetrahydrobenzo[*c*][1,2,3]triazolo[1,5-*a*]azocine (4c)
Yield: 0.116 g (38%); yellow solid; mp 158–160 °C.

IR (KBr): 2926, 2851, 1614, 1516, 1471, 1356, 1297, 1251, 1179, 1108, 1010, 835, 759 cm^{-1}.

^1H NMR ($CDCl_3$, 600 MHz): δ = 1.52–1.59 (m, 1 H), 1.79–1.87 (m, 1 H), 2.11–2.16 (m, 2 H), 2.21–2.25 (m, 1 H), 2.94 (dd, *J* = 8.4, 13.8 Hz, 1 H), 3.59 (dd, *J* = 11.4, 14.4 Hz, 1 H), 3.78 (s, 3 H), 4.78 (dd, *J* = 6.0, 13.8 Hz, 1 H), 6.82 (app d, *J* = 9.0 Hz, 2 H), 7.19 (dd, *J* = 1.2, 7.8 Hz, 1 H), 7.25 (td, *J* = 1.2, 7.5 Hz, 1 H), 7.41 (br d, *J* = 7.8 Hz, 1 H), 7.46 (td, *J* = 1.2, 7.5 Hz, 1 H), 7.53 (app d, *J* = 9.0 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 29.1, 29.2, 32.6, 48.1, 55.1, 113.8, 123.7, 126.6, 126.7, 127.9, 130.0, 130.3, 130.5, 132.5, 143.5, 143.6, 159.1.

MS (ESI): *m*/*z* = 306.28 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{19}N_3NaO$: 328.1426; found: 328.1425.

Synthesis of 5-(5,6-Dihydro[1,2,3]triazolo[5,1-*a*]isoquinolin-1-yl)pyrimidine-2,4(1*H*,3*H*)-dione (11a); Typical Procedure

To a well-stirred solution of **2d** (309 mg, 1.0 mmol) in anhydrous MeCN (7.0 mL) was added anhydrous NaI (90 mg, 3.0 mmol) followed by chlorotrimethylsilane (0.4 mL, 3.0 mmol) under an argon atmosphere. The reaction mixture was then stirred at r.t. for 20 h. The solvent was evaporated under reduced pressure and the residue was triturated with aqueous sodium metabisulfite solution (3 mL) and filtered, washed with H_2O (3 mL) and dried to furnish the pure product **11a**.

The same procedure was adopted for the conversion of compound **3d** into product **11b**.

Yield: 0.239 g (85%); colourless solid; mp >300 °C.

IR (KBr): 3427, 3159, 3052, 2830, 1716, 1672, 1485, 1425, 1209, 1181, 993, 773, 637 cm^{-1}.

^{1}H NMR (DMSO-d_6, 500 MHz): δ = 3.21, 4.56 (2 H each, comprising AA′XX′ system), 7.26–7.34 (m, 3 H), 7.39 (br d, *J* = 7.5 Hz, 1 H), 7.69 (d, *J* = 6.0 Hz, 1 H), 11.24 (d, *J* = 4.5 Hz, 1 H), 11.35 (s, 1 H).

^{13}C NMR (DMSO-d_6, 75 MHz): δ = 28.3, 44.5, 104.6, 124.5, 125.0, 127.3, 128.3, 128.9, 130.9, 132.9, 134.6, 142.6, 151.2, 162.5.

MS (ESI): *m*/*z* = 304.03 $[M + Na]^+$.

Anal. Calcd for $C_{14}H_{11}N_5O_2$: C, 59.78; H, 3.94; N, 24.90. Found: C, 59.83; H, 3.91; N, 24.87.

5-(6,7-Dihydro-5*H*-benzo[*c*][1,2,3]triazolo[1,5-*a*]azepine-1-yl)pyrimidine-2,4(1*H*,3*H*)-dione (11b)

Yield: 0.242 g (82%); light-yellow solid; mp >300 °C.

IR (KBr): 3475, 3169, 3059, 2827, 1716, 1671, 1504, 1416, 1204, 1176, 990, 768, 638 cm^{-1}.

^{1}H NMR (DMSO-d_6, 500 MHz): δ = 2.33, 2.59, 4.26 (2 H each, forming AA′BB′XX′ system), 7.24 (d, *J* = 7.5 Hz, 1 H), 7.28 (t, *J* = 7.5 Hz, 1 H), 7.34 (t, *J* = 7.3 Hz, 1 H), 7.39 (d, *J* = 7.5 Hz, 1 H), 7.62 (d, *J* = 6.0 Hz, 1 H), 11.13 (d, *J* = 5.0 Hz, 1 H), 11.19 (s, 1 H).

^{13}C NMR (DMSO-d_6, 75 MHz): δ = 29.6, 30.6, 45.7, 104.0, 126.9, 127.8, 129.2, 129.6, 135.3, 136.4, 138.4, 142.2, 151.1, 162.4.

MS (ESI): *m*/*z* = 318.06 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{13}N_5NaO_2$: 318.0967; found: 318.0963.

Synthesis of Bisheteroannulated Products 13a–d; General Procedure

To a well-stirred solution of *o*-iodo-azide **7a**–**d** (1 mmol) in anhydrous DMF (8 mL) were added successively $[Pd(PPh_3)_2Cl_2]$ (24.6 mg, 0.035 mmol), CuI (13.3 mg, 0.07 mmol) and Et_3N (0.71 mL, 5.0 mmol). The reaction mixture was then stirred under argon for 20 min. A solution of 1,3-diethynyl benzene **12** (0.6 mmol) dissolved in anhydrous DMF (1 mL) was then added dropwise and the reaction mixture was heated at 115 °C (except for **7d**, for which heating was carried out at 150 °C) for a few hours until consumption of the starting materials was observed (TLC). Upon completion of the reaction, the solvent was removed in vacuo, the residue was mixed with H_2O (30 mL) and then extracted with EtOAc (2 × 25 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified through silica gel (100–200 mesh) column chromatography (EtOAc–PE, 40–50% v/v) to afford the corresponding product **13a**–**d**.

1,3-Bis(8*H*-[1,2,3]triazolo[5,1-*a*]isoindol-3-yl)benzene (13a)

Yield: 0.210 g (54%); greenish solid; mp 226–228 °C.

IR (KBr): 3398, 1664, 1616, 1343, 1179, 891, 767 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.42 (s, 4 H), 7.41–7.57 (m, 6 H), 7.69 (t, *J* = 7.7 Hz, 1 H), 7.99–8.05 (m, 4 H), 8.59 (s, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 50.9, 121.7, 124.1, 125.5, 126.5, 128.0, 128.5, 129.0, 129.5, 132.0, 139.0, 139.3, 141.1.

FAB-MS: *m*/*z* = 389.4 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{24}H_{16}N_6Na$: 411.1334; found: 411.1339.

1,3-Bis(5,6-dihydro[1,2,3]triazolo[5,1-*a*]isoquinolin-1-yl)benzene (13b)

Yield: 0.208 g (50%); yellow solid; mp 262–264 °C.

IR (KBr): 3052, 2928, 1732, 1610, 1347, 1241, 1190, 910, 770, 739 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.26, 4.61 (4 H each, comprising two identical AA′XX′ systems), 7.17 (t, *J* = 7.4 Hz, 2 H), 7.26–7.35 (m, 4 H), 7.57–7.65 (m, 3 H), 7.79 (d, *J* = 7.5 Hz, 2 H), 8.07 (s, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 29.3, 44.9, 124.6, 124.9, 127.7, 128.4, 128.66, 128.7, 129.18, 129.2, 129.5, 132.3, 132.7, 142.6.

FAB-MS: *m*/*z* = 417.5 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{26}H_{20}N_6Na$: 439.1647; found: 439.1649.

1,3-Bis(6,7-dihydro-5*H*-benzo[*c*][1,2,3]triazolo[1,5-*a*]azepin-1-yl)benzene (13c)

Yield: 0.209 g (47%); yellow solid; mp 158–160 °C.

IR (KBr): 2944, 2867, 2096, 1603, 1448, 1356, 1248, 768 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.38, 2.61, 4.30 (4 H each, forming two identical AA′BB′XX′ systems), 7.13–7.17 (m, 2 H), 7.23–7.26 (m, 2 H), 7.29–7.30 (m, 4 H), 7.39 (t, *J* = 7.8 Hz, 1 H), 7.77 (dd, *J* = 1.0, 7.5 Hz, 2 H), 7.93 (s, 1 H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 30.2, 30.9, 45.8, 125.5, 126.7, 127.0, 127.6, 128.9, 129.1, 129.5, 129.8, 131.3, 133.0, 138.6, 143.2.

FAB-MS: *m*/*z* = 445.5 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{28}H_{24}N_6Na$: 467.1960; found: 467.1982.

1,3-Bis(5,6,7,8-tetrahydrobenzo[*c*][1,2,3]triazolo[1,5-*a*]azocin-1-yl)benzene (13d)

Yield: 0.128 g (27%); white solid; mp 240–242 °C.

IR (KBr): 3048, 2948, 2092, 1616, 1450, 1352, 1251, 889, 771 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.46–1.60 (m, 2 H), 1.73–1.83 (m, 3 H), 2.03–2.08 (m, 1 H), 2.11–2.22 (m, 4 H), 2.73 (dd, *J* = 8.3, 13.8 Hz, 1 H), 2.94 (dd, *J* = 8.5, 13.5 Hz, 1 H), 3.52–3.64 (m, 2 H), 4.72–4.82 (m, 2 H), 7.02 (d, *J* = 7.5 Hz, 1 H), 7.13 (t, *J* = 7.0 Hz, 2 H), 7.20 (br, 1 H), 7.30 (d, *J* = 7.5 Hz, 2 H), 7.39–7.51 (m, 4 H), 7.60 (br, 1 H), 7.87 (br, 1 H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 28.9, 29.0, 29.1, 29.2, 30.9, 32.6, 48.4, 124.7, 125.9, 126.5, 126.7, 126.76, 126.82, 128.8, 129.3, 129.9, 130.1, 130.3, 130.37, 130.40, 130.6, 130.8, 143.0; additional peaks are attributed to conformational equilibrium.

MS (ESI): *m*/*z* = 495.32 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{30}H_{28}N_6Na$: 495.2273; found: 495.2292.

Synthesis of 1a′

To a well-stirred solution of *o*-iodo-azide **7a** (259 mg, 1 mmol) in anhydrous DMF (6 mL) were added successively $[Pd(PPh_3)_2Cl_2]$ (10.5 mg, 0.015 mmol), CuI (5.7 mg, 0.03 mmol) and K_2CO_3 (276

mg, 2.0 mmol), and the reaction mixture was heated at 60 °C for 4 h under balloon pressure of acetylene gas. After completion of the reaction (TLC), the solvent was removed in vacuo; the residue was mixed with H_2O (50 mL) and extracted with EtOAc (2 × 25 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified through silica gel (100–200 mesh) column chromatography (EtOAc–PE, 20% v/v) to afford the product **1a′** (95 mg, 60%). The acyclic product **14a** (n = 1) was also isolated (69 mg, 24%) from this reaction mixture.

8*H*-[1,2,3]Triazolo[5,1-*a*]isoindole (1a′)
Yield: 0.094 g (60%); black solid; mp 84–86 °C.

IR (KBr): 3131, 2932, 1447, 1410, 1263, 1217, 1151, 1093, 974, 850, 772 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 5.35 (s, 2 H), 7.39–7.55 (m, 3 H), 7.66 (d, *J* = 7.2 Hz, 1 H), 7.84 (s, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 50.9, 121.5, 124.0, 127.4, 128.3, 128.7, 140.9, 142.7.

MS (ESI): *m*/*z* = 158.14 $[M + H]^+$.

HRMS (EI, 70 eV): *m*/*z* $[M]^+$ calcd for $C_9H_7N_3$: 157.064; found: 157.0646.

1-(2-Iodobenzyl)-1*H*-1,2,3-triazole (14a)
Yield: 0.068 g (24%); white solid; mp 63–64 °C.

IR (KBr): 3078, 1469, 1435, 1209, 1114, 1084, 1010, 736 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 5.66 (s, 2 H), 7.03–7.08 (m, 2 H), 7.34 (t, *J* = 7.5 Hz, 1 H), 7.60 (s, 1 H), 7.73 (s, 1 H), 7.90 (d, *J* = 7.8 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 58.2, 98.5, 123.7, 129.0, 129.5, 130.3, 134.1, 137.3, 139.8.

MS (ESI): *m*/*z* = 307.95 $[M + Na]^+$.

Anal. Calcd for $C_9H_8IN_3$: C, 37.92; H, 2.83; N, 14.74. Found: C, 37.88; H, 2.81; N, 14.78.

Synthesis of products 2–4a′
To a well-stirred solution of *o*-iodo-azide **7b**–**d** (0.5 mmol) in anhydrous DMF (6 mL) were added successively CuI (2.9 mg, 0.015 mmol) and K_2CO_3 (138 mg, 1.0 mmol), and the reaction mixture was then heated at 60 °C for 4 h under balloon pressure of acetylene gas. After completion of the reaction (TLC), the solvent was removed in vacuo; the residue was mixed with H_2O (30 mL) and extracted with EtOAc (2 × 25 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the corresponding crude product **14b**–**d**, which was used directly without further chromatographic purification.

To a well-stirred solution of crude intermediate **14b**/**14c** in anhydrous DMF (5 mL) were added successively $[Pd(PPh_3)_2Cl_2]$ (17.5 mg, 0.025 mmol), K_2CO_3 (207 mg, 1.5 mmol) and TBAB (16 mg, 0.05 mmol). The reaction mixture was then heated (110 °C for **14b**, 130 °C for **14c**) for 4 h under an argon atmosphere. After completion of the reaction (TLC), the solvent was removed in vacuo; the residue was mixed with H_2O (30 mL) and then extracted with EtOAc (2 × 25 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified through silica gel (100–200 mesh) column chromatography (EtOAc–PE, 10–20% v/v) to afford the corresponding product **2a′**/**3a′**.

The same reaction procedure was adopted for the synthesis of product **4a′** using crude intermediate **14d**; however, in this case, $Pd(OAc)_2$ (11 mg, 0.05 mmol) and $NaHCO_3$ (84 mg, 1.0 mmol) were employed in place of $[Pd(PPh_3)_2Cl_2]$ and K_2CO_3 and the reaction was heated at 130 °C for 2.5 h.

5,6-Dihydro[1,2,3]triazolo[5,1-*a*]isoquinoline (2a′)
Yield: 0.070 g (82%); white solid; mp 94–96 °C.

IR (KBr): 3117, 3066, 3023, 2975, 1666, 1485, 1457, 1425, 1346, 1295, 1244, 1183, 1107, 960, 835, 773 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 3.25, 4.61 (2 H each, comprising AA′XX′ system), 7.34–7.38 (m, 3 H), 7.58–7.59 (m, 1 H), 7.95 (s, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 28.6, 44.4, 124.2, 124.5, 127.7, 128.35, 128.39, 129.2, 131.8, 133.7.

MS (ESI): *m*/*z* = 172.18 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{10}H_9N_3Na$: 194.0694; found: 194.0685.

6,7-Dihydro-5*H*-benzo[*c*][1,2,3]triazolo[1,5-*a*]azepine (3a′)
Yield: 0.048 g (52%); pale-yellow liquid.

IR (neat): 3129, 3065, 2942, 2862, 1451, 1359, 1246, 1200, 1108, 1022, 981, 768 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 2.45, 2.72, 4.44 (2 H each, forming AA′BB′XX′ system), 7.32–7.38 (m, 3 H), 7.39–7.47 (m, 1 H), 7.80 (s, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 30.3, 30.6, 46.3, 127.0, 127.2, 128.2, 129.6, 129.8, 131.4, 137.8, 138.3.

MS (ESI): *m*/*z* = 208.01 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{11}H_{11}N_3Na$: 208.0851; found: 208.0844.

5,6,7,8-Tetrahydrobenzo[*c*][1,2,3]triazolo[1,5-*a*]azocine (4a′)
Yield: 0.042 g (42%); pale-yellow solid; mp 114–116 °C.

IR (KBr): 3132, 3012, 2939, 2854, 1440, 1354, 1237, 1202, 1104, 964, 855, 767 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 1.98 (br, 4 H), 2.45 (br, 2 H), 4.27 (br, 2 H), 7.29–7.32 (m, 2 H), 7.34 (d, *J* = 7.5 Hz, 1 H), 7.43–7.47 (m, 1 H), 7.68 (s, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 28.6, 28.9, 32.7, 48.4, 126.1, 126.3, 129.6, 130.2, 130.5, 132.4, 137.6, 142.8.

MS (ESI): *m*/*z* = 222.04 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{12}H_{13}N_3Na$: 222.1007; found: 222.1003.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis. Included are the preparation and characterization data of **7a**–**d**, X-ray crystallographic data of **4a** and copies of ^1H and ^{13}C NMR spectra of compounds **7a**–**d**, **1**–**4**, **11a**–**b**, **13a**–**d**, **1a′**–**4a′**, **14a**.

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