

Three-Component Synthesis of Cryofluorescent 2,4-Disubstituted 3*H*-1,5-Benzodiazepines – Conformational Control of Emission Properties

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Keywords: Benzodiazepines / C–C coupling / Cyclocondensation / Fluorescence / Microwave-assisted reactions / Multicomponent reactions

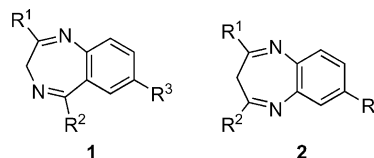
2,4-Disubstituted benzodiazepines are readily synthesized in good yields from acyl chlorides, terminal alkynes, and benzene-1,2-diamines by a consecutive one-pot, three-component Sonogashira coupling/Michael addition/cyclocondensation sequence. These diazepines display intense solid-state fluorescence, but only weak emission in solution at room temperature. The absorption and emission maxima can be controlled by the substitution pattern. Upon cooling, how-

ever, the phenomenon of cryofluorescence can be observed. X-ray structure analysis and temperature-dependent NMR indicate that freezing out of conformational interconversions is the source of the thermochromicity observed upon UV excitation.

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Introduction

3*H*-1,4-Benzodiazepines **1** and 3*H*-1,5-benzodiazepines **2** and their dihydro derivatives constitute an important class of psychopharmaca.^[1] In particular, derivatives of **2** have aroused considerable interest as CNS-active anticonvulsant drugs^[2] and as antianxiety, analgesic, sedative, antidepressive, and hypnotic agents,^[3] and also as anti-inflammatory agents.^[4] In addition, their use as in vitro non-nucleoside inhibitors of HIV-1 reverse transcriptase has also been reported.^[5] Besides their biological relevance, benzodiazepine derivatives have also found application as dyes for acrylic fibers.^[6] Moreover, benzodiazepine derivatives **2** are also valuable synthons in the preparation of annelated systems such as triazolo-, oxadiazolo-, oxazino-, or furo-benzodiazepines.^[7] With respect to expected enhanced pharmacological activity, syntheses of this class of heterocycles are currently being intensively pursued.



Among the most frequently used methods for the synthesis of benzodiazepines **2** is the cyclocondensation of benzene-1,2-diamines with 1,3-dicarbonyl compounds^[8] or equivalent 1,3-biselectrophiles such as epoxy ketones, α,β -unsaturated carbonyl compounds,^[9] or β -haloketones.^[1a] A broad variety of Brønsted and Lewis acids – such as InBr₃, CeCl₃/SiO₂, lanthanoide triflates, Amberlyst 15, Al₂O₃/P₂O₅, or acetic acid – have been utilized to catalyze these cyclocondensation reactions.^[10] In addition, approaches with ionic liquids^[11] or on solid supports have also been reported.^[12] With respect to the interesting pharmaceutical properties of diazepines, and moreover to the increasing quest for tailor-made functional π -systems through diversity-oriented strategies,^[13] we set out to develop and explore a concise one-pot synthesis of 1,5-benzodiazepines. As part of our program directed towards the design of new multicomponent syntheses of heterocycles initiated by Sonogashira cross coupling, we have focused on a cross coupling-cyclocondensation approach.^[14] Here we report on a concise, consecutive one-pot, three-component synthesis of 3*H*-1,5-benzodiazepines with flexibility of substitution pattern, their absorption and emission properties, as well as their unusual conformationally dependent cryofluorescence.

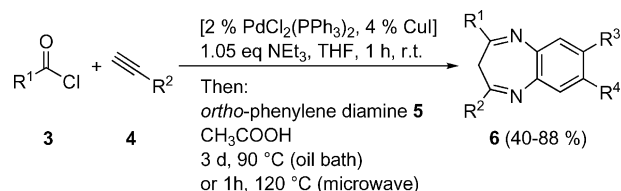
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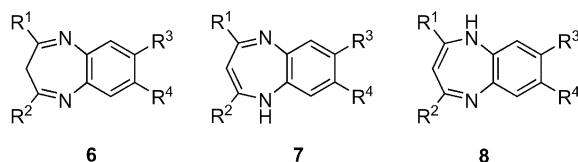
Results and Discussion

Alkynones are easily accessible through Sonogashira couplings^[15] between acyl chlorides and terminal alkynes.^[16] We have reported that the use of THF as a solvent enables a variation in which only one equivalent of triethylamine is applied as a base to achieve an efficient alkynone synthesis.^[17] The resulting alkynones are reactive towards cyclocondensations with binucleophiles, such as hydrazines, in a one-pot fashion.^[14b,14c,18] Therefore, after reactions between acyl chlorides **3** and terminal alkynes **4** under modified Sonogashira conditions for 1 h at room temperature to furnish the expected alkynones, subsequent addition of benzene-1,2-diamines **5** and acetic acid gives rise to the formation of benzodiazepines **6**, which can be obtained in moderate to very good yields as yellow solids and oils (Scheme 1, Table 1). In some cases dielectric heating in a microwave cavity turned out to be favorable and led to shorter reaction times (Table 2). However, in most cases conductive heating proved to give better yields.



Scheme 1. One-pot three-component synthesis of 1,5-benzodiazepines **6**.

The structures of the 1,5-benzodiazepines **6** were unambiguously assigned by ¹H, ¹³C, and 2D NMR spectroscopy and mass spectroscopy. Considerable line broadening for the methylene protons and carbon nuclei at room temperature suggests that, of the possible tautomers **6–8**, only tautomer **6** appears to be populated, but in conjunction with a dynamic phenomenon (vide infra).^[19] In addition, the structural assignment was corroborated by an X-ray analysis of compound **6f** (Figure 1 and Table 6).^[20]



The X-ray crystal structure analysis of **6f** clearly shows a locked half-boat conformation with a folding angle of 96°. 1,5-Benzodiazepines **6** would be expected to be prone to rapid conformational interconversion at elevated temperature, leveling out the non-equivalence of the methylene protons. This dynamic process was therefore studied by temperature-dependent NMR spectroscopy in CDCl₃ between 218 and 323 K (Figure 2).

At room temperature the methylene protons appear as extremely broad singlets. The resonances of protons H_a and H_b of the benzodiazepine **6j** are thus barely visible at this temperature, whereas with increasing temperature a sharp singlet at δ = 3.30 ppm gradually evolves.

Table 1. One-pot, three-component synthesis of 1,5-benzodiazepines **6** under conductive heating conditions.

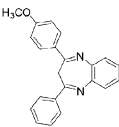
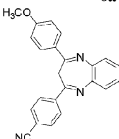
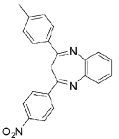
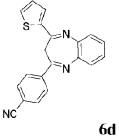
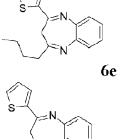
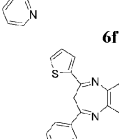
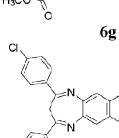
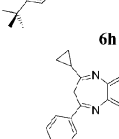
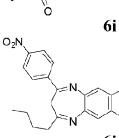
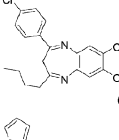
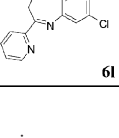
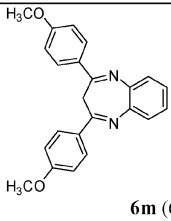
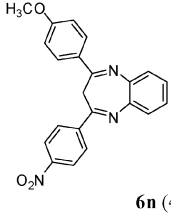
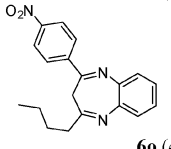
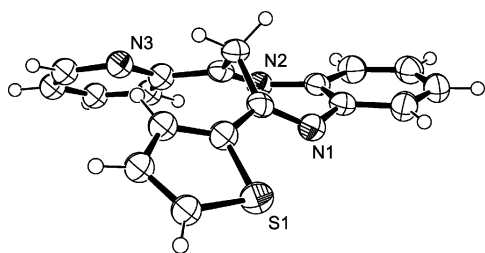
Entry	Acyl chloride 3	Alkyne 4	Diamine 5	Benzodiazepine 6
1	3a : R ¹ = 4-MeOC ₆ H ₄	4a : R ² = C ₆ H ₅	5a : R ³ = R ⁴ = H	 6a (88 %)
2	3a	4b : R ² = 4-NCC ₆ H ₄	5a	 6b (53 %)
3	3b : R ¹ = 4-H ₃ CC ₆ H ₄	4c : R ² = 4-O ₂ NC ₆ H ₄	5a	 6c (45 %)
4	3c : R ¹ = 2-thienyl	4b	5a	 6d (54 %)
5	3c	4d : R ² = <i>n</i> Bu	5a	 6e (58 %)
6	3c	4e : R ² = 2-pyridyl	5a	 6f (54 %)
7	3c	4f : R ² = 4-H ₃ CO ₂ CC ₆ H ₄	5b : R ³ = R ⁴ = Cl	 6g (64 %)
8	3d : R ¹ = 4-ClC ₆ H ₄	4g : R ² = 4-Me ₃ CC ₆ H ₄	5b	 6h (54 %)
9	3e : R ¹ = cyclopropyl	4f	5b	 6i (81 %)
10	3f : R ¹ = 4-O ₂ NC ₆ H ₄	4d	5b	 6j (86 %)
11	3d	4d	5b	 6k (59 %)
12	3c	4e	5b	 6l (44 %)

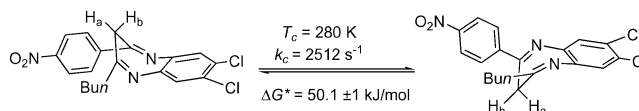
Table 2. One-pot, three-component synthesis of 1,5-benzodiazepines **6** under dielectric heating conditions.

Entry	3	Alkyne 4	5	Benzodiazepine 6
1	3a	4h : $R^2 =$ 4-MeOC ₆ H ₄	5a	 6m (63 %)
2	3a	4c	5a	 6n (40 %)
3	3f	4d	5a	 6o (47 %)

Figure 1. Molecular structure of compound **6f**.

Lowering the temperature to 250 K results in a splitting into two signals, which upon further cooling to 218 K resolve further into two doublets at $\delta = 2.19$ and 4.46 ppm. The coupling constants, with $J = 11$ Hz, are characteristic for geminal coupling. The huge signal separation ($\Delta\nu$) of the two methylene resonances, by 1131 Hz, can be attributed

to the anisotropic shielding by the annelated benzene ring. Consequently, the signal at lower field can be assigned to the *endo* proton. The coalescence temperature (T_c) is observed at ca. 280 K. Through application of the Eyring equation the ring flip barrier ($\Delta G^\ddagger$) can be calculated to be 50.1 ± 1 kJ mol⁻¹, which is in good agreement with literature precedence.^[19] Hence, the ring flip rate constant at T_c equals 2512 s⁻¹ (Scheme 2). Likewise, the carbon resonances of the characteristic methylene groups appearing at $\delta = 38$ ppm are difficult to assign at room temperature. However, below -20 °C this signal becomes sharp and can be unambiguously assigned by HETCOR spectra.

Scheme 2. Ring flip of 1,5-benzodiazepine **6j**, together with barrier and kinetic data.

Furthermore, the ring flip barrier ($\Delta G^\ddagger$) for the 2,4-diphenyl-substituted 1,5-benzodiazepine was calculated at the DFT level by use of the B3LYP functional^[21] and different Pople basis sets. The optimized transition state shows a completely planar 1,5-benzodiazepine structure of C_{2v} symmetry (Figure 3).

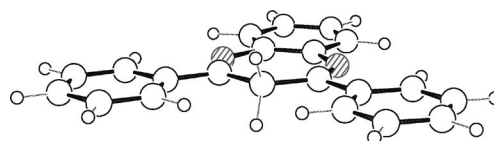


Figure 3. Optimized transition state of the 2,4-diphenyl-substituted 1,5-benzodiazepine.

Use of the triple-zeta basis set 6-311G furnishes a ring flip barrier ($\Delta G_{298}^\ddagger$) of 47.3 kJ mol⁻¹ (Table 3). Again, these results reproduce well the experimental data of this work and other literature precedence.^[19]

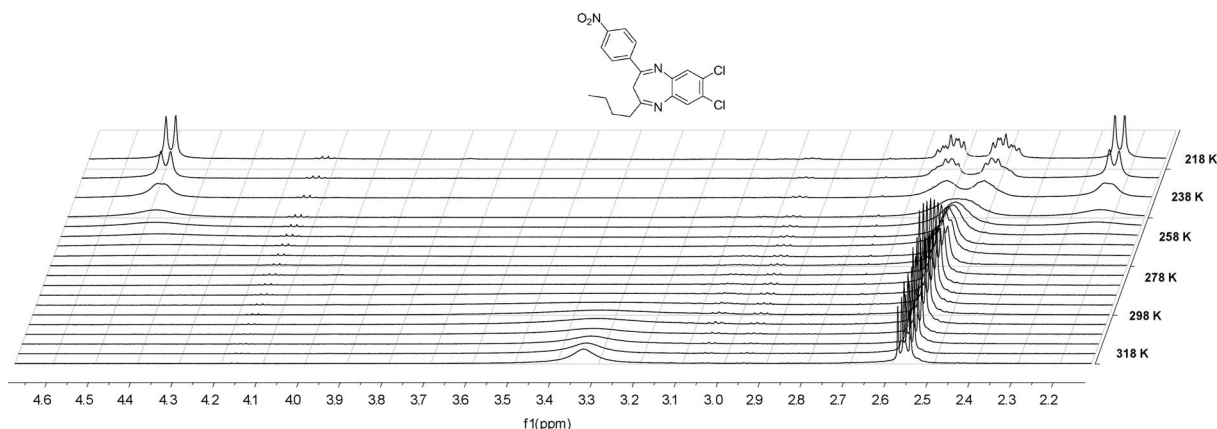
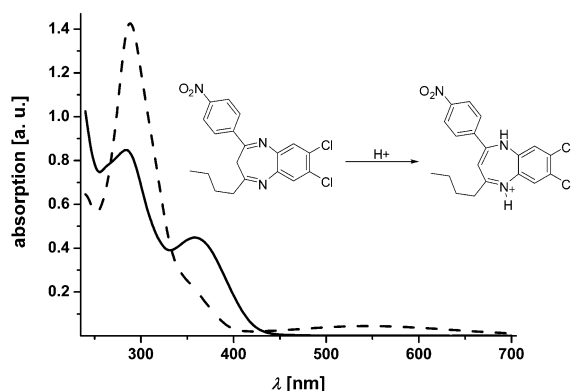
Figure 2. Temperature-dependent ¹H NMR spectra of compound **6j**, selected signals (recorded in CDCl₃, 500 MHz).

Table 3. Energies of the ring flip barrier ($\Delta G^\ddagger$) of the 2,4-diphenyl-substituted 1,5-benzodiazepine as computed with the B3LYP functional.

Entry	Method	$\Delta G^\ddagger_{298}[\text{kJ mol}^{-1}]$
1	B3LYP/3-21G	36.8
2	B3LYP/3-21G*	39.6
3	B3LYP/6-31G	41.2
4	B3LYP/6-31G**	44.0
5	B3LYP/6-311G	47.3

The 1,5-benzodiazepines **6** are intensively yellow to orange solids. Upon addition of trifluoroacetic acid to a dichloromethane solution of **6i** the deep violet benzodiazepinium salt is formed (Figure 4). Protonation causes a decrease in the absorption band at 359 nm and a concomitant increase in the band at 550 nm, caused by the formation of a horseshoe-shaped trimethine cyanine system.^[22]


 Figure 4. Absorption (recorded in CH_2Cl_2 at 293 K) spectra of **6i** (solid line) and **6i-H⁺** (dotted line).

Our diversity-oriented one-pot approach to 1,5-benzodiazepines gives rise to flexibility in substitution patterns, and the structure/property relationships can be studied for electronic absorption and emission spectra (Table 4). Minute substituent variations strongly affect both absorption and

emission properties. In solution, the longest-wavelength absorption maxima ($\lambda_{\text{max,abs}}$) of **6** are found in the near UV between 270 and 300 nm, with molar extinction coefficients (ϵ) ranging from 16400 to 44400 $\text{L mol}^{-1} \text{cm}^{-1}$. In solution at room temperature, all compounds are essentially nonfluorescent. At concentrations such as those used for the absorption measurements (10^{-3} to 10^{-4} M) weak emission signals can just be detected, revealing large Stokes shifts ranging from 2800 to 8000 cm^{-1} . These emission maxima ($\lambda_{\text{max,em}}$) lie between 385 and 516 nm. For compound **6c**, the fluorescence quantum yield (Φ_f) was determined and found to be less than 0.01 (Table 4). Interestingly, the intensities of the fluorescence signals increase slightly with dilution of the solutions, but at a concentration of 10^{-5} M the residual fluorescence vanishes completely. From the NMR dynamic behavior, the origin of minimal fluorescence can be attributed to the ring flip, which opens up a facile pathway for deactivation of the excited state by internal conversion. Therefore, in the solid state, in which the ring flip is frozen out, fluorescence occurs to its greatest extent, all solid 1,5-benzodiazepines **6** hence displaying intense fluorescence. The emission maxima of compounds **6** in the solid state ($\lambda_{\text{max,em}}$) are found between 420 and 535 nm (i.e., they are red-shifted by approximately 100 nm in comparison with the maxima in solution; Figure 5, Table 4).

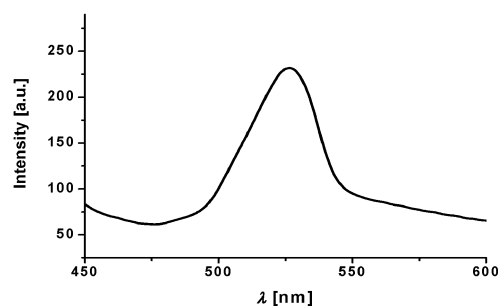

 Figure 5. Solid state emission spectrum of **6c** (recorded at 293 K).

 Table 4. Selected electronic properties (UV/Vis and fluorescence data, and Stokes shifts $\Delta\tilde{\nu}$) of the 1,5-benzodiazepines **6**.

Compound	Absorption ^[a] $\lambda_{\text{max,abs}}$ [nm] (ϵ)	Emission in solution ^[a] $\lambda_{\text{max,em}}$ [nm]	Stokes shift $\Delta\tilde{\nu}$ ^[b] [cm^{-1}]	Emission solid state $\lambda_{\text{max,em}}$ [nm]
6a	345 (sh), 285 (29900)	442	6400	502
6b	347 (sh), 275 (16400)	385	2800	509
6c	370 (sh), 284 (44400)	516	7600	527
6d	348 (sh), 266 (21600)	388	3000	508
6e	335 (sh), 268 (18800)	458	8000	535
6f	341 (sh), 291 (41300)	420	5500	493
6g	349 (sh), 272 (29200)	418	4700	510
6h	337 (sh), 276 (45400)	412	5400	426
6i	345 (sh), 276 (23100)	385	3000	420
6j	359 (sh), 284 (27200)	450	5600	525
6k	333 (sh), 272 (30900)	447	7700	490
6l	348 (sh), 294 (14500)	416	4700	510
6m	331 (sh), 285 (33700)	388	4400	495
6n	366 (sh), 292 (29300)	436	4400	530
6o	357 (sh), 284 (24500)	494	7800	517

[a] Recorded in CH_2Cl_2 , 293 K at $c = 10^{-3}$ to 10^{-4} M. Emissions in solution are measured without further dilution. [b] $\Delta\tilde{\nu} = \lambda_{\text{max,abs}} - \lambda_{\text{max,em}}$ [cm^{-1}].

Besides locking the ring flip by crystallization, decreasing the temperature should also cause thermochromic fluorescence in solution, and solutions of 1,5-benzodiazepines **6** cooled to $-78\text{ }^{\circ}\text{C}$ thus indeed show the phenomenon of cryofluorescence; at low temperature the ring flip is frozen and fluorescence appears. The emissions at $-78\text{ }^{\circ}\text{C}$ are found at about the same wavelengths as in the solid state, indicating significant aggregation of the fluorophores.

The spectral properties suggested that a closer look should be taken at the electronic structure of 1,5-benzodiazepines. Calculations based upon a starting geometry derived from the X-ray structure analysis of **6f** were therefore carried out with use of the B3LYP functional^[21] and the Pople 6-311++G basis set for geometry optimization. The same methodology was then used to scrutinize the influence of push–pull substitution on the properties of the electronic ground and excited states. These computations were carried out for 1,5-benzodiazepine **6n** and the corresponding benzodiazepinium cation **6n-H⁺**. The frontier orbitals of the push–pull systems **6n** and **6n-H⁺** thus clearly show that the longest-wavelength absorption band, which can be assigned to HOMO–LUMO transitions, possesses significant charge transfer character (Figure 6). For structure **6n**, electron density is shifted upon photonic excitation from the *p*-methoxyphenyl donor moiety and the benzo ring, localized in the HOMO, to the *p*-nitrophenyl acceptor unit, where LUMO coefficients are largest.

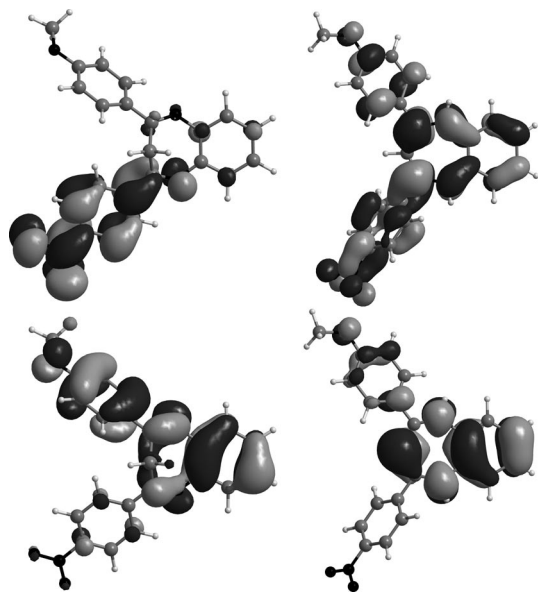
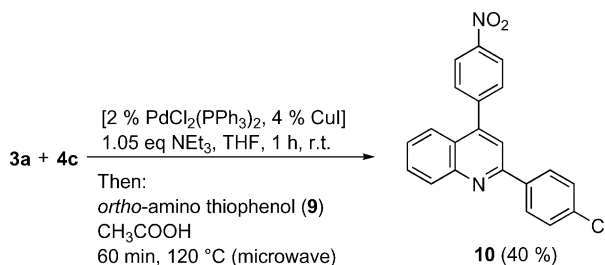


Figure 6. DFT-computed frontier orbitals of 1,5-benzodiazepines **6n** (left) and **6n-H⁺** (right), LUMOs (top) and HOMOs (bottom).

As might be expected, push–pull substitution causes red shifts both in absorption and in emission. Therefore, this facile and versatile synthetic route is perfectly suited for fine-tuning of the solid-state fluorescence colors of 1,5-benzodiazepines. For the cyanine system **6n-H⁺**, not only is planarization of the conjugated seven-membered ring found, as indicated by a small folding angle of 18° , but the electronic structure has also changed significantly. The

HOMO is predominantly localized in the central benzodiazepinium core, whereas the LUMO is delocalized over the whole structural framework. In the LUMO the central methine carbon atom is part of the nodal plane, and no coefficient is therefore found (Figure 6).

Finally, we sought to expand the scope of the three-component reaction to *ortho*-aminothiophenol (**9**) as a bisnucleophile, giving rise to benzo-thiazepine. However, upon subsection of acyl chloride **3a**, alkyne **4c** and *ortho*-aminothiophenol (**9**) to the sequence the yellow quinoline **10** was obtained in 40% yield. According to literature precedence the initially formed benzo-thiazepine is not stable under the reaction conditions, and after sulfur extrusion the quinoline is generated (Scheme 3).^[23]



Scheme 3. One-pot three-component synthesis of quinoline **10**.

Conclusions

In conclusion, we have established a versatile one-pot, three-component synthesis of 2,4-disubstituted 3*H*-benzo-[*b*][1,4]-diazepines in a consecutive coupling/addition/cyclocondensation sequence. Interestingly, all representatives are highly fluorescent in the solid state, but essentially non-fluorescent in solution at room temperature. Upon cooling the solutions show cryofluorescence that can be attributed to a freezing of the ring flip and aggregation. This thermoresponsive behavior of fluorophores as a consequence of restricted conformational changes opens new avenues for the development of tailor-made emitters in thermosensors and the fluorescence labeling of biomolecules, surfaces, or mesoporous materials. Studies expanding this novel modular approach to enhancing molecular diversity in targets of special interest to pharmaceutical and materials science applications are currently underway.

Experimental Section

General Considerations: All reactions involving water-sensitive compounds were carried out in flame-dried glassware under argon. Reagents and catalysts were purchased as reagent grade and were used without further purification. Solvents were dried with a solvent purification system. Flash column chromatography: silica gel 60, mesh 230–400. TLC: silica gel plates (60 F₂₅₄). ¹H NMR, ¹³C NMR, DEPT, NOESY, COSY, HMQC, and HMBC spectra were recorded with a 500 MHz NMR spectrometer in CDCl₃ as solvent. The assignments of quaternary C_{quat}, CH, CH₂, and CH₃ were made on the basis of DEPT spectra. Mass spectra were recorded with a quadrupole spectrometer. The melting points are un-

corrected. Elemental analyses were carried out in the microanalytical laboratory of the Pharmazeutisches Institut of the Heinrich-Heine-Universität Düsseldorf. Dielectric heating was performed in a single-mode microwave cavity producing continuous irradiation at 2450 MHz.

General Procedure for the Synthesis of 2,4-Disubstituted 3*H*-1,5-Benzodiazepines **6 under Conductive Heating Conditions (GP A):** In a 20 mL Schlenk tube, PdCl₂(PPh₃)₂ (15 mg, 0.02 mmol) and CuI (8 mg, 0.04 mmol) were dissolved in degassed THF (4 mL). Acyl chloride **3** (1.00 mmol), alkyne **4** (1.00 mmol), and triethylamine (1.05 mmol) were then added to this orange solution. The reaction mixture was stirred at room temperature for 1 h. Finally, the benzene-1,2-diamine **5** (1.10 mmol), followed by glacial acetic acid (1.0 mL), were added to this suspension, and the reaction mixture was heated at 90 °C in an oil bath for 16 h. After the system had cooled to room temperature, the solvent was removed under reduced pressure and the crude products were purified by flash chromatography on silica gel (hexane/ethyl acetate) to afford the analytically pure benzodiazepines **6** (for experimental details see Table 5, Entries 1–12).

General Procedure for the Synthesis of 2,4-Disubstituted 3*H*-1,5-Benzodiazepines **6 under Microwave Conditions (GP B):** In a 10 mL microwave tube, PdCl₂(PPh₃)₂ (15 mg, 0.02 mmol) and CuI (8 mg, 0.04 mmol) were dissolved in degassed THF (4 mL). Acyl chloride **3** (1.00 mmol), alkyne **4** (1.00 mmol), and triethylamine (1.05 mmol) were then added to this orange solution. The reaction mixture was stirred at room temperature for 1 h. Finally, the benzene-1,2-diamine **5** (1.10 mmol), followed by glacial acetic acid (1.0 mL), were added to this suspension, and the reaction mixture was heated at 120 °C in the microwave cavity for 1 h. After the system had cooled to room temperature, the solvent was removed under reduced pressure and the crude products were purified by flash chromatography on silica gel (hexane/ethyl acetate) to afford the analytically pure 1,5-benzodiazepines **6** or the quinoline **10** (for experimental details see Table 5, Entries 13–16).

2-(4-Methoxyphenyl)-4-phenyl-3*H*-1,5-benzodiazepine (6a**):** Compound **6a** was obtained as a yellow resin by GP A. ¹H NMR (500 MHz, CDCl₃): δ = 3.85 (s, 3 H), 6.95 (d, ³J = 8.7 Hz, 2 H), 7.30–7.36 (m, 5 H), 7.37 (dq, ³J = 7.1, ⁴J = 1.3 Hz, 2 H), 7.60 (dd, ³J = 7.5, ⁴J = 1.6 Hz, 2 H), 7.94 (d, ³J = 8.7 Hz, 2 H) ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 34.7 (CH₂), 55.4 (CH₃), 123.8 (2 × CH), 125.4 (CH), 126.3 (CH), 128.7 (CH), 128.7 (2 × CH), 128.8 (CH), 129.2 (2 × CH), 129.4 (C_{quat}), 130.0 (2 × CH), 131.0

(CH), 139.8 (C_{quat}), 141.0 (C_{quat}), 142.9 (C_{quat}), 148.7 (C_{quat}), 152.7 (C_{quat}), 161.9 (C_{quat}) ppm. IR (KBr): ν̄ = 2958 (m), 1561 (w), 1522 (w), 1463 (m), 1409 (w), 1274 (s), 1177 (w), 1125 (m), 1073 (m), 1029 (m), 910 (m), 847 (m), 800 (m), 759 (s), 695 (s), 602 (w) cm⁻¹. UV/Vis (CH₂Cl₂): λ_{max} (ε) = 285 (29900), 313 (25000), 345 nm (12200). Emission (CH₂Cl₂): λ_{max} (Stokes shift) = 442 nm (6400 cm⁻¹). Emission (solid state): λ_{max} = 502 nm. EI MS (70 eV): *m/z* (%) = 326 (13) [M]⁺, 272 (16), 244 (22), 238 (100), 90 (23), 107 (21), 92 (32), 77 (55), 76 (14), 64 (14), 57 (14). C₂₂H₁₈N₂O (326.39): calcd. C 80.96, H 5.56, N 8.58; found C 80.44, H 5.60, N 8.45.

4-[(4-Methoxyphenyl)-3*H*-1,5-benzodiazepin-2-yl]benzonitrile (6b**):** Compound **6b** was obtained as a yellow powder by GP A. m.p. 168 °C. ¹H NMR (500 MHz, CDCl₃): δ = 3.80 (s, 3 H), 6.90 (d, ³J = 8.9 Hz, 2 H), 7.31 (dq, ³J = 7.2, ⁴J = 2.2 Hz, 2 H), 7.53–7.56 (m, 2 H), 7.64 (d, ³J = 8.6 Hz, 2 H), 7.86 (d, ³J = 8.9 Hz, 2 H), 8.01 (d, ³J = 8.6 Hz, 2 H) ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 34.5 (CH₂), 55.4 (CH₃), 113.6 (C_{quat}), 114.1 (2 × CH), 118.3 (C_{quat}), 125.3 (CH), 126.1 (CH), 128.4 (2 × CH), 128.68 (CH), 128.74 (CH), 129.3 (C_{quat}), 130.0 (2 × CH), 132.3 (2 × CH), 139.9 (C_{quat}), 141.0 (C_{quat}), 141.2 (C_{quat}), 151.6 (C_{quat}), 152.8 (C_{quat}), 161.8 (C_{quat}) ppm. IR (KBr): ν̄ = 2954 (s), 2230 (s), 1601 (m), 1510 (w), 1463 (s), 1381 (m), 1285 (s), 1123 (s), 1074 (s), 1038 (m), 841 (m), 745 (s), 705 (m), 652 (w), 544 (w) cm⁻¹. UV/Vis (CH₂Cl₂): λ_{max} (ε) = 275 (16400), 324 (9100), 347 nm (6300). Emission (CH₂Cl₂): λ_{max} (Stokes shift) = 385 nm (2800 cm⁻¹). Emission (solid state): λ_{max} = 509 nm. EI MS (70 eV): *m/z* (%) = 352 (25), 351 (100) [M]⁺, 350 (53), 336 (28), 320 (21), 307 (13), 299 (19), 298 (24), 297 (57), 296 (49), 271 (18), 270 (10), 269 (52), 263 (14), 262 (19), 253 (13), 252 (56), 249 (23), 219 (10), 191 (11), 190 (30), 135 (82), 133 (37), 127 (16), 107 (12), 92 (14), 77 (22). C₂₃H₁₇N₃O (351.40): calcd. C 78.61, H 4.88, N 11.96; found: C 78.60, H 4.80, N 12.17.

2-(4-Nitrophenyl)-4-*p*-tolyl-3*H*-1,5-benzodiazepine (6c**):** Compound **6c** was obtained as a yellow powder by GP A; m.p. 161 °C. ¹H NMR (500 MHz, CDCl₃): δ = 2.39 (s, 3 H), 7.26 (d, ³J = 8.2 Hz, 2 H), 7.35–7.40 (m, 2 H), 7.60–7.62 (m, 2 H), 7.86 (d, ³J = 8.2 Hz, 2 H), 8.11 (d, ³J = 9.0 Hz, 2 H), 8.24 (d, ³J = 9.0 Hz, 2 H) ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 21.4 (CH₃), 34.8 (CH₂), 123.8 (2 × CH), 125.5 (CH), 126.3 (CH), 128.2 (2 × CH), 128.8 (4 × CH), 129.6 (2 × CH), 134.0 (C_{quat}), 139.9 (C_{quat}), 141.0 (C_{quat}), 141.6 (C_{quat}), 142.9 (C_{quat}), 148.7 (C_{quat}), 151.3 (C_{quat}), 153.3 (C_{quat}) ppm. IR (KBr): ν̄ = 2923 (m), 2853 (w), 1595 (m), 1562 (w), 1542 (w), 1521 (s), 1458 (w), 1436 (m), 1407 (w), 1376 (w), 1341 (s), 1323 (m), 1257 (m), 1186 (w), 1112 (m), 1051 (w), 1005 (m),

Table 5. Experimental details of the synthesis of 2,4-disubstituted 3*H*-1,5-benzodiazepines **6**.

Entry	mg (mmol) of acyl chloride 3	mg (mmol) of alkyne 4	mg (mmol) of benzene-1,2-diamine 5	mg (% yield) of 1,5-benzodiazepines 6
1	171 (1.00), 3a	103 (1.00), 4a	119 (1.10), 5a	287 (88), 6a
2	171 (1.00), 3a	128 (1.00), 4b	119 (1.10), 5a	187 (53), 6b
3	155 (1.00), 3b	148 (1.00), 4c	119 (1.10), 5a	160 (45), 6c
4	147 (1.00), 3c	128 (1.00), 4b	119 (1.10), 5a	177 (54), 6d
5	147 (1.00), 3c	83 (1.00), 4d	119 (1.10), 5a	164 (58), 6e
6	147 (1.00), 3c	104 (1.00), 4e	119 (1.10), 5a	164 (54), 6f
7	147 (1.00), 3c	161 (1.00), 4f	195 (1.10), 5b	275 (64), 6g
8	176 (1.00), 3d	159 (1.00), 4g	195 (1.10), 5b	246 (54), 6h
9	105 (1.00), 3e	161 (1.00), 4f	195 (1.10), 5b	314 (81), 6i
10	186 (1.00), 3f	83 (1.00), 4d	195 (1.10), 5b	336 (86), 6j
11	176 (1.00), 3d	83 (1.00), 4d	195 (1.10), 5b	224 (59), 6k
12	147 (1.00), 3c	104 (1.00), 4e	195 (1.10), 5b	164 (44), 6l
13	171 (1.00), 3a	133 (1.00), 4h	119 (1.10), 5a	225 (63), 6m
14	171 (1.00), 3a	148 (1.00), 4c	119 (1.10), 5a	149 (40), 6n
15	186 (1.00), 3f	83 (1.00), 4d	119 (1.10), 5a	151 (47), 6o
16	176 (1.00), 3d	148 (1.00), 4c	138 (1.10), 9	145 (40), 10

867 (m), 854 (s), 786 (w), 767 (s), 753 (m), 733 (w), 691 (m), 614 (w), 578 (m) cm^{-1} . UV/Vis (CH_2Cl_2): λ_{max} (ϵ) = 268 (44400), 284 (40100), 313 (30300), 343 (22000), 370 nm (16600). Emission (CH_2Cl_2): λ_{max} (Stokes shift) = 516 nm (7600 cm^{-1}). Emission (solid state): λ_{max} = 527 nm. EI MS (70 eV): m/z (%) = 356 (27) [$\text{M} + \text{H}$] $^{+}$, 355 (100) [M] $^{+}$, 354 (35) [$\text{M} - \text{H}$] $^{+}$, 341 (11), 340 (42), 309 (11), 308 (24), 307 (10), 294 (17), 293 (11), 292 (22), 233 (22), 117 (35), 116 (10), 115 (23), 102 (11), 91 (22), 90 (14), 89 (12), 76 (11). $\text{C}_{22}\text{H}_{17}\text{N}_3\text{O}_2$ (355.39): calcd. C 74.35, H 4.82, N 11.82; found C 74.05, H 4.94, N 11.61.

4-[(Thien-2-yl)-3H-1,5-benzodiazepin-2-yl]benzonitrile (6d): Compound **6d** was obtained as a yellow solid by GP A; m.p. 155 °C. ^1H NMR (500 MHz, CDCl_3): δ = 3.60 (br. s, 2 H), 7.09 (dd, 3J = 5.1, 3J = 3.8 Hz, 1 H), 7.34–7.37 (m, 2 H), 7.48 (dd, 3J = 5.1, 4J = 1.0 Hz, 1 H), 7.55–7.59 (m, 2 H), 7.63 (dd, 3J = 3.8, 4J = 1.0 Hz, 1 H), 7.74 (d, 3J = 8.7 Hz, 2 H), 8.15 (d, 3J = 8.7 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, CDCl_3): δ = 35.1 (CH_2), 113.9 (C_{quat}), 118.3 (C_{quat}), 125.7 (CH), 126.4 (CH), 127.9 (CH), 128.5 (2 $\times$ CH), 128.7 (CH), 128.87 (CH), 128.91 (CH), 131.7 (CH), 132.4 (2 $\times$ CH), 140.2 (C_{quat}), 140.3 (C_{quat}), 140.9 (C_{quat}), 143.6 (C_{quat}), 148.0 (C_{quat}), 151.7 (C_{quat}) ppm. IR (KBr): $\tilde{\nu}$ = 2956 (w), 2230 (s), 1542 (w), 1425 (w), 1289 (s), 1124 (m), 1076 (m), 852 (s), 803 (s), 763 (s), 701 (s), 621 (m), 559 (m), 537 (w), 517 (w) cm^{-1} . UV/Vis (CH_2Cl_2): λ_{max} (ϵ) = 266 (21600), 304 (14400), 325 (13100), 348 nm (10400). Emission (CH_2Cl_2): λ_{max} (Stokes shift) = 338 nm (3000 cm^{-1}). Emission (solid state): λ_{max} = 508 nm. EI MS (70 eV): m/z = 328 [$\text{M} + \text{H}$] $^{+}$ (24), 327 [M] $^{+}$ (100), 326 (81), 295 (17), 294 (76), 275 (21), 274 (37), 273 (56), 272 (80), 252 (13), 239 (15), 238 (20), 219 (16), 210 (30), 209 (19), 190 (14), 164 (10), 149 (15), 128 (11), 127 (22), 111 (69), 109 (49), 102 (10), 84 (14), 83 (15), 39 (20). $\text{C}_{20}\text{H}_{13}\text{N}_2\text{S}$ (327.40): calcd. C 73.37, H 4.00, N 12.83; found C 73.51, H 4.19, N 12.81.

2-Butyl-4-(thien-2-yl)-3H-1,5-benzodiazepine (6e): Compound **6e** was obtained as a yellow resin by GP A. ^1H NMR (500 MHz, CDCl_3): δ = 0.91 (t, 3J = 7.4 Hz, 3 H), 1.38 (sext, 3J = 7.4 Hz, 2 H), 1.73 (q, 3J = 7.6 Hz, 2 H), 2.57 (t, 3J = 7.6 Hz, 2 H), 3.23 (br. s, 2 H), 7.14–7.16 (m, 1 H), 7.26–7.30 (m, 2 H), 7.44–7.47 (m, 1 H), 7.51–7.53 (m, 2 H), 7.64–7.65 (m, 1 H) ppm. ^{13}C NMR (125 MHz, CDCl_3): δ = 13.8 (CH_3), 22.3 (CH_2), 28.2 (CH_2), 38.4 (CH_2), 40.1 (CH_2), 125.0 (CH), 125.1 (CH), 127.7 (CH), 127.8 (CH), 128.4 (CH), 128.8 (CH), 131.3 (CH), 140.0 (C_{quat}), 140.7 (C_{quat}), 144.2 (C_{quat}), 148.4 (C_{quat}), 161.4 (C_{quat}) ppm. IR (KBr): $\tilde{\nu}$ = 2956 (s), 2927 (s), 2870 (m), 1630 (m), 1603 (m), 1573 (s), 1544 (w), 1525 (w), 1460 (m), 1424 (s), 1358 (w), 1313 (m), 1265 (m), 1206 (m), 1110 (w), 1059 (w), 981 (w), 856 (m), 762 (s), 714 (s), 622 (w) cm^{-1} . UV/Vis (CH_2Cl_2): λ_{max} (ϵ) = 268 (18800), 288 (14500), 335 nm (12300). Emission (CH_2Cl_2): λ_{max} (Stokes shift) = 458 nm (8000 cm^{-1}), 500. Emission (solid state): λ_{max} = 535 nm. EI MS (70 eV): m/z (%) = 282 (5) [M] $^{+}$, 241 (18), 240 (100), 207 (14), 200 (11), 109 (15). $\text{C}_{17}\text{H}_{18}\text{N}_2\text{S}$ (282.40): calcd. C 72.30, H 6.42, N 9.92; found C 72.05, H 6.44, N 9.81.

2-(Pyridin-2-yl)-4-(thien-2-yl)-3H-1,5-benzodiazepine (6f): Compound **6f** (Table 6) was obtained as light yellow crystals by GP A; m.p. 130 °C. ^1H NMR (500 MHz, CDCl_3): δ = 4.03 (br. s, 2 H), 7.05–7.08 (m, 1 H), 7.32–7.38 (m, 3 H), 7.43 (d, 3J = 5.0 Hz, 1 H), 7.57–7.61 (m, 2 H), 7.76 (dt, 3J = 8.0, 4J = 1.0 Hz, 1 H), 8.11 (d, 3J = 3.7 Hz, 1 H), 8.34 (d, 3J = 8.0 Hz, 1 H), 8.76 (d, 3J = 4.8 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, CDCl_3): δ = 32.8 (CH_2), 123.2 (CH), 124.8 (CH), 125.2 (CH), 126.0 (CH), 127.7 (CH), 128.7 (CH), 128.8 (CH), 130.9 (CH), 131.2 (CH), 136.6 (CH), 140.8 (C_{quat}), 140.9 (C_{quat}), 144.0 (C_{quat}), 148.7 (CH), 150.3 (C_{quat}), 153.7 (C_{quat}), 154.9 (C_{quat}) ppm. IR (KBr): $\tilde{\nu}$ = 3054 (w), 1596 (m), 1576

(s), 1466 (m), 1425 (s), 1356 (w), 1325 (s), 1263 (m), 1215 (m), 1198 (m), 1155 (w), 1115 (w), 1089 (w), 1054 (m), 1037 (m), 1089 (m), 994 (w), 981 (m), 898 (w), 874 (m), 758 (s), 741 (m), 705 (s), 681 (s), 656 (w), 622 (m), 517 (s) cm^{-1} . UV/Vis (CH_2Cl_2): λ_{max} (ϵ) = 259 (40900), 274 (40100), 291 (41300), 341 nm (26000). Emission (CH_2Cl_2): λ_{max} (Stokes shift) = 420 nm (5500 cm^{-1}). Emission (solid state): λ_{max} = 493 nm. EI MS (70 eV, m/z): 304 [$\text{M} + \text{H}$] $^{+}$ (25), 303 [M] $^{+}$ (100), 302 (40), 271 (11), 270 (37), 225 (12), 195 (34), 194 (38), 167 (14), 109 (25), 90 (17), 89 (19), 79 (11), 78 (55), 77 (12), 76 (14), 69 (12), 65 (24), 64 (13), 63 (18), 52 (12), 51 (32), 50 (12), 45 (13), 39 (26). $\text{C}_{18}\text{H}_{13}\text{N}_2\text{S}$ (303.38): calcd. C 71.26, H 4.32, N 13.85; found C 70.81, H 4.40, N 13.57.

Table 6. Crystal data and structure refinement for **6f**.

Structure	6f
Empirical formula	$\text{C}_{18}\text{H}_{13}\text{N}_2\text{S}$
Formula weight	303.37
Temperature	200(2) K
Wavelength	0.71073 Å
Crystal system	orthorhombic
Space group	$Pnma$
Z	4
Unit cell dimensions	$a = 17.721(3)$ Å, $\alpha = 90^\circ$ $b = 16.894(3)$ Å, $\beta = 90^\circ$ $c = 4.8192(9)$ Å, $\gamma = 90^\circ$
Volume	1442.7(4) Å ³
Density (calculated)	1.40 g cm^{-3}
Absorption coefficient μ	0.22 [mm^{-1}]
Crystal shape	polyhedron
Crystal size	$0.31 \times 0.20 \times 0.12$ mm ³
Crystal color	yellow
Theta range for data collection	2.6–28.4°
Index ranges	$-8 \leq h \leq 23$, $-17 \leq k \leq 18$, $-6 \leq l \leq 3$
Reflections collected	4911
Independent reflections	1602 [$R(\text{int}) = 0.0356$]
Observed reflections	1062 [$I > 2\sigma(I)$]
Absorption correction	semiempirical from equivalents
Max. and min. transmission	0.97 and 0.93
Refinement method	full-matrix least-squares on F^2
Data/restraints/parameters	1602/47/108
Goodness-of-fit on F^2	1.04
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.048$, $wR_2 = 0.119$
Largest diff. peak and hole	0.37 and -0.23 e Å ⁻³

Methyl 4-[7,8-Dichloro-4-(thien-2-yl)-3H-1,5-benzodiazepin-2-yl]-benzoate (6g): Compound **6g** was obtained as a yellow solid by GP A; m.p. 192 °C. ^1H NMR (500 MHz, CDCl_3): δ = 3.94 (s, 3 H), 3.96 (br. s, 2 H), 7.08 (dd, 3J = 5.0, 3J = 3.8 Hz, 1 H), 7.49 (dd, 3J = 5.0, 4J = 1.0 Hz, 1 H), 7.65 (dd, 3J = 3.8, 4J = 1.0 Hz, 1 H), 7.676 (s, 1 H), 7.684 (s, 1 H), 8.08–8.13 (m, 4 H) ppm. ^{13}C NMR (125 MHz, CDCl_3): δ = 35.6 (CH_2), 52.4 (CH_3), 127.3 (CH), 128.0 (CH), 128.2 (2 $\times$ CH), 128.9 (C_{quat}), 129.5 (C_{quat}), 129.6 (CH), 129.7 (CH), 129.9 (2 $\times$ CH), 132.2 (C_{quat}), 132.4 (CH), 139.5 (C_{quat}), 139.9 (C_{quat}), 140.3 (C_{quat}), 143.2 (C_{quat}), 149.3 (C_{quat}), 154.0 (C_{quat}), 166.3 (C_{quat}) ppm. IR (KBr): $\tilde{\nu}$ = 2961 (s), 2873 (s), 1723 (s), 1654 (w), 1583 (s), 1517 (w), 1447 (m), 1379 (w), 1277 (s), 1192 (w), 1277 (s), 1121 (s), 1074 (m), 1017 (m), 879 (w), 855 (w), 798 (w), 768 (m), 744 (m), 721 (m), 552 (w), 520 (w) cm^{-1} . EI MS (70 eV): m/z (%) = 432 (16), 431 (20), 430 (69), 429 (48), 428 (100), 427 (43) [M] $^{+}$, 397 (47), 396 (14), 395 (50), 371 (43), 370 (17), 369 (60), 268 (14), 109 (87). UV/Vis (CH_2Cl_2): λ_{max} (ϵ) = 272 (29200), 349 nm (13900). Emission (CH_2Cl_2): λ_{max} (Stokes shift) = 418 nm (4700 cm^{-1}). Emission (solid state): λ_{max} = 510 nm. $\text{C}_{21}\text{H}_{14}\text{Cl}_2\text{N}_2\text{O}_2\text{S}$ (429.32): calcd. C 58.75, H 3.29, N 6.53; found C 58.56, H 3.38, N 6.40.

2-(4-*tert*-Butylphenyl)-7,8-dichloro-4-(4-chlorophenyl)-3H-1,5-benzodiazepine (6h): Compound **6h** was obtained as a light yellow solid by GP A; m.p. 97 °C. ¹H NMR (500 MHz, CDCl₃): δ = 1.33 (s, 9 H), 3.72 (br. s, 2 H), 7.40 (d, ³J = 8.4 Hz, 2 H), 7.45 (d, ³J = 8.3 Hz, 2 H), 7.67 (s, 1 H), 7.68 (s, 1 H), 7.88 (d, ³J = 8.3 Hz, 2 H), 7.88 (d, ³J = 8.4 Hz, 2 H) ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 32.1 (3 × CH₃), 34.8 (CH₂), 34.9 (C_{quat}), 125.9 (2 × CH), 128.0 (2 × CH), 128.7 (C_{quat}), 128.98 (C_{quat}), 129.04 (2 × CH), 129.5 (2 × CH), 129.75 (CH), 129.80 (CH), 133.7 (C_{quat}), 135.1 (C_{quat}), 137.4 (C_{quat}), 139.7 (C_{quat}), 140.1 (C_{quat}), 154.0 (C_{quat}), 154.9 (C_{quat}), 155.0 (C_{quat}) ppm. IR (KBr): ν̄ = 2964 (s), 1590 (s), 1560 (s), 1491 (m), 1446 (s), 1400 (m), 1364 (w), 1306 (s), 1192 (s), 1119 (s), 1094 (s), 1012 (s), 942 (w), 888 (m), 858 (m), 839 (m), 807 (s), 750 (w), 723 (w), 678 (w), 648 (w), 571 (s) cm⁻¹. UV/Vis (CH₂Cl₂): λ_{max} (ε) = 276 (45400), 337 nm (15400). Emission (CH₂Cl₂): λ_{max} (Stokes shift) = 412 nm (5400 cm⁻¹). Emission (solid state): λ_{max} = 426 nm. EI MS (70 eV): m/z (%) = 458 (8), 456 (19), 454 (16) [M]⁺, 399 (19), 397 (21), 353 (17), 351 (21), 317 (19), 315 (14), 299 (14), 298 (11), 297 (12), 283 (19), 281 (19), 277 (42), 276 (15), 275 (60), 241 (24), 161 (26), 159 (13), 149 (11), 144 (20), 143 (19), 141 (36), 139 (100), 137 (19), 129 (17), 117 (12), 116 (17), 115 (32), 113 (19), 111 (59), 105 (26), 103 (17), 102 (16), 101 (17), 91 (22), 77 (17), 76 (12), 75 (24), 71 (11), 69 (10), 58 (17), 57 (51), 55 (16), 43 (84), 41 (50), 40 (12), 39 (12). C₂₅H₂₁Cl₃N₂ (455.81): calcd. C 65.88, H 4.64, N 6.15; found C 65.57, H 4.71, N 6.04.

Methyl 4-(7,8-Dichloro-4-cyclopropyl-3H-1,5-benzodiazepin-2-yl)-benzoate (6i): Compound **6i** was obtained as a light greenish powder by GP A; m.p. 118 °C. ¹H NMR (500 MHz, CDCl₃): δ = 0.89–0.96 (m, 4 H), 1.85–1.91 (m, 1 H), 3.32 (br. s, 2 H), 3.96 (s, 3 H), 7.49 (s, 1 H), 7.61 (s, 1 H), 8.09 (d, ³J = 8.3 Hz, 2 H), 8.15 (d, ³J = 8.3 Hz, 2 H) ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 12.2 (2 × CH₂), 15.9 (CH), 38.5 (CH₂), 52.4 (CH₃), 128.0 (C_{quat}), 128.2 (2 × CH), 129.0 (C_{quat}), 129.1 (CH), 129.6 (CH), 130.0 (2 × CH), 132.1 (C_{quat}), 139.4 (C_{quat}), 139.8 (C_{quat}), 140.7 (C_{quat}), 153.7 (C_{quat}), 163.7 (C_{quat}), 166.4 (C_{quat}) ppm. IR (KBr): ν̄ = 3007 (w), 2952 (w), 1722 (s), 1611 (s), 1439 (s), 1402 (m), 1374 (w), 1279 (s), 1193 (m), 1179 (m), 1117 (s), 1056 (w), 1018 (w), 970 (w), 948 (w), 887 (m), 767 (m), 698 (m), 669 (w), 611 (w), 557 (w) cm⁻¹. UV/Vis (CH₂Cl₂): λ_{max} (ε) = 255 (20500), 276 (23100), 345 nm (7500). Emission (CH₂Cl₂): λ_{max} (Stokes shift) = 385 nm (3000 cm⁻¹). Emission (solid state): λ_{max} = 420 nm. EI MS (70 eV): m/z (%) = 390 (14), 389 (26), 388 (67), 387 (54), 386 (100) [M]⁺, 385 (36), 373 (15), 371 (22), 360 (20), 359 (13), 358 (28), 329 (12), 327 (18), 291 (10), 251 (12), 227 (20), 226 (19), 225 (29), 161 (14), 115 (12), 102 (21), 101 (11), 77 (10), 76 (13), 67 (12), 65 (11), 59 (24), 41 (37), 39 (14). C₂₀H₁₆Cl₂N₂O₂ (387.26): calcd. C 62.03, H 4.16, N 7.23; found C 61.82, H 4.23, N 7.12.

2-Butyl-7,8-dichloro-4-(4-nitrophenyl)-3H-1,5-benzodiazepine (6j): Compound **6j** was obtained as a yellow solid by GP A; m.p. 143 °C. ¹H NMR (500 MHz, CDCl₃): δ = 0.85 (t, ³J = 7.4 Hz, 3 H), 1.30 (sext, ³J = 7.4 Hz, 2 H), 1.62 (q, ³J = 7.5 Hz, 2 H), 2.53 (t, ³J = 7.5 Hz, 2 H), 7.55 (s, 1 H), 7.62 (s, 1 H), 8.18 (d, ³J = 8.7 Hz, 2 H), 8.32 (d, ³J = 8.7 Hz, 2 H) ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 13.7 (CH₃), 22.2 (CH₂), 28.1 (CH₂), 37.9 (CH₂), 40.1 (CH₂), 123.9 (2 × CH), 128.6 (C_{quat}), 129.1 (3 CH), 129.4 (C_{quat}), 129.7 (CH), 139.2 (C_{quat}), 139.8 (C_{quat}), 141.9 (C_{quat}), 149.0 (C_{quat}), 152.1 (C_{quat}), 162.1 (C_{quat}) ppm. IR (KBr): ν̄ = 2997 (w), 1637 (m), 1598 (m), 1520 (s), 1443 (s), 1347 (s), 1302 (m), 1180 (m), 1119 (m), 1049 (w), 888 (s), 856 (s), 801 (m), 753 (m), 717 (m), 694 (s), 671 (w), 617 (w) cm⁻¹. UV/Vis (CH₂Cl₂): λ_{max} (ε) = 359 (14600), 284 nm (27200). Emission (CH₂Cl₂): λ_{max} (Stokes shift) = 450 nm (5600 cm⁻¹). Emission (solid state): λ_{max} = 525 nm. EI MS (70 eV): m/z (%) = 391 (2), 389 (3), 351 (13), 350 (14), 349 (68), 348

(30), 347 (100), 346 (17). C₁₉H₁₇Cl₂N₃O₂ (390.26): calcd. C 58.47, H 4.39, N 10.77; found C 58.50, H 4.33, N 11.21.

2-Butyl-7,8-dichloro-4-(4-chlorophenyl)-3H-1,5-benzodiazepine (6k): Compound **6k** was obtained as a yellow resin by GP A. ¹H NMR (500 MHz, CDCl₃): δ = 0.85 (t, ³J = 7.4 Hz, 3 H), 1.29 (sext, ³J = 7.4 Hz, 2 H), 1.60 (q, ³J = 7.5 Hz, 2 H), 2.49 (t, ³J = 7.5 Hz, 2 H), 3.10 (br. s, 2 H), 7.45 (d, ³J = 8.6 Hz, 2 H), 7.54 (s, 1 H), 7.60 (s, 1 H), 7.94 (d, ³J = 8.6 Hz, 2 H) ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 13.7 (CH₃), 22.2 (CH₂), 28.0 (CH₂), 37.7 (CH₂), 40.0 (CH₂), 128.3 (C_{quat}), 128.6 (C_{quat}), 129.0 (CH), 129.1 (2 × CH), 129.5 (3 × CH), 134.9 (C_{quat}), 137.5 (C_{quat}), 139.66 (C_{quat}), 139.72 (C_{quat}), 153.3 (C_{quat}), 162.5 (C_{quat}) ppm. IR (KBr): ν̄ = 2957 (s), 2870 (s), 1655 (m), 1592 (s), 1490 (s), 1449 (s), 1399 (m), 1290 (m), 1179 (m), 1092 (s), 1011 (s), 886 (m), 842 (m), 752 (w), 675 (m) cm⁻¹. UV/Vis (CH₂Cl₂): λ_{max} (ε) = 272 (30900), 330 nm (10200). Emission (CH₂Cl₂): λ_{max} (Stokes shift) = 447 nm (7700 cm⁻¹). Emission (solid state): λ_{max} = 490 nm. EI MS (70 eV): m/z (%) = 382 [³⁷Cl,³⁷Cl,³⁵Cl M]⁺ (2), 380 [³⁷Cl,³⁵Cl,³⁵Cl M]⁺ (4), 378 [³⁵Cl,³⁵Cl,³⁵Cl M]⁺ (4), 340 [³⁷Cl,³⁷Cl,³⁵Cl M – C₃H₆]⁺ (32), 338 [³⁷Cl,³⁵Cl,³⁵Cl M – C₃H₆]⁺ (97), 336 [³⁵Cl,³⁵Cl,³⁵Cl M – C₃H₆]⁺ (100), 300 (10), 299 (10), 298 (13), 296 (12), 200 (14), 193 (12), 191 (37), 139 (13), 137 (14). C₁₉H₁₇Cl₃N₂ (379.71): calcd. C 60.10, H 4.51, N 7.38; found C 60.41, H 4.19, N 7.35.

7,8-Dichloro-2-(pyridin-2-yl)-4-(thien-2-yl)-3H-1,5-benzodiazepine (6l): Compound **6l** was obtained as a light yellow crystals by GP A; m.p. 269 °C. ¹H NMR (500 MHz, CDCl₃): δ = 1.65 (br. s, 2 H), 7.08 (t, ³J = 4.4 Hz, 1 H), 7.39 (dd, ³J = 6.7, ⁴J = 4.9 Hz, 1 H), 7.46 (d, ³J = 5.0 Hz, 1 H), 7.69 (s, 2 H), 7.78 (dt, ³J = 7.6, ⁴J = 1.0 Hz, 1 H), 8.14 (d, ³J = 3.7 Hz, 1 H), 8.32 (d, ³J = 14.0 Hz, 1 H), 8.76 (d, ³J = 4.8 Hz, 1 H) ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 33.2 (CH₂), 123.3 (CH), 125.2 (CH), 127.9 (CH), 128.5 (C_{quat}), 129.8 (CH), 129.9 (CH), 131.8 (CH), 132.0 (CH), 136.7 (CH), 140.1 (C_{quat}), 140.3 (C_{quat}), 143.4 (C_{quat}), 148.8 (2 × C_{quat}), 153.3 (C_{quat}), 156.0 (C_{quat}), 165.9 (C_{quat}) ppm. IR (KBr): ν̄ = 2924 (w), 1694 (w), 1591 (m), 1564 (s), 1524 (m), 1464 (m), 1448 (s), 1427 (s), 1376 (m), 1353 (m), 1316 (s), 1255 (m), 1193 (s), 1156 (m), 1122 (s), 1089 (m), 1059 (m), 1037 (m), 995 (w), 958 (w), 933 (w), 882 (s), 858 (w), 846 (m), 807 (s), 787 (s), 776 (s), 741 (m), 714 (s), 682 (w), 663 (w), 621 (m), 566 (m), 548 (m), 520 (m) cm⁻¹. UV/Vis (CH₂Cl₂): λ_{max} (ε) = 264 (14600), 294 (14500), 348 nm (9300). Emission (CH₂Cl₂): λ_{max} (Stokes shift) = 416 nm (4700 cm⁻¹). Emission (solid state): λ_{max} = 510 nm. EI MS (70 eV): m/z (%) = 375 (12), 374 (16), 373 (60), 372 (36), 371 (100) [M]⁺, 370 (20), 340 (16), 338 (27), 267 (10), 265 (20), 264 (21), 263 (29), 262 (23), 109 (40), 105 (11), 97 (13), 79 (11), 78 (56), 69 (13), 65 (23), 45 (12), 39 (11). C₁₈H₁₁Cl₂N₃S (372.27): calcd. C 58.07, H 2.98, N 11.29; found C 57.92, H 3.06, N 11.10.

2,4-Bis(4-methoxyphenyl)-3H-1,5-benzodiazepine (6m): Compound **6m** was obtained as a yellow powder by GP B; m.p. 173 °C. ¹H NMR (500 MHz, CDCl₃): δ = 3.83 (s, 6 H), 6.92 (d, ³J = 8.9 Hz, 4 H), 7.31 (dd, ³J = 6.1, ⁴J = 3.5 Hz, 2 H), 7.57 (d, ³J = 6.1, ⁴J = 3.5 Hz, 2 H), 7.95 (d, ³J = 8.9 Hz, 4 H) ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 34.5 (CH₂), 55.4 (2 × CH₃), 114.0 (4 × CH), 125.0 (2 × CH), 128.6 (2 × CH), 129.9 (4 × CH), 130.0 (2 × C_{quat}), 140.8 (2 × C_{quat}), 153.6 (2 × C_{quat}), 161.6 (2 × C_{quat}) ppm. IR (KBr): ν̄ = 3012 (w), 2968 (w), 2840 (w), 1605 (s), 1593 (s), 1514 (s), 1458 (m), 1434 (m), 1323 (s), 1231 (s), 1214 (m), 1172 (s), 1110 (m), 1023 (s), 854 (m), 837 (m), 815 (w), 801 (w), 763 (s), 722 (w), 644 (w), 563 (w), 561 (w), 516 (s) cm⁻¹. UV/Vis (CH₂Cl₂): λ_{max} (ε) = 285 (33700), 331 nm (13700). Emission (CH₂Cl₂): λ_{max} (Stokes shift) = 388 nm (4400 cm⁻¹), 440. Emission (solid state): λ_{max} = 495 nm. EI MS (70 eV): m/z (%) = 357 (25) [M + H]⁺, 356 (88) [M]⁺, 355 (35),

341 (15), 249 (13), 224 (39), 209 (15), 192 (10), 181 (12), 178 (11), 134 (11), 133 (100), 118 (17), 103 (13), 90 (20), 89 (14), 77 (22). $C_{23}H_{20}N_2O_2$ (356.42): calcd. C 77.51, H 5.66, N 7.86; found C 77.15, H 5.69, N 7.76.

2-(4-Methoxyphenyl)-4-(4-nitrophenyl)-3H-1,5-benzodiazepine (6n):

Compound **6n** was obtained as a yellow solid by GP B; m.p. 156 °C. 1H NMR (500 MHz, $CDCl_3$): δ = 3.85 (s, 3 H), 6.95 (d, 3J = 8.7 Hz, 2 H), 7.37 (dq, 3J = 7.1, 4J = 1.3 Hz, 2 H), 7.60 (dd, 3J = 7.5, 4J = 1.6 Hz, 2 H), 7.94 (d, 3J = 8.7 Hz, 2 H), 8.12 (d, 3J = 8.6 Hz, 2 H), 8.24 (d, 3J = 8.6 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 34.7 (CH_2), 55.4 (CH_3), 123.8 ($2 \times CH$), 125.4 (CH), 126.3 (CH), 128.7 (CH), 128.77 ($2 \times CH$), 128.83 (CH), 129.4 (C_{quat}), 130.0 ($2 \times CH$), 139.8 (C_{quat}), 141.0 (C_{quat}), 142.9 (C_{quat}), 148.7 (C_{quat}), 151.3 (C_{quat}), 152.7 (C_{quat}), 161.9 (C_{quat}) ppm. IR (KBr): $\tilde{\nu}$ = 2923 (w), 2844 (w), 1686 (w), 1607 (s), 1585 (s), 1563 (m), 1515 (s), 1458 (m), 1436 (m), 1345 (s), 1325 (s), 1261 (s), 1216 (w), 1203 (w), 1172 (m), 1056 (w), 1031 (m), 867 (m), 855 (m), 841 (s), 767 (m), 732 (w), 692 (m), 617 (w), 534 (w), 519 (m) cm^{-1} . UV/Vis (CH_2Cl_2): λ_{max} (ϵ) = 277 (27000), 292 (29300), 313 (22700), 366 nm (8300). Emission (CH_2Cl_2): λ_{max} (Stokes shift) = 436 (4400 cm^{-1}), 512 nm. Emission (solid state): λ_{max} = 530 nm. EI MS (70 eV): m/z (%) = 371 (12) $[M]^+$, 317 (16), 292 (10), 289 (22), 283 (26), 255 (12), 165 (17), 136 (11), 135 (100), 107 (21), 92 (32), 77 (46), 76 (14), 71 (12), 64 (14), 63 (11), 57 (14), 43 (11). $C_{22}H_{17}N_3O_3$ (371.39): calcd. C 71.15, H 4.61, N 11.31; found C 70.87, H 4.66, N 11.18.

2-Butyl-4-(4-nitrophenyl)-3H-1,5-benzodiazepine (6o):

Compound **6o** was obtained as a yellow resin by GP B. 1H NMR (500 MHz, $CDCl_3$): δ = 0.84 (t, 3J = 7.3 Hz, 3 H), 1.30 (sext, 3J = 7.5 Hz, 2 H), 1.62 (q, 3J = 7.6 Hz, 2 H), 2.53 (t, 3J = 7.6 Hz, 2 H), 3.29 (br. s, 2 H), 7.29–7.31 (m, 2 H), 7.44–7.47 (m, 1 H), 7.52–7.54 (m, 1 H), 8.19 (d, 3J = 8.8 Hz, 2 H), 8.32 (d, 3J = 8.8 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.7 (CH_3), 22.2 (CH_2), 28.3 (CH_2), 37.5 (CH_2), 40.1 (CH_2), 123.8 ($2 \times CH$), 125.2 (CH), 126.1 (CH), 127.8 (CH), 128.7 (CH), 128.9 ($2 \times CH$), 140.0 (C_{quat}), 140.3 (C_{quat}), 142.6 (C_{quat}), 148.8 (C_{quat}), 151.0 (C_{quat}), 160.8 (C_{quat}) ppm. IR (KBr): $\tilde{\nu}$ = 2958 (m), 1662 (m), 1599 (s), 1521 (s), 1461 (m), 1346 (s), 1109 (m), 1048 (m), 1011 (m), 855 (s), 765 (s), 713 (m), 696 (w) cm^{-1} . UV/Vis (CH_2Cl_2): λ_{max} (ϵ) = 266 (24100), 284 (24500), 357 nm (14700). Emission (CH_2Cl_2): λ_{max} = 494 nm (7800 cm^{-1}). Emission (solid state): λ_{max} = 517 nm. EI MS (70 eV): m/z (%) = 321 (2) $[M]^+$, 280 (20), 279 (100), 278 (16), 264 (11), 239 (13), 233 (10), 232 (23), 231 (22), 219 (12), 217 (11), 193 (14), 192 (19), 190 (10), 145 (11), 132 (32), 131 (22), 130 (20), 104 (14), 103 (14), 102 (28), 90 (22), 89 (30), 78 (11), 77 (26), 76 (33), 75 (13), 65 (11), 63 (14), 55 (12), 51 (12), 50 (14), 43 (17), 42 (14), 41 (41), 39 (20). $C_{19}H_{19}N_3O_2$ (321.37): calcd. C 71.01, H 5.96, N 13.08; found C 70.75, H 5.98, N 12.93.

2-(4-Chlorophenyl)-4-(4-nitrophenyl)quinoline (10):

Compound **10** was obtained as a yellow solid by GP B; m.p. 145 °C. 1H NMR (500 MHz, $CDCl_3$): δ = 7.41–7.49 (m, 4 H), 7.63–7.74 (m, 5 H), 8.10 (d, 3J = 8.6 Hz, 2 H), 8.36 (d, 3J = 8.8 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 118.7 ($2 \times CH$), 123.9 ($2 \times CH$), 124.3 (C_{quat}), 124.8 ($2 \times CH$), 125.0 (C_{quat}), 127.3 (CH), 128.8 ($2 \times CH$), 129.1 ($2 \times CH$), 130.5 ($2 \times CH$), 132.3 (C_{quat}), 133.4 (C_{quat}), 144.8 (C_{quat}), 148.0 (C_{quat}), 150.5 (C_{quat}), 155.5 (C_{quat}) ppm. IR (KBr): $\tilde{\nu}$ = 1587 (s), 1544 (m), 1520 (s), 1488 (m), 1422 (w), 1347 (s), 1106 (m), 1090 (m), 1016 (m), 971 (w), 857 (m), 830 (m), 766 (m), 716 (w), 699 (m), 581 (w), 539 (w) cm^{-1} . UV/Vis (CH_2Cl_2): λ_{max} (ϵ) = 265 nm (7300), 287 (4100), 330 (2900), 343 (2600), 367 (900). EI MS (70 eV): m/z (%) = 362 (11), 361 (12) $[M]^+$, 360 (33), 359 (14), 313 (14), 292 (17), 257 (17), 256 (100),

235 (15), 226 (12), 210 (41), 209 (27), 198 (14), 139 (20), 91 (13), 43 (12). $C_{21}H_{13}ClN_2O_2$ (360.79): calcd. C 69.91, H 3.63, N 7.76; found C 69.64, H 3.69, N 7.67.

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