Synthesis of Tetrazolo-Fused Benzodiazepines and Benzodiazepinones by a Two-Step Protocol Using an Ugi-Azide Reaction for Initial Diversity Generation

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Abstract

A two-step strategy for the synthesis of arrays of tricyclic tetrazolo-fused benzodiazepines and benzodiazepinones has been investigated. The protocol uses *ortho-N*-Boc phenylisocyanides and phenylglyoxaldehydes or ethyl glyoxylate in the 4-component Ugi-Azide reaction to afford MCR (Multi Component Reactions) derived adducts equipped with the desired diversity inputs. A subsequent acidic treatment (TFA/DCE) allows a simultaneous deprotection-cyclization leading to the final products.

Keywords

1. Introduction

The benzodiazepine family represents one of the most prominent classes of privileged scaffolds in medicinal chemistry.[1] Other than their well-known properties as psychoactive drugs, which function as sedative-hypnotics, anxiolytic, muscle relaxants, and anticonvulsants,[2] they display a plethora of further activity patterns ranging from anticancer[3] and anti-HIV properties[4] to cholecystokinin receptors antagonism.[5] Furthermore, this class possesses several examples of diverse biological activities of closely related structural analogs. One such example can be seen by comparing activities of compounds **1** and **2**. Lotrafiban[6] interacts highly selectively with the integrin GP$_{IIbIIIa}$, whereas **2** binds highly preferentially to the integrin $\alpha v\beta 3$ receptor.[7] This change was merely initiated by simple modification of the 'west-side' amine group, thought to recognize the RGD motif.

Multicomponent reactions have recently met renewed interest due to their capability to generate high molecular diversity through conceptually and operationally simple chemistry, able to build complex molecules incorporating diversity reagents in an atom economic

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fashion.[8] Indeed, since a widely exploited approach to elaborate MCR adducts consists of rigidifying them into nitrogen-containing heterocycles,[9] a number of MCR based benzodiazepine syntheses have been reported.[10]

2. Results and Discussion

In continuation of our studies on the generation of potentially medicinally relevant chemotypes *via* the efficient post-condensation modifications of the Ugi reaction,[11] we envisioned the possibility of fusing the multipurpose benzodiazepine core with the similarly interesting tetrazole moiety. Lately, we have explored the use of the Ugi-azide reaction to fruitfully embed the afore-mentioned scaffold in multicomponent derived backbones, which were subsequently submitted to secondary transformations resulting in drug-like entities.[12] In fact, the 1,5-disubstituted tetrazole ring has been identified as a surrogate of the *cis*-amide peptide bond,[13] opening new scenarios toward the preparation of peptidomimetics with enhanced *in vivo* stability.

The well-established TMS-N_3 variant of the Ugi 4-component condensation also constitutes the first and key step of this work. The process differs from the regular Ugi reaction with azidotrimethylsilane being used as a replacement for the carboxylic acid, while the other three inputs remain the same.

In this case, azide plays the role of the nucleophile instead of the carboxylate ion and traps the nitrilium intermediate species **4**, resulting in the formation of the 1,5-disubstututed tetrazole **6** upon intramolecular cyclization.[14] We initially decided to employ cyclic secondary amines and ethyl glyoxylate as the carbonyl input, along with the azide source and *ortho-N*-Boc phenylisocyanides, our plan being to endow the resulting products **7** with both an electrophilic ester functionality and a masked amino nucleophile. According to our experience, subsequent acidic treatment was most likely to cleave the Boc group and trigger cyclization rendering benzodiazepinones **8**. The multicomponent step proceeded smoothly under mild conditions, especially when trifluoroethanol (TFE) was used as the solvent. Indeed, such a phenomenon is well-known and is the outcome of the low nucleophilicity of TFE, still a polar protic solvent suitable for the Ugi reaction, but unlike methanol unable to attack the electrophilic Schiff base intermediate.[15] In order to keep the whole process simple and tailored for high-throughput applications, crude products were only quickly passed through flash chromatography and the semi-purified compounds **7** were directly submitted to the cyclization step. Predictably, the secondary transformation was readily promoted by dissolving **7** in a 10% TFA/DCE solution at elevated temperature (MW, 10 min, 120 °C). Hence, validation of the protocol was performed by preparing a small five member (**8a–e**) collection with good overall yields.

Whereas characterization of Ugi product **7** was skipped for the sake of procedural simplicity, unambiguous X-ray structural assignment was achieved for **8a** (Figure 3).[16]

With a validated route in hand for five examples, we then proceeded with a parallel synthesis production campaign of 48 compounds (general structure **8**) on a 0.2 millimolar scale. To our delight, after high-throughput purification by preparative HPLC-MS systems, all but one reaction was found to be successful, even if recovered amounts were extremely variable. From high-throughput perspective, extreme robustness of the strategy was demonstrated, at least for the amine input. In fact, while no additional isocyanides other than the two used in the validation phase were tried, 48 different secondary amines made up the diversity-enhancing pool.

Having developed an operationally friendly fast entry into an interesting fused heterocyclic scaffold containing a benzodiazepine and a tetrazole,[17] our next goal was to investigate replacement of ethyl glyoxylate with arylglyoxaldehydes to pave the way toward other chemotypes (**10** and **11**), and also to increase the number of diversity reagents by one over the first methodology. Arylglyoxaldehydes are indeed commercially available, and the additional carbonyl group they contain is ideal for reaction with unmasked internal amino nucleophiles. In this case, use of trifluoroethanol proved to be unnecessary, as methanol was capable to provide comparable yields under the same conditions, and cyclization step turned out to be even easier to accomplish, (MW, 10 min, 80 °C). Although good overall yields were obtained and the scope was extended to both primary and secondary amines, two distinct sets of compounds were isolated. Indeed, while adducts **9** derived from primary amines constantly led to enamine-type structures **10**, their analogues stemming from the incorporation of a secondary amine input furnished either adducts **10** or **11**. Over and above this issue, both **10** and **11** showed marked tendency to instability and after long term storage as dried solids at room temperature or short term exposure to silica gel or other acidic media, conversion into a plethora of degradation products was observed, probably *via* both hydrolysis and oxidation. Consequently, progression to parallel production of benzotetrazolodiazepines **10** and **11** was not carried out. Interconversion of structures **10** and **11** under acidic, basic or thermal conditions was never observed.

3. Conclusions

In summary, we have described herein an efficient and straightforward preparation of tetrazolo-fused benzodiazepines and benzodiazepinones involving an Ugi-azide multicomponent reaction for initial diversity generation followed by an acid-promoted post-condensation cyclization step. The procedure is perfectly amenable for high-throughput applications and library production for the benzodiazepinones **8** and, notwithstanding the previously discussed limitations, it represents a useful tool to gain access to richly substituted benzodiazepines **10** and **11** which are relatively stable when stored at low temperature.

4. Experimental Section

Solvents were purchased from commercial providers and used without further purification. Other reagents were used as obtained from commercial providers except when otherwise noted. Analytical thin layer chromatography (TLC) was performed on pre-coated silica gel plates. Visualization was accomplished with UV light or by staining with basic $KMnO_4$ solution. Column chromatography was performed using automated chromatographic systems. Melting points were determined in an open glass capillary and are uncorrected. NMR spectra were recorded in $CDCl_3$ at 400 MHz (^{1}H NMR) and 100 MHz (^{13}C NMR). Low and high resolution mass spectra were obtained using ESI methods.

General procedure for the preparation of benzotetrazolodiazepinones 8

Ethyl glyoxylate (1 mmol, 102 mg), amine (1 mmol), azidotrimethylsilane (1 mmol, 115 mg) and isocyanide (1 mmol) were dissolved in trifluoroethanol (0.5 mL) in a 10 mL MW vial. The reaction was allowed to run at room temperature for 24 h. Crude mixture was concentrated *in vacuo* and purified by flash chromatography (Hexane/EtOAc). Ugi adduct was then dissolved in a 10% TFA/DCE solution and heated at 120 °C for 10 min by means of microwave irradiation. Reaction mixture was diluted with EtOAc (15 mL) and washed with $NaHCO_3$ sat. solution (15 mL). The aqueous phase was then re-extracted with EtOAc (15 mL), combined organics were dried over $MgSO_4$ and crude mixture was purified by flash chromatography (Hexane/EtOAc) to afford expected benzotetrazolodiazepinones.

4-(piperidin-1-yl)-4*H*-benzo[*b*]tetrazolo[1,5-*d*][1,4]diazepin-5(6*H*)-one (8a): white solid, 54% yield; product purified using 5 to 50% EtOAc in Hexane gradient; m.p. 225 – 227 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm 9.23 (s, 1H), 7.95 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.53 (td, *J* = 7.8, 1.5 Hz, 1H), 7.40 (td, *J* = 7.8, 1.3 Hz, 1H), 7.25 (dd, *J* = 8.0, 1.3 Hz, 1H), 4.78 (s, 1H), 2.59 – 2.21 (m, 2H), 2.20 – 1.91 (m, 2H), 1.34 – 1.01 (m, 6H).; ^{13}C NMR (100 MHz, CDCl$_3$) δ ppm 168.1, 150.8, 130.7, 129.6, 126.3, 122.8, 121.3, 66.4, 52.2, 25.8, 24.1; [M+H]$^+$ = 285.2; HRMS (ESI): m/z calcd for C$_{14}$H$_{17}$N$_6$O [M+H]$^+$: 285.1459, found: 285.1459.

4-(4-benzylpiperidin-1-yl)-4*H*-benzo[b]tetrazolo[1,5-*d*][1,4]diazepin-5(6*H*)-one (8b): white solid, 63% yield; product purified using 5 to 40% EtOAc in Hexane gradient; m.p. 198 – 199 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm 9.49 (s, 1H), 7.97 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.55 (td, *J* = 7.6, 1.2 Hz, 1H), 7.43 (td, *J* = 7.6, 0.9 Hz, 1H), 7.30 – 7.11 (m, 5H), 7.02 (d, *J* = 6.8 Hz, 1H), 4.79 (s, 1H), 2.89 (d, *J* = 10.8 Hz, 1H), 2.33 (d, *J* = 6.8 Hz, 2H), 2.21 – 1.90 (m, 3H), 1.69 – 1.33 (m, 3H), 0.98 – 0.49 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ ppm 168.4, 150.7, 140.4, 130.8, 129.6, 129.3, 128.6, 126.4, 126.3, 126.2, 122.8, 121.5, 66.1, 51.7, 51.3, 43.0, 37.7, 32.0, 31.9; [M+H]$^+$ = 375.2; HRMS (ESI): m/z calcd for C$_{21}$H$_{23}$N$_6$O [M+H]$^+$: 375.1928, found: 375.1924.

8,9-dimethyl-4-(piperidin-1-yl)-4*H*-benzo[b]tetrazolo[1,5-*d*][1,4]diazepin-5(6*H*)-one (8c): white solid, 34% yield; product purified using 5 to 45% EtOAc in Hexane gradient; m.p. >250 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm 9.16 (s, 1H), 7.72 (s, 1H), 7.00 (s, 1H), 4.76 (s, 1H), 2.54 – 2.24 (m, 2H), 2.38 (s, 6H), 2.20 – 2.02 (m, 2H), 1.26 (m, 6H); ^{13}C NMR (100 MHz, CDCl$_3$) δ ppm 168.3, 150.4, 140.0, 135.3, 127.0, 123.7, 123.1, 122.1, 66.5, 52.3, 25.7, 24.1, 20.1, 19.7; [M+H]$^+$ = 313.3; HRMS (ESI): m/z calcd for C$_{16}$H$_{21}$N$_6$O [M+H]$^+$: 313.1771, found: 313.1766.

4-(4-benzylpiperidin-1-yl)-8,9-dimethyl-4*H*-benzo[b]tetrazolo[1,5-*d*] [1,4]diazepin-5(6*H*)-one (8d): white solid, 28% yield; product purified using 5 to 50% EtOAc in Hexane gradient; m.p. 207 – 208 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm 9.27 (b, s, 1H), 7.71 (s, 1H), 7.27 – 7.13 (m, 4H), 7.07 – 6.97 (m, 3H), 4.75 (s, 1H), 2.90 (d, *J* = 10.9 Hz, 1H), 2.39 (s, 6H), 2.35 (s, 1H), 2.22 – 1.91 (m, 3H), 1.57 – 1.29 (m, 3H), 0.97 – 0.61 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ ppm 168.2, 150.3, 140.5, 140.0, 135.4, 129.4, 128.6, 126.9, 126.3, 123.60, 123.1, 122.1, 66.1, 51.8, 51.5, 43.0, 37.8, 31.9, 31.8, 20.1, 19.7; [M+H]$^+$ = 403.2; HRMS (ESI): m/z calcd for C$_{23}$H$_{27}$N$_6$O [M+H]$^+$: 403.2241, found: 403.2245.

8,9-dimethyl-4-(pyrrolidin-1-yl)-4*H*-benzo[b]tetrazolo[1,5-*d*][1,4]diazepin-5(6*H*)-one (8e): white solid, 39% yield; product purified using 5 to 80% EtOAc in Hexane gradient; m.p. >250 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm 9.39 (s, 1H), 7.74 (s, 1H), 7.01 (s, 1H), 4.78 (s, 1H), 2.63 – 2.52 (b, m, 4H), 2.36 (s, 6H), 1.67 – 1.56 (b, m, 4H); ^{13}C NMR (100 MHz, CDCl$_3$) δ ppm 168.5, 150.7, 140.1, 135.4, 126.8, 123.34, 123.28, 122.4, 64.5, 52.1, 24.0, 20.1, 19.7. [M+H]$^+$ = 299.1; HRMS (ESI): m/z calcd for C$_{15}$H$_{19}$N$_6$O: 299.1615, found: 299.1613.

General procedure for the preparation of benzotetrazolodiazepines 10 and 11

Aryl glyoxaldehyde (1 mmol), amine (1 mmol), azidotrimethylsilane (1 mmol, 115 mg) and isocyanide (1 mmol) were dissolved in methanol (1 mL) in a 10 mL MW vial. The reaction was allowed to run at room temperature for 24 h. Crude mixture was concentrated *in vacuo* and purified by flash chromatography (Hexane/EtOAc). Ugi adduct was then dissolved in a 10% TFA/DCE solution and heated at 80 °C for 10 min by means of microwave irradiation. Reaction mixture was diluted with EtOAc (15 mL) and washed with NaHCO$_3$ sat. solution (15 mL). The aqueous phase was then re-extracted with EtOAc (15 mL), combined organics

were dried over MgSO$_4$ and crude mixture was purified by flash chromatography (Hexane/EtOAc or EtOAc/MeOH) to afford title compounds.

**5-(benzo[*d*][1,3]dioxol-5-yl)-4-(piperidin-1-yl)-6*H*-benzo[b]tetrazolo[1,5-*d*]
[1,4]diazepine (10a):** yellow solid, 44% yield; product purified using 5 to 40% EtOAc in
Hexane gradient; m.p. 203 – 204 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm 7.76 (d, *J* = 8.0
Hz, 1H), 7.30 – 7.25 (m, 1H), 7.17 – 7.12 (m, 1H), 6.97 (d, *J* = 1.2 Hz, 1H), 6.93 (dt, J = 8.0,
1.5 Hz, 1H), 6.86 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 1H), 6.03 (s, 1H), 4.77 (s,
1H), 2.90 (s, 4H), 1.40 (s, 6H); ^{13}C NMR (100 MHz, CDCl$_3$) δ ppm 153.1, 149.4, 148.0,
147.3, 140.6, 131.9, 130.3, 127.3, 124.6, 123.5, 121.5, 120.7, 120.1, 108.8, 108.0, 101.4,
52.6, 26.1, 23.80; [M+H]$^+$ = 389.1; HRMS (ESI): m/z calcd for C$_{21}$H$_{21}$N$_6$O$_2$ [M+H]$^+$:
389.1721, found: 389.1724.

5-phenyl-4-(piperidin-1-yl)-6*H*-benzo[*b*]tetrazolo[1,5-*d*][1,4]diazepine (10b): yellow
solid, 51% yield; product purified using 10 to 40% EtOAc in Hexane gradient; m.p. 195 –
197 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm 7.76 (dd, J = 8.0, 1.5 Hz, 1H), 7.47 – 7.38 (m,
5H), 7.29 – 7.24 (m, 1H), 7.16 – 7.11 (m, 1H), 6.76 (dd, *J* = 7.9, 1.3 Hz, 1H), 4.82 (s, 1H),
3.02 – 2.79 (m, 4H), 1.40 – 1.22 (m, 6H); ^{13}C NMR (100 MHz, CDCl$_3$) δ ppm 153.2, 150.3,
140.5, 138.2, 130.4, 128.9, 128.3, 127.7, 127.2, 124.6, 123.6, 120.8, 120.2, 52.6, 26.1, 23.8;
[M+H]$^+$ = 345.3; HRMS (ESI): m/z calcd for C$_{20}$H$_{21}$N$_6$ [M+H]$^+$: 345.1822, found:
345.1819.

**5-phenyl-*N*-(4-(trifluoromethoxy)phenyl)-6*H*-benzo[*b*]tetrazolo[1,5-*d*][1,4]diazepin-4-
amine (10c):** yellow solid, 48% yield; product purified using 0 to 30% MeOH in EtOAc
gradient; m.p. 193 – 195°C; ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm 7.79 (dd, *J* = 8.0, 1.4 Hz,
1H), 7.70 – 7.36 (m, 5H), 7.32 (td, *J* = 7.7, 1.5 Hz, 1H), 7.19 (td, *J* = 7.9, 1.3 Hz, 1H), 6.89
(d, *J* = 8.9 Hz, 2H), 6.83 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.58 (d, *J* = 9.0 Hz, 2H).5.30 (s, 1H), 5.19
(s, 1H); ^{13}C NMR (400 MHz, CDCl$_3$) δ ppm 151.5, 152.9, 144.6, 138.4, 136.1, 133.8 –
131.2 (m), 130.8, 130.1, 129.0, 128.8, 127.6, 127.2, 127.0, 126.6, 125.3, 123.6, 122.1, 121.9,
121.6, 121.2, 114.5, 105.5; [M+H]$^+$ = 437.1; HRMS (ESI): m/z calcd for C$_{22}$H$_{16}$F$_3$N$_6$O [M
+H]$^+$: 437.1332, found: 437.1331.

***N*,5-bis(4-methoxyphenyl)-6*H*-benzo[*b*]tetrazolo[1,5-*d*][1,4]diazepin-4-amine (10d):**
yellow solid, 62% yield; product purified using 0 to 30% MeOH in EtOAc gradient; m.p.
195 – 197°C; ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm 9.65 (s, 1H), 7.40 (d, *J* = 8.9 Hz, 1H),
7.06 – 6.86 (m, 6H), 6.76 (d, *J* = 11.7 Hz, 2H), 6.64 – 6.48 (m, 4H), 3.82 (s, 3H), 3.77 (s,
3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ ppm 158.5, 155.0, 149.6, 141.3, 132.2, 131.31, 131.1,
130.0, 127.7, 126.1, 125.4, 121.3, 120.0, 118.6, 117.4, 116.2, 116.1, 114.3, 114.2, 112.8,
101.0, 55.8, 55.4; [M+H]$^+$ = 413.3; HRMS (ESI): m/z calcd for C$_{23}$H$_{21}$N$_6$O$_2$: 413.1721,
found: 413.1723.

***N*-(3,4-dimethoxyphenyl)-5-phenyl-6*H*-benzo[*b*]tetrazolo[1,5-*d*][1,4]diazepin-4-amine
(10e):** yellow solid, 59% yield; product purified using 0 to 30% MeOH in EtOAc gradient;
m.p. 126 – 128°C; ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm 10.17 (s, 1H), 7.28 – 7.14 (m, 4H),
7.04 (s, 1H), 7.03 – 6.96 (m, 3H), 6.93 (s, 1H), 6.61 – 6.35 (m, 3H), 3.93 (s, 3H), 3.82 (s,
3H), 3.30 (b, s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ ppm 149.8, 149.5, 146.3, 141.34,
141.27, 133.4, 132.1, 130.9, 128.8, 128.71, 128.67, 126.7, 126.1, 121.9, 120.1, 119.9, 118.5,
117.4, 113.9, 100.7, 94.4, 56.2, 56.1; [M+H]$^+$ = 413.3; HRMS (ESI): m/z calcd for
C$_{23}$H$_{21}$N$_6$O$_2$ [M+H]$^+$: 413.1721, found: 413.1717.

**5-(benzo[*d*][1,3]dioxol-5-yl)-8,9-dimethyl-4-(piperidin-1-yl)-4*H*-benzo[*b*]tetrazolo[1,5-*d*]
[1,4]diazepine (11a):** yellow solid, 59% yield; product purified using 10 to 40% EtOAc in
Hexane gradient; m.p. 195 – 197 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm 7.80 (s, 1H), 7.58

(dd, J = 8.3, 1.9 Hz, 1H), 7.52 (d, J = 1.8 Hz, 1H), 7.33 (s, 1H), 6.86 (d, J = 8.2 Hz, 1H), 6.03 (dd, J = 3.6, 1.3 Hz, 2H), 5.58 (s, 1H), 2.40 (s, 3H), 2.39 (s, 3H), 2.40 – 2.33 (m, 2H), 2.05 – 1.96 (m, 2H), 1.29 – 1.20 (m, 3H), 1.17 – 1.09 (m, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ ppm 159.7, 150.6, 150.1, 148.4, 138.1, 136.9, 135.1, 132.4, 127.6, 123.4, 121.4, 121.2, 108.2, 108.00, 101.8, 60.1, 51.9, 25.5, 24.00, 19.6, 19.5; [M+H]$^+$ = 417.2; HRMS (ESI): m/z calcd for C$_{23}$H$_{25}$N$_6$O$_2$ [M+H]$^+$: 417.2034, found: 417.2034.

4-(8,9-dimethyl-5-phenyl-4H-benzo[b]tetrazolo[1,5-d][1,4]diazepin-4-yl)morpholine (11b): yellow solid, 51% yield; product purified using 10 to 100% EtOAc in Hexane gradient; m.p. 154 – 156°C; ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm 8.05 – 7.94 (m, 2H), 7.84 (s, 1H), 7.56 – 7.43 (m, 3H), 7.38 (s, 1H), 5.72 (s, 1H), 3.26 (t, J = 4.5 Hz, 4H), 2.50 – 2.43 (m, 2H), 2.42 (s, 3H), 2.41 (s, 3H), 2.15 – 2.07 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ ppm 159.8, 149.4, 138.4, 137.7, 136.6, 136.0, 131.6, 128.9, 128.0, 127.9, 121.52, 121.50, 121.3, 66.3, 59.7, 50.9, 19.6, 19.5; [M+H]$^+$ = 375.3; HRMS (ESI): m/z calcd for C$_{21}$H$_{23}$N$_6$O [M+H]$^+$: 375.1928, found: 375.1935.

5-(benzo[d][1,3]dioxol-5-yl)-4-(3,4-dihydroisoquinolin-2(1H)-yl)-8,9-dimethyl-4H-benzo[b]tetrazolo[1,5-d][1,4]diazepine (11c): yellow viscous oil, 23% yield; product purified using 10 to 100% EtOAc in Hexane gradient; ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm 7.80 (s, 1H), 7.58 – 7.53 (m, 2H), 7.34 (s, 1H), 7.12 – 7.00 (m, 2H), 6.99 – 6.91 (m, 1H), 6.91 – 6.80 (m, 2H), 6.04 (dd, J = 4.2, 1.3 Hz, 2H), 5.82 (s, 1H), 3.62 (d, J = 14.9 Hz, 1H), 3.32 (d, J = 14.9 Hz, 1H), 2.59 – 2.41 (m, 4H), 2.34 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ ppm 158.6, 150.8, 149.6, 148.6, 138.4, 136.3, 135.7, 133.7, 133.0, 132.3, 128.4, 128.2, 126.6, 126.3, 125.9, 123.5, 121.5, 121.1, 108.3, 108.0, 101.9, 58.9, 53.3, 48.0, 28.1, 19.6, 19.5; [M+H]$^+$ = 465.3; ; HRMS (ESI): m/z calcd for C$_{27}$H$_{25}$N$_6$O$_2$ [M+H]$^+$: 465.2034, found: 465.2027.

5-(benzo[d][1,3]dioxol-5-yl)-8,9-dimethyl-4-(4-(pyridin-2-yl)piperazin-1-yl)-4H-benzo[b]tetrazolo[1,5-d][1,4]diazepine (11d): yellow solid, 41% yield; product purified using 10 to 100% EtOAc in Hexane gradient; m.p. 228 – 230°C; ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm 8.10 (dd, J = 4.9, 1.1 Hz, 1H), 7.82 (s, 1H), 7.59 (dd, J = 8.3, 1.8 Hz, 1H), 7.54 (d, J = 1.8 Hz, 1H), 7.43 – 7.38 (m, 1H), 7.35 (s, 1H), 6.88 (d, J = 8.2 Hz, 1H), 6.58 (dd, J = 6.9, 5.0 Hz, 1H), 6.49 (d, J = 8.6 Hz, 1H), 6.03 (dd, J = 8.6, 7.6 Hz, 3H), 5.68 (s, 1H), 3.16 – 3.02 (m, 4H), 2.62 – 2.48 (m, 2H), 2.38 (s, 3H), 2.37 (s, 2H), 2.26 – 2.14 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ ppm 159.2, 158.8, 150.9, 149.7, 148.6, 147.9, 138.4, 137.4, 136.8, 135.6, 132.1, 127.7, 123.5, 121.4, 121.3, 113.7, 108.2, 108.0, 107.2, 101.9, 59.3, 50.3, 44.9, 19.7, 19.5; [M+H]$^+$ = 495.3; HRMS (ESI): m/z calcd for C$_{27}$H$_{27}$N$_8$O$_2$ [M+H]$^+$: 495.2252, found: 495.2251.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

References and notes

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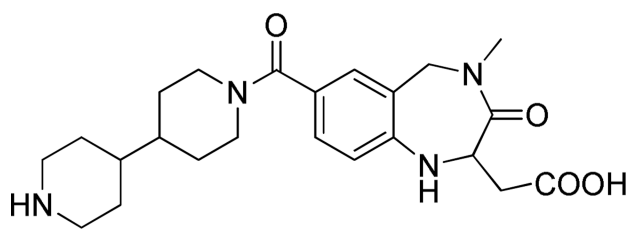
1
Lotrafiban
Fibrinogen receptor antagonist
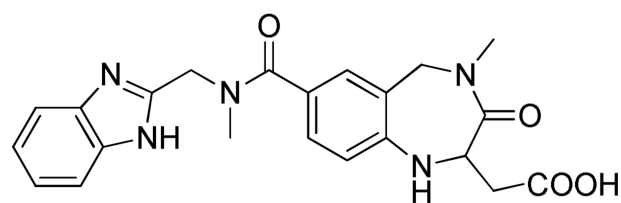
2
Vitronectin receptor antagonist $\alpha v \beta 3$

Figure 1.
Structurally close benzodiazepine-based drugs showing different activities.

8a (54%) **8b** (63%) **8c** (34%)
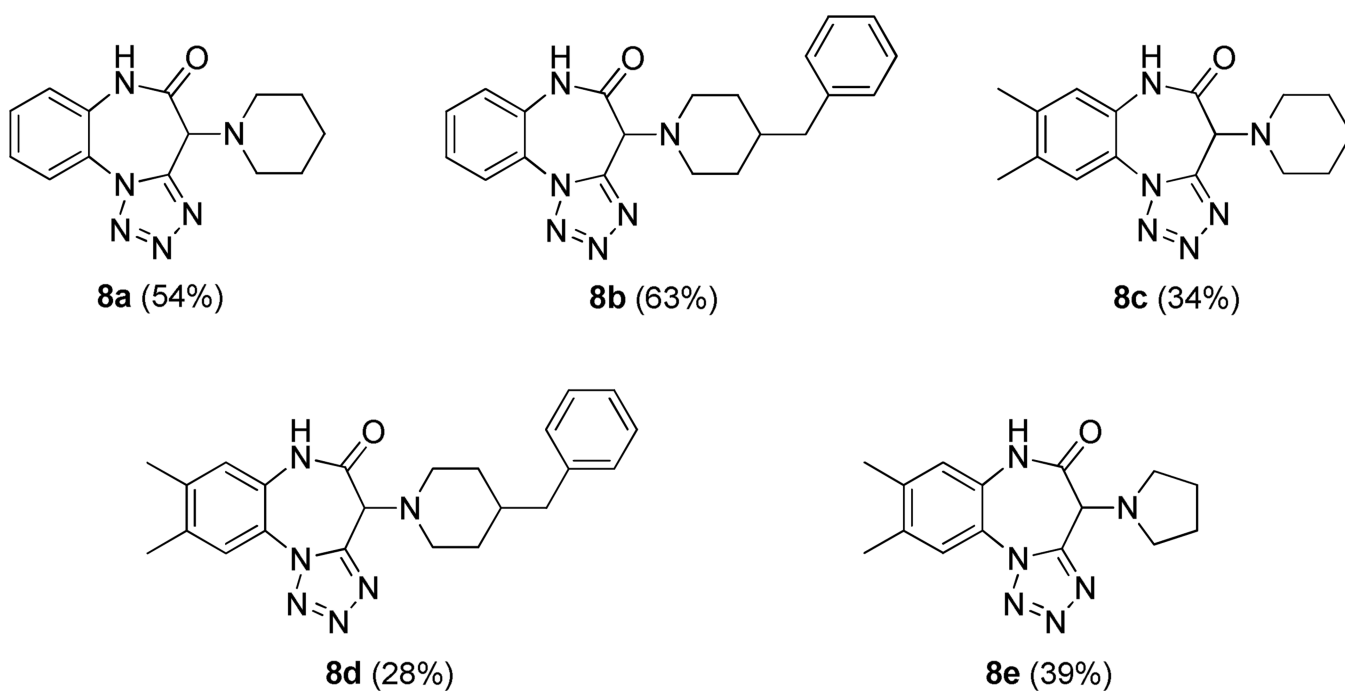
8d (28%) **8e** (39%)

Figure 2.
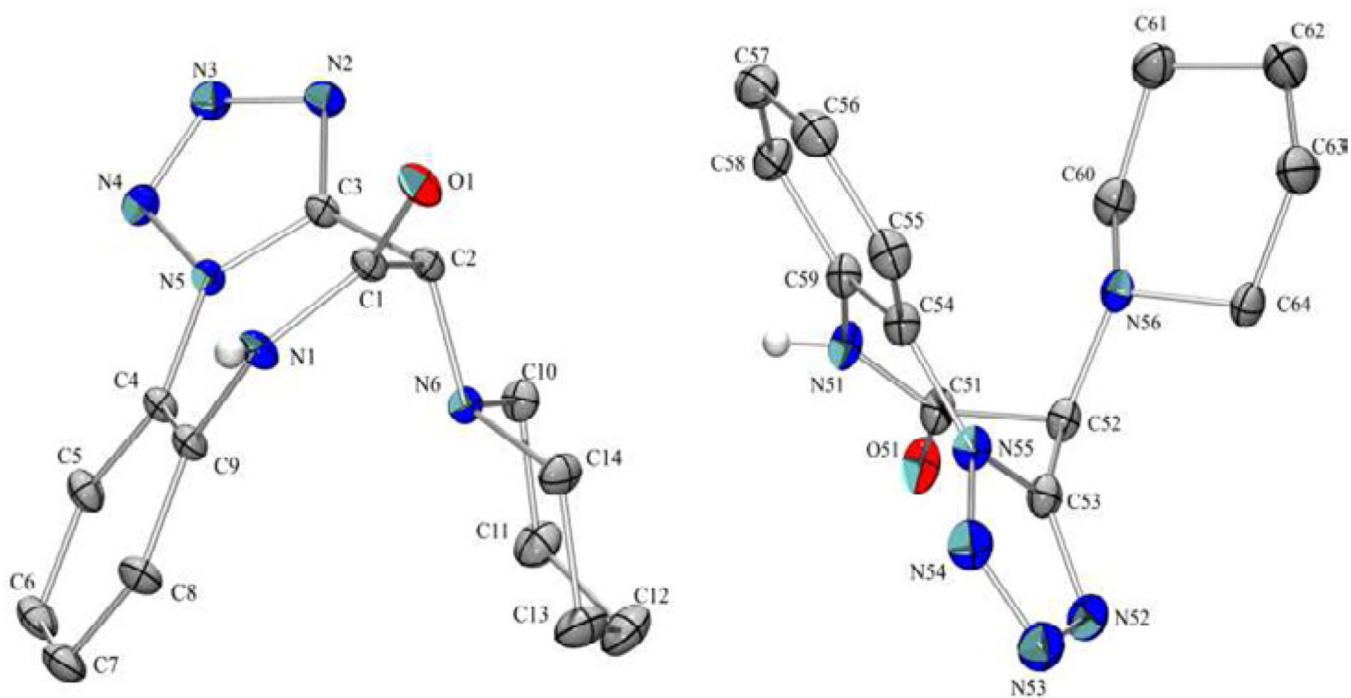The pivotal collection of benzodiazepinones **8**. Yields represent the combined two overall steps.

Figure 3.
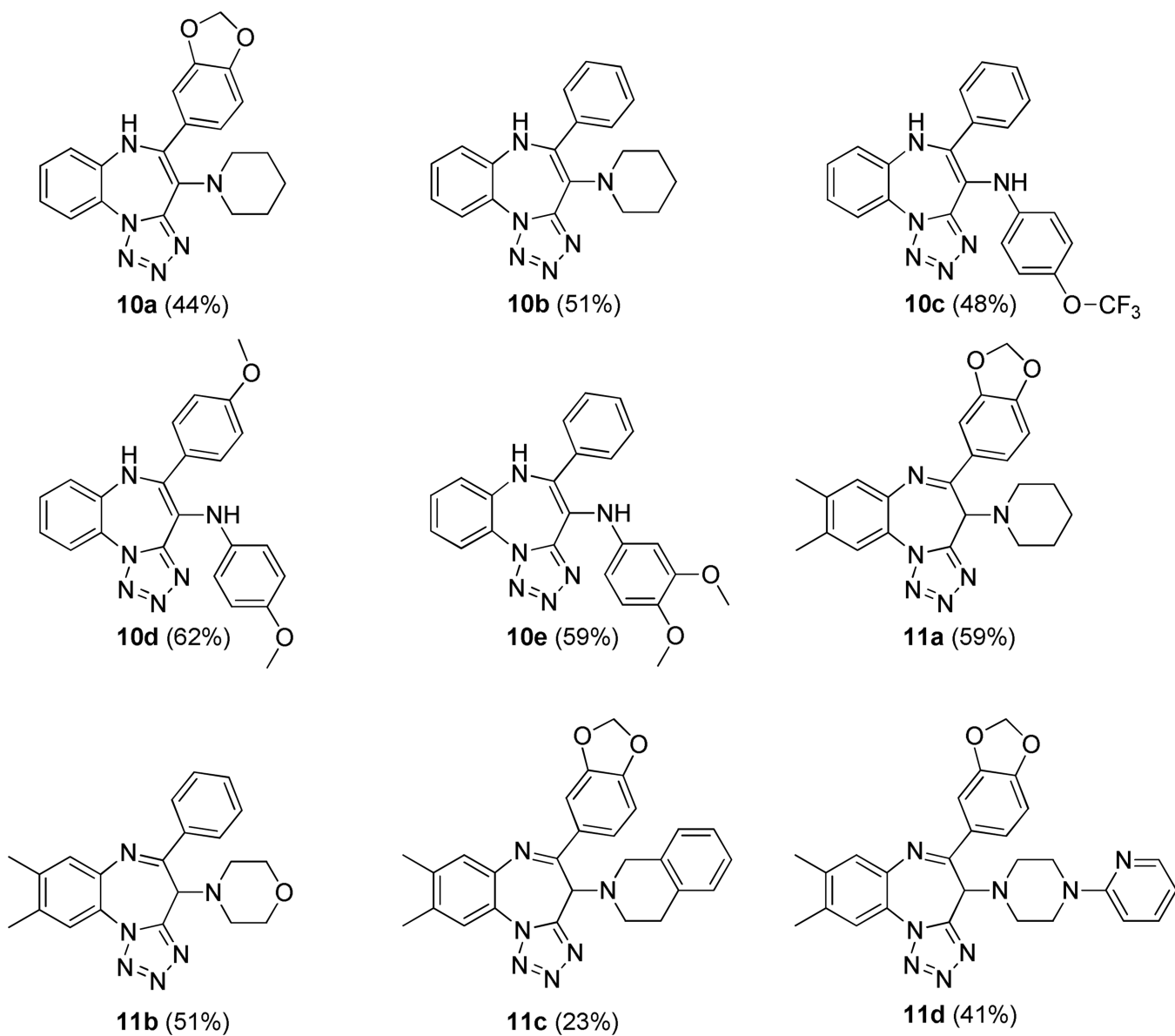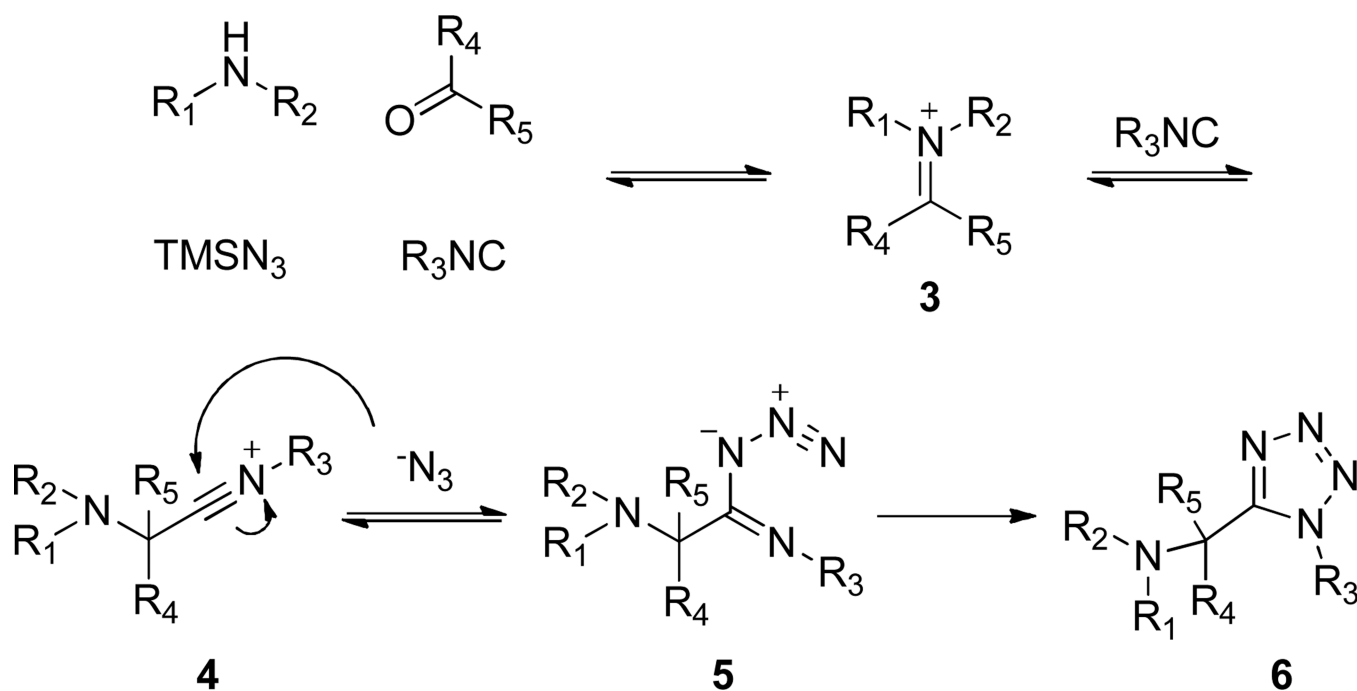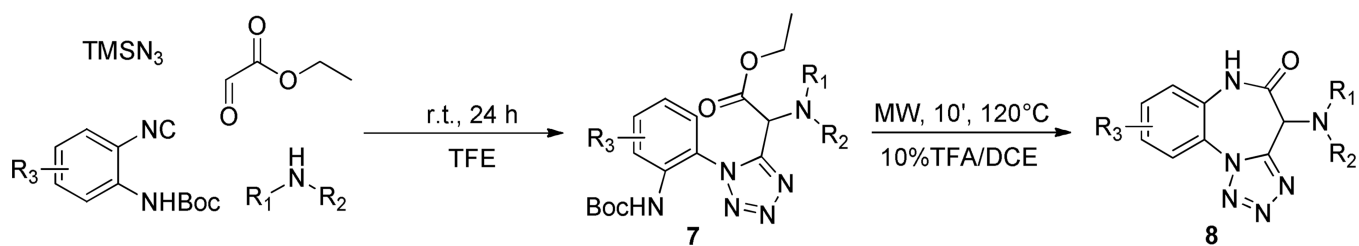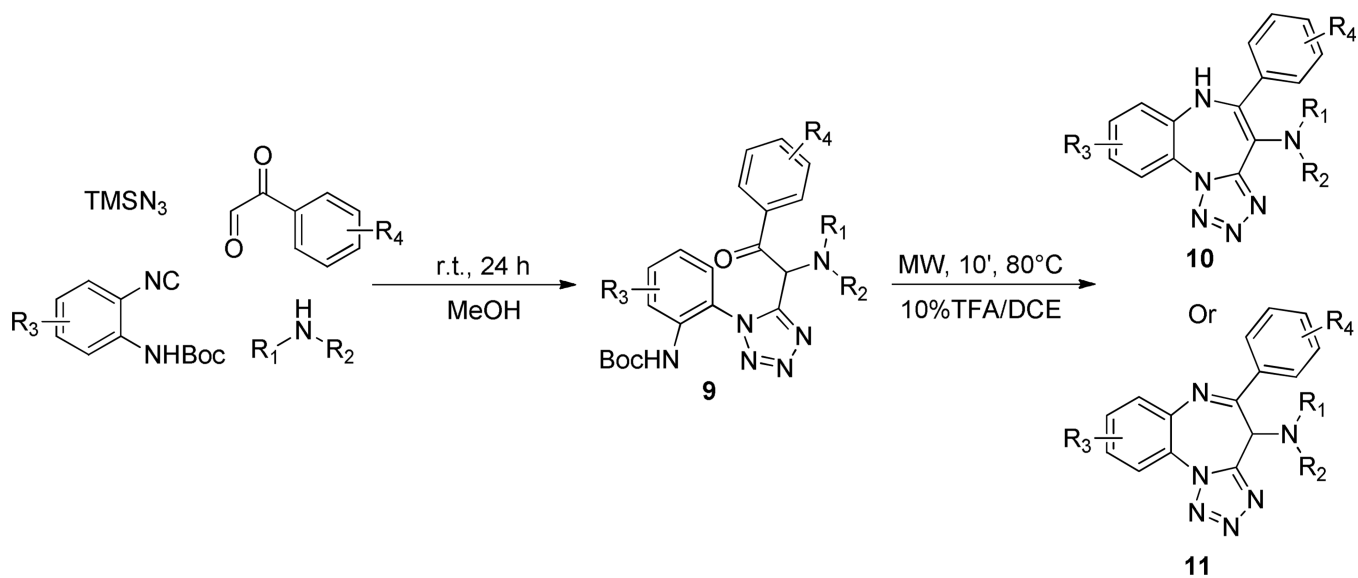Solved crystal structure of **8a** showing two unique molecules in the asymmetric unit.

Figure 4.
Synthesized benzodiazepines **10** and **11**. Yields represent the combined two overall steps.

Scheme 1.
Mechanism of the 4-component Ugi-Azide reaction (compatible with 1^{ry} or 2^{ry} amines).

Scheme 2.
Synthetic route toward tetrazolo-fused benzodiazepinones **8**.

Scheme 3.
Synthetic route toward tetrazolo-fused benzodiazepines **10** and **11**.