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Synthesis of novel fused 4,5-dihydro-1,2,3-triazolo[1,5-*a*][1,4] benzodiazepine derivatives via four-component Ugi–Smiles-type reaction

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ABSTRACT

Using 2-azidobenzaldehyde and propargylamine in a Ugi–Smiles coupling gave easy access to 4,5-dihydro-1,2,3-triazolo[1,5-*a*][1,4]benzodiazepine derivatives. This novel approach is based on the reaction between 2-azidobenzaldehyde, propargylamine, isocyanides, and nitrophenols in methanol under reflux conditions without using additional reagents or catalysts.

1. Introduction

After the introduction of novel multicomponent reactions by Passerini[1] and Ugi,[2] the use of isocyanide-based multicomponent reactions (IMCRs) has attracted a great deal of attention in medicinal chemistry[3–6] owing to producing bifunctional starting materials. Although the classical versions of the above reactions lead to acyclic systems, development of IMCRs by replacing various bifunctional starting materials, such as 2-azidobenzaldehyde[7] allows researchers to develop efficient routes to a range of functionalized heterocyclic scaffolds.[8–10] Usually, these functional groups lead to the intramolecular reactions[11] and post-condensation or cyclizations[12] to produce new heterocyclic compounds.

One of the most important and efficient modifications of IMCRs was investigated by El Kaïm et al.[13] in which traditional carboxylic acids were replaced by electron-deficient phenols as suitable surrogates in the Ugi reaction. The key step is an irreversible Smiles rearrangement in the last step of these reactions. For this reason, the reaction was termed Ugi–Smiles coupling.

Fused triazolo-benzodiazepines are of significant medical interests due to their effective properties. Two common anxiolytic agents, Alprazolam (**A**) and Estazolam (**B**) belong to this family of compounds (Fig. 1).[14] Some triazolo-benzodiazepine derivatives are known to bind weakly to the benzodiazepine receptor[15] and also to inhibit serine proteases.[16] It seems the use of this class of compounds with useful therapeutic purposes is of importance and designing libraries of fused triazolo-benzodiazepines with maximum diversity is one of the major medicinal chemistry researchers' goals.

Herein, as a continuation of our research into the synthesis of novel heterocycles,[17] especially promising bioactive compounds,[18] we report a Ugi–Smiles reaction, which provides an expedient route to novel and potentially bioactive fused 1,2,3-triazolo-1,4-benzodiazepine scaffolds **5** through a one-step reaction (Scheme 1).

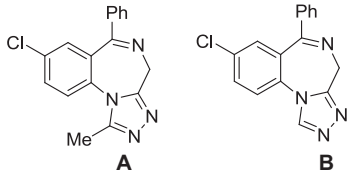

Fig. 1. Alprazolam (**A**) and Estazolam (**B**).

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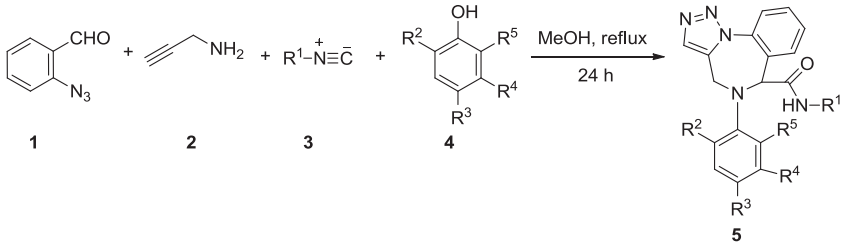


Scheme 1. Synthesis of 4,5-dihydro-1,2,3-triazolo[1,5-*a*][1,4]benzodiazepines **5**.

2. Results and discussion

In this work, we used 2-azidobenzaldehyde **1** and propargylamine **2** as the aldehyde and amine in the Ugi–Smiles coupling (Scheme 1). We found that intramolecular cyclization happened spontaneously without the need for additional reagents or catalysts to give the final compound **5**. We first studied the reaction of 2-azidobenzaldehyde (1 mmol), propargylamine (1 mmol), phenol (1 mmol), and cyclohexylisocyanide (1 mmol) in MeOH as the solvent. As we expected, phenol did not conduct the reaction due to lack of sufficient acidity. Thus, we utilized *para* and different *ortho*-nitrophenols, which are sufficiently acidic to take part in the reaction. When a mixture of 2-azidobenzaldehyde (1 mmol), propargylamine (1 mmol), *para*-nitrophenol (1 mmol) and cyclohexylisocyanide (1 mmol) in MeOH was heated at reflux for 24 h, the corresponding 4,5-dihydro-1,2,3-triazolo[1,5-*a*][1,4]benzodiazepine derivative **5a** was obtained in 50% yield. It was found that the reaction did not go to completion when stoichiometric amounts of starting materials were used. However, when 1.2 equiv isocyanide was used the desired product **5a** was obtained in good yield (75%, Table 1, entry 1).

The combination of all analytical information confirmed the given structure **5a**. The peak at 432 in mass spectrum is associated with the molecular ion and it is in accordance with calculated mass for $C_{23}H_{24}N_6O_3$. Also the spectrum shows a strong peak at 306 (M−126), which is related to elimination of −CONH−cyclohexyl group. A fairly strong peak is observed at 278 resulting from loss of N_2 from the M−126. The strong peak at 232 indicates elimination of NO_2 from the latter.

It should be noted that when *meta*-nitrophenols were used, there was no reaction and we concluded that neither unsubstituted phenol nor *m*-nitrophenols are suitable surrogates for carboxylic acids.

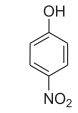
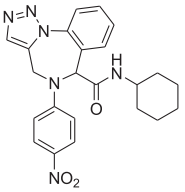
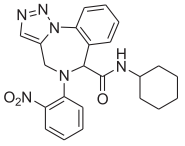
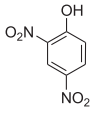
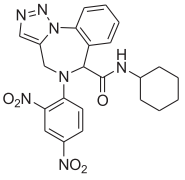
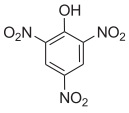
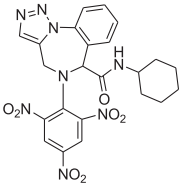
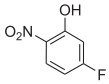
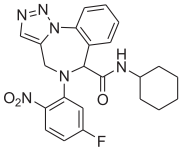
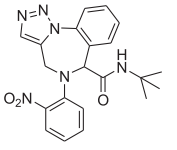
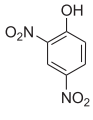
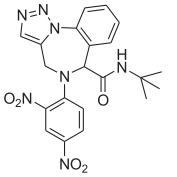
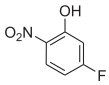
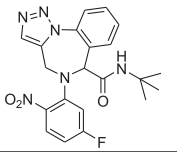
In spite of the fact that methanol usually is the solvent of choice for Ugi-type multicomponent reactions,[7b,12a,13a,13b,19] we screened other solvents, such as toluene, dichloromethane and ethanol in the reaction. Low yields and by-products resulted; therefore, we continued our experiment using methanol.

Considering the results, we expanded the scope of this promising reaction by using various nitrophenols and isocyanides. As can be seen in Table 1, they behaved similarly in the Ugi–Smiles coupling. *ortho*-Nitrophenols, particularly the derivatives with more electron-withdrawing groups, showed higher reactivity.

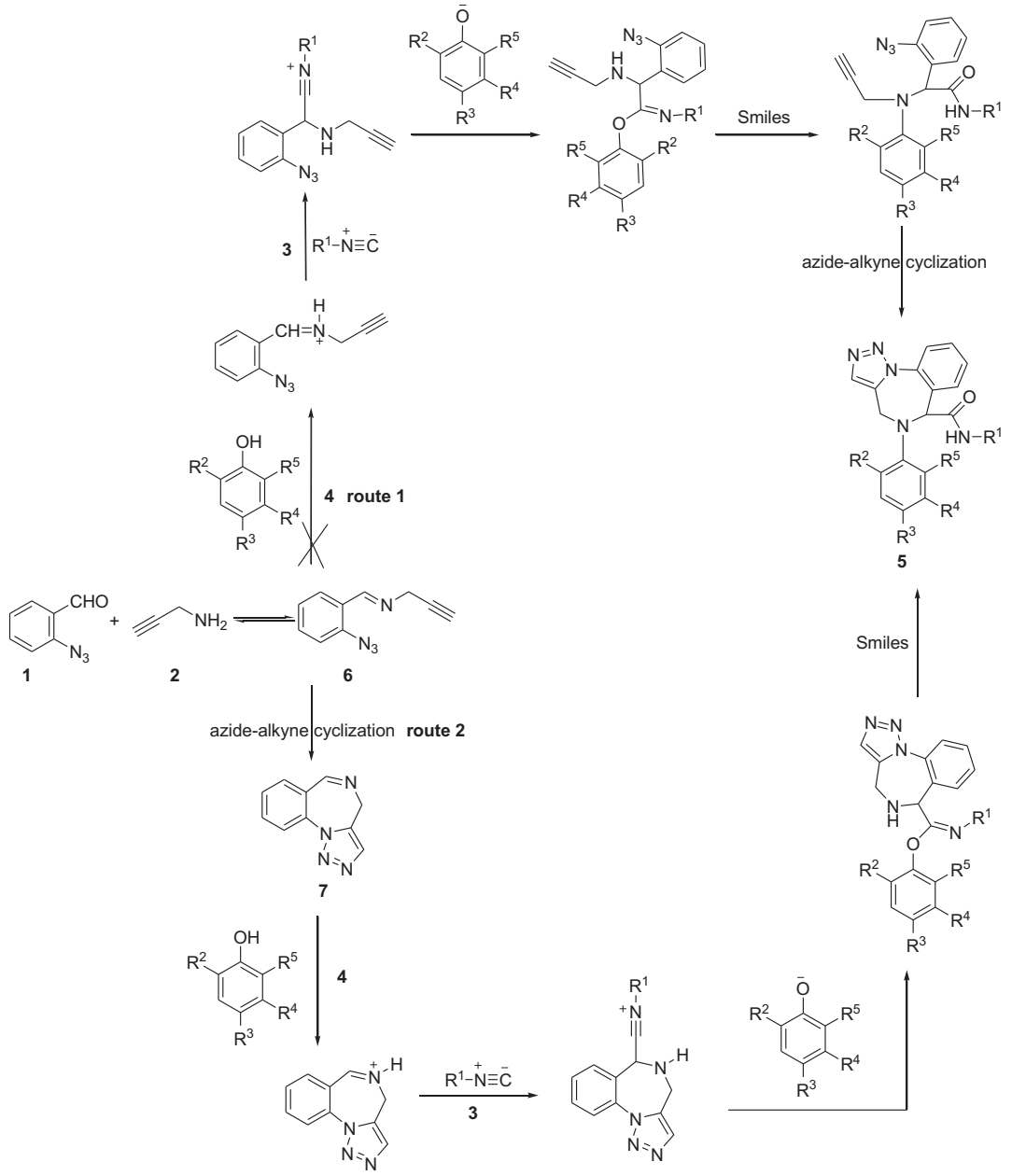
In the next step, we investigated the mechanism of reaction. A proposed sequences, has been depicted schematically in Scheme 2. According to the literature,[20] the first step in the Ugi reaction involves condensation of aldehyde **1** and amine **2** to form imine **6**. Presence of azido group in imine **6** suggests that there are two possible mechanisms for the reaction (routes 1 and 2 in Scheme 2).

The first mechanism (route 1, Scheme 2) shows that the formation of Ugi adduct takes place before azide-alkyne cyclization; while according to the second mechanism (route 2, Scheme 2), cyclization reaction and the formation of benzodiazepine ring is prior to Ugi reaction. To distinguish between mechanisms, a mixture of 2-azidobenzaldehyde **1** and propargylamine **2** in MeOH was

Table 1
Synthesis of 4,5-dihydro-1,2,3-triazolo[1,5-*a*][1,4]benzodiazepine derivatives **5**

Entry	Nitrophenols	Isocyanides	Product	Yield[a] (%)
1			**5a** 	75
2			**5b** 	80
3			**5c** 	85
4			**5d** 	88
5			**5e** 	85
6			**5f** 	80
7			**5g** 	85
8			**5h** 	85

[a] Isolated yield.



Scheme 2. Formation of 4,5-dihydro-1,2,3-triazolo[1,5-*a*][1,4]benzodiazepine derivatives **5**.

heated at reflux. After completion of reaction (checked by TLC), 4*H*-[1,2,3]triazolo[1,5-*a*][1,4]benzodiazepine **7**, the known compound reported by Alajarín et al.,[21] was obtained. Then, it was reacted with cyclohexylisocyanide **3a** and 4-nitrophenol **4a** under the conditions described in Section 4.2. The results revealed that **5a**, the corresponding product in one-pot four-component reaction (4.2.1) is the only product and thus, the second mechanism (route 2, Scheme 2) is acceptable.

3. Conclusion

In conclusion, we have shown that 4,5-dihydro-1,2,3-triazolo[1,5-*a*][1,4]benzodiazepine derivatives can be efficiently synthesized by modification of the four-component Ugi–Smiles type reaction of 2-azidobenzaldehyde, propargylamine, isocyanides, nitrophenols. The reaction was accomplished without using additional reagents or catalysts. The ease of preparation of compounds and the isolation of products, and the good chemical yields of the described transformation are the remarkable synthetic aspects of this procedure for the synthesis of new 1,2,3-triazolo-1,4-benzodiazepines.

4. Experimental section

4.1. General

Melting points were taken on a *Kofler* hot stage apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on *Bruker FT-500*, using TMS as an internal standard. The IR spectra were obtained on a *Nicolet Magna FTIR 550* spectrophotometer (in KBr). Mass spectra were determined on an *Agilent Technology* (HP) mass spectrometer operating at an ionization potential of 70 eV. The elemental analysis was performed with an Elementar Analysensystem GmbH *VarioEL* CHNS mode. All reagents and solvents were obtained from Merck and Aldrich and used without any purification. Silica gel 60

(0.040–0.063 mm) were used for column chromatography Thin layer chromatography (TLC) was performed using silica gel 60/Kieselguhr F254 precoated on Aluminum sheets (thickness 0.2 mm), commercially available from Merck. Visualization of spots on TLC plate was accomplished with UV light.

4.2. Synthesis of *N*-alkyl-4,5-dihydro-5-(substituted phenyl)-1,2,3-triazolo[1,5-*a*][1,4]benzodiazepine-6-carboxamide 5

General procedure: A mixture of 2-azidobenzaldehyde[22] **1** (1 mmol), propargylamine **2** (1 mmol), isocyanides **3** (1.2 mmol) and nitrophenol **4** (1 mmol) in MeOH (10 mL) was heated at reflux for 24 h. The solvent was then removed under reduced pressure and the crude reaction mixture was purified by column chromatography on silica gel (petroleum ether–ethyl acetate/6:1) to give pure products **5**.

4.2.1. N-Cyclohexyl-4,5-dihydro-5-(4-nitrophenyl)-1,2,3-triazolo[1,5-a][1,4]benzodiazepine-6-carboxamide ***5a***. Yield: 75%; yellow crystals; mp 160–161 °C; R_f value: 0.15. IR (KBr): 3367, 2930, 2854, 1660, 1593, 1497, 1389 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ=0.87–1.58 (m, 10H, cyclohexyl), 3.45–3.47 (m, 1H, NCH), 4.19 (d, J=13.5 Hz, 1H, H_{4a}), 5.01 (d, J=13.5 Hz, 1H, H_{4b}), 5.38 (s, 1H, H_6), 5.73 (d, J=7.7 Hz, 1H, NH), 6.94 (d, J=9.1 Hz, 2H, $H_{2'}$, $H_{6'}$), 7.53 (t, J=7.5 Hz, 1H, H_{11}), 7.56 (d, J=7.5 Hz, 1H, H_{12}), 7.69 (t, J=7.5 Hz, 1H, H_{10}), 7.85 (s, 1H, H_3), 7.98 (d, J=7.5 Hz, 1H, H_9), 8.21 (d, J=9.1 Hz, 2H, $H_{3'}$, $H_{5'}$). ^{13}C NMR (125 MHz, $CDCl_3$): δ=24.2, 24.3, 24.7, 31.8, 32.2, 39.7, 48.2, 68.4, 112.9, 123.3, 125.6, 127.0, 129.6, 130.6, 130.8, 132.6, 132.9, 133.8, 139.8, 153.0, 166.2. MS: m/z (%)=432.19 $[M]^+$ (1), 306 (95, M–CONHcyclohexyl), 278 (40), 232 (100), 129 (15), 103 (22), 77 (13), 76 (20), 55 (55). Anal. Calcd for $C_{23}H_{24}N_6O_3$: C, 63.88; H, 5.59; N, 19.43. Found: C, 64.05; H, 5.45; N, 19.21.

4.2.2. N-Cyclohexyl-4,5-dihydro-5-(2-nitrophenyl)-1,2,3-triazolo[1,5-a][1,4]benzodiazepine-6-carboxamide ***5b***. Yield: 80%; yellow crystals; mp 243–244 °C; R_f value: 0.18. IR (KBr): 3377, 2929, 2855, 1675, 1603, 1520, 1448, 1356 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ=0.90–1.61 (m, 10H, cyclohexyl), 3.37–3.43 (m, 1H, NCH), 3.87 (d, J=13.5 Hz, 1H, H_{4a}), 4.48 (d, J=13.5 Hz, 1H, H_{4b}), 4.91 (s, 1H, H_6), 7.34 (d, J=8.3 Hz, 1H, NH), 7.42 (dt, J=8.0, 1.0 Hz, 1H, $H_{4'}$), 7.53 (dd, J=8.0, 1.0 Hz, 1H, $H_{6'}$), 7.60–7.69 (m, 4H, H_9, H_{10}, H_{11}, H_{12}), 7.79 (s, 1H, H_3), 7.91–7.94 (m, 2H, $H_{3'}$, $H_{5'}$). ^{13}C NMR (125 MHz, $CDCl_3$): δ=24.2, 24.3, 24.8, 31.8, 31.9, 45.5, 47.8, 69.2, 123.3, 125.1, 125.8, 126.4, 128.3, 129.5, 130.1, 130.6, 131.8, 132.3, 134.1, 134.7, 144.1, 145.8, 166.9. MS: m/z (%)=432.19 $[M]^+$ (1), 332 (14), 306 (94, M–CONHcyclohexyl), 278 (38), 260 (23), 231 (100), 205 (10), 151 (12), 129 (26), 102 (22), 77 (29), 55 (56). Anal. Calcd for $C_{23}H_{24}N_6O_3$: C, 63.88; H, 5.59; N, 19.43. Found: C, 63.69; H, 5.65; N, 19.55.

4.2.3. N-Cyclohexyl-4,5-dihydro-5-(2,4-dinitrophenyl)-1,2,3-triazolo[1,5-a][1,4]benzodiazepine-6-carboxamide ***5c***. Yield: 85%; yellow crystals; mp 150–151 °C; R_f value: 0.15. IR (KBr): 3371, 2930, 2854, 1673, 1601, 1526, 1449, 1335 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ=0.87–1.56 (m, 10H, cyclohexyl), 3.40–3.43 (m, 1H, NCH), 4.12 (d, J=13.5 Hz, 1H, H_{4a}), 4.38 (d, J=13.5 Hz, 1H, H_{4b}), 5.26 (s, 1H, H_6), 6.30 (d, J=7.8 Hz, 1H, NH), 7.55 (d, J=9.1 Hz, 1H, $H_{6'}$), 7.65–7.75 (m, 3H, H_{10}, H_{11}, H_{12}), 7.77 (s, 1H, H_3), 7.98 (d, J=7.8 Hz, 1H, H_9), 8.41 (dd, J=9.1, 2.5 Hz, 1H, $H_{5'}$), 8.78 (d, J=2.5 Hz, 1H, $H_{3'}$). ^{13}C NMR (125 MHz, $CDCl_3$): δ=24.2, 24.7, 31.9, 32.0, 44.0, 48.3, 59.9, 67.8, 122.2, 123.4, 123.6, 126.6, 128.2, 129.9, 130.1, 131.0, 131.8, 132.8, 134.4, 141.1, 141.5, 148.0, 165.8. MS: m/z (%)=477.18 $[M]^+$ (1), 351 (8, M–CONHcyclohexyl), 318 (63), 290 (17), 260 (12), 243 (100), 216 (21), 190 (14), 155 (19), 129 (20), 102 (40), 76 (33), 55 (58). Anal. Calcd for $C_{23}H_{23}N_7O_5$: C, 57.86; H, 4.86; N, 20.53. Found: C, 57.60; H, 4.72; N, 20.75.

4.2.4. N-Cyclohexyl-4,5-dihydro-5-(2,4,6-trinitrophenyl)-1,2,3-triazolo[1,5-a][1,4]benzodiazepine-6-carboxamide ***5d***. Yield: 88%; yellow crystals; mp 238–239 °C; R_f value: 0.21. IR (KBr): 3461, 2932, 2855, 1690, 1603, 1519, 1492, 1369 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ=1.10–1.99 (m, 10H, cyclohexyl), 2.95 (br s, 1H, NH), 3.59 (d, J=13.4 Hz, 1H, H_{4a}), 4.01–4.03 (m, 1H, NCH), 4.17 (d, J=13.4 Hz, 1H, H_{4b}), 4.49 (s, 1H, H_6), 7.53–7.54 (m, 2H, H_9, H_{12}), 7.77 (s, 1H, H_3), 7.82–7.87 (m, 2H, H_{10}, H_{11}), 8.62 (s, 1H, $H_{3'}$), 8.73 (s, 1H, $H_{5'}$). ^{13}C NMR (125 MHz, DMSO-d_6): δ=24.8, 25.4, 28.2, 28.7, 37.7, 53.8, 59.7, 62.2, 118.3, 122.8, 128.1, 128.4, 128.5, 128.6, 128.9, 129.2, 132.0, 133.7, 135.7, 167.3. MS: m/z (%)=522.16 $[M]^+$ (1), 396 (1, M–CONHcyclohexyl), 391 (55), 270 (13), 242 (20), 215 (16), 185 (30), 155 (24), 129 (26), 102 (21), 83 (85), 55 (100). Anal. Calcd for $C_{23}H_{22}N_8O_7$: C, 52.87; H, 4.24; N, 21.45. Found: C, 52.95; H, 4.44; N, 21.66.

4.2.5. N-Cyclohexyl-4,5-dihydro-5-(5-fluoro-2-nitrophenyl)-1,2,3-triazolo[1,5-a][1,4]benzodiazepine-6-carboxamide ***5e***. Yield: 85%; yellow crystals; mp 182–183 °C; R_f value: 0.22. IR (KBr): 3355, 2929, 2854, 1669, 1613, 1582, 1520, 1341 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ=0.93–1.65 (m, 10H, cyclohexyl), 3.41–3.43 (m, 1H, NCH), 3.87 (d, J=13.5 Hz, 1H, H_{4a}), 4.49 (d, J=13.5 Hz, 1H, H_{4b}), 4.95 (s, 1H, H_6), 7.09 (ddd, J=9.1, 8.0, 2.5 Hz, 1H, $H_{4'}$), 7.21 (dd, J=9.2, 2.5 Hz, 1H, $H_{6'}$), 7.28 (s, 1H, NH), 7.65–7.71 (m, 3H, H_{10}, H_{11}, H_{12}), 7.81 (s, 1H, H_3), 7.95 (d, J=7.6 Hz, 1H, H_9), 8.05 (dd, J=9.1, 5.5 Hz, 1H, $H_{3'}$). ^{13}C NMR (125 MHz, $CDCl_3$): δ=24.2, 24.3, 24.8, 31.8, 31.9, 45.2, 47.9, 69.0, 112.7 (d, $^2J_{C-F}$=23.1 Hz), 113.1 (d, $^2J_{C-F}$=23.0 Hz), 123.5, 127.7, 128.2 (d, $^3J_{C-F}$=10.5 Hz), 129.7, 130.2, 130.4, 131.8, 132.5, 134.6, 141.2, 146.7 (d, $^4J_{C-F}$=9.8 Hz), 164.8 (d, $^1J_{C-F}$=258.8 Hz), 166.5. MS: m/z (%)=451.18 $[M+1]^+$ (6), 324 (75, M–CONHcyclohexyl), 308 (16), 249 (100), 158 (12), 130 (14), 83 (28), 55 (65). Anal. Calcd for $C_{23}H_{23}FN_6O_3$: C, 61.32; H, 5.15; N, 18.66. Found: C, 61.55; H, 5.32; N, 18.50.

4.2.6. N-tert-Butyl-4,5-dihydro-5-(2-nitrophenyl)-1,2,3-triazolo[1,5-a][1,4]benzodiazepine-6-carboxamide ***5f***. Yield: 80%; yellow crystals; mp 221–223 °C; R_f value: 0.15. IR (KBr): 3353, 2966, 2829, 1678, 1602, 1521, 1476, 1361 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ=1.10 (s, 9H, *t*-butyl), 3.84 (d, J=13.0 Hz, 1H, H_{4a}), 4.52 (d, J=13.0 Hz, 1H, H_{4b}), 4.86 (s, 1H, H_6), 7.32 (s, 1H, NH), 7.42 (dt, J=8.1, 1.0 Hz, 1H, $H_{4'}$), 7.55 (dd, J=8.1, 1.0 Hz, 1H, $H_{6'}$), 7.61–7.69 (m, 4H, H_9, H_{10}, H_{11}, H_{12}), 7.83 (s, 1H, H_3), 7.92–7.95 (m, 2H, $H_{3'}$, $H_{5'}$). ^{13}C NMR (125 MHz, $CDCl_3$): δ=27.5, 45.4, 50.5, 70.1, 123.4, 125.1, 126.0, 126.4, 128.6, 129.4, 130.1, 130.6, 132.1, 132.3, 134.2, 134.6, 144.4, 145.8, 167.2. MS: m/z (%)=406.18 $[M]^+$ (1), 306 (42, M–CONH^{t}Bu), 285 (12), 231 (77), 170 (10), 129 (21), 91 (100), 57 (61). Anal. Calcd for $C_{21}H_{22}N_6O_3$: C, 62.06; H, 5.46; N, 20.68. Found: C, 62.22; H, 5.60; N, 20.73.

4.2.7. N-tert-Butyl-4,5-dihydro-5-(2,4-dinitrophenyl)-1,2,3-triazolo[1,5-a][1,4]benzodiazepine-6-carboxamide ***5g***. Yield: 85%; yellow crystals; mp 130–132 °C; R_f value: 0.19. IR (KBr): 3372, 2969, 2829, 1678, 1601, 1527, 1389 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ=1.09 (s, 9H, *tert*-butyl), 4.05 (d, J=14.0 Hz, 1H, H_{4a}), 4.42 (d, J=14.0 Hz, 1H, H_{4b}), 5.18 (s, 1H, H_6), 6.44 (s, 1H, NH), 7.59 (d, J=9.0 Hz, 1H, $H_{6'}$), 7.65–7.74 (m, 3H, H_{10}, H_{11}, H_{12}), 7.81 (s, 1H, H_3), 8.00 (d, J=7.8 Hz, 1H, H_9), 8.45 (dd, J=9.0, 2.5 Hz, 1H, $H_{5'}$), 8.80 (d, J=2.5 Hz, 1H, $H_{3'}$). ^{13}C NMR (125 MHz, $CDCl_3$): δ=28.0, 44.6, 51.7, 69.1, 122.6, 124.1, 124.3, 127.4, 128.8, 130.3, 130.5, 131.4, 132.4, 133.3, 134.8, 142.1, 142.3, 148.8, 166.3. MS: m/z (%)=451.16 $[M]^+$ (1), 351 (20, M–CONH^{t}Bu), 335 (14), 318 (18), 276 (21), 230 (79), 202 (16), 180 (10), 164 (14), 145 (30), 129 (29), 102 (45), 77 (52), 57 (100). Anal. Calcd for $C_{21}H_{21}N_7O_5$: C, 55.87; H, 4.69; N, 21.72. Found: C, 55.70; H, 4.80; N, 21.90.

4.2.8. N-tert-Butyl-4,5-dihydro-5-(5-fluoro-2-nitrophenyl)-1,2,3-triazolo[1,5-a][1,4]benzodiazepine-6-carboxamide ***5h***. Yield: 85%; yellow crystals; mp 218–220 °C; R_f value: 0.20. IR (KBr): 3430, 2925, 2856, 1637, 1607, 1492, 1468, 1381 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ=1.10 (s, 9H, *tert*-butyl), 3.83 (d, J=13.0 Hz, 1H, H_{4a}), 4.53 (d, J=13.0 Hz, 1H, H_{4b}), 4.90 (s, 1H, H_6), 7.09 (ddd, J=9.0, 8.0, 2.2 Hz, 1H, $H_{4'}$), 7.23 (dd, J=9.2, 2.2 Hz, 1H, $H_{6'}$), 7.31 (s, 1H, NH), 7.65–7.69 (m, 3H, H_{10}, H_{11}, H_{12}), 7.85 (s, 1H, H_3), 7.95 (d, J=7.6 Hz, 1H, H_9), 8.06

(dd, J=9.0, 5.7 Hz, 1H, $H_{3'}$). ^{13}C NMR (125 MHz, $CDCl_3$): δ=28.0, 45.5, 51.1, 70.2, 113.3 (d, $^2J_{C-F}$=23.2 Hz), 113.7 (d, $^2J_{C-F}$=23.3 Hz), 124.0, 127.9, 128.4, 128.7 (d, $^3J_{C-F}$=10.6 Hz), 130.1, 130.8, 132.5, 132.9, 134.9, 141.7, 147.4 (d, $^4J_{C-F}$=9.5 Hz), 165.3 (d, $^1J_{C-F}$=258.5 Hz), 167.3. MS: m/z (%)=425.17 $[M+1]^+$ (11), 324 (86, M−CONH^{t}Bu), 308 (25), 296 (20), 249 (100), 237 (24), 158 (15), 146 (16), 130 (20), 57 (95). Anal. Calcd for $C_{21}H_{21}FN_6O_3$: C, 59.43; H, 4.99; N, 19.80. Found: C, 59.25; H, 5.10; N, 19.95.

4.2.9. 4H-[1,2,3]Triazolo[1,5-a][1,4]benzodiazepine **7**. Yield: 60%; yellow crystals; mp 159–162 °C; R_f value: 0.15. ^{1}H NMR (500 MHz, $CDCl_3$): δ=4.73 (s, 2H, H_4), 7.57–7.62 (m, 2H, H_8, H_{10}), 7.68 (s, 1H, H_3), 7.72 (dt, J=7.5, 2.1 Hz, 1H, H_9), 8.22 (d, J=8.1 Hz, 1H, H_7), 8.48 (s, 1H, H_6). ^{13}C NMR (125 MHz, $CDCl_3$): δ=43.5, 122.5, 124.8, 128.5, 131.0, 131.6, 132.5, 134.7, 136.1, 163.2. Anal. Calcd for $C_{10}H_8N_4$: C, 65.21; H, 4.38; N, 30.42. Found: C, 64.95; H, 4.60; N, 30.20.

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Supplementary data

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References and notes

1. (a) Passerini, M.; Simone, L. *Gazz. Chim. Ital.* **1921**, *51*, 126; (b) Passerini, M.; Ragni, G. *Gazz. Chim. Ital.* **1931**, *61*, 964.
2. (a) Ugi, I.; Meyr, R.; Fetzer, U.; Steinbrückner, C. *Angew. Chem.* **1959**, *71*, 386; (b) Ugi, I.; Steinbrückner, C. *Angew. Chem.* **1960**, *72*, 267.
3. Akritopoulou-Zanze, I. *Curr. Opin. Chem. Biol.* **2008**, *12*, 324.
4. Evans, C. G.; Smith, M. C.; Carolan, J. P.; Gestwicki, J. E. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 2587.
5. Wang, W.; Dömling, A. *J. Comb. Chem.* **2009**, *11*, 403.
6. Borthwick, A. D.; Davies, D. E.; Exall, A. M.; Hatley, R. J. D.; Hughes, J. A.; Irving, W. R.; Livermore, D. G.; Sollis, S. L.; Nerozzi, F.; Valko, K. L.; Allen, M. J.; Perren, M.; Shabbir, S. S.; Woollard, P. M.; Price, M. A. *J. Med. Chem.* **2006**, *49*, 4159.
7. (a) He, P.; Wu, J.; Nie, Y.-B.; Ding, M.-W. *Tetrahedron* **2009**, *65*, 8563; (b) He, P.; Nie, Y.-B.; Wu, J.; Ding, M.-W. *Org. Biomol. Chem.* **2011**, *9*, 1429; (c) Zhong, Y.; Wang, L.; Ding, M.-W. *Tetrahedron* **2011**, *67*, 3714.
8. Shaabani, A.; Maleki, A.; Mofakham, H.; Khavasi, H. R. *J. Comb. Chem.* **2008**, *10*, 323.
9. Rodríguez-Borges, J. E.; Goncalves, S.; do Vale, M. L.; García-Mera, X.; Coelho, A.; Sotelo, E. *J. Comb. Chem.* **2008**, *10*, 372.
10. Shaabani, A.; Soleimani, E.; Sarvary, A.; Rezayan, A. H. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3968.
11. Cho, S.; Keum, G.; Kang, S. B.; Han, S.-Y.; Kim, Y. *Mol. Diversity* **2003**, *6*, 283.
12. (a) Banfi, L.; Basso, A.; Guanti, G.; Lecinska, P.; Riva, R. *Mol. Diversity* **2008**, *12*, 187; (b) Donald, J. R.; Martin, S. F. *Org. Lett.* **2011**, *13*, 852; (c) El Kaïm, L.; Grimaud, L.; Miranda, L. D.; Vieu, E.; Cano-Herrera, M.-A.; Perez-Labrada, K. *Chem. Commun.* **2010**, *46*, 2489; (d) Akritopoulou-Zanze, I.; Gracias, V.; Djuric, S. W. *Tetrahedron Lett.* **2004**, *45*, 8439.
13. (a) El Kaïm, L.; Grimaud, L.; Oble, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 7691; (b) El Kaïm, L.; Gizolme, M.; Grimaud, L.; Oble, J. *J. Org. Chem.* **2007**, *72*, 4169; (c) El Kaïm, L.; Grimaud, L.; Purumandla, S. R. *Tetrahedron Lett.* **2010**, *51*, 4962; (d) El Kaïm, L.; Gizzi, M.; Grimaud, L. *Org. Lett.* **2008**, *10*, 3417; (e) El Kaïm, L.; Gizolme, M.; Grimaud, L.; Oble, J. *Org. Lett.* **2006**, *8*, 4019.
14. (a) Hester, J. B., Jr.; Rudzik, A. D.; Kamdar, B. V. *J. Med. Chem.* **1971**, *14*, 1078; (b) Schweitzer, P. K.; Koshorek, G.; Muehlbach, M. J.; Morris, D. D.; Roehrs, T.; Walsh, J. K.; Roth, T. *Hum. Psychopharmacol. Clin. Exp.* **1991**, *6*, 99; (c) Levine, J.; Cole, D. P.; Chengappa, K. N. R.; Gershon, S. *Depression Anxiety* **2001**, *14*, 94; (d) Snyder, P. J.; Werth, J.; Giordani, B.; Caveney, A. F.; Feltner, D.; Maruff, P. *Hum. Psychopharmacol. Clin. Exp* **2005**, *20*, 263.
15. Bertelli, L.; Biagi, G.; Giorgi, I.; Livi, O.; Manera, C.; Scartoni, V.; Martini, C.; Giannaccini, G.; Trincavelli, L.; Barili, P. L. *Farmaco* **1998**, *53*, 305.
16. Mohapatra, D. K.; Maity, P. K.; Shabab, M.; Khan, M. I. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5241.
17. (a) Khoobi, M.; Alipour, M.; Zarei, S.; Jafarpour, F.; Shafiee, A. *Chem. Commun.* **2012**, 2985; (b) Mahdavi, M.; Asadi, M.; Saeedi, M.; Rezaei, Z.; Moghbel, H.; Foroumadi, A.; Shafiee, A. *Synlett* **2012**, 2521; (c) Mahdavi, M.; Asadi, M.; Saeedi, M.; Ebrahimi, M.; Rasouli, M. A.; Ranjbar, P. R.; Foroumadi, A.; Shafiee, A. *Synthesis* **2012**, *44*, 3649.
18. (a) Foroumadi, A.; Emami, S.; Mansouri, S.; Javidnia, A.; Saeid-Adeli, N.; Shirazi, F. H.; Shafiee, A. *Eur. J. Med. Chem.* **2007**, *42*, 985; (b) Fallah-Tafti, A.; Foroumadi, A.; Tiwari, R.; Shirazi, A. N.; Hangauer, D. G.; Bu, Y.; Akbarzadeh, T.; Parang, K.; Shafiee, A. *Eur. J. Med. Chem.* **2011**, *46*, 4853.
19. (a) Ilyn, A. P.; Trifilenkov, A. S.; Kuzovkova, J. A.; Kutepov, S. A.; Nikitin, A. V.; Ivachtchenko, A. V. *J. Org. Chem.* **2005**, *70*, 1478; (b) Gulevich, A. V.; Balenkova, E. S.; Nenajdenko, V. G. *J. Org. Chem.* **2007**, *72*, 7878.
20. Ugi, I.; Offermann, K. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 624.
21. Alajarín, M.; Cabrera, J.; Pastor, A.; Villalgordo, J. M. *Tetrahedron Lett.* **2007**, *48*, 3495.
22. 2-Azidobenzaldehyde was prepared according to Pelkey, E. T.; Gribble, G. W. *Tetrahedron Lett.* **1997**, *38*, 5603.