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A simple and one-pot synthesis of 2,3,4,5-tetrasubstituted 4,5-dihydro-3*H*-1,4-benzodiazepines

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ABSTRACT

2,3,4,5-Tetrasubstituted 4,5-dihydro-3*H*-1,4-benzodiazepines were synthesized in one-pot by a new sequential Ugi 4CC/Staudinger/aza-Wittig reaction, starting from easily accessible *o*-azidobenzaldehyde, α-amino ketone hydrochloride, isocyanide and carboxylic acid.

1. Introduction

1,4-Benzodiazepines are one of the most important and widely used scaffolds in medicinal chemistry, especially for the treatment of anxiety and sleep disorders.[1] A large number of 1,4-benzodiazepine derivatives have also been found to show other biological activities, such as antiarrhythmic,[2] anticonvulsant,[3] anticancer[4] and anti-HIV activities.[5] Several new synthetic approaches have been reported in literature recently. For example, some 1,4-benzodiazepines can be prepared either by reaction of bromoethylsulfonium salt with 1,3-diamines,[6] or by a one-pot reaction of methyl 1-arylaziridine-2-carboxylates with *N*-[2-bromomethyl(aryl)]trifluoroacetamides.[7] Another 1,4-benzodiazepines were obtained from Pd-catalyzed coupling of *N*-allyl-2-aminobenzylamine derivatives with aryl bromides,[8] or by the reaction of 2-aminobenzylamine with 1,2-diaza-1,3-dienes.[9] Although much effort has been directed toward the construction of 1,4-benzodiazepines, fewer methods for the synthesis of 4,5-dihydro-3*H*-1,4-benzodiazepines have been developed. To further discover molecules with potent and selective biological activity, it is of importance to explore new methodology for the synthesis of novel 4,5-dihydro-3*H*-1,4-benzodiazepine entities.

The Ugi reaction is a powerful, atom-economical reaction between isocyanide, amine, aldehyde (or ketone) and carboxylic acid components that generates a significantly more complex α-acylamino amide adduct.[10] The sequence of Ugi isocyanide multicomponent reaction, followed by post-condensation transformations, constitutes an extremely powerful synthetic tool for the preparation of structurally diverse complex molecules, especially heterocyclic compounds.[11] The aza-Wittig reactions of iminophosphoranes have received increased attention in view of their utility in the synthesis of *N*-heterocycles.[12] Recently the sequence of Ugi and Passerini reaction, followed by post-condensation Staudinger and aza-Wittig reaction, has been utilized in synthesis of a series of biologically useful heterocycles.[13–19] Continuing our interest in the synthesis of various heterocycles via aza-Wittig reaction,[20] we wish to report herein a one-pot synthetic approach to 2,3,4,5-tetrasubstituted 4,5-dihydro-3*H*-1,4-benzodiazepines by a sequential Ugi 4CC–Staudinger–aza-Wittig reaction, starting from the easily accessible *o*-azidobenzaldehyde, α-amino ketone hydrochloride, isocyanide and carboxylic acid.

2. Results and discussion

It has been reported that α-amino ketone hydrochloride **1a** can be used as one reactant in some Ugi reactions to produce normal products albeit in low to moderate yields (38%–78%).[21] However, 2-azidobenzaldehyde **2** has not been used previously in the reaction to prepare corresponding azide **7**. Initially, we selected the phenacylamine hydrochloride **1a**, 2-azidobenzaldehyde **2**, 4-methylbenzoic acid **3a** and *tert*-butylisocyanide **4a** as the reactants (Scheme 1).

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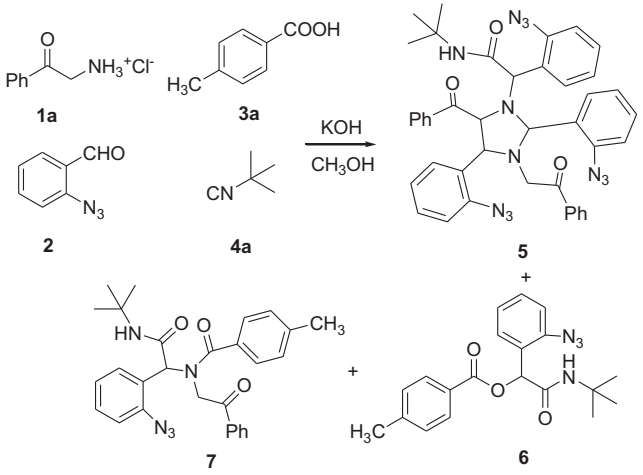
When the phenacylamine hydrochloride **1a**, potassium hydroxide, 2-azidobenzaldehyde **2**, 4-methylbenzoic acid **3a** and *tert*-butylisocyanide **4a** was stirred in methanol at room temperature, the reaction solution became red and a white solid precipitated, which was verified unexpectedly to be the tetrahydroimidazole adduct **5** (42%). The normal Passerini product **6** (16%) and Ugi product **7** (25%) was also isolated from the reaction mixture. The structure of tetrahydroimidazole adduct **5** was confirmed by its spectrum data. Furthermore a single crystal of **5** was obtained from the CH_2Cl_2 solution, and X-ray structure analysis verified the proposed structure (Fig. 1). The formation of the adduct **5** might be rationalized in terms of an initial condensation of **1a** and **2** to give the Schiff base intermediate **8**, which undergoes self-condensation under the reaction condition to produce tetrahydroimidazole **9** through the condensation of the methylene group of intermediate **8**, further reaction of **9** with aldehyde **2** and isocyanide **4a** give the adduct **5**[22] (Scheme 2).



Scheme 1. Ugi reaction of phenacylamine hydrochloride **1a**.

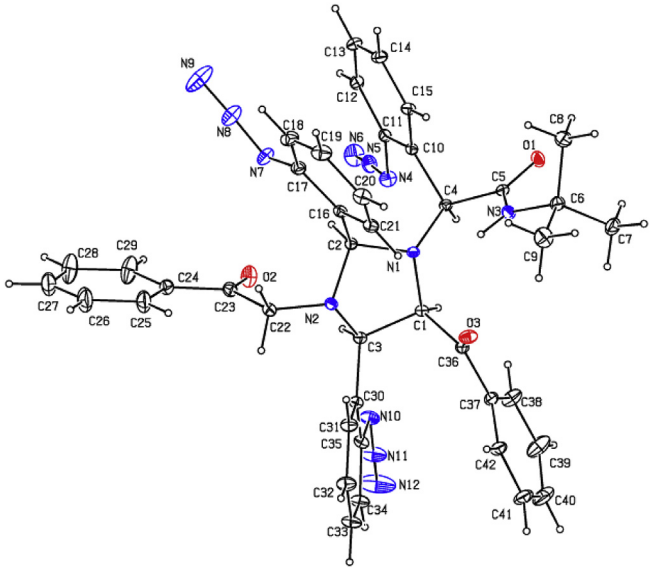
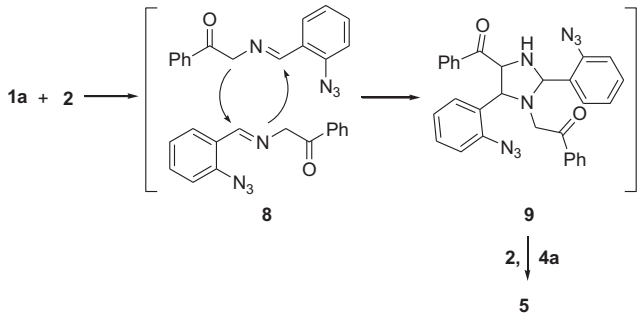
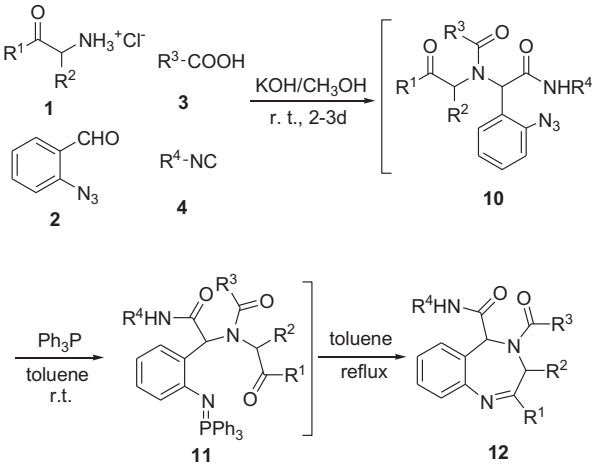


Fig. 1. X-ray crystal structure of compound **5**.



Scheme 2. Possible mechanism for formation of adduct **5**.

We speculated that the formation of adduct **5** would be diminished if a α-substituted α-amino ketone **1** ($R^2 \neq H$) was used. The α-amino ketone hydrochloride **1** (1 equiv), 2-azidobenzaldehyde **2** (1 equiv), acid **3** (1 equiv) and isocyanide **4** (1 equiv) were then employed for the reaction (Scheme 3). We were pleased to find that, in these cases, the Ugi reaction proceeds smoothly and some of the products **10** can be isolated in 67–79% yields, but the obtained azides **10** were found not stable when stored. So the best result was obtained when the reaction was carried out in one-pot fashion: after monitoring the formation of the azides **10**, the formed inorganic salt (KCl) was removed by filtration and the solvent was changed from methanol to toluene, then triphenylphosphine was added and the resulted solution was refluxed. The final products obtained were verified to be 4,5-dihydro-3*H*-1,4-benzodiazepines **12** (in 65–81% overall yields) (Table 1). The starting material, which was left over has little affection on the proceeding one-pot reaction.



Scheme 3. Synthesis of 4,5-dihydro-3*H*-1,4-benzodiazepines **12**.

The compounds **12a**–**p** were confirmed by their spectrum data. For example, the ^1H NMR spectrum of **12b** shows the signals of CONH and COCH at 5.85 and 5.00 ppm as singlet. The signals of NCH appear at 4.95–4.92 ppm as multiplets. The signals of CH_2CH_3 and *t*-Bu appear at 1.66–0.58 as multiplets. The signals attributable to the Ar–Hs are found at 7.96–7.24 ppm as multiplets. The ^{13}C NMR spectrum data in **12b** showed the signals of C=O and C=N carbon at 172.4, 167.8 and 167.7 ppm. The MS spectrum of **12b** shows M^+–CONHBu-*t* at *m*/*z* 387 with 14% abundance. Furthermore a single crystal of 2,3,4,5-tetrasubstituted 4,5-dihydro-3*H*-1,4-benzodiazepine **12a** was obtained from the CH_2Cl_2/petroleum

Table 1
Preparation of compounds **12**

	R^1	R^2	R^3	R^4	Yield[a] (%)
12a	Ph	Et	4-$CH_3C_6H_4$	*t*-Bu	74
12b	Ph	Et	4-ClC_6H_4	*t*-Bu	68
12c	Ph	Et	2-$CH_3C_6H_4$	*t*-Bu	73
12d	Ph	Et	Ph	*t*-Bu	65
12e	Ph	Et	4-FC_6H_4	*t*-Bu	68
12f	Ph	Et	2-ClC_6H_4	*t*-Bu	72
12g	Ph	Et	2-FC_6H_4	*t*-Bu	73
12h	Ph	Et	4-$CH_3OC_6H_4$	*t*-Bu	78
12i	Ph	Et	4-ClC_6H_4	*c*-C_6H_{11}	70
12j	Ph	Et	Ph	*c*-C_6H_{11}	77
12k	Ph	Et	4-FC_6H_4	*c*-C_6H_{11}	71
12l	Ph	Me	4-$CH_3C_6H_4$	*t*-Bu	65
12m	Ph	Et	*c*-C_6H_{11}	*t*-Bu	81
12n	4-ClC_6H_4	Et	4-$CH_3C_6H_4$	*t*-Bu	65
12o	4-ClC_6H_4	Et	4-$CH_3OC_6H_4$	*t*-Bu	76
12p	4-ClC_6H_4	*n*-Bu	4-ClC_6H_4	*t*-Bu	75
12q	Me	$PhCH_2$	4-ClC_6H_4	*t*-Bu	78
12r	Me	$PhCH_2$	4-$CH_3C_6H_4$	*t*-Bu	79

[a] Isolated yields based on azide **2**.

ether solution of **12a**, and X-ray structure analysis verified the proposed structure (Fig. 2).

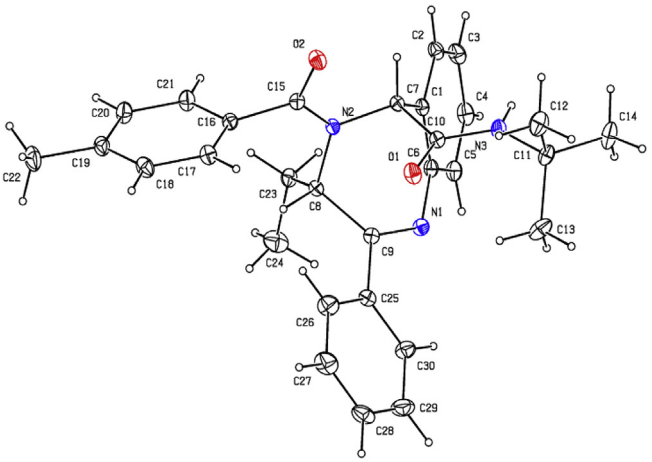


Fig. 2. X-ray crystal structure of compound **12a**.

3. Conclusion

We have successfully synthesized a series of 2,3,4,5-tetrasubstituted 4,5-dihydro-3*H*-1,4-benzodiazepines in one-pot fashion by a sequential Ugi 4CC–Staudinger–aza-Wittig reaction, starting from the corresponding α-alkyl α-amino ketone hydrochlorides as the amino component. The used aminoketones, isocyanides and acids can be varied broadly, producing products with three potential points of diversity, in combination to the easy availability of the synthetic approach and the large scope of the reaction makes it useful in synthetic and medicinal chemistry.

4. Experimental

4.1. General

Melting points were determined using a X-4 model apparatus and were uncorrected. MS were measured on a Finnigan Trace MS spectrometer. IR were recorded on a PE-983 infrared spectrometer as KBr pellets with absorption in cm^{-1}. NMR were recorded in $CDCl_3$ or DMSO-d_6 on a Varian Mercury 600 spectrometer and resonances relative to TMS. Elementary analyses were taken on a Vario EL III elementary analysis instrument. The X-ray diffraction data were collected on a *Bruker SMART AXS CCD* diffractometer, MoKα, 2θ=1.86–27.50°.

4.2. Synthesis of compounds 5, 6 and 7

Finely powdered 4-methylbenzoic acid **3** (R^3=4-$CH_3C_6H_4$, 0.68 g, 5 mmol) was added to a well-stirred solution of potassium hydroxide (0.28 g, 5 mmol) in MeOH (15 mL), the phenacylamine hydrochloride **1** (R^1=C_6H_5, R^2=H, 0.86 g, 5 mmol) was added to the above suspension at 5 °C and stirring was continued for 10 min. The resulting suspension was treated with 2-azidobenzaldehyde **2** (0.74 g, 5 mmol) and then with *tert*-butylisocyanide **4** (R^4=*t*-Bu, 0.42 g, 5 mmol). The reaction solution became red and a white solid precipitated when the reaction mixture was stirred at room temperature for 5–6 h. After stirring for 24 h, the solid precipitated was filtered, washed with water (30 mL) and dried to give the adduct **5**. The filtrate was then condensed and the residue was purified by column chromatography (4:1, petroleum ether/diethyl ether) to give compounds **6** and **7**.

*4.2.1. 2-(2-Azidophenyl)-2-(2,4-bis(2-azidophenyl)-5-benzoyl-3-(2-oxo-2-phenylethyl)imidazolidin-1-yl)-N-(tert-butyl)acetamide (**5**).* White solid (1.01 g, 42%). Mp 196–197 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ=8.85 (s, 1H, NH), 7.54–7.15 (m, 16H, Ar–H), 6.91–6.83 (m, 2H, Ar–H), 6.68 (s, 1H, Ar–H), 6.60 (d, *J*=7.2 Hz, 2H, Ar–H), 6.51 (d, *J*=7.8 Hz, 1H, Ar–H), 5.75 (d, *J*=9.6 Hz, 1H, CH), 5.32 (d, *J*=9.0 Hz, 1H, CH), 5.28 (s, 1H, CH), 5.00 (s, 1H, CH), 3.68 (d, *J*=17.4 Hz, 1H, CH_2^a), 3.49 (d, *J*=18.0 Hz, 1H, CH_2^b), 1.12 (s, 9H, *t*-Bu). ^{13}C NMR (150 MHz, $CDCl_3$): δ=201.6, 197.3, 170.1, 140.2, 138.8, 138.3, 136.9, 136.0, 133.1, 132.7, 132.5, 132.4, 130.2, 129.3, 129.2, 129.0, 128.2, 127.6, 127.5, 127.2, 126.7, 126.5, 124.9, 124.5, 123.6, 117.8, 117.7, 117.3, 116.4, 74.7, 71.5, 60.6, 50.8, 50.1, 28.2, 28.1. IR (KBr): 3319, 2972, 2905, 2127, 1695, 1698, 1598, 1583 cm^{-1}. Elemental Anal. Calcd for $C_{42}H_{38}N_{12}O_3$: C, 66.48; H, 5.05; N, 22.15. Found: C, 66.21; H, 5.24; N, 22.01.

*4.2.2. 1-(2-Azidophenyl)-2-(tert-butylamino)-2-oxoethyl 4-methylbenzoate (**6**).* Light yellow solid (0.39 g, 16%). Mp 140–141 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ=7.98 (d, *J*=7.2 Hz, 2H, Ar–H), 7.59–7.16 (m, 6H, Ar–H), 6.41 (s, 1H, CH), 6.16 (s, 1H, NH), 2.40 (s, 3H, CH_3), 1.37 (s, 9H, *t*-Bu). ^{13}C NMR (150 MHz, $CDCl_3$): δ=167.0, 165.0, 144.2, 137.9, 129.8, 129.6, 129.2, 129.1, 127.3, 126.4, 125.0, 118.2, 51.5, 28.5, 28.6, 21.6. IR (KBr): 3283, 3086, 2970, 2925, 2129, 1727, 1664, 1612, 1563, 1293, 1274, 1111 cm^{-1}. Elemental Anal. Calcd for $C_{20}H_{22}N_4O_3$: C, 65.56; H, 6.05; N, 15.29. Found: C, 65.46; H, 5.83; N, 15.24.

*4.2.3. N-(1-(2-Azidophenyl)-2-(tert-butylamino)-2-oxoethyl)-4-methyl-N-(2-oxo-2-phenylethyl) benzamide (**7**).* Light yellow solid (0.61 g, 25%). Mp 168–169 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ=8.79 (s, 1H, NH), 7.92 (d, *J*=7.8 Hz, 2H, Ar–H), 7.58–7.10 (m, 11H, Ar–H), 5.65 (s, 1H, CH), 4.88 (d, *J*=16.8 Hz, 1H, NCH_2^a), 3.64 (d, *J*=16.8 Hz, 1H, NCH_2^b), 2.40 (s, 2.5H, 0.83CH_3), 2.27 (s, 0.5H, 0.17CH_3), 1.56 (s, 8H, 0.8*t*-Bu), 1.45 (s, 1H, 0.1*t*-Bu). ^{13}C NMR ($CDCl_3$, 150 MHz): δ=196.7, 173.6, 168.2, 140.7, 139.4, 135.2, 133.8, 132.0, 130.6, 129.9, 129.1, 128.6, 128.2, 127.2, 127.0, 125.0, 118.5, 63.6, 52.0, 50.0, 28.7, 21.4. IR (KBr): 3314, 3066, 2974, 2129, 1694, 1674, 1614 cm^{-1}. Elemental Anal. Calcd for $C_{28}H_{29}N_5O_3$: C, 69.55; H, 6.04; N, 14.48. Found: C, 69.74; H, 5.97; N, 14.35.

4.3. One-pot synthesis of 2,3,4,5-tetrasubstituted 4,5-dihydro-3*H*-1,4-benzodiazepines 12

*4.3.1. N-(tert-Butyl)-3-ethyl-4-(4-methylbenzoyl)-2-phenyl-4,5-[dihydro-3H-1,4-benzodiazepine-5-carboxamide (**12a**).* Finely

powdered 4-methylbenzoic acid **3** (R^3=4-$CH_3C_6H_4$, 0.27 g, 2 mmol) was added to a well-stirred solution of potassium hydroxide (0.11 g, 2 mmol) in MeOH (10 mL), α-alkyl α-amino ketone hydrochlorides **1** (R^1=C_6H_5, R^2=Et, 0.33 g, 2 mmol) was added to the above suspension at 5 °C and stirring was continued for 10 min. The resulting suspension was treated with 2-azidobenzaldehyde **2** (0.29 g, 2 mmol) and then with isocyanide **4** (R^4=*t*-Bu, 0.17 g, 2 mmol). The reaction mixture was stirred at room temperature, monitoring the reactions by thin-layer chromatography (TLC) until the reactants disappeared. The formed inorganic salt was removed by filtration. After removing the solvent under reduced pressure, dry toluene (5 mL) was added. To the above solution was added dropwise the solution of triphenylphosphine (0.63 g, 2.4 mmol) in dry toluene (5 mL) at room temperature. The mixture was then heated to reflux, monitoring the reactions by thin-layer chromatography (TLC) until the reaction completed. The solvent was then evaporated under reduced pressure and the residue was purified by column chromatography to give 4,5-dihydro-3*H*-1,4-benzodiazepines **12a**. Light yellow solid (0.69 g, 74%). Mp 175–176 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ=8.12–7.11 (m, 13H, Ar–H), 6.22–6.13 (m, 1H, NH), 5.13 (s, 1H, CH), 5.06 (s, 0.2H, 0.2CH), 4.84 (s, 0.8H, 0.8CH), 2.40 (s, 3H, CH_3), 1.65–0.38 (m, 14H, CH_2CH_3 and *t*-Bu). ^{13}C NMR ($CDCl_3$, 150 MHz): δ=171.8, 170.0, 167.8, 148.2, 147.8, 140.1, 139.4, 133.6, 133.2, 130.3, 129.2, 129.1, 128.2, 128.0, 126.4, 125.8, 124.7, 64.8, 55.4, 51.4, 28.0, 24.7, 21.3, 10.8. MS: *m*/*z* (%)=367 (13, M^+–CONHBu-*t*), 232 (3), 120 (9), 119 (100). Elemental Anal. Calcd for $C_{30}H_{33}N_3O_2$: C, 77.06; H, 7.11; N, 8.99. Found: C, 77.21; H, 7.12; N, 9.22.

*4.3.2. N-(tert-Butyl)-4-(4-chlorobenzoyl)-3-ethyl-2-phenyl-4,5-dihydro-3H-1,4-benzodiazepine-5-carboxamide (**12b**).* Operation as above with 4-chlorobenzoic acid **3** (R^3=4-ClC_6H_4, 0.31 g, 2 mmol) and isocyanide **4** (R^4=*t*-Bu, 0.17 g, 2 mmol), compound **12b** (0.66 g, 68%) was isolated as light yellow solid. Mp 172–173 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ=7.96–7.24 (m, 13H, Ar–H), 5.85 (s, 1H, NH), 5.00 (s, 1H, CH), 4.95–4.92 (m, 1H, CH), 1.66–1.61 (m, 1H, CH_2^a), 1.39 (s, 8H, 0.88*t*-Bu), 1.16 (s, 1H, 0.12*t*-Bu), 0.86–0.84 (m, 1H, CH_2^b), 0.60 (t, *J*=7.2 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 150 MHz): δ=172.4, 167.8, 167.7, 149.3, 137.9, 136.6, 133.7, 131.0, 129.4, 128.8, 128.7, 128.6, 128.4, 127.3, 127.2, 126.2, 125.0, 124.0, 61.3, 60.0, 51.7, 29.0, 28.4, 27.9, 24.2, 11.0. MS: *m*/*z* (%)=387 (14, M^+–CONHBu-*t*), 232 (6), 207 (3), 193 (6), 165 (8), 139 (100). Elemental Anal. Calcd for $C_{29}H_{30}ClN_3O_2$: C, 71.37; H, 6.20; N, 8.61. Found: C, 71.32; H, 6.12; N, 8.87.

*4.3.3. N-(tert-Butyl)-3-ethyl-4-(2-methylbenzoyl)-2-phenyl-4,5-dihydro-3H-1,4-benzodiazepine-5-carboxamide (**12c**).* Operation as above with 2-methylbenzoic acid **3** (R^3=2-$CH_3C_6H_4$, 0.27 g, 2 mmol) and isocyanide **4** (R^4=*t*-Bu, 0.17 g, 2 mmol), compound **12c** (0.68 g, 73%) was isolated as light yellow solid. Mp 173–174 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ=8.11–7.04 (m, 13H, Ar–H), 6.16–6.12 (m, 1H, NH), 5.16–4.76 (m, 2H, 2CH), 2.55 (s, 1H, 0.33CH_3), 2.30 (s, 2H, 0.67CH_3), 1.78–0.36 (m, 14H, CH_2CH_3 and *t*-Bu). ^{13}C NMR ($CDCl_3$, 150 MHz): δ=170.5, 169.6, 167.1, 147.6, 140.0, 136.0, 133.1, 130.4, 130.2, 129.7, 128.7, 128.1, 128.0, 127.7, 126.4, 126.3, 125.8, 125.6, 124.6, 64.3, 55.3, 51.2, 27.9, 24.3, 18.7, 10.7. MS: *m*/*z* (%)=367 (11, M^+–CONHBu-*t*), 247 (2), 232 (2), 193 (1), 165 (3), 119 (100). Elemental Anal. Calcd for $C_{30}H_{33}N_3O_2$: C, 77.06; H, 7.11; N, 8.99. Found: C, 77.27; H, 7.32; N, 8.82.

*4.3.4. 4-Benzoyl-N-(tert-butyl)-3-ethyl-2-phenyl-4,5-dihydro-3H-1,4-benzodiazepine-5-carboxamide (**12d**).* Operation as above with benzoic acid **3** (R^3=C_6H_5, 0.24 g, 2 mmol), compound **12d** (0.59 g, 65%) was isolated as light yellow solid. Mp 225–226 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ=7.50–7.23 (m, 14H, Ar–H), 5.70 (s, 1H, NH), 5.04–5.01 (m, 2H, 2CH), 1.43 (s, 9H, *t*-Bu), 1.20–1.18 (m, 1H, CH_2^a), 0.93–0.86 (m, 1H, CH_2^b), 0.59 (t, *J*=7.4 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 150 MHz): δ=173.4, 167.9, 167.7, 149.4, 138.0, 135.4, 130.8, 130.4, 129.1, 128.5, 128.3, 127.3, 127.2, 125.9, 125.3, 124.3, 124.1, 61.7, 59.8, 51.5, 28.5, 24.2, 11.1. MS: *m*/*z* (%)=353 (13, M^+–CONHBu-*t*), 248 (6), 232 (4), 207 (6), 193 (4), 135 (7), 122 (4), 105 (100). Elemental Anal. Calcd for $C_{29}H_{31}N_3O_2$: C, 76.79; H, 6.89; N, 9.26. Found: C, 76.57; H, 7.02; N, 9.23.

*4.3.5. N-(tert-Butyl)-3-ethyl-4-(4-fluorobenzoyl)-2-phenyl-4,5-dihydro-3H-1,4-benzodiazepine-5-carboxamide (**12e**).* Operation as above with 4-fluorobenzoic acid **3** (R^3=4-FC_6H_4, 0.28 g, 2 mmol) and isocyanide **4** (R^4=*t*-Bu, 0.17 g, 2 mmol) in the first step, compound **12e** (0.64 g, 68%) was isolated as light yellow solid. Mp 177–178 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ=8.10–7.12 (m, 13H, Ar–H), 6.20–6.12 (m, 1H, NH), 5.08–4.78 (m, 2H, 2CH), 1.62–1.60 (m, 1H, CH_2^a), 1.24–1.20 (m, 1H, CH_2^b), 1.12 (s, 2H, 0.22*t*-Bu), 0.94 (s, 7H, 0.78*t*-Bu), 0.71–0.42 (m, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 150 MHz): δ=170.7, 170.3, 167.6, 163.9, 162.3, 147.8, 140.1, 132.7, 130.6, 130.2, 128.7, 128.3, 128.2, 128.0, 125.9, 124.6, 124.3, 115.6, 115.5, 64.7, 59.6, 55.5, 51.4, 28.5, 27.9, 27.3, 10.7. MS: *m*/*z* (%)=471 (1) $[M]^+$, 371 (53), 343 (3), 309 (7), 247 (4), 232 (8), 218 (8), 193 (3), 165 (2), 123 (100). Elemental Anal. Calcd for $C_{29}H_{30}FN_3O_2$: C, 73.86; H, 6.41; N, 8.91. Found: C, 73.57; H, 6.33; N, 9.16.

*4.3.6. N-(tert-Butyl)-4-(2-chlorobenzoyl)-3-ethyl-2-phenyl-4,5-dihydro-3H-1,4-benzodiazepine-5-carboxamide (**12f**).* Operation as above with 2-chlorobenzoic acid **3** (R^3=2-ClC_6H_4, 0.31 g, 2 mmol) and isocyanide **4** (R^4=*t*-Bu, 0.17 g, 2 mmol), compound **12f** (0.70 g, 72%) was isolated as light yellow solid. Mp 176–177 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ=8.23–7.06 (m, 13H, Ar–H), 6.22–6.13 (m, 1H, NH), 5.15–4.74 (m, 2H, 2CH), 1.73–1.69 (m, 1H, CH_2^a), 1.30–0.92 (m, 10H, CH_2^b and *t*-Bu), 0.72–0.33 (m, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 150 MHz): δ=169.9, 167.8, 167.1, 147.8, 140.0, 135.6, 131.3, 131.1, 130.4, 130.3, 130.1, 129.5, 129.3, 129.0, 128.2, 128.1, 128.0, 127.7, 126.8, 125.7, 124.2, 64.4, 55.5, 55.2, 51.3, 27.9, 24.3, 24.2, 11.2, 10.7. MS: *m*/*z* (%)=387 (17, M^+–CONHBu-*t*), 232 (6), 193 (2), 165 (5), 141 (33), 139 (100). Elemental Anal. Calcd for $C_{29}H_{30}ClN_3O_2$: C, 71.37; H, 6.20; N, 8.61. Found: C, 71.53; H, 6.23; N, 8.44.

*4.3.7. N-(tert-Butyl)-3-ethyl-4-(2-fluorobenzoyl)-2-phenyl-4,5-dihydro-3H-1,4-benzodiazepine-5-carboxamide (**12g**).* Operation as above with 2-fluorobenzoic acid **3** (R^3=2-FC_6H_4, 0.28 g, 2 mmol) and isocyanide **4** (R^4=*t*-Bu, 0.17 g, 2 mmol), compound **12g** (1.03 g, 73%) was isolated as light yellow solid. Mp 178–179 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ=7.47–7.06 (m, 11H, Ar–H), 6.84 (t, *J*=7.2 Hz, 1H, Ar–H), 6.71 (d, *J*=8.4 Hz, 1H, Ar–H), 6.62 (s, 1H, NH), 5.80–5.58 (m, 2H, 2CH), 2.14–1.81 (m, 2H, CH_2), 1.28 (s, 9H, *t*-Bu), 1.05–0.44 (m, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 150 MHz): δ=166.9, 166.3, 159.9, 158.3, 140.9, 138.0, 134.9, 131.3, 131.2, 129.2, 128.9, 128.7, 125.7, 125.6, 123.5, 122.5, 119.4, 118.3, 116.7, 115.8, 115.6, 65.9, 65.8, 51.3, 28.8, 28.3, 11.4. MS: *m*/*z* (%)=371 (65, M^+–CONHBu-*t*), 343 (7), 232 (9), 193 (2), 165 (2), 123 (100). Elemental Anal. Calcd for $C_{29}H_{30}FN_3O_2$: C, 73.86; H, 6.41; N, 8.91. Found: C, 73.94; H, 6.18; N, 8.73.

*4.3.8. N-(tert-Butyl)-3-ethyl-4-(4-methoxybenzoyl)-2-phenyl-4,5-dihydro-3H-1,4-benzodiazepine-5-carboxamide (**12h**).* Operation as above with 4-methoxybenzoic acid **3** (R^3=4-$CH_3OC_6H_4$, 0.30 g, 2 mmol) and isocyanide **4** (R^4=*t*-Bu, 0.17 g, 2 mmol), compound **12g** (0.75 g, 78%) was isolated as light yellow solid. Mp 168–169 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ=8.12–7.76 (m, 2H, Ar–H), 7.50–7.12 (m, 9H, Ar–H), 6.94 (d, *J*=7.8 Hz, 2H), 6.21–6.13 (m, 1H, CH), 5.17 (s, 1H, NH), 5.05 (s, 0.2H, 0.2CH), 4.84 (s, 0.8H, 0.8CH), 3.85 (s, 3H, OCH_3), 1.98–1.26 (m, 2H, CH_2), 1.10 (s, 2H, 0.22*t*-Bu), 0.93 (s, 7H, 0.78*t*-Bu), 0.70–0.41 (m, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 150 MHz): δ=171.6, 170.1, 167.9, 160.4, 147.8, 140.1, 130.5, 130.3, 130.2, 128.7, 128.3, 128.2, 128.0, 125.9, 124.7, 124.6, 113.8, 64.8, 55.4, 55.3, 51.4, 27.9, 24.7, 10.7.

MS: *m*/*z* (%)=383 (25, M^+−CONHBu-*t*), 247 (4), 232 (3), 193 (1), 165 (1), 135 (100). Elemental Anal. Calcd for $C_{30}H_{33}N_3O_3$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.25; H, 6.94; N, 8.76.

*4.3.9. 4-(4-Chlorobenzoyl)-N-cyclohexyl-3-ethyl-2-phenyl-4,5-dihydro-3H-1,4-benzodiazepine-5-carboxamide (**12i**).* Operation as above with 4-chlorobenzoic acid **3** (R^3=4-ClC_6H_4, 0.31 g, 2 mmol) and isocyanocyclohexane **4** (R^4=*c*-C_6H_{11}, 0.22 g, 2 mmol), compound **12i** (0.72 g, 70%) was isolated as light yellow solid. Mp 223–224 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): *δ*=8.06–7.67 (m, 2H, Ar–H), 7.49–7.12 (m, 11H, Ar–H), 6.20–6.10 (m, 1H, NH), 5.06 (s, 1H, CH), 4.92–4.76 (m, 1H, CH), 3.58–3.35 (m, 1H, NCH), 1.74–0.45 (m, 15H, CH_2CH_3 and $(CH_2)_5$). ^{13}C NMR ($CDCl_3$, 150 MHz): *δ*=170.7, 170.5, 167.5, 148.0, 140.1, 135.4, 135.1, 130.7, 130.2, 128.8, 128.4, 128.2, 128.1, 127.8, 127.4, 125.9, 124.7, 124.0, 64.2, 55.5, 48.8, 32.2, 24.8, 24.6, 24.3, 10.3. MS: *m*/*z* (%)=513 (2, M^+), 387 (85), 359 (5), 249 (2), 248 (3), 232 (7), 193 (3), 165 (3), 139 (100). Elemental Anal. Calcd for $C_{31}H_{32}ClN_3O_2$: C, 72.43; H, 6.27; N, 8.17. Found: C, 72.14; H, 6.47; N, 8.03.

*4.3.10. 4-Benzoyl-N-cyclohexyl-3-ethyl-2-phenyl-4,5-dihydro-3H-1,4-benzodiazepine-5-carboxamide (**12j**).* Operation as above with benzoic acid **3** (R^3=C_6H_5, 0.22 g, 2 mmol) and isocyanocyclohexane **4** (R^4=*c*-C_6H_{11}, 0.22 g, 2 mmol), compound **12j** (0.74 g, 77%) was isolated as light yellow solid. Mp 171–172 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): *δ*=7.48–7.20 (m, 14H, Ar–H), 6.06 (s, 1H, NH), 5.16 (s, 1H, CH), 5.03 (s, 1H, CH), 3.91–3.87 (m, 1H, NCH), 1.98–1.92 (m, 2H, CH_2), 1.66–1.09 (m, 10H, $(CH_2)_5$), 0.87–0.59 (m, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 150 MHz): *δ*=173.3, 167.9, 167.6, 149.1, 137.9, 135.2, 130.8, 130.4, 129.4, 129.1, 128.3, 127.2, 127.1, 126.6, 125.9, 125.0, 124.3, 61.2, 59.7, 48.7, 47.9, 32.6, 25.0, 11.4, 10.4. MS: *m*/*z* (%)=479 (1, M^+), 353 (76), 325 (5), 247 (2), 232 (6), 193 (2), 165 (2), 105 (100). Elemental Anal. Calcd for $C_{31}H_{33}N_3O_2$: C, 77.63; H, 6.94; N, 8.76. Found: C, 77.69; H, 7.13; N, 8.64.

*4.3.11. N-Cyclohexyl-3-ethyl-4-(4-fluorobenzoyl)-2-phenyl-4,5-dihydro-3H-1,4-benzodiazepine-5-carboxamide (**12k**).* Operation as above with 4-fluorobenzoic acid **3** (R^3=4-FC_6H_4, 0.28 g, 2 mmol), and isocyanocyclohexane **4** (R^4=*c*-C_6H_{11}, 0.22 g, 2 mmol), compound **12k** (0.70 g, 71%) was isolated as light yellow solid. Mp 223–224 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): *δ*=8.07–7.65 (m, 2H, Ar–H), 7.55–7.13 (m, 11H, Ar–H), 6.21–6.12 (m, 1H, NH), 5.10 (s, 1H, CH), 4.94–4.78 (m, 1H, CH), 3.59–3.36 (m, 1H, NCH), 1.82–0.44 (m, 15H, CH_2CH_3 and $(CH_2)_5$). ^{13}C NMR ($CDCl_3$, 150 MHz): *δ*=170.8, 170.5, 167.6, 164.0, 162.3, 148.0, 140.2, 132.7, 131.2, 130.7, 130.3, 128.8, 128.3, 128.0, 127.4, 126.3, 126.0, 124.7, 124.1, 115.7, 115.6, 64.4, 59.3, 55.6, 48.8, 32.0, 25.2, 24.8, 24.4, 24.2, 10.7. MS: *m*/*z* (%)=497 (2, M^+), 371 (63), 353 (3), 343 (5), 247 (3), 232 (8), 218 (4), 123 (100). Elemental Anal. Calcd for $C_{31}H_{32}FN_3O_2$: C, 74.83; H, 6.48; N, 8.44. Found: C, 74.74; H, 6.33; N, 8.62.

*4.3.12. N-(tert-Butyl)-3-methyl-4-(4-methylbenzoyl)-2-phenyl-4,5-dihydro-3H-1,4-benzodiazepine-5-carboxamide (**12l**).* Operation as above with 4-methylbenzoic acid **3** (R^3=4-$CH_3C_6H_4$, 0.27 g, 2 mmol), α-alkyl α-amino ketone hydrochlorides **1** (R^1=C_6H_5, R^2=Me, 0.37 g, 2 mmol) and isocyanide **4** (R^4=*t*-Bu, 0.17 g, 2 mmol), compound **12l** (0.59 g, 65%) was isolated as light yellow solid. Mp 173–174 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): *δ*=8.07–7.77 (m, 2H, Ar–H), 7.49–7.08 (m, 11H, Ar–H), 6.24–6.20 (m, 1H, NH), 5.28–5.12 (m, 1H, CH), 5.03–4.84 (m, 1H, CH), 2.40 (s, 3H, CH_3), 1.08–0.83 (m, 12H, CH_3 and *t*-Bu). ^{13}C NMR ($CDCl_3$, 150 MHz): *δ*=171.2, 170.7, 167.7, 147.5, 139.5, 139.0, 133.5, 130.6, 130.2, 129.3, 129.1, 128.2, 128.0, 126.5, 126.4, 125.9, 125.1, 64.9, 64.6, 51.5, 50.8, 50.4, 28.4, 28.0, 21.3. MS: *m*/*z* (%)=453 (4, M^+), 353 (34), 261 (3), 234 (9), 218 (10), 194 (5), 165 (4), 119 (100). Elemental Anal. Calcd for $C_{29}H_{31}N_3O_2$: C, 76.79; H, 6.89; N, 9.26. Found: C, 76.64; H, 6.93; N, 9.47.

*4.3.13. N-(tert-Butyl)-4-(cyclohexanecarbonyl)-3-ethyl-2-phenyl-4,5-dihydro-3H-1,4-benzodiazepine-5-carboxamide (**12m**).* Operation as above with cyclohexanecarboxylic acid **3** (R^3=*c*-C_6H_{11}, 0.26 g, 2 mmol), α-alkyl α-amino ketone hydrochlorides **1** (R^1=C_6H_5, R^2=Et, 0.40 g, 2 mmol) and isocyanide **4** (R^4=*t*-Bu, 0.17 g, 2 mmol), compound **12m** (0.74 g, 81%) was isolated as light yellow solid. Mp 163–164 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): *δ*=8.06–7.94 (m, 2H, Ar–H), 7.49–7.23 (m, 7H, Ar–H), 6.12–6.04 (m, 1H, NH), 5.28–5.18 (m, 2H, 2CH), 2.60–2.51 (m, 1H, NCH), 2.01–0.95 (m, 21H, CH_2, $(CH_2)_5$ and *t*-Bu), 0.71–0.59 (m, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 150 MHz): *δ*=175.8, 169.2, 167.8, 148.2, 139.6, 131.0, 130.3, 130.2, 128.5, 128.3, 127.9, 127.6, 126.0, 125.8, 124.9, 124.5, 63.5, 53.8, 51.5, 41.1, 28.8, 27.8, 27.5, 26.0, 24.1, 10.8. MS: *m*/*z* (%)=359 (24, M^+−CONHBu-*t*), 331 (5), 249 (100), 247 (3). Elemental Anal. Calcd for $C_{29}H_{37}N_3O_2$: C, 75.78; H, 8.11; N, 9.14. Found: C, 75.81; H, 7.93; N, 9.33.

*4.3.14. N-(tert-Butyl)-2-(4-chlorophenyl)-3-ethyl-4-(4-methylbenzoyl)-4,5-dihydro-3H-1,4-benzodiazepine-5-carboxamide (**12n**).* Operation as above with 4-methylbenzoic acid **3** (R^3=4-$CH_3C_6H_4$, 0.27 g, 2 mmol), α-alkyl α-amino ketone hydrochlorides **1** (R^1=4-ClC_6H_5, R^2=Et, 0.40 g, 2 mmol) and isocyanide **4** (R^4=*t*-Bu, 0.17 g, 2 mmol), compound **12n** (0.65 g, 65%) was isolated as light yellow solid. Mp 202–203 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): *δ*=8.08–7.70 (m, 2H, Ar–H), 7.49–7.12 (m, 10H, Ar–H), 6.21–6.08 (m, 1H, NH), 5.12–5.03 (m, 1H, CH), 4.99–4.75 (m, 1H, CH), 2.39 (s, 3H, CH_3), 1.64–1.60 (m, 1H, CH_2^a), 1.31–1.12 (m, 1H, CH_2^b), 1.10 (s, 2H, 0.22*t*-Bu), 0.94 (s, 7H, 0.78*t*-Bu), 0.68 (t, *J*=7.2 Hz, 2.5H, 0.83CH_3), 0.37 (t, *J*=7.2 Hz, 0.5H, 0.17CH_3). ^{13}C NMR ($CDCl_3$, 150 MHz): *δ*=171.7, 169.2, 167.7, 147.5, 139.4, 138.6, 136.5, 133.5, 130.4, 130.1, 129.3, 129.0, 128.3, 128.2, 126.4, 126.0, 124.6, 64.5, 55.3, 51.3, 28.5, 28.0, 27.9, 24.6, 21.3, 10.7. MS: *m*/*z* (%)=401 (24, M^+−CONHBu-*t*), 373 (3), 266 (3), 227 (2), 119 (100), 91 (16). Elemental Anal. Calcd for $C_{30}H_{32}ClN_3O_2$: C, 71.77; H, 6.42; N, 8.37. Found: C, 71.73; H, 6.35; N, 8.61.

*4.3.15. N-(tert-Butyl)-2-(4-chlorophenyl)-3-ethyl-4-(4-methoxybenzoyl)-4,5-dihydro-3H-1,4-benzodiazepine-5-carboxamide (**12o**).* Operation as above with 4-methoxybenzoic acid **3** (R^3=4-$CH_3OC_6H_4$, 0.30 g, 2 mmol), α-alkyl α-amino ketone hydrochlorides **1** (R^1=4-ClC_6H_5, R^2=Et, 0.40 g, 2 mmol) and isocyanide **4** (R^4=*t*-Bu, 0.17 g, 2 mmol), compound **12o** (0.78 g, 76%) was isolated as yellow solid. Mp 180–181 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): *δ*=8.07–7.70 (m, 2H, Ar–H), 7.49–7.13 (m, 8H, Ar–H), 6.94 (d, *J*=7.8 Hz, 2H, Ar–H), 6.20–6.07 (m, 1H, NH), 5.16–5.08 (m, 1H, CH), 4.97 (s, 0.2H, 0.2CH), 4.75 (s, 0.8H, 0.8CH), 3.85 (s, 3H, OCH_3), 1.62–1.60 (m, 1H, CH_2^a), 1.28–1.27 (m, 1H, CH_2^b), 1.10 (s, 2H, 0.22*t*-Bu), 0.94 (s, 7H, 0.78*t*-Bu), 0.67–0.39 (m, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 150 MHz): *δ*=171.6, 169.3, 167.9, 160.4, 147.6, 138.7, 136.6, 130.5, 130.2, 129.5, 129.4, 128.6, 128.3, 126.1, 126.0, 124.6, 124.5, 113.7, 64.8, 64.6, 55.2, 51.4, 28.0, 24.6, 10.7. MS: *m*/*z* (%)=517 (2, M^+), 417 (11), 282 (5), 266 (2), 227 (3), 135 (100). Elemental Anal. Calcd for $C_{30}H_{32}ClN_3O_3$: C, 69.55; H, 6.23; N, 8.11. Found: C, 69.74; H, 6.28; N, 8.23.

*4.3.16. N-(tert-Butyl)-3-butyl-4-(4-chlorobenzoyl)-2-(4-chlorophenyl)-4,5-dihydro-3H-1,4-benzodiazepine-5-carboxamide (**12p**).* Operation as above with 4-chlorobenzoic acid **3** (R^3=4-ClC_6H_4, 0.31 g, 2 mmol), α-alkyl α-amino ketone hydrochlorides **1** (R^1=4-ClC_6H_5, R^2=Et, 0.40 g, 2 mmol) and isocyanide **4** (R^4=*t*-Bu, 0.17 g, 2 mmol), compound **12p** (0.82 g, 75%) was isolated as yellow solid. Mp 146–147 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): *δ*=8.03 (t, *J*=8.4 Hz, 2H, Ar–H), 7.65–7.10 (m, 10H, Ar–H),

6.17–6.11 (m, 1H, NH), 4.97 (s, 1H, CH), 4.69 (s, 1H, CH), 1.52–1.26 (m, 2H, CH_2), 1.17–0.86 (m, 13H, CH_2CH_2 and *t*-Bu), 0.67–0.53 (m, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 150 MHz): δ=170.6, 169.5, 167.5, 147.8, 138.4, 136.8, 135.4, 135.0, 130.6, 129.5, 128.8, 128.7, 128.5, 128.4, 128.1, 126.1, 124.3, 64.5, 53.9, 51.5, 28.4, 28.1, 27.9, 22.2, 13.6. MS: *m*/*z* (%)=449 (26, M^+–CONHBu-*t*), 392 (3), 308 (2), 267 (3), 141 (27), 139 (100). Elemental Anal. Calcd for $C_{31}H_{33}Cl_2N_3O_2$: C, 67.63; H, 6.04; N, 7.63. Found: C, 67.72; H, 6.21; N, 7.89.

*4.3.17. 3-Benzyl-N-(tert-butyl)-4-(4-chlorobenzoyl)-2-methyl-4,5-dihydro-3H-1,4-benzodiazepine-5-carboxamide (**12q**).* Operation as above with 4-chlorobenzoic acid **3** (R^3=4-ClC_6H_4, 0.31 g, 2 mmol), α-alkyl α-amino ketone hydrochlorides **1** (R^1=CH_3, R^2=$PhCH_2$, 0.40 g, 2 mmol) and isocyanide **4** (R^4=*t*-Bu, 0.17 g, 2 mmol), compound **12q** (0.76 g, 78%) was isolated as yellow solid. Mp 214–215 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ=7.55–6.45 (m, 13H, Ar–H), 6.20–5.42 (m, 1H, NH), 4.92–4.54 (m, 2H, 2CH), 2.92–2.08 (m, 2H, CH_2), 1.85–1.82 (m, 3H, CH_3), 1.22–1.16 (m, 9H, *t*-Bu). ^{13}C NMR ($CDCl_3$, 100 MHz): δ=173.8, 170.0, 167.9, 147.5, 136.7, 135.5, 134.9, 130.9, 130.2, 129.0, 128.9, 1284, 126.7, 126.0, 125.1, 124.5, 64.6, 59.8, 51.7, 36.2, 30.9, 28.2. MS: *m*/*z* (%)=487 (1, M^+), 387 (53), 184 (11), 141 (27), 140 (8), 139 (100). Elemental Anal. Calcd for $C_{29}H_{30}ClN_3O_2$: C, 71.37; H, 6.20; N, 8.61. Found: C, 71.46; H, 6.21; N, 8.73.

*4.3.18. 3-Benzyl-N-(tert-butyl)-2-methyl-4-(4-methylbenzoyl)-4,5-dihydro-3H-1,4-benzodiazepine-5-carboxamide (**12r**).* Operation as above with 4-chlorobenzoic acid **3** (R^3=4-$CH_3C_6H_4$, 0.27 g, 2 mmol), α-alkyl α-amino ketone hydrochlorides **1** (R^1=CH_3, R^2=$PhCH_2$, 0.40 g, 2 mmol) and isocyanide **4** (R^4=*t*-Bu, 0.17 g, 2 mmol), compound **12r** (0.74 g, 79%) was isolated as yellow solid. Mp 209–210 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ=7.53–6.40 (m, 13H, Ar–H), 6.24–5.44 (m, 1H, NH), 5.06–4.63 (m, 2H, 2CH), 2.98–2.09 (m, 5H, CH_2 and CH_3), 1.85–1.77 (m, 3H, CH_3), 1.23–1.17 (m, 9H, *t*-Bu). ^{13}C NMR ($CDCl_3$, 100 MHz): δ=173.7, 171.0, 168.1, 147.5, 139.4, 136.9, 133.4, 130.6, 130.6, 130.1, 129.1, 129.0, 128.3, 126.6, 126.3, 126.0, 125.8, 125.4, 124.3, 64.5, 59.9, 51.5, 36.1, 30.9, 28.1, 21.3. MS: *m*/*z* (%)=367 (37, M^+–CONHBu-*t*), 247 (3), 233 (4), 207 (6), 184 (3), 129 (4), 119 (100). Elemental Anal. Calcd for $C_{31}H_{33}N_3O_2$: C, 77.06; H, 7.11; N, 8.99. Found: C, 77.12; H, 7.36; N, 8.87.

4.4. Isolation of some azides 10

*4.4.1. N-(1-(2-Azidophenyl)-2-(tert-butylamino)-2-oxoethyl)-2-methyl-N-(1-oxo-1-phenylbutan-2-yl)benzamide (**10c**).* Finely powdered 2-methylbenzoic acid **3** (R^3=2-$CH_3C_6H_4$, 0.27 g, 2 mmol) was added to a well-stirred solution of potassium hydroxide (0.11 g, 2 mmol) in MeOH (10 mL), α-alkyl α-amino ketone hydrochlorides **1** (R^1=C_6H_5, R^2=Et, 0.33 g, 2 mmol) was added to the above suspension at 5 °C and stirring was continued for 10 min. The resulting suspension was treated with 2-azidobenzaldehyde **2** (0.29 g, 2 mmol) and then with isocyanide **4** (R^4=*t*-Bu, 0.17 g, 2 mmol). The reaction mixture was stirred at room temperature for 24 h, monitoring the reactions by thin-layer chromatography (TLC) until the reactants disappeared. After removing the solvent under reduced pressure, the residues were purified by column chromatography (4:1, petroleum ether/diethyl ether) to give the azides **10c** (0.81 g, 79%), which was analyzed by spectral method immediately. White solid (yield 79%). Mp 134–136 °C. ^1H NMR ($CDCl_3$, 600 MHz): δ=7.53–6.81 (m, 13H, Ar–H), 5.38–5.14 (m, 2H, NH and NCH), 5.05–5.03 (m, 1H, NCH), 2.58–2.51 (m, 2H, CH_2), 2.34–2.14 (m, 3H, CH_3), 1.34–1.26 (m, 9H, $3CH_3$), 0.87–0.83 (m, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 150 MHz): δ=196.4, 172.1, 166.8, 138.5, 136.4, 135.4, 134.9, 133.1, 130.9, 129.5, 129.1, 128.3, 128.1, 127.6, 127.5, 127.1, 125.7, 124.9, 117.8, 62.1, 58.3, 51.2, 28.2, 22.4, 19.7, 18.9, 18.8, 10.3. IR (KBr): 3272, 2968, 2131, 1695, 1678, 1617 cm^{-1}. Elemental Anal. Calcd for $C_{30}H_{33}N_5O_3$: C, 70.43; H, 6.50; N, 13.69. Found: C, 70.47; H, 6.36; N, 13.93.

*4.4.2. N-(1-(2-Azidophenyl)-2-(tert-butylamino)-2-oxoethyl)-2-fluoro-N-(1-oxo-1-phenylbutan-2-yl)benzamide (**10g**).* Operation as above with 2-fluorobenzoic acid **3** (R^3=2-FC_6H_4, 0.28 g, 2 mmol), compound **10g** (0.80 g, 78%) was isolated as white solid. Mp 188–189 °C. ^1H NMR ($CDCl_3$, 600 MHz): δ=7.79–7.12 (m, 12H, Ar–H), 6.74 (t, *J*=7.2 Hz, 1H, Ar–H), 5.24 (s, 1H, NCH), 5.22–5.00 (m, 2H, NH and NCH), 2.56–2.34 (m, 1H, CH_2^a), 2.14–2.07 (m, 1H, CH_2^b), 1.38 (s, 2H, $3CH_3$), 1.26 (s, 7H, $3CH_3$), 1.10–1.08 (m, 1H, CH_3), 0.87 (t, *J*=6.6 Hz, 2H, CH_3). ^{13}C NMR ($CDCl_3$, 150 MHz): δ=195.6, 167.6, 166.6, 138.2, 135.7, 133.1, 133.0, 131.6, 129.3, 129.2, 128.2, 128.0, 127.8, 127.6, 127.4, 126.2, 124.9, 124.3, 123.9, 117.4, 116.2, 62.3, 58.7, 51.2, 28.3, 22.9, 22.8, 22.7, 10.7. IR (KBr): 2099, 1710, 1679, 1637 cm^{-1}. Elemental Anal. Calcd for $C_{29}H_{30}FN_5O_3$: C, 67.56; H, 5.86; N, 13.58. Found: C, 67.44; H, 5.63; N, 13.59.

*4.4.3. N-(1-(2-Azidophenyl)-2-(tert-butylamino)-2-oxoethyl)-4-methyl-N-(1-oxo-1-phenylpropan-2-yl)benzamide (**10l**).* Operation as above with 4-methylbenzoic acid **3** (R^3=4-$CH_3C_6H_4$, 0.27 g, 2 mmol) and α-alkyl α-amino ketone hydrochlorides **1** (R^1=C_6H_5, R^2=Me, 0.37 g, 2 mmol), compound **10l** (0.67 g, 67%) was isolated as white solid. Mp 181–183 °C. ^1H NMR ($CDCl_3$, 600 MHz): δ=8.67–7.13 (m, 13H, Ar–H), 6.02–4.21 (m, 3H, 2NCH and NH), 2.39 (s, 3H, CH_3), 1.51–0.84 (m, 12H, $4CH_3$). ^{13}C NMR ($CDCl_3$, 150 MHz): δ=170.5, 167.6, 163.9, 162.3, 148.0, 140.1, 132.7, 130.7, 130.3, 128.8, 128.3, 127.9, 127.4, 126.0, 124.7, 124.1, 115.6, 64.4, 55.6, 48.8, 32.0, 25.2, 24.8, 24.2, 10.7. IR (KBr): 2091, 1630, 1562 cm^{-1}. Elemental Anal. Calcd for $C_{29}H_{31}N_5O_3$: C, 70.00; H, 6.28; N, 14.07. Found: C, 70.21; H, 6.02; N, 14.04.

5. Crystallographic material

Compound **5**: formula $C_{42}H_{38}N_{12}O_3$, colourless crystal. The crystal is of triclinic, space group *P*–1 with *a*=9.1637 (16) Å, *b*=14.864 (3) Å, *c*=14.891 (3) Å, α=97.570 (3)°, β=94.437 (3)°, γ=100.613 (3)°, *V*=1965.4 (6) Å, *Z*=2, D_x=1.282 g/cm^3, *F*(000)=796.28, μ=0.085 mm^{-1}, *R*=0.0485 and *wR*=0.1411 for 6831 observed reflections with $I>2\sigma(I_0)$.

Compound **12a**: formula $C_{30}H_{33}N_3O_2$, colourless crystal. The crystal is of triclinic, space group *P*–1 with *a*=10.323 (2) Å, *b*=12.260 (3) Å, *c*=12.331 (3) Å, α=105.404 (4)°, β=102.235 (4)°, γ=110.466 (3)°, *V*=1326.9 (5) Å, *Z*=2, D_x=1.170 g/cm^3, *F*(000)=500.0, μ=0.074 mm^{-1}, *R*=0.0480 and *wR*=0.1590 for 4889 observed reflections with $I>2\sigma(I_0)$.

Crystallographic datas for **5** and **12a** have been deposited in the Cambridge Crystallographic Data Center as supplementary publication numbers CCDC 939798, 939799. Copies of the data may be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

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Supplementary data

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