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Facile Synthesis of 3-Arylidene-3*H*-1,4-benzodiazepines by a Sequential Ugi/Staudinger/Aza-Wittig Reaction

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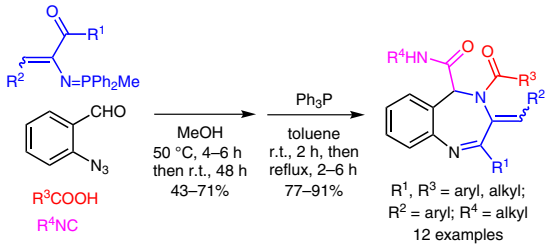

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Abstract *N*-[2-(Alkylamino)-1-(2-azidophenyl)-2-oxoethyl]-*N*-(3-oxoprop-1-en-2-yl)amides, obtained from the Ugi reaction of a vinyliminophosphorane, 2-azidobenzaldehyde, a carboxylic acid, and an alkyl isocyanide, reacted with triphenylphosphine to give various 3-arylidene-3*H*-1,4-benzodiazepine in good yields via sequential Staudinger and intramolecular aza-Wittig reaction.

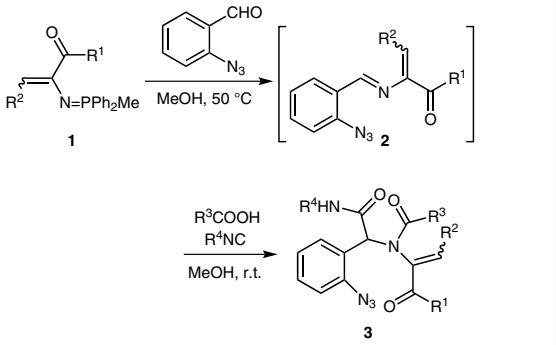
Key words 3*H*-1,4-benzodiazepine, Ugi reaction, Staudinger reaction, aza-Wittig reaction, vinyliminophosphorane, azides

Benzodiazepines have attracted great attention in medicinal chemistry because of their broad spectrum of biological activities. Some 1,4-benzodiazepine derivatives have been found recently to exhibit good antiseizure,[1] antianxiety,[2] antileishmanial,[3] antitubulin,[4] and antitumor activities.[5] Much effort has been invested in the synthesis of benzodiazepine derivatives to deduce structure–activity relationships and discover new analogues with improved properties. The most frequently employed synthetic approaches to 1,4-benzodiazepine skeletons include the reaction of 2-aminobenzophenones with α-amino acids,[6] cyclocondensation of 2-halobenzoic acids or 2-halobenzophenones with some diamines,[7] and Pictet–Spengler reaction of *N*,*N*′-dimethyl-*N*-phenyl-1,2-ethanediamine with aldehydes.[8] In addition, the preparation of these compounds can be carried out via an indium-catalyzed multicomponent reaction.[9] The sequential Ugi and aza-Wittig reactions were also used successfully to prepare some 1,4-benzodiazepines by using arylglyoxals, α-amino ketones, or 2-aminobenzophenones as Ugi starting materials.[10] Although much effort has been directed toward the construction of 1,4-benzodiazepines, 3-arylidene-substituted 3*H*-1,4-benzodiazepines were not easily accessible by currently existing synthetic methods.

The Ugi reaction is a powerful multicomponent reaction that has been used widely to prepare α-acylamino amides starting from an aldehyde, amine, acid, and isocyanide.[11] The combination of Ugi reaction with other post-condensation reactions constitutes an extremely powerful synthetic method for the preparation of many complex molecules, especially heterocyclic compounds.[10b,12] The aza-Wittig reactions of iminophosphoranes have received considerable attention due to their efficient application in heterocyclic synthesis.[13] Owing to its good stability, vinyliminophosphorane may be regarded as an equivalent of the unstable enamine and it has been used in the synthesis of various heterocycles, such as isoquinolines, dihydropyrimidines, and oxazoles.[14] Continuing our interests in multicomponent reactions[15] and aza-Wittig reactions of vinyliminophosphoranes,[14c–f] we wish to report herein a new facile synthesis of 3-arylidene-substituted 3*H*-1,4-benzodiazepines via an Ugi/Staudinger/aza-Wittig sequence by using vinyliminophosphoranes as an Ugi starting material.

Although many primary amines have been used in the Ugi reaction, vinylamines have not been utilized for the reaction due to their instability. We have reported that the aza-Wittig reactions of some stable diphenyl(methyl)iminophosphoranes **1** with 2-azidobenzaldehyde produced *N*-vinylimines **2** at 50 °C in good yields,[14f] which may be used in further Ugi reactions. The one-pot reaction of diphenyl(methyl)iminophosphorane **1**, 2-azidobenzaldehyde, carboxylic acid, and isocyanide were then investigated (Scheme 1): after the aza-Wittig reaction of diphenyl(methyl)iminophosphorane **1** with 2-azidobenzaldehyde was complete at 50 °C, the carboxylic acid and isocyanide were added to the reaction mixture at room temperature.

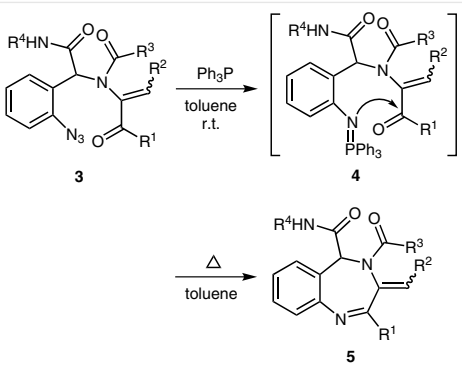
The Ugi reaction took place to give azides **3** in only moderate yields (43–71%, Table 1) probably due to some side reactions.



Scheme 1 Preparation of azides 3 via Ugi reaction

The Staudinger reactions of azides **3** with triphenylphosphine occurred smoothly at room temperature to generate iminophosphoranes **4** with nitrogen evolution. Intramolecular aza-Wittig reactions of **4** took place partially at room temperature, but completely at refluxing temperature, to produce 3-arylidene-substituted 3*H*-1,4-benzodiazepines **5** in 77–91% yields (Scheme 2,Table 1). The yields of the products were always good regardless of the R^1, R^2, R^3, and R^4 substituents.

The structure of 3-arylidene-substituted 3*H*-1,4-benzodiazepines **5** was confirmed by their spectral data. For example, the ^{1}H NMR spectrum of **5a** at room temperature shows multiplets at δ = 8.44–6.43 due to the aromatic and alkenyl hydrogen. The signal of CH is found at δ = 6.19 and



Scheme 2 Preparation of compounds **5** via Staudinger/aza-Wittig reaction

5.83 as two singlets (2:1). The signals of NH appear at δ = 5.40 and 4.97 as two singlets (2:1). The *tert*-butyl protons absorb at δ = 1.20 and 0.92 as two singlets (8:1). Such two singlets might be due to the different conformation and *E*/*Z* configuration of the 3*H*-1,4-benzodiazepines **5a**. However, the ^{1}H NMR spectrum of **5a** at higher temperature (50 °C) shows only one singlet at δ = 1.19 for *tert*-butyl protons, indicating the former two singlets (8:1) may be resulted from the different conformation. The two singlets (2:1) of CH and NH did not change, implying that it may be due to the different *E*/*Z* configuration. The ^{13}C NMR spectrum data of **5a** show the signals of two CON and C-2 of the benzodiazepine at δ =171.0, 166.8, and 166.0. These results indicated that the products **5** obtained were a mixture of isomers and the data reported are for major isomer in the mixture of two. The MS spectrum of **5a** shows molecular ion peak at *m*/*z* 513 with 5% abundance. Furthermore a single crystal of

Table 1 Preparation of Azides **3** and 3-Arylidene-3*H*-1,4-benzodiazepines **5**

Entry	R^1	R^2	R^3	R^4	Compd	Yield[a] (%)	Ratio[b] *Z*/*E*	Compd	Yield[c] (%)	Ratio[b] *Z*/*E*
1	Ph	Ph	Ph	*t*-Bu	**3a**	69	4.1	**5a**	88	1.9
2	4-ClC_6H_4	Ph	Ph	*t*-Bu	**3b**	43	3.8	**5b**	80	1.4
3	Ph	Ph	4-$NO_2C_6H_4$	*t*-Bu	**3c**	58	3.8	**5c**	77	3.3
4	Ph	Ph	Ph	Cy	**3d**	57	4.2	**5d**	91	1.7
5	Ph	Ph	4-ClC_6H_4	Cy	**3e**	65	4.0	**5e**	78	2.4
6	Ph	Ph	Ph	*n*-Bu	**3f**	51	3.3	**5f**	84	2.3
7	Ph	Ph	Me	Cy	**3g**	71	2.9	**5g**	86	7.1
8	Ph	Ph	4-MeC_6H_4	Cy	**3h**	69	3.5	**5h**	83	1.5
9	Ph	Ph	Et	Cy	**3i**	64	2.8	**5i**	81	4.3
10	Ph	Ph	2-ClC_6H_4	Cy	**3j**	65	4.4	**5j**	87	–
11	Ph	4-FC_6H_4	Me	*t*-Bu	**3k**	46	2.5	**5k**	85	5.5
12	Me	Ph	Ph	*t*-Bu	**3l**	52	3.6	**5l**	82	2.1

[a] Isolated yields based on iminophosphoranes **1**.
[b] Determined by ^{1}H NMR but the major isomer of the products not being determined.
[c] Isolated yields based on azides **3**.

compound **5a** was obtained from the CH_2Cl_2 solution, and X-ray crystal structure analysis verified the proposed structure (Figure 1). The carbon–carbon double bond of the vinyl group was observed to be *Z*-configuration, showing one of the *E*/*Z* isomers was obtained occasionally after recrystallization.

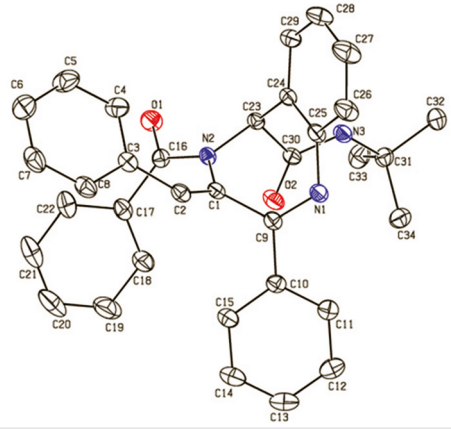


Figure 1 ORTEP diagram of the crystal structure of 5a (30% thermal ellipsoids)

In conclusion, we report herein a facile synthesis of 3-arylidene-substituted 3*H*-1,4-benzodiazepines using the Ugi reaction followed by Staudinger/aza-Wittig reactions. The Ugi reaction involving the *N*-vinylimine was also investigated first. Due to the easy availability of the synthetic approach and the neutral ring-closure condition, this new synthetic approach discussed here has potential for the synthesis of various benzodiazepines, which are of considerable interest in chemical biology study and drug discovery.

Melting points were determined using a X-4 model apparatus and are uncorrected. MS were measured on a Finnigan Trace MS spectrometer. IR spectra were recorded on a PE-983 infrared spectrophotometer as KBr pellets. NMR were recorded in $CDCl_3$ or DMSO-d_6 on a Varian Mercury 600 or 400 spectrometer and resonances relative to TMS. Elemental 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°.

Azides 3a–l via Ugi Reaction; General Procedure

A mixture of diphenyl(methyl)iminophosphoranes **1**[14f] (2 mmol) and 2-azidobenzaldehyde (0.29 g, 2 mmol) in MeOH (10 mL) was stirred at 50 °C for 4–6 h. Then the carboxylic acid (2 mmol) and isocyanide (2 mmol) were added sequentially to the mixture at r.t. The mixture was stirred at r.t. for 48 h until the solid had precipitated completely. After the solvent had been evaporated, the crude mixture was purified by recrystallization (CH_2Cl_2/petroleum ether) to give azides **3a–l**.

N-[1-(2-Azidophenyl)-2-(*tert*-butylamino)-2-oxoethyl]-*N*-(3-oxo-1,3-diphenylprop-1-en-2-yl)benzamide (3a)

White crystals; yield: 0.77 g (69%).

IR (KBr): 3441, 2133, 1685, 1658, 1638, 1448, 1290, 1122, 1069 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.80 (s, 0.8 H, 0.8 NH), 8.59 (s, 0.2 H, 0.2 NH), 8.57–6.77 (m, 19 H, Ar-H), 6.57 (s, 1 H, =CH), 6.25 (s, 0.8 H, 0.8 CH), 5.38 (s, 0.2 H, 0.2 CH), 1.52 (s, 7 H, 7/9 × 3 CH_3), 1.43 (s, 2 H, 2/9 × 3 CH_3).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 197.5, 171.5, 168.2, 144.1, 140.8, 136.4, 135.6, 132.7, 132.2, 131.6, 130.9, 130.5, 130.2, 130.0, 129.1, 128.9, 128.7, 128.5, 128.4, 128.0, 127.4, 126.2, 125.0, 124.6, 118.1, 62.0, 51.2, 28.6.

Anal. Calcd for $C_{34}H_{31}N_5O_3$: C, 73.23; H, 5.60; N, 12.56. Found: C, 73.38; H, 5.79; N, 12.66.

N-[1-(2-Azidophenyl)-2-(*tert*-butylamino)-2-oxoethyl]-*N*-[3-(4-chlorophenyl)-3-oxo-1-phenylprop-1-en-2-yl]benzamide (3b)

White crystals; yield: 0.51 g (43%).

IR (KBr): 3442, 2132, 1685, 1648, 1602, 1490, 1292, 1125, 1069 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.67 (s, 0.8 H, 0.8 NH), 8.54 (s, 0.2 H, 0.2 NH), 8.53–6.77 (m, 18 H, Ar-H), 6.61 (s, 0.2 H, 0.2 =CH), 6.50 (s, 0.8 H, 0.8 =CH), 6.24 (s, 0.8 H, 0.8 CH), 5.38 (s, 0.2 H, 0.2 CH), 1.51 (s, 7 H, 7/9 × 3 CH_3), 1.42 (s, 2 H, 2/9 × 3 CH_3).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 195.7, 169.3, 167.5, 148.3, 143.4, 141.3, 141.1, 139.8, 135.8, 133.9, 132.4, 131.5, 131.1, 130.6, 130.4, 129.1, 129.0, 128.9, 128.5, 127.3, 125.2, 123.9, 122.6, 122.5, 118.3, 62.3, 51.4, 28.5.

Anal. Calcd for $C_{34}H_{30}ClN_5O_3$: C, 68.97; H, 5.11; N, 11.83. Found: C, 69.21; H, 5.24; N, 12.00.

N-[1-(2-Azidophenyl)-2-(*tert*-butylamino)-2-oxoethyl]-4-nitro-*N*-(3-oxo-1,3-diphenylprop-1-en-2-yl)benzamide (3c)

White crystals; yield: 0.70 g (58%).

IR (KBr): 3442, 2128, 1687, 1664, 1645, 1490, 1292, 1137, 1070 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.63 (s, 0.8 H, 0.8 NH), 8.48 (s, 0.2 H, 0.2 NH), 7.87–6.66 (m, 18 H, Ar-H), 6.57 (s, 1 H, =CH), 6.25 (s, 0.8 H, 0.8 CH), 5.46 (s, 0.2 H, 0.2 CH), 1.52 (s, 7 H, 7/9 × 3 CH_3), 1.42 (s, 2 H, 2/9 × 3 CH_3).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 197.0, 169.3, 167.6, 165.7 (minor), 148.3, 143.8, 142.5 (minor), 141.4, 140.9, 138.8 (minor), 137.3 (minor), 135.9, 135.6, 133.2, 132.3, 131.3, 131.2, 130.6, 130.4, 129.2, 129.1, 128.9, 128.6, 128.1, 127.3, 125.2, 123.9, 122.6, 122.5, 118.3, 62.3, 59.6 (minor), 51.3, 28.5.

Anal. Calcd for $C_{34}H_{30}N_6O_5$: C, 67.76; H, 5.02; N, 13.95. Found: C, 67.93; H, 5.27; N, 13.89.

N-[1-(2-Azidophenyl)-2-(cyclohexylamino)-2-oxoethyl]-*N*-(3-oxo-1,3-diphenylprop-1-en-2-yl)benzamide (3d)

White crystals; yield: 0.66 g (57%).

IR (KBr): 3443, 2132, 1687, 1650, 1491, 1287, 1133, 1069 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.88 (d, *J* = 7.8 Hz, 0.8 H, 0.8 NH), 8.51 (d, *J* = 7.2 Hz, 0.2 H, 0.2 NH), 7.78–6.72 (m, 19 H, Ar-H), 6.57 (s, 1 H, =CH), 6.35 (s, 0.8 H, 0.8 CH) , 5.51 (s, 0.2 H, 0.2 CH), 3.95–3.82 (m, 1 H, NCH), 2.14–1.26 (m, 10 H, 5 CH_2).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 197.5, 171.4, 168.2, 166.3 (minor), 144.1, 140.7, 136.4, 135.5, 132.6, 132.2, 131.6, 130.9, 130.5, 130.3, 130.0, 129.8, 129.0, 128.7, 128.4, 128.0, 127.3, 126.3, 126.2, 124.9, 124.4, 118.1, 61.5, 59.7 (minor), 48.0, 32.9, 25.6, 24.7, 24.6.

Anal. Calcd for $C_{36}H_{33}N_5O_3$: C, 74.08; H, 5.70; N, 12.00. Found: C, 74.06; H, 5.62; N, 12.24.

_N_-[1-(2-Azidophenyl)-2-(cyclohexylamino)-2-oxoethyl]-4-chloro-_N_-(3-oxo-1,3-diphenylprop-1-en-2-yl)benzamide (3e)

White crystals; yield: 0.80 g (65%).

IR (KBr): 3440, 2131, 1682, 1637, 1490, 1295, 1070 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.79 (d, *J* = 7.8 Hz, 0.8 H, 0.8 NH), 8.47 (d, *J* = 7.8 Hz, 0.2 H, 0.2 NH), 7.80–6.74 (m, 18 H, Ar-H), 6.58 (s, 1 H, =CH), 6.34 (s, 0.8 H, 0.8 CH), 5.53 (s, 0.2 H, 0.2 CH), 3.94–3.81 (m, 1 H, NCH), 2.18–1.27 (m, 10 H, 5 CH_2).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 197.3, 170.4, 167.9, 143.8, 142.6 (minor), 140.8, 138.6 (minor), 136.3, 136.1, 136.0, 133.8, 132.9, 132.3, 131.4, 131.0, 130.4, 129.1, 128.8, 128.5, 128.0, 127.7, 127.5, 125.0, 124.1, 118.1, 61.6, 48.0, 32.8, 25.5, 24.6, 24.5.

Anal. Calcd for $C_{36}H_{32}ClN_5O_3$: C, 69.95; H, 5.22; N, 11.33. Found: C, 70.11; H, 5.43; N, 11.41.

_N_-[1-(2-Azidophenyl)-2-(butylamino)-2-oxoethyl]-_N_-(3-oxo-1,3-diphenylprop-1-en-2-yl)benzamide (3f)

White crystals; yield: 0.57 g (51%).

IR (KBr): 3443, 2109, 1679, 1657, 1633, 1488, 1298, 1134, 1069 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.92 (br, 0.75 H, 0.75 NH), 8.50 (br, 0.25 H, 0.25 NH), 7.78–6.75 (m, 19 H, Ar-H), 6.59 (s, 1 H, =CH), 6.40 (s, 0.8 H, 0.8 CH), 5.55 (s, 0.2 H, 0.2 CH), 3.49–3.26 (m, 2 H, NCH_2), 1.70–1.35 (m, 4 H, CH_2CH_2), 0.94–0.87 (m, 3 H, CH_3).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 197.6, 171.4, 169.2, 167.3 (minor), 144.2, 142.8 (minor), 140.6, 138.0 (minor), 136.8 (minor), 136.3, 135.3, 132.7, 132.2, 131.5, 130.9, 130.4, 130.3, 130.0, 129.8, 129.2, 129.0, 128.6, 128.4, 128.0, 127.3, 126.3, 124.9, 124.4, 118.1, 61.5, 59.7 (minor), 39.4, 20.1, 13.7.

Anal. Calcd for $C_{34}H_{31}N_5O_3$: C, 73.23; H, 5.60; N, 12.56. Found: C, 73.47; H, 5.75; N, 12.59.

2-(2-Azidophenyl)-_N_-cyclohexyl-2-[_N_-(3-oxo-1,3-diphenylprop-1-en-2-yl)acetamido]acetamide (3g)

White crystals; yield: 0.74 g (71%).

IR (KBr): 3442, 2137, 1677, 1633, 1489, 1310, 1121, 1070 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.55 (d, *J* = 6.6 Hz, 0.8 H, 0.8 NH), 7.96 (d, *J* = 7.8 Hz, 0.2 H, 0.2 NH), 7.92–6.77 (m, 15 H, Ar-H, =CH), 6.11 (s, 0.8 H, 0.8 CH), 5.49 (s, 0.2 H, 0.2 CH), 3.89–3.79 (m, 1 H, NCH), 2.42–1.26 (m, 13 H, 5 CH_2, CH_3).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 196.6, 193.9 (minor), 172.1 (minor), 171.1, 168.0, 145.2, 142.4 (minor), 140.3, 138.4 (minor), 137.0 (minor), 136.3, 135.3, 132.7, 131.7, 131.1, 130.8, 130.0, 129.2, 129.1, 128.9, 128.2, 125.3, 124.8, 118.2, 60.8, 59.2 (minor), 47.9, 32.7, 32.6, 30.8 (minor), 25.5, 24.6, 21.9.

Anal. Calcd for $C_{31}H_{31}N_5O_3$: C, 71.38; H, 5.99; N, 13.43. Found: C, 71.62; H, 6.14; N, 13.54.

_N_-[1-(2-Azidophenyl)-2-(cyclohexylamino)-2-oxoethyl]-4-methyl-_N_-(3-oxo-1,3-diphenylprop-1-en-2-yl)benzamide (3h)

White crystals; yield: 0.82 g (69%).

IR (KBr): 3443, 2131, 1683, 1655, 1641, 1450, 1287, 1125, 1070 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.90 (d, *J* = 7.8 Hz, 0.8 H, 0.8 NH), 8.52 (d, *J* = 7.8 Hz, 0.2 H, 0.2 NH), 7.80–6.58 (m, 19 H, Ar-H, =CH), 6.35 (s, 0.8 H, 0.8 CH), 5.48 (s, 0.2 H, 0.2 CH), 3.94–3.82 (m, 1 H, NCH), 2.18 (s, 3 H, CH_3), 1.95–1.27 (m, 10 H, 5 CH_2).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 197.6, 196.0 (minor), 171.5, 170.7 (minor), 168.2, 166.3 (minor), 144.1, 142.7 (minor), 140.7, 140.1, 136.5, 132.6, 132.5, 132.2, 131.6, 130.8, 130.5, 130.2, 129.1, 129.0, 128.6, 128.3, 127.9, 126.3, 124.9, 124.5, 118.1, 61.5, 59.6 (minor), 47.9, 32.8, 30.8 (minor), 25.5, 24.6, 24.5, 21.2.

Anal. Calcd for $C_{37}H_{35}N_5O_3$: C, 74.35; H, 5.90; N, 11.72. Found: C, 74.55; H, 5.87; N, 11.91.

_N_-[1-(2-Azidophenyl)-2-(cyclohexylamino)-2-oxoethyl]-_N_-(3-oxo-1,3-diphenylprop-1-en-2-yl)propionamide (3i)

White crystals; yield: 0.68 g (64%).

IR (KBr): 3441, 2135, 1686, 1657, 1640, 1449, 1291, 1125, 1069 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.54 (d, *J* = 5.4 Hz, 0.75 H, 0.75 NH), 7.97 (d, *J* = 7.2 Hz, 0.25 H, 0.25 NH), 7.84–6.77 (m, 15 H, Ar-H), 6.13 (s, 0.75 H, 0.75 CH), 5.48 (s, 0.25 H, 0.25 CH), 3.89–3.80 (m, 1 H, NCH), 2.28–0.98 (m, 15 H, 5 CH_2, CH_2CH_3).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 196.8, 175.2 (minor), 174.5, 168.2, 145.3, 142.7 (minor), 140.4, 138.4 (minor), 136.4, 135.0, 132.6, 132.5, 131.7, 131.1, 130.9, 130.0, 129.8, 129.2, 129.1, 128.9, 128.2, 128.0, 126.2 (minor), 125.4, 124.8, 124.7, 118.2, 60.9, 59.4, 48.2 (minor), 47.9, 32.7, 30.8 (minor), 27.0, 26.3 (minor), 25.6, 24.6, 9.3.

Anal. Calcd for $C_{32}H_{33}N_5O_3$: C, 71.75; H, 6.21; N, 13.07. Found: C, 72.02; H, 6.29; N, 13.25.

_N_-[1-(2-Azidophenyl)-2-(cyclohexylamino)-2-oxoethyl]-2-chloro-_N_-(3-oxo-1,3-diphenylprop-1-en-2-yl)benzamide (3j)

White crystals; yield: 0.80 g (65%).

IR (KBr): 3442, 21313, 1687, 1659, 1647, 1450, 1290, 1130, 1072 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.08 (br, 0.8 H, 0.8 NH), 8.36 (d, *J* = 7.2 Hz, 0.2 H, 0.2 NH), 7.48–6.65 (m, 19 H, Ar-H, =CH), 6.31 (s, 0.8 H, 0.8 CH), 5.63 (s, 0.2 H, 0.2 CH), 4.13–3.87 (m, 1 H, NCH), 2.18–1.25 (m, 10 H, 5 CH_2).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 197.6, 171.0, 168.8, 144.0, 139.5, 136.8, 135.2, 134.9, 132.4, 131.4, 131.2, 131.1, 130.8, 130.5, 129.6, 128.8, 128.7, 128.3, 128.2, 128.0, 125.4, 125.1, 124.6, 123.8, 117.7, 61.1, 53.4, 51.1, 30.8, 28.5, 19.4.

Anal. Calcd for $C_{36}H_{32}ClN_5O_3$: C, 69.95; H, 5.22; N, 11.33. Found: C, 70.07; H, 5.40; N, 11.36.

2-(2-Azidophenyl)-_N_-_tert_-butyl-2-{_N_-[1-(4-fluorophenyl)-3-oxo-3-phenylprop-1-en-2-yl]acetamido}acetamide (3k)

White crystals; yield: 0.47 g (46%).

IR (KBr): 3445, 2130, 1678, 1641, 1490, 1306, 1122, 1073 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.41 (s, 0.7 H, 0.7 NH), 7.96 (br, 0.3 H, 0.3 NH), 7.78–6.57 (m, 14 H, Ar-H, =CH), 6.01 (s, 0.8 H, 0.8 CH), 5.39 (s, 0.2 H, 0.2 CH), 1.99–1.87 (m, 3 H, CH_3), 1.48 (s, 7 H, 7/9 × 3 CH_3), 1.37 (s, 2 H, 2/9 × 3 CH_3).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 196.3, 194.0 (minor), 171.0, 168.0, 167.5 (minor), 165.0, 163.3, 143.6, 140.1, 138.3, 136.3, 136.0, 134.8, 133.1, 132.6, 131.1, 130.0, 129.1, 128.2, 127.3, 126.2, 125.3, 124.9, 124.8, 118.2, 116.2, 61.2, 50.9, 28.8, 28.2, 27.8, 22.0, 21.6 (minor).

Anal. Calcd for $C_{29}H_{28}FN_5O_3$: C, 67.82; H, 5.50; N, 13.64. Found: C, 67.96; H, 5.72; N, 13.81.

N-[1-(2-Azidophenyl)-2-(*tert*-butylamino)-2-oxoethyl]-*N*-(3-oxo-1-phenylbut-1-en-2-yl)benzamide (3l)

White crystals; yield: 0.51 g (52%).

IR (KBr): 3442, 2137, 1677, 1633, 1489, 1310, 1121, 1070 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.63 (s, 0.7 H, 0.7 NH), 8.46 (br, 0.3 H, 0.3 NH), 7.89–6.71 (m, 15 H, Ar-H, =CH), 6.08 (s, 0.8 H, 0.8 CH), 5.26 (s, 0.2 H, 0.2 CH), 2.49–1.92 (m, 3 H, CH_3), 1.48 (s, 7 H, 7/9 × 3 CH_3), 1.41 (s, 2 H, 2/9 × 3 CH_3).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 200.3, 171.1, 170.1 (minor), 168.1, 166.0 (minor), 140.8, 140.4, 139.2 (minor), 137.0, 135.5, 131.6, 131.2, 130.7, 130.6, 130.0, 129.9, 129.2 (minor), 128.5, 127.4, 126.1, 124.4, 124.2, 118.0, 117.9, 61.7, 50.9, 29.4 (minor), 28.9, 28.4, 27.9, 25.6, 25.2 (minor).

Anal. Calcd for $C_{29}H_{29}N_5O_3$: C, 70.28; H, 5.90; N, 14.13. Found: C, 70.47; H, 6.03; N, 14.29.

3-Arylidene-Substituted 4,5-Dihydro-3*H*-1,4-benzodiazepines 5a–l; General Procedure

Ph_3P (0.26 g, 1 mmol) was added to a stirred solution of azide **3** (1 mmol) in dry toluene (10 mL) at r.t. The mixture was stirred for about 2 h; iminophosphorane **4** was formed (TLC monitoring). Then the solution was heated to reflux for 2–6 h. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography to give 3-arylidene-substituted 4,5-dihydro-3*H*-1,4-benzodiazepines **5a–l**.

4-Benzoyl-3-benzylidene-*N*-*tert*-butyl-2-phenyl-4,5-dihydro-3*H*-1,4-benzodiazepine-5-carboxamide (5a)

White crystals; yield: 0.45 g (88%).

^1H NMR (600 MHz, $CDCl_3$, r.t.): δ = 8.44–6.43 (m, 20 H, Ar-H, =CH), 6.19 (s, 0.3 H, 0.3 CH), 5.83 (s, 0.7 H, 0.7 CH), 5.40 (s, 0.3 H, 0.3 NH), 4.97 (s, 0.7 H, 0.7 NH), 1.20 (s, 8 H, 8/9 × 3 CH_3), 0.92 (s, 1 H, 1/9 × 3 CH_3).

^1H NMR (600 MHz, $CDCl_3$, 50 °C): δ = 8.02–6.41 (m, 20 H, Ar-H, =CH), 6.19 (s, 0.3 H, 0.3 CH), 5.82 (s, 0.7 H, 0.7 CH), 5.35 (s, 0.3 H, 0.3 NH), 4.97 (s, 0.7 H, 0.7 NH), 1.19 (s, 9 H, 3 CH_3).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.0, 166.8, 166.0, 149.1, 136.1, 134.7, 133.8, 131.5, 130.7, 130.5, 130.1, 129.7, 129.3, 129.0, 128.5, 128.2, 128.1, 128.0, 127.7, 126.9, 126.5, 126.0, 125.3, 124.7, 61.1, 51.5, 28.5.

MS: *m*/*z* (%) = 513 (5, M^+), 413 (10), 165 (10), 105 (100), 77 (21).

Anal. Calcd for $C_{34}H_{31}N_3O_2$: C, 79.51; H, 6.08; N, 8.18. Found: C, 79.74; H, 6.25; N, 8.31.

4-Benzoyl-3-benzylidene-*N*-*tert*-butyl-2-(4-chlorophenyl)-4,5-dihydro-3*H*-1,4-benzodiazepine-5-carboxamide (5b)

White crystals; yield: 0.44 g (80%).

^1H NMR (600 MHz, $CDCl_3$): δ = 8.39–6.41 (m, 19 H, Ar-H, =CH), 6.19–6.13 (m, 0.4 H, 0.4 CH), 5.78 (s, 0.6 H, 0.6 CH), 5.38–5.28 (m, 0.4 H, 0.4 NH), 4.90 (s, 0.6 H, 0.6 NH), 1.20 (s, 7 H, 7/9 × 3 CH_3), 0.94–0.86 (m, 2 H, 2/9 × 3 CH_3).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.1, 166.8, 165.0. 149.0, 137.9, 136.3, 133.8, 133.4, 131.1, 130.7, 130.5, 130.4, 130.3, 130.2, 130.1, 129.8, 128.6, 128.5, 128.4, 128.2, 127.7, 127.0, 126.1, 125.5, 124.8, 61.1, 51.6, 28.5.

MS: *m*/*z* (%) = 547 (2, M^+), 446 (10), 105 (100), 77 (18).

Anal. Calcd for $C_{34}H_{30}ClN_3O_2$: C, 74.51; H, 5.52; N, 7.67. Found: C, 74.68; H, 5.41; N, 7.85.

3-Benzylidene-*N*-*tert*-butyl-4-(4-nitrobenzoyl)-2-phenyl-4,5-dihydro-3*H*-1,4-benzodiazepine-5-carboxamide (5c)

Yellow crystals; yield: 0.43 g (77%).

^1H NMR (600 MHz, $CDCl_3$): δ = 8.40–6.36 (m, 19 H, Ar-H, =CH), 6.22 (s, 0.2 H, 0.2 CH), 5.89 (s, 0.8 H, 0.8 CH), 5.39 (s, 0.2 H, 0.2 NH), 4.85 (s, 0.8 H, 0.8 NH), 1.23 (s, 8 H, 8/9 × 3 CH_3), 0.95–0.86 (m, 1 H, 1/9 × 3 CH_3).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 168.7, 166.3, 165.7, 149.1, 148.2, 142.3, 134.5, 133.4, 131.8, 130.6, 130.4, 130.0, 128.9, 128.7, 128.6, 128.4, 128.2, 126.7, 126.2, 125.5, 124.7, 122.2, 122.1, 61.1, 51.7, 28.5.

MS: *m*/*z* (%) = 558 (5, M^+), 308 (20), 215 (18), 165 (41), 149 (100), 103 (26).

Anal. Calcd for $C_{34}H_{30}N_4O_4$: C, 73.10; H, 5.41; N, 10.03. Found: C, 73.37; H, 5.53; N, 10.18.

4-Benzoyl-3-benzylidene-*N*-cyclohexyl-2-phenyl-4,5-dihydro-3*H*-1,4-benzodiazepine-5-carboxamide (5d)

White crystals; yield: 0.49 g (91%).

^1H NMR (600 MHz, $CDCl_3$): δ = 8.40–6.47 (m, 20 H, Ar-H, =CH), 6.20 (s, 0.4 H, 0.4 =CH), 5.83 (s, 0.6 H, 0.6 =CH), 5.48 (d, *J* = 5.4 Hz, 0.4 H, 0.4 NH), 4.98 (d, *J* = 7.2 Hz, 0.6 H, 0.6 NH), 3.79–3.63 (m, 1 H, NCH), 1.85–0.84 (m, 10 H, 5 CH_2).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.2, 166.9, 166.1, 149.3, 136.3, 135.3, 134.7, 133.9, 131.6, 130.7, 130.5, 130.2, 129.7, 129.1, 128.9, 128.6, 128.3, 127.7, 127.0, 126.9, 126.5, 126.1, 125.0, 62.3 (minor), 60.9, 48.8, 32.9, 32.4, 25.3, 24.5, 24.4.

MS: *m*/*z* (%) = 539 (4, M^+), 412 (28), 308 (7), 165 (12), 105 (100), 77 (18).

Anal. Calcd for $C_{36}H_{33}N_3O_2$: C, 80.12; H, 6.16; N, 7.79. Found: C, 80.22; H, 6.41; N, 7.98.

3-Benzylidene-4-(4-chlorobenzoyl)-*N*-cyclohexyl-2-phenyl-4,5-dihydro-3*H*-1,4-benzodiazepine-5-carboxamide (5e)

White crystals; yield: 0.45 g (78%).

^1H NMR (600 MHz, $CDCl_3$): δ = 8.40–6.43 (m, 19 H, Ar-H, =CH), 6.22 (s, 0.3 H, 0.3 CH), 5.87 (s, 0.7 H, 0.7 CH), 5.47 (s, 0.3 H, 0.3 NH), 4.93 (s, 0.7 H, 0.7 NH), 3.78–3.63 (m, 1 H, NCH), 1.83–0.86 (m, 10 H, 5 CH_2).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.0, 168.8 (minor), 166.7, 165.8, 149.1, 144.9 (minor), 140.9 (minor), 136.1 (minor), 135.5, 134.7, 134.5, 133.6, 131.6, 130.6, 130.2, 129.1, 128.9, 128.6, 128.2, 127.8, 127.2, 127.0, 126.5, 126.0, 125.0, 124.6, 62.2 (minor), 60.7, 48.8, 32.6, 32.5, 25.0, 24.3.

MS: *m*/*z* (%) = 573 (2, M^+), 446 (25), 165 (20), 139 (100), 111 (16).

Anal. Calcd for $C_{36}H_{32}ClN_3O_2$: C, 75.31; H, 5.62; N, 7.32. Found: C, 75.45; H, 5.82; N, 7.58.

4-Benzoyl-3-benzylidene-*N*-butyl-2-phenyl-4,5-dihydro-3*H*-1,4-benzodiazepine-5-carboxamide (5f)

White crystals; yield: 0.43 g (84%).

^1H NMR (600 MHz, $CDCl_3$): δ = 8.40–6.49 (m, 20 H, Ar-H, =CH), 6.20 (s, 0.3 H, 0.3 CH), 5.84 (s, 0.7 H, 0.7 CH), 5.67 (br, 0.3 H, 0.3 NH), 5.16 (s, 0.7 H, 0.7 NH), 3.24–3.05 (m, 2 H, NCH_2), 1.36–0.73 (m, 7 H, $CH_2CH_2CH_3$).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.1, 169.9 (minor), 167.8, 166.1, 149.2, 145.2 (minor), 141.2 (minor), 136.2, 134.7, 133.8, 131.6, 130.7, 130.4, 130.2, 129.7, 129.5, 129.1, 128.9, 128.8, 128.6, 128.2, 127.7, 126.9, 126.5, 126.1, 124.9, 62.2 (minor), 60.8, 40.0, 31.5, 19.8, 13.6.

MS: *m*/*z* (%) = 513 (4, M^+), 412 (25), 165 (10), 105 (100), 77 (19).

Anal. Calcd for $C_{34}H_{31}N_3O_2$: C, 79.51; H, 6.08; N, 8.18. Found: C, 79.54; H, 6.35; N, 8.39.

4-Acetyl-3-benzylidene-*N*-cyclohexyl-2-phenyl-4,5-dihydro-3*H*-1,4-benzodiazepine-5-carboxamide (5g)

White crystals; yield: 0.41 g (86%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.13 (d, *J* = 7.2 Hz, 2 H, Ar-H), 7.58–7.18 (m, 12 H, Ar-H), 6.68 (s, 0.1 H, 0.1 =CH), 6.30 (s, 0.1 H, 0.1 CH), 6.22 (s, 0.9 H, 0.9 =CH), 6.09 (s, 0.9 H, 0.9 CH), 5.41 (d, *J* = 6.6 Hz, 0.1 H, 0.1 NH), 4.89 (d, *J* = 7.2 Hz, 0.9 H, 0.9 NH), 3.77–3.50 (m, 1 H, NCH), 2.01 (s, 3 H, CH_3), 1.65–0.86 (m, 10 H, 5 CH_2).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.2, 166.6, 166.0, 149.1, 135.9, 133.9. 132.2, 131.3, 130.7, 130.0, 128.9, 128.6, 128.3, 127.7, 126.3, 125.7, 125.5, 124.8, 61.3, 48.6, 48.5, 32.7, 32.4, 24.7, 21.3.

MS: *m*/*z* (%) = 477 (4, M^+), 350 (30), 308 (6), 231 (11), 165 (21).

Anal. Calcd for $C_{31}H_{31}N_3O_2$: C, 77.96; H, 6.54; N, 8.80. Found: C, 78.21; H, 6.64; N, 8.64.

3-Benzylidene-*N*-cyclohexyl-4-(4-methylbenzoyl)-2-phenyl-4,5-dihydro-3*H*-1,4-benzodiazepine-5-carboxamide (5h)

Light yellow crystals; yield: 0.46 g (83%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.43–6.47 (m, 19 H, Ar-H, =CH), 6.19 (s, 0.4 H, 0.4 CH), 5.83 (s, 0.6 H, 0.6 CH), 5.47 (br, 0.4 H, 0.4 NH), 5.00 (br, 0.6 H, 0.6 NH), 3.79–3.63 (m, 1 H, NCH), 2.31 (s, 2.2 H, CH_3), 2.17 (s, 0.8 H, CH_3), 1.84–0.86 (m, 10 H, 5 CH_2).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.2, 170.0 (minor), 166.9, 166.0, 149.1, 145.0 (minor), 141.1 (minor), 139.6, 136.7 (minor), 136.1 (minor), 134.6, 133.8, 133.3, 131.4, 130.7, 130.5, 130.0, 129.6, 128.8, 128.4, 128.1, 127.6, 127.4, 126.9, 126.4, 125.9, 125.0, 124.6, 62.2 (minor), 60.7, 48.7, 32.8, 32.4, 25.0, 24.5, 21.4.

MS: *m*/*z* (%) = 553 (1, M^+), 426 (15), 165 (10), 119 (100), 91 (16).

Anal. Calcd for $C_{37}H_{35}N_3O_2$: C, 80.26; H, 6.37; N, 7.59. Found: C, 80.38; H, 6.51; N, 7.84.

3-Benzylidene-*N*-cyclohexyl-2-phenyl-4-propionyl-4,5-dihydro-3*H*-1,4-benzodiazepine-5-carboxamide (5i)

Light yellow crystals; yield: 0.40 g (81%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.32–8.13 (m, 2 H, Ar-H), 7.77–7.18 (m, 12 H, Ar-H), 6.26 (s, 1 H, =CH), 6.09 (s, 1 H, CH), 5.40 (br, 0.2 H, 0.2 NH), 4.93 (d, *J* = 3.0 Hz, 0.8 H, 0.8 NH), 3.77–3.52 (m, 1 H, NCH), 2.65–2.10 (m, 2 H, CH_2), 1.71–0.86 (m, 13 H, CH_3, 5 CH_2).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.8, 166.3, 166.1, 149.1, 135.8, 133.7, 131.7, 131.2, 130.7, 129.6, 129.2, 128.7, 128.4, 128.2, 127.7, 127.4, 126.1, 125.6, 124.7, 61.4, 48.2, 32.2, 31.9, 26.5, 25.1, 24.2, 24.0, 9.1.

MS: *m*/*z* (%) = 491 (4, M^+), 364 (19), 309 (100), 231 (9), 165 (21).

Anal. Calcd for $C_{32}H_{33}N_3O_2$: C, 78.18; H, 6.77; N, 8.55. Found: C, 78.32; H, 6.79; N, 8.77.

3-Benzylidene-4-(2-chlorobenzoyl)-*N*-cyclohexyl-2-phenyl-4,5-dihydro-3*H*-1,4-benzodiazepine-5-carboxamide (5j)

Yellow crystals; yield: 0.50 g (87%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.29–6.03 (m, 20 H, Ar-H, =CH, CH), 5.51–4.63 (m, 1 H, NH), 3.79–3.28 (m, 1 H, NCH), 2.17–0.70 (m, 10 H, 5 CH_2).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 168.9, 167.6 (minor), 166.6, 165.4, 149.1, 146.3 (minor), 137.1 (minor), 136.3 (minor), 135.0, 130.4, 130.1, 130.0, 129.6, 129.4, 129.0, 128.7, 128.5, 128.2, 127.9, 127.8, 127.6, 127.3, 126.9, 126.6, 126.1, 125.8, 125.3, 64.4, 62.2, 48.7, 32.5, 32.3, 25.1, 24.6, 24.3.

MS: *m*/*z* (%) = 573 (2, M^+), 447 (10), 309 (9), 165 (12), 139 (100), 111 (8).

Anal. Calcd for $C_{36}H_{32}ClN_3O_2$: C, 75.31; H, 5.62; N, 7.32. Found: C, 75.48; H, 5.81; N, 7.52.

4-Acetyl-*N*-*tert*-butyl-3-(4-fluorobenzylidene)-2-phenyl-4,5-dihydro-3*H*-1,4-benzodiazepine-5-carboxamide (5k)

White crystals; yield: 0.40 g (85%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.29–6.90 (m, 13 H, Ar-H), 6.65 (s, 0.2 H, 0.2 =CH), 6.26 (s, 0.2 H, 0.2 CH), 6.19 (s, 0.8 H, 0.8 =CH), 6.04 (s, 0.8 H, 0.8 CH), 5.34–4.85 (m, 1 H, NH), 2.03 (s, 2.5 H, 2.5/3 × CH_3) 1.68 (s, 0.5 H, 0.5/3 × CH_3), 1.27–0.87 (m, 9 H, 3 CH_3).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 168.8, 166.2, 165.8, 162.7, 161.1, 148.9, 135.5, 131.9, 131.4, 131.2, 130.6, 130.5, 130.0, 129.4, 129.3, 128.5, 128.4, 128.2, 126.2, 126.1, 125.6, 125.4, 123.3, 123.2, 115.9, 61.3, 51.3, 28.4, 22.2.

MS: *m*/*z* (%) = 469 (4, M^+), 370 (30), 327 (100), 165 (31), 89 (18).

Anal. Calcd for $C_{29}H_{28}FN_3O_2$: C, 74.18; H, 6.01; N, 8.95. Found: C, 74.21; H, 6.24; N, 9.08.

4-Benzoyl-3-benzylidene-*N*-*tert*-butyl-2-methyl-4,5-dihydro-3*H*-1,4-benzodiazepine-5-carboxamide (5l)

White crystals; yield: 0.37 g (82%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.77–6.34 (m, 15.3 H, Ar-H, =CH, 0.3 CH), 5.57 (s, 0.7 H, 0.7 CH), 5.40 (s, 0.3 H, 0.3 NH), 4.86 (s, 0.7 H, 0.7 NH), 2.64–2.24 (m, 3 H, CH_3), 1.25 (s, 9 H, 3 CH_3).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.0, 169.4 (minor), 166.9, 166.0 (minor), 162.1 (minor), 148.5, 144.6, 135.9 (minor), 135.4, 135.2, 134.3, 133.7, 132.4 (minor), 130.6, 130.5, 129.9, 129.5, 129.3, 128.9, 128.3, 128.2, 127.6, 127.3, 127.0, 126.7, 126.0, 125.9, 125.0, 120.6 (minor), 62.1 (minor), 60.5, 51.4, 28.6, 27.8, 26.8, 26.0.

MS: *m*/*z* (%) = 451 (3, M^+), 351 (13), 247 (5.6), 105 (100), 77 (25).

Anal. Calcd for $C_{29}H_{29}N_3O_2$: C, 77.13; H, 6.47; N, 9.31. Found: C, 77.28; H, 6.56; N, 9.50.

Crystallographic Data

Compound **5a**: formula $C_{34}H_{31}N_3O_2$, colorless crystal. The crystal is of monoclinic, space group *P*2(1)/*c* with *a* = 9.4058(6) Å, *b* = 19.4857(12) Å, *c* = 15.9018(10) Å, α = 90°, β = 101.9670(10)°, γ = 90°, *V* = 2851.1(3) Å^3, *Z* = 4, D_c = 1.197 g/cm^3, *F*(000) = 1088, μ = 0.075 mm^{-1}, *R* = 0.0633, and w*R* = 0.1479 for 5598 observed reflections with $I > 2\sigma(I_0)$. CCDC 1447870 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588308.

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