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Design and synthesis of novel 1,4-benzodiazepine surrogates as potential CCKA and CCKB antagonists via palladium-catalyzed three-component cascade reactions

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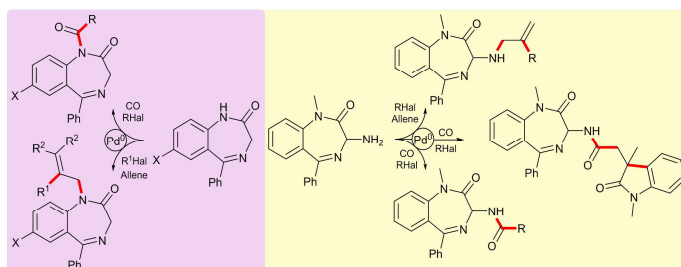
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Design and synthesis of novel 1,4-benzodiazepine surrogates as potential CCKA and CCKB antagonists *via* palladium-catalyzed three component cascade reactions

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Design and synthesis of novel 1,4-benzodiazepine surrogates as potential CCKA and CCKB antagonists via palladium-catalyzed three-component cascade reactions

H. Ali Dondas,^{a,*} Samet Belveren,^a Samet Poyraz,^a Ronald Grigg,^b Colin Kilner,^b Marcos Ferrándiz-Saperas,^c Elisabet Selva^c and José M. Sansano.^c

^a Department of Chemistry, Faculty of Pharmacy, Mersin University, 33342, Mersin, Turkey.

^b School of Chemistry, Leeds University, Leeds LS2 9JT, UK

^c Departamento de Química Orgánica, Universidad de Alicante, Apdo. 99, E-03080-Alicante, Spain.

Instituto de Síntesis Orgánica (ISO), Universidad de Alicante, Centro de Innovación en Química Avanzada (ORFEO-CINQA), Spain.

Fax: +(90) 324 341 30 22; phone: +(90) 324 341 28 15 / 12103.

Corresponding author; e-mail: yakdas25@mersin.edu.tr, yakdas25@hotmail.com

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ABSTRACT

Structurally diverse novel 1,4-benzodiazepine analogues related to selective CCKA antagonist MK-329, and CCKB antagonists L-365,260 and YM022 are prepared via palladium-catalyzed three component domino reactions involving allenylation-carbonylation-anion capture in one-pot cascade protocol in good to excellent yields.

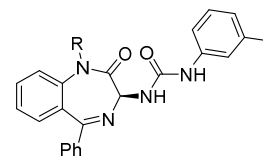
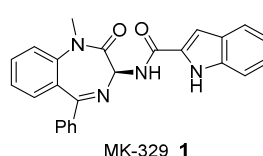
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1. Introduction

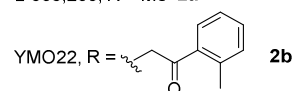
1,4-Benzodiazepin-2-ones are privileged structures possessing an outstanding range of important medicinal and pharmaceutical properties¹ including uses as gastrin/cholecystokinin-B antagonists,² anticonvulsant,³ anxiolytic agent,⁴ anti-HIV,⁵ and HIV-Tat antagonist,⁶ oxytocin antagonist,⁷ anti-ischemic agents,⁸ neuroprotective effect,⁹ and antitrypanosomal activity.¹⁰ In addition, the treatment of neurologic disorders such as Down's syndrome and Alzheimer's disease has been successfully completed by employing these heterocyclic families.¹¹ Several palladacycle complexes derived from 1,4-benzodiazepin-2-ones and pyrrolo[2,1-c][1,4]benzodiazepinones were found to be potent antitumor agents,^{1b,12} whilst another benzodiazepine surrogates were used as antileishmanial agents.¹³ But 1,4-benzodiazepin-2-ones and its analogues are predominantly active in the central nervous system. For example, it has been reported potent nonpeptidic receptor antagonist of the peptide hormone cholecystokinin,¹⁴ the selective cholecystokinin-A (CCKA) antagonist MK-329 **1**,¹⁵ and the selective cholecystokinin-B (CCKB) antagonists L-365,260 **2**,¹⁶ and YM022 **3**¹⁷ and a selective translocator protein (TSPO) agonist Ro5-4864 **4** (Figure 1).^{8,9,18}

Recently, there have been reported many synthetic strategies to investigate novel and/or structurally diverse privileged scaffold

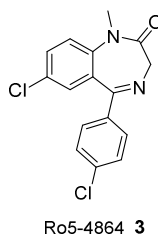
containing 1,4-benzodiazepin-2-one frameworks. The most employed strategy consist in the synthesis of the fully functionalized heterocycle.¹⁹



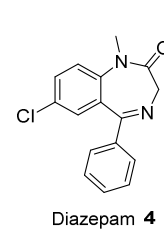
L-365,260, R = Me **2a**



YM022, R = **2b**



Ro5-4864 **3**

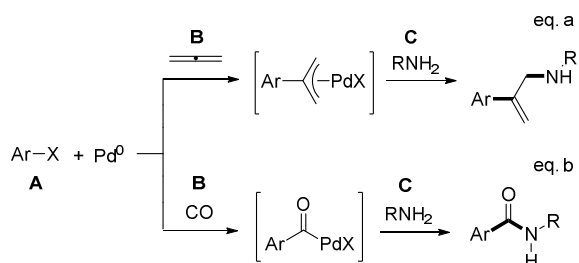


Diazepam **4**

Figure 1. Several biologically important 1,4-benzodiazepin-2-ones.

Alternatively, benzodiazepine-2-ones can be used as the pharmacophore whose substituents are ready to be introduced or modified by conventional synthetic procedures. In this sense, we have reported that an amino group bonded to the 3-position of benzodiazepine ring reacted with aldehyde to generate the corresponding imine, which was the precursor of the azomethine ylide *via* thermal or by metal-catalyzed processes. In this contribution, 1,3-dipolar cycloaddition cascade reactions occurred with chiral and achiral dipolarophiles affording spirocycloadducts in good to excellent yields.²⁰

In addition, Grigg's group experience concerning multicomponent²¹ palladium cascades ($A \rightarrow B \rightarrow C$) have been widely demonstrated,²² especially, in those involving oxidative addition-intermolecular allene insertion (Scheme 1, eq. a) or carbon monoxide insertion (Scheme 1, eq. b) followed by nucleophilic addition as terminating reactions.^{22a,c,h,e,23,24}

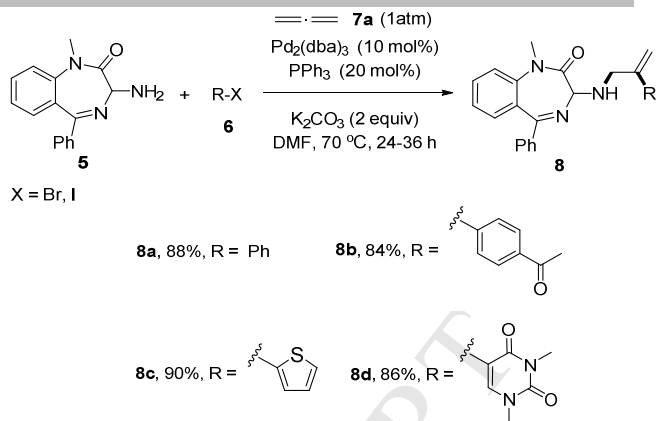


Scheme 1. Domino reactions involved in this contribution.

In this work, novel 1,4-benzodiazepine-2-one analogues are synthesized from benzodiazepine-2-one precursors *via* palladium(0)-catalyzed multicomponent reactions based on oxidative addition onto species **A**, followed by allene **B** insertion and final capture with nucleophile **C**, as well as oxidative addition onto species **A** followed by carbon monoxide **B** insertion and final capture with nucleophile **C**. In all cases, and according to Scheme 1, the terminating step is performed through the amino/amido group anchored to the benzodiazepine-2-one nucleus.

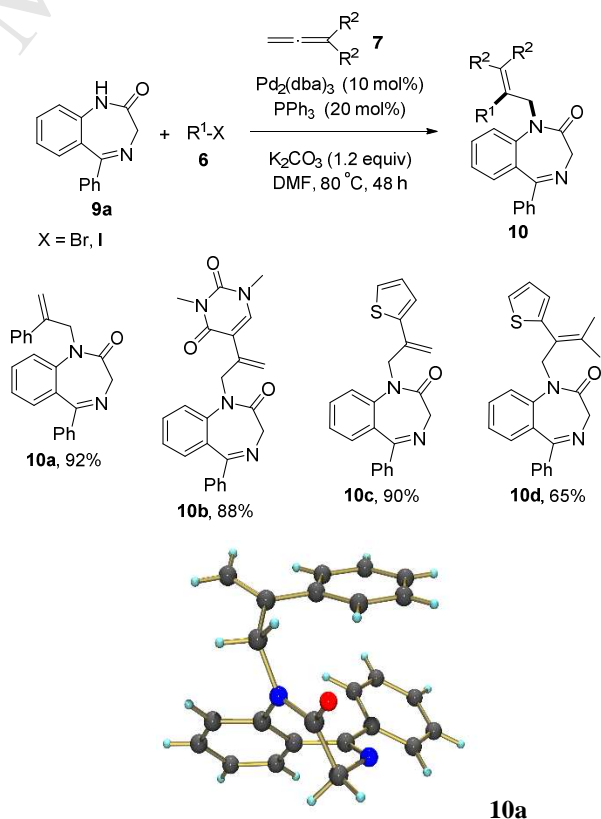
2. Results and Discussion

Palladium(0)-catalyzed allenylation-anion capture cascade reactions: The three-component reaction involving free amine 1-methyl-3-amino-1,3-dihydro-5-phenyl-(2*H*)-1,4-benzodiazepine-2-one **5**,^{22,23} aryl halides **6** and allene **7a** was performed in the presence of a catalytic system comprised by Pd₂(dba)₃ (10 mol%) and PPh₃ (20 mol%). The final conditions were selected according to previous optimizations done in previous works,^{22b,c} that means, DMF at 70 °C for 24-36 h and K₂CO₃ as base (2 equiv). Compounds **8a-d** were obtained in 84-90% yield (Scheme 2). Using this methodology, the incorporation of new biologically interesting substituents, as 5-uracil²⁵ or 2-thienyl,²⁶ was available increasing the potential activity of products **8a-d**.



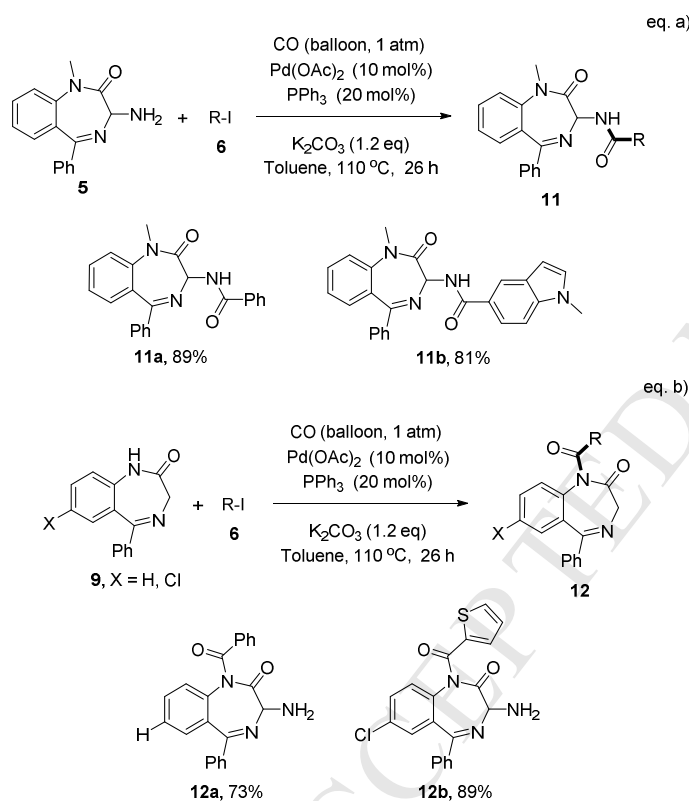
Scheme 2. Palladium(0)-catalyzed allenylation-anion capture cascade reactions involving amine **5**.

A second version of this cascade palladium-catalyzed allenylation-anion capture was successfully attempted with benzodiazepinone **9a** as nucleophilic terminating agent.²⁷ Using identical reaction conditions than those described before, substituted and unsubstituted allenes **7** were allowed to react with aryl halides **6** and heterocycle **9a**, in the presence of Pd₂(dba)₃ (10 mol%) and PPh₃ (20 mol%) in DMF at 80 °C for 48 h. Functionalized compounds **10a-d** were obtained in 65-92% yield in one pot cascade reaction (Scheme 3). X-Ray diffraction analysis of structure **10a**²⁸ also confirmed the skeleton drawn in Scheme 3.



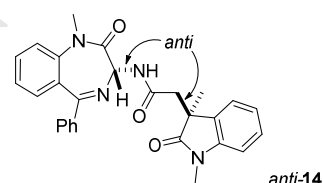
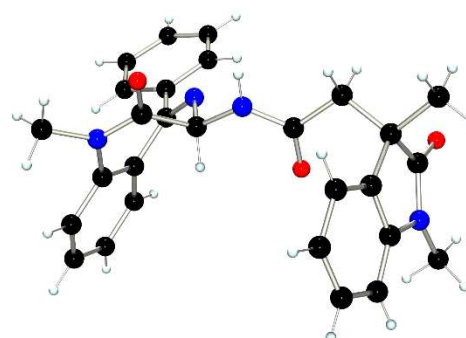
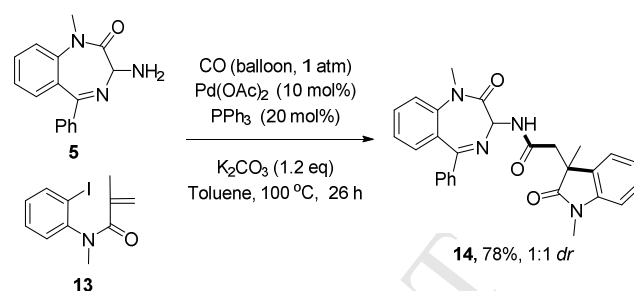
Scheme 3. Palladium(0)-catalyzed allenylation-anion capture cascade reactions involving benzodiazepine **9** and X-ray diffraction structure of compound **10a**.

Palladium-catalyzed carbonylation-anion capture cascade reactions: A third series of benzodiazepine-2-one analogues were prepared from **5** or **9** but employing carbon monoxide instead of allenes as relay species in the cascade processes. These reactions were accomplished with potassium carbonate (1.2 equiv) and a catalytic system comprised by palladium(II) acetate (10 mol%), and triphenylphosphine (20 mol%) in toluene at 110 °C for 26 h. First, amine **5** was employed as terminating agent in the palladium(0)-catalyzed oxidative addition-carbonylation obtaining products **11a** and **11b** in 89% and 81% yields, respectively (Scheme 3, eq. a). Similarly, benzodiazepine-2-ones **9a** (X = H) and **9b** (X = Cl)²⁹ were submitted to palladium catalyzed carbonylation anion capture reaction affording products **12a** and **12b** in 73% and 89% yields, respectively (Scheme 3, eq. b). Despite of being a trivial transformation introducing a benzoyl group, this procedure permit the use of more complex iodoarenes, which are much more accessible than the corresponding benzoyl chlorides. In this series a variety of reactions conditions were evaluated, such as different catalyst systems, but yields were not improved.



Scheme 4. Palladium-catalyzed carbonylation-anion capture cascade reactions employing molecules **5** and **9** as starters.

An example of double relay system in a palladium-catalyzed cyclization-carbonylation-anion capture reaction was studied. Thus the aryl iodide **13**³⁰ smoothly reacted with palladium(II) acetate (10 mol%) and triphenylphosphine (20 mol%), of potassium carbonate (1.2 equiv) in toluene at 100 °C for 26 h furnishing product **14** in 78% yield as a 1:1 mixture of diastereoisomers (Scheme 5). A similar ratio was observed in the earlier stages of the reaction, even at low temperatures. The reaction proceeds *via* 5-*exo-trig* cyclisation as starting process of the palladium cascade reaction.³¹ Both isomers were separated by column chromatography (flash silica) and one of them (*anti*-**14**)



Scheme 5. Palladium-catalyzed cyclization-carbonylation-anion capture from compounds **5** and **13** and X-ray diffraction structure of diastereoisomer *anti*-**14**.

3. Conclusion

In conclusion, a variety of 1,4-benzodiazepine-2-one derivatives can be accessed through a simple one-pot molecularly diverse multicomponent cascade protocol proceeding via palladium(0)-catalyzed allenylation anion capture and cascade palladium-catalyzed carbonylation anion capture reactions. In these processes C(sp²)-C(sp²) + C(sp³)-N(sp³) new bonds and C(sp²)-C(sp²) + C(sp²)-N(sp³) new bonds are generated, respectively. In addition, with a double relay system, C(sp²)-C(sp³) + C(sp³)-C(sp²) + C(sp²)-N(sp³) new bonds are easily formed using the appropriate starter. With this methodology a range of allenes and aryl halides can be employed in good to excellent yields tolerating many functional groups. The molecular complexity of each component can be increased in order to build sophisticated architectures or even natural core products.

4. Experimental Section

4.1. General information

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Mass spectra were recorded at 70 eV on a VG Autospec mass spectrometer. Nuclear magnetic resonance spectra and decoupling experiments were determined at 250 MHz

on a Q.E 300 instrument and at 500 MHz on a Bruker AM500 spectrometer as specified. Chemical shifts are given in parts per million (δ) downfield from tetramethylsilane as internal standard. Spectra were determined in CDCl_3 except where otherwise stated. The structurally most important peaks of the IR spectra (recorded using a Nicolet 510 P-FT-ATR) are listed and wavenumbers are given in cm^{-1} . Flash column chromatography was performed using silica gel 60 (230-400 mesh). Kieselgel columns were packed with silica gel GF254 (Merck 7730). Petroleum ether refers the fraction with bp 40-60 °C unless otherwise specified. Microanalyses were obtained using a Carlo-Erba Model 1106 instrument. Arylhalides were purchased from Aldrich and used as received. In the case of aryl iodide **13** was prepared according to literature procedure.³⁰

4.2. Synthetic procedures and characterization data

4.2.1. General procedure for allenylation-anion capture reaction. Synthesis of compounds **8**

In a Schlenk tube a solution of aryl halide (1.2 mmol), $\text{Pd}_2(\text{dba})_3$ (92 mg, 0.1 mmol), PPh_3 (52 mg, 0.2 mmol) and K_2CO_3 (276 mg, 2 mmol) in dry DMF (10 mL) was prepared. Then free amine **5** (318, 1.2 mmol) was added and the mixture was degassed once by the freeze thaw pump. Allene was introduced (1 atm) and the solution stirred at 70 °C for 24-36 h. The Schlenk was cooled to ambient temperature and internal pressure was released slowly before filtering the crude mixture through a filter paper. The solvent was evaporated under reduced pressure to give a solid which was purified by column chromatography (flash silica) obtaining compounds **8**.

4.2.1.1. 3-[2-Phenyl-2-propenylamino]-1-methyl-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one (**8a**). Yield: 402 mg (88%). Colourless prisms; mp 98-100 °C (petroleum ether/EtOAc). IR (neat): 1792, 1698, 1650 cm^{-1} . δ_{H} (500 MHz): 7.86 (m, 1H, ArH), 7.70 (m, 2H, ArH), 7.40-7.60 (m, 5H, ArH), 7.35 (m, 3H, ArH), 7.14-7.43 (m, 4H, ArH), 6.83 (m, 2H, ArH), 5.08, 5.53 (2 br. s, $\text{CH}_2=\text{C}$), 5.37 (s, 1H, NCHN), 3.22, 3.41 (2d, J 12.5 Hz, 2H, CH_2N), 3.42 (s, 3H, NMe), 3.32 (br. s, 1H, NH). δ_{C} (126 MHz): 35.8 (Me), 53.9 (CH_2N), 83.6 (NCHN), 113.4 ($\text{CH}_2=\text{C}$), 115.8, 126.4, 126.5, 127.2, 127.9, 128.6, 129.0, 129.2, 130.9, 131.0, 131.2, 131.9, 139.6, 146.4 ($\text{C}=\text{CH}_2$ and ArC), 166.7 ($\text{C}=\text{N}$), 168.6 ($\text{C}=\text{O}$). m/z (%) (EI): 381 (M^+ , 2), 319 (20), 229 (100) Anal. calcd. for $\text{C}_{25}\text{H}_{23}\text{N}_3\text{O}_2$: C, 78.70; H, 6.00; N, 11.00, found C, 78.85; H, 6.30; N, 11.10.

4.2.1.2. 3-[[2-(4-Acetylphenyl)-2-propenyl]amino]-1-methyl-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one (**8b**). Yield: 355 mg (84%). Colourless prisms; mp 77-78 °C (petroleum ether/EtOAc). IR (neat): 1790, 1698, 1650, 1604, 1446, 1340 cm^{-1} . δ_{H} (500 MHz): 7.89 (d, 2H, J 7.7 Hz, ArH), 7.64-7.58 (m, 5H, ArH), 7.40 (m, 1H, ArH), 7.39-7.34 (m, 2H, ArH), 7.32-7.36 (m, 2H, ArH), 7.21 (m, 1H, ArH), 5.53 (s, 1H, $\text{C}=\text{CH}_2\alpha$), 5.51 (s, 1H, $\text{C}=\text{CH}_2\beta$), 4.40 (s, 1H, CHNH), 4.0 (d, 1H, J 13.6 Hz, $\text{NHCH}_2\alpha$), 3.9 (d, 1H, J 13.6 Hz, $\text{NHCH}_2\beta$), 3.44 (s, 3H, NMe), 3.05 (br. s, 1H, NH), 2.57 (s, 3H, Me). δ_{C} (126 MHz): 26.6 (28-C), 35.1 (4-C), 48.6 (20-C), 74.7 (1-C), 115.9 (23-C), 121.5 (6-C), 124.1 (24-C), 126.4 (16-C, 14-C), 128.1 (22-C, 17-C), 128.3 (13-C), 128.5 (10-C, 15-C), 129.1 (8-C), 129.7 (7-C), 130.2 (9-C), 131.7 (25-C), 131.7 (29-C), 136.2 (12-C), 138.4 (5-C), 143.2 (26-C), 144.8 (21-C), 144.9 (30-C), 166.6 (11-C=N), 168.8 (2-C=O), 197.7 (27-C=O). m/z (%) (EI): 423 (M^+ , 10), 389 (6), 260 (17), 237 (100), 221 (85), 201 (62), 174 (19),

115 (26). HRMS (ES): $\text{C}_{27}\text{H}_{25}\text{N}_3\text{O}_2\text{Na}$ requires: 446.1844, found: 446.1864. Anal. calcd. for $\text{C}_{27}\text{H}_{25}\text{N}_3\text{O}_2 \cdot 0.25\text{H}_2\text{O}$ (%): C, 75.75; H, 5.95; N, 9.80, found C, 75.45; H, 5.95; N, 9.30.

4.2.1.3. 1-Methyl-5-phenyl-1,3-[[2-(2-thienyl)-2-propenyl]amino]-1,3-dihydro-2H-1,4-benzodiazepin-2-one (**8c**). Yield: 348 mg (90%). Colourless prisms; mp 133-135 °C (petroleum ether/EtOAc). IR (neat): 1793, 1690, 1604, 1446, 1340 cm^{-1} . δ_{H} (500 MHz): 7.65-7.60 (m, 2H, ArH), 7.55 (m, 1H, ArH), 7.44 (m, 1H, ArH), 7.41-7.21 (m, 4H, ArH), 7.20-7.15 (m, 2H, ArH), 7.13 (m, 1H, ArH), 6.95 (m, 1H, ArH), 5.46 (br. s, 1H, $\text{C}=\text{CH}_2\alpha$), 5.28 (br. s, 1H, $\text{C}=\text{CH}_2\beta$), 4.41 (s, 1H, CHNH), 3.97 (d, 1H, J 13.7 Hz, $\text{NHCH}_2\alpha$), 3.85 (d, 1H, J 13.8 Hz, $\text{NHCH}_2\beta$), 3.44 (s, 3H, NMe), 2.95 (br. s, 1H, NH). δ_{C} (126 MHz): 35.1 (4-C), 48.8 (20-C), 74.6 (1-C), 112.0 (22-C), 121.4 (24-C), 123.7 (6-C), 124.0 (26-C), 124.2 (8-C), 127.3 (9-C), 128.3 (14-C, 16-C), 129.1(10-C), 129.7 (13-C, 17-C), 130.2 (15-C), 130.5 (7-C), 131.6 (25-C), 138.5 (12-C), 139.5 (5-C), 143.2 (21-C), 143.9 (23-C), 166.5 ($\text{C}=\text{O}$), 169.0 ($\text{C}=\text{N}$). m/z (%) (EI): 387 (M^+ , 10), 371 (5), 238 (17), 221 (91), 194 (25), 165 (100), 138 (21), 97 (50), 77 (29) and 51 (9). Anal. calcd. for $\text{C}_{23}\text{H}_{21}\text{N}_3\text{OS}$ (%): C, 71.10; H, 5.60; N, 10.90; S, 8.30; found: C, 71.30; H, 5.50; N, 10.90; S, 8.30.

4.2.1.4. 1,3-Dimethyl-5-(1-[[1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl] amino] methyl)vinyl)-2,4-(1H, 3H)-pyrimidinedione (**8d**). Yield: 381 mg (86%). Colourless prisms; mp 101-103 °C (petroleum ether/EtOAc). IR (neat): 3100, 2900, 1698, 1650, 1604, 1446, 1345 cm^{-1} . δ_{H} (500 MHz): 7.70 (s, 1H, $\text{C}=\text{CH}$), 7.65-7.21 (m, 9H, ArH), 5.68 (br. s, 1H, $\text{C}=\text{CH}_2\alpha$), 5.45 (br. s, 1H, $\text{C}=\text{CH}_2\beta$), 4.47 (s, 1H, CHNH), 3.95 (d, 1H, J 13.0 Hz, $\text{NHCH}_2\alpha$), 3.84 (d, J 12.9 Hz, $\text{NHCH}_2\beta$), 3.47 (br. s, 1H, NH), 3.44 (s, 3H, NMe), 3.41 (s, 3H, NMe), 3.32 (s, 3H, NMe). δ_{C} (126 MHz): 28.0 (NMe), 35.1 (NMe), 37.1 (NMe), 49.2 (20-C, CH_2NH), 74.4 (1-C, CHNH), 112.9 (22-C), 118.9 (23-C), 121.5 (6-C), 124.5 (24-C), 128.2 (14-C, 16-C), 128.5 (10-C), 128.9 (13-C, 17-C), 129.6 (9-C), 130.3 (8-C), 130.6 (7-C), 131.8 (15-C), 138.2 (12-C), 141.3 (5-C), 142.9 (21-C), 151.3 (27-C=O), 162.5 (30-C=O), 166.9 (2-C=O), 168.4 (11-C=N). m/z (%) (EI): 443 (M^+ , 7), 409 (9), 260 (11), 237 (33), 221 (100), 194 (37), 165 (15), 109 (8), 77 (14) and 42 (31). HRMS (ES): $\text{C}_{25}\text{H}_{25}\text{N}_5\text{O}_3\text{Na}$ requires 444.2050; found: 444.2036 (M + H). Anal. calcd. for $\text{C}_{25}\text{H}_{25}\text{N}_5\text{O}_3 \cdot 5\text{H}_2\text{O}$ (%): C, 66.40; H, 5.75; N, 15.45; found: C, 66.45; H, 5.70; N, 15.40.

4.2.2. General procedure for allenylation-anion capture reaction. Synthesis of compounds **10**

The method to prepare compounds **10** was the analogous one described for the synthesis if compounds **8** but employing K_2CO_3 (130 mg, 1.2 mmol) at 80 °C for 48 h.

4.2.2.1. 5-Phenyl-1-(2-phenyl-2-propenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one (**10a**): Yield: 324 mg (92%). Colourless prisms; mp 107-109 °C (petroleum ether/EtOAc). IR (neat): 3050, 2900, 1673, 1608, 1594, 1447, 1371, 1321 cm^{-1} . δ_{H} (500 MHz): 7.14-6.97 (m, 14H, ArH), 5.65 (d, 1H, J 16.3 Hz, $\text{NCH}_2\alpha\text{C}=\text{CH}_2$), 5.41 (s, 1H, $\text{C}=\text{CH}_2\alpha$), 5.16 (s, 1H, $\text{C}=\text{CH}_2\beta$), 4.80 (d, 1H, J 10.5 Hz, $\text{NCH}_2\alpha\text{C}=\text{O}$), 4.55 (d, 1H, J 16.3 Hz, $\text{NCH}_2\beta\text{C}=\text{CH}_2$), 3.80 (d, 1H, J 10.5 Hz, $\text{NCH}_2\beta\text{C}=\text{O}$). δ_{C} (126 MHz): 48.7 (18-C), 56.9 (1-C), 115.4 (20-C), 122.2 (5-C), 123.9 (7-C), 125.6 (12-C, 16-C), 127.8 (13-C, 15-C), 128.2 (9-C), 128.3 (23-C, 25-C), 129.4 (22-C, 26-C), 129.9 (6-C), 130.0 (14-C), 130.3 (8-C), 130.7 (24-C), 137.3 (19-C), 138.3 (11-C), 141.3 (4-C), 142.8 (21-C), 169.5 (2-C=O), 170.3 (10-C=N). m/z (%) (EI): 423 (M^+ , 10), 389 (6), 260 (17), 237 (100), 221 (85), 201 (62), 174 (19), 115 (26). 352 (M, 100), 323 (73), 235

(29), 207 (23), 165 (18), 115 (20), 91 (56), 43 (8). Anal. calcd. for $C_{24}H_{20}N_2O \cdot 0.25H_2O$ (%): C, 81.80; H, 5.70; N, 7.95; found: C, 81.35; H, 5.80; N, 7.90.

4.2.2.2. *1,3-Dimethyl-5-[1-[2-oxo-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-1-yl]vinyl]-2,4(1H,3H)-pyrimidinedione (10b)*: Yield: 364 mg (88%). Colourless prisms; mp 197-199 °C (petroleum ether/EtOAc). IR (neat): 3050, 1703, 1654, 1448, 1371 cm^{-1} . δ_H (500 MHz): 7.55 (m, 1H, ArH), 7.45-7.39 (m, 4H, ArH), 7.33-7.25 (m, 2H, ArH), 7.20-7.18 (m, 2H, ArH), 6.96 (s, 1H, C=CHNMe), 5.97 (s, 1H, C=CH α), 5.50 (d, 1H, *J* 15.7 Hz, NCH α C=CH β), 5.23 (s, 1H, C=CH β), 4.77 (d, 1H, *J* 10.3 Hz, NCH α C=O), 4.35 (d, 1H, *J* 15.8 Hz, NCH β C=CH α), 3.80 (d, 1H, *J* 10.2 Hz, NCH β C=O), 3.11 (s, 3H, NMe), 2.95 (s, 3H, NMe). δ_C (126 MHz): 27.9 (CNMe), 36.6 (CNMe), 49.3 (18-C), 57.0 (1-C), 108.6 (21-C), 119.7 (20-C), 123.1 (5-C), 124.8 (7-C), 128.2 (12-C, 16-C), 128.8 (13-C, 15-C), 129.9 (9-C), 130.1 (8-C), 130.9 (14-C), 131.2 (6-C), 134.6 (11-C), 137.51 (19-C), 140.7 (4-C), 141.0 (28-C), 150.1 (25-C), 162.0 (22-C), 169.8 (10-C), 170.14 (2-C). *m/z* (%) (EI): 414 (M^+ , 63), 385 (42), 371 (36), 207 (100), 194 (34), 180 (94), 165 (48), 91 (46), 42 (47). Anal. calcd. for $C_{24}H_{22}N_4O_3$ (%): C, 69.55; H, 5.30; N, 13.50; found: C, 69.40; H, 5.40; N, 13.30.

4.2.2.3. *5-Phenyl-1-[2-(2-thienyl)-2-propenyl]-1,3-dihydro-2H-1,4-benzodiazepin-2-one (10c)*: Yield: 322 mg (90%). Colourless prisms; mp 59-61 °C (petroleum ether/EtOAc). IR (neat): 3000, 1674, 1607, 1447, 1372 cm^{-1} . δ_H (250 MHz): 7.58-7.10 (m, 9H, ArH), 6.90-6.86 (m, 2H, ArH), 6.60 (m, 1H, ArH) 5.50 (d, 1H, *J* 15.8 Hz, NCH α C=CH β), 5.43 (s, 1H, C=CH α), 5.0 (s, 1H, C=CH β), 4.85 (d, 1H, *J* 10.5 Hz, NCH α C=O), 4.50 (d, 1H, *J* 15.8 Hz, NCH β C=CH α), 3.82 (d, 1H, *J* 10.5 Hz, NCH β C=O). δ_C (126 MHz): 48.9 (18-C), 57.0 (1-C), 114.0 (20-C), 122.3 (5-C), 124.2 (7-C), 124.3 (22-C), 124.5 (23-C), 127.6 (13-C, 15-C), 128.0 (12-C, 16-C), 129.3 (14-C), 130.1 (8-C), 130.2 (24-C), 130.2 (6-C), 130.9 (9-C), 136.2 (19-C), 138.4 (11-C), 141.0 (4-C), 141.3 (21-C), 169.3 (2-C=O), 170.6 (10-C=N). *m/z* (%) (EI): 358 (M^+ , 41), 329 (14), 297 (34), 235 (52), 165 (34), 124 (71), 91 (100) and 45 (17). Anal. calcd. for $C_{22}H_{18}N_2OS$ (%): C, 73.75; H, 5.05; N, 7.80; S, 8.95; found: C, 73.50; H, 5.10; N, 7.70; S, 8.75.

4.2.2.4. *1-[3-Methyl-2-(2-thienyl)-2-butenyl]-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one (10d)*: Yield: 250 mg (65%). Pale brown amorphous prisms; mp 49-51 °C (petroleum ether/EtOAc). IR (neat): 3100, 2900, 1674, 1653, 1607, 1447, 1373 cm^{-1} . δ_H (250 MHz): 7.48-7.18 (m, 9H, ArH), 6.91 (m, 1H, ArH), 6.50 (m, 1H, ArH), 6.41 (m, 1H, ArH), 5.43 (d, 1H, *J* 15.2 Hz, NCH α C=C), 4.72 (d, 1H, *J* 10.7 Hz, NCH α C=O), 4.55 (d, 1H, *J* 15.2 Hz, NCH β C=C), 3.69 (d, 1H, *J* 10.6 Hz, NCH β C=O), 1.86, 1.65 (2xs, 6H, 2xCMe). δ_C (126 MHz): 21.2 (Me), 23.1 (Me), 48.4 (18-C), 57.0 (1-C), 122.4 (21-C), 123.3 (20-C), 123.8 (5-C), 124.3 (7-C), 126.3 (25-C), 126.4 (9-C), 127.9 (13-C, 15-C), 129.7 (12-C, 16-C), 129.9 (26-C), 130.0 (14-C), 130.2 (8-C), 130.4 (6-C), 137.3 (19-C), 138.3 (11-C), 142.1 (4-C), 142.3 (23-C), 169.8 (C=O), 170.0 (C=N). *m/z* (%) (EI): 386 (M^+ , 100), 371 (15), 357 (10), 325 (13), 304 (8), 249 (12). Anal. calcd. for $C_{24}H_{22}N_2OS \cdot 0.5H_2O$ (%): C, 72.90; H, 5.40; N, 7.05; found: C, 73.45; H, 4.95; N, 7.00.

4.2.3. General procedure for the carbonylation anion capture reaction. Synthesis of compounds **11**, **12** and **14**.

A solution of iodoarene **6** or **13** (1.1 mmol), $Pd_2(dba)_3$ (92 mg, 0.1 mmol), PPh_3 (52 mg, 0.2 mmol) and K_2CO_3 (166 mg, 1.2 mmol) and the corresponding benzodiazepine-2-one derivative **5** or **9** (1 mmol) in dry toluene was prepared in a round-bottomed flask. Then, a balloon containing carbon monoxide was adapted

and the mixture heated to 100-105 °C for 24-32 h. The reaction was cooled to ambient temperature and filtered through filter paper. The solvent was evaporated under reduced pressure to give a solid which was purified by column chromatography (flash silica) obtaining pure compounds **11**, **12** and **14**.

4.2.3.1. *N-[1-Methyl-2-oxo-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl] benzamide (11a)*: Yield: 329 mg (89%). Colourless prisms; mp 223-225 °C (petroleum ether/EtOAc). IR (neat): 3108, 2890, 1698, 1688, 1659, 1604, 1445 cm^{-1} . δ_H (250 MHz): 8.07 (br. d, 1H, *J* 7.9 Hz, NH), 7.97-7.22 (m, 14H, ArH), 5.74 (d, 1H, *J* 7.9 Hz, NCH), 3.50 (s, 3H, NMe). δ_C (126 MHz): 35.41 (NMe), 67.6 (1-C, NCH), 121.6 (24-C), 124.6 (15-C), 127.3 (13-C, 17-C), 128.3 (14-C, 16-C), 128.5 (22-C, 26-C), 129.1 (10-C), 129.8 (23-C, 25-C), 130.7 (6-C), 130.7 (8-C), 131.8 (7-C), 132.0 (9-C), 134.0 (12-C), 138.1 (5-C), 142.7 (21-C), 167.1 (2-C=O), 167.7 (20-C=O), 167.9 (11-C=N). *m/z* (%) (FAB): 370 (M^+ +1, 100), 249 (8), 221 (19), 147 (8), 105 (25), 69 (22), 55 (28). HRMS (ES): $C_{23}H_{19}N_3O_3Na$ requires 392.1363; found: 392.1365. Anal. calcd. for $C_{23}H_{19}N_3O_3 \cdot 0.5H_2O$ (%): C, 73.00; H, 5.30; N, 11.10; found: C, 72.90; H, 5.30; N, 10.80.

4.2.3.2. *1-Methyl-N-(1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-1H-indole-6-carboxamide (11b)*: Yield: 342 mg (81%). Pale brown amorphous prisms; mp 136-138 °C (petroleum ether/EtOAc). IR (neat): 3113, 2888, 1695, 1685, 1659, 1600, 1440 cm^{-1} . δ_H (250 MHz): 8.30 (s, 1H, Hc), 8.14 (d, 1H, *J* 7.9 Hz, NH), 7.83-7.23 (m, 11H, ArH), 7.10 (d, 1H, *J* 3.1 Hz, CHa=CHb), 6.58 (d, 1H, *J* 3.1 Hz, CHa=CHb), 5.81 (d, 1H, *J* 8.0 Hz, CHNH), 3.78 (s, 3H, NMe), 3.49 (s, 3H, NMe). δ_C (126 MHz): 33.0 (NMe), 35.3 (NMe), 67.6 (1-CH), 102.3, 109.0, 120.9, 121.0, 121.5, 124.5, 125.2, 128.0, 128.2, 128.3, 129.1, 129.8, 129.9, 130.2, 130.6, 130.7, 131.9, 138.2, 138.5 (ArC), 142.8 (C=N), 167.4, 168.1 (2xC=O). *m/z* (%) (EI): 422 (M^+ , 15), 264 (24), 237 (37), 223 (19), 158 (100), 130 (33), 84 (55) and 47 (10). HRMS (ES): $C_{26}H_{22}N_4O_2Na$ requires 445.1640; found: 445.1623. Anal. calcd. for $C_{26}H_{22}N_4O_2 \cdot 0.5CH_2Cl_2$ (%): C, 68.45; H, 4.95; N, 12.05; found C, 68.15; H, 5.05; N, 11.60.

4.2.3.3. *1-Benzoyl-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one (12a)*: Yield: 245 mg (72%). Pale yellow prisms; mp 73-75 °C (petroleum ether/EtOAc). IR (neat): 3118, 2901, 1692, 1682, 1679, 1604, 1455 cm^{-1} . δ_H (250 MHz): 7.80-7.30 (m, 14H, ArH), 4.86 (d, 1H, *J* 11.1 Hz, NCH α), 4.0 (d, 1H, *J* 11.1 Hz, NCH β). δ_C (126 MHz): 57.7 (1-CH α), 125.6, 126.34, 127.41, 128.35, 128.5, 128.6, 128.6, 128.7, 128.8, 129.5, 129.6, 129.6, 130.3, 130.4, 130.9, 131.4, 133.25, 133.8 (ArC), 170.76 (C=O), 170.80 (C=O), 171.10 (C=N). *m/z* (%) (EI): 340 (M^+ , 6), 312 (16), 235 (91), 207 (12), 105 (100), 91 (54), 77 (66), 51 (16). HRMS (ES): $C_{22}H_{16}N_2O_2Na$ requires 363.1109; found: 363.1105. Anal. calcd. for $C_{22}H_{16}N_2O_2 \cdot 0.5H_2O$ (%): C, 75.65; H, 4.90; found: C, 75.15; H, 4.90.

4.2.3.4. *(7-Chloro-5-phenyl-1-(thiophene-2-carbonyl)-1H-benzo[e][1,4]diazepin-2(3H)-one (12b)*: Yield: 338 mg (89%). Pale yellow amorphous prisms; mp 79-81 °C (petroleum ether/EtOAc). IR (neat): 3100, 2910, 1698, 1688, 1670, 1624, 1446, 1342 cm^{-1} . δ_H (500 MHz): 7.71-7.70 (d, 2H, ArH), 7.62 (d, 1H, *J* 4.9 Hz, ArH), 7.55-7.35 (m, 7H, ArH), 6.99 (d, 1H, *J* 4.2 Hz, ArH), 4.91 (d, 1H, *J* 10.0 Hz, NCH α), 3.96 (d, 1H, *J* 9.10 Hz, NCH β). δ_C (126 MHz): 57.4 (1-CH α), 125.5, 128.4, 128.7, 128.8, 129.5, 129.6, 130.2, 131.1, 131.7, 131.8, 135.9, 136.0, 137.1, 137.3, 137.8 (ArC), 164.6 (C=O), 169.5 (C=O), 169.5 (C=N). *m/z* (%) (ES): 380 (M^+ , 100). Anal. calcd. for $C_{20}H_{13}ClN_2O_2S$ (%): C, 63.05; H, 3.40; N, 7.35; found: C, 62.95; H, 3.40; N, 7.20.

4.2.3.5. 2-(1,3-Dimethyl-2-oxo-2,3)-dihydro-1H-indol-3-yl)-N-[methyl-2-oxo-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)acetamide (*anti-14*): Yield: 177 mg (38%). Colourless prisms; mp > 230 °C (petroleum ether/EtOAc). IR (neat): 3050, 2900, 1713, 1670, 1610, 1494, 1145 cm⁻¹. δ_{H} (250 MHz): 7.55- 7.25 (m, 12H, ArH), 7.0 (m, 1H, ArH), 6.82 (d, 1H, *J* 7.7 Hz, NH), 5.38 (d, 1H, *J* 8.3 Hz, 1-C), 3.42 (s, 3H, NMe), 3.24 (s, 3H, NMe), 3.10 (d, 1H, *J* 15.4 Hz, CH₂C=O), 2.90 (d, 1H, *J* 15.5 Hz, CH₂C=O), 1.43 (s, 3H, NMe). δ_{C} (126 MHz): 24.3, 24.4 (26-C, NMe), 26.4, 26.5 (4-C, N-Me), 35.4, 35.5 (23-C, Me), 43.4 (21-C), 45.8 (22-C), 66.9 (1-C), 108.1 (30-C), 121.6 (29-C), 122.4 (6-C), 122.7 (15-C), 124.4 (9-C), 127.9 (7-C), 128.1 (13-C), 128.2 (14-C, 16-C), 128.9 (27-C), 129.8 (13-C, 17-C), 130.6 (3-C, 28-C), 131.8 (8-C), 133.3 (32-C), 138.0 (12-C), 142.7 (10-C), 143.3 (5-C), 167.2 (2-C=O), 167.6 (20-C=O), 168.8 (11-C=N), 180.2 (24-C=O). *m/z* (%) (EI): 466 (M⁺, 46), 409 (8), 264 (53), 248 (100), 222 (86), 174 (65), 160 (51), 130 (16), 77 (23). HRMS (ES): C₂₈H₂₆N₄O₃Na requires 489.1903; found: 489.1898. Anal. calcd. for C₂₈H₂₆N₄O₃·H₂O (%): C, 69.40; H, 5.75; N, 11.55; found: C, 69.20; H, 5.60; N, 11.55.

4.2.3.6. 2-(1,3-Dimethyl-2-oxo-2,3)-dihydro-1H-indol-3-yl)-N-[methyl-2-oxo-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)acetamide (*syn-14*): Yield: 186 mg (40%). Colourless prisms; mp > 230 °C (petroleum ether/EtOAc). IR (neat): 3050, 2905, 1712, 1670, 1610, 1490, 1145 cm⁻¹. δ_{H} (250 MHz): 7.71-7.03 (m, 13H, ArH), 6.85 (d, 1H, *J* 7.7 Hz, NH), 5.36 (d, 1H, *J* 8.2 Hz, NCH), 3.41 (s, 3H, NMe), 3.23(s, 3H, NMe), 3.08 (d, 1H, *J* 15.6 Hz, CH₂C=O), 2.96 (d, 1H, *J* 15.6 Hz, CH₂C=O), 1.43 (s, 3H,

NMe). δ_{C} (126 MHz): 24.6, 24.7 (26-C, NMe), 26.4, 26.5 (4-C, NMe), 35.3, 35.4 (23-C, Me), 43.3 (21-C), 45.8 (22-C), 66.9 (1-C), 108.1 (30-C), 121.6 (29-C), 122.3 (6-C), 122.6 (15-C), 124.4 (9-C), 127.9 (7-C), 128.1 (13-C), 128.6, 128.7 (14-C, 16-C), 129.7 (27-C), 131.9 (31-C), 132.0 (28-C), 132.2, 132.3 (8-C, 17-C), 133.4 (32-C), 138.1 (12-C), 142.7 (10-C), 143.4 (5-C), 167.2 (2-C=O), 167.4 (20-C=O), 169.0 (11-C=N), 180.3 (24-C=O). *m/z* (%) (FAB): 467 (M⁺+1, 100), 221(28), 174(18), 133(25), 109(12), 57(12). HRMS (ES): C₂₈H₂₆N₄O₃Na requires 489.1903; found: 489.1884. Anal. calcd. for C₂₈H₂₆N₄O₃·H₂O (%): C, 69.40; H, 5.75; N, 11.55; found: C, 69.60; H, 5.95; N, 11.05.

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