An expedient and facile route for the general synthesis of 3-aryl substituted 1,2,3-triazolo[1,5-*a*][1,4]benzodiazepin-6-ones and 1,2,3-triazolo[1,5-*a*][1,5]benzodiazocin-7-ones†

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We describe herein a convenient approach for the general synthesis of novel tricyclic scaffolds incorporating a fusion of the 1,2,3-triazole ring with difficultly obtainable medium sized rings such as [1,4]benzodiazepin-5-ones and [1,5]benzodiazocin-6-ones through Sonogashira coupling of an aryl iodide with 2-amino-*N*-methyl-*N*-(prop-2-ynyl)benzamide or homologue followed by *in situ* diazotisation, azidation and cycloaddition reactions. The strategy also allows easy accessibility of the corresponding amide-reduced analogues. The operational simplicity and easy substrate availability make the process cost effective and practical.

Introduction

The development of novel therapeutic agents and identification of molecular probes depend primarily on the availability of libraries of small molecules. This in turn requires efficient synthetic transformations that allow the synthesis of complex molecules from relatively simple starting materials by enabling several bond forming events to occur in the same reaction pot. Nitrogen-rich and medium-sized heterocyclic rings are found abundantly in many drugs, preclinical leads and bio-active natural products. Owing to this and other reasons, there has been considerable effort towards establishing practical and elegant syntheses of such heterocyles over the last few years. However, seven-, eight- and larger-membered rings are generally more difficult to prepare due to their torsional, transannular and large-angle strain combined with enthalpic and entropic constraints for ring closure[1] and thus pose a tremendous synthetic challenge in organic chemistry.

Among the large varieties of heterocycles, 1,4-benzodiazepines[2] have been integral parts of many drugs,[2a-c] therapeutic leads,[2d-f] and bioactive naturally occurring substances[2g-h] and this structural moiety is considered a "privileged structure"[2f] in medicinal chemistry. One of the most important subclasses of 1,4-benzodiazepines is 1,4-benzodiazepin-5-ones, which have been well recognized for their ever evolving and broad range of biological activities, such as antitumor,[3a] anti-insectan,[3b] fibrinogenic receptor antagonist,[3c] muscarinic receptor ligands,[3d] human neurokinin NK1 receptors,[3e] and others.[3f] More importantly, the spectrum of these therapeutic activities has been enhanced significantly by developing scaffolds made through the fusion of 1,4-benzodiazepinone moiety with some specific heterocycles, *e.g.* pyrrole,[2e,4a-c] imidazole,[4d] triazole,[4d-e] and oxazole.[4f] Indeed, it resulted in the discovery of many clinically and commercially successful drugs used for the treatment of central nervous system (CNS) disorders and other diseases. Notable amongst them are the triazolobenzodiazepines Alprazolam (**1a**) and Estazolam (**1b**), which have found use as anxiolytic agents,[5a-c] and triazolam (**1c**), known as an anti-depressant[5d] (Fig. 1). Besides, Flumazenil (**2**) belongs to the family of cognition enhancers[6] and Bretazenil (**3**) is popular due to its potency against neurodegenerative diseases.[7] In addition, a tetrazole-annulated derivative G-7453 (**4**) has emerged as a potential fibrinogen antagonist in recent past.[8] On the other hand 1,5-benzodiazocines, the next higher homologue of 1,4-benzodiazepines, are comparatively less studied, despite having various impressive activities,[9] as these eight-membered rings are relatively difficult to access. In view of the immense biological activities of these classes of compounds coupled with our own interest in lead evaluation studies, we became interested in the general synthesis of 1,2,3-triazolo[1,5-*a*][1,4]benzodiazepin-6-ones **5** and 1,2,3-triazolo[1,5-*a*][1,5]benzodiazocin-7-ones **6** (Fig. 1), which could serve as potent pharmacophores in medicinal chemistry. Careful examination of the literature indicates that the majority of syntheses[8,10] have been developed for specific derivatives (R_1 = H) of **5** through inter- or intra-molecular cycloaddition between terminal acetylene and aryl azide, limiting

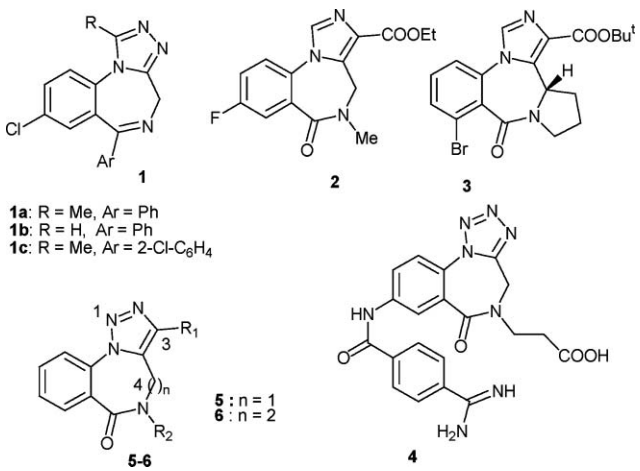

Fig. 1 Fused 1,4-benzodiazepines/1,5-benzodiazocines of interest.

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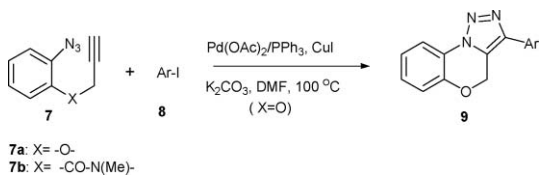
the scope for general synthetic utility. Surprisingly, synthesis of the 3-substituted derivatives (R_1 = aryl/alkyl) of **5** is rarely pursued.[11] Moreover, most of the aforementioned syntheses are multi-step procedures resulting in poor overall yields, while others require harsh reaction conditions and/or are sluggish in nature. Regarding 1,5-benzodiazocinones, although few syntheses are known,[9b,12] to the best of our knowledge there is no report on the synthesis of 3-substituted-1,2,3-triazolo[1,5-*a*][1,5]benzodiazocin-7-ones **6**.

As a part of our interest in the synthesis of novel triazole fused systems through palladium catalysed reactions,[13] we recently reported[13b] the synthesis of [1,2,3]triazolo[5,1-*c*][1,4]benzoxazines **9** through palladium-copper catalysis (Scheme 1). In continuation of these studies, we felt that replacement of 1-azido-2-(prop-2-ynyloxy)benzene **7a** in Scheme 1 by 2-azido-*N*-methyl-*N*-(prop-2-ynyl)benzamide **7b** followed by palladium catalyzed reaction with aryl iodide **8** would lead to the formation of 1,2,3-triazole annulated 1,4-benzodiazepinone **5** (R_1 = Ar, R_2 = Me). Surprisingly, repeated attempts to synthesise the requisite starting substrate **7b** through diazotisation followed by *in situ* azidation of the corresponding amine precursor did not lead to the expected azido substrate **7b**; instead, the intramolecular cycloadduct of **7b** was isolated each time. The propensity of such self cycloaddition is attributable to the HOMO–LUMO energy gap (between azide and acetylene) which is perhaps too low in the substrate **7b** for it to be stable at room temperature or even at lower ones. This is in line with the observations of similar type by other research groups.[14]



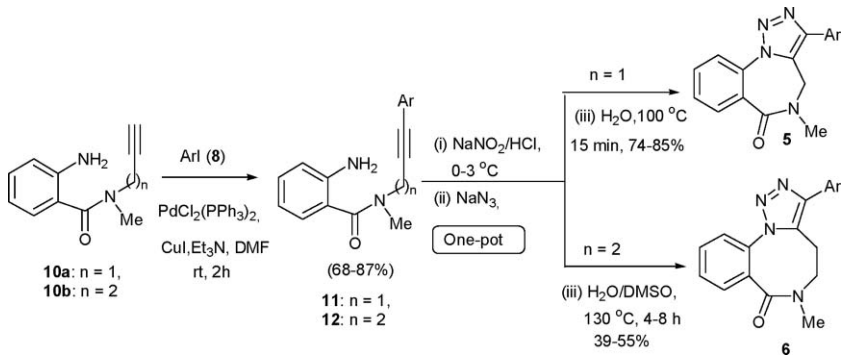
Scheme 1 Synthesis of 1,2,3-triazolo-benzoxazine.[13b]

We then decided to change the strategy and explore the findings noted in our general synthesis of compounds **5–6**. More specifically, we decided to employ the Sonogashira coupling reaction[15] of aryl iodides **8** with 2-amino-*N*-methyl-*N*-(prop-2-ynyl)benzamide **10a** (or higher homologue **10b**) in order to get the corresponding aryl-substituted alkyne **11** (or **12**), which upon subsequent diazotisation/azidation followed by concurrent cycloaddition would lead to the formation of the desired product **5** (or **6**) (Scheme 2). Herein, we report the results obtained in this pursuit.

Results and discussion

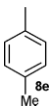
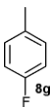
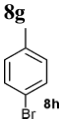
Our synthetic approach started with the preparation of 2-amino-*N*-methyl-*N*-(prop-2-ynyl)benzamide **10a**, which was in turn synthesised in a one-step reaction between commercially available isatoic anhydride and *N*-methylpropargylamine as reported[16] earlier. The reactions of **10a** with aryl iodides **8** were carried out under very mild conditions by stirring the mixture at room temperature (27–32 °C) for 2 h in the presence of $Pd(PPh_3)_2Cl_2$ (4.0 mol%), CuI (6.0 mol%), and triethylamine (7.0 equiv.) in DMF (Scheme 2). C-arylation of the terminal alkyne of **10a** took place efficiently leading to the formation of the disubstituted alkynes **11a–g** with good to excellent yields (entries 1–7, Table 1). Bis-triphenylphosphine palladium(II) chloride and copper(I) iodide appeared to be the catalyst and co-catalyst of choice. After screening various solvents and bases, DMF and triethylamine were found to be the best. Various aryl, hetero-aryl and substituted aryl iodides also could be used in the C-arylation reactions under palladium-copper catalysis, although the yields were somewhat lower (entry 1 *vs.* entries 4–7; Table 1). We then focused our attention on *in situ* diazotisation/azidation followed by cycloaddition reaction in order to get access to the desired seven-membered 1,2,3-triazolo[1,5-*a*][1,4]benzodiazepin-6-ones **5**. Accordingly, phenyl-substituted alkyne **11a** was subjected to diazotisation reaction using sodium nitrite in dilute HCl. Subsequent treatment of the generated diazonium salt with sodium azide furnished the corresponding azido derivative as expected, which was confirmed through isolation followed by spectroscopic characterizations. We then decided to heat the reaction mixture without isolating the intermediate azido compound in order to carry out the cycloaddition *in situ*. Pleasingly, the reaction was found to be complete within 15 min upon heating at 100 °C, leading to the formation of the desired *N*-methyl-3-phenyl-1,2,3-triazolo[1,5-*a*][1,4]benzodiazepin-6-one **5a** with 85% yield (entry 1, Table 1). The same reaction protocol was adopted in the general synthesis of the products **5b–g**, starting from their amine precursors **11b–g** (entries 2–7, Table 1) with 74–85% yields.

Encouraged by the results obtained, we next turned our attention to synthesise 1,2,3-triazolo[1,5-*a*][1,5]benzodiazocin-7-ones **6**, the eight-membered analogues of products **5**, employing



Scheme 2 Synthesis of 1,2,3-triazolo[1,5-*a*][1,4]benzodiazopin-6-ones and 1,2,3-triazolo[1,5-*a*][1,5]benzodiazocin-7-ones (**5–6**).

Table 1 Sonogashira coupling followed by *in situ* diazotisation, azidation, and cycloaddition reactions leading to the formation of products **5–6**

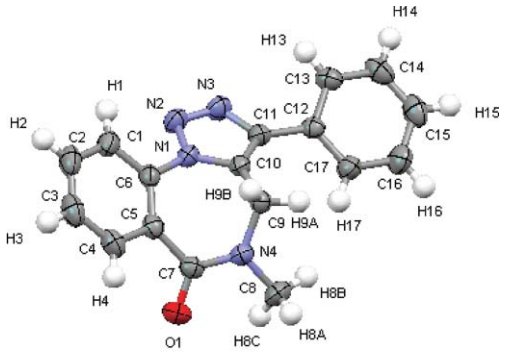
Entry	Aryl Iodide (ArI) Ar, **8**	Products[a] **11–12** (Yield%)[b]	Products[c] **5–6** (Yield%)[b]	Heating time	Overall Yield(%)
1	 **8a**	**11a** (85)	**5a** (85)	15 min	73
2	 **8b**	**11b** (87)	**5b** (85)	15 min	74
3	 **8c**	**11c** (85)	**5c** (84)	15 min	72
4	 **8d**	**11d** (71)	**5d** (83)	15 min	59
5	 **8e**	**11e** (82)	**5e** (80)	15 min	65
6	 **8f**	**11f** (72)	**5f** (80)	15 min	58
7	 **8g**	**11g** (72)	**5g** (74)	15 min	52
8	**8a**	**12a** (81)	**6a** (39)	7 h	32
9	**8e**	**12b** (79)	**6b** (46)	8 h	37
10	**8f**	**12c** (75)	**6c** (41)	4.5 h	31
11	**8g**	**12d** (68)	**6d** (51)	5 h	35
12	 **8h**	**12e** (76)	**6e** (55)	5 h	42

[a] Reaction conditions: Iodide **8** (1.0 equiv.), Acetylene **10a** or **10b** (1.05 equiv.), $Pd(PPh_3)_2Cl_2$ (0.04 equiv.), CuI (0.06 equiv.), Et_3N (7.0 equiv.) in dry DMF (4 mL) stirred at rt for 2 h. [b] Chromatographically isolated pure products. [c] Reaction conditions: **11** or **12** (1.0 equiv.), 2 N HCl (8 mL), a solution of $NaNO_2$ (1.4 equiv.) in water (2.0 mL), stirred at 0–3 °C for 30 min. Stirring another 1 h after the addition of a solution of NaN_3 (1.4 equiv.) in water (2.0 mL) followed by heating at 100 °C (for entries 1–7) or 130 °C after addition of DMSO (8.0 mL) (for entries 8–12).

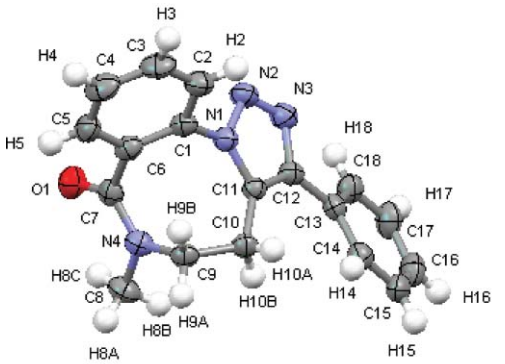
the aforesaid reaction strategy. Accordingly, 2-amino-*N*-methyl-*N*-(but-3-ynyl)benzamide **10b**, the requisite starting compound, was prepared by the reaction of isatoic anhydride and *N*-methylhomopropargylamine under the same reaction conditions as used in the synthesis of **10a**. The C-arylation reactions were carried out efficiently using various aryl iodides **8** at room temperature for 2 h through palladium-copper catalysis affording (68–81%) the di-substituted alkynes **12a–e** (Scheme 2 and entries 8–12, Table 1). Interestingly, when 1-bromo-4-iodobenzene **8h** was employed as substrate, the iodo group selectively participated in the reaction as coupling partner (entry 12, Table 1). The intermediate amines **12a–e** could easily be converted to the corresponding azido derivatives following the diazotisation/azidation protocol as described earlier. However, in contrast to observations in the synthesis of seven-membered ring products **5**, *in situ* cycloaddition occurred (entries 8–12, Table 1) only upon addition of some amount of DMSO (8 mL) to the reaction mixture (12 mL) containing azide followed by immediate heating at 130 °C for few hours. The yields (39–55%) of eight membered ring products **6** were found to be somewhat lower compared to their seven-membered analogues **5**.

Products **5–6** were well characterised by spectroscopic and analytical data. Further structural confirmation came from X-ray diffraction analysis of the products **5a** and **6a** (Fig. 2).[17]

Because of the importance of 6*H*-1,2,3-triazolobenzodiazepines[18a-c] and their corresponding eight-membered variants,[18d-e] which serve as core structures in various compounds having interesting pharmacological properties,[18]



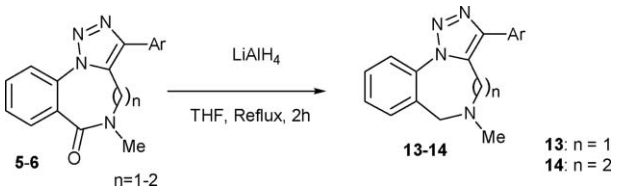
ORTEP representation of **5a**.



ORTEP representation of **6a**.

Fig. 2 Crystal structure of products **5a** and **6a**.

we became interested in getting easy access to 1,2,3-triazolo[1,5-*a*][1,4]benzodiazepines/[1,5]benzodiazocines **13–14** as a sequel to this work. When the products **5–6** were treated with lithium aluminium hydride (LAH) in dry THF under reflux for 2 h, reduction of the amide functionality took place smoothly affording the corresponding amine derivatives **13–14** with moderate to good yields (Scheme 3 and Table 2). Structures of all the products could easily be assigned through spectroscopic and analytical evidences. In IR, disappearance of a peak around



Scheme 3 Reduction of products **5–6**.

Table 2 Reduction of products **5–6** using $LiAlH_4$[a]

Entry	1	2	3	4	5	6	7
Substrate	**5a**	**5b**	**5e**	**5f**	**5g**	**6a**	**6b**
Product	**13a**	**13b**	**13c**	**13d**	**13e**	**14a**	**14b**
Yield(%)[b]	60	63	69	66	70	36	42

[a] Reaction conditions: Product **5** or **6** (0.25 equiv.), $LiAlH_4$ (1.0 equiv.) in dry THF (7.0 mL) was heated under reflux for 2 h. [b] Chromatographically isolated pure products.

1640 cm^{-1} attributable to cyclic amide was observed, while in ^{1}H-NMR, the appearance of appropriate signals for the newly generated benzylic protons besides the other protons provided evidence regarding the formation of targeted products **13–14**. It was further confirmed by other spectroscopic and analytical data. Thus, the success of our work has been extended through the synthesis of these important classes of compounds.

Conclusions

In summary, we have described an established approach for the general synthesis of 1,2,3-triazolo[1,5-*a*][1,4]benzodiazepin-6-ones/[1,5]benzodiazocin-7-ones with moderate to good overall yields. The amides could be smoothly reduced, affording the corresponding amine analogues. The reaction protocol requires cheap starting materials and is carried out under mild reaction conditions. It utilizes one-pot reactions involving diazotisation/azidaton followed by concurrent cycloaddition in water (or using some amount of DMSO as co-solvent in few cases) and is very easy to operate. Overall, this reaction approach is very simple, convenient and cost effective.

Experimental section

General procedure for the synthesis of products 5 through *in situ* diazotisation/azidation followed by concurrent cycloaddition

To a stirred and cooled (0–3 °C) solution of **11** (0.90 mmol) in 2 N HCl (8.0 mL) was added $NaNO_2$ (87 mg, 1.26 mmol) in 2 mL H_2O dropwise during 35 min and the mixture was allowed to stir for another 30 min at the same temperature. A solution of NaN_3 (82 mg, 1.26 mmol) in 2 mL H_2O was added dropwise during 35 min under ice-cooled condition and the stirring was continued for another 15 min. The reaction mixture was allowed to come to room temperature during about 45 min. It was then heated at 100 °C for 15 min. After completion of the reaction, as checked by TLC, it was extracted with chloroform (2 × 30 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The resulting crude residue was purified by silica gel (100–200 mesh) column chromatography using 30–45% ethyl acetate in hexane (v/v) as eluent to afford the product **5**.

5-Methyl-3-phenyl-[1,2,3]triazolo[1,5-*a*][1,4]benzodiazepin-6(4*H*)-one (5a). Yield, 85%; solid, mp 178–180 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.27 (s, 3H), 4.62 (s, 2H), 7.46–7.61 (m, 4H), 7.72–7.75 (m, 3H), 8.06 (d, J = 8.1 Hz, 1H), 8.11 (d, J = 7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.1, 41.8, 122.4, 127.0, 127.2, 128.6, 128.9, 129.0, 129.7, 130.7, 131.9, 132.6, 143.4, 166.2; IR (KBr, cm^{-1}) 3048, 2935, 1640, 1484, 1451, 1393; MS (ESI) (m/z) 313.13 ($M+Na^+$). Anal. Calcd for $C_{17}H_{14}N_4O$: C, 70.33; H, 4.86; N, 19.30. Found: C, 70.26; H, 4.88; N, 19.35.

5-Methyl-3-(1-naphthyl)-[1,2,3]triazolo[1,5-*a*][1,4]benzodiazepin-6(4*H*)-one (5b). Yield 85%, Solid, mp 200–202 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.13 (s, 3H), 4.40 (s, 2H), 7.50–7.63 (m, 5H), 7.76 (t, J = 7.2 Hz, 1H), 7.95–8.01 (m, 3H), 8.13–8.16 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.4, 41.6, 122.4, 125.1, 125.2, 126.3, 126.5, 126.8, 127.0, 128.1, 128.3, 128.9, 129.6, 131.9, 132.2, 132.7, 132.8, 133.7, 142.6, 166.4; IR (KBr, cm^{-1}) 3053, 1643, 1488, 1393,

1254, 1134; MS (ESI) (*m*/*z*) 341.13 (M+H$^+$), 363.11 (M+Na$^+$). Anal. Calcd for $C_{21}H_{16}N_4O$: C, 74.10; H, 4.74; N, 16.46; Found: C, 74.05; H, 4.76; N, 16.49.

5-Methyl-3-(3-pyridyl)-[1,2,3]triazolo[1,5-*a*][1,4]benzodiazepin-6(4*H*)-one (5c). Yield 84%, Solid, mp 159–161 °C; ^{1}H NMR (600 MHz, DMSO-d_6) 3.06(s, 3H), 4.73 (s, 2H), 7.62 (t, J = 7.2 Hz, 1H), 7.74 (t, J = 7.2 Hz, 1H), 7.84 (d, J = 7.8 Hz, 1H), 7.89–7.91 (m, 2H), 8.57 (d, J = 7.2 Hz, 1H), 8.72 (br s, 1H), 9.03 (br s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6)δ 36.7, 41.9, 123.4, 127.5, 127.8, 128.8, 130.7, 132.5,132.6,134.2, 134.6, 139.0, 141.4, 143.3, 145.1, 167.0; IR (KBr, cm^{-1}) 1640, 1482, 1385, 1263, 1134; MS (ESI) (*m*/*z*) 292.04 (M+H$^+$), 314.02 (M+Na$^+$). Anal. Calcd for $C_{16}H_{13}N_5O$: C, 65.97; H, 4.50; N, 24.04; Found: C, 65.93; H, 4.47; N, 23.98.

5-Methyl-3-(2-methylphenyl)-[1,2,3]triazolo[1,5-*a*][1,4]benzodiazepin-6(4*H*)-one (5d). Yield 83%, Solid, mp 136–138 °C;^{1}H NMR (300 MHz, $CDCl_3$) δ 2.38 (s, 3H), 3.19 (s, 3H), 4.39 (s, 2H), 7.24–7.38 (m, 4H), 7.59 (t, J = 7.35 Hz, 1H), 7.73 (t, J = 7.5 Hz, 1H), 8.10 (t, J = 7.8 Hz, 2H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.2, 36.2, 41.5, 122.3, 125.8, 127.0, 128.5, 128.8, 129.1, 130.0, 130.8, 131.8, 132.1, 132.7, 132.8, 137.9, 143.7, 166.3; IR (KBr, cm^{-1}) 2916, 1639, 1487, 1396, 1252, 1136; MS (ESI) (*m*/*z*) 305.06 (M+H$^+$), 327.04 (M+Na$^+$). Anal. Calcd for $C_{18}H_{16}N_4O$: C, 71.04; H, 5.30; N, 18.41; Found: C, 71.08; H, 5.27; N, 18.37.

5-Methyl-3-(4-methylphenyl)-[1,2,3]triazolo[1,5-*a*][1,4]benzodiazepin-6(4*H*)-one (5e). Yield 80%, Solid, mp 221–223 °C;^{1}H NMR (300 MHz, $CDCl_3$) δ 2.44 (s, 3H), 3.26 (s, 3H), 4.60 (s, 2H), 7.33 (d, J = 7.5 Hz, 2H), 7.56–7.64 (m, 3H), 7.72 (t, J = 7.4 Hz, 1H), 8.05 (d, J = 8.1 Hz, 1H), 8.11 (d, J = 7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.1, 36.1, 42.0, 122.5, 127.2, 128.8, 129.7, 130.5, 132.1, 132.6, 133.0, 138.6, 143.6, 166.3; IR (KBr, cm^{-1}) 2916, 1639, 1486, 1393, 1255, 1136; MS (ESI) (*m*/*z*) 305.14 (M+H$^+$), 327.11 (M+Na$^+$). Anal. Calcd for $C_{18}H_{16}N_4O$: C, 71.04; H, 5.30; N, 18.41; Found: C, 71.08; H, 5.27; N, 18.46.

5-Methyl-3-(3-methoxyphenyl)-[1,2,3]triazolo[l,5-*a*][1,4]benzodiazepin-6(4*H*)-one (5f). Yield 80%, Solid, mp 168–170 °C;^{1}H NMR (300 MHz, $CDCl_3$) 3.28(s, 3H), 3.90 (s, 3H), 4.63 (s, 2H), 7.00 (dd, J = 7.35, 1.5 Hz, 1H), 7.26 (m, 1H), 7.33–7.36 (m, 1H), 7.44 (t, J = 7.8 Hz, 1H), 7.59 (t, J = 7.5 Hz, 1H), 7.72 (t, J = 7.05 Hz, 1H), 8.05 (d, J = 7.8 Hz, 1H), 8.11 (d, J = 7.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.0, 41.7, 55.1, 112.7, 114.2, 119.1, 122.3, 126.9, 128.9, 130.0, 130.8, 130.9, 131.9, 132.60, 132.63, 143.1, 159.9, 166.2; IR (KBr, cm^{-1}) 3071, 2935, 1631, 1482, 1392, 1256, 1146; MS (ESI) (*m*/*z*) 321.04 (M+H$^+$), 343.02 (M+Na$^+$). Anal. Calcd for $C_{18}H_{16}N_4O_2$: C, 67.49; H, 5.03; N, 17.49; Found: C, 67.59; H, 5.06; N, 17.54.

5-Methyl-3-(4-fluorophenyl)-[1,2,3]triazolo[1,5-*a*][1,4]benzodiazepin-6(4*H*)-one (5g). Yield 74%, Solid, mp 229–231 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.26 (s, 3H), 4.59 (s, 2H), 7.20–7.26 (m, 2H), 7.60 (t, J = 7.5 Hz, 1H), 7.70–7.73 (m, 3H), 8.05 (d, J = 7.8 Hz, 1H), 8.12 (d, J = 7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.2, 41.8, 116.2 (d, J = 21.8 Hz), 122.5, 126.0 (d, J = 3.8 Hz), 127.1, 129.1, 129.2, 130.7, 132.1, 132.7, 132.8, 142.7, 162.9 (d, J = 247.5 Hz), 166.3; IR (KBr, cm^{-1}) 3071, 1638, 1483, 1393, 1226, 1134; MS (ESI) (*m*/*z*) 309.09 (M+H$^+$), 331.06 (M+Na$^+$). Anal. Calcd for $C_{17}H_{13}FN_4O$: C, 66.23; H, 4.25; N, 18.17; Found: C, 66.19; H, 4.29; N, 18.12.

General procedure for the synthesis of products 6 through *in situ* diazotisation/azidation followed by concurrent cycloaddition

To a well-stirred and cooled (0–3 °C) solution of **12** (0.90 mmol) in 2 N HCl (8.0 mL) was added a solution of $NaNO_2$ (87 mg, 1.26 mmol) in 2 mL H_2O dropwise during 35 min and the mixture was allowed to stir for another 30 min at the same temperature. A solution of NaN_3 (82 mg, 1.26 mmol) in 2 mL H_2O was added dropwise during 35 min under ice-cooled condition and the stirring was continued for another 15 min at the same temperature. The reaction mixture was then allowed to come to room temperature during about 45 min and DMSO (8 mL) was added to the reaction mixture. The resulting mixture was then heated at 130 °C until the completion of the reaction (monitored by TLC). It was then cooled and extracted with chloroform (2 × 20 mL); the extract was washed with brine (15 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product was purified through column chromatography over silica gel (100–200 mesh) using 20–50% ethyl acetate in hexane (v/v) as eluent to furnish the product **6**.

6-Methyl-3-phenyl-[1,2,3]triazolo[1,5-*a*][1,5]benzodiazocin-7-(4*H*)-one (6a). Yield 39%; Solid, mp 204–206 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.97 (s, 3H), 3.05 (dd, J = 16.8, 4.2 Hz, 1H), 3.38 (ddd, J = 15.3, 6.6, 0.8 Hz, 1H), 3.68 (ddd, J = 17.1, 13.5, 6.9 Hz, 1H), 4.08 (ddd, J = 15.3, 13.5, 5.1 Hz, 1H), 7.42 (t, J = 7.2 Hz, 1H), 7.49 (t, J = 7.5 Hz, 2H), 7.60–7.66 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 23.0, 32.6, 46.3, 127.3, 127.9, 128.2, 128.6, 128.7, 129.3, 130.5, 130.6, 131.0, 132.2, 134.4, 146.0, 167.8; IR (KBr, cm^{-1}) 3065, 2959, 1646, 1486, 1267, 1075; MS (EI) (*m*/*z*) 304, 276, 261, 204; Anal. Calcd. for $C_{18}H_{16}N_4O$: C, 71.04; H, 5.30; N, 18.41; Found C, 71.10; H, 5.34; N, 18.37.

6-Methyl-3-(4-methylphenyl)-[1,2,3]triazolo[1,5-*a*][1,5]benzodiazocin-7-(4*H*)-one (6b). Yield 46%; Solid, mp 203–205 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.42 (s, 3H), 2.97–3.06 (m, 4H), 3.37 (dd, J = 15.1, 6.7 Hz, 1H), 3.66 (ddd, J = 16.4, 13.2, 6.6 Hz, 1H), 4.08 (td, J = 14.3, 4.8 Hz, 1H), 7.30 (d, J = 8.1 Hz, 2H), 7.54 (d, J = 7.8 Hz, 2H), 7.63 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2, 22.9, 32.5, 46.3, 127.3, 127.5, 127.8, 128.5, 129.0, 129.4, 130.5, 130.9, 132.1, 134.4, 138.0, 145.9, 167.8; IR (KBr, cm^{-1}) 3071, 2923, 1642, 1482, 1267, 1073; MS (EI) (*m*/*z*) 318, 290, 275, 217, 204; Anal. Calcd. for $C_{19}H_{18}N_4O$: C, 71.68; H, 5.70; N, 17.60; Found C, 71.62; H, 5.74; N, 17.63.

6-Methyl-3-(3-methoxyphenyl)-[1,2,3]triazolo[1,5-*a*][1,5]benzodiazocin-7-(4*H*)-one (6c). Yield 41%; Solid, mp 177–179 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.97 (s, 3H), 3.03 (ddd, J = 16.6, 4.9, 0.9 Hz, 1H), 3.38 (ddd, J = 15.3, 6.9, 1.2 Hz, 1H), 3.69 (ddd, J = 17.1, 13.5, 6.9 Hz, 1H), 3.88 (s, 3H), 4.08 (ddd, J = 15.4, 13.6, 5.2 Hz, 1H), 6.96 (ddd, J = 8.2, 2.5, 0.7 Hz, 1H), 7.18 (dt, J = 7.5, 1.0 Hz, 1H), 7.25 (td, J = 2.1, 0.6 Hz, 1H), 7.39 (t, J = 7.8 Hz, 1H), 7.60–7.64 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 23.1, 32.6, 46.3, 55.3, 113.4, 114.0, 120.1, 127.4,128.6, 129.4, 129.7, 130.6, 131.0, 131.8, 132.2, 134.4, 145.8, 159.8, 167.8; IR (KBr, cm^{-1}) 3059, 2925, 1644, 1488, 1252, 1078; HRMS (ESI) (*m*/*z*) Calcd. For $C_{19}H_{18}N_4O_2Na$ 357.1327. Found: 357.1326.

6-Methyl-3-(4-fluorophenyl)-[1,2,3]triazolo[1,5-*a*][1,5]benzodiazocin-7(4*H*)-one (6d). Yield 51%; Solid, mp 218–220 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.97 (s, 3H), 3.03 (ddd, J = 16.6, 4.9, 0.7 Hz, 1H), 3.39 (ddd, J = 15.6, 7.2, 1.2 Hz, 1H), 3.62 (ddd, J = 16.8, 13.5, 6.9 Hz, 1H), 4.08 (ddd, J = 15.3, 13.5, 5.1 Hz, 1H), 7.18 (tt, J = 8.7, 2.3 Hz, 2H), 7.59–7.63 (m, 6H);^{13}C NMR (150 MHz, $CDCl_3$) δ 23.0, 32.6, 46.2, 115.8 (d, J = 21 Hz), 126.6 (d, J = 3.0 Hz), 127.3, 128.6, 129.2, 129.7 (d, J = 7.5 Hz), 130.7, 131.0, 132.1, 134.3, 145.1, 162.7 (d, J = 246 Hz), 167.7; IR (KBr, cm^{-1}) 3071, 2924, 1645, 1496, 1224, 1075; MS (EI) (*m*/*z*) 322, 294, 222; Anal. Calcd. For $C_{18}H_{15}FN_4O$: C, 67.07; H, 4.69; N, 17.38; Found C, 67.11; H, 4.66; N,17.34.

6-Methyl-3-(4-bromophenyl)-[1,2,3]triazolo[1,5-*a*][1,5]benzodiazocin-7-(4*H*)-one (6e). Yield 55%; Solid, mp 274–276 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.97 (s, 3H), 3.04 (dd, J = 16.8, 4.8 Hz, 1H), 3.39 (dd, J = 15.0, 6.6 Hz, 1H), 3.62 (ddd, J = 16.7, 13.4, 6.9 Hz, 1H), 4.09 (ddd, J = 15.0, 13.6, 4.9 Hz, 1H), 7.47–7.66 (m, 8H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 22.3, 31.8, 45.6, 121.4, 127.2, 128.1, 129.5, 129.6, 130.86, 130.89, 131.2, 131.7, 132.3, 133.6, 143.7, 166.8; IR (KBr, cm^{-1}) 1636, 1484, 1393; HRMS (ESI) (*m*/*z*) Calcd. for $C_{18}H_{15}BrN_4ONa$ 405.0327 (M + Na$^+$); Found: 405.0324.

General procedure for the synthesis of products 13 or 14 through reduction using $LiAlH_4$

To a well stirred solution of product **5** or **6** (0.25 mmol) in dry THF (7.0 mL), lithium aluminium hydride (38 mg, 1.0 mmol) was added and allowed to heat under reflux under argon atmosphere for 2 h. It was cooled, diethyl ether (60 mL) was added followed by seven to ten drops of water and the reaction mixture was kept under stirring for five to ten min. A solid residue that appeared was filtered and the organic layer from the filtrate was collected. The organic layer was washed with water (15 mL) and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the crude product was purified through column chromatography over silica gel (100–200 mesh) using 30–40% ethyl acetate in hexane (v/v) as eluent to afford the desired product **13** or **14**.

5-Methyl-3-phenyl-(4*H*)-[1,2,3]triazolo[1,5-*a*][1,4]benzodiazepine (13a). Yield 60%; Solid, mp 124–126 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.53 (s, 3H), 3.62 (s, 2H), 3.73 (s, 2H), 7.41 (tt, J = 7.5, 1.4 Hz, 1H), 7.47 (td, J = 6.9, 1.2 Hz, 1H), 7.49–7.51 (m, 3H), 7.58 (td, J = 7.8, 1.8 Hz, 1H), 7.85 (dd, J = 7.8, 1.2 Hz, 2H), 7.95 (dd, J = 7.8, 1.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 44.0, 47.3, 56.7, 122.8, 127.3, 128.3, 128.5, 128.9, 129.0, 129.6, 129.9, 130.6, 131.0, 136.6, 145.3; IR (neat, cm^{-1}) 2947, 2778, 1484, 1252, 1131; MS (FAB+) (*m*/*z*) 277 (M+H$^+$); Anal. Calcd. for $C_{17}H_{16}N_4$: C, 73.89; H, 5.84; N, 20.27. Found C, 73.86; H, 5.81; N, 20.32.

5-Methyl-3-(1-naphthyl)-(4*H*)-[1,2,3]triazolo[1,5-*a*][1,4]benzodiazepine (13b). Yield 63%; Oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.40 (s, 3H), 3.59 (s, 2H), 3.69 (s, 2H), 7.49–7.67 (m, 7H), 7.91–7.96 (m, 2H), 8.03 (d, J = 7.5 Hz, 1H), 8.18 (t, J = 4.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 43.9, 46.9, 56.7, 122.8, 125.2, 125.8, 126.1, 126.6, 127.4, 128.1, 128.2, 128.6, 129.0, 129.2, 129.5, 131.0, 131.9, 132.0, 133.8, 136.7, 144.7; IR (neat, cm^{-1}) 3051, 2933, 2788, 1491, 1251; MS (ESI) (*m*/*z*) 327.25 (M + H$^+$). Anal. Calcd. for $C_{21}H_{18}N_4$: C, 77.28; H, 5.56; N, 17.17. Found C, 77.34; H, 5.59; N, 17.19.

5-Methyl-3-(4-methylphenyl)-(4*H*)-[1,2,3]triazolo[1,5-*a*][1,4]-benzodiazepine (13c). Yield 69%; Oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.42 (s, 3H), 2.52 (s, 3H), 3.61 (s, 2H), 3.72 (s, 2H), 7.30 (d, J = 7.8 Hz, 2H), 7.46–7.51 (m, 2H), 7.58 (td, J = 7.2, 2.4 Hz, 1H), 7.73 (d, J = 8.1 Hz, 2H), 7.95 (t, J = 7.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2, 43.9, 47.1, 56.6, 122.7, 127.1, 127.7, 128.3, 128.9, 129.4, 129.5, 131.0, 136.6, 138.1, 145.4; IR (neat, cm^{-1}) 2949, 1484, 1455, 1253, 1132, 1005; MS (FAB+) (*m*/*z*) 291 (M + H$^+$), 290, 262, 261; Anal. Calcd. for $C_{18}H_{18}N_4$: C, 74.46; H, 6.25; N, 19.30. Found C, 74.52; H, 6.23; N, 19.35.

5-Methyl-3-(3-methoxyphenyl)-(4*H*)-[1,2,3]triazolo[1,5-*a*][1,4]-benzodiazepine (13d). Yield 66%; Oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.53 (s, 3H), 3.60 (s, 2H), 3.74 (s, 2H), 3.89 (s, 3H), 6.95–6.97 (m, 1H), 7.39–7.54 (m, 5H), 7.58 (td, J = 6.52, 2.1 Hz, 1H), 7.95(d, J = 7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 44.0, 47.2, 55.3, 56.7, 112.5, 114.3, 119.5, 122.7, 128.6, 129.0, 129.5, 129.8, 130.0, 131.0, 131.9, 136.6, 145.1, 160.0; IR (neat, cm^{-1}) 2944, 1487, 1246, 1032; MS (FAB+) (*m*/*z*) 307 (M + H$^+$); Anal. Calcd. for $C_{18}H_{18}N_4O$: C, 70.57; H, 5.92; N, 18.29. Found C, 70.52; H, 5.98; N, 18.27.

5-Methyl-3-(4-fluorophenyl)-(4*H*)-[1,2,3]triazolo[1,5-*a*][1,4]benzodiazepine (13e). Yield 70%; Oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.53 (s, 3H), 3.62 (s, 2H), 3.69 (s, 2H), 7.19 (t, J = 8.1 Hz, 2H), 7.45–7.52 (m, 2H), 7.59 (td, J = 7.1, 1.8 Hz, 1H), 7.79–7.84 (m, 2H), 7.94 (d, J = 7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 43.9, 47.2, 56.6, 115.9 (d, J = 21.0 Hz), 122.7, 126.8 (d, J = 3.0 Hz), 128.4, 129.13, 129.14 (d, J = 8.3 Hz), 129.6, 129.8, 131.1, 136.5, 144.4, 162.8 (d, J = 246 Hz); IR (neat, cm^{-1}) 2931, 1497, 1226, 1155, 1003; MS (FAB+) (*m*/*z*) 295 (M+H$^+$), 266, 265; Anal. Calcd. for $C_{17}H_{15}FN_4$: C, 69.37; H, 5.14; N, 19.04. Found C, 69.41; H, 5.17; N, 18.98.

6-Methyl-3-(phenyl)-(4*H*)-[1,2,3]triazolo[1,5-*a*][1,5]benzodiazocine (14a). Yield 36%; Oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.52 (s, 3H), 2.56 (br, 1H), 2.89 (br, 1H), 3.14 (br, 1H), 3.31(br, 2H), 3.78 (br, 1H), 7.39 (tt, J = 7.5, 1.2 Hz, 1H), 7.47–7.54 (m, 5H), 7.62–7.64 (m, 1H), 7.74–7.76 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.0, 44.1, 56.0, 56.4, 126.6, 127.2, 127.9, 128.8, 128.9, 129.9, 131.2, 132.2, 133.5, 134.6, 135.1, 144.1; IR (neat, cm^{-1}) 3057, 2937, 1494, 1448, 1255; MS (ESI) (*m*/*z*) 291.22 (M + H$^+$); MS (EI) (*m*/*z*) 290, 261, 218, 133; Anal. Calcd. For $C_{18}H_{18}N_4$: C, 74.46; H, 6.25; N, 19.30. Found C, 74.41; H, 6.28; N, 19.36.

6-Methyl-3-(4-methylphenyl)-(4*H*)-[1,2,3]triazolo[1,5-*a*][1,5]-benzodiazocine (14b). Yield 42%; Oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.41 (s, 3H), 2.54 (s, 3H), 2.57 (br, 1H), 2.92 (br, 1H), 3.16 (br, 1H), 3.35 (br, 2H), 3.83 (br, 1H), 7.29 (d, J = 8.4 Hz, 2H), 7.50–7.53 (m, 3H), 7.61–7.64 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 20.7, 21.2, 43.8, 55.7, 56.1, 126.6, 127.1, 128.1, 129.2, 129.5, 129.9, 132.4, 134.5, 134.8, 137.9, 144.3; IR (neat, cm^{-1}) 3029, 2926, 1498, 1461, 1255; HRMS (ESI) (*m*/*z*) Calcd. For $C_{19}H_{21}N_4$ 305.1766 (M + H$^+$). Found 305.1762.

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Notes and references

1 (*a*) E. L. Eliel and S. H. Wilen, in *Stereochemistry of Organic Compounds*, Wiley, New York, NY, 1994; (*b*) P. Appukkuttan, W. Dehaen and E. Van Der Eycken, *Org. Lett.*, 2005, **7**, 2723; (*c*) D. R. Spring, S. Krishna, H. E. Blackwell and S. L. Schreiber, *J. Am. Chem. Soc.*, 2002, **124**, 1354; (*d*) K. C. Majumder, I. Ansary, B. Sinha and B. Chattopadhyay, *Synthesis*, 2009, 3593.

2 (*a*) D. J. Greenblatt and R. I. Shader, in *Benzodiazepines in Clinical Practice*, Raven Press, New York, 1974; (*b*) L. H. Sternbach, in *The Benzodiazepine Story*, ed. F. Hoffmann-La Roche, Roche Scientific Services, Basel, 2nd edn, 1983, P. 5; (*c*) J. K. Landquist, in *Comprehensive Heterocyclic Chemistry*, ed. A. R. Katritzky and C. W. Rees, Pergamon, Oxford, 1984, Vol. 1, p. 170; (*d*) G. Mohiuddin, P. S. Reddy, K. Ahmed and C. V. Ratnam, *Heterocycles*, 1986, **24**, 3489; (*e*) D. E. Thurston and D. S. Bose, *Chem. Rev.*, 1994, **94**, 433; (*f*) A. A. Patchet and R. P. Nargund, *Annu. Rep. Med. Chem.*, 2000, **35**, 289; (*g*) A. Witt and J. Bergman, *J. Org. Chem.*, 2001, **66**, 2784; (*h*) S. Eguchi, *Arkivoc*, 2005, (part ii), 98.

3 (*a*) T. Kaneko, H. Wong, T. W. Doyle, W. C. Rose and W. T. Bradner, *J. Med. Chem.*, 1985, **28**, 388; (*b*) W. Zhang, J. P. William, Y. Lu, T. Nagashima and Q. Chu, *Tetrahedron Lett.*, 2007, **48**, 563; (*c*) R. M. Keenam, J. F. Callaham, J. M. Samanen, W. E. Bondinell, R. R. Calvo, I. Chen, C. DeBrosse, D. S. Eggleston, R. C. Haltiwanger, S. M. Hwang, D. R. Jakes, T. W. Ku, W. H. Miller, K. A. Newlander, A. Nichols, M. F. Parker, L. S. Southhall, I. Uzinskas, J. A. Vasko-Moser, J. W. Venslavsky, A. S. Wong and W. F. Huffmann, *J. Med. Chem.*, 1999, **42**, 545; (*d*) F. Novelli, A. Sparatore, B. Tass and F. Sparatore, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 3031; (*e*) T. Sugimori, T. Okawa, S. Eguchi, A. Kakehi, E. Yashima and Y. Okamoto, *Tetrahedron*, 1998, **54**, 7997; (*f*) A. Walser and R. I. Fryer, in *Chemistry of Heterocyclic Compounds, Bicyclic Diazepines*, ed. E. C. Taylor and A. Weissberger, Wiley, Chichester, UK, 1991, Vol. 50, P. 431, Chapters V-VIII.

4 (*a*) K. M. Rahman, A. S. Thomson, C. H. James, M. Narayanaswamy and D. E. Thurston, *J. Am. Chem. Soc.*, 2009, **131**, 13756; (*b*) T. Wang, A. S. Lui and I. S. Cloudsdale, *Org. Lett.*, 1999, **1**, 1835; (*c*) A. Kamal, V. Devaiah, K. L. Reddy and N. Shankaraiah, *Adv. Synth. Catal.*, 2006, **348**, 249; (*d*) For a review article on azole-fused benzodiazepines, see: M. Gerecke, E. Kyburz, R. Borer and W. Gassner, *Heterocycles*, 1994, **39**, 693; (*e*) D. K. Mohapatra, P. K. Maity, M. Shabab and M. I. Khan, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 5241; (*f*) S. Kobayashi, *Bull. Chem. Soc. Jpn.*, 1975, **48**, 302.

5 (*a*) P. J. Snyder, J. Werth, B. Giordani, A. F. Caveney, D. Feltner and P. Maruff, *Hum. Psychopharmacol. Clin. Exp.*, 2005, **20**, 263; (*b*) J. Levine, D. P. Cole, K. N. Roy Chengappa and S. Gerson, *Depress. Anxiety*, 2001, **14**, 94; (*c*) G. L. Post, R. O. Patrick, J. E. Crowder, J. Houston, J. M. Ferguson, R. J. Bielski, L. Bailey, H. G. Pearlman, V. S. Shu and M. W. Pierce, *J. Clin. Psychopharmacol.*, 1991, **11**, 249; (*d*) D. J. Greenblatt, J. S. Harmatz, L. Shapiro, N. Engelhardt, T. A. Gouthro and T. A. Shader, *N. Engl. J. Med.*, 1991, **324**, 1691.

6 (*a*) W. Frostl and L. Maitre, *Pharmacopsychiatry*, 1989, **22**, 54; (*b*) S. R. Donohue and R. F. Dannals, *Tetrahedron Lett.*, 2009, **50**, 7271.

7 A. G. Katsifis, M. E. McPhee, F. Mattner and D. D. Ridley, *Aust. J. Chem.*, 1999, **52**, 1061 and see also reference 4e.

8 A. W. Thomas, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 1881.

9 (*a*) T. Howard, in *Comprehensive Heterocyclic Chemistry II*, vol. 7., ed. A. R. Katritzky, C. W. Rees and E. F. V. Scriven, Pergamon, New York, 1996, p. 151; (*b*) P. Herold, J. W. Herzig, P. Wenk, T. Leutert, P. Zbinden, W. Fuhrer, S. Stutz, K. Schenker, M. Meier and G. Rihs, *J. Med. Chem.*, 1995, **38**, 2946; (*c*) W. Heitmann, H. Liepmann, U. Matzel, H. Zeugner, A. M. Fuchs, H. Krahling, M. Ruhland, F. Mol and M. T. M. Tulp, *Eur. J. Med. Chem.*, 1988, **23**, 249.

10 (*a*) M. Alajarin, J. Cabrera, A. Pastor and J. M. Villalgordo, *Tetrahedron Lett.*, 2007, **48**, 3495; (*b*) I. Akritopoulou-Zanze, V. Gracias and S. W. Djuric, *Tetrahedron Lett.*, 2004, **45**, 8439; (*c*) D. L. Coffen, R. I. Fryer, D. A. Katonak and F. Wong, *J. Org. Chem.*, 1975, **40**, 894; (*d*) G. Broggini, G. Molteni, A. Terraneo and G. Zecchi, *Tetrahedron*, 1999, **55**, 14803; (*e*) G. Broggini, I. De Marchi, M. Martinelli, G. Paladino and A. Penoni, *Lett. Org. Chem.*, 2004, **1**, 221; (*f*) G. Broggini, I. De Marchi, M. Martinelli, G. Paladino, T. Pilati and A. Terraneo, *Synthesis*, 2005, 2246.

11 Zecchi and coworkers synthesised few specific derivatives (R_1 = Ph/Me/H, R_2 = Ph) of [1,2,3]triazolo[1,5-*a*][1,4]benzodiazepines **5** through multi-step approach using alkynyl bromide, which is not easily accessible. For details see: G. Broggini, G. Molteni and G. Zecchi, *Synthesis*, 1995, 647.

12 (*a*) H. Yoshida, E. Shirakawa, Y. Honda and T. Hiyama, *Angew. Chem., Int. Ed.*, 2002, **41**, 3247; (*b*) J. B. Bremner and W. Sengpracha, *Tetrahedron*, 2005, **61**, 941; (*c*) I. O'Neil, C. L. Murray, A. J. Potter and S. B. Kalindjian, *Tetrahedron Lett.*, 1997, **38**, 3609.

13 (*a*) C. Chowdhury, S. Mukherjee, B. Das and B. Achari, *J. Org. Chem.*, 2009, **74**, 3612; (*b*) C. Chowdhury, A. K. Sasmal and P. K. Dutta, *Tetrahedron Lett.*, 2009, **50**, 2678; (*c*) C. Chowdhury, S. B. Mandal and B. Achari, *Tetrahedron Lett.*, 2005, **46**, 8531.

14 L. Garanti, G. Molteni and G. Broggini, *J. Chem. Soc., Perkin Trans. 1*, 2001, 1816; See also ref. 4e and 10d.

15 (*a*) K. Sonogashira, Y. Tohda and N. Haghihara, *Tetrahedron Lett.*, 1975, **16**, 4467; (*b*) K. Sonogashira, in *Comprehensive Organic Synthesis*, ed. B. M. Trost, Pergamon, Oxford, 1991, vol 3, p. 521.

16 M. C. Venuti, *Synthesis*, 1982, 266.

17 The crystal data has been deposited at Cambridge Crystallographic Data Centre [CCDC No: 774490 for product **5a** and 775332 for product **6a**]. Copies of the data can be obtained free of charge *via* www.ccdc.ac.uk/conts/retrieving.html or CCDC, 12 union Road, Cambridge CB2 1EZ, UK.

18 For preclinical antitumor activities, see: (*a*) J. T. Hunt, C. Z. Ding, R. Batorsky, M. Bednarz, R. Bhide, Y. Cho, S. Chong, S. Chao, J. Gullo-Brown, P. Guo, S. H. Kim, F. Y. F. Lee, K. Leftheris, A. Miller, T. Mitt, M. Patel, B. A. Penhallow, C. Ricca, W. C. Rose, R. Schmidt, W. A. Slusarchyk, G. Vite and V. Manne, *J. Med. Chem.*, 2000, **43**, 3587; For anti-HIV activities, see: (*b*) K. A. Perker and C. A. Coburn, *J. Org. Chem.*, 1992, **57**, 97; For antifungal agents, see: (*c*) L. Meerpoel, J. V. Gestel, F. V. Gerven, F. Woestenborghs, P. Marichal, V. Sipido, G. Terence, R. Nash, D. Corens and R. D. Richards, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 3453; For inhibitors of hepatitis C virus, see: (*d*) I. Stansfield, C. Ercolani, A. Mackay, I. Conte, M. Pompei, U. Koch, N. Gennari, C. Giuliano, M. Rowley and F. Narjes, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 627; For other activities, see: (*e*) J. Rujirawanich and T. Gallagher, *Org. Lett.*, 2009, **11**, 5494.