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Fe_3O_4/SiO_2 nanoparticles: an efficient and magnetically recoverable nanocatalyst for the one-pot multicomponent synthesis of diazepines

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ABSTRACT

In this research, a new protocol for the one-pot multicomponent synthesis of diazepine derivatives using a 1,2-diamine, a linear or cyclic ketone, and an isocyanide in the presence of a catalytic amount of silica-supported iron oxide (Fe_3O_4/SiO_2) nanoparticles at ambient temperature in excellent yields is described.

1. Introduction

Metal nanoparticles (MNPs), especially supported magnetic metal nanoparticles (S-MMNPs), have emerged as a new class of nanocatalyst. An important feature of these catalysts is simple separation of them using an external magnet without filtration. Furthermore, S-MMNPs catalysts showed not only high catalytic activity but also a high degree of chemical stability in various organic solvents.[1–5]

Iron, the most ubiquitous of the transition metals and the fourth most plentiful element in the Earth's crust, is the structural backbone of our modern infrastructure. Iron however has a great deal to offer at the nanoscale, including very potent magnetic and catalytic properties.[6]

Diazepines[7–9] have been the object of intense investigation in medicinal chemistry, because of their remarkable central nervous system depressant activity, and are now one of the most widely prescribed class of psychotropics.[10] More recently, the area of biological interest of 1,5-benzodiazepines[11–15] have been extended to antibiotics,[16,17] and various diseases, such as cancer,[18] viral infection (HIV),[19–21] and cardiovascular disorders.[22,23] The 1,5-benzodiazepine core is found in compounds active against a variety of target types including peptide hormones (**A**),[24] interleukin converting enzymes (**B**),[25] and potassium blockers (**C**).[23] Two recently published patents indicate that 2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine derivatives carrying carboxamide substituents (**D**) are potentially important as a therapeutic and prophylactic agent for diabetes, diabetic nephropathy or glomerulosclerosis (Fig. 1).[26,27]

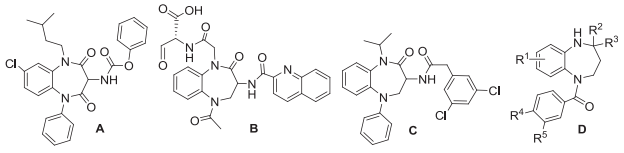

Fig. 1. The structure of some medicinally and biologically important diazepines.

Multicomponent reactions (MCRs) offer significant advantages over conventional linear step syntheses, by reducing time, saving money, energy, and raw-materials, thus resulting in both economical and environmental benefits. On the other side, because of the unique reactivity of the isocyanide functional group, isocyanide-based MCRs (I-MCRs) are among the most versatile, in terms of the number and variety of compounds, which can be generated.[28–30]

In continuing our interest in MCRs,[31–33] in this work, we wish to introduce a new approach for the one-pot multicomponent synthesis of 2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-2-carboxamide derivatives **4a**–**l** and 4,5,6,7-tetrahydro-1*H*-1,4-diazepine-5-carboxamide derivatives **4m**–**o** starting from simple and readily available

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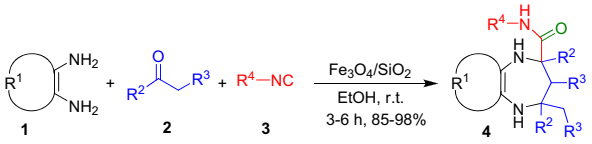
inputs including a 1,2-diamine **1**, a linear or cyclic ketone **2**, and an isocyanide **3** in the presence of a catalytic amount of silica-supported iron oxide (Fe_3O_4/SiO_2) nanoparticles in ethanol at ambient temperature in excellent yields (Scheme 1).



R^1 = CN, Ar-Cl_2, Ar-NO_2 and Ar-COOH
R^2 and R^3 = acetone, cyclohexanone and acetophenone
R^4 = aliphatic, alicyclic and aromatic

Scheme 1. Synthesis of diazepine-2-carboxamide derivatives **4a**–**o** in the presence of Fe_3O_4/SiO_2 nanocatalyst.

To the best of our knowledge, this is the first report of the use of MNPs in I-MCRs, and this new approach opens an important field to the use of economically and environmentally efficient S-MMNPs in heterocyclic synthesis.

2. Results and discussion

S-MMNPs were readily prepared according to the literature procedure,[1–5,34,35] by the addition of water dispersed Fe_3O_4 nanoparticles into a basic solution of tetraethylorthosilicate (TEOS) and stirring overnight. After heating the resulted gel, the magnetic material was isolated by centrifugation and vacuum dried to obtain the S-MMNPs, which were stable under reaction conditions.

The particle size was studied by transmission electron microscope (TEM) and the identification of S-MMNPs were based on the analysis of TEM images. The obtained TEM images of nanoparticles clearly showed a monodispersed spherical shape in which Fe_3O_4 nanoparticles were supported on silica (Fig. 2).

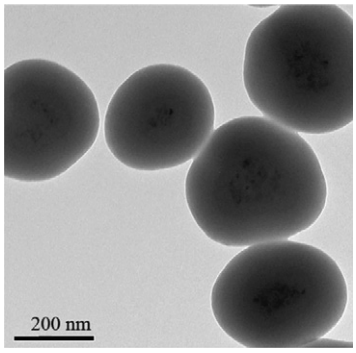


Fig. 2. TEM image of the S-MMNPs.

In order to optimize the reaction conditions, a pilot experiment was carried out using *o*-phenylenediamine and acetone stirred in ethanol at room temperature in the presence of Fe_3O_4/SiO_2 nanocatalyst. The progress of the reaction was monitored by TLC. After 1 h, benzyl isocyanide was added to the reaction mixture and stirring was continued for 4 h. After completion of the reaction, a physical magnetic filtration of the catalyst and after that an aqueous workup afforded compound **4a** in 92% yield.

As can be seen in Table 1, the results showed that the efficiency and the yield of the reaction in EtOH was higher than those obtained in other solvents, such as H_2O, MeOH, CH_3CN, CH_2Cl_2, and toluene, or under solvent-free conditions.

As indicated in Table 2, the reaction of *o*-phenylenediamine, acetone, and benzyl isocyanide was also carried out in the presence of various protic solid acids (Amberlyst-21 and Montmorillonite-K_{10}), liquid acids (HCl, H_2SO_4, and HOAc), Lewis acid ($AlCl_3$), Fe_3O_4, and SiO_2. The best yield was obtained with S-MMNPs. To illustrate the need of S-MMNPs for these reactions, an experiment was conducted in the absence of S-MMNPs (Table 2, entry 8). The yield in this case was trace after 6 h. Obviously, S-MMNPs is an important component of the reaction.

Table 1
Effect of solvent on the model reaction[a]

Entry	Solvent	Time (h)	Yield[b] (%)
1	H_2O	8	57
2	EtOH	5	92
3	MeOH	5	90
4	CH_2Cl_2	10	35
5	Toluene	12	27
6	Solvent-free	12	42

[a] *o*-Phenylenediamine (1 mmol), acetone (2 mmol), and benzyl isocyanide (1 mmol) at room temperature in the presence of S-MMNPs (0.05 mmol).
[b] Isolated yield.

Due to the success of the above reaction, we explored the scope and limitations of this promising reaction by varying the structure of the diamine, ketone, and isocyanide component (Table 3). The reaction proceeds very cleanly under mild conditions at room temperature, and no undesirable side reactions were observed under these reaction conditions.

An important aspect of this reaction was the high purity of the product. All of the products were sufficiently pure after workup, but they were crystallized from acetone to give highly pure crystalline products.

A possible mechanism for the formation of products **4a**–**o** is shown in Scheme 2. It is conceivable that the initial event is the formation of diimine **5** from condensation between *o*-phenylenediamine **1** and 2 mol of ketone **2** in the presence of a catalytic amount of S-MMNPs.[28–30] Then, an intramolecular imine–enamine cyclization of **5** affords seven-membered ring **6**. On the basis of the well-established chemistry of reaction of isocyanides with imines,[28–30] intermediate **7** was produced by nucleophilic attack of isocyanide **3** to iminium **6** followed by nucleophilic attack of a H_2O molecule on the nitrilium moiety and production of compound **8**. Finally, tautomerization of intermediate **8** produces the diazepine-2-carboxamide derivatives **4**.

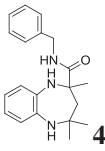
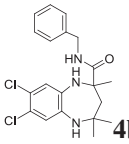
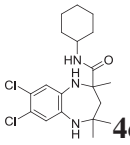
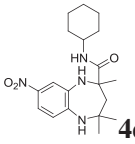
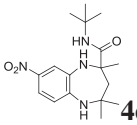
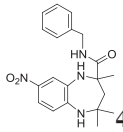
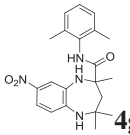
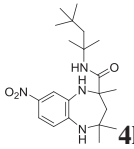
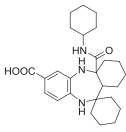
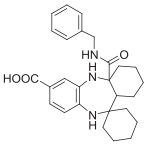
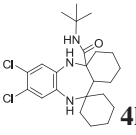
In the case of asymmetric aromatic diamines as the 1,2-diamine component of starting materials, this reaction was highly regioselective. The ^1H NMR and ^{13}C NMR spectra obtained from **4d**–**j** were consistent with the presence of only one isomer. It may be explained that the selectivity is due to the electronic effect of the electron-withdrawing groups, such as NO_2 and COOH, which deactivates the *p*-amino group and the reaction is initiated by the *m*-

Table 2
Monitoring of the catalyst effect on the model reaction[a]

Entry	Catalyst	Time (h)	Yield[b] (%)
1	Amberlyst-21	8	40
2	Montmorillonite-K_{10}	8	34
3	HCl	6	73
4	H_2SO_4	6	55
5	HOAc	7	48
6	$AlCl_3$	6	62
7	S-MMNPs	5	92
8	—	6	Trace
9	Fe_3O_4	6	35
10	SiO_2	6	28

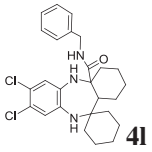
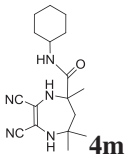
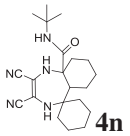
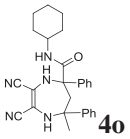
[a] *o*-Phenylenediamine (1 mmol), acetone (2 mmol), and benzyl isocyanide (1 mmol) at room temperature in the presence of 0.05 mmol of nanocatalyst.
[b] Isolated yield.

Table 3
Synthesis of diazepine-2-carboxamides **4a**–**o** in the presence of S-MMNPs

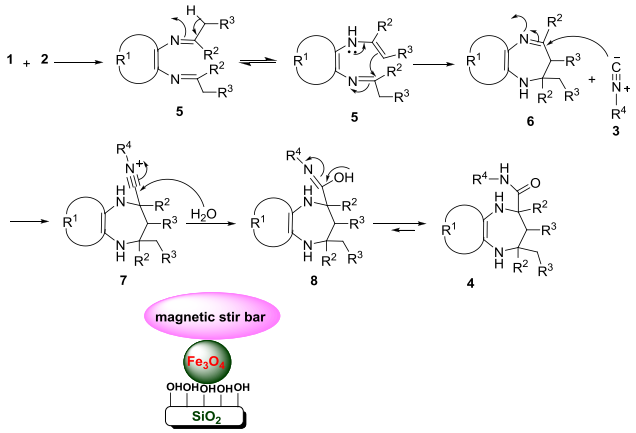
Entry	Diamine	Ketone	Isocyanide	Product	Time (h)	Yield[a] (%)
1	*o*-Phenylenediamine	Acetone	Benzyl	 **4a**	5	92
2	4,5-Dichloro-1,2-phenylenediamine	Acetone	Benzyl	 **4b**	5	97
3	4,5-Dichloro-1,2-phenylenediamine	Acetone	Cyclohexyl	 **4c**	4	85
4	4-Nitro-1,2-phenylenediamine	Acetone	Cyclohexyl	 **4d**	3	98
5	4-Nitro-1,2-phenylenediamine	Acetone	*tert*-Butyl	 **4e**	3	96
6	4-Nitro-1,2-phenylenediamine	Acetone	Benzyl	 **4f**	4	95
7	4-Nitro-1,2-phenylenediamine	Acetone	2,6-Dimethylphenyl	 **4g**	6	86
8	4-Nitro-1,2-phenylenediamine	Acetone	1,1,3,3-Tetramethylbutyl	 **4h**	5	93
9	3,4-Diaminobenzoic acid	Cyclohexanone	Cyclohexyl	 **4i**	5	90
10	3,4-Diaminobenzoic acid	Cyclohexanone	Benzyl	 **4j**	6	86
11	4,5-Dichloro-1,2-phenylenediamine	Cyclohexanone	*tert*-Butyl	 **4k**	4	94

(*continued on next page*)

Table 3 (*continued*)

Entry	Diamine	Ketone	Isocyanide	Product	Time (h)	Yield[a] (%)
12	4,5-Dichloro-1,2-phenylenediamine	Cyclohexanone	Benzyl	 **4l**	4	91
13	2,3-Diaminomaleonitrile	Acetone	Cyclohexyl	 **4m**	3	97
14	2,3-Diaminomaleonitrile	Cyclohexanone	*tert*-Butyl	 **4n**	4	90
15	2,3-Diaminomaleonitrile	Acetophenone	Cyclohexyl	 **4o**	5	87

[a] Isolated yield.



Scheme 2. Possible mechanism for the formation of products **4a**–**o**.

amino group to give iminium ion **6** as favored intermediate (Fig. 3).[11–15]

The catalyst is very active, non-toxic, economically efficient, and environmentally benign. One of the advantages of the heterogeneous catalysts is their ability to perform as a recyclable reaction medium. The S-MMNPs were adsorbed onto the magnetic stirring bar when the magnetic stirring was stopped. The nanoparticles were then washed with EtOH, air-dried, and used directly for the next round of reactions without further purification. It was shown that the S-MMNPs catalyst could be recovered and reused in subsequent reactions several times without considerable loss of catalytic activity (Table 4). Thus, this process could be interesting for large-scale synthesis.

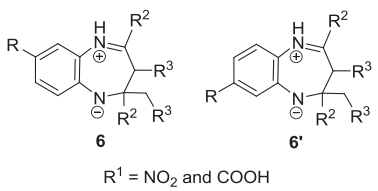


Fig. 3. The structure of intermediates **6** and **6′**.

Table 4
Reusability of Fe_3O_4/SiO_2 nanoparticles for the synthesis of compound **4a**

Run	Yield[a] (%)
1	92
2	91
3	90
4	88
5	90
6	89

[a] Isolated yields of the subsequent runs by using the same recovered catalyst.

3. Conclusion

In summary, we have introduced a new approach for the one-pot multicomponent synthesis of diazepine derivatives starting from simple and readily available precursors including a 1,2-diamine, a linear or cyclic ketone, and an isocyanide using magnetically recoverable Fe_3O_4/SiO_2 nanocatalyst. This new and efficient protocol for the preparation of synthetically, biologically and pharmaceutically relevant diazepine derivatives includes some important aspects like the easy workup procedure, reusability of catalyst, high atom economy, excellent yields, and mild reaction conditions.

4. Experimental

4.1. General

All solvents, chemicals, and reagents were purchased from Merck, Fluka and Sigma–Aldrich international chemical

companies. Melting points were measured on an Electrothermal 9200 apparatus and are uncorrected. Mass spectra were recorded on a Finnigan-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. The ^{1}H NMR spectra were recorded at 300.13 MHz on Bruker DRX-300 Avance spectrometer; chemical shifts (δ scale) are reported in parts per million (ppm). ^{1}H NMR spectra are reported in order: number of protons, multiplicity and approximate coupling constant (J value) in hertz (Hz); signals were characterized as s (singlet), d (doublet), t (triplet), m (multiplet), br s (broad signal), and Ar (aryl). The ^{13}C NMR spectra were recorded at 75.47 MHz; chemical shifts (δ scale) are reported in parts per million (ppm). The elemental analyses were performed with an Elementar Analysensysteme GmbH VarioEL. TEM images were obtained on a Philips EM208.

All of the products were characterized by IR, ^{1}H NMR and ^{13}C NMR spectra and Mass spectral data.

4.2. Preparation of silica-supported Fe_3O_4 nanoparticles (S-MMNPs)

Fe_3O_4 (<50 nm particle size (TEM), ≥98%) (10 mL) in water dispersion was adjusted to pH 11 with NaOH (1 M). Then, TEOS (2.10 mL) was added and the reaction stirred overnight. After that, the resulted gel was heated at 60 °C during 30 min. The magnetic material was isolated by centrifugation (8000 rpm, 15 min) and vacuum dried during 24 h to obtain the S-MMNPs.

4.3. Typical procedure for the synthesis of compound 4a

To a reaction tube charged with a magnetic stir bar and Fe_3O_4/SiO_2 nanoparticles (0.05 mmol, 5 mol %) in ethanol (5 mL), *o*-phenylenediamine (0.108 g, 1 mmol) and acetone (0.116 g, 2 mmol) were added. The tube was then stoppered. The reaction mixture was stirred for 1 h at ambient temperature. After completion of the reaction, as indicated by TLC (ethyl acetate/*n*-hexane, 3/1), benzyl isocyanide (0.117 g, 1 mmol) was added to the reaction mixture. Then, the resulting mixture was stirred for 4 h at ambient temperature. After completion of the reaction, as indicated by TLC (ethyl acetate/*n*-hexane, 4/1), the S-MMNPs catalyst was adsorbed on to the magnetic stirring bar when the stirring was stopped. The S-MMNPs were then washed with EtOH, air-dried, and used directly for the next round of reactions without further purification. After that, the reaction solution was filtered off and the residue was purified by washing further with water, and then crystallized from acetone to give *N*-benzyl-2,4,4-trimethyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepine-2-carboxamide **4a** as yellow crystals (0.297 g, 92%): mp 136–138 °C. IR (KBr) cm^{-1}: 3410, 3382, 3292, 3025, 2936, 2853, 1635, 1545, 1442. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ 1.05 (3H, s, CH_3), 1.08 (3H, s, CH_3), 1.28 (3H, s, CH_3), 1.56 (1H, d, J=14.2 Hz, CH_2), 2.25 (1H, d, J=14.1 Hz, CH_2), 4.12 (1H, br s, NH), 4.26–4.31 (2H, m, CH_2 of benzyl), 4.98 (1H, br s, NH), 6.55–6.75 (4H, m, H–Ar), 7.15–7.25 (5H, m, H–Ar), 7.95 (1H, m, NH–CO). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ 30.1, 30.4, 32.2, 42.9, 48.7, 52.8, 60.2, 119.4, 120.1, 121.6, 127.0, 127.5, 128.6, 138.2, 139.9, 176.4. MS *m*/*z* 323 (M$^+$, 12), 189 (100), 133 (60), 91 (25), 65 (18). Anal. Calcd for $C_{20}H_{25}N_3O$: C, 74.37; H, 7.49; N, 12.53. Found C, 74.42; H, 7.64; N, 12.85.

4.3.1. N-Benzyl-7,8-dichloro-2,4,4-trimethyl-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-2-carboxamide ***4b*** Light yellow crystals; mp 194-197 °C. IR (KBr) cm^{-1}: 3411, 3377, 3338, 3183, 3018, 2971, 2928, 2870, 1647, 1590, 1522, 1426, 1365. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 1.11 (6H, s, $2CH_3$), 1.29 (3H, s, CH_3), 1.58 (1H, br s, CH_2), 2.42 (1H, br s, CH_2), 4.29 (2H, m, CH_2 of benzyl), 4.62 (1H, br s, NH), 5.39 (1H, br s, NH), 6.90-7.15 (7H, m, H-Ar), 7.91 (1H, br s, NH-CO). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 30.2, 30.5, 32.1, 43.0, 48.6, 53.2, 60.5, 119.5, 119.9, 121.3, 127.0, 127.4, 128.5, 137.5, 138.7, 140.0, 175.7. MS *m*/*z*: 393 (M$^+$, ^{37}Cl, 6), 391 (M$^+$, ^{35}Cl, 8), 259 (85), 257 (100), 203 (48), 201 (72), 166 (12), 91 (30), 65 (12), 41 (22). Anal. Calcd for $C_{20}H_{23}Cl_2N_3O$: C, 61.23; H, 5.91; N, 10.71. Found C, 61.35; H, 5.80; N, 10.48.

4.3.2. 7,8-Dichloro-N-cyclohexyl-2,4,4-trimethyl-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-2-carboxamide ***4c***. Pink crystals; mp 169–172 °C. IR (KBr) cm^{-1}: 3378, 3286, 3130, 3018, 2961, 2929, 2852, 1651, 1587, 1513, 1491, 1448, 1366. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 1.04 (3H, s, CH_3), 1.11 (3H, s, CH_3), 1.23 (3H, s, CH_3), 1.00–1.63 (11H, m, $5CH_2$ of cyclohexyl and 1H of CH_2), 2.30 (1H, d, J=14.1 Hz, CH_2), 3.50 (1H, m, CH of cyclohexyl), 4.67 (1H, br s, NH), 5.37 (1H, br s, NH), 6.85 (1H, s, H–Ar), 6.98 (1H, s, H–Ar), 7.04 (1H, d, J=7.1 Hz, NH–CO). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 24.5, 24.6, 25.6, 29.6, 30.2, 32.2, 32.3, 32.4, 47.8, 48.8, 53.0, 60.2, 119.8, 120.3, 121.2, 138.3, 138.7, 174.6. MS *m*/*z*: 385 (M$^+$, ^{37}Cl, 5), 391 (M$^+$, ^{35}Cl, 7), 259 (80), 257 (100), 166 (10), 55 (20), 41 (34). Anal. Calcd for $C_{19}H_{27}Cl_2N_3O$: C, 59.37; H, 7.08; N, 10.93. Found C, 59.50; H, 7.23; N, 10.66.

4.3.3. N-Cyclohexyl-2,4,4-trimethyl-8-nitro-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-2-carboxamide ***4d***. Red crystals; mp 185–187 °C. IR (KBr) cm^{-1}: 3412, 3365, 3320, 3018, 2931, 2847, 1641, 1592, 1531, 1492, 1450, 1318. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 0.99–1.61 (20H, m, $3CH_3$, $5CH_2$ of cyclohexyl and 1H of CH_2), 2.48 (1H, d, J=13.7 Hz, CH_2), 3.50 (1H, m, CH of cyclohexyl), 5.34 (1H, br s, NH), 6.13 (1H, br s, NH), 6.64 (1H, d, J=8.8 Hz, H–Ar), 7.06 (1H, d, J=7.6 Hz, H–Ar), 7.51 (1H, d, J=6.9 Hz, NH–CO), 7.70 (1H, s, H–Ar). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 24.5, 24.7, 25.6, 29.3, 30.8, 32.3, 32.4, 32.9, 47.2, 47.9, 53.6, 60.8, 116.0, 117.2, 118.3, 134.1, 138.1, 147.3, 174.4. MS *m*/*z*: 360 (M$^+$, 5), 234 (100), 218 (12), 178 (50), 132 (45), 55 (20), 41 (30). Anal. Calcd for $C_{19}H_{28}N_4O_3$: C, 63.31; H, 7.83; N, 15.54. Found C, 63.57; H, 7.66; N, 15.28.

4.3.4. N-tert-Butyl-2,4,4-trimethyl-8-nitro-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-2-carboxamide ***4e***. Red crystals; mp 224–226 °C. IR (KBr) cm^{-1}: 3423, 3363, 3331, 3047, 2970, 2929, 2870, 1655, 1592, 1529, 1473, 1450, 1365, 1324. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 1.16 (9H, s, $3CH_3$), 1.24 (9H, s, $3CH_3$), 1.54 (1H, d, J=14.3 Hz, CH_2), 2.48 (1H, d, J=13.8 Hz, CH_2), 5.38 (1H, br s, NH), 6.18 (1H, br s, NH), 6.66 (1H, d, J=8.8 Hz, H–Ar), 6.71 (1H, br s, NH), 7.52 (1H, d, J=8.8 Hz, H–Ar), 7.68 (1H, br s, NH–CO). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 28.6, 29.2, 30.8, 33.0, 47.2, 47.0, 50.4, 53.6, 61.2, 116.0, 117.0, 118.5, 133.8, 137.9, 147.5, 174.7. MS *m*/*z*: 334 (M$^+$, 7), 234 (100), 218 (20), 178 (85), 132 (76), 57 (24), 41 (40). Anal. Calcd for $C_{17}H_{26}N_4O_3$: C, 61.06; H, 7.84; N, 16.75. Found C, 60.82; H, 7.95; N, 16.48.

4.3.5. N-Benzyl-2,4,4-trimethyl-8-nitro-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-2-carboxamide ***4f***. Red crystals; mp 150–152 °C. IR (KBr) cm^{-1}: 3376, 3326, 3271, 3015, 2976, 2929, 2847, 1649, 1590, 1536, 1497, 1474, 1327. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 1.19 (3H, s, CH_3), 1.26 (3H, s, CH_3), 1.34 (3H, s, CH_3), 1.68 (1H, d, J=14.6 Hz, CH_2), 2.52 (1H, d, J=16.5 Hz, CH_2), 4.17–4.64 (2H, AB-system, J_{AB}=11.3 Hz, CH_2 of benzyl), 6.78 (1H, d, J=8.4 Hz, H–Ar), 7.11 (3H, m, H–Ar), 7.20 (3H, m, 2H–Ar and NH), 7.48 (1H, d, J=7.2 Hz, H–Ar), 7.59 (1H, d, J=7.6 Hz, H–Ar), 7.75 (1H, br s, NH–CO), 8.09 (1H, br s, NH). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 29.1, 30.4, 32.5, 40.8, 43.0, 47.0, 54.2, 61.1, 116.5, 118.4, 118.5, 126.0, 127.1, 127.5, 128.5, 128.6, 138.3, 139.3, 139.7, 175.2. MS *m*/*z*: 368 (M$^+$, 3), 234 (100), 205 (30), 178 (30), 132 (35), 106 (55), 91 (40), 77 (26), 63 (24), 55 (25), 41 (70). Anal. Calcd for

$C_{20}H_{24}N_4O_3$: C, 65.20; H, 6.57; N, 15.21. Found C, 65.52; H, 6.74; N, 15.02.

4.3.6. N-(2,6-Dimethylphenyl)-2,4,4-trimethyl-8-nitro-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-2-carboxamide ***4g***. Light red crystals; mp 183–185 °C. IR (KBr) cm^{-1}: 3408, 3318, 3095, 2967, 2924, 2847, 1663, 1619, 1593, 1578, 1525, 1504, 1426, 1370. ^1H NMR (300.13 MHz, DMSO-d_6) δ: 1.25 (3H, s, CH_3), 1.30 (3H, s, CH_3), 1.46 (3H, s, CH_3), 1.73 (1H, d, J=14.1 Hz, CH_2), 1.96 (3H, s, CH_3), 2.04 (3H, s, CH_3), 2.65 (1H, d, J=14.7 Hz, CH_2), 4.46 (1H, br s, NH), 5.19 (1H, br s, NH), 6.74 (1H, d, J=8.5 Hz, H–Ar), 7.00 (3H, m, H–Ar), 7.52 (1H, d, J=7.1 Hz, H–Ar), 7.67 (1H, d, J=8.4 Hz, H–Ar), 8.73 (1H, br s, NH–CO). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 18.3, 18.4, 29.9, 31.8, 32.5, 49.0, 53.6, 61.6, 116.1, 116.6, 118.3, 118.6, 126.6, 128.1, 135.2, 135.7, 135.9, 136.3, 137.9, 146.9, 173.4. MS m/z: 382 (M^+, 1), 365 (5), 349 (5), 309 (45), 293 (100), 247 (70), 234 (60), 178 (42), 132 (30), 103 (14), 77 (32), 57 (15), 41 (22), 39 (24). Anal. Calcd for $C_{21}H_{26}N_4O_3$: C, 65.95; H, 6.85; N, 14.65. Found C, 66.22; H, 6.69; N, 14.52.

4.3.7. 2,4,4-Trimethyl-8-nitro-N-(2,4,4-trimethylpentan-2-yl)-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-2-carboxamide ***4h***. Yellow crystals; mp 175–178 °C. IR (KBr) cm^{-1}: 3431, 3346, 3311, 3018, 2964, 2871, 1645, 1592, 1517, 1499, 1479, 1453, 1366. ^1H NMR (300.13 MHz, DMSO-d_6) δ: 0.89 (9H, s, $3CH_3$), 1.17 (6H, s, $2CH_3$), 1.24 (9H, s, $3CH_3$), 1.29 (1H, d, J=15.3 Hz, CH_2), 1.51 (1H, d, J=14.3 Hz, CH_2), 1.80 (1H, d, J=14.6 Hz, CH_2), 2.53 (1H, d, J=14.4 Hz, CH_2), 5.44 (1H, br s, NH), 6.10 (1H, br s, NH), 6.58 (1H, br s, NH–CO), 6.66 (1H, d, J=8.8 Hz, H–Ar), 7.51 (1H, dd, J=8.7 and 1.3 Hz, H–Ar), 7.69 (1H, d, J=1.9 Hz, H–Ar). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 28.6, 29.0, 29.1, 31.4, 31.6, 32.8, 47.0, 51.5, 53.6, 54.4, 61.3, 115.5, 117.3, 118.1, 134.2, 138.2, 147.0, 174.1. MS m/z: 391 (M^++1, 10), 234 (100), 218 (12), 178 (48), 132 (46), 57 (38), 41 (40). Anal. Calcd for $C_{21}H_{34}N_4O_3$: C, 64.59; H, 8.78; N, 14.35. Found C, 64.82; H, 8.39; N, 14.46.

4.3.8. 4a′-(Cyclohexylcarbamoyl)-1′,2′,3′,4′,4a′,5′,10′,11a′-octahydrospiro[cyclohexane-1,11′-dibenzo[b,e][1,4]diazepine]-7′-carboxylic acid ***4i***. Colorless crystals; mp 213–214 °C. IR (KBr) cm^{-1}: 3415, 3355, 3287, 3082, 2930, 2855, 1682, 1644, 1608, 1514, 1450, 1425, 1357. ^1H NMR (300.13 MHz, DMSO-d_6) δ: 1.00–1.70 (28H, m, $14CH_2$ of cyclohexyls), 2.49 (1H, br s, 1H of CH_2), 3.47 (1H, m, CH of cyclohexyl), 4.45 (1H, br s, NH), 5.19 (1H, br s, NH), 6.21 (1H, d, J=8.0 Hz, H–Ar), 6.72 (1H, d, J=8.0 Hz, H–Ar), 7.07 (1H, d, J=8.0 Hz, H–Ar), 7.70 (1H, br s, NH–CO), 12.10 (1H, br s, COOH). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 21.1, 21.5, 24.1, 24.3, 25.6, 26.4, 31.9, 32.6, 32.8, 37.4, 47.0, 47.8, 57.9, 63.2, 117.6, 120.5, 120.6, 122.2, 138.3, 140.2, 168.2, 176.4. MS m/z: 439 (M^+, 8), 313 (100), 189 (35), 55 (32), 41 (33). Anal. Calcd for $C_{26}H_{37}N_3O_3$: C, 71.04; H, 8.48; N, 9.56. Found C, 70.85; H, 8.63; N, 9.44.

4.3.9. 4a′-(Benzylcarbamoyl)-1′,2′,3′,4′,4a′,5′,10′,11a′-octahydrospiro[cyclohexane-1,11′-dibenzo[b,e][1,4]diazepine]-7′-carboxylic acid ***4j***. Colorless crystals; mp 213–215 °C. IR (KBr) cm^{-1}: 3410, 3363, 3310, 3015, 2931, 2847, 1640, 1590, 1531, 1492, 1455, 1340. ^1H NMR (300.13 MHz, DMSO-d_6) δ: 1.00–2.00 (18H, m, $9CH_2$ of cyclohexyls), 2.41 (1H, br s, CH), 4.09 (1H, d, J=14.3 Hz, 1H of CH_2 of benzyl), 4.28 (1H, d, J=9.2 Hz, 1H of CH_2 of benzyl), 4.42 (1H, br s, NH), 5.08 (1H, br s, NH), 6.75 (1H, d, J=6.9 Hz, H–Ar), 6.90 (2H, m, H–Ar), 7.13 (5H, m, H–Ar), 7.30 (1H, br s, NH–CO), 12.03 (1H, br s, COOH). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 21.1, 21.5, 24.3, 25.6, 26.3, 32.5, 37.7, 43.0, 47.8, 58.1, 63.5, 118.0, 120.3, 120.7, 122.5, 126.9, 127.3, 128.4, 138.5, 139.7, 139.9, 168.2, 177.6. MS m/z: 447 (M^+, 2), 340 (14), 313 (100), 257 (12), 204 (30), 106 (55), 91 (30), 84 (58), 66 (68), 55 (18), 48 (22), 41 (32). Anal. Calcd for $C_{27}H_{33}N_3O_3$: C, 72.46; H, 7.43; N, 9.39. Found C, 72.33; H, 7.65; N, 9.44.

4.3.10. N-tert-Butyl-7′,8′-dichloro-1′,2′,3′,4′,4a′,5′,10′,11a′-octahydrospiro[cyclohexane-1,11′-dibenzo[b,e][1,4]diazepine]-4a′-carboxamide ***4k***. Colorless crystals; mp 168–170 °C. IR (KBr) cm^{-1}: 3435, 3310, 3294, 3059, 2936, 2871, 1638, 1603, 1505, 1456, 1410, 1363. ^1H NMR (300.13 MHz, DMSO-d_6) δ: 1.10 (9H, s, $3CH_3$), 1.18–1.70 (18H, m, $9CH_2$ of cyclohexyls), 2.28 (1H, t, J=7.7 Hz, CH), 4.24 (1H, br s, NH), 5.30 (1H, br s, NH), 6.03 (1H, s, H–Ar), 6.90 (1H, s, H–Ar), 6.99 (1H, s, NH–CO). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 21.1, 21.5, 23.9, 25.6, 26.3, 28.6, 32.9, 37.2, 48.0, 49.9, 57.6, 63.7, 116.7, 118.5, 121.0, 121.4, 136.3, 176.2. MS m/z: 418 (M^+–19, ^{37}Cl, 1), 416 (M^+–19, ^{35}Cl, 2), 338 (20), 336 (24), 295 (30), 293 (52), 240 (45), 213 (100), 200 (82), 172 (40), 107 (32), 77 (32), 65 (46), 55 (26), 41 (77). Anal. Calcd for $C_{23}H_{33}Cl_2N_3O$: C, 63.01; H, 7.59; N, 9.58. Found C, 62.87; H, 7.85; N, 9.45.

4.3.11. N-Benzyl-7′,8′-dichloro-1′,2′,3′,4′,4a′,5′,10′,11a′-octahydrospiro[cyclohexane-1,11′-dibenzo[b,e][1,4]diazepine]-4a′-carboxamide ***4l***. Colorless crystals; mp 193–195 °C. IR (KBr) cm^{-1}: 3392, 3339, 3094, 3029, 2929, 2853, 1623, 1589, 1518, 1492, 1452, 1351. ^1H NMR (300.13 MHz, DMSO-d_6) δ: 1.00–2.00 (18H, m, $9CH_2$ of cyclohexyls), 2.37 (1H, m, CH), 4.06–4.28 (2H, m, CH_2 of benzyl), 4.32 (1H, br s, NH), 5.26 (1H, br s, NH), 6.80 (1H, s, H–Ar), 6.90 (1H, s, H–Ar), 7.18–7.26 (5H, m, H–Ar), 7.95 (1H, br s, NH–CO). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 21.1, 21.5, 24.5, 25.5, 26.4, 32.1, 38.0, 43.0, 48.2, 58.1, 63.6, 116.8, 117.8, 121.5, 121.9, 126.9, 127.4, 128.4, 135.2, 140.2, 177.1. MS m/z: 473 (M^+, ^{37}Cl, 3), 471 (M^+, ^{35}Cl, 5), 364 (3), 337 (100), 213 (30), 91 (38), 55 (20), 41 (25). Anal. Calcd for $C_{26}H_{31}Cl_2N_3O$: C, 66.10; H, 6.61; N, 8.89. Found C, 66.28; H, 6.54; N, 8.54.

4.3.12. 2,3-Dicyano-N-cyclohexyl-5,7,7-trimethyl-4,5,6,7-tetrahydro-1H-1,4-diazepine-5-carboxamide ***4m***. Colorless crystals; mp 169–172 °C. IR (KBr) cm^{-1}: 3414, 3329, 3223, 2934, 2850, 2216, 1650, 1626, 1574, 1512, 1449. ^1H NMR (300.13 MHz, DMSO-d_6) δ: 1.06 (3H, s, CH_3), 1.17 (3H, s, CH_3), 1.22 (3H, s, CH_3), 1.00–1.70 (10H, m, $5CH_2$ of cyclohexyl), 1.56 (1H, d, J=14.3 Hz, CH_2), 2.37 (1H, d, J=14.5 Hz, CH_2), 3.51 (1H, m, C*H* of cyclohexyl), 5.56 (1H, br s, N*H*), 5.83 (1H, br s, N*H*), 7.27 (1H, d, J=7.6 Hz, N*H*–CO). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 24.3, 25.1, 25.2, 25.7, 29.5, 32.1, 32.2, 32.8, 48.6, 54.6, 61.9, 110.1, 110.4, 117.5, 117.6, 173.5. MS m/z: 315 (M^+, 5), 258 (2), 242 (4), 189 (100), 160 (20), 133 (64), 56 (30), 43 (70). Anal. Calcd for $C_{17}H_{25}N_5O$: C, 64.73; H, 7.99; N, 22.20; found C, 64.85; H, 8.10; N, 22.09.

4.3.13. N-tert-Butyl-2,3-dicyano-1,4,5a,6,7,8,9,9a-octahydrospiro[benzo[e][1,4]diazepine-5,1′-cyclohexane]-9a-carboxamide ***4n***. White crystals; mp 170–173 °C. IR (KBr) cm^{-1}: 3380, 3292, 2934, 2855, 2220, 2203, 1635, 1617, 1544, 1448. ^1H NMR (300.13 MHz, DMSO-d_6) δ: 1.00–2.00 (27H, m, $9CH_2$ of cyclohexyls and 9H of $C(CH_3)_3$), 2.20–2.30 (1H, m, CH of cyclohexyl), 4.66 (1H, m, N*H*), 5.89 (1H, m, N*H*), 6.98 (1H, br s, N*H*–CO). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 21.1, 21.5, 23.9, 25.2, 26.0, 28.5, 32.3, 38.3, 47.9, 48.5, 59.6, 65.2, 106.1, 113.6, 117.3, 118.1, 173.2. MS m/z: 369 (M^+, 35), 298 (25), 268 (100), 208 (20), 98 (22), 81 (14), 67 (40), 55 (60), 41 (50). Anal. Calcd for $C_{21}H_{31}N_5O$: C, 68.26; H, 8.46; N, 18.95; found C, 68.22; H, 8.40; N, 19.01.

4.3.14. 2,3-Dicyano-N-cyclohexyl-7-methyl-5,7-diphenyl-4,5,6,7-tetrahydro-1H-1,4-diazepine-5-carboxamide ***4o***. Light yellow crystals; mp 221–222 °C. IR (KBr) cm^{-1}: 3350, 3258, 3054, 2929, 2859, 2217, 1570, 1543, 1513, 1451. ^1H NMR (300.13 MHz, DMSO-d_6) δ: 1.10–2.00 (10H, m, $5CH_2$ of cyclohexyl), 2.25 (3H, s, CH_3), 2.90 (1H, d, J=14.6 Hz, CH_2), 3.85 (1H, m, CH of cyclohexyl), 4.07 (1H, d,

J=14.5 Hz, CH_2), 6.94–7.58 (10H, m, H–Ar), 7.34 (1H, d, J=7.6 Hz, N*H*–CO), 7.96 (1H, br s, N*H*), 9.06 (1H, br s, N*H*). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 20.8, 21.3, 25.2, 31.8, 32.1, 46.6, 50.7, 55.4, 66.2, 104.2, 110.3, 118.0, 120.5, 121.1, 125.0, 125.1, 127.5, 129.1, 129.2, 129.5, 136.5, 137.5, 139.9, 140.6, 142.7, 166.5. MS m/z: 341 (M^+–98, 2), 333 (32), 318 (54), 313 (26), 272 (10), 236 (100), 209 (30), 132 (84), 105 (82), 98 (5), 91 (75), 77 (24), 65 (40), 55 (65), 43 (80). Anal. Calcd for $C_{27}H_{29}N_5O$: C, 73.78; H, 6.65; N, 15.93; found C, 73.80; H, 6.75; N, 15.82.

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