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# One-pot multicomponent synthesis of diazepine derivatives using terminal alkynes in the presence of silica-supported superparamagnetic iron oxide nanoparticles

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ABSTRACT

A new, efficient, one-pot multicomponent reaction for the synthesis of diazepine derivatives in excellent yields is described. The reactions of various 1,2-diamines, terminal alkynes, and an isocyanide take place in the presence of a catalytic amount of magnetically recoverable silica-supported superparamagnetic $Fe_3O_4$ nanoparticles in ethanol (as a green reaction medium) at ambient temperature.



Multicomponent reactions (MCRs) and sequential transformations offer significant advantages over conventional linear-step syntheses, by reducing time, and saving money, energy, and raw-materials, thus resulting in both economic and environmental benefits. Due to the unique reactivity of the isocyanide functional group, isocyanide-based MCRs (IMCRs) are among the most versatile in terms of the number and variety of compounds which can be generated.[1–3]

As a consequence of the advantages of monodispersed and size-controllable nanoscale magnetic materials, such as core/shell nanoparticles, highly functional materials with modified properties, techniques, and procedures for their production have advanced considerably. They have provided many exciting opportunities which have led to an active exploration of magnetic nanoparticles in a wide range of nanotechnology applications, in material chemistry and many other fields, such as electronics, biomedical, pharmaceutical, optics, and catalysis.[4]

Nanomaterials, especially metal nanoparticles (MNPs) and supported magnetic metal nanoparticles (S-MMNPs) have emerged as new classes of nanocatalysts. Some important features of these catalysts are simple separation using an external magnet without the need for filtration, high catalytic activity, and a high degree of chemical stability in various organic solvents.[5–8] Iron has a great deal to offer on the nanoscale, including very potent catalytic properties.[9]

Biological interest in diazepines has been extended to antibiotics,[10,11] cancer,[12] viral infection (HIV),[13–15] and cardiovascular disorders.[16,17] Figure 1 shows the structures of the commercial diazepine-core drugs diazepam (**1**), clobazam (**2**), and triflubazam (**3**). The 1,5-benzodiazepine core is found in compounds active against a variety of target types including peptide hormones (**4**),[18] interleukin-converting enzymes (**5**),[19] and potassium blockers (**6**).[17] Tetrahydro-1*H*-1,5-benzodiazepine derivatives with carboxamide substituents (**7**) are potentially important as therapeutic and prophylactic agents for diabetes, diabetic nephropathy, or glomerulosclerosis.[20,21]

In addition, diazepines are especially useful synthons for the rapid construction of heterocyclic systems due to the presence of a possible electrophilic C=N site. This structural feature could allow the diversity-oriented synthesis[22] of small libraries of diazepine-based compounds for pharmacological testing toward a wide range of biological targets.[23]

In the literature, the syntheses of diazepine derivatives are reported using variations of reagents and catalysts such as the condensation reaction of a 1,2-diamine with various ketones in the presence of ceric ammonium nitrate (CAN),[24] $Yb(OTf)_3$,[25] $Sc(OTf)_3$,[26] $SiO_2/ZnCl_2$,[27] and silica sulfuric acid,[28] with alkynoates in the presence of $Ga(OTf)_3$,[29] and also with terminal alkynes in the presence of $Hg(OTf)_2$.[30] In addition, examples of metal-free mild syntheses of diazepines have been disclosed in the literature.[31]

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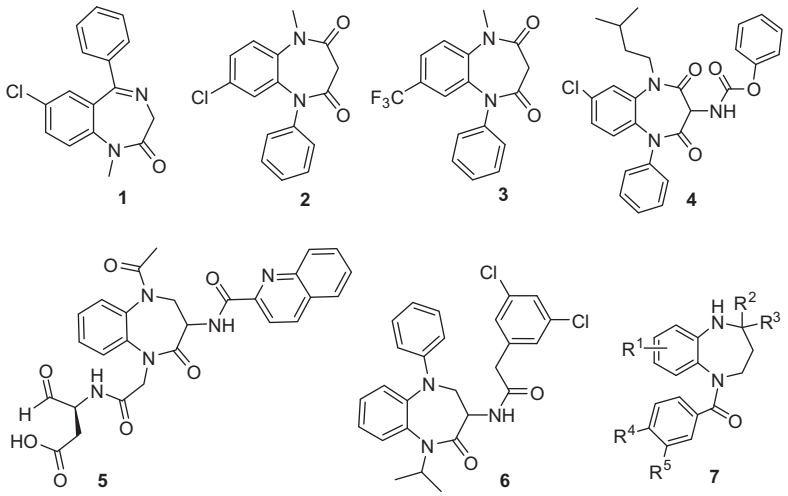


**Figure 1.** Some examples of medicinally and biologically important diazepine derivatives.

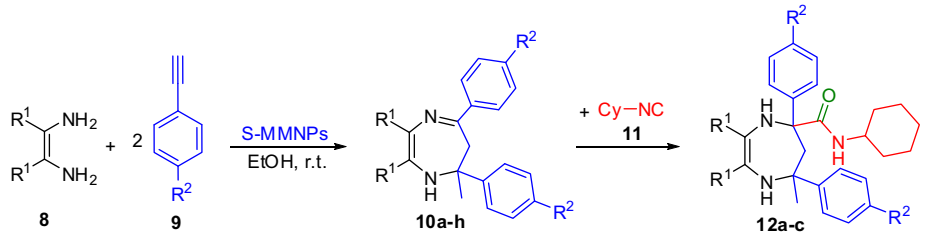
Due to the importance of the introduction of new, efficient, and inexpensive methods for chemical transformations, and also in continuation of our research on MCRs,[32–34] herein, a new approach for the one-pot multicomponent synthesis of diazepine derivatives **10a–h** and diazepine carboxamide derivatives **12a–c**, starting from simple and readily available substrates including 1,2-diamines **8**, terminal alkynes **9**, and isocyanide **11**, in the presence of a catalytic amount of silica-supported iron oxide ($Fe_3O_4/SiO_2$) nanoparticles (S-MMNPs) is reported. The reaction takes place in ethanol as a green reaction medium at ambient temperature (Scheme 1).

This method represents a useful extension of our previous work (Scheme 2),[32–34] where a carbonyl input, such as a cyclic or acyclic ketone, is replaced by a terminal alkyne.

To the best of our knowledge, this is the first synthesis of diazepines and diazepine carboxamides using terminal alkynes catalyzed by superparamagnetic MNPs via IMCRs. This new approach opens an important field involving the use of economically and environmentally efficient nanoscale magnetic materials in organic synthesis.

S-MMNPs were readily prepared according to the literature procedure,[4–8,34–36] by the addition of water-dispersed $Fe_3O_4$ nanoparticles into a basic solution of tetraethylorthosilicate (TEOS) and stirring overnight. Next, the resulting gel was heated for 30 min at 60 °C and the magnetic material was isolated by centrifugation, and dried under vacuum to give the S-MMNPs, which were stable under the employed reaction conditions.

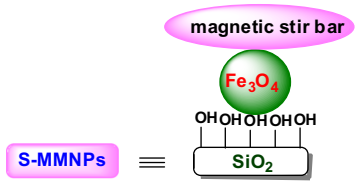
The particle size was studied by transmission electron microscopy (TEM) and the identification of the S-MMNPs was based on the analysis of TEM images. The obtained TEM images showed clearly monodispersed spherical-shaped nanoparticles in which the $Fe_3O_4$ nanoparticles were supported on silica (Fig.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



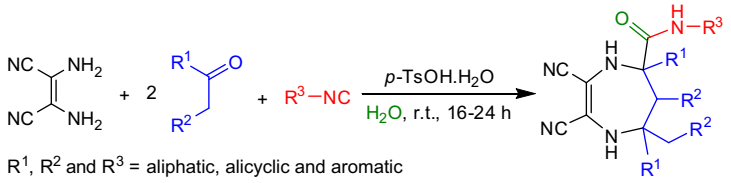

| Product | $R^1$ | $R^2$ | Time (h) | Yield (%) |
|---|---|---|---|---|
| **10a** | CN | H | 4 | 94 |
| **10b** | CN | $CH_3$ | 5 | 95 |
| **10c** | CN | Br | 5 | 90 |
| **10d** |  | H | 4 | 92 |
| **10e** |  | H | 8 | 85 (95:5)[a] |
| **10f** |  | H | 6 | 89 |
| **10g** |  | $CH_3$ | 8 | 82 (88:12)[a] |
| **10h** |  | H | 10 | 70 (96:4)[a] |

| Product | $R^1$ | $R^2$ | Time (h) | Yield (%) |
|---|---|---|---|---|
| **12a** | CN | H | 6 | 90 |
| **12b** | CN | $CH_3$ | 7 | 92 |
| **12c** | CN | Br | 7 | 83 |

[a] The regioisomeric ratio.




**Scheme 1.** Synthesis of diazepines **10a–h** and diazepine carboxamides **12a–c** in the presence of the supported $Fe_3O_4/SiO_2$ nanocatalyst.




**Scheme 2.** Our earlier work.[32]

A pilot experiment was carried out using 2,3-diaminomaleonitrile and phenyl acetylene via stirring in ethanol at room temperature in the presence of the $Fe_3O_4/SiO_2$ nanocatalyst. The progress of the reaction was monitored by TLC. After completion of the reaction (4 h), the S-MMNP catalyst became attached to the magnetic stir bar when the stirring was stopped. Then, the reaction solution was filtered and the residue was purified by washing with water, and then crystallization from ethanol to give product **10a**.

Due to the reactivity of the imine site of product **10**, a further reaction could be performed in the same reaction pot. In this step, cyclohexyl isocyanide was added to the reaction mixture and stirring was continued. After completion of the reaction, removal of

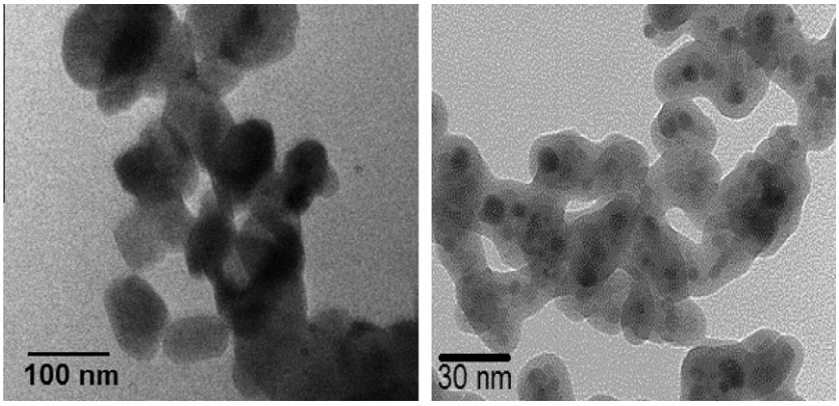
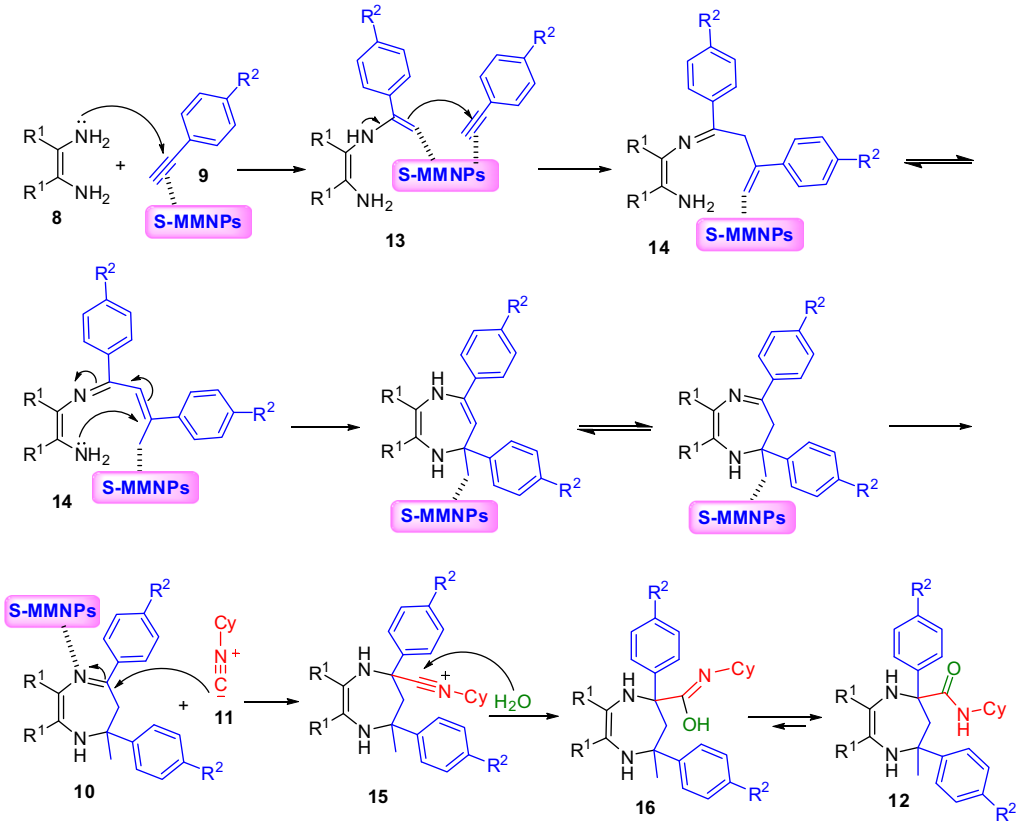



**Figure 2.** TEM images of silica-supported $Fe_3O_4$ (S-MMNPs) at two magnifications.




**Scheme 3.** Possible mechanism for the formation of products **10a–h** and **12a–c**.

the catalyst (using a magnet) and subsequent aqueous work-up afforded compounds **12a–c** in good to excellent yields. The S-MMNP catalyst was washed with EtOH, air-dried, and used directly in following reactions without further purification.

In the absence of S-MMNPs, only a trace of the desired product was obtained after 24 h.

As indicated in Scheme 1, we explored the scope and limitations of this reaction by varying the structure of the diamine **8** and phenyl acetylene **9** components. The reactions proceeded very cleanly under mild conditions at room temperature, and no undesirable side reactions were observed.

In the case of unsymmetrical substituted diamines, inseparable regioisomeric mixtures of **10e**, **10g,** and **10h** were obtained. The approximate regioisomeric ratios in each case are indicated in Scheme 1. At present, the structures of the major and minor isomers of **10e**, **10g,** and **10h** have not been assigned.

All the products were characterized from $^{1}H$, $^{13}C$ NMR, and IR spectral data and elemental analysis, and in some cases, by comparison of the melting points with those of authentic samples.

The catalyst is very active, nontoxic, economically efficient, and environmentally benign. One of the advantages of heterogeneous catalysts is their recyclability. It was shown that the S-MMNP catalyst could be recovered and reused in subsequent reactions, several times, and without considerable loss of the catalytic activity (Scheme 1, product **12a**: yields of the five runs using the same recovered catalyst were 88, 86, 89, 87, and 85%, respectively). Thus, this process could be interesting for large-scale synthesis.

A possible mechanism for the formation of products **10a–h** and **12a–c** is shown in Scheme 3. It is conceivable, that the initial event is the formation of complex **13** via condensation between 1,2-diamine **8** and phenyl acetylene **9** (as a keto-methyl equivalent) in the presence of a catalytic amount of S-MMNPs.[30] Next, imine–enamine tautomerization and intramolecular cyclization of **14** via a 1,4- or a Michael addition affords seven-membered diazepines **10a–h**. On the basis of the well-established chemistry of the reactions of isocyanides with imines,[1–3,32–34] intermediate **15** was produced by nucleophilic attack of isocyanide **11** on imine **10** followed by nucleophilic attack of an $H_2O$ molecule on the nitrilium moiety and production of compound **16**. Finally, tautomerization of **16** produces the diazepine carboxamide derivatives **12a–c**.

In conclusion, we have introduced a new, one-pot multicomponent synthesis of diazepine and diazepine carboxamide derivatives starting from simple and readily available precursors including various 1,2-diamines, terminal alkynes, and an isocyanide in the presence of a catalytic amount of a magnetically recoverable $Fe_3O_4/SiO_2$ nanocatalyst. This efficient protocol for the preparation of synthetically, biologically, and pharmaceutically relevant diazepine derivatives includes some important aspects such as the easy work-up procedure, reusability of the catalyst, high atom economy, excellent yields, and mild reaction conditions.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.01.123. These data include MOL files and InChiKeys of the most important compounds described in this article.

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36. *Preparation of silica-supported $Fe_3O_4$ nanoparticles (S-MMNPs):* $Fe_3O_4$ [<50 nm particle size (TEM), ⩾98%] (10 mL) as a $H_2O$ dispersion was adjusted to pH 11 with NaOH (1 M). Then, 2.10 mL of TEOS was added and the mixture was stirred overnight. The resulting gel was heated at 60 °C over 30 min. The magnetic material was isolated by centrifugation (8000 rpm, 15 min) and dried under vacuum over 24 h to obtain the S-MMNPs.
*General procedure for the synthesis of compounds **10a–h**:* To a reaction tube containing a magnetic stir bar and $Fe_3O_4/SiO_2$ nanoparticles (5 mol %) in 5 mL of EtOH, 1,2-diamine **8** (1 mmol) and a terminal alkyne **9** (2 mmol) were added. The reaction mixture was stirred at ambient temperature for the appropriate time. After completion of the reaction, as indicated by TLC (EtOAc/*n*-hexane, 3/1), stirring was stopped and the S-MMNP catalyst became attached to the magnetic stir bar. The S-MMNPs were then washed with EtOH, air-dried, and used directly for subsequent reactions without further purification. The reaction solution was filtered and the residue purified by washing with $H_2O$, and then crystallized from EtOH to give products **10a–h**.
*Typical procedure for the synthesis of compound **12a**:* To a reaction tube containing a magnetic stir bar and $Fe_3O_4/SiO_2$ nanoparticles (5 mol %) in 5 mL of EtOH, 2,3-diaminomaleonitrile (0.108 g, 1 mmol) and phenyl acetylene (0.205 g, 2 mmol) were added. The mixture was stirred for 4 h at ambient temperature. After completion of the reaction, as indicated by TLC (EtOAc/*n*-hexane, 3/1), cyclohexyl isocyanide (0.109 g, 1 mmol) was added. The resulting mixture was stirred for 6 h at ambient temperature. After completion of the reaction, as indicated by TLC (EtOAc/*n*-hexane, 4/1), stirring was stopped and

the S-MMNP catalyst became attached to the magnetic stir bar. The S-MMNPs were then washed with EtOH, air-dried, and used directly for subsequent reactions without further purification. The reaction solution was filtered and the residue purified by washing with $H_2O$, and then crystallized from acetone to give product **12a**.

*Spectral data for selected products:*

Compound **10d**: Light yellow crystals; mp 150–151 °C; IR (KBr) $cm^{-1}$: 3332, 1637, 1598, 1426. $^1H$ NMR (300 MHz, $CDCl_3$), $\delta$: 1.70 (3H, s, $CH_3$), 2.95 (1H, d, $J$ = 13.2 Hz, $CH_2$), 3.15 (1H, d, $J$ = 13.2 Hz, $CH_2$), 3.35 (1H, br s, NH), 6.65–7.10 (2H, m, $C_6H_4$), 7.25–7.48 (10H, m, $C_6H_5$), 7.55–7.68 (2H, m, $C_6H_4$). $^{13}C$ NMR (75 MHz, $CDCl_3$), $\delta$: 29.7, 41.4, 74.3, 121.6, 122.0, 125.4, 126.7, 127.3, 127.4, 128.3, 128.5, 128.8, 129.6, 138.1, 139.2, 140.6, 145.3, 166.3. Anal. Calcd for $C_{22}H_{20}N_2$: C, 84.58; H, 6.45; N, 8.97; Found; C, 84.62; H, 6.40; N, 8.86. **10e**: Light yellow crystals; mp 123–124 °C; IR (KBr) $cm^{-1}$: 3340, 1620, 1585, 1436. $^1H$ NMR (300 MHz, $CDCl_3$), $\delta$ (major regioisomer): 1.76 (3H, s, $CH_3$), 2.96 (1H, d, $J$ = 13.2 Hz, $CH_2$), 3.18 (1H, d, $J$ = 13.2 Hz, $CH_2$), 3.45 (1H, br s, NH), 3.77 (3H, s, $OCH_3$), 6.35 (1H, d, $J$ = 1.9 Hz, $C_6H_3$), 6.62 (1H, dd, $J$ = 8.0, 1.9 Hz, $C_6H_3$), 7.10–7.63 (11H, m, $C_6H_3$ and $2C_6H_5$). $^{13}C$ NMR (75 MHz, $CDCl_3$), $\delta$ (major regioisomer): 29.5, 42.3, 54.4, 74.2, 104.8, 109.4, 123.6, 126.5, 127.2, 127.6, 128.1, 128.5, 128.8, 129.6, 137.3, 145.3, 146.3, 161.2, 165.3. Anal. Calcd for $C_{23}H_{22}N_2O$: C, 80.67; H, 6.48; N, 8.18; Found: C, 80.54; H, 6.42; N, 8.21. Compound **10f**: Light yellow crystals; mp 115–116 °C; IR (KBr) $cm^{-1}$: 3290, 1615, 1548, 1442, 1360. $^1H$ NMR (300 MHz, $CDCl_3$), $\delta$: 1.70 (3H, s, $CH_3$), 2.24 (6H, s, $2CH_3$), 2.95 (1H, d, $J$ = 13.2 Hz, $CH_2$), 3.12 (1H, d, $J$ = 13.2 Hz, $CH_2$), 3.38 (1H, br s, NH), 6.60 (1H, s, $C_6H_2$), 7.10 (1H, s, $C_6H_2$), 7.15–7.61 (10H, m, $C_6H_5$). $^{13}C$ NMR (75 MHz, $CDCl_3$), $\delta$: 18.6, 19.3, 29.6, 43.1, 75.1, 122.3, 125.4, 126.8, 126.9, 127.8, 128.2, 129.5, 129.6, 129.7, 134.8, 135.8, 137.7, 139.8, 147.7, 166.8. Anal. Calcd for $C_{24}H_{24}N_2$: C, 84.67; H, 7.11; N, 8.23; Found: C, 84.63; H, 7.06; N, 8.32. **12a**: Yellow crystals; mp 221–223 °C. IR (KBr) $cm^{-1}$: 3352, 3256, 3054, 2927, 2859, 2217, 1570, 1543, 1513, 1451. $^1H$ NMR (300 MHz, DMSO-$d_6$) $\delta$: 1.00–2.00 (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 MHz, DMSO-$d_6$) $\delta$: 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. Anal. Calcd for $C_{27}H_{29}N_5O$: C, 73.78; H, 6.65; N, 15.93; Found: C, 73.81; H, 6.72; N, 15.85. Compound **12b**: Yellow crystals; mp 210–212 °C. IR (KBr) $cm^{-1}$: 3352, 3255, 3053, 2927, 2857, 2218, 1578, 1542, 1513, 1454. $^1H$ NMR (300 MHz, DMSO-$d_6$) $\delta$: 1.10–2.00 (10H, m, $5CH_2$ of cyclohexyl), 1.66 (3H, s, $CH_3$), 2.12 (3H, s, $CH_3$), 2.26 (3H, s, $CH_3$), 2.89 (1H, d, $J$ = 14.4 Hz, $CH_2$), 3.86 (1H, m, CH of cyclohexyl), 4.07 (1H, d, $J$ = 14.3 Hz, $CH_2$), 6.90–7.60 (8H, m, H-Ar), 7.56 (1H, d, $J$ = 7.2 Hz, N*H*–CO), 7.96 (1H, br s, N*H*), 9.07 (1H, br s, N*H*). $^{13}C$ NMR (75 MHz, DMSO-$d_6$) $\delta$: 20.8, 21.0, 21.3, 25.3, 25.4, 31.6, 31.8, 32.1, 46.6, 50.7, 55.4, 66.2, 104.2, 110.3, 115.5, 120.5, 121.1, 125.1, 127.5, 128.9, 129.1, 129.2, 129.5, 129.7, 136.5, 137.5, 140.6, 142.7, 153.5, 166.5. Anal. Calcd for $C_{29}H_{33}N_5O$: C, 74.49; H, 7.11; N, 14.98; Found: C, 74.55; H, 7.28; N, 14.80. Compound **12c**: Yellow crystals; mp 202–205 °C. IR (KBr) $cm^{-1}$: 3350, 3250, 3063, 2929, 2859, 2223, 1550, 1544, 1485, 1453. $^1H$ NMR (300 MHz, DMSO-$d_6$) $\delta$: 0.83–2.07 (10H, m, $5CH_2$ of cyclohexyl), 1.70 (3H, s, $CH_3$), 2.90 (1H, d, $J$ = 14.3 Hz, $CH_2$), 3.84 (1H, m, CH of cyclohexyl), 4.12 (1H, d, $J$ = 14.0 Hz, $CH_2$), 7.07–8.04 (10H, m, 8H-Ar, N*H*–CO and N*H*), 9.23 (1H, br s, N*H*). $^{13}C$ NMR (75 MHz, DMSO-$d_6$) $\delta$: 25.2, 25.6, 25.7, 31.2, 31.8, 32.1, 46.3, 50.8, 55.4, 66.9, 104.2, 111.9, 115.3, 120.1, 120.7, 121.5, 124.7, 127.5, 127.6, 129.4, 131.4, 131.6, 132.0, 138.0, 142.4, 144.7, 165.6. Anal. Calcd for $C_{27}H_{27}Br_2N_5O$: C, 54.29; H, 4.56; N, 11.72; Found: C, 54.35; H, 4.40; N, 11.84.