Synthesis of new 3-phenyl substituted dibenzo-1,4-diazepin-1-one derivatives

Fang-Ming Wang[a]*, Dan Bao[a], Ming Wang[a], Ming-Jun Li[a], Li-Zhuang Chen[a] and Guang-Fan Han[a,b]

[a]*School of Environmental and Chemical Engineering, Jiangsu University of Science and Technology, Zhenjiang, Jiangsu 212003, P.R. China*

[b]*Department of Chemical Engineering, Zhen Jiang College, Zhenjiang, Jiangsu 212003, P.R. China*

A new series of 3-phenyl substituted dibenzo-1,4-diazepin-1-one derivatives were synthesised by condensation of 5-phenylcyclohexane-1,3-dione, *o*-phenylenediamine and benzaldehydes. All the compounds were characterised by IR, MS, ^{1}H NMR and elemental analysis. The crystal structure of 3-phenyl-11-(2-chlorophenyl)-2,3,4,5,10,11-hexahydro-1H-dibenzo[b,e][1,4]diazepin-1-one was determined by X-ray single-crystal diffraction.

Keywords: 3-phenyldibenzo-1,4-diazepin-1-one, 5-phenylcyclohexane-1,3-dione, condensation, crystal structure

Benzodiazepines are well-known nitrogen heterocyclic compounds. They have wide range of therapeutic and pharmacological properties, and are used as anticonvulsant, antianxiety, analgesic, sedative, antidepressive, hypnotic agents, anti-inflammatory agents, *etc*.[1–3]

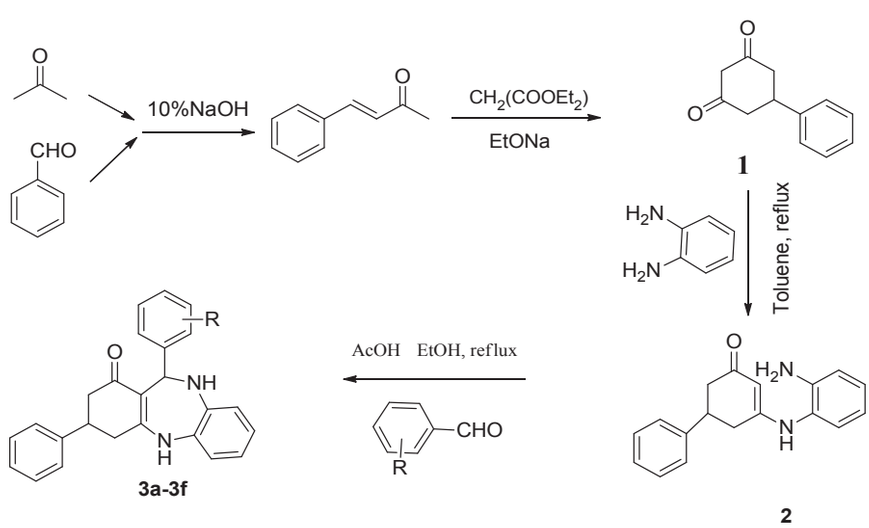
Research on the synthesis of benzodiazepines mainly focuses on two directions. One direction focuses on fusing benzodiazepines with other heterocyclic systems, such as pyrrolo, triazole, oxazino, or furanobenzodiazepines.[4–7] They have exhibited anxiolytic activities,[8] and serve as cholecystokinin A and B antagonists,[9] platelet-activating factor antagonists,[10] anticancer agents.[11] The other direction focuses on the preparation of benzodiazepine derivatives, which includes catalysis,[12–16] solid state reaction,[17] and microwave irradiation.[18,19]

We now report a new series of 3-phenyl substituted dibenzo-1,4-diazepin-1-one derivatives. They were synthesised by condensation of 5-phenyl-1,3-cyclohexane-dione, *o*-phenylenediamine and benzaldehydes (Scheme 1). The crystal structure of **3a** was determined by X-ray single-crystal diffraction.

Results and discussion

As shown in Scheme 1, 5-phenylcyclohexane-1,3-dione was obtained from benzaldehyde, acetone and diethyl malonate as the reference.[20] 5-Phenylcyclohexane-1,3-dione was mixed with *o*-phenylenediamine in toluene and refluxed for 8 hours to prepare the intermediate enamine **2** with high yield. 3-Phenyldibenzo-1,4-diazepin-1-one derivatives, were obtained by condensation of **2** with different benzaldehydes, using acetic acid as the catalyst in ethanol. The data show that the reaction proceeded smoothly to afford the corresponding products in good yields.

The MS, IR, ^{1}H NMR and elemental analysis shown in the experimental section, confirmed the structures of the compounds. The broad peak at δ 4.92 of **2** was attributed to the two proton shifts of the NH_2 group, while the single peak at δ 8.35 was attributed to the imino group –NH– in its ^{1}H NMR spectrum. The 3-phenyldibenzo-1,4-diazepin-1-one derivatives showed broad absorption bands at 3316–3332 cm^{-1}, typical absorptions of an imino group, and the absorption bands at 1592–1638 cm^{-1} were the absorptions of a carbonyl group (C=O), in the IR spectrum. In their ^{1}H NMR spectrum, the



a: R=2-Cl; b: R=4-Cl; c: R=4-OCH_3; d: R=3-OCH_3, 4-OCH_3; e: R=C_4H_4; f: R=H

Scheme 1 Synthesis of 3-phenyldibenzo-1,4-diazepin-1-ones.

* Correspondent. E-mail: wangfmzj@just.edu.cn

broad single peak at δ 8.77–9.10, was attributed to the proton shifts of the imino group at the 5-position. The broad peak at δ 5.96–6.29 split into two peaks due to the 10-imino group. In the ESI-MS spectrum, the ion adducts were usually observed as the primary fragment peaks of the title compounds.

The two chiral carbon atoms C3 and C11, indicate that isomers will exist. When we used the column chromatography to purify the crude products of **3b**, **3c** and **3f**, we obtained two isomers, **3b-1**, **3b-2**, **3c-1**, **3c-2**, **3f-1** and **3f-2**, which were confirmed by MS and ^{1}H NMR spectroscopy. With compounds **3a**, **3d** and **3e**, we obtained only one structure. The single crystal structure of **3a** was determined by X-ray diffraction analysis. The ORTEP and packing diagrams are shown in Figs 1 and 2. Figure 1 shows that the diazepine 7-member rings of **3a** have a nearly half-boat conformation. Also, the two chiral atoms C3 and C11 in **3a** existed in *S*- and *R*-configurations, similarly. It meant that the (3*S*,11*R*)-configuration of the compound was its present conformations.

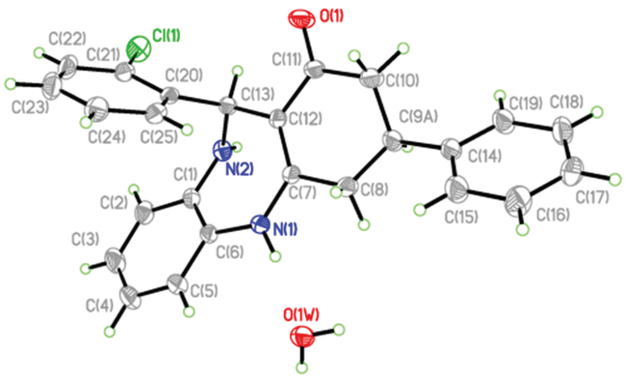


Fig. 1 ORTEP representation of compound **3a** showing 30% probability ellipsoids.

Conclusion

In summary, we have successfully synthesised a new series of 3-phenyl substituted 2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b*,*e*][1,4]diazepin-1-one derivatives by the condensation reaction. All the compounds were characterised and confirmed. Moreover, the crystal structure of **3a** was determined by X-ray single-crystal diffraction. We believe that it will be very useful to study the relationship between their biological activities and structures in the future.

Experimental

The 5-phenyl-l, 3-cyclohexanedione **1** was synthesised as described in the literature.[20] Other chemicals were of analytical reagent grade and purchased from commercial sources, which were used directly without further purification. Melting points were determined on a capillary tube method and the temperature was not calibrated. IR spectra were recorded as thin films on KBr using a Digilab FTS 2000 spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker AVANCE III 500 spectrometer. Element analysis was determined by Elementar Vario EL III analysers. The electrospray ionisation mass spectrometry (ESI-MS) were determined on an Aglient-6100 equipment.

Synthesis of intermediate **2**

A mixture of 5-phenyl-,3-cyclohexanedione **1** (5 mmol) and *o*-phenylenediamine (5 mmol) were dissolved in toluene and refluxed for 8 h. When the reaction was complete, it was cooled to room temperature. The yellowish solid product **2** was collected by filtration and purified by recrystallisation from 95% ethanol.

Synthesis of 3-phenyl-dibenzo[b,e][1,4]diazepin-1-ones **3***; general procedure*

The intermediate **2** (5 mmol), benzaldehyde (5 mmol) were mixed in ethanol (25 mL), refluxed for 3–4 h and catalysed by acetic acid (2.5 mL). After cooling, the solvent were dried by rotavaporation to obtain a pale-yellowish solid. The crude products were purified by column chromatography (ethyl acetate/cyclohexane=2 : 1) to afford the title compounds. After purifying the crude products **3b**, **3c** and **3f**, two very close isomer compounds, **3b-1**, **3b-2**, **3c-1**, **3c-2**, **3f-1**and **3f-2** were obtained.

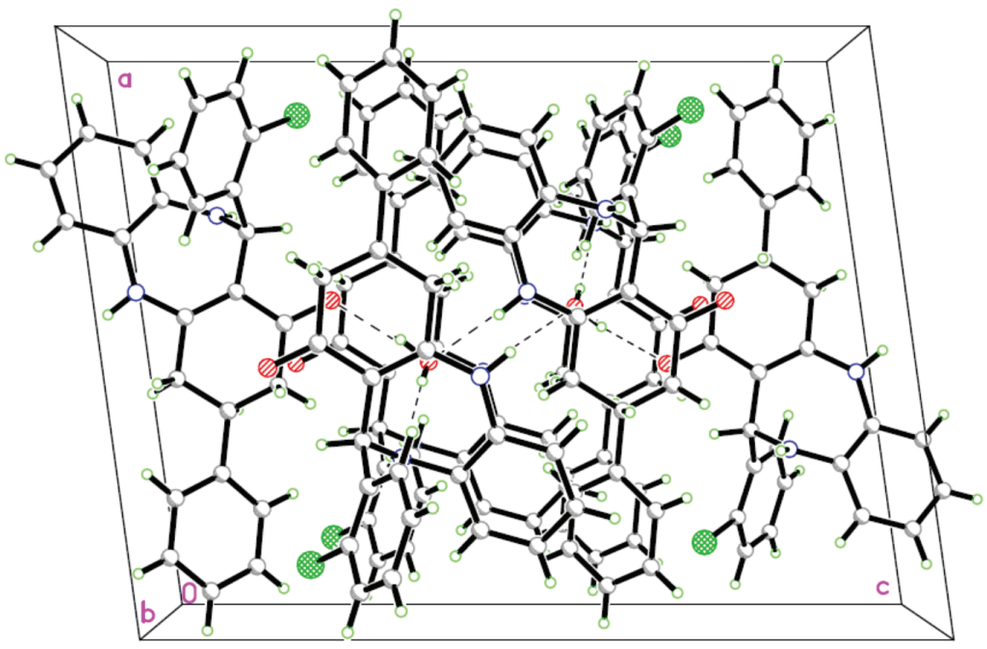


Fig. 2 Packing diagram of compound **3a** in unit-cell as viewed along *b*-axis.

Single-crystal x-ray crystallography

Crystallographic data of **3a** were collected using a Bruker SMART APEX II CCD-based diffractometer with graphite-monochromatic Mo*Kα* radiation (λ=0.71073 Å) at 291(2)K. Data reductions and absorption corrections were performed using SAINT and SADABS software packages,[21] respectively. The structure was determined using the SHELXL-97 software package.[22] Non-hydrogen atoms were refined anisotropically using the full-matrix least-squares method on F^2. All hydrogen atoms were placed at calculated positions and refined riding on the parent atoms. Crystallographic data for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC No.1008694. The crystallographic data of **3a** are shown in Table 1.

5-((2-Aminophenyl)amino)-1,6-dihydro-[1,1′-biphenyl]-3(2H)-one (**2**): Yield 92%; m.p. 208–210 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 2.26 (m, 1H, 4a-H), 2.53 (m, 1H, 4b-H), 2.66 (m, 1H, 6a-H), 2.85 (m, 1H, 6b-H), 4.72 (s, 1H, 2-H), 4.92 (br, 2H, 14-NH), 6.57 (m, 1H, 5-H), 6.76–7.35 (m, 9H, PhH), 8.35 (s, 1H, 7-NH). IR (KBr) υ: 3306 br, 1638 s, 1176 m, 1108 m, 738 m. Anal. calcd for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.06; found: C, 77.32; H, 6.45; N, 9.84%. MS (ESI) *m/z*: 279.2 (M+1).

3-Phenyl-11-(2-chlorophenyl)-2,3,4,5,10,11-hexahydro-1H-dibenzo[b,e][1,4]diazepin-1-one (**3a**): Yield 65%; m.p. 136–138 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 2.50 (m, 2H, 2-H), 2.95 (m. 1H, 4a-H), 3.13 (m, 1H, 4b-H), 3.45 (m, 1H, 3-H), 5.60 (d, 1H, *J*=6.0 Hz, 11-H), 5.96 (d, 1H, *J*=6.0 Hz, 10-NH), 6.48–6.64 (m, 4H, PhH), 9.10 (s, 1H, 5-NH); 6.88–7.38 (m, 9H, PhH, 3′-H, 4′-H, 5′-H, 6′-H); IR (KBr) υ: 3325 br, 1602 m, 1529 s, 1386 m, 754 m, 700 m. Anal. calcd for $C_{25}H_{21}ClN_2O$: C, 74.90; H, 5.28; N, 6.99; found: C, 74.75; H, 5.07; N, 6.95%. MS (ESI) *m/z*: 401.2 (M+1).

3-Phenyl-11-(4-chlorophenyl)-2,3,4,5,10,11-hexahydro-1H-dibenzo[b,e][1,4]diazepin-1-one (**3b**)

3b-1: Yield 40%; m.p. 222–224 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 2.46 (m, 1H, 2a-H), 2.60 (m, 1H, 2b-H), 2.91 (m, 1H, 4a-H), 3.09 (m, 1H, 4b-H), 3.46 (m, 1H, 3-H), 5.67 (d, 1H, *J*=6.0 Hz, 11-H), 6.26 (d, 1H, *J*=6.0 Hz, 10-NH), 7.04–7.39 (m, 13H, PhH, 2′-H, 3′-H, 5′-H, 6′-H), 8.92 (s, 1H, 5-NH). IR (KBr) υ: 3318 br, 1604 m, 1511 s, 1386 m, 752 m, 700 m. Anal. calcd for $C_{25}H_{21}ClN_2O$: C, 74.90; H, 5.28; N, 6.99; found: C, 74.69; H, 5.04; N, 6.85%. MS (ESI) *m/z*: 401.2 (M+1).

3b-2: Yield 36%; m.p. 222–224 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 2.42 (m, 1H, 2a-H), 2.69 (m, 1H, 2b-H), 2.87 (m, 1H, 4a-H), 3.01 (m, 1H, 4b-H), 3.39 (m, 1H, 3-H), 5.77 (d, 1H, *J*=6.0 Hz, 11-H), 6.31 (d, 1H, *J*=6.0 Hz, 10-NH), 6.59–6.91 (m, 11H, PhH, 2′-H, 6′-H), 7.12 (m, 2H, 3′-H, 5′-H); 8.87 (s, 1H, 5-NH). IR (KBr) υ: 3318 br, 1604 m, 1511 s, 1386 m, 752 m, 700 m. Anal. calcd for $C_{25}H_{21}ClN_2O$: C, 74.90; H, 5.28; N, 6.99; found: C, 74.65; H, 5.11; N, 6.89%. MS (ESI) *m/z*: 401.2 (M+1).

3-Phenyl-11-(4-methoxyphenyl)-2,3,4,5,10,11-hexahydro-1H-dibenzo[b,e][1,4]diazepin-1-one (**3c**)

3c-1: Yield 35%; m.p. 212–214 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 2.53 (m, 2H, 2-H), 2.91 (m, 1H, 4a-H), 3.06 (m, 1H, 4b-H), 3.45 (m, 1H, 3-H), 3.62 (s, 3H, 4′-OCH_3), 5.64 (d, 1H, *J*=6.0 Hz, 11-H), 6.16 (d, 1H, *J*=6.0 Hz, 10-NH), 6.88–7.35 (m, 13H, PhH, 2′-H, 3′-H, 5′-H, 6′-H), 8.82 (s, 1H, 5-NH); IR (KBr) υ: 3316 br, 1597 m, 1389 s, 1290 m, 770 m. Anal. calcd for $C_{26}H_{24}N_2O_2$: C, 78.76; H, 6.10; N, 7.07; found: C, 78.57; H, 5.83; N, 6.88%. MS (ESI) *m/z*: 397.2 (M+1).

3c-2: Yield 28%; m.p. 212–214 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 2.42 (m, 1H, 2a-H), 2.68 (m, 1H, 2b-H), 2.87 (m, 1H, 4a-H), 2.99 (m, 1H, 4b-H), 3.38 (m, 1H, 3-H), 3.64 (s, 3H, 4′-OCH_3), 5.74 (d, 1H, *J*=5.5 Hz, 11-H), 6.22 (d, 1H, *J*=6.5 Hz, 10-NH), 6.58–6.69 (m, 11H, PhH, 2′-H, 6′-H), 7.09 (d, 2H, *J*=8.5 Hz, 3′-H, 5′-H), 8.78 (s, 1H, 5-NH). IR (KBr) υ: 3316 br, 1597 m, 1389 s, 1290 m, 770 m. Anal. calcd for $C_{26}H_{24}N_2O_2$: C, 78.76; H, 6.10; N, 7.07; found: C, 78.53; H, 5.86; N, 6.93%. MS (ESI) *m/z*: 397.2 (M+1).

3-Phenyl-11-(3,4-dimethoxyphenyl)-2,3,4,5,10,11-hexahydro-1H-dibenzo[b,e][1,4]diazepin-1-one (**3d**): Yield 61%; m.p. 134–136 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 2.66 (m, 2H, 2-H), 2.99 (m, 1H, 4a-H), 3.64 (m, 6H, 3′-OCH_3, 4′-OCH_3), 3.86 (m, 1H, 4b-H), 3.86 (m, 1H, 3-H), 5.73 (d, 1H, *J*=6.0 Hz, 11-H), 6.23 (d, 1H, *J*=6.0 Hz, 10-NH), 6.59–7.35 (m, 12H, PhH, 2′-H, 5′-H, 6′-H), 8.77 (s, 1H, 5-NH). IR (KBr) *υ*: 3332 m, 2935 m, 1592 m, 1533 s, 1384 m, 1267 m, 757 m. Anal. calcd for $C_{27}H_{26}N_2O_3$: C, 76.03; H, 6.14; N, 6.57; found: C, 75.87; H, 5.80; N, 6.43%. MS (ESI) *m/z*: 427.1 (M+1).

3-Phenyl-11-(naphthalen-1-yl)-2,3,4,5,10,11-hexahydro-1H-dibenzo[b,e][1,4]diazepin-1-one (**3e**): Yield 80%; m.p. 166–168 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 2.50 (m, 2H, 2-H), 2.98 (m, 1H, 4a-H), 3.17 (m, 1H, 4b-H), 3.49 (m, 1H, 3-H), 5.90 (d, 1H, *J*=6.5 Hz, 11-H), 6.06 (d, 1H, *J*=8.0 Hz, 10-NH), 6.46–6.78 (m, 4H, PhH), 7.04–8.55 (m, 12H, PhH+Naph–H), 9.01 (s, 1H, 5-NH). IR (KBr) *υ*: 3329 m, 3025 m, 1598 m, 1390 s, 1290 m, 775 m, 700 m. Anal. calcd for $C_{29}H_{24}N_2O$: C, 83.63; H, 5.81; N, 6.73; found: C, 83.52; H, 5.65; N, 6.63%. MS (ESI) *m/z*: 417.1 (M+1).

3,11-Diphenyl-2,3,4,5,10,11-hexahydro-1H-dibenzo[b,e][1,4]diazepin-1-one (**3f**)

3f-1: Yield 50%; m.p. 206–208 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 2.46 (m, 1H, 2a-H), 2.60 (m, 1H, 2b-H), 2.89 (m, 1H, 4a-H), 3.09 (m, 1H, 4b-H), 3.46 (m, 1H, 3-H), 5.70 (d, 1H, *J*=6.0 Hz, 11-H), 6.24 (d, 1H, *J*=6.0 Hz, 10-NH), 6.89–7.36 (m, 14H, PhH), 8.88 (s, 1H, 5-NH). IR (KBr) *υ*: 3295 m, 1594 m, 1529 s, 1388 m, 754 m, 698 m. Anal. calcd for $C_{25}H_{22}N_2O$: C, 81.94; H, 6.05; N, 7.64; found: C, 81.80; H, 5.78; N, 7.56%. MS (ESI) *m/z*: 367.2 (M+1).

3f-2: Yield 25%; m.p. 206–208 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 2.43 (m, 1H, 2a-H), 2.69 (m, 1H, 2b-H), 2.96 (m, 2H, 4-H), 3.38 (m, 1H, 3-H), 5.80 (d, 1H, *J*=6.0 Hz,11-H), 6.29 (d, 1H, *J*=4.0 Hz, 10-NH), 6.58–7.16 (m, 14H, PhH), 8.84 (s, 1H, 5-NH). IR (KBr) *υ*: 3295 m, 1594 m, 1529 s, 1388 m, 754 m, 698 m. Anal. calcd for $C_{25}H_{22}N_2O$: C, 81.94; H, 6.05; N, 7.64; found: C, 81.77; H, 5.83; N, 7.45%. MS (ESI) *m/z*: 367.2 (M+1).

Table 1 Crystallographic data for compound **3a**

Identification	**3a**
Empirical formula	$C_{25}H_{23}ClN_2O_2$
Formula weight	418.90
Temperature/K	291(2)
Wavelength/Å	0.71073
Crystal system, space group	Monoclinic, $P2_1/c$
Unit cell dimensions	*a*=14.3192(17) Å, α=90°
	b=7.9273(9)Å, β=97.831(2) °
	c=18.744(2) Å, γ=90°
Volume/Å^3	2107.8(4)
Z	4
Calculated density/g cm^{-3}	1.320
Absorption coefficient/ mm^{-1}	0.206
F(000)	880
Crystal size/mm	0.25×0.22×0.18
Theta range for data collection	2.78 to 25.00°.
Limiting indices	$-17\le h\le 17$, $-9\le k\le 9$, $-20\le l\le 22$
Reflections collected/unique	14569/3705 (R_{int}=0.0201)
Completeness to theta=25.00	99.6%
Max. and min. transmission	0.9639 and 0.9504
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3705/0/275
Goodness-of-fit on F^2	1.015
Final *R* indices [*I*>2sigma(*I*)]	R^1=0.0507, wR^2=0.1357
R indices (all data)	R^1=0.0614, wR^2=0.1472
Largest diff. peak and hole/e Å^{-3}	0.548 and −0.511

This work was supported by the National Natural Science Foundation of China for Young Scholars (Grant No. 21201087), the Natural Science Foundation of Jiangsu Province (No. BK20131244) and a start-up grant from Jiangsu University of Science and Technology, P.R. of China.

Received 25 August 2014; accepted 8 October 2014
Paper 1402852 doi: 10.3184/174751914X14138073011066
Published online: 13 November 2014

References

1 V.J. Merluzzi, K.D. Hargrave, M. Labadia, K. Grozinger, M. Skoog, J.C. Wu, C.-K. Shih, K. Eckner, S. Hattox, J. Adams, A.S. Rosenthal, R. Faanes, R.J. Eckner, R.A. Koup and J.L. Sullivan, *Science,* 1990, **250**, 1411.
2 R. Ramajayam, R. Giridhar and M.R. Yadav, *Mini-Rev. Med. Chem.,* 2007, **7**, 793.
3 N. Kaur and D. Kishore, *Synth. Commun*., 2014, **44**, 1375.
4 K. Ahmed, G. Ramesh, O. Srinivas and P. Ramulu, *Bioorg. Med. Chem. Lett.,* 2004, **14**, 471.
5 M. Essaber, A. Baouid, A. Hasnaoui, A. Benharreb and J.P. Lavergne, *Synth. Commun.,* 2000, **28**, 4097.
6 A.M. El-snyed, H. Abdel-ghany and A.M.M. El-snghier, *Synth. Commun.,* 1999, **29**, 3561.
7 K.V. Reddy, P.S. Rao and D. Ashok, *Synth. Commun.,* 2000, **30**, 1825.
8 L.H. Sternbach, *J. Med. Chem.,* 1979, **22**, 1.
9 M.G. Bock, R.M. Dipardo, B.E. Evans, K.E. Rittle, W.L. Whitter, D.F. Veber, P.S. Anderson and R.M. Freidinger, *J. Med. Chem.,* 1989, **32**, 13.
10 E. Korneki, Y.H. Erlich and R.H. Lenox, *Science,* 1984, **226**, 1454.
11 M.C. Hsu, A.D. Schutt, M. Holly, L.W. Slice, M.I. Sherman, D.D. Richman, J.M. Potash and D.F. Volsky, *Science,* 1991, **254**, 1799.
12 L.-T. An, F.-Q. Ding, J.-P. Zou and X.-H. Lu, *Synth. Commun.,* 2008, **38**, 1259.
13 G. Sabitha, G.S.K.K. Reddy, K.B. Reddy, N.M. Reddy and J.S. Yadav, *Adv. Synth. Catal.,* 2004, **346**, 921.
14 B.P. Bandgar, S.V. Bettigeri and N.S. Joshi, *Synth. Commun.,* 2004, **34**, 1447.
15 W.Y. Chen and J. Lu, *Synlett.,* 2005, 1337.
16 M.A. Pasha and V.P. Jayashankara, *Heterocycles,* 2006, **68**, 1017.
17 M.S. Balakrishna and B. Kaboudin, *Tetrahedron Lett.,* 2001, **42**, 1127.
18 B. Kaboudin and K. Navaee, *Heterocycles,* 2001, **55**, 1443.
19 M. Pozarentzi, J.S. Stephanatou and C.A. Tsoleridis, *Tetrahedron Lett.,* 2002, **43**, 1755.
20 G.-F. Han, J.-K. Dong, F.-M. Wang, Z. Xing and Y.-Y. Zhao, *Chin. J. Org. Chem.,* 2008, **28**, 750.
21 Software packages SMART and SAINT, Bruker AXS Inc., Madison, WI (2000).
22 G.M. Sheldrick. SHELXL-97, Program for the Refinement of Crystal Structure, University of Gottingen, Germany (1997).