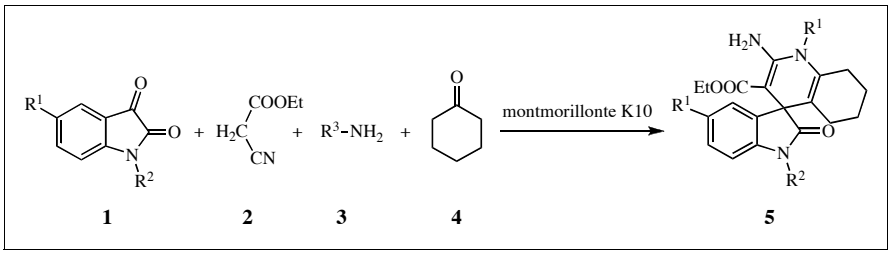
Four Component and Solvent-free Synthesis of Some New Spiro-1,4-Dihydropyridines on Solid Support Montmorillonite K10

Javad Azizian,*[a] Farhad Hatamjafari,[b] Ali Reza Karimi[c]

[a]Chemistry Department, Shahid Beheshti University, Postal Code 1983963113, Tehran, Iran. [b]Department of Chemistry, Faculty of Science, Islamic Azad University-Tonekabon Branch, P. O. Box 46815-375, Tonekabon, Iran. [c]Department of Chemistry, Faculty of Science, Islamic Azad University-Karaj Branch, P. O. Box 31485-313, Karaj, Iran.

Received October 15, 2005



A series of some new spiro-1,4-dihydropyridine derivatives have been synthesized in good yields in a four component, and solvent-free process by condensation of isatins, primary amines, ethyl cyanoacetate and cyclohexanone on solid support montmorillonite K10

J. Heterocyclic Chem., **43**, 1349 (2006).

One-pot multicomponent processes have recently gained considerable and steadily increasing academic, economic and ecological interest because they address fundamental principles of synthetic efficiency and reaction design [1]. Additionally, the prospect of extending one-pot reactions into combinatorial and solid-phase synthesis [1,2] promises many opportunities for developing novel lead structures for pharmaceuticals, catalysts and even novel molecule based materials.

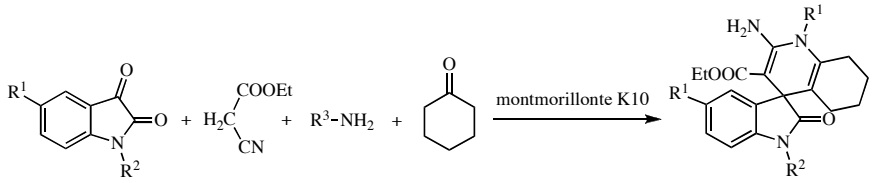
Nitrogen heterocycles are frequently found in privileged structures (pharmacophores) [3], but their incorporation sometimes poses special problems (multistep sequences, lack of generality, preparation from acyclic precursors, *etc.*); thus, only a limited number of strategies have been successfully applied in the synthesis of heterocyclic scaffolds [4]. The development of new, rapid, and clean synthetic routes toward focused libraries of such compounds is therefore of great importance to both medicinal and synthetic chemists [5]. Undoubtedly, the most efficient strategies involve multicomponent reactions (MCRs), which have manifested as a powerful tool for the rapid introduction of molecular diversity [6]. Consequently, the design and development of MCRs for the generation of heterocycles receives growing interest [6a]. In this context, isatin [7] show interesting features that make them attractive for use in MCR: the variety of available derivatives and the rich chemistry of the amine and ketone moieties, which may be exploited for a wide variety of synthetically useful transformations.

In recent years, an increasing interest has been focused on the synthesis of 1,4-dihydropyridyl compounds owing to their significant biological activity [8]. In particular, dihydropyridine drugs such as nifedipine, nicardipine, amlodipine and others are effective cardiovascular agents for the treatment of hypertension [9]. 4-Aryl-1,4-dihydropyridines have been explored for their calcium channel activity and the heterocyclic rings are found in a variety of bioactive compounds such as vasodilator, bronchodilator, antiatherosclerotic, antitumour, anti-diabetic, geroprotective and heptaprotective agents [10]. Moreover studies have discovered that these compounds exhibit diverse medical functions such as neuroprotectants, compounds with platelet antiaggregators, cerebral antiischaemic agents and chemosensitizers [11]. The remarkable drug activity of these compounds not only attracted many chemists to synthesize this heterocyclic nucleus but also became an active research area of continuing interest. Consequently, the development of general and facile methods for the synthesis of such compounds is an active field of research [8].

Oxindole derivatives have been shown to possess antibacterial and antiinflammatory activities [12] and are used as laxatives [13].

In the context of our general interest in multiple component reactions [14] and as part of our ongoing research programmes in the area of heterocyclic compounds containing nitrogen [14,15], and due to the resultant pharmacological interest in compounds which belong to the 1,4-dihydropyridines and oxindoles, herein, we report four-component and solvent-free synthesis of some new spiroindoline-1,4-dihydropyridines, *via* condensation of isatins, primary amines, ethyl cyanoacetate and cyclohexanone on solid support montmorillonite K10 (Scheme 1).

Scheme 1



1 **2** **3** **4** **5**

For example, by mixing of isatin, benzyl amine, ethyl cyanoacetate and cyclohexanone on solid support montmorillonite K10 we obtained the spiroindoline-1,4-dihydropyridine **5a** (97% yield) after heating the mixture for 15 min at 100 ºC then stirring for 2 h at room temperature (Table 1).

In summary, the multicomponent reaction described herein provides a simple and direct entry into a number interesting novel spiroindoline-1,4-dihydropyridine derivatives that may be of value in medicinal chemistry.

Table 1

Synthesis of Spiroindoline-1,4-dihydropyridines

5a-h	R^1	R^2	R^3	Yield (%) with K10	Yield (%) without K10	m. p.
5a	H	H	benzyl	97	50	257-258 °C
5b	H	H	n-butyl	86	45	244-245 °C
5c	H	H	cyclohexyl	78	40	249-250 °C
5d	H	benzyl	benzyl	89	50	289-290 °C
5e	H	H	methyl	96	50	229-230 °C
5f	H	H	ethyl	92	50	232-233 °C
5g	Br	H	benzyl	82	45	280-281 °C

Montmorillonite K10 is one of the solids most efficiently heated by microwaves and is also known for its adsorbing properties of organic molecules. We showed that heating of the mixture of starting material, adsorbed on montmorillonite K10, led to the expected products **5** in a higher yield (80-97%) than for the purely heating procedure (40-50%). This indicates in the absence of solvent, montmorillonite K10 is needed for this reaction.

The structures of compounds **5a-g** were deduced from their elemental analyses and their IR, ^{1}H and ^{13}C NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at the appropriate *m/z* values. The ^{1}H NMR spectrum of **5a** exhibited two broad single lines readily recognized to arise from NH_2 (δ 7.73) and NH (δ 10.02) protons along with multiplets (δ 6.66-7.44) for the aromatic protons. The triplet and quartet at 0.68 ppm and 4.85 ppm related to CH_3 and O-CH_2, respectively. The two doublets at 3.56-3.59 ppm related to N-CH_2. The ^{1}H decoupled ^{13}C NMR spectrum of **5a** showed 24 distinct resonances in agreement with the proposed structure. Mass spectra were recorded on a FINNIGAN-MAT 8430 Mass spectrometer operating at on ionization potential of 70 eV.

EXPERIMENTAL

Melting points were measured on an Electro thermal 9100 apparatus and are uncorrected. IR spectra were measured on a Shimadzu IR-470 Spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were determined on Bruker 300 DRX AVANCE instrument at 300 and 75 MHz, respectively. Elemental analyses were performed using a Heracus CHN-O-Rapid analyzer.

General Procedure for the Preparation of **5a**.

Montmorillonite K10 (0.3 g) was placed in a mortar followed by isatin (0.147 g, 1 mmol), ethyl cyanoacetate (0.113 g, 1 mmol), cyclohexanone (0.98 g, 1 mmol) and benzyl amine (0.107 g, 1 mmol). These materials were then mixed using a pestle for *ca*. 5 min. The homogenised mixture was placed in a pyrex test tube to which was added five drops of ethanol and the mixture heated for 15 min at 100 ºC, then stirred for 2 h at room temperature. The contents were mixed thoroughly with 20 mL of $CHCl_3$. The solution was dried under high vacuum and the resulting solid residue, recrystallised from ethanol to give the pure crystalline solid **5a** (0.417 g).

Spectral Data for products.

2'-Amino-1'-benzyl-3'-ethoxycarbonyl-1',4',5',6',7',8'-hexahydrospiro[indoline-3,4'(1*H*)-quinolin]-2-one (**5a**).

White crystalline solid, m.p. 257-258 °C, IR (KBr) (ν_{max}, cm^{-1}): 3345 (NH), 3182 (NH_2), 1651, 1686 (2C=O); ^{1}H NMR

(DMSO-d_6, 300 MHz) δ_H: 0.68 (3H, t, ^3J=7.1 Hz, CH_3), 0.83-2.03 (8H, m, cyclohexyl), 3.56 and 3.58 (2H, 2d, ^2J=3.8 Hz, N-CH_2), 4.86 (2H, q, ^3J=7.1 Hz, O-CH_2), 6.66-7.44 (9H, m, H_{arom}), 7.73 (2H, bs, NH_2), 10.02 (1H, bs, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ_C: 14.0 (CH_3), 22.3, 23.4, 23.9, 26.7, 45.9, 54.7 ($6CH_2$), 58.6 (C_{spiro}), 76.2, 108.7, 111.9, 122.1, 123.6, 126.9, 127.6, 127.9, 129.4, 130.8, 139.1, 139.2, 143.8, 156.4 (Aromatic and alkene carbons), 169.6, 182.7 (2C=O); MS (m/z, %): 429 (M^+, 10), 356 (100), 310 (20), 264 (100), 91 (100).

Anal. Calcd. for $C_{26}H_{27}N_3O_3$: C, 72.71; H, 6.34; N, 9.78. Found: C, 72.65; H, 6.25; N, 9.70.

2'-Amino-1'-buthyl-3'-ethoxycarbonyl-1',4',5',6',7',8'-hexahydrospiro[indoline-3,4'(1*H*)-quinolin]-2-one (**5b**).

White crystalline solid, m.p. 244-245 °C, IR (KBr) (ν_{max}, cm^{-1}): 3366 (NH), 3198 (NH_2), 1646, 1692 (2C=O); ^{1}H NMR (DMSO-d_6, 300 MHz) δ_H: 0.43 (3H, t, ^3J =7.1 Hz, CH_3), 0.91 (3H, t, ^3J =7.2 Hz, CH_3), 0.99-2.26 (14H, m, cyclohexyl and $2CH_2$), 3.65 (2H, m, N-CH_2), 4.57 (2H, q, ^3J =7.2 Hz, O-CH_2), 6.64-7.07 (4H, m, H_{arom}), 7.71 (2H, bs, NH_2), 10.03 (1H, bs, NH) ; ^{13}C NMR (DMSO-d_6, 75 MHz) δ_C: 14.0, 14.7 ($2CH_3$), 20.2, 21.6, 24.2, 25.3, 30.1, 41.6, 46.1, 52.5 ($8CH_2$), 58.0 (C_{spiro}), 75.3, 106.9, 108.9, 121.3, 121.8, 127.1, 136.4, 138.4, 144.0, 157.0 (Aromatic and alkene carbons), 169.0, 181.0 (2C=O); MS (m/z, %): 395 (M^+, 20), 322 (100), 264 (10), 97 (30), 57 (40).

Anal. Calcd for $C_{23}H_{29}N_3O_3$: C, 69.85; H, 7.39; N, 10.62. Found: C, 69.75; H, 7.35; N, 10.58.

2'-Amino-1'-cyclohexyl-3'-ethoxycarbonyl-1',4',5',6',7',8'-hexahydrospiro[indoline-3,4'(1*H*)-quinolin]-2-one (**5c**).

White crystalline solid, m.p. 249-250 °C, IR (KBr) (ν_{max}, cm^{-1}): 3334 (NH), 3122 (NH_2), 1686, 1698 (2C=O); ^{1}H NMR (DMSO-d_6, 300 MHz) δ_H: 1.12 (3H, t, ^3J =7.05 Hz, CH_3), 1.05-2.76 (19H, m, cyclohexyl), 4.12 (2H, q, ^3J =7.05 Hz, O-CH_2), 6.72-7.25 (4H, m, H_{arom}), 7.86 (2H, bs, NH_2), 10.35 (1H,bs, NH) ; ^{13}C NMR (DMSO-d_6, 75 MHz) δ_C: 14.7 (CH_3), 20.2, 22.1, 23.9, 24.8, 25.5, 26.1, 26.2, 31.3, 33.7, 52.5 ($10CH_2$), 50.1 (CH), 58.6 (C_{spiro}), 75.3, 110.4, 120.2, 121.9, 124.3, 124.7, 125.4, 129.3, 130.2, 142.4, 150.3 (Aromatic and alkene carbons), 167.8, 178.0 (2C=O); MS (m/z, %): 421 (M^+, 50), 347 (100), 264 (40), 132 (100), 56 (80).

Anal. Calcd for $C_{25}H_{31}N_3O_3$: C, 71.23; H, 7.41; N, 9.97. Found: C, 71.19; H, 7.35; N, 9.91.

2'-Amino-1'-benzyl-3'-ethoxycarbonyl-1',4',5',6',7',8'-hexahydrospiro[1-benzylindoline-3,4'(1*H*)-quinolin]-2-one (**5d**).

White crystalline solid, m.p. 289-290 °C, IR (KBr) (ν_{max}, cm^{-1}): 3354 (NH), 3184 (NH_2), 1658, 1680 (2C=O); ^{1}H NMR (DMSO-d_6, 300 MHz) δ_H: 0.45 (3H, t, ^3J =9.1 Hz, CH_3), 0.73-2.17 (8H, m, cyclohexyl), 3.58 (4H, m, 2N-CH_2), 4.95 (2H, q, ^3J =9.1 Hz, O-CH_2), 6.89-7.42 (14H, m, H_{arom}), 7.81 (2H, bs, NH_2); ^{13}C NMR (DMSO-d_6, 75 MHz) δ_C: 14.4 (CH_3), 23.3, 24.2, 41.6, 44.3, 49.8, 52.1, 54.2 ($7CH_2$), 58.4 (C_{spiro}), 75.9, 108.2, 111.6, 123.0, 126.8, 126.8, 127.8, 128.1, 128.6, 128.9, 129.2, 129.3, 129.5, 131.3, 137.9, 138.0, 138.4, 139.1, 143.7, 144.4, 156.1 (Aromatic and alkene carbons), 169.4, 179.3 (2C=O); MS (m/z, %): 520 (M^++1, 10), 446 (40), 356 (15), 236 (10), 91 (100).

Anal. Calcd for $C_{33}H_{33}N_3O_3$: C, 76.13; H, 6.58; N, 8.07. Found: C, 76.10; H, 6.54; N, 8.00.

2'-Amino-3'-ethoxycarbonyl-1'-methyl-1',4',5',6',7',8'-hexahydrospiro[indoline-3,4'(1*H*)-quinolin]-2-one (**5e**).

White crystalline solid, m.p. 229-230 °C, IR (KBr) (ν_{max}, cm^{-1}): 3335 (NH), 3178 (NH_2), 1652, 1696 (2C=O); ^{1}H NMR (DMSO-d_6, 300 MHz) δ_H: 0.45 (3H, t, ^3J =7.07 Hz, CH_3), 1.01-1.99 (8H, m, cyclohexyl), 2.88 (3H, s, N-CH_3), 4.18 (2H, q, ^3J =7.07 Hz, O-CH_2), 6.67-7.04 (4H, m, H_{arom}), 7.74 (2H, bs, NH_2), 10.04 (1H, bs, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ_C: 14.0, 41.2 ($2CH_3$), 24.0, 25.1, 28.7, 34.7, 55.2 ($5CH_2$), 58.1 (C_{spiro}), 75.3, 107.8, 108.6, 121.5, 121.9, 127.1, 137.7, 138.4, 144.0, 157.7 (Aromatic and alkene carbons), 169.0, 181.2 (2C=O); MS (m/z, %): 353 (M^+, 40), 280 (100), 252 (20), 148 (20), 91 (20).

Anal. Calcd for $C_{20}H_{23}N_3O_3$: C, 67.97; H, 6.56; N, 11.89. Found: C, 67.92; H, 6.52; N, 11.84.

2'-Amino-3'-ethoxycarbonyl-1'-ethyl-1',4',5',6',7',8'-hexahydrospiro[indoline-3,4'(1*H*)-quinolin]-2-one (**5f**).

White crystalline solid, m.p. 232-233 °C, IR (KBr) (ν_{max}, cm^{-1}): 3362 (NH), 3200 (NH_2), 1662, 1692 (2C=O); ^{1}H NMR (DMSO-d_6, 300 MHz) δ_H: 0.45 (3H, t, ^3J =7.05 Hz, CH_3), 0.63 (3H, t, ^3J =7.05 Hz, CH_3), 0.85-2.12 (8H, m, cyclohexyl), 3.50 (2H, m, N-CH_2), 4.86 (2H, q, ^3J =7.02 Hz, O-CH_2), 6.53-7.08 (4H, m, H_{arom}), 7.68 (2H, bs, NH_2), 10.05 (1H, bs, NH) ; ^{13}C NMR (DMSO-d_6, 75 MHz) δ_C: 13.9, 14.0 ($2CH_3$), 21.6, 24.2, 25.3, 41.2, 41.6, 52.5 ($6CH_2$), 58.0 (C_{spiro}), 75.2, 106.3, 108.9, 121.3, 121.8, 127.1, 136.2, 138.4, 143.9, 156.7 (Aromatic and alkene carbons), 169.1, 181.1 (2C=O); MS (m/z, %): 367 (M^+, 40), 294 (100), 265 (60), 252 (20), 91 (100).

Anal. Calcd for $C_{21}H_{25}N_3O_3$: C, 68.64; H, 6.86; N, 11.44. Found: C, 68.60; H, 6.82; N, 11.40.

2'-Amino-1'-benzyl-5-bromo-3'-ethoxycarbonyl-1',4',5',6',7',8'-hexahydrospiro[indoline-3,4'(1*H*)-quinolin]-2-one (**5g**).

White crystalline solid, m.p. 280-281 °C, IR (KBr) (ν_{max}, cm^{-1}): 3348 (NH), 3234 (NH_2), 1681, 1726 (2C=O); ^{1}H NMR (DMSO-d_6, 300 MHz) δ_H: 0.68 (3H, t, ^3J =7.05 Hz, CH_3), 0.89-2.16 (8H, m, cyclohexyl), 3.54 and 3.56 (2H, 2d, ^2J =3.3 Hz, N-CH_2), 4.80 (2H, q, ^3J =7.05 Hz, O-CH_2), 6.86-7.44 (8H, m, H_{arom}), 8.16 (2H, bs, NH_2), 11.14 (1H, bs, NH) ; ^{13}C NMR (DMSO-d_6, 75 MHz) δ_C: 14.8 (CH_3), 23.1, 24.9, 26.1, 28.8, 43.5, 53.0 ($6CH_2$), 61.8 (C_{spiro}), 76.8, 117.39, 126.0, 127.2, 127.8, 127.9, 128.1, 128.2, 128.8, 129.1, 129.2, 129.4, 139.4, 158.7 (Aromatic and alkene carbons), 163.0, 170.7 (2C=O); MS (m/z, %): 508 (M^+, 10), 435 (35), 289 (10), 106 (20), 91 (100).

Anal. Calcd for $C_{26}H_{26}BrN_3O_3$: C, 61.42; H, 5.15; Br, 15.72; N, 8.27. Found: C, 61.38; H, 5.12; Br, 15.69; N, 8.23.

REFERENCES

[1a] G. H. Posner, *Chem. Rev*., **86**, 831 (1986); [b] A. Domling and Ugi, I. *Angew. Chem. Int. Ed*., **39**, 3167 (2000); [c] I. Ugi, A. Domling and B. Werner, *J. Heterocyclic Chem*., **37**, 647 (2000); [d] H. Bienayme, C. Hulme, G. Oddon and P. Schmitt, *Chem. Eur. J*., **6**, 3321 (2000); [e] I. Ugi and S. Heck, *Comb. Chem. High Throughput Screen*, **4**, 1 (2001); [f] V. Nair, C. Rajesh, A. U. Vinod, S. Bindu, A. R. Sreekanth, J. S. Mathen and L. Balagopala, *Acc. Chem. Res*., **36**, 899 (2003); [g] T. Hudlicky, D. A. Entwistle, K. K. Pitzer and A. J. Thorpe, *Chem. Rev*., **96**, 1195 (1996).

[2] S. Kobayashi, *Chem. Soc. Rev*., **28**, 1 (1999).

[3a] G. Wess, N. Urmann and B. Sickenberger, *Angew. Chem. Int. Ed*., **40**, 3341 (2001); [b] I. Muegge, *Chem. Eur. J*., **8**, 1977 (2002); [c] C. Anies, A. Pancrazi and J.-Y. Lallemand, *Tetrahedron Lett*., **35**, 7771 (1994).

[4] For recent successful approaches dealing with nitrogen heterocycles, see: [a] I. Collins, *J. Chem. Soc. Perkin Trans. 1,* 1921 (2002; [b] M. F. Gordeev, D. V. Patel and E. M. Gordon, *J. Org. Chem.*, **61**, 924 (1996); [c] B. A. Lorsbach, J. T. Bagdanoff, R. B. Miller and M. J. Kurth, *J. Org. Chem.*, **63**, 2244 (1998); [d] B. Munoz, C. Chen and I. A. McDonald, *Biotechnol. Bioeng.,* **71**, 78 (2000); [e] H. E. Pelish, N. J. Westwood, Y. Feng, T. Kirchhausen and M. D. Shair, *J. Am. Chem. Soc.*, **123**, 6740 (2001); [f] S. Ding, N. S. Gray, X. Wu, Q. Ding and P. G. Schultz, *J. Am. Chem. Soc.*, **124**, 1594 (2002); [g] S. Nagashima and K. Kanematsu, *Tetrahedron Asymmetry*, **1**, 743 (1990).

[5a] R. Newton, *sp2* (2002), November, 16-18 (see: http://www. sp2.uk.com); [b] S. J. Teague, A. M. Davis, P. D. Leeson and T. Oprea, *Angew. Chem. Int. Ed.*, **38**, 3743 (1999); [c] R. W. Armstrong, A. P. Combs, P. A. Tempest, S. D. Brown and T. A. Keating, *Acc. Chem. Res.*, **29**, 123 (1996); [d] S. L. Schreiber, *Science*, **287**, 1964 (2000).

[6a] R. V. A. Orru and M. de Greef, *Synthesis,* 1471 (2003); [b] A. Dömling and I. Ugi, *Angew. Chem. Int. Ed.*, **39**, 3168 (2000); [c] H. Bienayme´, C. Hulme, G. Oddon and P. Schmitt, *Chem. Eur. J.*, **6**, 3321 (2000).

[7] J. F. M. da Silva, S. J. Garden and A. C. Pinto, *J. Braz. Chem. Soc.,* **12**, 273 (2001).

[8a] D. Mauzeral and F. H. Westheimer, *J. Am. Chem. Soc.*, **77**, 2261 (1955); [b] P. G. Baraldi, A. Chiarini, R. Budriesi, M. Roberti, A. Casolar, S. Manfredini, D. Simoni, V. Zanirato, K. Varani and P. A. Borea, *Drug. Des. Delivery.*, **5**, 13 (1989); [c] P. G. Baraldi, R. Budriesi, B. Cacciari, A. Chiarini, L. Garuti, G. Giovanninetti, A. Leoni and M. Roberti, *Collect. Czech. Chem. Commun.*, 169 (1992); [d] A. Di Stilo, S. Visentin, C. Clara, A. M. Gasco, G. Ermondi and A. Gasco, *J. Med. Chem.*, **41**, 5393 (1998); [e] M. Kawase, A. Shah, H. Gaveriya, N. Motohashi, H. Sakagami, A. Varga and J. Molnar, *J. Bioorg. Chem.*, **10**, 1051 (2002); [f] M. Suarez, Y. Verdecia, B. Illescas, R. Martinez-Alvarez, A. Avarez, E. Ochoa, C. Seoane, N. Kayali and N. Martin, *Tetrahedron*, **59**, 9179 (2003); [g] L. D. Quin, A Guide to Organophophorus Chemistry, Wiley Interscience, New York, 2000; [h] X. Y. Xu, G. W. Qin, R. S. Xu and X. Z. Zhu, *Tetrahedron*, **54**, 14179 (1998).

[9a] F. R. Buhler and W. Kiowski, *J. Hypertens*, **S3**, 5 (1987); [b] J. L. Reid, P. A. Meredith and F. Pasanisi, *J. Cardiovasc. Pharmacol.*, **S18**, 7 (1985).

[10a] T. Godfraid, R. Miller and M. Wibo, *Pharmacol. Rev.*, **38**, 321 (1986); [b] A. Sausins and G. Duburs, *Heterocycles*, **27**, 269 (1988); [c] P. P. Mager, R. A. Coburn, A. J. Solo, D. J. Triggle and H. Rothe, *Drug Des. Discovery*, **8**, 273 (1992); [d] R. Mannhold, B. Jablonka, W. Voigdt, K. Schoenafinger and K. Schravan, *Eur. J. Med. Chem.*, **27**, 229 (1992).

[11a] V. Klusa, *Drugs Future*, **20**, 135 (1995); [b] R. G. Bretzel, C. C. Bollen, E. Maeser and K. F. Federlin, *Am. J. Kidney Dis.*, **21**, 53 (1993); [c] R. G. Bretzel, C. C. Bollen, E. Maeser, and K. F. Federlin, *Drugs Future*, **17**, 465 (1992); [d] R. Boer and V. Gekeler, *Drugs Future*, **20**, 499 (1995).

[12a] F. D. Popp, *J. Heterocyclic Chem.*, **21**, 1367 (1984); [b] H. Pajouhesh, R. Parsons and F. D. Popp, *J. Pharm. Sci.,* **72**, 318 (1983).

[13] F. Garrido, J. Ibanez, E. Gonalons and A. Giraldez, *Eur. J. Med. Chem.*, **10**, 143 (1975).

[14a] J. Azizian, A. R. Karimi, Z. Kazemizadeh, A. A. Mohammadi and M. R. Mohammadizadeh, *Tetrahedron Lett.*, **46**, 6155 (2005); [b] J. Azizian, A. A. Mohammadi, A. R. Karimi and M. R. Mohammadizadeh, *J. Org. Chem.*, **70**, 350 (2005); [c] J. Azizian, M. R. Mohammadizadeh, N. Karimi, A. A. Mohammadi and A. R. Karimi, *Heterocycles*, **65**, 143 (2005); [d] J. Azizian, A. R. Karimi, A. A. Mohammadi and M. R. Mohammadizadeh, *Heterocycles*, **63**, 2225 (2004); [e] J. Azizian, A. R. Karimi, A. A. Mohammadi and M. R. Mohammadizadeh, *Synthesis*, 2263 (2004); [f] J. Azizian, A. R. Karimi and A. A. Mohammadi, *Synth. Commun.,* **33**, 383 (2003); [g] J. Azizian, A. R. Karimi, H. Arefrad, A. A. Mohammadi and M. R. Mohammadizadeh, *Mol. Diversity,* **6**, 223 (2003); [h] J. Azizian, A. A. Mohammadi and A. R. Karimi, *Synth. Commun.*, **33**, 415 (2003); [i] J. Azizian, A. V. Morady and A. Asadi, *Tetrahedron Lett.*, **43**, 9721 (2002).

[15a] J. Azizian, A. R. Karimi, Z. Kazemizadeh, A. A. Mohammadi and M. R. Mohammadizadeh, *J. Org. Chem.*, **70**, 1471 (2005); [b] J. Azizian, A. A. Mohammadi, A. R. Karimi, M. R. Mohammadizadeh and M. Koohshari, *Heterocycls*, **63**, 2013 (2004).