Indian Journal of Chemistry
Vol. 46B, January 2007, pp. 216-220

Note

Synthesis of novel 1,2,4-oxadiazole heterocyclic compounds containing 2-*H* pyranopyridine-2-one moiety and related compounds

N Vasanth Kumar & Uday C Mashelker*

Organic Research Laboratory, SS & LS Patkar College, S V Road, Goregaon (West), Mumbai 400 062, India

E-mail: vknalam@yahoo.com

Received 23 *January* 2006*; accepted (revised)* 1 *Sepember* 2006

7-Hydroxy/Amino-5-methyl-6-(5-substituted-[1,2,4]oxadiazol-3-yl)-2-oxo-2*H*-pyrano[2,3-*b*]pyridine-3-carboxylic acid amides **5a-c** and **6a-c** have been prepared starting from ethyl 2*H*-pyrano [2,3-*b*] pyridine-3-carboxylate **1** and **2**, compounds **1** and **2** are treated with aqueous ammonia solution to afford 2*H*-pyrano[2,3-*b*] pyridine-3-carboxamide **3a-b**, which are converted to 6-carboxamidoxime 2*H*-pyrano [2,3-*b*] pyridine-3-carboxamide **4a-b** by treating with hydroxyl amine in refluxing ethanol. Carboxamidoximes **4a-b** are treated with various acid chlorides to obtain 1,2,4-oxadiazole derivatives **5a-c** and **6a-c**. Carboxamide **3a** is reacted with triethyl orthoformate to give 4-amino-5-methyl pyrano [3",2':5,6] pyrido [2,3-*d*] pyrimidine-7-carboximde **7**. Carboxamidoxime **4a** is allowed to react with *N*,*N*-dimethyl formamide dimethyl acetal under reflux to obtain *N*-(6-carbonyl-4-methyl-7-oxo-1,7-dihydropyrano[2,3-*b*]pyrazolo[4,3-*e*]pyridine-3-yl)methanamide **8**. These compounds are expected to have better hypertensive activity.

Keywords: 1,2,4-oxadiazole, carboxamide, 2*H*-pyranopyridine -2-one, anti-hypertensive, hydroxyl amine, tyrosine kinase, cyclocondensation, carboxamidoxime.

IPC: Int.Cl.[8] C07D

1,2,4-Oxadiazole rings occur widely in biologically active compounds[1] such as analgesics, anti-inflammatory agents[2,3], antimicrobials[3], antivirals[4,5], pesticides and insecticides[6,7]. Numerous 1,2,4-oxadiazoles have been suggested as potential agonists for cortical muscarinic[8,9] benzodiazepine[10] and 5-HT_{1D} (5-hydroxytryptamine) receptors[11] and as antagonists for 5-HT_3[12], or histamine H_3 receptors[13]. They also inhibit the SH2 domain of tyrosine kinase[14], monoamine oxidase[15], human nuetrophil elastase[16], and human DNA topoisomerases[17]. Keeping in mind the biological significance of 1,2,4-oxadiazole derivatives, The synthesis of some new 1,2,4-oxadiazole containing 2*H*-pyranopyridine-2-one derivatives are reported.

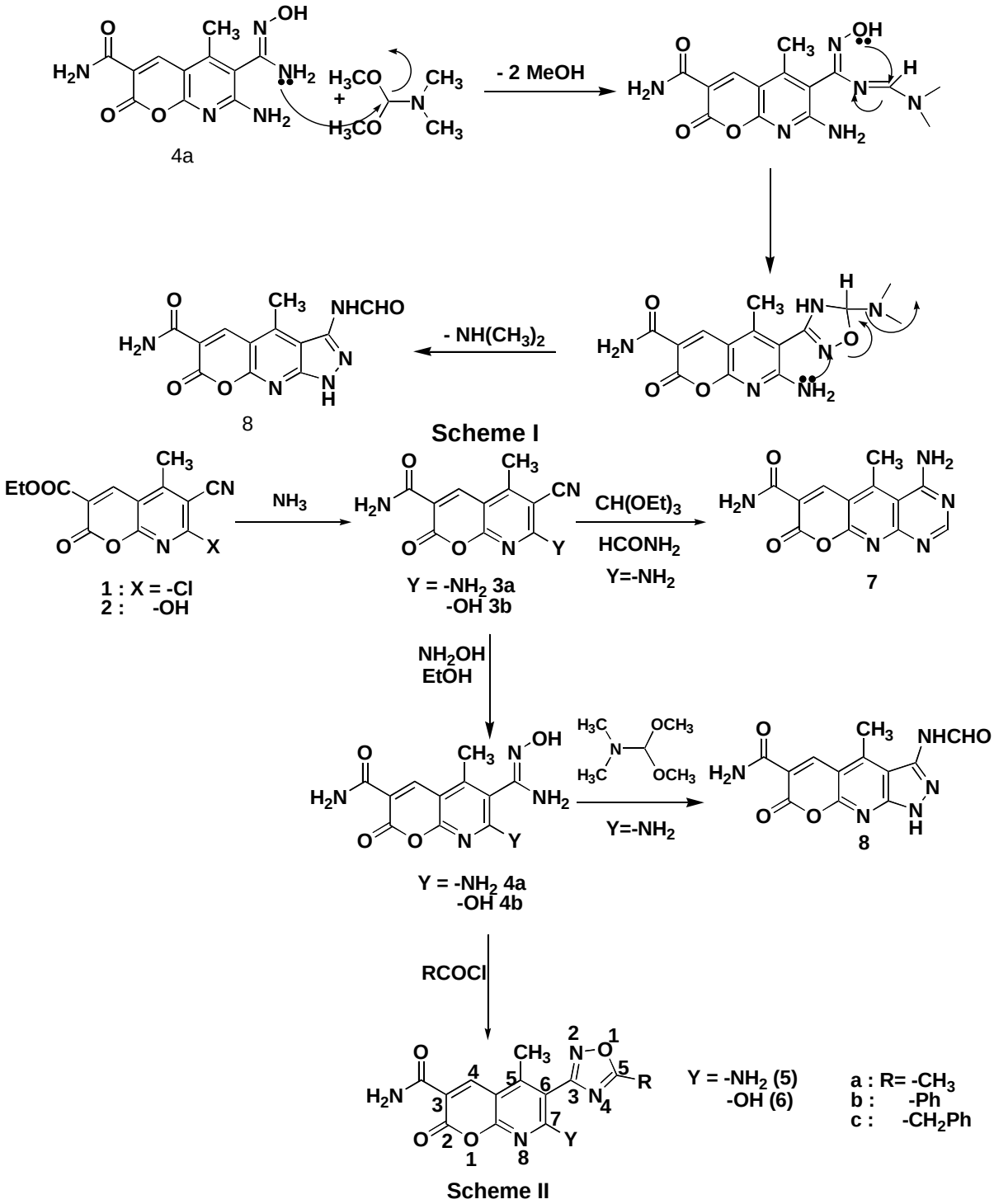
Results and Discussion

In the present work, 2*H*-pyrano [2,3-*b*] pyridine-3-carboxylates **1** and **2**, which were previously prepared[18], were used as the key intermediate for further synthesis. Thus, when compound **1** and **2** were treated separately with aqueous ammonia 2*H*-pyrano [2,3-*b*] pyridine-3-carboxamides **3a** and **3b** were obtained. Compounds **3a** and **3b** were characterized by its IR and ^{1}H NMR, the IR showed the disappearance of ester absorption at 1750 observed a new absorption at 1704 and 1706 cm^{-1} correspond to amide, also the ^{1}H NMR showed the disappearance of ester protons δ 1.22-1.29 (t, 3H, -CH_2-CH_3), 4.1-4.2 (q, 2H, -CH_2-CH_3) observed new peak at δ 10.42 and 10.85 (D_2O exchangeable) corresponds amide of **3a** and **3b** respectively.

The compounds **3a** and **3b** were reacted with hydroxylamine[19] in absolute ethanol, which afforded 6-carboxamidoxime 2*H*-pyrano [2,3-*b*] pyridine-3-carboxamides **4a** and **4b**. These carboxamides **4a** and **4b** were allowed to react with different acid chlorides namely, acetyl chloride, benzoyl chloride and phenyl acetyl chloride to give compounds **5a-c** and **6a-c** respectively. On the other hand carboxamide **3a** was treated with triethyl orthoformate[19] to give 4-amino-5-methyl Pyrano [3",2':5,6] pyrido [2,3-*d*] pyrimidine-7-carboximde **7** (**Schemes I** and **II**). Also the cyclocondensation of carboxamidoximes[19] **4a** with *N*, *N*-dimethyl form amide dimethyl acetal to afforded the *N*-(6-carbonyl-4-methyl-7-oxo-1,7-dihydropyrano [2,3-*b*] pyrazolo [4,3-*e*] pyridine-3-yl) methanamide **8** (**Scheme II**).

Experimental Section

Melting points were determined on a Buchi 545 melting point apparatus and are uncorrected. IR spectra were recorded in KBr on a Perkin-Elmer 1650 spectrometer, ^{1}H NMR was recorded in DMSO-d_6 using 200 MHz Bruker spectrometer (chemical shifts in δ, ppm) with TMS as internal standard and mass spectra on a HP-5989A spectrometer. The Analytical Research Department of Lupin Limited (Lupin Research Park) carried out all analytical work. All the organic extracts were dried over sodium sulfate after work-up.



The dry reactions were carried out under nitrogen with magnetic/mechanical stirring. Unless otherwise mentioned all the solvents and reagents used were of LR grade. TLC was performed on precoated silica-gel plates, which were visualized using UV light.

General procedure for the preparation of 3a,b. To the solution of suitable ethyl pyrano [2,3-*b*] pyridine-3-carboxylate **1** or **2** (0.01 mole) in ethanol (50 mL) was added aqueous ammonia solution (10 mL). This resulting mixture was stirred at room temperature for 7-12 hr. After completion of the reaction the precipitate was collected by filtration, washed with ethanol, and then dried under reduced pressure. The solid so obtained was recrystallized

from ethanol to give compound **3a** or **b** as a white solid.

7-Amino-6-cyano-5-methyl-2-oxo-2*H*-pyrano-[2,3-*b*]pyridine-3-carboxamide 3a. m.p. 326-28°C; yield 95%; IR (KBr, cm^{-1}): 3153.2 (-NH_2), 2215.8 (-CN), 1704 (-C=O, lactone), 1663.1 (-C=O, amide); ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.30 (s, -CH_3), 8.10 (s, 1H, C_4-H), 10.42 (brs, 1H, -$CONH_2$, exchangeable). Anal. Found: C, 54.10; H, 3.30; N, 22.94. Calcd for $C_{11}H_8N_4O_3$: C, 54.16; H, 3.36; N, 22.98%.

7-Hydroxy-6-cyano-5-methyl-2-oxo-2*H*-pyrano-[2,3-*b*]pyridine-3-carboxamide 3b. m.p. 342-44°C; yield 92%; IR (KBr, cm^{-1}): 3426 (-OH), 2221 (-CN), 1706 (-C=O, lactone), 1655 (-C=O, amide); ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.37 (s, 3H, -CH_3), 8.30 (s, 1H, C_4-H), 10.42 (brs, 1H, -$CONH_2$, exchangeable), Anal. Found: C, 53.88; H, 2.88; N, 17.14. Calcd for $C_{11}H_7N_3O_4$: C, 53.80; H, 2.91; N, 17.22%.

General procedure for the preparation of 4a-b. A mixture of pyrano [2,3-*b*] pyridine-3-carboxamide (**3a** or **3b**, 0.061 mole) and ethanolic hydroxylamine [20] (6.62 g in 150 mL ethanol) was heated under reflux for 7 hr. After this period, the reaction mixture was concentrated under reduced pressure. The residue was crystallized from ethanol to give **4a** or **b**.

7-Amino-6-carboxamidoxime-5-methyl-2-oxo-2*H*-pyrano[2,3-*b*]pyridine-3-arboxamide 4a. m.p. 269-71°C; yield 83%; IR (KBr, cm^{-1}): 3256.3 (-NH_2), 1710 (-C=O, lactone), 1633.6 (-C=N amide); ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.30 (s, 3H, -CH_3), 7.08 (brs, -OH, D_2O exchangeable), 8.10 (s, 1H, C_4-H), 9.90 (s, -$CONH_2$, exchangeable). Anal. Found: C, 47.66; H, 4.0; N, 25.26. Calcd for $C_{11}H_{11}N_5O_4$: C, 47.69; H, 4.09; N, 25.3%.

7-Hydroxy-6-carboxamidoxime-5-methyl-2-oxo-2*H*-pyrano[2,3-*b*]pyridine-3-carboxamide 4b. m.p. 280-82°C; yield 87%; IR (KBr, cm^{-1}): 3235 (-OH), 1704 (C=O, lactone), 1658 (-C=O, amide); ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.37 (s, 3H, -CH_3), 7.08 (s, -OH, D_2O exchangeable), 8.10 (s, 1H, C_4-H), 9.90 (s, -NH_2, exchangeable), 10.0 (s, -$CONH_2$, exchangeable). Anal. Found: C, 47.49; H, 3.62; N, 20.14. Calcd for $C_{11}H_{10}N_4O_5$: C, 47.53; H, 3.67; N, 20.10%.

General procedure for the preparation of 5a-c, 6a-c. A mixture of carboxamidoxime **4** (0.01 mole) and suitable acid chlorides (10 mL) was refluxed for 10-12 hr. The progress of reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured into crushed ice, stirred the reaction mass for 2 hr and the solid formed was collected by filtration, washed with small amounts of water. The obtained crude solid was crystallized from ethanol.

7-Amino-5-methyl-6-(5-methyl-1,2,4-oxadiazolyl-3-yl)-2-oxo-2*H*-pyrano[2,3-*b*]yridine-3carboxymide 5a. m.p. 305-07°C; yield 68%; IR (KBr, cm^{-1}): 3488.9 (-NH_2), 1702 (-C=O, lactone), 1641.7 (-C=O, amide); ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.9 (s, 3H, -CH_3), 2.35 (s, 3H, -CH_3), 8.16 (s, 1H, C_4-H), 11.3 (s, -$CONH_2$, exchangeable). Anal. Found: C, 51.83; H, 3.68; N, 23.25. Calcd for $C_{13}H_{11}N_5O_4$: C, 51.89; H, 3.72; N, 23.20%.

7-Amino-5-methyl-6-(5-phenyl-1,2,4-oxadiazolyl-3-yl)-2-oxo-2*H*-pyrano[2,3-*b*] pyridine-3carboxy-mide 5b. m.p. 292-94°C; yield 69%; IR (KBr, cm^{-1}): 3452.3 (-NH_2), 1706 (-C=O, lactone), 1682 (-C=O, amide); ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.39 (s, 3H, -CH_3), 7.45 (m, 3H, Ar), 8.06 (s, 1H, C_4-H), 8.21 (d, 2H, Ar), 10.3 (s, -$CONH_2$, exchangeable). Anal. Found: C, 59.50; H, 3.61; N, 19.28. Calcd for $C_{18}H_{13}N_5O_4$: C, 59.61; H, 3.69; N, 19.32%.

7-Amino-5-methyl-6-(5-benzyl-1,2,4-oxadiazol-yl-3-yl)-2-oxo-2*H*-pyrano[2,3-*b*] yridine-3-carboxy-mide 5c. m.p. 359-61°C; yield 70%; IR (KBr, cm^{-1}): 3326 (-NH_2), 1700 (-C=O, lactone), 1623 (-C=O, amide); ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.39 (s, 3H, -CH_3), 3.90 (s, 2H, -CH_2Ph) 7.18-7.31(m, 5H, Ar), 8.06 (s, 1H, C_4-H), 10.30 (s, -$CONH_2$, exchangeable). Anal. Found: C, 60.48; H, 4.01; N, 18.56. Calcd for $C_{19}H_{15}N_5O_4$: C, 60.53; H, 4.16; N, 18.61%.

7-Hydroxy-5-methyl-6-(5-methyl-1,2,4-oxadiazol-yl-3-yl)-2-oxo-2H-pyrano[2,3-b]pyridine-3-carboxy-mide 6a. m.p. 285-87°C; yield 70%; IR (KBr, cm^{-1}): 3415 (-OH), 1708 (-C=O, lactone), 1644 (-C=O, amide); ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.39 (s, 3H, -CH_3), 2.60 (s, 3H, -CH_3), 8.06 (s, 1H, C_4-H), 10.30 (s, -$CONH_2$, exchangeable). Anal. Found: C, 51.66; H, 33.3; N, 18.54. Calcd for $C_{13}H_{10}N_4O_5$: C, 51.69; H, 3.39; N, 18.61%.

7-Hydroxy-5-methyl-6-(5-phenyl-1,2,4-oxadiazol-yl-3-yl)-2-oxo-2H-pyrano[2,3-b]pyridine-3-carboxy-mide 6b. m.p. 292-94°C; yield 72%; IR (KBr, cm^{-1}): 3432 (-OH), 1710 (-C=O, lactone), 1620 (-C=O, amide); ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.39 (s, 3H, -CH_3), 7.45 (m, 3H, Ar), 8.06 (s, 1H, C_4-H), 8.21 (d, 2H, Ar,), 10.3 (s, -$CONH_2$, exchangeable). Anal. Found: C, 59.34; H, 3.32; N, 15.38. Calcd for $C_{18}H_{12}N_4O_5$: C, 59.41; H, 3.38; N, 15.42%.

7-Hydroxy-5-methyl-6-(5-benzyl-1,2,4-oxadiazo-lyl-3-yl)-2-oxo-2*H*-pyrano[2,3-*b*]pyridine-3-carbo-

xymide 6c. m.p. 321-23°C; yield 75%; IR (KBr, cm^{-1}): 3446 (-OH), 1715 (C=O, lactone), 1685 (-C=O, amide); ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.39 (s, 3H, -CH_3), 3.90 (s, 2H, -CH_2Ph) 7.18-7.31 (m, 5H, Ar), 8.06 (s, 1H, C_4-H), 10.3 (s, -$CONH_2$, exchangeable). Anal. Found: C, 60.32; H, 3.73; N, 14.81. Calcd for $C_{19}H_{14}N_4O_5$: C, 60.38; H, 3.80; N, 14.86%.

Preparation of 4-amino-5-methyl-8-oxo-8*H*-pyrano[3",2':5,6]pyrido[2,3-*d*]pyrimidine-7-carboximde 7. A mixture of 7-Amino-6-cyano-5-methyl-2-oxo-2*H*-pyrano [2,3-*b*] pyridine-3-carboxamide **3a**, (10.0 g, 0.04 mole) and triethyl orthoformate (100 mL) was refluxed for 8-10 hr. After completion of the reaction, the reaction mixture was cooled and excess reagent was removed under reduced pressure. The residue was dissolved in chloroform, treated with charcoal and filtered. The filtrate was added slowly into petroleum ether and stirred for 3 hr to precipitate the solid. The solid was filtered off and residue was washed with petroleum ether. The crude compound was crystallized from ethanol. m.p. 364-66°C; yield 52%; IR (KBr, cm^{-1}): 3147 (-NH_2), 1701 (-C=O, lactone), 1659 (-C=O, amide); ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.27 (s, 3H, -CH_3), 7.80 (s, 1H), 8.66 (s, 1H, -NH_2), 10.0 (s, -$CONH_2$, exchangeable). Anal. Found: C, 53.14; H, 3.34; N, 25.82. Calcd for $C_{12}H_9N_5O_3$: C, 53.22; H, 3.34; N, 25.90%.

Preparation of *N*-(6-carbonyl-methyl-7-oxo-1,7-dihydropyrano[2,3-*b*]pyrazolo[4,3-*e*]pyridine-3-yl) methanamide 8. To a stirred solution of 7-amino-6-carboxamidoxime-5-methyl-2-oxo-2*H*-pyrano [2,3-*b*] pyridine-3-carboxamide **4a**, (1.0 g, 0.0028 mole) in toluene (15 mL) was added *N*, *N*-dimethylformamide dimethyl acetal (0.47 g, 0.004 mole) and the reaction mixture was heated under reflux for 4-5 hr. The resulting solution was then allowed to cool to room temperature and the solvent was concentrated under reduced pressure. Purification of the residue by crystallization from ethanol to get **8**, m.p. 400-02°C; yield 58%; IR (KBr, cm^{-1}): 3435.1(-NH_2), 1689 (-C=O, lactone), 1638.1 (-C=O, amide); ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.17 (s, 3H, -CH_3), 7.90 (s, 1H), 8.4 (s, 1H, -CHO), 10.30 (s, -$CONH_2$, exchangeable). Anal. Found: C, 50.18; H, 3.16; N, 24.38. Calcd for $C_{12}H_9N_5O_4$: C, 50.23; H, 3.19; N, 24.43%.

Acknowledgement

The authors are thankful to Lupin Limited (Lupin Research Park) for supporting this work. Co-operation extended by all the colleagues of the analytical R & D division is gratefully acknowledged.

References

1 Clapp L B, in *Comprehensive Heterocyclic Chemistry*, edited by A R Katritzky & C W Rees, (Pergamom Press), 6, **1984**, p 365 and references cited therein.

2 Afiatpour P, Srivastva R M, de Oliverira M L & Barreiro E J, *Braz J Med Biol Res,* 27, **1994**, 1403.

3 Lima A A, *M A Thesis*, Departamento de Quimica Fundamental-Universidade Federal de Pernambuco, Recife, **1994**.

4 Diana G D & Nitz T J, *U S Pat*. 5,464,848 (Cl. 514-364; C07D413/12), 7 Nov **1995**; *US Appl.* 869, 287, 15 Apr **1992**, 34 pp; *Chem Abstr*, 124, **1996**, 124,176114h.

5 Aldous D J, Bailey T R, Diana G D, Nitz T J & Kuo, G-H. *PCT Int Appl WO* 95 31,452 (Cl.C07D403/12), 23 Nov **1995**; *US appl* 242,752, 13 May **1994**, 74 pp; *Chem Abstr* 124, **1996**, 232462j.

6 Jeschke P, Wachendorff-Neumann U, Erdelen C, Mencke N & Turberg A, *Ger Offen. DE* 4; 401.107 (Cl.C07D271/06), 20 Jul 1995, Appl. 17 Jan **1994**, 40 pp; *Chem Abstr* 123, **1995**, 340135t.

7 Jeschke P, Wachendorff-Neumann U, Erdelen C, Mencke N, *Ger Offen DE* 4,401,108 (Cl.C07D271/06), 20 Jul 1995, Appl. 17 Jan 1994, 35 pp; *Chem Abstr* 123, **1995**, 340136u.

8 a) Andersen K E, Jorgensen A S, Braestrup C, *Eur J Med Chem,* 29, **1994**, 393; b) Saunders J, Cassidy M, Freedman S B, Harley E A, Iversen L L, Kneen C, MacLeod A M, Merchant K J, Snow R J & Baker R, *J Med Chem,* 33, **1990**, 1128.

9 a) Showell G A, Gibbons T L, Kneen C O, MacLeod A M, Merchant K, Saunders J, Freedman S B, Patel S & Baker R, *J Med Chem* 34, **1991**, 1086; b) Messer Jr W S, Abuh Y F, Liu Y, Periysamy, Nagur D O, Edgar M A A, Ei-Assadi A A, Sbeih S, Dumbar P G, Roknich S, Ryo T, Fang Z, Ojo B, Zhang H, Huzl III J J & Nagy P I, *J Med Chem*, 40, **1997**, 1230; c) OrleK B S, Blaney F E, Brown F, Clark M S G, Hadley M S, Hatcher J, Riley G J, Rosenberg H E, Wadsworth H J & Wyman P, *J Med Chem*, 34, **1991**, 2726; Macor J E, Ordway T, Smith R L, Verhoest P R & Mack R A, *J Org Chem*, 61, **1996**, 3228.

10 Watjen F, Baker R, Engelstoff M, Herbert R, MacLeod A, Knight A, Merchant K, Moseley J, Saunders J, Swain C J, Wang E & Springer J P, *J Med Chem*, 32, **1989**, 2282; b) Tully W R, Gardner C R, Gillespie R J & Westwood R, *J Med Chem*, 34, **1991**, 2060.

11 Chen C Y, Senanayake C H, Bill T J, Larsen R D, Verhoeven T R & Reider P J, *J Org Chem*, 59, **1994**, 3738.

12 Swain C J, Baker R, Kneen C, Moseley J, Saunders J, Seward E M, Stevenson G, Beer M, Stanton J & Watling K, *J Med Chem*, 34, **1991**, 140.

13 Clitherow J W, Beswick P, Irving W J, Scopes D I C, Barnes J C, Clapham J, Brown J D, Evans D J, & Hanesn T K, *Bioorg Med Chem Lett*, 6, **1996**, 833.

14 a) Buchanan J L, Vu C B, Merry T J, Corpuz E G, Pradeepan S G, Main U N, Yang M, Plake H R, Varkhedkar V M, Lynch B A, Loiacono , Tiong C L & Holt D A, *Bioorg Med Chem Lett,* 9, **1999**, 2359; b) Vu C B, Corpuz E G, Merry T J, Pradeep S G, Bartlett C, Bohacek R S, Botfield M C, Eyermann C J, Lynch B A, MacNeil I A, Ram M K, van Schravendijk M R, Violette S & Sawyer T K, *J Med Chem*, 42, **1999**, 4088.

15 Matsumoto J, Takahashi T, Agata M, Toyofuku H & Sasada N, *Japanese Journal of Pharmacology*, 65 (1), **1994**, 51.

16 Ohmoto K, Yamamoto T, Imanishi H, Odagaki Y, Kawabata K, Sekioka T, Hirota Y, Matsuoka S, Nakai H & Toda M, *J Med Chem*, 43, **2000**, 4927.

17 Rudolph J, Theis H, Hanke R, Endermann R, Johannsen L & Geschke F U, *J Med Chem*, 44, **2001**, 619.

18 N Vasanth Kumar & Uday C Mashelker, *Indian J Chem*, communicated.

19 Vercek B, Leban I, Stanovnik B & Tisler M, *J Org Chem*, 44, **1979**, 1695.

20 Hydroxylamine was prepared from 6.62 g of hydroxylamine hydrochloride and an ethanolic solution of sodium ethoxide 13.2 g stirred for 15 min and filtered the NaCl, the ethanolic solution of hydroxylamine used as such.