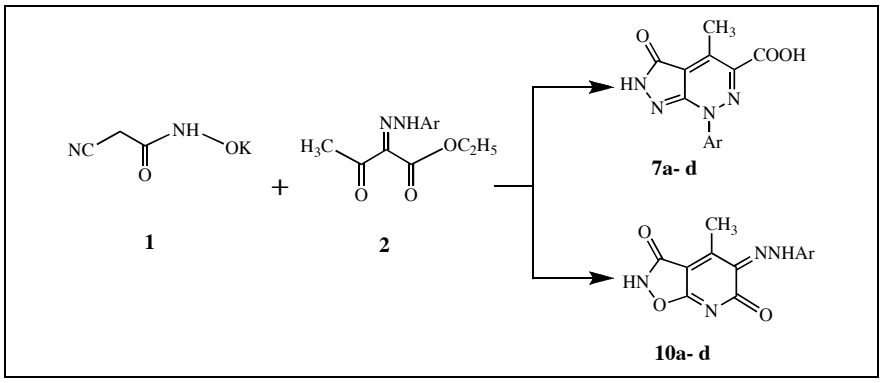
New One- Pot Synthesis of Pyrazolo[3,4-*c*]pyridazine and Isoxazolo-[5,4-*b*]pyridine Derivatives from Potassium Cyanoacetahydroxamate

Eman A. El-Rady * and Magda A. Barsy†

Chemistry Department, Faculty of Science, South Valley University, Aswan, Egypt.
emanelradi@hotmail.com

Recevied July 24, 2007



The reaction of potassium cyanoacetohydroxamate **1** with ethyl 2-aryl-hydrazono-3-oxobutyrates **2** gave the unexpected pyrazolo[3,4-*c*]pyridazines **7** and isoxazolo[5,4-*b*]pyridines **10** *via* a one-pot reaction. A mechanistic proof is suggested to account for the products.

J. Heterocyclic Chem., **45**, 1233 (2008).

INTRODUCTION

Pyrazole derivatives have attracted attention because of their use as a precursor for many drug substances, covering a broad spectrum of medicinal and pharmacological applications [1-6]. Such derivatives have antibacteriales, antifungicals, anticonvulsants [7], hypotensives [8], antidepressants [9] and neuroprotective [10] activities. They are also used as novel ligands for the estrogen recpetor [11]. Introduction of the azole ring to other heterocyclic compounds is expected to influence their biological activities significantly. Thus, the synthesis of pyrazolopyridazine derivatives [12-14] and their biological activities have attracted interest because they have shown remarkable effects on the central nervous system [15], they posses anti-inflammatory [16,17], anti-HSV-1 [18] activity and they are also used as selective inhibitors of cyclin-dependent kinases [19], recently they were investigated as ERK2 inhibitors [20] and found to be useful as peripheral vasodilators and evaluated as inhibitors of PDE5 extracted from human platelets [21]. On the other hand, the isoxazolopyridine revealed auxin activity [22] and cytotoxic activity against various human and mouse tumor cells. They also have potential as antiproliferative [23] and as HMG-CoA reductase inhibitors [24].

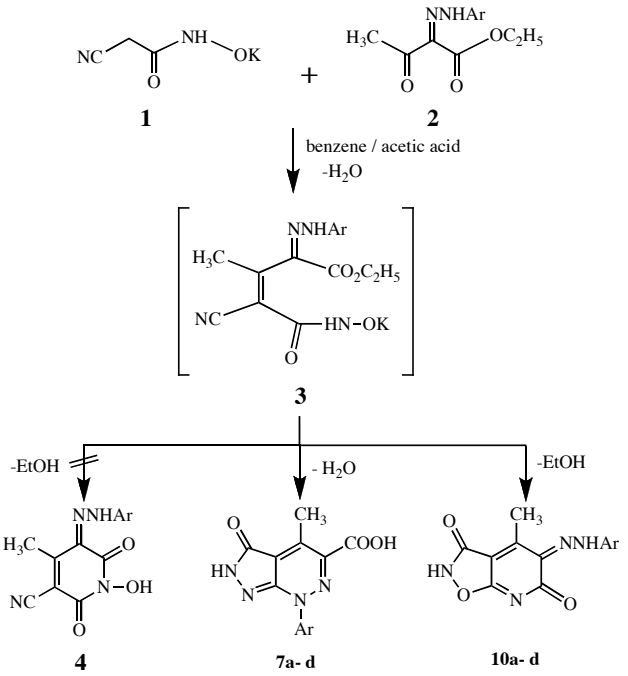
RESULTS AND DISCUSSION

Ethyl 2-arylhydrazono-3-oxobutyrates represent versatile reagents in organic synthesis. Recently, we reported their utility to prepare pyridine, pyridazine, cinnoline, phthalazine and other condensed heterocyclic derivatives [25-29]. Many new reported synthetic methods for pyrazolo-pyridazine and/or isoxazolo-pyridine derivatives have been based on using one functionalized pyrazole (pyridazine/isoxazole) ring to react with different reagents to construct the second heterocyclic ring. However, the strategy reported in this paper is based on the new and facile reaction of potassium cyanoacetohydroxamate **1** which was not used before in analogous synthesis with ethyl 2-arylhydrazono-3-oxobutyrates **2** to deliver pyrazolo-pyridazine and isoxazolo-pyridines analogs *via* a one-pot synthesis.

The first look on the two reactants led us to expect that the pyridine ring **4** would be the product *via* condensation - elimination reaction in accordance with our previous results [27, 29] as shown in Scheme 1.

However, potassium cyanoacetohydroxamate **1** reacted with ethyl 2-arylhydrazono-3-oxobutyrates **2a-d** under reflux in a mixture of benzene-acetic acid-ammonium acetate to give two products and no pyridine **4** was detected. Red crystals were formed during reflux, which had melting point > 350 °C, and lustrous yellow needles that melt at 200 °C were precipitated at room temperature, careful analysis of the filtrate showed that no other products were present. Each of the two products showed the same *m/z* at 270, compatible with the expected pyridine compound **4** which would formed *via* condensation-elimination reaction through formation of the intermediate **3**, formed *via* condensation step between the active

Scheme 1

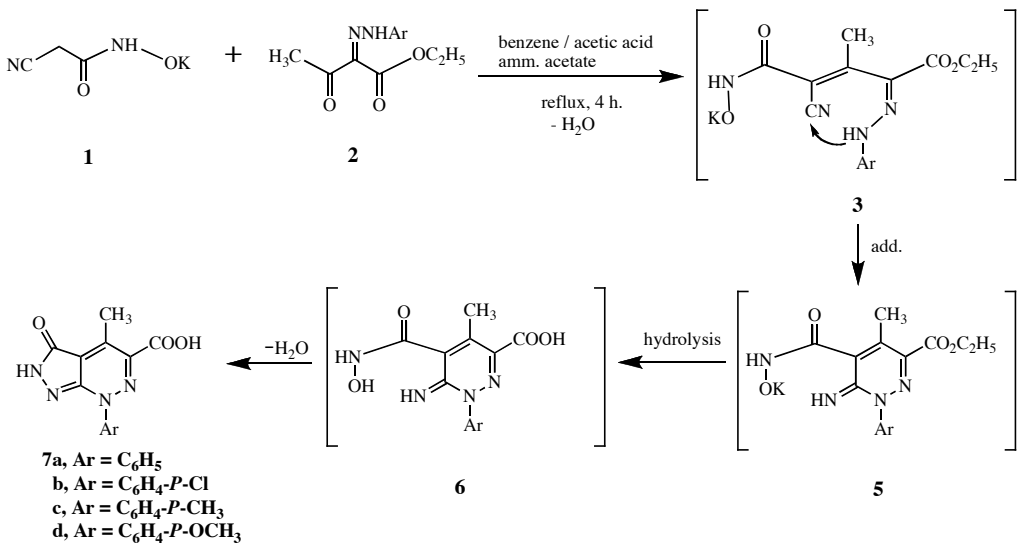


methylene of potassium cyanoacetohydroxamate **1** and the carbonyl oxygen of ester **2**, followed by elimination of ethanol (Scheme 1). However, the IR spectra showed no absorption band characteristic for the cyano function, as expected for compound **4**, and consequently formation of compound **4** was ruled out. On the other hand, the IR spectra revealed bands assigned for carbonyl and NH groups. Meanwhile, ^{1}H- and ^{13}C NMR spectra showed the absence of the characteristic absorption pattern of ethoxy protons of ester group. In this light, we assumed that the precursor of products **7a-d** and **10 a-d** can be the Knoevenagel intermediate **3**. To account for the formation of the products, it is plausible that intermediate **3** undergos intramolecular cycloaddition of the hydrazo hydrogen to the cyano function yielding the pyridazine intermediate **5**, which is hydrolyzed to the hydroxamic acid intermediate **6**, followed by loss of water to afford the red pyrazolo[3,4-*c*]pyridazine **7a-d**, (Scheme 2). The ^{1}H NMR spectra of **7a-d** showed singlet signals assigned for methyl and NH protons at δ 2.3-2.7 and 12.1-12.5 ppm, respectively. The ^{13}C NMR of **7a** showed signal at δ 15.2 ppm assigned for *C*H$_3$, 122.2-127.8 (*aryl-C*), 128.2 (*C*-6), 132.1 (*C*-5), 135.6 (*C*-6a), 140.3 (*C*-2a), 165.5 (*C*-7), 170.1 (*C*O$_2$H), while revealed the disappearance of any signal at 115-118 ppm of cyano carbon, which would be present in structure **4**.

On the other hand, in the key intermediate **3** the potassium of hydroxamate moiety may be hydrolyzed to the hydroxamic acid intermediate **8**. The latter readily is cyclized to the iminoisoxazolone intermediate **9** *via* an intramolecular cycloaddition of the hydrogen of hydroxamic acid to the cyano function. However, elimination of ethanol from **9** yielded the yellow isoxazolo[5,4-*b*]pyridine derivatives **10a-d**, (Scheme 3). The ^{1}H NMR spectrum of **10a** revealed two singlet signals at δ 2.3 and 12.6 ppm due to methyl and hydrazo protons respectively, beside multiplet at δ 7.1-7.9 ppm for aromatic and NH of isoxazolone.

Scheme 2

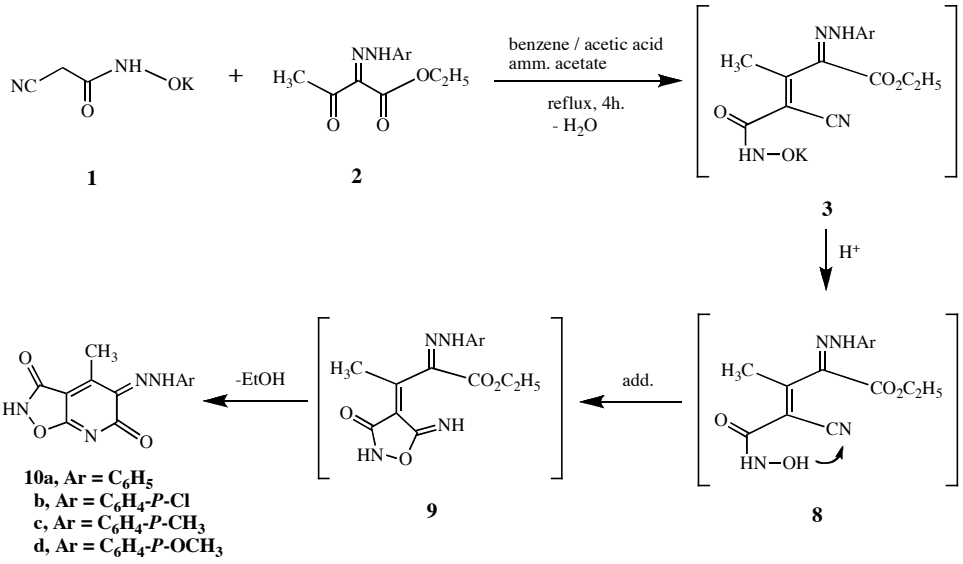
Formation of Pyrazolopyridines



7a, Ar = C$_6$H$_5$
b, Ar = C$_6$H$_4$-*P*-Cl
c, Ar = C$_6$H$_4$-*P*-CH$_3$
d, Ar = C$_6$H$_4$-*P*-OCH$_3$

Scheme 3

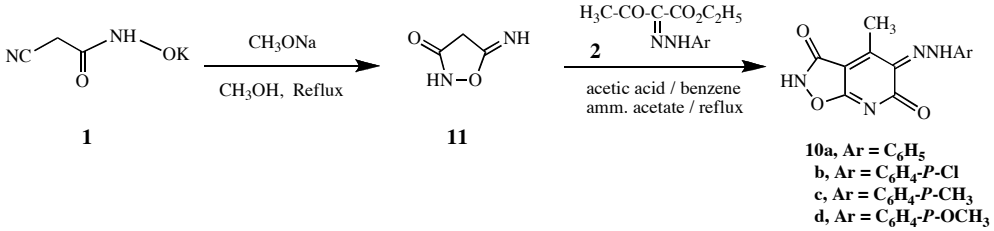
Formation of Isoxazolopyridines



Structure of **10** can be ascertained unequivocally as shown in scheme 4. The hydroxamate **1** was cyclized to isoxazolone **11** under reflux in methanolic sodium methoxide according to Khan [30] then allowed to react with the butyrates **2** using the same reaction conditions. The same isoxazolo[5,4-*b*]pyridines **10** were isolated as the sole products. This may confirm that the intermediate **8** underwent intramolecular cycloaddition forming the isoxazolone ring before ethanol elimination occurred.

Reaction of arylhydrazones (2a-d) with potassium cyanacetamidehydroxmate (1). A mixture of equimolar amounts **(1a)** (2.3 g, 0.01 mol), **(2a)** (1.8 g, 0.01 mol) and anhydrous ammonium acetate (0.77 g, 0.01mol) in acetic acid/benzene mixture (50:10 v/v) was heated for 4 hours under reflux using a Dean-Stark apparatus. The red crystals, which formed during reflux, were collected by filtration and identified as compounds **(7a-d)**. The filtrate was cooled to room temperature and the resulting crystals were collected by filtration to give compounds **(10a-d)**.

Scheme 4



EXPERIMENTAL

Melting points were determined on a Gallenkamp electrothermal melting point apparatus and are uncorrected. IR spectra were recorded as potassium bromide pellets on a Pye Unicame SP 3-300 and FT IR 8101 PC Shimadzu infrared spectrophotometer. The ^{1}H NMR, ^{13}C NMR spectra were obtained in deuterated dimethyl sulfoxide and/or chloroform on a Varian Gemini 200 NMR spectrometer using tetramethylsilane (TMS) as an internal reference. Mass spectra were recorded on a GC MS-QP 1000 EX Shimadzu mass spectrometer at 70 eV. Elemental analysis was carried out at the Microanalytical Center of Cairo University, Giza, Egypt. Potassium cyanacetamidehydroxmate **1** was prepared according to a published procedure [30].

4-Methyl-3-oxo-7-phenyl-2*H*-pyrazolo[3,4-*c*]pyridazine-5-carboxylic acid (7a). mp: >350 °C, Yield: 1g, 38 % (DMF/H_2O). IR: ν 1651-1700 (CO), 3106-3115 (NH), 3469 (OH) cm^{-1}; ^{1}H nmr (DMSO): δ 2.6 (*s*, 3H, CH_3), 7.3-7.9 (*m*, 5H, Ar-H), 12.5 (*s*, 1H, NH), 14.1 (*s*, 1H, OH); ^{13}C nmr: 15.2 (CH_3), 122.2-127.8 (aryl-C), 128.2 (C-6), 132.1 (C-5), 135.6 (C-6a), 140.3 (C-2a), 165.5 (C-7), 170.1 (COOH); MS (70 eV) *m/z* (%): 270 (M^+, 60). Anal. Calcd. For $C_{13}H_{10}N_4O_3$ (270.25): C, 57.78; H, 3.73; N, 20.73. Found: C, 57.88; H, 3.50; N, 20.60.

4-Methyl-3-oxo-7-(*p*-chlorophenyl)-2*H*-pyrazolo[3,4-*c*]-pyridazine-5-carboxylic acid (7b). mp: 315-17 °C, Yield: 0.8 g, 27 % (DMF / H_2O). IR: ν 1680-1698 (CO), 3185-3190 (NH), 3390 (OH) cm^{-1}; ^{1}H nmr (DMSO): δ 2.7 (*s*, 3H, CH_3), 7.0-7.7 (*m*, 4H, Ar-H), 12.2 (*s*, 1H, NH), 14.4 (*s*, 1H, OH); MS (70 eV)

m/z (%): 304 (M^+, 50). Anal. Calcd. For $C_{13}H_9ClN_4O_3$ (304.69): C, 51.25; H, 2.98; N, 18.39. Found: C, 51.47; H, 2.51; N, 18.60.

4-Methyl-3-oxo-7-(*p*-methylphenyl)-2*H*-pyrazolo[3,4-*c*]-pyridazine-5-carboxylic acid (7c). mp: 297- 99 °C, Yield: 0.9 g, 32 % (DMF / H_2O). IR: ν 1685-1695 (CO), 3184-3190 (NH), 3400 (OH) cm^{-1}; ^1H nmr (DMSO): δ 2.3 (*s*, 3H, CH_3), 2.6 (*s*, 3H, CH_3), 7.0-7.7 (*m*, 4H, Ar-H), 12.1 (*s*, 1H, NH), 14.1 (*s*, 1H, OH); MS (70 eV) *m/z* (%): 284 (M^+, 50). Anal. Calcd. For $C_{14}H_{12}N_4O_3$ (284.28): C, 59.15; H, 4.25; N, 19.71. Found: C, 59.32; H, 4.55; N, 19.68.

4-Methyl-3-oxo-7-(*p*-methoxyphenyl)-2*H*-pyrazolo[3,4-*c*]-pyridazine-5-carboxylic acid (7d). mp: 300 - 2 °C, Yield: 0.9 g, 26 % (DMF / H_2O). IR: ν 1695-1702 (CO), 3188-3199 (NH), 3420 (OH) cm^{-1}; ^1H nmr (DMSO): δ 2.3 (*s*, 3H, CH_3), 3.7 (*s*, 3H, CH_3), 7.1-7.6 (*m*, 4H, Ar-H), 12.2 (*s*, 1H, NH), 14.2 (*s*, 1H, OH); MS (70 eV) *m/z* (%): 300 (M^+, 40). Anal. Calcd. For $C_{14}H_{12}N_4O_4$(300.27): C, 56.00; H, 4.03; N, 18.66. Found: C, 56.16; H, 4.23; N, 18.88.

3,6-Dioxo-4-methyl-5-phenylhydrazo-2*H*-5,6-dihydroisoxazolo[5,4-*b*]pyridine (10a). mp: 200 - 2 °C, Yield: 0.9 g, 34 % (EtOH). IR: ν 1690-1701 (CO), 3194-3200 (NH) cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.3 (*s*, 3H, CH_3), 7.1-7.9 (*m*, 6H, Ar-H + NH), 12.6 (*s*, 1H, NH); ^1C nmr: 15.5 (CH_3), 127-130 (aryl-C), 132.9 (C-4), 142.2 (C-5),165.9 (C-6), 170.2 (C-3); MS (70 eV) *m/z* (%): 270 (M^+, 70). Anal. Calcd. For $C_{13}H_{10}N_4O_3$ (270.25): C, 57.78; H, 3.73; N, 20.73. Found: C, 57.85; H, 3.59; N, 20.65.

3,6-Dioxo-4-methyl-5-(*p*-chlorophenylhydrazo)-2*H*-5,6-dihydro-isoxazolo[5,4-*b*]pyridine (10b). mp: 210- 12 °C, Yield: 0.9 g, 30 % (EtOH). IR: ν 1689-1699 (CO), 3189-3190 (NH) cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.4 (*s*, 3H, CH_3), 7.0-7.6 (*m*, 5H, Ar-H + NH), 12.1 (*s*, 1H, NH); MS (70 eV) *m/z* (%): 304 (M^+, 60). Anal. Calcd. For $C_{13}H_9ClN_4O_3$ (304.69): C, 51.25; H, 2.98; N, 18.39. Found: C, 51.45; H, 2.59; N, 18.65.

3,6-Dioxo-4-methyl-5-(*p*-methylphenylhydrazo)-2*H*-5,6-dihydro-isoxazolo[5,4-*b*]pyridine (10c). mp: 190 - 92 °C, Yield: 1 g, 35 % (EtOH). IR: ν 1688-1702 (CO), 3184-3190 (NH) cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.4 (*s*, 3H, CH_3), 2.6 (*s*, 3H, CH_3), 7.0-7.7 (*m*, 5H, Ar-H + NH), 12.3 (*s*, 1H, NH); MS (70 eV) *m/z* (%): 284 (M^+, 40). Anal. Calcd. For $C_{14}H_{12}N_4O_3$ (284.28): C, 59.15; H, 4.25; N, 19.71. Found: C, 59.35; H, 4.50; N, 19.65.

3,6-Dioxo-4-methyl-5-(*p*-methoxyphenylhydrazo)-2*H*-5,6-dihydro-isoxazolo[5,4-*b*]pyridine (10d). mp: 195 - 97 °C, Yield: 1 g, 33 % (EtOH). IR: ν 1698-1702 (CO), 3184-3195 (NH) cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.3 (*s*, 3H, CH_3), 3.5 (*s*, 3H, CH_3), 7.0-7.6 (*m*, 5H, Ar-*H* + *NH*), 12.4 (*s*, 1H, NH); MS (70 eV) *m/z* (%): 300 (M^+, 40). Anal. Calcd. For $C_{14}H_{12}N_4O_4$ (300.27): C, 56.00; H, 4.03; N, 18.66. Found: C, 56.15; H, 4.13; N, 18.85.

REFERENCES

† The author is indebted to the Royal Society of Chemistry, Awards and Lectureships International Affairs for funding this research.

[1] Baldwin, J. J.; Lumma, P. K.; Novello, F. C.; Ponticello, G. S.; Sprague, J. M.; Duggan, D. E. *J. Med. Chem.* **1977**, *20*, 1189.

[2] Beck, J. R.; Lynch, M. P.; Patent , G. B. 2, 149, 402, 1985; *Chem. Abstr.* **1985**, *103*, 141938.

[3] Okada, I.; Okui, S.; Takahashi, Y.; Fukuchi, T.; Patent, E. P. 289, 879 1989; *Chem. Abstr.* **1989**, *110*, 96234.

[4] Ishikawa, H.; Moritia, T.; Oono, T.; Nakamura, T.; Taniguchi, M.; Yoshizawa, H.; Yochihara, M.; Patent, J. P. 1993, 5, 255, 316, *Chem. Abstr.* **1994**, *120*, 99438.

[5] Gursoy, A.; Demirayak, S.; Capan, G.; Erol, K. *Euro. J. Med. Chem.* **2000**, *35*, 359.

[6] Kucukguzel, S. G.; Rollas, S.; Erdeniz, H.; Kiraz, M.; Ekinci, A. C.; Vidin, A. *Euro. J. Med. Chem.* **2000**, *35*, 761.

[7] Londershausen, M. *Pestic. Sci.* **1996**, *48*, 269.

[8] Turan-Zitouni, G.; Chevallet, P.; Kilic, S.F.; Erol, K.; *Eur. J. Med. Chem.* **2000**, *35*, 635.

[9] Plaska, E.; Erol, D.; Demirdamar, R. *Eur. J. Med. Chem.* **1996**, *31*, 43.

[10] Shimada, F.; Shiga, Y.; Morikawa, M.; Kowazura, H.; Morikawa, O.; Matsuoka, T.; Nishizaki, T.; Saito, N. *Eur. J. Pharmacol* **1999**, *386*, 263.

[11] Katzenellenbogen, A. J.; Ying, H. R.; *Organic Letter* **2000**, *2(18)*, 2833.

[12] Ozer, I.; Emin, S.; Yunus, A.; *J. Heterocyclic Chem.* **2005**, *42*, 117.

[13] Shawali, A. S. *J. Heterocyclic Chem.* **1997**, *14*, 375.

[14] Shalaby, A. A.; *Phosphorus, Sulfur and Silicon* **2003**, *178(2)*, 199.

[15] Zabska, R.; Kolodziejczyk, A.; Sieklucka, D. M.; Morawska, D.; Kleinrok, Z. *Acta Pol Pharm* **1998**, *55(4)*, 305.

[16] Tewari, A. K. ; Mishra, A. *Bioorg. Med. Chem.* **2001**, *9(3)*, 715.

[17] Tewari, K. A.; Mishra, A. *Bioorg. Med. Chem.* **2001**, *9*, 715.

[18] Baraldi, G. P.; Manfredini, S.; Romagnoli, R.; Stevanato, L.; Zaid, N. A.; Manservigi, R. *Nucleos. Nucleot* **1998**, *17*, 2165.

[19] Brana, M. F.; Cacho, M.; Garcia, M. L.; Mayoral, E. P.; Lopez, B.; Depascual-eresa, B.; Romas, A.; Acero, N.; linares, F. L.; Munoz-Mingarro, D.; Lozach, O.; Meijer, L. *J. Med. Chem.* **2005**, *48(22)*, 6843.

[20] Kinoshita, T.; Warizaya, M.; Ohori, M.; Soto, K.; Neya, M.; Fujii, T. *Bioorg Med. Chem. Lett.* **2006**, *16(1),* 55.

[21] Dal Piaz, V.; Castellana, C. M.; Vergelli, C.; Giovannoni, P. M.; Gavalda, A.; Segarra,V.; Beleta, J; Ryder, H.; Palacios**,** M. J. *J. Enzyme Inhib Med. Chem.* **2002**, *17(4),* 277.

[22] Abignente, E.; Caprariis, P. De *Farmaco* **1975**, *30(12*), 992.

[23] Poreba, K. ; Wietrzyk, J. ; Opolski, A. *Acta Pol Pharm.* **2003**, *60(4)*, 293.

[24] Suzuki, M.; Iwasaki, H.; Fujikawa,Y.; Sakashita, M.; Kitahara, M.; Sakoda, R. *Bioorg. Med. Chem. Lett.* **2001**, *11(10)*, 1285.

[25] Barsy, M. A.; El Maghraby, M. A.; Ahmed, S. M. *J. Chinese Chem. Soc.* **1998**, *45*, 655.

[26] El Nagdi, M. H.; Barsy, M. A.; Abed El Latif, F. M.; Sadek, K.U. *J. Chem. Res(S)* **1998**, 26.

[27] Barsy, M. A. *J. Chinese Chem. Soc.* **2000**, *47*, 951.

[28] Barsy, M. A.; Abd El Latif, F. M.; El Rady, E. A.; Hassan, M. E.; El Maghraby, M. A. *Synthetic Commun.* **2001**, *31(17)*, 2569.

[29] El Rady, E. A.; Barsy, M. A. *J. Heterocyclic Chem.* **2006**, *43*, 243

[30] Khan, M. A.; Rafla, F. K. *J. Chem. Soc., Perkin 1*, **1974**, 327.