

The conversion of the 2(3*H*)-furanone into the oxazinone and pyrimidinone derivatives is studied. A 2-(furan-2-ylmethylene)-4-oxo-4-phenylbutanoyl azide **3** was synthesized to carry out these conversions through its thermolysis in dry benzene and/or base-catalyzed decomposition of this azide in the presence of different amines. The structures of all compounds were demonstrated from their spectral data and elemental analyses.

J. Heterocyclic Chem., **00**, 00 (2017).

INTRODUCTION

In the last decades, our research group was interested in the conversion of 2(3*H*)-furanones into a variety of heterocyclic systems of synthetic and biological importance. Based on their facile ring opening by nitrogen nucleophiles, these furanones were converted into acyclic products that, via ring closure, afforded many heterocycles, namely, pyrrolones, pyridazinones, triazoles, oxadiazoles, thiazolidinones, and benzoxazinones [1–17]. To our knowledge, the conversion of 2(3*H*)-furanones into pyrimidine derivatives has not been reported. Pyrimidine derivatives have a wide spectrum of

biological activities. These derivatives are reported to have antiviral [18], antibacterial [19], anti-inflammatory [20], antimalarial [21], anticancer [22], and antihypertensive activities [23]. In view of the foregoing facts, we report herein the conversion of 2(3*H*)-furanones into oxazinone and pyrimidinone derivatives.

RESULTS AND DISCUSSION

Conventionally, 2-(furan-2-ylmethylene)-4-oxo-4-phenylbutanoyl azide **3** was previously prepared *via* the following two steps: (i) The 2(3*H*)-furanone **1** reacted with hydrazine

hydrate at room temperature in ethanol to give the acid hydrazide **2**. (ii) The hydrazide was converted into the corresponding acyl azide **3** by the action of sodium nitrite in AcOH [7] (Scheme 1). The structure of **3** was inferred from its IR spectrum that displayed ν_{N_3} of azide at 2142 cm^{-1} and devoid from NH and NH_2 absorption bands.

Acyl azides are known to be suitable candidates for the synthesis of many acyclic and heterocyclic derivatives via their acid or base-catalyzed decompositions. Thus, it was of interest to the authors to construct oxazinone and pyrimidinone derivatives using the azide **3** as a key starting material. The reactions of **3** with benzylamine, hydrazine, and *p*-toluidine were studied (Scheme 2). Thermolysis of the azide in dry benzene led to the construction of oxazinone derivative **4** as a sole product (Scheme 1). The formation of **4** can be postulated *via* loss of nitrogen gas then Curtius rearrangement of the resulting nitrene to afford the isocyanate intermediate (non-isolable) followed by exo-trig ring closure (Scheme 3). The structure of **4** was substantiated from its IR spectrum that lacked $\nu_{\text{N}=\text{C}=\text{O}}$ of isocyanate group and only displayed the stretching absorption bands of oxazinone CO and NH at ν 1732 and 3175 cm^{-1} , respectively. The $^1\text{H-NMR}$ spectrum was a good evidence for its existence as a mixture of lactam-lactim tautomers in the ratio 9:1 as it shows two singlet signals at δ 13.28 and 13.25 ppm displayed, both integrated to one exchangeable proton of $\text{NH-CO}\rightleftharpoons\text{N}=\text{C-OH}$ grouping. Moreover, the mass spectrum exhibited the correct molecular ion peak at m/z 253 (46%) as well as the base peak at m/z 252 (100%) representing $[\text{M}-1]$ cation. The same product **4** was obtained via pyrolysis of the azide by fusion in neat.

When azide **3** was allowed to react with benzylamine in dry benzene at room temperature, the benzylurea derivative **5** was obtained. While the reaction in refluxing benzene for 1 h resulted in the formation of pyrimidinone derivative **6**.

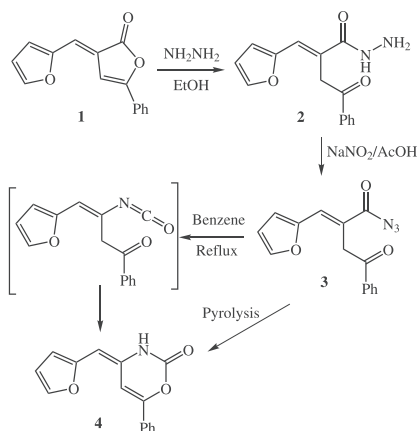
The structures of **5** and **6** were deduced from their analytical and spectral data. The IR spectrum of **5** revealed a broad band at 3247 cm^{-1} attributable to NH groups, as well as the characteristic absorption bands for $\text{C}=\text{O}$ of ketone and amide groups at 1671 and 1643 cm^{-1} , respectively. The $^1\text{H-NMR}$ spectrum of **5** showed that CH_2CO protons were magnetically non-equivalent, which may be attributed to hydrogen bonding between $\text{PhC}=\text{O}$ and NH groups. The appearance of two singlet signals corresponding to the olefinic proton in the ratio of 2:1 is a good evidence for the existence of compound **5** as E/Z-mixture respectively (Cf. Experimental). The $^1\text{H-NMR}$ spectrum of **6** was devoid of the splitting pattern of CH_2CO group and showed a singlet band at δ 4.8 ppm due to benzyl- CH_2 protons, as well as two singlet signals at δ 10.03 and 10.04 ppm , both integrated to one exchangeable proton of $\text{NH-CO}\rightleftharpoons\text{N}=\text{C-OH}$ grouping in the ratio of 5:1, respectively.

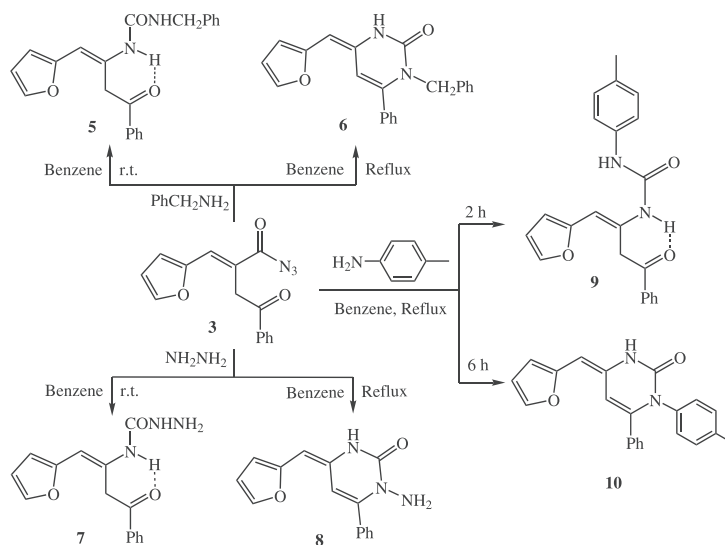
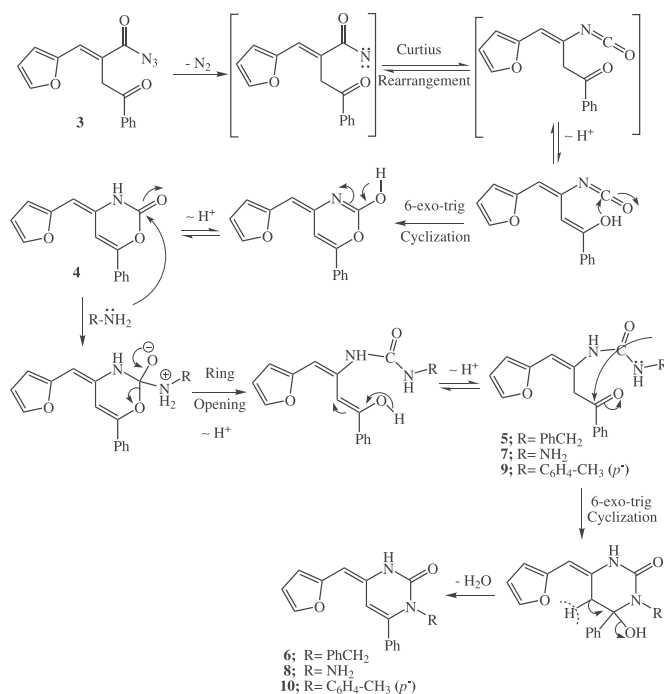
The reaction of **3** with hydrazine was also dependent on the reaction conditions. Thus, stirring of **3** with hydrazine in benzene at room temperature afforded the semicarbazide derivative **7** while at refluxing conditions; 1-aminopyrimidinone derivative **8** was produced. The IR spectrum of **7** showed broad bands at 3331 and 3208 cm^{-1} attributable to NH and NH_2 groups, as well as the characteristic absorption bands for $\text{C}=\text{O}$ of ketone and hydrazide groups at 1700 and 1659 cm^{-1} . The $^1\text{H-NMR}$ spectrum of **7** exhibited geminal coupling of two magnetically non-equivalent protons of CH_2 ($J = 16.4\text{ Hz}$) as an evidence for the aforementioned hydrogen bonding. This compound exists as E/Z-mixture as it shows two singlet signals for the olefinic proton in the ratio 2:1, respectively (Cf. Experimental).

The aromatic amine, *p*-toluidine, failed to affect decomposition of the azide **3** at room temperature, a behavior that may be attributed to the weak nucleophilicity of the *p*-toluidine nitrogen atom. But when the reaction was carried out in dry benzene at 90°C for 2 h, base-catalyzed decomposition occurred with the formation of the *p*-tolylurea derivatives **9**. On the other hand, carrying out the reaction under reflux conditions for 6 h led to the construction of *p*-tolylpyrimidinone derivative **10**. The IR spectrum of **9** provided the characteristic absorption bands for two NH and two $\text{C}=\text{O}$ of ketone and amide groups at 3317 and 3209 cm^{-1} and 1699 and 1650 cm^{-1} , respectively. Also, the geminal coupling between CH_2 protons ($J = 16.0\text{ Hz}$) was clearly shown in its $^1\text{H-NMR}$ spectrum indicating to hydrogen bonding. Similarly, this compound exists as E/Z-mixture in the ratio 3:1 as it shows two singlet signals for the olefinic proton in the ratio 3:1, respectively (Cf. Experimental).

The formation of the oxazinone and pyrimidinone derivatives may be represented by Scheme 3.

Scheme 1. Synthesis of azide **3**.



Scheme 2. Reactions of azide **3**.**Scheme 3.** Formation of the oxazinone and pyrimidinone derivatives.

EXPERIMENTAL

Melting points were measured on Gallen Kamp electric melting point apparatus. The IR spectra were recorded using potassium bromide disks on Fourier transform infrared Thermo Electron Nicolet 7600 spectrometer (Thermo Fisher Scientific Inc., Waltham, MA) at the Central Laboratory of Faculty of Science, Ain Shams University. The ^1H -NMR spectra were run at 400 MHz on a GEMINI 400 BB NMR spectrometer (GEMINI,

Manufacturing & Engineering Inc., Anaheim, CA) using tetramethyl silane (TMS) as an internal standard in deuterated dimethylsulphoxide ($\text{DMSO}-d_6$) at the Main Defense Chemical Laboratory, Cairo. The mass spectra were recorded on Shimadzu GC-MS-QP-1000EX mass spectrometer (Shimadzu Scientific Instruments, Inc., Columbia, MD) operating at 70 eV at the Micro-analytical Center of Cairo University. The progress of all reactions was monitored by the thin-layer chromatography using Merck Kiesel gel 60 F254 aluminum backed plates.

General procedure for preparation of 4-(furan-2-ylmethylene)-6-phenyl-3,4-dihydro-2H-1,3-oxazin-2-one (4). A solution of the azide **3** (5 mmol) in dry benzene (20 mL) was heated under reflux for 1 h. The separated solid after cooling was collected by filtration and recrystallized from petroleum ether, 80–100/benzene, (2:1) to afford oxazinone **4** as red crystals; mp. 170–172°C, yield 49%. IR (KBr) (ν , cm^{-1}): 3175 (NH), 3057, 3040 (Aryl-H), 1732 ($\text{C}=\text{O}_{\text{Oxazinone}}$), 730, 684 (δ_{5H}). $^1\text{H-NMR}$ (DMSO- d_6): δ_{H} (ppm) 13.28 (br.s, 1H, OH, Lactim form, *exchangeable*), 13.25 (br.s, 1H, NH, Lactam form, *exchangeable*), 8.10–6.91 (m, 8H, Ar-H), 6.78 (s, 1H, C-H_{Oxazinone}), 6.48 (s, 1H, CH=). MS (m/z , %): 253 (M^+ , 46), 252 (100), 222 (62), 194 (67), 115 (34), 104 (23), 81 (36), 77 (64). Anal. Calcd. for $\text{C}_{15}\text{H}_{11}\text{NO}_3$ (253.07): C, 71.14; H, 4.38; N, 5.53. Found: C, 71.08; H, 4.27; N, 5.42.

Pyrolysis of azide 3. In a 10-mL round-bottomed flask fitted with an air condenser, 0.5 g of the azide **3** was placed. The flask was heated on a sand bath whereby the azide was fused. Heating was continued for another 1 h. The product obtained after recrystallization from petroleum ether, 80–100/benzene, (2:1) was proved by direct comparison (mp., mixed mp. and TLC) to be the oxazinone **4**.

Reaction of the azide 3 with benzylamine. Benzylamine (2 mmol) was added dropwise to a solution of azide **3** (2 mmol) in dry benzene (20 mL) and the mixture was stirred at room temperature for 2 h or heated under reflux for 1 h. The precipitated solid was collected by filtration and recrystallized from petroleum ether, 80–100/benzene (3:1) to give benzylurea **5** and *N*-benzylpyrimidine **6**, respectively.

E,Z-1-Benzyl-3-(1-(furan-2-yl)-4-oxo-4-phenylbut-1-en-2-yl)urea (5). Brown crystals, mp. 195–197°C, yield 52%. IR (KBr) (ν , cm^{-1}): 3247 (NH), 3059, 3028 (Aryl-H), 2937, 2922 (Alkyl-H), 1671 ($\text{C}=\text{O}_{\text{Ketone}}$), 1643 ($\text{C}=\text{O}_{\text{Amide}}$), 759, 692 (δ_{5H}). $^1\text{H-NMR}$ (DMSO- d_6): δ_{H} (ppm) 9.51 (br.s, 1H, NHCO, *exchangeable*), 9.20 (br.s, 1H, NHCH_2 , *exchangeable*), 7.75–7.05 (m, 13H, Ar-H), 6.73, 6.56 (*Two singlets*, 1H, *E* and *Z* isomers, CH=), 4.33 (s, 2H, NHCH_2), 3.19–3.01 (dd, 2H, CH_2CO , $J = 16.4$ Hz). MS (m/z , %): 360 (M^+ , 10), 253 (42), 210 (50), 192 (60), 106 (3), 91 (100), 77 (51). Anal. Calcd. for $\text{C}_{22}\text{H}_{20}\text{N}_2\text{O}_3$ (360.15): C, 73.32; H, 5.59; N, 7.77. Found: C, 73.21; H, 5.43; N, 7.68.

1-Benzyl-4-(furan-2-ylmethylene)-6-phenyl-3,4-dihydropyrimidin-2(1H)-one (6). Yellow crystals, mp. 148–150°C, yield 47%. IR (KBr) (ν , cm^{-1}): 3259 (NH), 3065, 3021 (Aryl-H), 2955, 2935 (Alkyl-H), 1652 ($\text{C}=\text{O}$), 738, 692 (δ_{5H}). $^1\text{H-NMR}$ (DMSO- d_6): δ_{H} (ppm) 10.04 (s, 1H, OH, *Lactim form*, *D₂O-Exchangeable*), 10.03 (s, 1H, NH, *Lactam form*, *D₂O-Exchangeable*), 7.75–7.05 (m, 13H, Ar-H), 6.83 (s, 1H, C-H_{pyrimidine}), 6.66 (s, 1H, CH=), 4.81 (s, 2H, CH_2). MS (m/z , %): 342 (M^+ , 100), 251 (40),

223 (55), 208 (42), 166 (29), 91 (80), 77 (32). Anal. Calcd. for $\text{C}_{22}\text{H}_{18}\text{N}_2\text{O}_2$ (342.14): C, 77.17; H, 5.30; N, 8.18. Found: C, 77.08; H, 5.21; N, 8.02.

Reaction of the azide 3 with hydrazine hydrate: synthesis of E,Z-N-(1-(furan-2-yl)-4-oxo-4-phenylbut-1-en-2-yl)hydrazinecarboxamide (7). Hydrazine (2 mmol) was added dropwise to a solution of azide **3** (2 mmol) in dry benzene (20 mL) and the mixture was stirred at room temperature. The obtained solid was collected by filtration and recrystallized from benzene to give the semicarbazide derivative **7** as brown crystals, mp. 205–207°C, yield 39%. IR (KBr) (ν , cm^{-1}): 3331, 3208 (NH, NH_2), 3064, 3032 (Aryl-H), 2923, 2859 (Alkyl-H), 1700 ($\text{C}=\text{O}_{\text{Ketone}}$), 1659 ($\text{C}=\text{O}_{\text{Amide}}$), 743, 699 (δ_{5H}). $^1\text{H-NMR}$ (DMSO- d_6): δ_{H} (ppm) 9.01 (br.s, 1H, NH, *exchangeable*), 7.34 (s, 1H, NHNH_2 , *D₂O-Exchangeable*), 7.75–6.72 (m, 8H, Ar-H), 6.56, 6.45 (*Two singlets*, 1H, *E* and *Z* isomers, CH=), 4.50 (br.s, 2H, NH_2 , *exchangeable*), 3.19–3.00 (dd, 2H, CH_2 , $J = 16.4$ Hz). MS (m/z , %): 285 (M^+ , 14), 255 (39), 227 (21), 150 (12), 180 (10), 119 (20), 77 (100). Anal. Calcd. for $\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}_3$ (285.11): C, 63.15; H, 5.30; N, 14.73. Found: C, 63.04; H, 5.19; N, 14.61.

Synthesis of 1-amino-4-(furan-2-ylmethylene)-6-phenyl-3,4-dihydropyrimidin-2(1H)-one (8). A solution of the azide **3** (2 mmol) and hydrazine (2 mmol) in dry benzene (20 mL) was heated at 90°C for 1 h. The reaction mixture was concentrated and then cooled. The obtained solid was collected by filtration and recrystallized from petroleum ether, 60–80/benzene (2:1) to give 1-aminopyrimidinone derivative **8** as faint brown crystals, mp. 160–162°C, yield 35%. IR (KBr) (ν , cm^{-1}): 3330, 3204 (NH, NH_2), 3063, 3032 (Aryl-H), 1659 ($\text{C}=\text{O}$), 743, 699 (δ_{5H}). $^1\text{H-NMR}$ (DMSO- d_6): δ_{H} (ppm) 13.10 (br.s, 1H, NH, *exchangeable*), 7.94–6.81 (m, 8H, Ar-H), 6.69 (s, 1H, $\text{CH}_{\text{pyrimidine}}$), 6.39 (s, 1H, CH=), 4.99 (br.s, 2H, NH_2 , *exchangeable*). MS (m/z , %): 267 (M^+ , 100), 239 (21), 162 (28), 102 (19), 81 (15), 77 (30). Anal. Calcd. for $\text{C}_{15}\text{H}_{13}\text{N}_3\text{O}_2$ (267.10): C, 67.40; H, 4.90; N, 15.72. Found: C, 67.28; H, 4.75; N, 15.58.

Reaction of the azide 3 with p-toluidine; synthesis of 1-(1-(furan-2-yl)-4-oxo-4-phenylbut-1-en-2-yl)-3-p-tolylurea (9).

p-Toluidine (2 mmol) was added to a solution of the azide **3** (2 mmol) in dry benzene (20 mL), and the mixture was heated on water bath for 2 h. The obtained solid was collected by filtration and recrystallized from petroleum ether, 80–100/benzene (2:1) to give *p*-tolylurea derivative **9** as brown crystals, mp. 220–222°C, yield 49%. IR (KBr) (ν , cm^{-1}): 3316, 3209 (2 NH), 3088, 3025 (Aryl-H), 2915, 2858 (Alkyl-H), 1699 ($\text{C}=\text{O}_{\text{Ketone}}$), 1650 ($\text{C}=\text{O}_{\text{Amide}}$), 733, 687 (δ_{5H}). $^1\text{H-NMR}$ (DMSO- d_6): δ_{H} (ppm) 9.80 (s, 1H, NHTolyl , *D₂O-Exchangeable*), 9.05 (s, 1H, NH, *D₂O-Exchangeable*), 7.75–6.83 (m, 8H, Ar-H), 7.19–7.17 (d, 2H, HTolyl , $J = 8$ Hz), 7.05–7.03 (d, 2H, HTolyl , $J = 8$ Hz), 6.73, 6.56 (*Two singlets*, 1H, *E* and *Z* isomers, CH=), 3.20–3.05 (dd, 2H, CH_2 , $J = 16$ Hz), 2.27 (s, 3H, CH_3). MS (m/z , %): 360 (M^+ , 51), 345 (41), 270 (25),

193 (15), 119 (28), 91 (100), 77 (50). Anal. Calcd. for $C_{22}H_{20}N_2O_3$ (360.15): C, 73.32; H, 5.59; N, 7.77. Found: C, 73.20; H, 5.42; N, 7.64.

Synthesis of 4-(furan-2-ylmethylene)-6-phenyl-1-p-tolyl-3,4-dihydropyrimidin-2(1H)-one (10). A solution of the azide **3** (2 mmol) and *p*-toluidine (2 mmol) in dry benzene (20 mL) was refluxed for 6 h. The obtained solid after cooling was collected by filtration and recrystallized from benzene to give *N*-*p*-tolylpyrimidine derivative **10** as orange crystals, mp. 178–180°C, yield 38%. IR (KBr) (ν , cm^{-1}): 3317 (NH), 3061, 3025 (Aryl-H), 2974, 2918 (Alkyl-H), 1649 (C=O), 733, 687 (δ_{5H}). 1H -NMR (DMSO- d_6): δ_H (ppm) 12.16 (br.s, 1H, NH, *exchangeable*), 7.94–7.02 (m, 8H, Ar-H), 7.27–7.25 (d, 2H, H_{Tolyl} , $J = 8$ Hz), 7.08–7.06 (d, 2H, H_{Tolyl} , $J = 8$ Hz), 6.68 (s, 1H, C-H_{pyrimidine}), 6.38 (s, 1H, CH=), 2.33 (s, 3H, CH₃). MS (m/z , %): 342 (M^+ , 40), 327 (100), 252 (50), 146 (18), 102 (10), 90 (21), 77 (100). Anal. Calcd. for $C_{22}H_{18}N_2O_2$ (342.14): C, 77.17; H, 5.30; N, 8.18. Found: C, 77.05; H, 5.18; N, 8.04.

REFERENCES AND NOTES

- [1] Abou-Elmagd, W. S. I.; El-Ziaty, A. K.; El-Zahar, M. I.; Ramadan, S. K.; Hashem, A. I. *Synth Commun* 2016, 46, 1197.
- [2] Abou-Elmagd, W. S. I.; Hashem, A. I. *J Heterocyclic Chem* 2016, 53, 202.
- [3] El-Ziaty, A. K.; Abou-Elmagd, W. S. I.; Ramadan, S. K.; Hashem, A. I. *Synth. Commun* 2017, 47, 471.
- [4] Hashem, A. I.; Youssef, A. S. A.; Kandeel, K. A.; Abou-Elmagd, W. S. I. *Eur J Med Chem* 2007, 42, 934.
- [5] Kandeel, K. A.; Youssef, A. S. A.; Abou-Elmagd, W. S. I.; Hashem, A. I. *J Heterocyclic Chem* 2006, 43, 957.
- [6] Abou-Elmagd, W. S. I.; El-Ziaty, A. K.; Abdalha, A. A. *Heterocycl Commun* 2015, 21, 179.
- [7] Abou-Elmagd, W. S. I.; Hashem, A. I. *J Heterocyclic Chem* 2012, 49, 947.
- [8] Abou-Elmagd, W. S. I.; Hashem, A. I. *Synth Commun* 2013, 43, 1083.
- [9] Abou-Elmagd, W. S. I.; Hashem, A. I. *Med Chem Res* 2013, 22, 2005.
- [10] Sayed, H. H.; Hashem, A. I.; Youssef, N. M.; El-Sayed, W. A. *Arch Pharm Chem* 2007, 340, 315.
- [11] El-Kousy, S. M.; El-Torgoman, A. M.; El-Bassiouny, A. A.; Hashem, A. I. *Pharmazie* 1988, 43, 80.
- [12] Hashem, A. I.; Shaban, M. E. *J Prakt Chem* 1981, 323, 164.
- [13] Hashem, A. I.; Senning, A. *Adv Heterocycl Chem* 1999, 73, 275.
- [14] Hamad, A. S.; Hashem, A. I. *Molecules* 2000, 5, 895.
- [15] Hamad, A. S.; Hashem, A. I. *J Heterocyclic Chem* 2002, 39, 1325.
- [16] Yassin, S.; Abd El-Aleem, H. A.; El-Sayed, I. E.; Hashem, A. I. *Rev Roum Chim* 1996, 41, 989.
- [17] Hamad, A. S.; Hashem, A. I.; El-Kafrawy, A. F.; Saad, M. M. *Phosphorus, Sulfur, Silicon and the Related Elements* 2000, 159, 157.
- [18] Haly, A.; Votruba, I.; Masojdjkova, M.; Andrei, G.; Snoeck, R.; Naesens, L.; De Clercq, E.; Balzarini, J. *J. Med Chem* 2002, 45, 1918.
- [19] Cieplik, J.; Stolarczyk, M.; Pluta, J.; Gubrynowicz, O.; Bryndal, I.; Lis, T.; Mikulewicz, M. *Acta Pol. Pharm.* 2011, 68, 57.
- [20] Nofal, Z. M.; Fahmy, H. H.; Zarea, E. S.; El-Eraky, W. *Acta Pol Pharm* 2011, 68, 507.
- [21] Agarwal, A.; Srivastava, K.; Puri, S. K.; Chanhani, P. M. *Bioorg Med Chem Lett* 2005, 15, 3130.
- [22] Yai-Yam, H.; Jim-Ni, Z.; Ruo, J.; Yung-Lan, Z.; Sheng-Yang, Y.; Luo-Ting, Y.; Li, Y. *Molecules* 2011, 16, 10685.
- [23] Alam, O.; Khan, S. A.; Siddiqui, N.; Ahsan, W.; Verma, S. P.; Gilani, S. J. *Eur J Med Chem* 2010, 45, 5113.