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[A0031]

Convenient synthesis of some methyl-*N*-[2-(6-oxo-3-p-tolyl-5,6-dihydro-4H-pyridazin-1-yl)-acetamide]alkanoates

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Abstract:

An efficient *one-pot* synthesis of methyl-*N*-[2-(6-oxo-3-p-tolyl-5,6-dihydro-4H-pyridazin-1-yl)-acetamide]alkanoates **5a-j** and dipeptides **8a-f** was successfully realized starting from amino acid esters **4** and azides **3**, **7,** respectively. The hydrazide **6a** was further reacted with selected aldehydes to give the corresponding hydrazones **9a-c**.

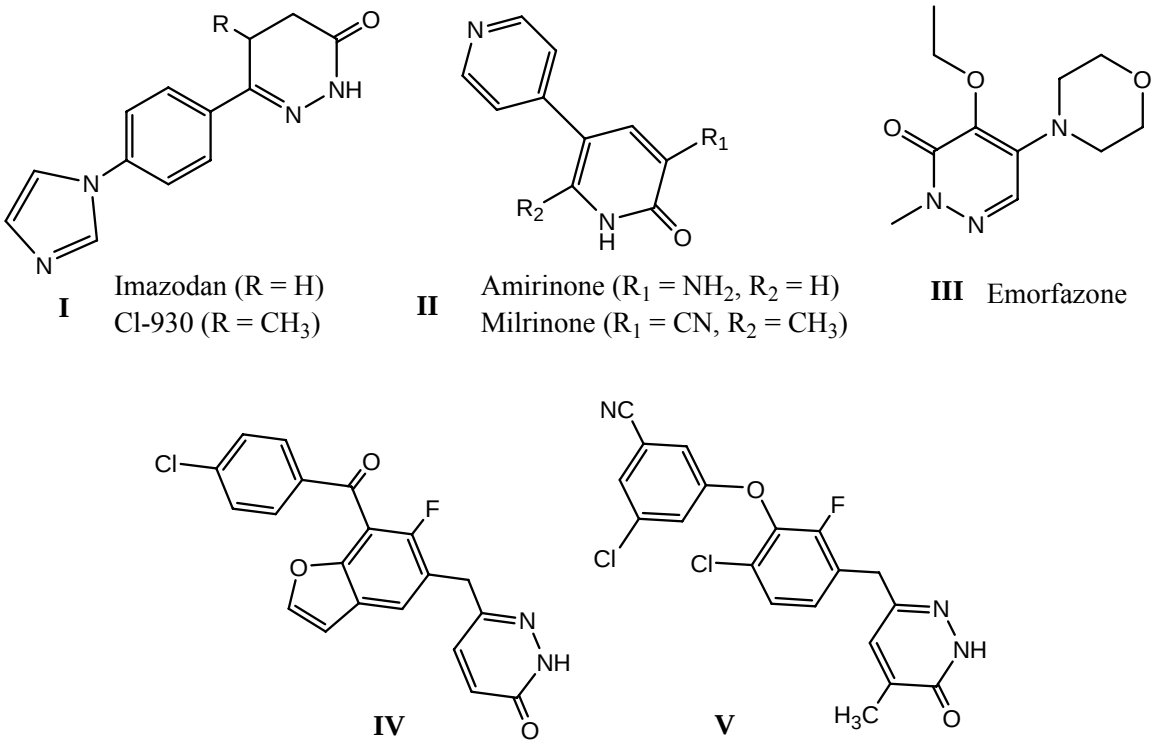
Keywords: amino acids, dipeptide, azide coupling, dihydro-2H-pyridazin-3-one, hydrazones.

Introduction

Pyridazines represent an important class of biologically active compounds. Recently, a substantial number of 6-aryl-3-(2*H*)-pyridazinones have been reported to possess antimicrobial[1,2], potent analgesic[3], anti-inflammatory[3-7], antifeedant[8], herbicidal[9], antihypertensive[10-12] and antiplatelet activities[13-15], anticancer effects[16] and other anticipated biological[17] and pharmacological properties[18,19]. Besides, arylsubstituted 4,5-dihydro-3(2*H*)-pyridazinones such as imazodan **I** are reported to show ionotropic properties comparable to milrinone and amrinone **II**. Emorfazone (4-ethoxy-2-methyl-5-morpholino-3(2*H*)-pyridazinone) **III** is an analgesic and anti-inflammatory compound marketed as pentoil and nandron[20-23].

Also, a series of benzyl pyridazinones **IV** were evaluated as HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTIs)[24]. Several members of this series showed good

activity against the wild-type virus and NNRTI resistant viruses. Crystal structures of inhibitors bound to HIV-RT demonstrated that the pyridazinones **V** interact with the protein backbone through a pair of hydrogen bonds between the amide of the K103 amino acid and the N-NH acceptor–donor motif of the pyridazinone. Inspection of the small molecule crystal structures of the inhibitors themselves revealed that in the solid state the pyridazinones were associated through extensive aromatic stacking interactions [25].



I Imazodan (R = H)
Cl-930 (R = CH_3)

II Amirinone (R_1 = NH_2, R_2 = H)
Milrinone (R_1 = CN, R_2 = CH_3)

III Emorfazone

IV

V

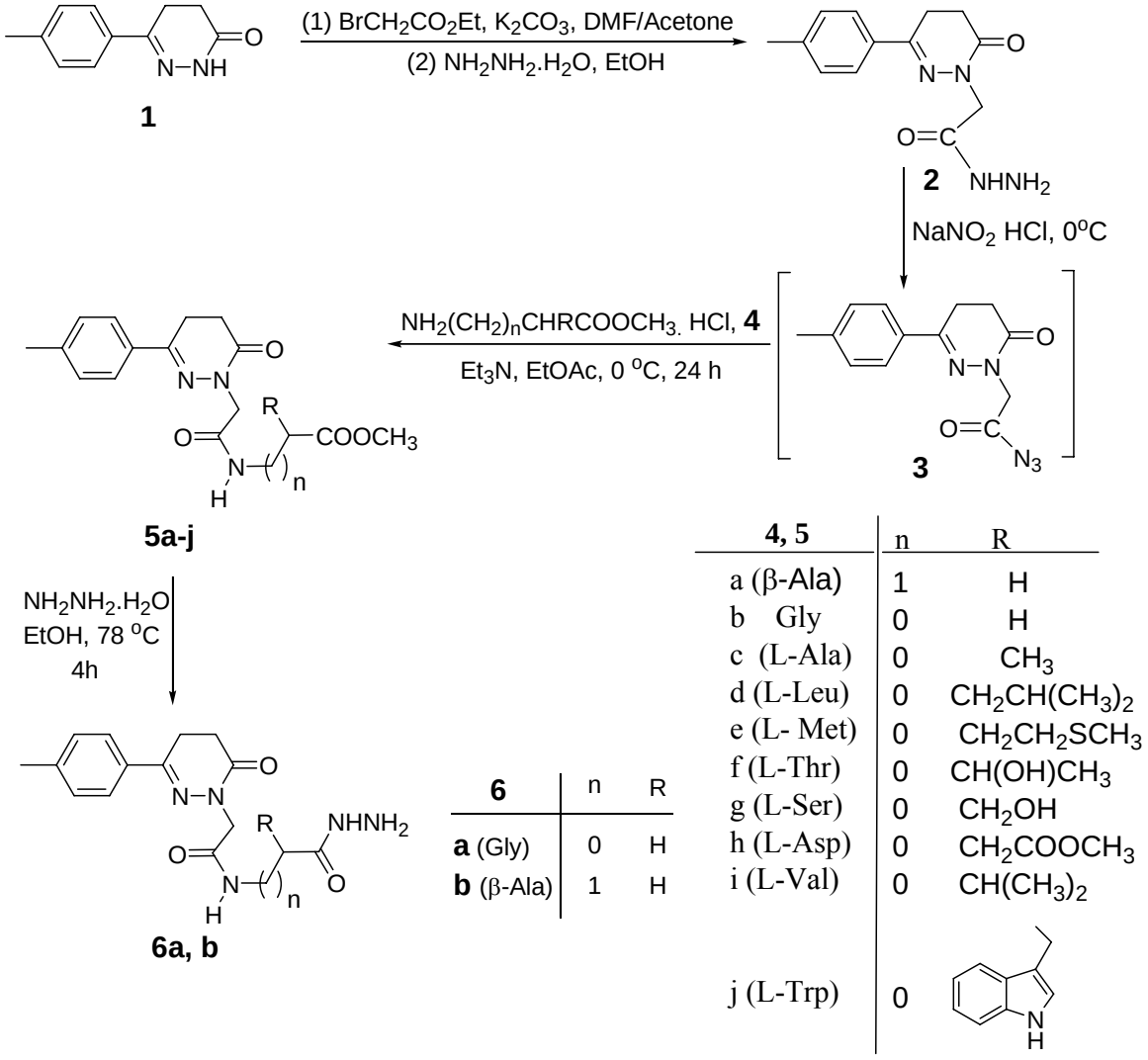
Figure 1. Biological active pyridazinones

In this paper, we describe the development of a new series of dihydro-2*H*-pyridazin-3-one derivatives, whose chemical modifications include *N*-terminal coupled amino acid and dipeptide derivatives as HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTIs).

Results and Discussion:

The synthesis of new amino acid derivatives coupled with biologically active heterocyclic moieties such as triazole quinazoline[26] and quinoline[27] attracted our attention. In this work we studied 6-p-tolyl-4,5-dihydro-2H-pyridazin-3-one (**1**) as biologically active heterocyclic moiety. The hydrazide **2** could be prepared by regioselective N alkylation for **1** with ethylbromoactetate which subsequently

hydrazinolyzed *via* hydrazine hydrate (Scheme 1). The procedures of those steps were already established in literature[28-30].



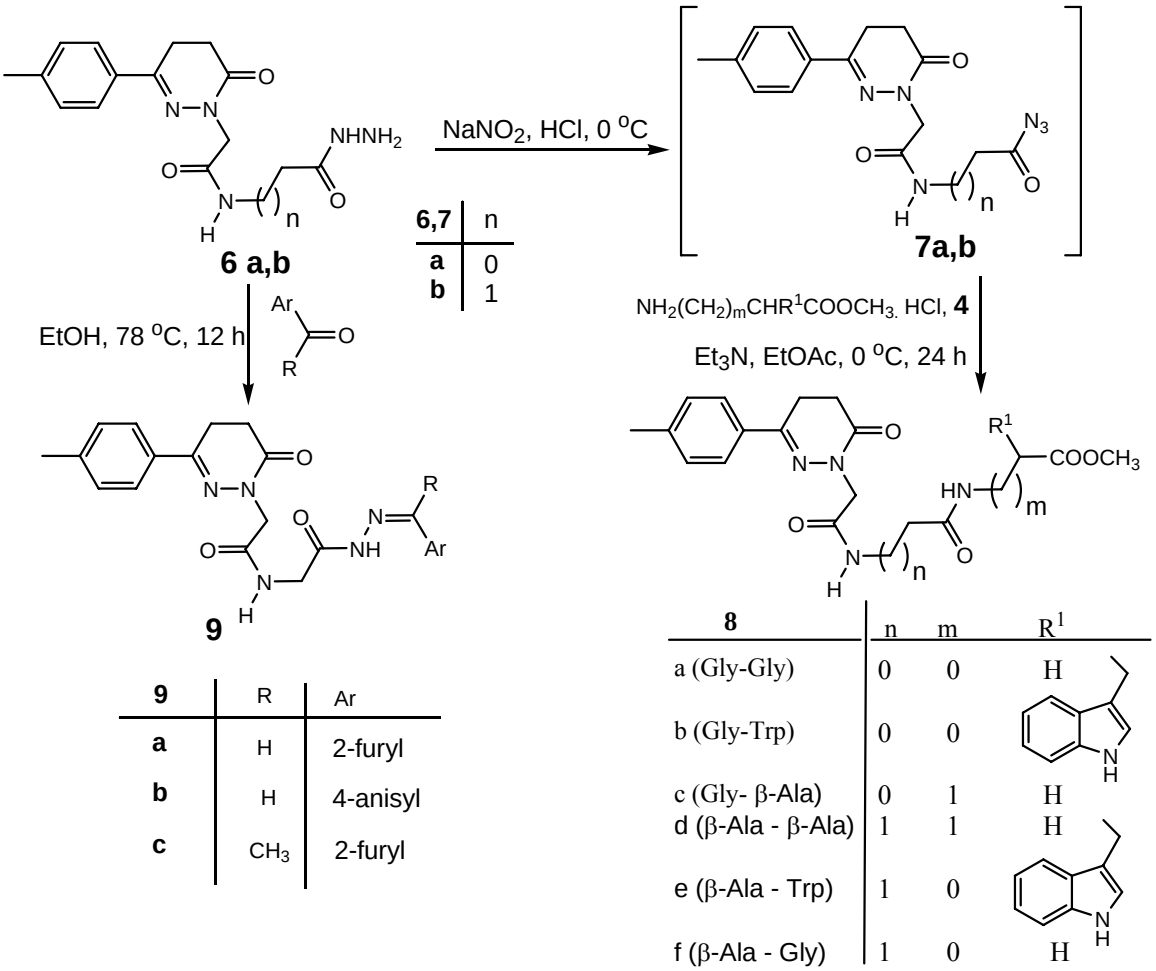
Scheme 1

The acyl azide route is one of the first developed for peptide coupling by Curtius[31]. The synthesis of the target amino acid derivatives **5a-j** were efficiently formed *via* azide coupling method,[26,27,32-34] which was reported to minimize the degree of racemization in amino acid coupling. The *in situ* generated azide **3** solution in ethyl acetate reacted with amino acid methyl ester hydrochloride **4** in the presence of triethyl amine to afford methyl-*N*-[2-(6-oxo-3-p-tolyl-5,6-dihydro-4H-pyridazin-1-yl)-acetamide]alkanoates **5a-j** in good yield. Further development of azide coupling was obtained by the synthesis of *N*-

substituted dipeptide derivatives **8a-f**. Thus, boiling the amino acid ester derivatives **5a,b** (β-Ala, Gly) with hydrazine hydrate gave acyl hydrazide **6a,b** (Scheme1).

Nitrosation of acyl hydrazide **6a,b** finally gave the acyl azide **7a,b** by treatment with $NaNO_2$ and HCl mixture. The *in situ* generated azides solution **7a,b** in ethyl acetate reacted with amino acid methyl esters hydrochloride **4** in the presence of triethyl amine produced dipeptide derivatives **8a-f** in good yield, scheme 2.

Various *N*-acylheteroarylhydrazones (NAH) have been synthesized and were found to possess very interesting biological activities[33,35]. The Glycyl hydrazide **6a** was condensed with aldehydes and 2-acetyl furan to exhibit the hydrazone **9a-c** (Scheme 2).



6,7	n
a	0
b	1

9	R	Ar
a	H	2-furyl
b	H	4-anisyl
c	CH_3	2-furyl

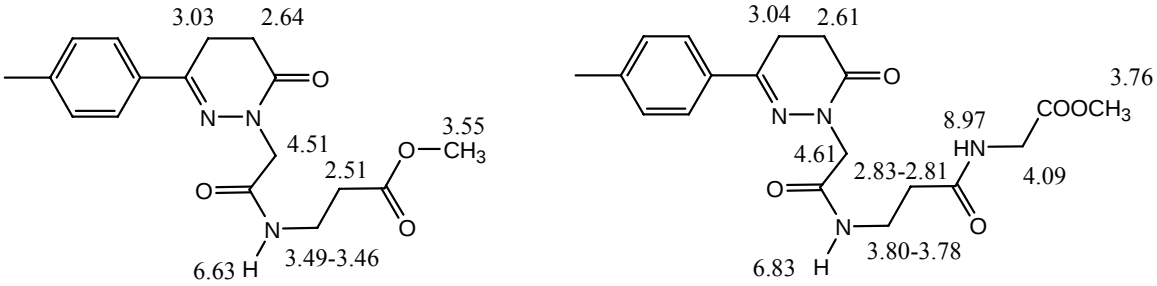
8	n	m	R^1
a (Gly-Gly)	0	0	H
b (Gly-Trp)	0	0	
c (Gly- β-Ala)	0	1	H
d (β-Ala - β-Ala)	1	1	H
e (β-Ala - Trp)	1	0	
f (β-Ala - Gly)	1	0	H

Scheme 2

The structure assignment of the *N*-substituted amino acid esters **5a-j**; acyl hydrazide **6;** the *N*-substituted dipeptides **8a-f** and acyl hydrazones **9a-c** is based on ^{1}H NMR spectral and physicochemical analysis, Figure 2.

The ^{1}H NMR spectra clearly confirm the regioselective *N*-alkylation for all isolated products. Thus, the ^{1}H NMR spectrum of **5a** gave a singlet signal at 4.51 ppm typically associated with NCH_2. Furthermore, a multilplet, a triblet, and two singlet signals at 3.49-3.46, 2.51, 3.55 and 6.63 ppm associated with two CH_2, OMe and NH groups, respectively. Also, the ^{1}H NMR spectra of all compounds showed two triplets at 2.64 and 3.01 ppm associated with the two CH_2 groups of the pyridazine skeleton.

The ^{1}H NMR spectrum of the *N*-substituted dipeptide **8f** exhibits signals at δ 2.83-2.81, 3.80-3.78, 4.09, 6.83 and 8.97 ppm corresponding to functionalities found at the dipeptide chain; two CH_2 (β-alaninyl residue), CH_2 (glycyl residue) and two NH groups, respectively.



5a **8f**

Figure 2. Selected ^{1}H NMR of compounds **5a** and **8f.**

The ^{1}H NMR spectrum of **9a** in DMSO gave two D_2O exchangeable broad signals at δ 11.32 and 8.32 ppm with similar intensities, in addition to two D_2O exchangeable broad signals at δ 11.42 and 3.84 ppm with larger intensities. We might conclude that the hydrazone **9a** solution in DMSO is present in the form of two tautomers (structure A) and (structure B)[26] with intramolecular hydrogen bonds of the type N–H···N=C stabilizing each form in 1:2. ratio, respectively. The participation of the NH group in the N–H···N=C system is confirmed by a signal at δ 11.32 (structure A). Structure B is induced by enolization of the hydrazide carbonyl which gave a signal at δ 11.42 and 3.84 ppm corresponding to NH group and an exocyclic OH group, respectively.

References

1. Sayed, G. H.; Sayed, M. A.; Mahmoud, M.R.; Shaaban, S. S. *Egypt. J. Chem*. **2002**, *45*, 767.
2. Katrusiak, A.; Katrusiak, A.; Baloniak, S. *Tetrahedron* **1994**, *50*, 12933.
3. Okcelik, B.; Unlu, S.; Banoglu, E.; Kupeli, E.; Yesilada, E.; Sahin, M.F. *Arch. Pharm. Pharm. Med. Chem.* **2003**, *336*, 406.
4. Dogruer, D. S.; Sahin, M. F.; Kupeli, E.; Yesilada, E. *Turk. J. Chem*. **2003**, *27*, 727.
5. Frolov, E. B.; Lakner, F. J.; Khvat, A. V.; Ivachtchenko, A. V. *Tetrahedron Lett*. **2004**, *45*, 4693.
6. Banoglu, E.; Akoglu, C.; Unlu, S.; Kupeli, E.; Yesilada, E.; Sahin, M.F.. *Arch. Pharm. Pharm. Med. Chem.* **2004**, *337*, 7.
7. Gokce, M.; Dogruer, D.; Sahin, M. F. *Il Farmaco* **2001**, *56*, 233.
8. Cao, S.; Qian, X.; Song, G.; Chai, B.; Jiang, Z. *J. Agric. Food Chem*. **2003**, *51*, 152.
9. Piaz, V. D.; Ciciani, G.; Giovannoni, M. P. *Synthesis* **1994**, 669.
10. Ogretir, C.; Yarligan, S.; Demirayak, S. *J. Chem. Eng. Data* **2002**, *47*, 1396.
11. Barbaro, R.; Betti, L.; Botta, M.; Corelli,F.; Giannaccini, G.; Maccari, L.; Manetti, F.; Strappaghetti, G.; Corsano, S. *J. Med. Chem.* **2001**, *44*, 2118.
12. Sircar, I. *J. Heterocyclic Chem*. **1985**, *22*, 1045.
13. Coelho, A.; Sotelo, E.; Fraiz, N.; Yanez, M.; Laguna, R.; Cano, E.; Ravina, E. *Bioorg. Med. Chem. Lett*. **2004**, *14*, 321.
14. Sotelo, E.; Centeno, N. B.; Rodrigo, J.; Ravina, E. *Tetrahedron Lett*. **2002**, *58*, 2389.
15. Sotelo, E.; Fraiz, N.; Yanez, M.; Terrades, V.; Laguna, R.; Cano, E.; Ravina, E. *Bioorg. Med. Chem.* **2002**, *10*, 2873.
16. Malinka, W.; Redzicka, A.; Lozach, O. *Il Farmaco* **2004**, *59*, 457.
17. Youssef, A. S.; Marzouk, M. I.; Madkour, H. M. F.; El-Soll, A. M. A.; El-Hashash, M. A. *Can. J. Chem*. **2005**, *83*, 251.
18. Sotelo, E.; Pita, B.; Ravina, E. *Tetrahedron Lett.* **2000**, *41*, 2863.
19. Sotelo, E.; Coelho, A.; Ravina, E. *Chem. Pharm. Bull*. **2003**, *51*, 427.
20. Deniz, S. D.; M. Fethi, S.; Esra, K.; Erdem, Y. *Turk. J. Chem*. **2003**, *27*, 727.

21. Beata, D. H.; Katrien, M.; Oliver, E.; Laszlo, K.; Pal Tapolcsanyi; Bert, U. W. M.; Zsuzsanna, R.; Gyorgy, H.; Roger A. D.; Guy, L. F. L.; Janez, K.; Peter M. *Tetrahedron* **2004**, *60* , 2283.
22. Karolin, A.; Annegret, T.; Nicolle, S.; Matthias, B. *Tetrahedron Letters* **2008**, *49,* 4607.
23. Samar, A. A. *Molecules* **2007***, 12,* 25.
24. Zachary, K. S.; Dunn, J. P.; Li, Y.; Heilek, G.; Dunten, P.; Elworthy, T. R.; Han, X.; Harris, S. F.; Hirschfeld, D. R.; Hogg, J. H.; Huber, W.; Kaiser, A.; Kertesz, D. J.; Kim, W.; Roepel, T.; Irzadegan, M. G.; Saito, Y. D.; Silva, T. M. P. C.; Swallow, S.; Tracy, J. L.; Villasenor, A.; Vora, H.; Zhou, A. S.; Klumpp, K. *Bioorg. Med. Chem. Lett*. **2008**, *18 (15)*, 4348.
25. Zachary K. S., James, P. D.; Li, Y; Gabrielle, H.; Pete, D.; Todd, R. E.; Xiaochun, H.; Seth, F. H.; Donald, R. H.; J. Heather, H.; Walter, H.; Ann C. K.; Denis, J. K.; Woongki, K.; Taraneh, M.; Michael, G. R.; Y. David, S.; Tania, M. P. C. S.; Steven, S.: Jahari, L.; Tracy, *et al. Bioorganic & Medicinal Chemistry Letters*, **2008**, 18, *(15)4352*.
26. Fathalla, W.; El Rayes, S. M.; Ali, I. A. I. *ARKIVOC* **2007**, *(xvi)*, 173.
27. Ali, I. A. I.; Fathalla, W.; El Rayes, S. M. *ARKIVOC* **2008**, *(xiii),* 179
28. Kolobov, A. V.; Panfilov, S. T.; Hohlev, A. L.; Borisov, P. V.; Krasovska, G. G.; Smirnov, A. A.; Sharova, A. I.; Kofanov, E. R. *Izvestiya Vysshikh Uchebnykh Zavedenii, Khimiyai Khimicheskaya Tekhnologiya* **2006**, *49(3)*, 24.
29. Sayed, A. A.; Jahine, H.; Zaher, H. A.; Sherif, O. *Indian Journal of Chemistry* **1975**, *13(11)*, 1142.
30. Kane, J. M.; Huber, E. W.; Miller, F. P.; Kehne, J. H. *Pharmazie* **1992**, *47(4)*, 249.
31. Curtius, Th. *Berichte der Deutschen Chemischen Gesellschaft* **1902**, *35*, 3226.
32. Fathalla, W.; Ali, A. I. *Heteroatom Chemistry* **2007**, *18*, 637.
33. Ali, I. A. I; Al-Masoudi, I. A.; Saeed, B.; Al-Masoudi, N. A.; La Colla, P. *Heteroatom Chemistry* **2005,** *16*, 148.
34. El Rayes, S. M.; Ali, I. A. I.; Fathalla, W. *ARKIVOC* **2008**, *(xi),* 86.
35. Todeschini, A. R.; Miranda, A. L. P.; Silva, K. C. M.; Parrini, S. C.; Barreiro, E. J. *Eur. J. Med. Chem.* **1997**, *33*, 189.