PYRIDAZINE AND ITS RELATED COMPOUNDS, SYNTHESIS OF SOME NOVEL CONDENSED PYRIDAZINES

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Abstract

A series of pyridazino[3,4-d][1,3]oxazin-5-one derivatives were designed and synthesized through a versatile method. Reaction of chloro-ester **1** with sodium azide has afforded azido-ester **2** which reacted with triphenylphosphine to produce compound **3**; amino-ester **4** was formed upon treatment of compound **3** with acetic acid 80%; this amino-ester **4** was then hydrolyzed to the amino-acid **5** which is considered the starting material. The approach involves treatment of pyridazinamino-acid **5** with acetic anhydride, benzoyl chloride, triethylorthoformate, ethyl chloroformate, diethyl oxalate, phthalic anhydride as well as succinic anhydride to yield pyridazino[3,4-d][1,3]oxazin-5-one derivatives **6, 8, 9, 10, 11, 12 and 13**. The new synthesized compounds were confirmed by their infrared, mass spectrum and ^{1}H-NMR.

Keywords: Pyridazine, 1,3-Oxazin-6-one, Pyridazino[3,4-d][1,3]oxazin-5-one, Synthesis, Condensation.

Introduction

Pyridazine and its fused heterocyclic derivatives have recently received much attention from their reactions, synthetic and effective biological importance [1–3]. It has been reported to possess antimicrobial [4], antituberculosis [5, 6], antifungal [7], anticancer [8], herbicidal [9] activities, and plant growth regulators and crop protecting agents [10].

In the light of these facts, our interest was focused on synthesizing new heterocyclic compounds including pyridazinoxazines moieties with suitable substituent of biological and pharmacological interest. The structures of the newly synthesized compounds were elucidated on the basis of various

spectroscopic methods and in some cases by comparison with samples previously prepared by unambiguous route.

Materials and methods

All melting points were determined in open glass capillaries and are uncorrected. IR spectra were recorded on a BRUKER Vector 22 Germany spectrometer (KBr). ^{1}H-NMR spectra were recorded on Varian Gemini 200 MHz spectrometer, using tetramethylsilane (TMS) as an internal reference. The Electron Impact mass spectra were obtained at 70 eV using Shimadzu QP-2010 Plus mass spectrometer. The reactions were followed up by thin layer chromatography (TLC) on silica gel F_{254} aluminum sheets (Merck), the spots were detected by UV lamp at 254–365 nm.

Synthesis of ethyl-3-azido-5,6-diphenylpyridazine-4- carboxylate (2)

To a solution of compound **1** (3.385 g, 0.01 mole) in ethanol (20 ml) sodium azide (1.95 g, 0.03 mole) was added. The reaction mixture was refluxed for 5 h., the solvent was evaporated under reduced pressure until dryness, 200 ml water was added then drops of conc HCl. The precipitate was filtered off and washed with water. After dryness the product was recrystallized from ethanol. White crystals, yield 71.3%, mp 118-120 ºC, IR (KBr, cm^{-1}): 1734 (C=O), 2338 (N_3), ^{1}H-NMR (DMSO-d_6): δ = 0.9 (t, 3H, CH_3), 4.13-4.22 (q, 2H, CH_2), 7.18–7.36 (m, 10H, 2Ph).

Synthesis of ethyl 5,6-diphenyl-3 ((triphenylphosphoranylidene)amino)pyridazine-4- carboxylate (3)

To a solution of compound **2** (3.45 g, 0.01 mole) in benzene (20 ml) triphenylphosphene (5.24 g, 0.02 mole) was added. The reaction mixture was refluxed for 8 h., the solvent was evaporated under reduced pressure until dryness, and the residue was treated with excess amount of diethylether. The precipitate was filtered off and washed with diethyl ether. After dryness the product was recrystallized from ethanol. White crystals, yield 86.35%, mp 178-180 ºC, IR (KBr, cm^{-1}): 1728(C=O), ^{1}H-NMR (DMSO-d_6): δ = 0.92-1.08 (t, 3H, CH_3), 4.12-4.18 (q, 2H, CH_2), 7.11–7.86 (m, 25H, 5Ph).

Synthesis of ethyl-3-amino-5,6-diphenylpyridazine-4- carboxylate(4)

A solution of compound **3** (1 g, 0.0017 mole) in glacial acetic acid 80 % (10 ml) was refluxed for 8 h., the reaction mixture was poured into ice water, drops of NH4OH solution was added. The precipitate was filtered off and recrystallized from ethanol. White crystals, yield 82.98%, mp 188-190 ºC, IR (KBr, cm^{-1}): 1708 (C=O), 3476,3272 (NH_2), ^{1}H-NMR (DMSO-d_6): δ = 0.79 -0.84(t, 3H, CH_3), 3.94-4.01 (q, 2H, CH_2), 7.04–7.29 (m, 10H, 2Ph), 6.7 (s, 2H, NH_2).

Synthesis of 3-amino-5,6-diphenylpyridazine-4-carboxylic acid (5)

A solution of compound **4** (1 g, 0.003 mole) in ethanolic sodium hydroxide 2N (10 ml) was refluxed for 5 h., the solvent was evaporated under reduced pressure until dryness, and the residue was treated with water. On acidification with conc HCl, a precipitate was obtained which was filtered off, washed several times with water and recrystallized from methanol. White crystals, yield 87.9%, mp 233-235 ºC, IR (KBr, cm^{-1}): 1658 (C=O), 3352,3270 (NH_2), ^{1}H-NMR (DMSO-d_6): δ = 7.18–7.36 (m, 10H, 2Ph), 6.9 (s, 2H, NH_2).

Synthesis of 7-methyl-3,4-diphenyl-5H-pyridazino[3,4-d][1,3]oxazin-5-one (6)

Method A:

A solution of compound **5** (1 g, 0.0034 mole) in acetic anhydride (5 ml) was refluxed for 18 h., the mixture was poured into water. The precipitate was filtered, dried and washed with diethyl ether. After dryness the product was recrystallized from ethanol. Brown crystals, yield 74%, mp 280-282 ºC, IR (KBr, cm^{-1}): 1695 (C=O), 1556 (C=N), ^{1}H-NMR (DMSO-d_6): δ = 2.49-2.51(s, 3H, CH_3), 7.2–7.3 (m, 10H, 2Ph). MS *m/z* (%): 316 [M^++1] (0.03), 274 [M^+ -N =CMe] (2.57, F_1), 230 [F_1 –CO_2] (0.54, F_2), 153[F_2 –Ph] (0.92).

Method B:

To a solution of compound **30** (3.19 g, 0.01 mole) in acetic acid (15 ml) acetic anhydride (24 ml) and sodium acetate (2 g) were added, the mixture was refluxed for 15 h., then poured into water. The precipitate was filtered, dried and washed with diethyl ether (2.44 g, 77.4 %). After dryness the product was recrystallized from ethanol,it was identical with that prepared by method **A**.

Synthesis of 3-benzamido- 5,6-diphenylpyridazine-4- carboxylic acid (7)

To a solution of compound **5** (0.3 g, 0.001 mole) in pyridine (5 ml) benzoyl chloride (0.28 g, 0.23 ml, 0.002 mole) was added drop by drop at room temperarure. The reaction mixture was stirred for additional 3 h., and the solid product formed upon pouring into ice water containing few drops of conc HCl was collected by filteration, washed with excess amount of water, dried and recrystallized from methanol. White crystals, yield 75%, mp 138-140 ºC, IR (KBr, cm^{-1}): 1685 (C=O), 3064 (NH), 3425(OH) ^{1}H-NMR (DMSO-d_6): δ = 7.15–8.06 (m, 15H, 3Ph), 11.4 (s, 1H, NH), 11.8 (s, 1H, OH). MS *m/z* (%): 395 [M^+] (0.11), 250 [M^+ -COOH] (49.76, F_1), 230 [F_1 –HNCOPh] (0.57, F_2), 153[F_2 –Ph] (0.14).

Synthesis of 3,4,7-triphenyl-5H-pyridazino[3,4-d]-1,3-oxazin-5-one (8)

To a solution of compound **5** (0.3 g, 0.001 mole) in pyridine (5 ml) benzoyl chloride (0.28 g, 0.23 ml, 0.002 mole) was added drop by drop at room

temperature. The reaction mixture was refluxed for 15 h. After cooling the reaction mixture was poured into ice water containing few drops of conc HCl and the precipitate was filtered, dried and washed with ethanol. After dryness the product was recrystallized from methanol. White crystals, yield 64.4%, mp 285-287 ºC, IR (KBr, cm^{-1}): 1769 (C=O), 1587 (C=N), ^{1}H-NMR (DMSO-d_6): δ = 7.15–8.31 (m, 15H, 3Ph). MS *m/z* (%): 377 [M^+] (5.25), 274 [M^+ -N =CPh] (1.46, F_1), 230 [F_1 –CO_2] (16.53, F_2), 153[F_2 –Ph] (0.13).

Synthesis of 3,4-diphenyl-5H-pyridazino[3,4-d]-1,3-oxazin-5-one (9)

A solution of compound **5** (1 g, 0.0034 mole) in triethylorthoformate (5 ml) was refluxed for 12 h., the mixture was evaporated to dryness in air and the residue was treated with diethyl ether. The precipitate was filtered off, dried and recrystallized from benzene. Brown crystals, yield 67.6%, mp 163-165 ºC, IR (KBr, cm^{-1}): 1675 (C=O), 1588 (C=N), MS *m/z* (%): 299 [M^+-2] (0.07), 274 [M^+ - CH=N] (0.09, F_1), 230[F_1 –CO_2] (0.09, F_2), 153 [F_2 –Ph] (3.40).

Synthesis of 7-ethoxy-3,4-diphenyl-5H-pyridazino[3,4-d]-1,3-oxazin-5-one (10)

To a solution of compound **5** (1 g, 0.0034 mole) in pyridine (5 ml) ethyl chloroformate (0.37 g, 0.32 ml, 0.0034 mole) was added drop by drop at room temperature. The reaction mixture was refluxed for 10 h. After cooling the reaction mixture was poured into ice water containing few drops of conc HCl and the precipitate was filtered, dried and washed with water . After dryness the product was recrystallized from ethanol. Brown crystals, yield 76.2%, mp 268-270 ºC, IR (KBr, cm^{-1}): 1695 (C=O), 1556 (C=N), MS *m/z* (%): 346 [M^++1] (0.61), 274 [M^+ - N=COEt] (0.61, F_1), 230 [F_1 –CO_2] (0.09, F_2), 153 [F_2 –Ph] (6.40).

Synthesis of ethyl 5-oxo-3,4-diphenyl-5H-pyridazino[3,4-d]-1,3-oxazine-7-carboxylate (11)

To a solution of compound **5** (1 g, 0.0034 mole) in dimethyl formamide (10 ml) diethyl oxalate (0.41 g, 0.0034 mole) was added. The reaction mixture was refluxed for 12 h. After cooling the reaction mixture was poured into ice water and the precipitate was filtered, dried and washed with water. After dryness the product was recrystallized from ethanol. White crystals, yield 70.3%, mp 140-142 ºC, IR (KBr, cm^{-1}): 1627 (C=O cyclic), 1663 (C=O ester), 1595 (C=N), MS *m/z* (%): 373 [M^+] (0.01), 300 [M^+ - COOEt] (0.11, F_1), 256 [F_1 –CO_2] (0.05, F_2), 179 [F_2 –Ph] (3.40).

Synthesis of 2-(5-oxo-3,4-diphenyl-5H-pyridazino[3,4-d]-1,3-oxazin-7-yl)benzoic acid (12)

To a solution of compound **5** (1 g, 0.0034 mole) in dimethyl formamide (10 ml) phthalic anhydride (0.5 g, 0.0034 mole) was added. The reaction mixture was refluxed for 9 h. After cooling the reaction mixture was poured into ice water and the precipitate was filtered, dried and washed with water. After dryness the product was recrystallized from ethanol. White crystals, yield 76.3%, mp 238-240 ºC, IR (KBr, cm^{-1}): 3433 (OH), 1725 (C=O cyclic), 1784 (C=O acid), 1578 (C=N), MS *m/z* (%): 421 [M^+] (0.03), 300 [M^+ -C6H4–COOH] (0.28, F_1), 256 [F_1 –CO_2] (2.68, F_2), 179 [F_2 –Ph] (6.03).

Synthesis of 3-(5-oxo-3,4-diphenyl-5H-pyridazino[3,4-d]-1,3-oxazin-7-yl)propanoic acid (13)

To a solution of compound **5** (1 g, 0.0034 mole) in dimethyl formamide (10 ml) succinic anhydride (0.34 g, 0.0034 mole) was added. The reaction mixture was refluxed for 10 h. After cooling the reaction mixture was poured into ice water and the precipitate was filtered, dried and washed with water. After dryness the product was recrystallized from ethanol. White crystals, yield 68.75%, mp 218-220 ºC, IR (KBr, cm^{-1}): 3438 (OH), 1641 (C=O cyclic), 1707 (C=O acid), 1555 (C=N), MS *m/z* (%): 374 [M^++1] (13.7), 328 [M^+ –COOH] (100, F_1), 300 [F_1 – C_2H_4] (6.09, F_2), 256 [F_2 –CO_2] (0.26, F_3), 179 [F_3 –Ph] (3.36).

Results and discussion

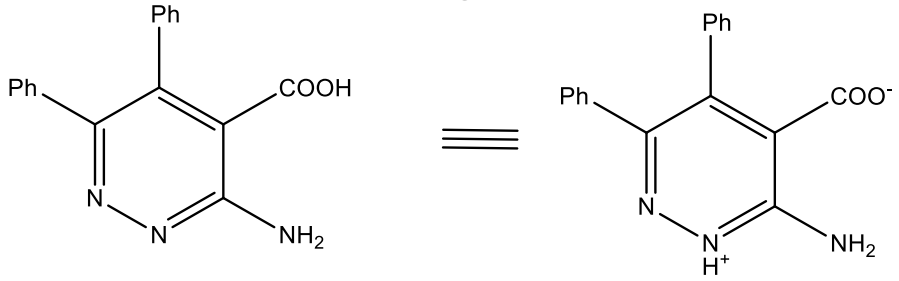
This paper is devoted to a discussion of preparation of oxazine derivatives which are useful intermediates for the preparation of heterocyclic compounds. The pyridazine derivatives **4** and **5** depicted in (Scheme 1) were obtained by the reaction of pyridazinechloro-ester **1** - prepared according to reported method [11]- with sodium azide in ethanol afforded the azido- ester **2**. Ethyl-3-azido-5,6-diphenylpyridazine-4- carboxylate **2** was confirmed on the basis of analytical and spectral data. Thus, the IR spectrum showed an absorption band at 1734 cm^{-1} for the ester carbonyl group and an absorption band at 2338 cm^{-1} for the azido group. Moreover, the ^{1}H-NMR spectrum revealed the presence of 3H triplet at δ 0 .9 corresponding to the ester methyl protons, 2H quartet at δ 4.13-4.227 for the methylene protons and 10H multiplet at δ 7.18-7.36 for the phenyl protons (2Ph).

The reaction of azido-ester **2** with triphenylphosphine in benzene provided triphenylphosphnium product **3**. Ethyl 5,6-diphenyl-3-((triphenylphosphoranylidene)amino)pyridazine-4- carboxylate **3** was assigned on the basis of analytical and spectral data. Thus, the IR spectrum of the reaction product showed an absorption band at for the ester carbonyl group at 1728 cm^{-1}. Moreover, the ^{1}H-NMR spectrum revealed the presence of 3H triplet at δ 0.928-

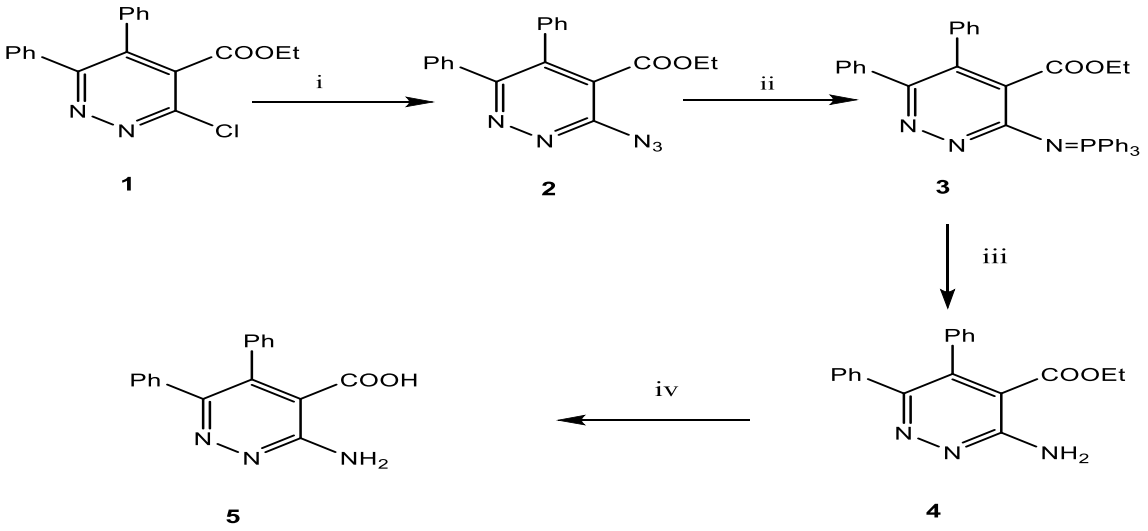
1.088 corresponding to the ester methyl protons, 2H quartet at δ 4.129-4.184 for the methylene protons and 25H multiplet at δ 7.108-7.866 for the phenyl protons (5 Ph).

Refluxing of triphenylphosphnium product **3** in acetic acid 80% led to the formation of the amino-ester product **4** in good yield. Ethyl-3-amino-5,6-diphenylpyridazine-4- carboxylate **4** was confirmed on the basis of analytical and spectral data. Its infrared spectrum showed the presence of NH_2 group at 3476,3272 cm^{-1} and C=O group at 1708 cm^{-1} and the ^{1}H-NMR spectrum showed the presence of signals at δ 7.049-7.298 (m, 10H, 2Ph), δ 6.715 (s, 2H, NH_2), δ 3.947-4.018 (q, 2H, CH_2) and δ 0.793-0.840 (t, 3H, CH_3).

Hydrolysis of ester group of compound **4** with ethanolic sodium hydroxide gave rise to the pyridazinamino-acid product **5**. 3-Amino-5,6-diphenylpyridazine-4-carboxylic acid **5** was confirmed on the basis of analytical and spectral data. Thus the IR spectrum showed an absorption band at 1658 cm^{-1} for the carbonyl group and an absorption band at 3352, 3270 cm^{-1} for the NH_2 group, two broad bands between 2495-1984 cm^{-1} and strong band at 1658 cm^{-1} for NH^+ , COO^{-1}



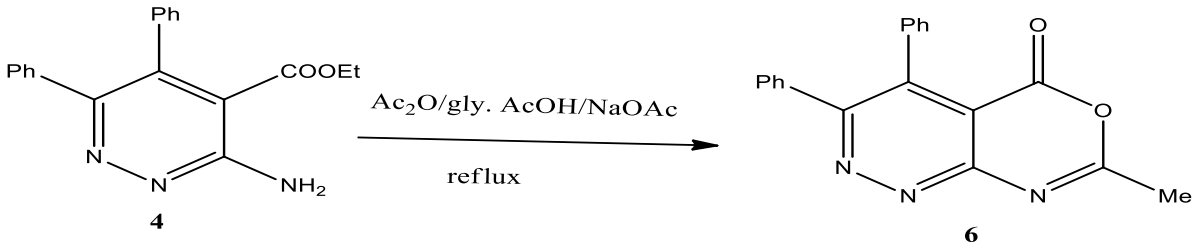
Moreover, the ^{1}H-NMR spectrum revealed the presence of 10H multiplet at δ 7.188-7.368 for the phenyl protons and 2H singlet at δ 6.9 for the NH_2 group, no signal for OH group as a result of presence of amino acid as zwitter ion.



Scheme 1 Synthesis of derivatives **4 , 5**. Reagents and conditions *i* NaN_3/EtOH; *ii* PPh_3, C_6H_6 ; iii AcOH 80% ; iv NaOH/EtOH

The pyridazinoxazine derivatives as the target compounds depicted in (Scheme 3). The precursor 7-methyl-3,4-diphenyl-5H-pyridazino[3,4-d][1,3]oxazin-5-one **6** was prepared by heating pyridazinamino-acid **5** in acetic anhydride under reflux. The infrared spectrum of the oxazine derivative **6** revealed presence of carbonyl group band at 1695 cm^{-1} and no absorption revealed to either NH group or acid carbonyl group. The ^{1}H-NMR showed the presence of 10H multiplet at δ 7.206-7.376 due to the aromatic phenyl groups and 3H singlet at δ 2.493-2.505 due to the methyl group. The mass spectrum could be accounted as follow: it gives the molecular ion+1 at m/z 316, the molecular ion could lose N=C-Me to give the ion at m/z 274, which in turn lose CO_2 to give the ion at m/z 230, then lose Ph radical to give an ion at m/z 153.

Pyridazinoxazine derivative **6** can also be prepared by, when a solution of this amino-ester **4** in glacial acetic acid containing a small excess of sodium acetate was heated with acetic anhydride under reflux, oxazine derivative **6** is obtained, it was identical (m.p,mixed m.p, IR) with that prepared from compound **5**. (Scheme 2)



Scheme 2

Benzoylation of the solution of amino-acid **5** in pyridine with benzoyl chloride at r.t gave rise to N-benzoylamino-acid **7**. However, when this reaction mixture is refluxed for a long time, pyridazinoxazine derivative **8** is formed in good yield.

3-Benzamido- 5,6-diphenylpyridazine-4- carboxylic acid **7** was assigned on the basis of analytical and spectral data. Thus, the IR spectrum of the reaction product showed an absorption band for the carbonyl group at 1685 cm^{-1}, an absorption band at 3425 cm^{-1} for OH group and an absorption band at 3064 cm^{-1} for NH group. Moreover, the ^{1}H-NMR spectrum revealed the presence of 1H singlet at δ 11.8 for the OH group, 1H singlet at δ 11.4 for the NH group and 15H multiplet at δ 7.151-8.063 for the aromatic phenyl protons (3 Ph). The mass spectrum could be accounted as follow: the molecular ion at m/z 395 underwent the following fragmentation, it could lose COOH to give the ion at m/z 350, which in turn could lose -NHCOPh to give the ion at m/z 230, then lose Ph radical to give the ion at m/z 153.

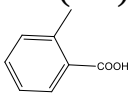
The infrared spectrum of the 3,4,7-triphenyl-5H-pyridazino[3,4-d]-1,3-oxazin-5-one **8** showed the presence of carbonyl group band at 1769 cm^{-1} and no absorption revealed to either NH group or acid carbonyl group. The ^{1}H-NMR showed the presence of 15H multiplet at δ 7.149-8.313 due to the aromatic phenyl group. The mass spectrum could be accounted as follow: the molecular ion at m/z 377 underwent the following fragmentation, it could lose N=CPh to give the ion at m/z 274, then lose CO_2 to give the ion at m/z 230 which could lose Ph to give the ion at m/z 153.

Reaction of pyridazinamino-acid **5** with triethylorthoformate at refluxed temperature led to the formation of pyridazinoxazine derivative **9**. The structure of 3,4-diphenyl-5H-pyridazino[3,4-d]-1,3-oxazin-5-one **9** was supported by its infrared and mass spectra. The infrared spectrum showed the presence of cyclic carbonyl group band at 1675 cm^{-1}. The mass spectrum could be accounted as follow: it gives the molecular ion-2 at m/z 299, the molecular

ion could lose N=CH to give the ion at m/z 274, then lose CO_2 to give the ion at 230 which lose Ph radical to give the ion at m/z 153.

It was found that pyridazinamino-acid **5** on reaction with ethyl chloroformate in presence of pyridine yielded 7-ethoxy-3,4-diphenyl-5H-pyridazino[3,4-d]-1,3-oxazin-5-one **10** in moderately yield. Identification of the structure **10** was achieved from its spectral data. The IR spectrum revealed band at 1695 cm^{-1} for the cyclic carbonyl group The mass spectrum could be accounted as follow : it give the molecular ion+1 at m/z 346, the molecular ion could lose N=COEt to give the ion at m/z 274, then lose CO_2 to give the ion at m/z 230, then lose Ph radical to give the ion at m/z 153.

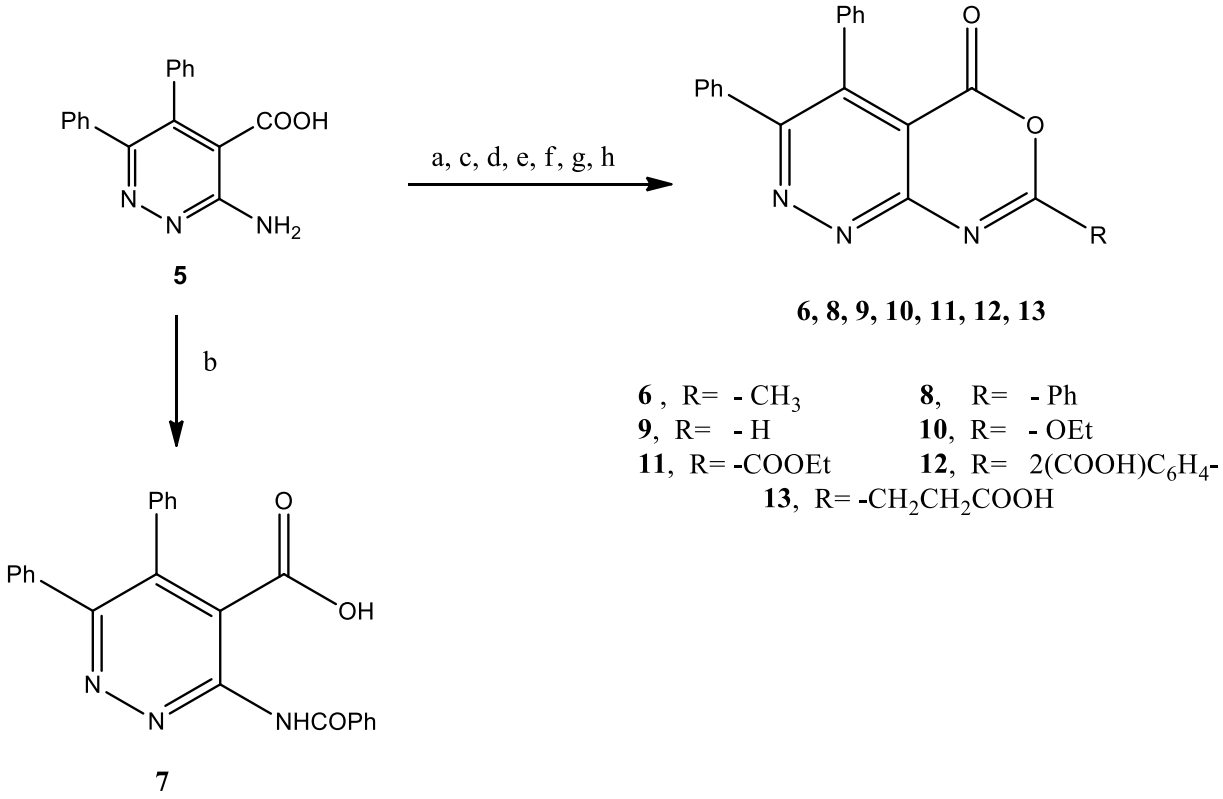
Refluxing a solution of pyridazinamino-acid **5** with diethyl oxalate in dimethyl formamide, undergoes cyclization by an intramolecular nucleophilic addition with elimination of ethanol molecule produces pyridazinoxazine derivative **11**. The isolated product was proven to be ethyl 5-oxo-3,4-diphenyl-5H-pyridazino[3,4-d]-1,3-oxazine-7-carboxylate **11** based on spectral data. The IR spectrum displays ester carbonyl group at 1663 cm^{-1}, cyclic carbonyl group at 1627 cm^{-1}. The mass spectrum could be accounted as follow: the molecular ion at m/z 373 underwent the following fragmentation, it could lose COOEt to give the ion at 300, which in turn gives rise to the ion at m/z 256 by the lose of CO_2, this could lose Ph to give the ion at m/z 179.

The pyridazinamino-acid **5** when reacted with phthalic anhydride in dimethyl formamide at refluxed temperature gave 2-(5-oxo-3,4-diphenyl-5H-pyridazino[3,4-d]-1,3-oxazin-7-yl)benzoic acid **12.** The structure of compound **12** is supported by its infrared and mass spectrum. The infrared spectrum revealed the presence of OH band at 3433 cm^{-1}, acid carbonyl at 1784 cm^{-1} and cyclic carbonyl at 1725 cm^{-1}. The mass spectrum gave a molecular ion at m/z 421(M^+) in accord with the proposed structure. The molecular ion could lose 

radical to give an ion at m/z 300, it also could lose CO_2 radical to give the ion at m/z 256 which in turn loses phenyl radical to give the ion at m/z 179.

The pyridazinamino-acid **5** reacts with succinic anhydride in dimethyl formamide at reflux temperature to give 3-(5-oxo-3,4-diphenyl-5H-pyridazino[3,4-d]-1,3-oxazin-7-yl)propanoic acid **13.** The structure of compound **13** was supported by its infrared and mass spectrum. The IR spectrum revealed the presence of OH group at 3438 cm^{-1}, acid carbonyl group at 1707 cm^{-1} and cyclic carbonyl group at 1641 cm^{-1}.The mass spectrum could be accounted as follows : it give the molecular ion+1 at m/z 374, the molecular ion could lose COOH to give the ion at m/z 328, then lose C_2H_4 to give the ion at m/z 300

which lose CO_2 to give the ion at m/z 256 which lose Ph radical to give the ion at m/z 179.



6 , R= - CH_3 **8**, R= - Ph
9, R= - H **10**, R= - OEt
11, R= -COOEt **12**, R= 2(COOH)C_6H_4-
13, R= -CH_2CH_2COOH

Scheme 3 Synthesis of derivatives **6 , 7, 8, 9, 10, 11, 12, 13**. Reagents and conditions *a.* Ac_2O; *b. BzCl/Py./r.t* ; c. *BzCl/Py./reflux*; d. $CH(OEt)_3$; e. ClCOOEt/Py. ; f.DEO/DMF ; g. Phthalic anhydride/DMF ; h. Succinic anhydride/DMF

Conclusion

In summary we have developed a novel class of pyridazino[3,4-d][1,3]oxazin-5-one derivatives which are useful intermediates for the preparation of heterocyclic compounds. It is known that 1,3-oxazin-6-ones which essentially are 5-aza-2-pyrones, are attractive due to their high reactivity towards nucleophiles as aromatic amines producing new pyrimidopyridazines.

References

1. M. Asif, A. Singh, L. Ratnakar, J Pharm Res. (2011), 4(3): 664–667.
2. I. I. Mangalagiu, Curr Org Chem. (2011), 15(5):730–752.

3. Deeb A, El-Eraky W, El-Awdan S, Mahgoub S (2014) Pyridazine and its related compounds, Part 34: hypoglycemic and hypolipidemic activity of some novel condensed pyridazine sulfonamides. Med Chem Res 23:34–41
4. Kandile NG, Mohamed MI, Zaky H, and Mohamed HM (2009) Novel pyridazine derivatives: synthesis and antimicrobial activity evaluation. Eur J Med Chem, 44 (5): 1989–1996.
5. Mangalagiu II (2011) Recent achievements in the chemistry of 1,2-diazines. Curr Org Chem, 15 (5):730–752.
6. Mantu D, Luca MC, Moldoveanu C, Zbancioc G and Mangalagiu II (2010) Synthesis and antituberculosis activity of some new pyridazine derivatives. Part II. Eur Med Chem, 45 (11): 5164–5168.
7. Drochioiu G, Sunel V, Oniscu C, Basu C and Murariu M (2007) The breakdown of plant biostructure followed by amino acids determination. Romanian Biotechnological Letters, 6 (2): 155–165.
8. Butnariu RM, Caprosu MD, Bejan V, Mangalagiu II, Ungureanu M, Poiata A, Tuchilus C, Florescu M (2007) Pyridazine and phthalazine derivatives with potential antimicrobial activity. J Hetrocycl Chem, 44 (5):1149–1152.
9. Han X, Hong YH, You Quan ZHU, Mao LIU Bim ZX, Fang Zhong HU, and Zheng YH (2010) Synthesis and herbicidal activities of novel 4- (3-trifluoromethylphenyl)-2*H*-pyridazin-3-one derivatives. Science China Chemistry, 53 (1): 157–166. Hansch C, Sammes PG, Taylor J B (1990) Comprehensive Medicinal Chemistry. Pergamon Press: Oxford, UK, Vol. 2, Chapter 7.1, pp 255–270.
10. Tucaliuc RB, Risca IM, Drochioiu G and Mangalagiu I (2008) Biological effect of some new pyridazine derivatives on wheat in germination experiments. Romanian Biotechnological Letters, 13 (4): 3837–3842.
11. Deeb A, Said S (1990) Studies on polyazaindenes synthesis of several new condensed pyridazine derivatives collect. Czech Chem Commun 55:2795–2799

تخليق وتفاعلات لبعض مشتقات البيريدازين

تم تصميم سلسلة من مشتقات بيريدازينو [4،3-3،1] [d] أوكسازين-5-وان وتجميعها من خلال طريقة متعددة الاستخدامات.عند تفاعل الكلورو استر 1 مع أزيد الصوديوم ينتج أزيدو أستر 2 التي تفاعلت مع ثلاثي سفينيل فوسفين لإنتاج مركب 3؛ أمينو-إستر 4 تم تكوينه عند معالجة المركب 3 مع حامض الخليك 80٪. ثم تم تحلل هذا الأمينو استر 4 إلى الحمض الامينى 5. ويشمل النهج معالجة حمض البيريدازينوامينو 5 مع أنهيدريد حمض الخليك، كلوريد البنزويل، ثلاثي إيثيل اورثوفورمات، كلوروفورمات الإيثيل، أوكسالات ثنائي إيثيل، أنهيدريد حمض الفثاليك وكذلك أنهيدريد حمض السكسينيك لانتاج مشتقات بيريدازينو أوكسازين 6 و 8 و 9 و 10 و 11 و 12 و 13. وقد تأكدت المركبات المصنعة الجديدة من خلال الأشعة تحت الحمراء، الطيف الكتلي و الرنين المغناطيسى.