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"Designing Synthesis and Biological Evaluation of Pyridazinone Derivatives"

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ABSTRACTS

Chemistry is the branch of science in which study of the molecules and their transformation; it deals with their composition, properties of substance element and molecule Chemistry is the science of matter and it occurs in three form solid liquid and gas.

Pharmaceutical chemistry is a science that gives the information of drug molecules their preparation, in vivo and vitro studies the properties of drugs. In this the study of the method of quality control and the condition of their usage. Or this is also called the chemistry of drugs.

Pharmaceutical chemistry is important for the quality of drug molecules and it should be safe for consumer and products. Pharmaceutical chemistry is the study of chemical properties of compounds. In this the study of drug designing, synthesizing and developing of drugs molecule in pharmaceutical chemistry. This is also called Medicinal chemistry. In which the study identification, synthesis and development of new chemical drug molecules which have therapeutic activity. It also studies of existing drugs and their biological effects and their quantitative structural activity relationship (QSAR).

Pharmaceutical Chemistry is the science the of drugs, in this the
Development of drugs entity. It also cover drug discovery, delivery and there are part of biomedical analysis. In this the study of pharmacokinetics and pharmacodynamics properties of drugs molecules Pharmaceutical chemistry work is based on the laboratory manual.

The chemistry of heterocyclic compounds is continuously exploring field of the organic chemistry. The synthesis of heterocyclic compounds have attention of scientist because of biological importance of its.

Pharmaceutical chemistry involves remedies and cures and for disease condition, analytical techniques, quality assurance pharmacology, metabolism, absorption and chemistry of the drug. Pharmaceutical chemistry leads to careers in biotechnology, organic chemistry and drug development, pharmaceutical companies, quality assurance, research facilities, and more.

Chemistry is the science of matter and its structure change properties is an important in pharmaceutical science and it include acids and bases. And other organic compounds, chemicals like soap, detergents, dyes, polymers and metals etc. In simple words, scope of chemistry is everywhere and every time

Medicinal chemistry is a discipline that covers the design, development, and synthesis of pharmaceutical drug molecules. This is a process in which scientist from chemistry or synthetic organic chemistry, pharmacology, medicinal chemistry and other biological sciences study the drug molecule. It is the evaluation of the properties of drugs.

The use of plants, animals and minerals as medicine from many years ago. New drug discovery methods are useful now days for synthesis of new molecule. New molecule with potential pharmaceutical

effects is called hits compounds. These are natural compound synthesis by computational chemistry and from screening methods.

The hit compound is improving pharmacokinetic, pharmacodynamic pharmacological effects of compounds from biotechnology. Then identify lead compound. The lead compound is further optimized to be a drug entity that is safe to use in human in clinical trials study.

Heterocyclic have largest of classical divisions of organic chemistry and are have many importance biological and industrial field.

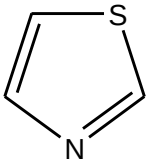
The majority of pharmaceuticals and biologically active agrochemicals are heterocyclic while countless additives and modifiers used in industrial applications ranging from cosmetics, reprography, information storage and plastics are also heterocyclic in nature. One striking structural feature inherent to heterocyclic, which is exploited to great advantage by the drug industry, lies in their ability to prepare substituent around a core scaffold in defined three dimensional representations.

For more than a century, heterocyclic have constituted one of the largest areas of research in organic chemistry. Heterocyclic have contributed to the development of society from a biological and industrial point of view as well as to the understanding of life processes to improve the quality of life. Among the approximately 20 million chemical compounds identified by the end of the second millennium, more than two-thirds are fully or partially aromatic and approximately half are heterocyclic. (Wonder nucleus) which posses almost all types of biological activities

Heterocyclic is a branch of organic chemistry which deals with the cyclic compounds in which at least one hetero atom is a member of its rings. Nitrogen, oxygen and sulphur are the common hetero atoms present in the heterocyclic compounds. Heterocyclic compounds also known as ring compounds and cyclic compounds. Heterocyclic compounds are said as cyclic compounds or ring compounds because its structure having one rings.

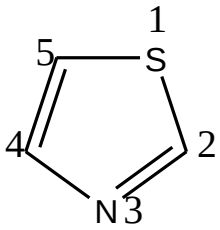
Now a day's heterocyclic compounds having great demands in the market of pharmaceutical company because of its great importance against the variety of common disease. Therefore day by day interested has been increases for synthesis of heterocyclic compounds. A heterocyclic compound is biological active compounds. Heterocyclic compounds having antifungal, anti-inflammatory antibacterial, antioxidant, anticonvulsant, antiallergic activity.

Thiazole is a example of heterocyclic compound. Thiazoles are a five-member heterocyclic compounds in which sulfur and nitrogen atom is the member of the rings atom.



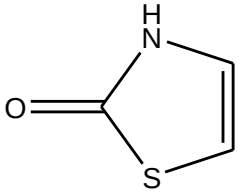
Thiazole

Nomenclature—Thiazole is also known as 1,3-thiazole because it contain sulfur atom in 1 position and nitrogen atom at 3 position in its structure



Thiazole

Derivatives --Thiazolone is a oxygenated derivatives of thiazole.

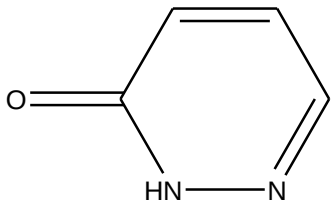


Thiazolone

Imporatance—thiazolone and its derivatives having a greater importance to curing many chronic disease specially bacterial, fungal. Bacterial and fungal resistivity is always a challenging problem because of the multi drug resistivity against pathogen is increase day by day. To overcome these problems is only by formation of new compound with active nucleus to deal resistivity against pathogens.

Pyridazinone:

Various pyridazin-3(2*H*) - ones have attracted considerable attention as they are endowed with a variety of pharmacological activities. These derivatives represent one of the most active classes of compounds possessing a wide spectrum of biological activity ranging from cardiovascular properties, anti inflammatory, anti diabetic, antidepressant, analgesic, anti-AIDS, anticancer, antimicrobial and anticonvulsant activities. As a result a number of pyridazinone derivatives have reached clinical trial level as cardio tonic and antihypertensive drug1. In present study, a review of different biological activities such as cardiovascular, anti-inflammatory, analgesic, antinociceptive, antiasthmatic, antidiabetic, antidepressant, anticonvulsant, anti-HIV-1, antiproliferative, antimicrobial and insecticidal activities have been dealt in detail. The pyridazinones have attracted a great deal of attention because of the wide spectrum of their pharmaceutical and agrochemical activities.[12]Pyridazinone are six-member heterocyclic compounds, 2 nitrogen atoms are present at adjacent positions. Pyridazin-3-one, a saturated or unsaturated form of pyridazine with carbonyl group on third carbon, has been considered as a magic moiety (wonder nucleus) which posses almost all types of biological activities.[13]



Pyridazinone

Pyridazine has been assumed to be a planar molecule for which two Kekule structures are given as mentioned. Pyridazine is a resonance hybrid in which the greater contribution is made by the structure containing = NN=configuration. The 1, 2 diazine systems that contain a carbonyl group in the ring are called pyridazinone. This nitrogen heterocyclic is included in chemicals with a wide range of biological activities and can also be used to link other pharmacophoric groups. Pyridazine is colorless liquid and boiling point 208 ^{0}C, density 1.1015, melting point -8 ^{0}C.[4]

The synthesis of novel pyridazinone derivatives and investigation of their chemical and activities have gained more importance in recent years. Pyridazinone derivatives have established a variety of pharmacological activities most of them are related to cardiovascular effects. In this field number of compounds such as zardaverine/imidazole, bemoradan, indolindan, pimobendan are few examples of pyridazinones that are active as cardiotonic agents/ platelet.1-9Literature survey revealed that substituted pyridazinones have reported to possess

Pharmacological activities such as antidepressant antihypertensive antithrombotic antifungal, antibacterial, antimicrobial, analgesic anti-inflammatory, antifeedant, antiplatelet, anticancer, diuretics, anti HIV, vasodilator and other anticipated biological and pharmacological properties.

Aminopyrine is a classical drug with strong analgesic and anti-inflammatory activities butreprted to have side effects. A series of pyridazinone derivatives are structurally related to aminopyrine with a pyrazolone ring. Among these4-alkoxy-2-methyl-5-morpholino-3(2H)-pyridazinones have been found to have strong analgesic and anti-inflammatory activities. In the present scenario, a large number of medications acting through different mechanisms for the treatment of hypertension are available. Even the one has to admit that blood pressure of majority of hypertensive patients is inadequately controlled, partly because the treatment is not conducted intensively enough, but partly also because the medication(s) are not taken as prescribed. Lowering blood pressure in hypertensive patients requires therefore not only a broad choice of effective and well-tolerated medications, but also skills to motivate them to comply lifelong with the treatment. hypertension is the most common cardiovascular disease. The definition of hypertension, therefore using any specific cut off point is arbitrary. The studies on the hydralazine group drugs led to the synthesis of many pyridazinone derivatives with a wide activity spectrum on cardiovascular system1-3. Pyridazinone derivatives, a class of compounds containing the N-N bond, exhibit a wide range of pharmacological activities such as antidepressant4, antihypertensive5-8, antithrombotic9, anticonvulsant10, cardiotonic11, antibacterial12, diuretics13, antiHIV14 and anticancer15. Some pyridazinone derivatives like indolidan16, bemoradan17, primobendan18,

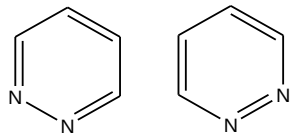
levosimendan19 (antihypertensive), already approved in the clinical market. The current work describes the synthesis of some new substituted pyridazine derivatives with encouraging antihypertensive activity by non-invasive method using Tail Cuff method.

The main objective present research work to synthesis, characterization and biological evaluation of pyridazine derivatives. All the synthesized compounds were obtained in good yield by optimizing various synthetic procedures. The structures of the compounds were established by elemental analysis, IR, 1H-NMR and Mass spectral data analysis. To study the different synthesized derivative by using different analytical parameters. And also to find out the good pharmacologically active synthesized compounds.

Chemistry of Pyridazinone and Pyridazine:

Pyridazine is one of the three possible isomeric diazines. The diazines are a group of compounds formally derived from benzene by the replacement of two of the ring carbon atom by nitrogen. It was obtained as early as 1886 by Fischer and was first synthesized by Tauber in 1895. The nitrogen atoms pyridazine displays properties different from the isomeric diazine.

Pyrdazine is a planer six membered ring and it is the represented as a resonance hybrid of two structure (1a) and (1b) with a greater contribution from the canonical structure (1a) (Figure: 8).

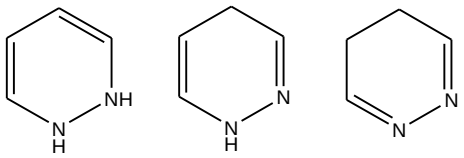


1(a) 1(b)

Figure : 8

This is supported by the result of microwave spectroscopy, electron diffraction data & X-ray crystallographic analysis, which all indicate that the N-N bond has single bond character. Bond length and bond angle have been also calculated by microwave spectroscopy, electron diffraction.

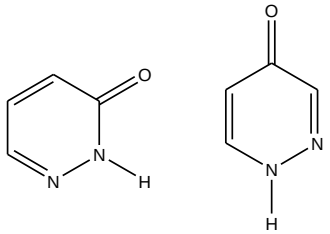
Six possible reduced pyridazines, 1, 2(4), 1, 4(5) and 4, 5(6) dihydropyridazines are known (Figure: 9).



4 5 6

Figure : 9

Appropriately substituted pyridazines exhibits tautomerism. This 3 & 4- hydroxyl pyridazines (7) and (8) exist predominantly in the oxo form.[2-4]



(7) (8)

Figure : 10

REFERENCE

[1]. Introduction of Heterocyclic compounds
[2]. Katritzky, Alan R. Chairman of the editorial board, Charles W. Rees, FRS Co chairman of the EB, FRS, Comprehensive hetrocyclic chemistry the structure reaction synthesis & use of hetrocyclic compounds,**1984** Vol-3 pergamon press, UK p-2.
[3]. Sir Deker Barton, FRS, David Ollis FRS., Chairman and deputy chairman of the editorial board. Comprehensive Organic Chemistry. The synthesis & reaction of the organic compound.
[4]. Matyus, P and Czako, K. Trend in heterocyclic chemistry, **1993** P-3, 249.
[5]. Tisler, M and Stanovic, B. advance in heterocyclic chemistry, Katritzky Alan R., and boulton A J. eds academic press, **1979** p-408.

[6]. Eddy Sotelo, Nuria Friaz, Matilde Yanez, Reyes Laguna, Ernesto Cano and Enrique Ravina. Synthesis and antiplatelet activity of 4, 5- disubstituted-6-phenyl-3(2H)- pyridazinones.Chem.Oharm.Bull.**2002**;50(12):574 1577.

[7]. Laguna R, Rodriguez-Linarez, B, Cano E, Estevez I, Ravina E, and Sotel, E. Pyridazines. XIII. Synthesis of 6-aryl-5-oxygenated substituted- 3(2H)-pyridazinones and evaluation as platelet aggregation inhibitors. Chem. Pharm.Bull.**1997**; 45:1151-1155.

[8]. Gaetano S. Epidemiology of cardiovascular disease inthe 21st century: Updated numbers and updated facts. JCardiovasc Dis **2013**; 1(1): 1-2.

[9]. Al-Sieni AI, Baghdadi MA, Al-Abbasi FA. Country widestatistical assessment of smoking inducedatherosclerotic and metabolic risk factors in Saudipopulation. Asian J Pharm Health Sci **2014**; 4(1): 916-920.(3 oxo derivatives)

[10]. Siddiqui AA., et al. "Synthesis and antiinflammatory activity of 6-(substituted aryl)-2,3,4,5-tetrahydro-3-thiopyridazinones". Indian Journal of Hetrocyclic Chemistry **2004**13: 257-260.

[11]. Asif Husain, Aftab Ahmad, Anil Bhandari, VeermaRam.Synthesis and Antitubercular activity of pyridazinone derivatives, J Chil Chem So,**2011** 56, 778-786.

[12]. Murty MSR, Ramalingeswara Rao B, Synthesis and preliminary evaluation activity studies of novel 4-(aryl/ heteroaryl-2-ylmethyl)-6-phenyl-2-[3-(4-substituted-piperazine-1-yl)propyl] pyridazine-3(2H)-one derivatives as anticancer agents, Med Chem Research, **2012**, 21, 3161-3169.

[13]. Mohammad Asif, Anita Singh. (2010). Exploring Potential, Synthetic Methods and General Chemistry of Pyridazine and Pyridazinone: A Brief Introduction, International Journal of Chem Tech Res. 2(2), 1112-1128.

[14]. B Chahkandi; SF Tayyari; M Bakhshaei; M Chahkandi. *J Mol Graphics Modell*, **2013**, 44(0), 120-128.

[15]. M Smith; J March. Wiley Interscience, **2001**, 329, 5083-5087.

[16]. Dogruer, D. S., Sahin, M. F., Kupeli, E., Yesilada, E. Synthesis and Analgesic and AntiInflammatory Activity of New Pyridazinones. Turk. J. Chem., **2003** 27: 727-738.

[17]. L Zare; N Mahmoodi; A Yahyazadeh; M Nikpassand. *UltrasonSonochem*, **2012**, 19(4), 740-44.

[18]. K Alex; a Tillack; N Schwarz; M Beller. *Tetrahedron Lett*, **2008**, 49(31), 4607-4609.

[19]. Imran. M., Abida, 6-(4-Aminophenyl)-4,5-dihydro-3(2H)-pyridazinone – An important chemical moiety for development of cardioactive agents: A review Tropical Journal of Pharmaceutical Research July **2016**; 15 (7): 1579-1590

[20]. Sotelo, E., Pita, B., Ravina, E. Pyridazines. Part 22:1 Highly Efficient Synthesis of Pharmacologically Useful 4-Cyano-6-Phenyl-5-Substituted-3(2*H*)-Pyridazinones. Tetrahedron Lett. **2008***41:*2863-2866.

[21]. Okcelik, B., Unlu, S., Banoglu, E., Kupeli, E., Yesilada, E., Sahin, M. F. Investigation of New Pyridazinone Derivatives for the Synthesis of Potent Analgesic and Anti-Inflammatory Compounds with Cyclooxygenase Inhibitory Activity. Arch. Pharm. Pharm. Med. Chem. **2003**336:406-412.

[22]. Frolov, E. B., Lakner, F. J., Khvat, A. V., Ivachtchenko, A. V. An Efficient Synthesis of Novel 1,3- oxazolo [4, 5-*d*] Pyridazinones. Tetrahedron Lett.**2004** 45:4693-4696.

[23]. Piaz, V. D., Ciciani, G., Giovannoni, M. P. 5-Acetyl-2-Methyl-4-Nitro-6-Phenyl-3(2*H*)-Pyriazinone: Versatile Precursor to Hetero-Condensed Pyridazinones.**1994** Synthesis. 669-671.

[24]. Sircar, I. Synthesis of New 1, 2, 4-Triazolo [4,3-b]pyridazines and Related Compound. J. Heterocyclic Chem., **1985** 22: 1045-1048.

[25]. Sotelo, E., Fraiz, N., Yanez, M., Terrades, V., Laguna, R., Cano, E., Ravina, E. Pyridazines. Part XXIX: Synthesis and Platelet Aggregation Inhibition Activity of 5-Substituted-6-Phenyl-3(2*H*)-Pyridazinones Novel Aspects of their Biological Action. Bioorg. Med. Chem., **2000** 10: 2873- 2882.

[26]. Siddiqui, A. A., Syed, R. A., Mohammed, S. M., Syed, A. H., Mohammed, R., Ravindra K. Synthesis and *In-vitro* Antifungal Activity of 6-substituted-phenyl-2-{[(4' SubstitutedPhenyl-5'-Thioxo)-1,2,4-Triazol-3-yl]-methyl}-2,3,4,5-Tetrahy- dropyridazin-3-One Derivatives, **2008** Acta Poloniae Pharmaceutica., 65(2): 223-228.

[27]. Sotelo, E., Coelho, A., Ravina, E. Pyridazine Derivatives 321): Stille-Based Approaches in the Synthesis of 5-Substituted-6-Phenyl-3(2*H*)-Pyridazinones. Chem. Pharm. Bull. **2003** 51: 427-430.

[28]. Siddiqui, A. A., Kushnoor, A., Wani, S. M. Synthesis and hypotensive activity of some 6-(substituted aryl)-4-methyl-2, n3-dihydropyridazin-3-ones. Indian J of Chem.**2004** B, 43B: 1574-1579.

[29]. Wang, T., Xiang, B., Wang, Y., Chen, C., Dong, Y., Fang, H., Wang, M. Spectroscopic investigation on the binding of bioactive pyridazinone derivative to human serum albumin and molecular modeling. Colloids Surf B Biointerfaces. **2008** 65(1):113-139.

[30]. Dawood, N. T., Abdel-Gawad, S. M., Soliman, F. M. Synthesis of some pyridone derivatives. Boll Chim Farm. **2001** 140(3):149-54.

[31]. Jing, T., Duo-Zhi, W., Ling-Hua, C. Synthesis of 5-(6-Pyridazinone-3-yl)-2-lycosylamino-1, 3,4-oxadiazoles. Journal of the Chinese Chemical Society, **2007** 54: 1287-1292.

[32]. Károlyházy, L., Horváth, G., Mátyus, P. [A novel pyridazino-fused ring system: synthesis of pyridazino[3,4-b]diazepam] [Article in Hungarian] Acta Pharm Hung. **2001** 71(2):168-170.

[33]. Li, L.S., Zhou, Y., Zhao, J., Dragovich, P. S., Stankovic, N., Bertolini, T. M., Murphy, D. E., Sun, Z., Tran C. V., Ayida, B. K., Ruebsam, F., Webber S. E. Synthesis of New Pyridazinone Derivatives: 2,6- Disubstituted 5-Hydroxy- 3(2*H*)-pyridazinone-4-carboxylic Acid Ethyl Esters. Journal of Synthetic Organic Chemistry. **2000** 21: 3301-3308.

[34]. Ravina, E., Teran, C., Santana, L., Garcia, N., Estevez, I. (1990) Pyridazine derivatives. 9. Synthesis of 2h-pyridazin-3-ones with aroylpiperazinyl groups. Heterocycles **1974** 31:1967-1972.

[35]. Miguel, F. B., Monica, C. M. L. G., Elena, P. M., Berta, L., Beatriz de, P. T., Ana, R., Nuria, A., Francisco, L., Dolores, M. M., Olivier, L., Laurent, M., Pyrazolo[3,4-c]pyridazines as Novel and Selective Inhibitors of Cyclin-Dependent Kinases. J. Med. Chem.**2005** 48: 6843-6854.

[36]. Li, L.S., Zhou, Y., Zhao, J., Dragovich, P. S., Stankovic, N., Bertolini, T. M., Murphy, D. E., Sun, Z., Tran C. V., Ayida, B. K., Ruebsam, F., Webber S. E., Synthesis of New Pyridazinone Derivatives: 2,6- Disubstituted 5-Hydroxy- 3(2H)-pyridazinone-4-carboxylic Acid Ethyl Esters. Journal of Synthetic Organic Chemistry. **2007** 21: 3301-3308.

[37]. Mojahidul, I., Anees, A. S, Ramadoss, R. Synthesis, Antitubercular, Antifungal and Antibacterial Activities of 6-Substituted Phenyl-2-(3'-Substituted Phenyl Pyridazin-6'-yl)-2, 3, 4, 5-Tetrahydropyridazin3-one Acta Poloniae Pharmaceutica, **2008** 65 (3): 353-362.

[38]. Siddiqui, A. A., Syed, R. A., Mohammed, S. M., Syed, A. H., Mohammed, R., Ravindra K. Synthesis and In-vitro Antifungal Activity of 6-substituted-phenyl-2-{[(4'-SubstitutedPhenyl-5'-Thioxo)-1,2,4-Triazol-3-yl]-methyl}-2,3,4,5-Tetrahy- dropyridazin-3-One Derivatives, 2008 Acta Poloniae Pharmaceutica.,**2008** 65(2): 223-228.

[39]. Laura, K., Wing, H. A., Behanna, L. J., Van, E. D., Martin, W., and Hantamalala, R. R. (2006) De Novo and Molecular Target-Independent Discovery of Orally Bioavailable Lead Compounds for Neurological Disorders. Current Alzheimer Research, 3: 205-214.

[40]. Mizzoni, R. H. and Spoerri, P. E. (1951) Synthesis in the pyridazine series. I. Pyridazine and 3,6- dichloropyridazine. J Am Chem Soc 73:1873- 1874.
[41]. Wermuth, C. G., Schlewer, G., Bourguignon, J. J., Maghioros, G., Bouchet, M. J., Moire, C., et al. (1989) 3-Aminopyridazine derivatives with atypical antidepressant, serotonergic, and dopaminergic activities. J Med Chem., 32: 528-537.
[42]. Li, Q., Lin, G., Liu, L., Yang, Z., Zhang, L. H. (2009) Methyl carbonium ion migration during the reaction of 4-chloro-5-methoxyl-3(2H)-pyridazinone with trifluoroethylation agents. Molecules. 14(2):777-84.
[43]. Bansal Ranju, Thota Sridhar, Pyridazin-3(2H)-ones: the versatile pharmacophore of medicinal significance, Med Chem Research, **2012**.
[44]. Miguel, F. B., Monica, C. M. L. G., Elena, P. M., Berta, L., Beatriz de, P. T., Ana, R., Nuria, A., Francisco, L., Dolores, M. M., Olivier, L., Laurent, M. (2005) Pyrazolo[3,4-c]pyridazines as Novel and Selective Inhibitors of Cyclin-Dependent Kinases. J. Med. Chem. 48: 6843-6854.
[45]. Abubshait, S. A. (2007) An efficient synthesis and reactions of novel indolylpyridazinone derivatives with expected biological activity. Molecules. 2007; 12(1):25-42.
[46]. Deniz, S. D. M. and Fethi, S. (2003) Synthesis and Analgesic and Anti-Inflammatory Activity of New Pyridazinones. Turk J Chem, 27: 727–738.
[47]. Lee, S. G., Kim, J. J., Kweon, D. H., Kang, Y. J., Cho, S. D., Kim, S. K., Yoon, Y. J., Recent progress in pyridazin-3(2H)-ones chemistry, Curr. Med. Chem., **2004** 8: 1463–1480.
[48]. Katrusiak, A., Baloniak, S. Reactivity of 6-Chloro-4- and 5-Hydrazino-2- Phenyl-3(2H)- Pyridazinones with Vilsmeier Reagent. Tetrahedron. **1994** 50:12933-12940.
[49]. Dury, K. (1965) new methods in the chemistry of pyridazones. Angew Chem, 77: 282-90. 94.
[50]. Li, Q., Lin, G., Liu, L., Yang, Z., Zhang, L. H. (2009) Methyl carbonium ion migration during the reaction of 4-chloro-5-methoxyl-3(2H)-pyridazinone with trifluoroethylation agents. Molecules. 14(2):777-84. 95.
[51]. Halasz, B. D., Monsieurs, K., Elias, O., Karolyhazy, L., Tapolcsanyi, P., Maes, B. U., Riedl, Z., Hajos, G., Dommisse, R. A., Lemiere, G. L., Kosmrlj, J., Matyus, P. (2004) Synthesis of 5HPyridazino[4,5-b]Indoles and their benzofurane analogues utilizing an intramolecular Heck-Type Reaction. Tetrahedron. 60: 2283- 2291.
[52]. D'Auria M., Electrophilic substitutions and HOMOs in azines and purines. Tetrahedron Lett., **2005** 46: 6333-6336.
[53]. Pattison G, Sandford G, Yufit DS, Howard JA, Christopher JA, Miller DD. Polysubstitutedpyridazinones from sequential nucleophilic substitution reactions of tetrafluoropyridazine. J Org Chem., **2009** 74 (15):5533-40.
[54]. Heinisch, G., and Frank, H, Pharmacologically active pyridazine derivatives. Prog. Med. Chem. **1990** 27: 1-35
[55]. Lee, S. G., Kim, J. J., Kweon, D. H., Kang, Y. J., Cho, S. D., Kim, S. K., Yoon, Y. J. Recent progress in pyridazin-3(2H)-ones chemistry, Curr. Med. Chem. **2004** 8: 1463–1480.
[56]. Pahernik, S. A., Schmid, J., Sauter, T., Schildberg, F. W., Koebe, H. G. Metabolism of pimobendan in long-term human hepatocyte culture: in vivo-in vitro comparison. Xenobiotica. **1995** (8):811-23.
[57]. Sayed, G. H, Sayed, M. A, Mahmoud, M. R, Shaaban, S. S. Synthesis and Reactions of New Pyidazinone Derivatives of Expected Antimicrobial Activities. Egypt. J. Chem. **2002** 45: 767- 776.
[58]. Tisler, M and Stanovic, B. advance in heterocyclic chemistry, Katritzky Alan R., and boulton A J. eds academic press.**1979** p408.
[59]. Katrusiak, A., Baloniak, S. Reactivity of 6-Chloro-4- and 5-Hydrazino-2- Phenyl-3(2H)Pyridazinones with Vilsmeier Reagent. Tetrahedron. **1994** 50:12933-12940.
[60]. Gokce, M., Dogruer, D., Sahin, F. Synthesis and Antinociceptive Activity of 6-Substituted-3pyridazinone Derivatives. Farmaco, **2001** 56: 233-237.