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Review Article

SYNTHESIS AND BIOLOGICAL EVALUATION OF SOME PYRIDAZINONE DERIVATIVES

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ABSTRACT

A series of pyridazinone derivatives were synthesized by a sequence of reactions starting from respective aryl hydrocarbons with anhydrides in the presence of anhydrous catalyst (Friedel-craft acylation). It was reported that derivatives of pyridazinones like triazole, phthalazinone, indolyl,6-(substituted-phenyl)-2-(substitutedmetjyl)-4,5-dihydropyridazine-3(2*H*)-ones were also synthesized by The Friedal-Craft Acylation of aromatic hydocabons with succinic anhydride gave β-substituted benzoyl propionic acid in presence of lewis acid, $AlCl_3$. These compounds were then characterized and screened for their respective pharmacological activities.

This review was an attempt to gather the different developments for synthesis and pharmacological activities of pyridazinone derivatives.

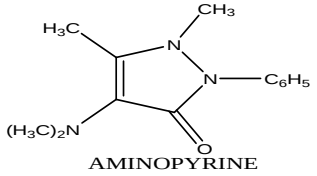
INTRODUCTION

The synthesis of novel pyridazinone derivatives and investigation of their chemical and biological 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 a number of compounds such as zardaverine/imidazole, bemoradan, indolindan, pimobendan are few examples of pyridazinones that are active as cardiotonic agents/ platelet.[1-9]

Literature survey revealed that substituted pyridazinones have reported to possess pharmacological activities such as antidepressant[10, 11], antihypertensive[12-27], antithrombotic[28], antifungal[29,50-54], antibacterial[30], antimicrobial[31-36], analgesic anti-inflammatory[37-43], antifeedant[44], antiplatelet[1-9], anticancer[45], diuretics[46], anti HIV[47], vasodilator and other anticipated biological and pharmacological properties[48].

CHEMISTRY

Aminopyrine is a classical drug with strong analgesic and anti-inflammatory activities but reprted to have side effects. A series of pyridazinone derivatives are structurally related to aminopyrine with a pyrazolone ring. Among these 4-alkoxy-2-methyl-5-morpholino-3(2*H*)-pyridazinones have been found to have strong analgesic and anti-inflammatory activities[49,55-58].

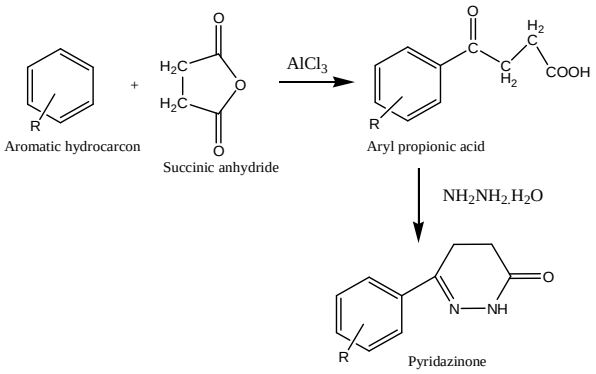


AMINOPYRINE

Synthesis

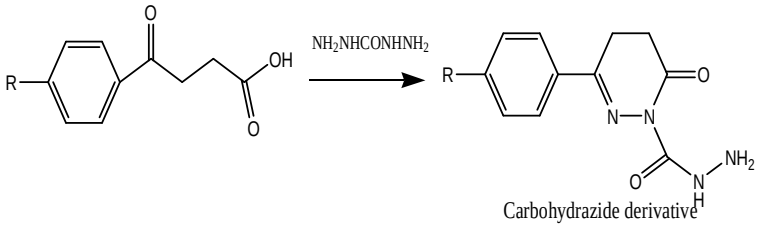
Some 6-(substituted phenyl)-4-5-dihydropyridazin-3(2*H*)-one derivatives were reported to synthesize according to scheme 1. The Friedal-Craft Acylation of aromatic hydrocarbons with succinic anhydride gave β-substituted benzoyl propionic acid in presence of lewis acid, $AlCl_3$.

1) The resulting β- benzoyl propionic acid on hydrazinolysis gave the pyridazinone.[12]



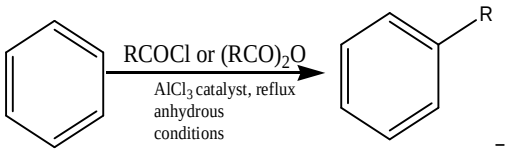
SCHEME 1

2) The resulting β- benzoyl propionic acid on hydrozinolysis with carbohydrazide gave pyridazinone carbohydrazide.[18]



Friedel-Crafts Acylation[59]

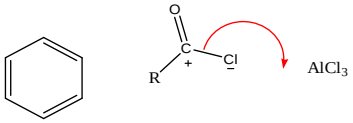
Friedel-Crafts acylation is the acylation of aromatic rings with an acyl chloride using a strong Lewis acid catalyst. Friedel-Crafts acylation is also possible with acid anhydrides. Reaction conditions are similar to the Friedel-Crafts alkylation. This reaction has several advantages over the alkylation reaction. Due to the electron-withdrawing effect of the carbonyl group, the ketone product is always less reactive than the original molecule, so multiple acylations do not occur. Also, there are no carbocation rearrangements, as the carbonium ion is stabilized by a resonance structure in which the positive charge is on the oxygen.



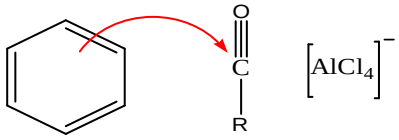
The feasibility of the Friedel-Crafts acylation depends on the stability of the acyl chloride reagent. formyl chloride, for example, is too unstable to be isolated. Thus, synthesis of benzaldehyde via the Friedel-Crafts pathway requires that formyl chloride be synthesized *in situ*. This is accomplished via the Gattermann-Koch reaction, accomplished by reacting benzene with carbon monoxide and hydrogen chloride under high pressure, catalyzed by a mixture of aluminium chloride and cuprous chloride.

Reaction mechanism

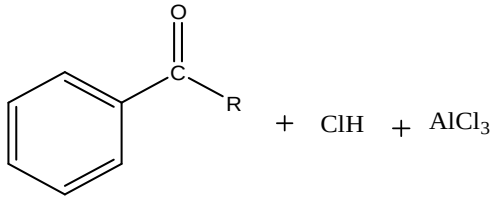
In a simple mechanistic view, the first step consists of dissociation of a chlorine atom to form an acyl cation.



This is followed by nucleophilic attack of the arene toward the acyl group.

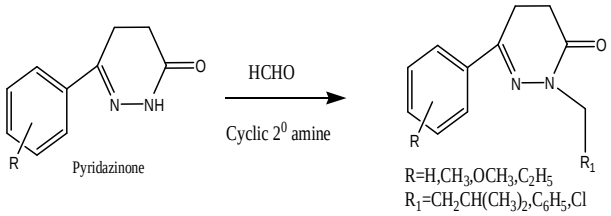


Lastly, a chlorine atom reacts to form HCl, and the $AlCl_3$ catalyst is regenerated.

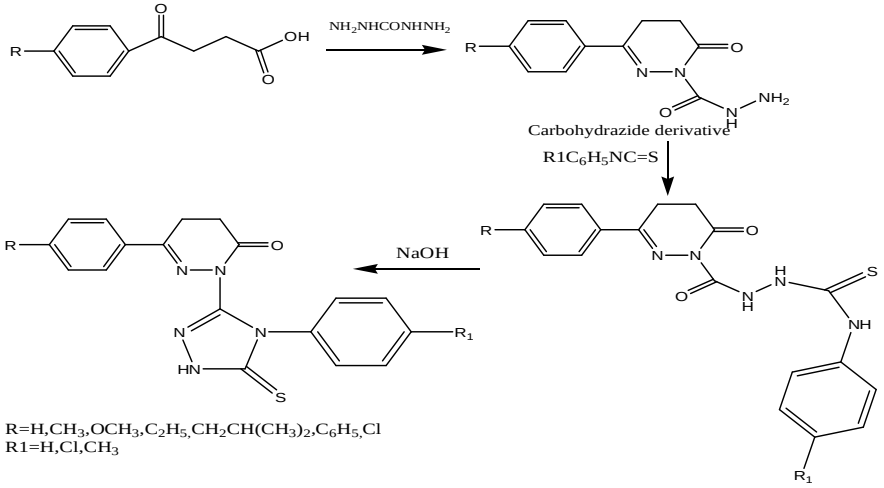


Different pyridazinone derivatives reported

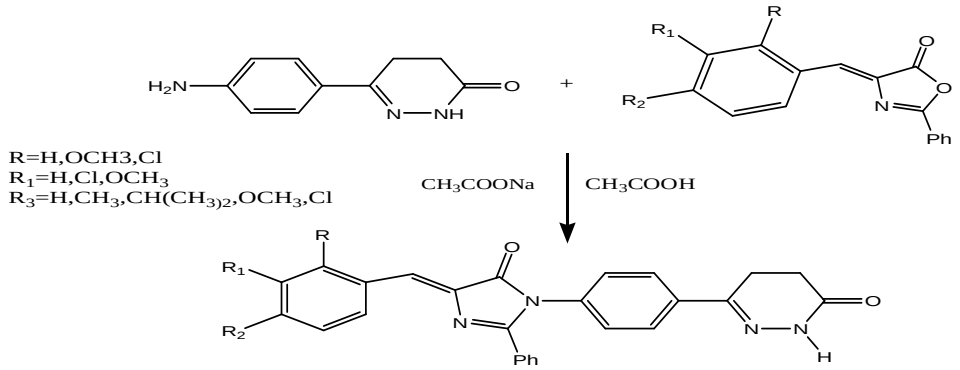
Pyridazinone was synthesized according to Scheme-I, which involves Friedel-craft Acylation of aromatic hydrocarbon with succinic anhydride to give β- benzoyl propionic acid in presence of $AlCl_3$ catalyst. The β-benzoyl propionic acid on hydrazinolysis gave pyridazinones. These 6-substituted-phenyl-4, 5-dihydropyridazin-3(2*H*)-one derivatives were then subjected to mannich reaction with cyclic secondary amine to give 6-(substituted-phenyl)-2-(substituted methyl)-4, 5-dihydro pyridazin-3(2*H*)-one derivatives. The compounds were evaluated for antihypertensive activities by Tail-Cuff method.[12.]



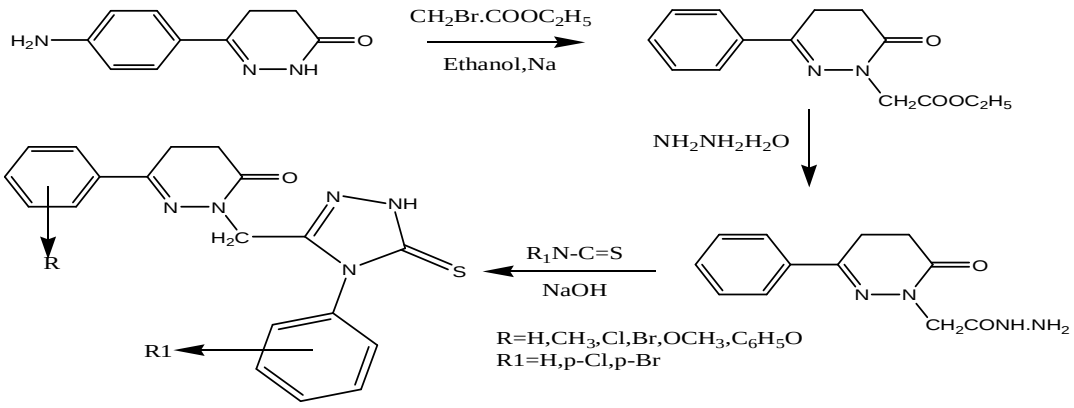
Triazole incorporated pyridazinones were designed and synthesized by a sequence of reaction from respective aryl hydrocarbons. The compounds were screened for antihypertensive activity using non-invasive Tail-Cuff Method.Friedel crafts acylation of hydrocarbons with succinic anhydride and anhydrous $AlCl_3$ gave β- aroyl propionic acids. This was then treated with carbohydrazide using ethanol, then treated with aryl isothiocyanate to give thiosemicarbazide derivatives which was refluxed with NaOH to give different triazole derivatives,i.e.6-(substituted phenyl)-2-(4-substituted phenyl-5-thioxo-4,5-dihydro-1H-1,2,4-triazole-3-yl)-4,5-dihydropyridazin-3(2*H*)-one derivatives.[18]



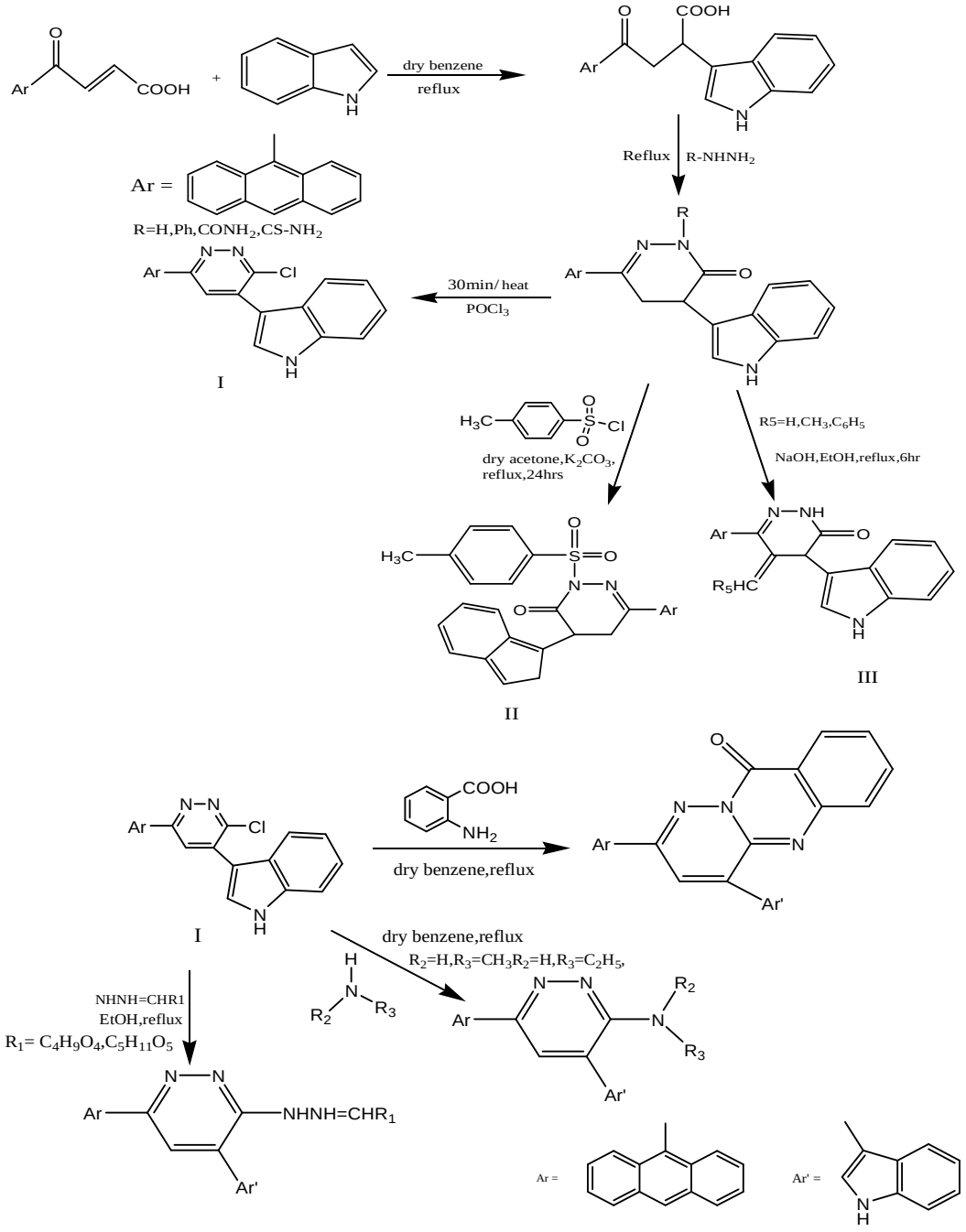
As the 6-arylpyridazinone structure is essential for the activity on cardio vascular system, a number of studies on substitution have been performed on both pyridazinone and aryl residues. Reports showed that the p-substituted compounds on aryl residue were more active than the m-substituted ones. Hence, the compounds were considerably antihypertensive by substituting the amino group (Thyes et al., 1983).This paper, reports the formation of the imidazolinone ring system using the amino group. For this purpose, the amino compounds were reacted with oxazolinones. Thus, some 6-[(4-arylidene-2-phenyl-5- oxoimidazolin-1-yl)phenyl]-4,5-dihydro-3(2H)-pyridazinone and 4-[(4-arylidene-2-phenyl-5-oxoimidazolin-1-yl)phenyl]- 1(2H)-phthalazinone derivatives were synthesized by reacting 6-(4-aminophenyl)-4,5-dihydro-3(2H)-pyridazinone or 4-(4-aminophenyl)-1(2H)-phthalazinone with different 4- arylidene-2-phenyl-5(4H)-oxazolone derivatives. The antihypertensive activities of the compounds were examined both in vitro and in vivo. Some pyridazinone derivatives showed appreciable activity.[19]



1, 2, 4-triazole derivatives show diverse pharmacological properties such as antimicrobial (1-4), anti-inflammatory (5), analgesic (6), anticancer (7), antihypertensives (8), anticonvulsant and antiviral (9). Some of antifungal azole derivatives used as common antibiotics such as amphotericin B possess toxic effect on humans along with their antimicrobial effects (10). Although antimicrobial agents having different structures are frequently used in the treatment of fungal infections, there is an increasing resistance to these drugs. To overcome the development of drug resistance it is necessary to synthesize a new class of antifungal compounds possessing different chemical properties from those of used commonly. 5-Thioxo-1, 2, 4-triazole containing a pyridazinone side chain is an ideal heterocyclic system for antifungal activity. The following antifungal 1, 2, 4-triazole derivatives are applicable in medicine like fluconazole (11), itraconazole and terconazole. A series of 1, 2, 4-triazole derivatives were synthesized and evaluated for their in vitro antifungal activity. The structures of the final triazoles were confirmed on the basis of their spectral data. The above triazoles were synthesized by four step reactions presented in Scheme.[29,50-54.]



A novel synthesis of some new indolypyridazinone derivatives by cyclocondensation of indolylbutyric acid with hydrazine hydrate and its derivatives to give pyridazinone derivatives is described. Further pyradizinones are treated with $PCl_5/POCl_3$, arylsulphonyl chloride derivatives and aliphatic or aromatic aldehydes gave chloropyridazine derivatives. Chloropyridazine derivatives when treated with carbohydrate hydrazones of ribose,glucose,galactose and lactose in ethanol gave hydralzonopyradazine derivatives and with aliphatic or aromatic amines i.e. methylamine, ethylamine, aniline etc, in dry benzene gave pyridazine derivatives. The pyridazinones can also be reacted with benzene or 4-toluenesulphonyl chloride and anhydrous K_2CO_3 in dry acetone gave 6-anthracene 9-yl-4-(1H indol-3-yl) -2-(benzenesulphonly or 4-toluenesulphonyl)-4,5-dihydro-2H-pyridazin-3-ones respectively. The structures of all new synthesized compounds were established from spectral data and elemental analysis. The antimicrobial activity of selected compounds against gram positive and negative bacteria were reported.[30]



PHARMACOLOGICAL EVALUATION

Vasodilator activity[19]

In vitro

Sheep carotid artery taken from a slaughterhouse were cut into 0.3 mm rings and put in an organ bath of 10 ml capacity containing Tyrod solution in a gas of 95% O_2 and 5% CO_2. Two g of tension was applied. The preparation was allowed to equilibrate for 60 min with regular washes every 15 min. In order to check the vasodilator activity, 8 mM potassium chloride was included in the concentrations. After thorough washing, this process was repeated until the amplitude of the concentrations became constant. The substances were investigated using the single dose technique. Between administrations of the individual substances, the preparations were washed until the initial situation was

reestablished and the potassium chloride concentrations were induced.[19]

By tail cuff method (in vivo) [12, 18, 19]

Albino rats of both sexes weighing 200±10 g were used in this study. There were seven animals in each group. The compounds were dissolved in DMSO. The arterial blood pressures of the conscious rats were measured by the tail-cuff method using an indirect blood pressure recorder system MAY 9610 (Turkey). The blood pressure of each rat was measured before and 30 min. after the intraperitoneal injection of the compounds. Each compound was given 20 mg/kg dose in 0.1 ml volume. 0.1 ml DMSO was administered to the animals in the control group. The reduction of blood pressure between two measurements was recorded as mmHg. The results were expressed as mean±S.E.M. Student's test was used for statistical analyses.[12, 18, 19.]

In vitro antifungal activity[29, 50-54]

The antifungal activities of the tested compounds against different fungal species were carried out by microdilution method. The results were compared with the standard drug ñ voriconazole. The minimum inhibitory concentration of voriconazole for all the fungal species was lower than 0.5 g/ml. Twelve compounds tested in the study were found to have significant antifungal activities against all the fungal species. The chloro substituent derivative showed the highest activity against all the fungal species. The MIC of the standard drug voriconazole was between 0.10 and 0.50 g/ml against all the fungal species. The two electronegative groups of Cl were found to increase the activity of 1, 2, 4-triazole but presence of bulky group or aromatic group on benzene ring, were found to decrease the activity.[29]

Anti-inflammatory activity[37-42]

Anti-inflammatory activity against carragenan-induced rat's paw oedema was determined by the method of Winter et al. The rats were divided into groups of five animals each. Compounds were screened for anti-inflammatory activity at 50 mg/kg p.o. The percentage of anti-inflammatory activity was calculated according to the following formula.

% Anti-inflammatory activity = $1-v_1/v_2 \times 100$

where v_1 and v_2 are volume of oedema in drug treated and control group, respectively.

RESULTS AND DISCUSSION

Pyridazinone were synthesized by Friedel-craft's acylation reaction. Several derivatives were synthesized by the given different schemes. Chemical structures of the title compounds were elucidated by ^{1}H-NMR, Mass spectral and elemental analysis and screening of the compounds for their biological activity was reported.

CONCLUSION

A novel synthesis of some pyridazinone derivatives by Friedel Craft's acylation is described. The reaction of aromatic hydrocarbons with succinic anhydride and lewis acid gave β-aroyl propionic acid which on treatment with hydrazine hydrate or carbohydrazide gave pyridazinone derivatives. The structures of all new synthesized compounds were established from their spectral data and elemental analysis. Further different pharmacological activities of these compounds were reported.

REFERENCES

1. 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.
2. 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..
3. Corsano S, Vezza R, Scapicchi R, Foresi S, Strappaghetti G, Nenci G. G, and Gresele P. New pyridazinone derivatives as inhibitors of platelet aggregation. Eur. J. Med. Chem., 30,627-631 (1995)
4. Montero-Lastres, A, Fraiz N, Laguna R, Cano E, Esteves I and Ravina E. Pyridazines XVIII. 6-aryl-3(2H)-pyridazinones inhibit calcium influx in stimulated platelets. Biol. Pharm. Bull. 1999;22:1376-1379.
5. Sotelo E, Fraiz N, Yanez M, Terrades, V, Laguna R., Cano E and Ravina E. Pyridazines. Part XXIX: Synthesis and platelet aggregation inhibition activity of 5-substituted-6- phenyl-3(2H)-pyridazinones. Novel aspects of their biological actions. Bioorg. Med. Chem. 2002;10:2873-2882..
6. Sotelo E, Fraiz N, Yanez M, Laguna R Cano E and E. Ravina, Pyridazines. Part 31: Synthesis and antiplatelet activity of 4,5-disubstituted-6-phenyl-

3(2H)-pyridazinones. Chem. Pharm. Bull. 2002;50:1574-1577.
7. Coelho, A.; Sotelo, E.; Fraiz, N.; Yanez, M.; Laguna, R.; Cano, E.; Ravina, E. Pyridazines. Part36: Synthesis and Antiplatelet Activity of 5-Substituted-6-Phenyl-3(2*H*)-Pyridazinones. Bioorg.Med. Chem. Lett. 2004, *14*, 321-324
8. Sotelo, E.; Fraiz, N.; Yanez, M.; Terrades, V.; Laguna, R.; Cano, E.; Ravina, E. Pyridazines. PartXXIX: Synthesis and Platelet Aggregation Inhibition Activity of 5-Substituted-6-Phenyl-3(2*H*)-Pyridazinones Novel Aspects of their Biological Action. Bioorg. Med. Chem. 2002, *10*, 2873-2882.
9. A.Coelho, E. Sotelo, E. Ravina, Tetrahedron 59(2003)2477-2484.
10. A.A Siddiqui, S.R, Ahmad, S.A. Hussian, Acta.Pol.Pharm.64 (2)2008, 223-228.
11. Anees A.Siddiqui, Ravinesh Mishra and Mohammad Shaharyar.Synthesis, characterization and antihypertensive activity of pyridazinone derivatives. European Journal of Medicinal Chemistry.Vol 45, Issue 6, June 2010, 2283-2290.
12. S. Demirayak, A.C. Karaburun, R. Beis, Eur. J. Med. Chem. 39 (2004) 1089–1095.
13. A.A. Siddiqui, S.M. Wani, Ind. J. Chem. 43B (2004) 1574–1579.
14. Ogretir, C.; Yarligan, S.; Demirayak, S. Spectroscopic Determination of Acid Dissociation Constants of Some Biologically Active 6-Phenyl-4, 5-Dihydro-3(2*H*)-Pyridazinone Derivatives. J.Chem. Eng. Data 2002, *47*, 1396-1400.
15. Barbaro, R.; Betti, L.; Botta, M.; Corelli,F.; Giannaccini, G.; Maccari, L.; Manetti, F.;Strappaghetti, G.; Corsano, S. Synthesis Biological Evaluation and Pharmacophore Generation ofNew Pyridazinone Derivatives with Affinity Toward α1- and α2- Adrenoceptors. J. Med. Chem. 2001, *44*, 2118-2132.
16. Sircar, I. Synthesis of New 1, 2, 4-Triazolo [4, 3-b]pyridazines and Related Compound. J. HeterocyclicChem. 1985, *22*, 1045-1048.
17. Anees A.Siddiqui,Ravinesh Mishra, Asif Husain, Mohd. Rashid, Palash Pal.Triazole incorporated pyridazinones as a new class of anti-hypertensive agents:design, Synthesis and in vivo screening. Bioorganic and Medicinal Chemistry Letters.2011,
18. Seref Demirayak, Ahmet Cagri Karaburun, Ismail Kayagil, Kevser Erol, and Basar Sirmagul.Some Pyridazinone and Phthalazinone Derivatives and Their Vasodilator Activities. Arch Pharm Res Vol 27, No 1, 13-18, 2004.
19. Betti, L., Floridi, M., Giannaccini, G., Manetti, F., Strappaghetti,G., Tafi, A., and Botta, M., a1-Adrenoceptor antagonists. 5.Pyridazinone-arylpiperazines. Probing the influence on affinity and selectivity of both ortho-Alkoxy groups at the arylpiperazine moiety and cyclic substituents at the pyridazinone nucleus. Bioorg. Med. Chem. Lett. 2003;13:171-173..
20. Cignarella, G., Barlocco, D., Pinna, G. A., Loriga, M., Curzu, M.,Tofanetti, O., Germini, M., Cazzulani, P., and Cavalletti, E.,Synthesis and biological evaluations of substituted benzo[h]-cinnolinones and 3-benzo[6,7]cyclohepta[1,2-c]pyridazinones: higher homologues of the antihypertensive and antithrombotic 5H-indeno[1,2-c]pyridazinones. J. Med. Chem.,32, 2277-2282 (1989).
21. Combs, D. W., Rampulla, M. S., Bell, S. C., Klaubert, D. H., Tobia, A. J., Falotico, R., Haertlein, B., Lakas-Weiss, C., and Moore, J. B., 6-Benzoxazinylpyridazin-3-ones, Potent, longacting positive inotrope and peripheral vasodilator agents. J.Med. Chem., 33, 380-386 (1990).
22. Curran, W. V. and Ross, A., 6-Phenyl-4,5-dihydro-3-(2H)- pyridazinones, A series of hypotensive agents, J. Med. Chem., 17, 273-281 (1974).
23. Foye, W. O., Lemke, T. L., and Williams, D. A., Principles of Medicinal Chemistry, 4th Ed., Williams and Wilkins. London, 345-387, 499-534 (1995).
24. Seki, T., Nakao, T., Masuda, T., Hasumi, K., Gotanda, K., Ishimori, T., Honma, S., Minami, N., Shibata, K., and Yasuda K., Studies on agents with vasodilator and b-blocking activities. IV, Chem. Pharm. Bull., 44, 2061-2069 (1996).
25. Szasz, G. and Budvavi-Bavauy, Z., Pharmaceutical Chemistry of Antihypertensive Agents, CRC Press, Boca Raton, 3-265 (1991).

26. Emilsson H., Salendar H., Gaarder J.: Eur. J.Med. Chem. 21, 333 (1985).
27. A.Monge,P.Parrado,M.Font,E.F.Alvare z,J.Med.Chem.30(6),1987,1029-1035.
28. Anees A Siddiqui,Syed Rizwan Ahmad, Mohammed Shehroz Mir, Syed Akhtar Hussain,Mohammed Raish and Ravindra Kaur.Synthesis and invitro antifungal activity of 6-substituted-phenyl2-{[(4'-substituted phenyl5'-thioxo)-1,2,4-triazol-3-yl]-methyl}-2,3,4,5-tetrahydropyridazin-3 one derivatives. Acta Poloniae Pharmaceutica - Drug Research, Vol. 65 No. 2 pp. 223-228, 2008.
29. Samar A. Abubshait, An Efficient Synthesis and Reactions of Novel Indolylpyridazinone derivatives with Expected Biological Activity. Molecules 2007*, 12,* 25-42.
30. 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.
31. Katrusiak, A.; Katrusiak, A.; Baloniak, S. Reactivity of 6-Chloro-4- and 5-Hydrazino-2- Phenyl-3(2*H*)-Pyridazinones with Vilsmeier Reagent. Tetrahedron 1994, *50*, 12933-12940.
32. Kassab, R.R. Simple Synthesis and Reactions of Some New Pyridazinono Derivatives and their Antimicrobial Activity. Egypt. J. Chem. 2002, *45*, 1055-1073.
33. Deniz S.. Dogruer.Synthesis of some pyridazinone derivatives carrying urea, thiourea and sulphonamide moieties and their antimicrobial activity. Turk j. Chem.34 (2010), 57-65.
34. Grare, M.; Mourer, M.; Fontanay, S.; Regnouf-de-Vains, J. B. Finance, C.; Duval, R. E. J. Antimicrob. Chemother.2007, *60*, 575-581.
35. Ghannoum, M.A.; Rice L. B. Clinical Microbiology Reviews 1999, *12*, 501-517.
36. Takaya M, Sato M, Terashima K, Tanizawa H, Maki Y. A new nonsteroidal analgesic-antiinflammatory agent. Synthesis and activity of 4-ethoxy-2-methyl-5-morpholino-3(2H)-pyridazinone and related compounds. J Med Chem. 1979 Jan*; 22(1):53-8.*
37. Sahina MF, Badiçoglu B, Gökçe M, Küpeli E, Yeşilada E. Synthesis and analgesic and antiinflammatory activity of methyl 6-substituted-3(2h)-pyridazinone-2-ylacetate derivatives. Arch Pharm (Weinheim). 2004 Aug; 337(8):445-52
38. Banoglu, E.; Akoglu, C.; Unlu, S.; Kupeli, E.; Yesilada, E.; Sahin, M.F. Amide Derivatives of [6-(5-Methyl-3-phenylpyrazole-1-yl)-3(2*H*)-Pyridazinone-2-yl]acetic Acids as Potential Analgesic anti-Inflammatory Compounds. Arch. Pharm. Pharm. Med. Chem. 2004, *337*, 7-14.
39. 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.
40. Dogruer, D.S.; Sahin, M.F.; Kupeli, E.; Yesilada, E. Synthesis and Analgesic and Anti- Inflammatory Activity of New Pyridazinones. Turk. J. Chem. 2003, *27*, 727-738. Molecules 2007*, 12,* 41
41. Tazkoparan B., Gokhan N., Aktay G., Yesilada E., Ertan M.: Eur. J. Med. Chem. 34, 743(2000).
42. Cao, S.; Qian, X.; Song, G.; Chai, B.; Jiang, Z. Synthesis and Antifeedant Activity of New Oxadiazolyl 3(2*H*)-pyridazinones. J. Agric. Food Chem. 2003, *51*, 152-155.
43. W.Malinka,A.Redzicka,O.Lozach,New Derivatives of pyrrolo[3,4-d]pyridazinone and their anticancer effects.Il Farmaco 59(2004)457-462.
44. Akahane, A; Katayama, H; Mitsunaga, T.J.Med.Chem.1999, 42,779-783.
45. Livermone, D.G.H.; Bethell, R.C.; Cammack, N.J.Med.Chem.1993, 36, 3784.
46. Youssef,A.S.;Marzouk,M.I.;Madkour,H .M.F.;El-Soll,A.M.A.;El-Hashash,M.A.Synthesis of some heterocyclic systems of anticipated biological activities via 6-aryl-4-pyrazol-1-yl-pyridazin-3-one.Can.J.Chem.2005,83,251-259.
47. Makoto Sato, Hisayuki Tanizawa,Tamotsu Fukuda and Tomokazu Yuizono.Japan.J.Pharmacol.29,303(1 979)
48. Williams DA, Lemke TL. Foye's Principles of Medicinal Chemistry, 5th ed. Lippincott Williams and Wilkins, 2002.
49. Holla B. S., Golsalves R., Shenoy, S.: Farmaco 53, 574 (1998).

50. Ersan S., Nacak S., Berkem R.: Farmaco 53, 773 (1998).
51. Yuksek H., Demirbas A., Ikizler A., Johansson C.B., Celik C., Ikizler A.A.: Arzneim.-Forsch.Drug Res. 47, 405 (1997).
52. Ikizler A.A., Ucar F., Demirbas N., Yasa I.,Ikizler A., Genzer T.: Indian J. Heterocycl. Chem. 61, 271 (1999).
53. Collin X., Sauleu A., Coulon J.: Bioorg. Med. Chem. 13, 2601 (2003).Chem. 13, 2601 (2003).
54. McEvoy, F. J. and Allen, Jr. G. R., 6-(Substituted phenyl)-5-substituted-4,5-dihydro-3(2H)-pyridazinones. J. Med. Chem.,17, 281-286 (1974). Tishler, M. and Stanovnik, B., Pyridazines. Adv. Heterocyclic Chem., 9, 121 (1968).
55. Tishler, M. and Stanovnik, B., Recent advances in pyridazine chemistry. Adv. Heterocyclic Chem., 24, 363 (1979).
56. Thyes, M., Lehmann, H. D., Gries, J., König, H., Kretzschmar, R., Kunze, J., Lebkücher, R., and Lenke, D., 6-Phenyl-4,5-dihydro-3-(2H)-pyridazinones. J. Med. Chem., 26, 800-807(1983).
57. Wolf, M.E., Burger's Medicinal Chemistry and Drug Discovery 5th ed. Vol. 2, p. 152-462. John Wiley and Sons, New York (1997).
58. Robert Thornton Morrisison,Robert Neilson Boyd.6th ed.,666-667.Prentice-Hall of India.1992.