Journal of Advanced Biomedical and Pharmaceutical Sciences

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Pyridazinones and pyrrolones as promising Scaffolds in Medicinal Chemistry

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Received: September 26, 2018; revised: October 23, 2018; accepted: November 5, 2018

Abstract

Pyridazinones and pyrrolones are important building blocks for some important drugs such as the naturally occurring antibacterial pyrrolone, althiomycin; the cardiotonic pyridazinones, pimobendan and levosimendan and the analgesic anti-inflammatory, emorfozan. Therefore, researchers all over the world paid attention to prepare various pyridazinones and pyrroolones derivatives. The variability in the biological response and ease of preparation from the corresponding furanones attracted attention of researchers to explore these two nuclei in the design and synthesis of different analogues. This review article focuses on different biological activities, structure activity relationship and mechanism of action of pyridazinones and pyrrolones derivatives.

Key words
Pyridazinones, Pyrrolones, Biological activities, Structure activity relationship

1. Introduction

Pyridazinones and pyrrolones are heterocyclic compounds having many biological activities such as anti-inflammatory [1], analgesic [1], antibacterial [2] and cardiotonic [3] activities. Both pyridazinones and pyrrolones could be synthesized by nucleophilic substitution from the corresponding furanones [1]. Pyridazinones and pyrrolones are fantastic moieties with wide application in clinical use. The most important examples are, Althiomycin **1** which is a naturally occurring alkaloid separated from *Streptomyces Althioticus* and used as antibiotic through inhibition of protein synthesis [2]. In addition, Pimobendan **2** is a phosphodiesterse III (PDE III) inhibitor and used in management of congestive heart failure[3]. Moreover, Emorfozan **3** was marketed in Japan as an analgesic and anti-inflammatory drug [4]. Also, literature reports have also revealed several pyridazinones with vasorelaxant activity such as SK&F-93741 **4** a dihydropyridazinone derivative having vasodilator properties [5]. Moreover, levosimendan **5** which is a cyano containing pyridazinone derivative exhibiting cardiotonic activity with dual inotropic and vasodilator activities, so levosimendan used in treatment of congestive heart failure [6-8]. **(Figure1)**

2. Pyridazinones

Pyridazine is the structural isomer of 1,3-diazine (pyrimidine) and 1,4-diazine (pyrazine). Pyridazine is a planer six membered ring and is considered as a resonance hybrid of two structures **6a** and **6b,** but the structure **6a** is the predominating one [9]. **(Figure 2)**

Moreover, oxo-pyridazines exhibit tautomerism, the 3 and 4-hydroxyl pyridazines **7a** and **7c** exist predominantly in the more stable oxo form **7b** and **7d**, respectively[10]. **(Figure 3)**
Pyridazin-3-one scaffold either saturated or unsaturated form has been considered as a magic moiety which possesses important types of biological activities. This variability in the biological response attracted attention of researchers to explore this nucleus to its multiple potential biological activities. Different synthetic methods of pyridazins and pyridazinones depend on reaction of 1,4-disubstituted aromatic hydrocarbons, furanones , diketons, ketoacids or ketoesters with hydrazine or its derivatives[11-15].

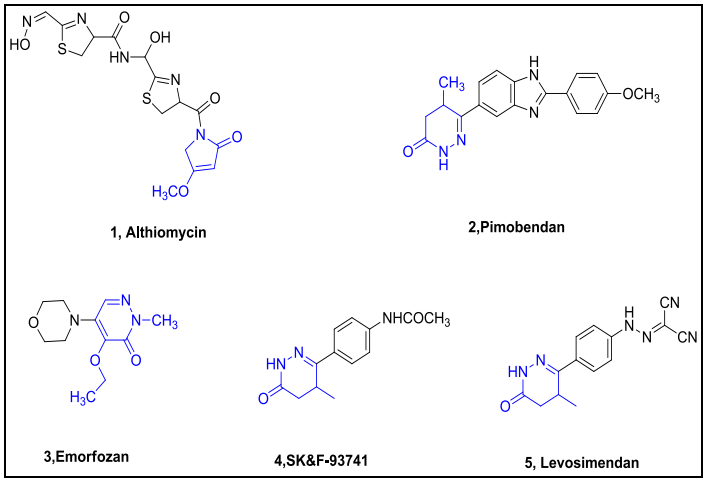

Figure 1: Clinically used pyrrolone and pyridazinone drugs.

3. Biological activities of pyridazin-3(*2H*)-one derivative

Pyridazin-3(*2H*)-one derivatives was attracted the attention of medicinal chemists due to the variable pharmacological

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activities of this moiety such as antihypertensive [16], platelet aggregation inhibitors [17], cardiotonic [5], antimicrobial[18], analgesic[19], anti-inflammatory agents. [19], anticonvulsant [20], anticancer [21] and (PDE III, V) inhibitors[5, 22]. **(Figure 4)**

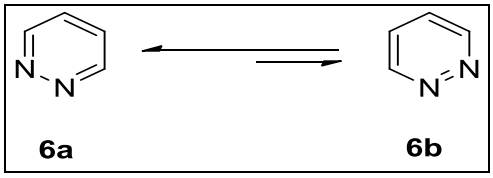

Figure 2: Structural isomers of pyridazin**.**

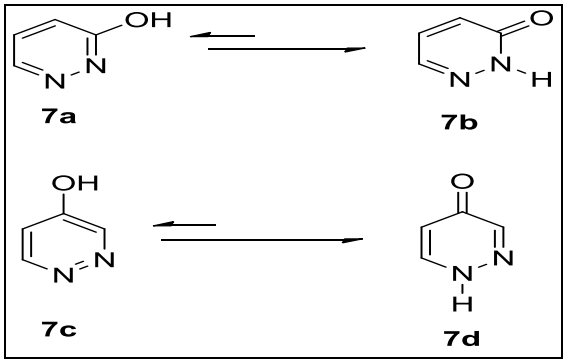

Figure 3: Keto-enol tautomerism of pyridazinones.

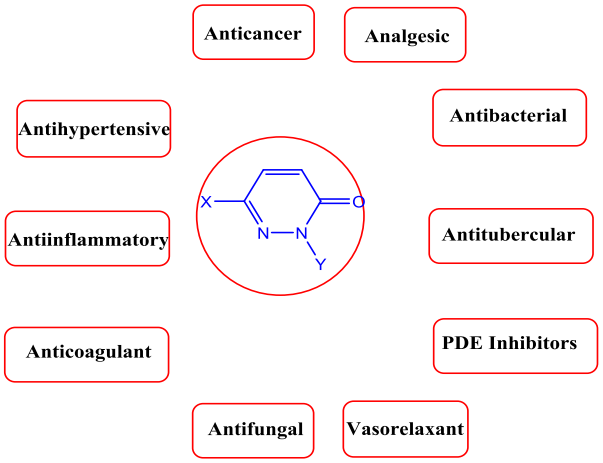

Figure 4: Biological activities of pyridazinones.

3.1. Anti-inflammatory Activity

K. Abouzid *et al.*, [23] synthesized a series of pyridazinones for comparison with diclofenac. Some of the tested compounds revealed more than 50% inhibition of carrageenan-induced rat paw edema at a dose 10 mg/kg. Compounds **8** and **9** showed comparable activity to declofenac after 4hr. The presence of bromine at position 2 in compound **8** or 2,6-dimethylphenyl group in compound **9** increased the anti-inflammatory activity. Meanwhile, A novel 6-aryl-2-(*p*-sulfamoylphenyl)-4,5-dihydropyridazin-3(2*H*)-ones was synthesized and tested for their anti-inflammatory activity in carrageenan-induced rat paw edema model by R. Bashir *et al.*, [24]. Compound **10** showed anti-inflammatory activity comparable to that of celecoxib after 5hr. Similarly, K. Abouzid *et al* ., [25] synthesized a series of compounds containing central bicyclic quinoxaline substituted with a phenyl ring and pyridazinone ring instead of sulfamoylphenyl or sulfonylphenyl group of celcoxib. The phenyl ring was used to fit in to the area occupied by the CF_3 group of celecoxib. Bicyclic quinoxaline nucleus attached to pyridazinone and phenyl substituents in compounds **11** and **12** produced potent anti-inflammatory activity especially chloro analogue **12**. Moreover, K. Abouzid *et al.*, [26] introduced a series of aryl ethenyl and aryl ethyl pyridazinone derivatives. The results indicated that synthesized compounds exhibited good anti-inflammatory activity with safe gastrointestinal profile and compound **13** in which ethyl linker between the dihydropyridazinone ring and the aryl moiety more potent than derivatives with ethyenyl linker. D.S. Dogruer *et al.*,[27] synthesized a series of 4,6-diphenyl-3(2*H*)-pyridazinones substituted at two position of pyridazinone with 4-arylpiperazin-1-yl-carbonylalkyl moieties. All synthesized compounds were tested for their anti-inflammtory activity using carrageenan-induced rat paw edema at a dose 10 mg/kg and compound **14** showed significant anti-infalammatory activity. Moreover, a novel series of 4-phenyl and 4-4-(2-chlorophenyl)-6-(5-chloro-2-oxo-3*H*-benzoxazol-7-yl)-3(2*H*)-pyridazinones were synthesized and tested for anti-infalammatory activity using rat paw edema method and in vitro screening assay against cyclooxygenases COX-1 and COX-2. Compounds **15** and **16** showed a comparable activity to indomethacin with inhibition% of 49.7, 53.6 and 56.8, respectively, which support the results of COX inhibitory activity screening, B. Okcelik *et al*., [28]. Also, Z. Ozdemir *et al*., [29] reported the synthesis of novel series of 6-substituted-3(2*H*)-pyridazinone-2-acetyl-2-(substituted-benzal)hydrazine derivatives and evaluated their anti-inflammatory activity using carrageenan-induced rat paw edema method. Compounds **17** and **18** gave inhibition % (35.0 and 36.0%), respectively comparable to that of indomethacin (39.4%). Sahin *et al*., [30] synthesized a series of 6-substituted-3(2*H*)-pyridazinone-2-ylacetate and tested for their anti-inflammatory activity using carrageenan-induced rat paw edema method. Compound **19** exhibited the highest inhibition (41.6%) comparable to indomethacin (43.1%). Additionally, it did not show gastric lesion in treated rats. M.M. Saeed *et al*., [31] synthesized a series of pyridazine and pyridazinone derivatives, the target compounds were tested for their anti-inflammatory and ulcerogenic properties using indomethacin as standard drug. Compounds **20** and **21** showed anti-inflammatory activity of (42.6 % and 31%), respectively, which are more comparable to indomethacin (40.3%). Moreover, both compounds exhibited a safe gastric profile and selective COX-2 inhibition in the MTT assay. C Barberot *et al*.,**[32]** synthesized a series of pyridazinones and tested as anti-inflammatory agents through reduction of IL-8 level and compound **22** was the most active compound. **(Figure 5)**

3.2. Analgesic activity

M. Asif *et al.*, [33] synthesized a series of 6-phenyl-4-substituted benzylidine tetrahydropyridazin-3(2*H*)-one derivatives and evaluated their analgesic activity against aspirin

using hot plate model. Compounds **23**, **24** and **25** exhibited significant analgesic activities when compared with the reference drug aspirin. C. Biancalani *et al.*,[34] synthesized a series of pyridazinones substituted with arylpiperazinylalkyl group and tested their analgesic activity in a model of acute nociception induced by thermal stimuli in mice. Compound **26** showed strong analgesic activity with ED_{50} of 3.5 µg, which about 3-fold more potent than morphine. Moreover, A. Singh *et al.*,[35] synthesized 6-aryl-4-substituted benzylidene/furfurylidene pyridazin(*2H*)-3-one derivatives and tested their analgesic activity against aspirin using hot plate model. Results indicated that compounds **27**, **28** and **29** exhibited analgesic activity comparable to aspirin. M. Sukuroglu *et al.*, [36] synthesized a series of amide derivatives of [6-(3,5-dimethyl-4-chloro-pyrazole-1-yl)-3(2*H*)-pyridazinone-2-yl]acetic acid and tested its *in vivo* analgesic activity using *p*-benzoquinone-induced writhing test. Results indicated that compounds **30** and **31**were equipotent to aspirin where the inhibition of writhing was (52.4, 54.3 and 52.9%), respectively. **(Figure 6)**

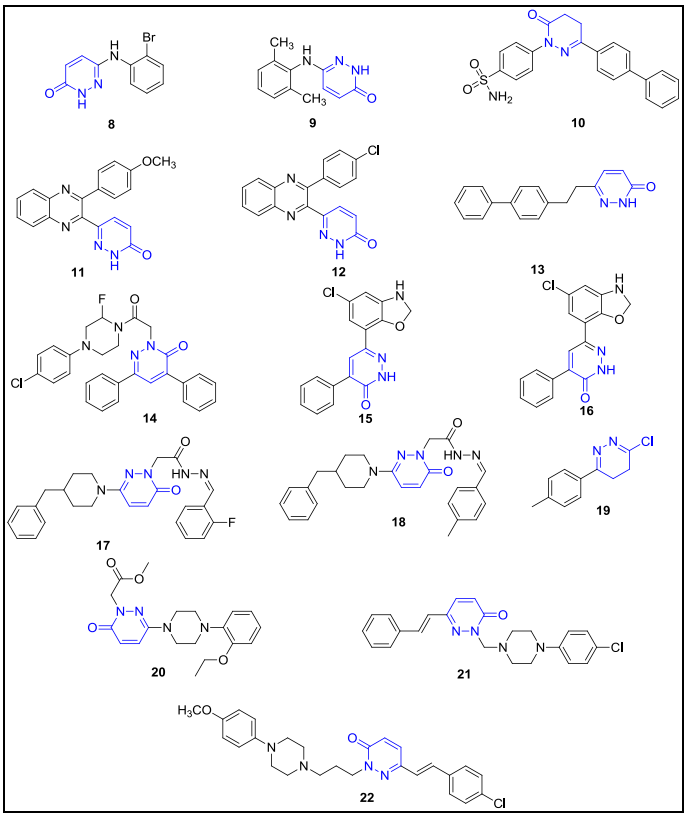

Figure 5: Pyridazinone derivatives with anti-inflammatory activity**.**

3.3. Antihypertensive Activity

A.A. Siddiqui *et al.*,[16] synthesized a group of 1,2,4-triazol-3-yl-4,5-dihydropyridazin-3(2*H*)-one derivatives. Results indicated that compounds with structural features of the general formula **32** showed the maximum antihypertensive activity. Indeed, M. Imran *et al.*, [37] synthesized four pyridazinone derivatives and molecular docking studies of these compounds was carried out on human angiotensin converting enzyme (ACE). Compound **33** exhibited the highest scores in docking study and so tested for ACE inhibitory activity using Dojindo ACE Kit-WST test kit and revealed promising activity (IC_{50} = 5.78 µg/mL) compared to that of lisinopril (IC_{50} = 0.85 µg/mL). From this research study, authors concluded that incorporation of amino and carboxylic acid groups into the structure of pyridazinone derivatives can enhance the ACE inhibitory activity of this class of compounds. Moreover, R. Mishra *et al.*, [38] introduced a series of 4,5-dihydro-1*H*-(1,2,4-triazol-3-yl)-4,5-dihydropyridazin-3(2*H*)-one derivatives and evaluated their antihypertensive activity using Tail Cuff method. This study revealed that compounds **34** and **35** reduced the mean arterial blood pressure (MABP) by (41.84 and 40.98%), respectively in comparable results to the standard drugs propranolol and hydralazine (41.40 and 41.76%), respectively. Vikas Jakhmola *et al.*, [39] synthesized a series of new 6-(substitutedphenyl)-2-(substitutedmethyl)-4,5-dihydropyridazin-3(*2H*)-one derivatives and evaluated their antihypertensive activity using Tail Cuff method. Results indicated that compounds **36** and **37** showed antihypertensive activity (reduction of MABP = 41.99 and 42.40%), respectively which are more potent than the used standard, hydralazine (reduction of MABP = 40.76%). **(Figure 7)**

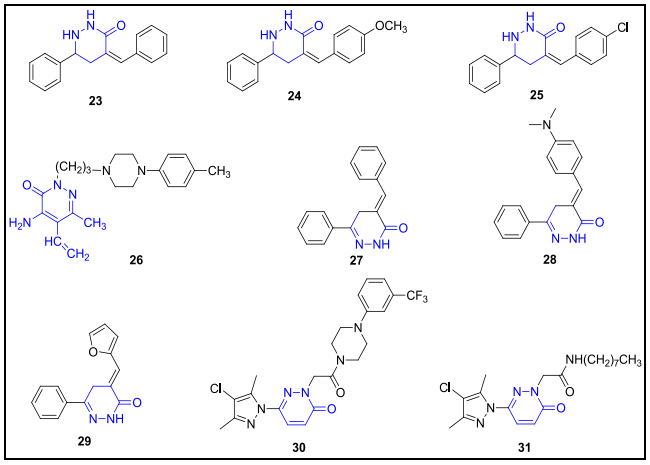

Figure 6: Pyridazinone derivatives with strong analgesic activity.

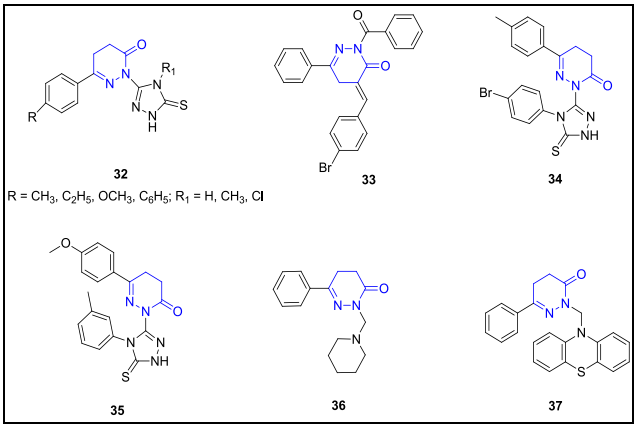

Figure 7: Pyridazinone derivatives with antihypertensive activity.

3.4. Vasorelaxant activity

K. Abouzid et al., [40] synthesized three series of pyridazinones to identify potential vasodilatory cardiotonic lead compounds. Compounds, **38** and **39** showed higher fit scores to the developed pharmacophore. The vasorelaxant activity was tested using isolated main pulmonary artery of the rabbit using Milrinone as a reference drug. R. Bansal *et al.*, [41] synthesized

a series of dihydropyridazin-3(2*H*)-ones and evaluated as vasodilators using rat thoracic aortic rings. Compound **40** revealed vasorelaxation activity higher than that of hydralazine and equal to SK&F-93741 (IC_{50} = 0.199, 0.316 and 0.199), respectively. SAR study of these compounds revealed that substitution of pyridazinone ring with phenyl moiety in position two or sex cancelled the vasorelaxant activity. **(Figure 8)**

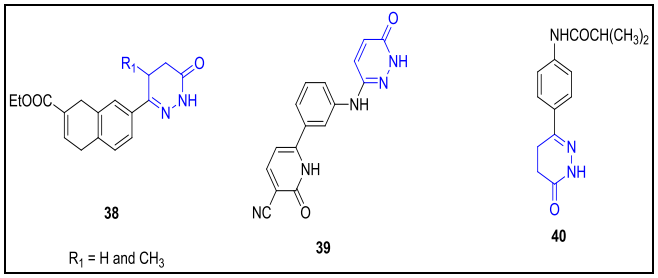

Figure 8: Pyridazinone derivatives with vasorelaxant activity.

3.5. Platelet aggregation inhibitory activity

T. Costas *et al.*,[42] synthesized new 2,6-disubstituted pyridazinone derivatives and tested their antiplatelet effect. Compound **41** showed a comparable antiplatelet activity to aspirin. Also, A series of 6-(4-(substituted–amino)phenyl)-4,5-dihydro-3(2*H*)-pyridazinones was synthesized by S. Thota *et al.*, [17]. All the tested compounds exhibited significant platelet aggregation inhibitory activity. Compounds **42** and **43** were found to be more potent than aspirin. Moreover, E. Sotelo *et al.*, [43] synthesized a series of 6-phenyl-3(2*H*)-pyridazinones with potential antiplatelet effect. Compound **44** showed the highest platelet aggregation inhibition with IC_{50} value of (15 µM). Additionally, R. Laguna *et al.*, [44] synthesized a series of 6-aryl-5-oxygenated substituted pyridazinones and evaluated as platelet aggregation inhibitors in a dose-dependent manner. Compounds **45** and **46** revealed higher potency than standard drug sulfinpyrazone (IC_{50} = 60 and 70 µM, respectively). Moreover, measurement of intracellular cAMP level indicated that activity is independent on cAMP PDEIII level in intact cells. Hence, authors suggested that the target pyridazinones may be acting by another mechanism. From the results, it is obvious that oxidation of alcoholic group into aldehydic group and further into carboxylic acid group diminishes the platelet aggregation inhibitory activity of these compounds. **(Figure 9)**

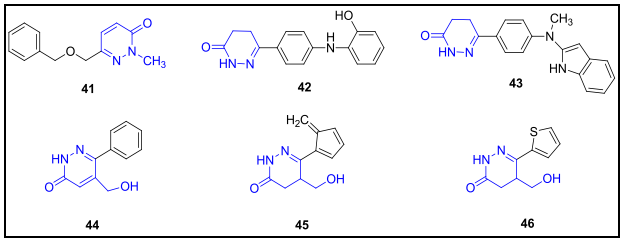

Figure 9: Pyridazinone derivatives with platelet aggregation inhibitory activity.

3.6. Phosphodiesterases inhibitory activity

D. Kumar *et al.,[5]* synthesized a group of 2-substituted-6-(4-acylaminophenyl)-4,5-dihydropyridazin-3 (2*H*)-ones as potent inotropic and vasorelaxant agents through inhibition of PDE III. The synthesized compounds was evaluated for cardiotonic activity using isolated rat atria and for vasorelaxant activity using descending thoracic aortic rings of Wistar rats precontracted with phenylephrine (10^{-6} mol/L). Compound **47** exhibited significant inodilatory properties and showed vasorelaxant activity. V. D. Piaz *et al.* ,[22] synthesized a series of pyrazolo[3,4-*d*]pyridazinones and tested as PDE V inhibitors. Compound **48** exhibited the highest activity among synthesized analogues with IC_{50} of 0.18 µM comparable to zaprinast (1.0 µM) and Sildenafil (0.005 µM). **(Figure 10)**

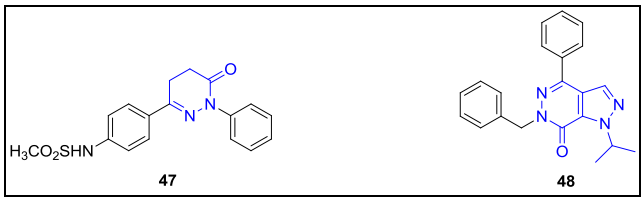

Figure 10: Pyridazinone derivatives with PDE inhibitory activity.

3.7. Anticancer activity

N.A. El-Ghaffar *et al.* [21] synthesized a series of pyridazine and pyridazinones substituted with 2-phenyl-1*H*-indolyl group and evaluated their anticancer activity. Compound **49** exhibited potent cytotoxic effect against breast carcinoma. T.H Al-Tel *et al.*,[45] synthesized a series of tetrahydro-2*H*-pyrano [3,2-*c*] pyridazin-3(6*H*)-one derivatives. Compounds **50** and **51** showed antiproliferative activity against the SK-BR-3 breast cancer cell line with 30 fold potency compared to other cancer cell lines tested (IC_{50} 0.21 and 0.15 µM, respectively). A. Pau *et al.*, [46] synthesized a series of hexahydrothieno-cycloheptapyridazinone derivatives and evaluated their cytotoxic activity. Compounds **52** showed significant activity against non-small cell lung cancer cell line HOP-92 and CNS cancer cell line SNB-75 with growth percentage of 20.09 and 22.69%, respectively. Also, compound **53** exhibited significant activity with growth percentage of 27.86 against CNS cancer cell line SNB-75. Moreover, P. Selvakumar *et al.*,[47] synthesized a series of pyridopyridazin-3(2*H*)-one derivatives and evaluated their anticancer activity against MCF-7 breast cancer. Compound **54** exhibited significant activities with IC_{50} of 61.3 µM. SAR results indicated that amidic group in the structure of pyridopyridazin-3(2*H*)-one is essential for anticancer activity. A novel pyridazinone derivatives carrying benzenesulfonamide moiety were prepared by I. Rathish *et al.*, [48] Compound **55** exhibited remarkable activity against leukemia cancer cell line SR and non-small cell lung cancer cell line NCI-H522 with GI_{50} less than 0.1 µM. Also, it showed significant activity against different cancer cell lines with GI_{50} less than 1.0 µM. Y. Liu *et al.*, [49] designed and synthesized 6-aryl-2-(3-(heteroarylamino) benzyl) pyridazinone derivatives and evaluated as a selective c-Met tyrosine kinase inhibitors. SAR results indicated that compound **56** was the highest selective c-Met tyrosine kinase inhibitor among the tested derivatives. This compound have good pharmacokinetic properties in mice and showed significant antitumor activity against a c-Met enzyme and EBC-cell with IC_{50} of 7.5 and 31.2 nM, respectively compared to crizotinib (1.4 and 19.0 nM). Also, S.H. Abbas *et al.*, [50]

synthesized a series of pyridazinones and tested their cytotoxicity and tubulin polymeras inhibition. Compound **57** exhibited good cytotoxic activity against Hep-G2 cancer cell line with IC_{50} of 14.80 µM comparable to Paclitaxel IC_{50} of 0.73 µM. additionally; this compound gave a promising inhibition for tubulin polymerase enzyme. Moreover, B Kummari *et al*.,[51] synthesizes a series of pyridazinones and compound **58** was more potent than standard drug doxorubicin (IC_{50} of 3.30 µM) against cancer cell lines A549 with IC_{50} of 2.42 µM. **(Figure 11)**

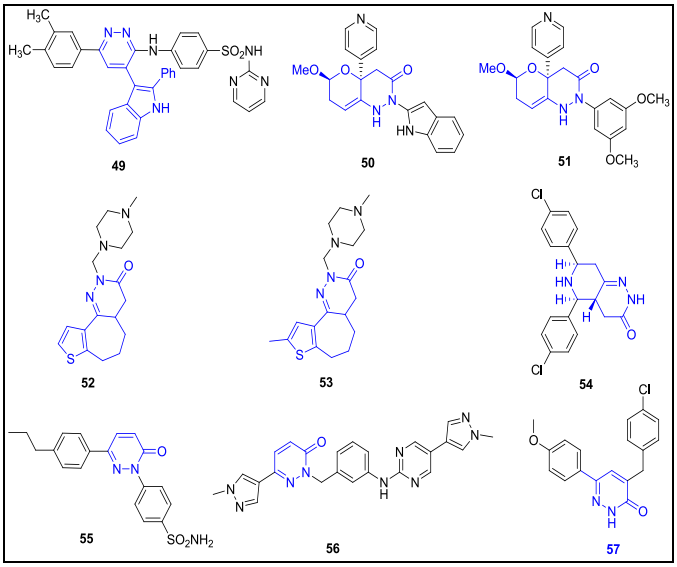

Figure 11: Pyridazinone derivatives with anticancer activity.

3.8. Antibacterial activity

A series of pyridazinones was prepared by G. Alang *et al.*, [52]. The antibacterial activity of synthesized compounds was carried out against *S. aureus*, *S. epidermis*, *P. Aeruginosa* and *E. coli*. Results showed that compounds **59a** and **59b** exhibited excellent activity against *E. coli* and *P. Aeruginosa* when compared to ampicillin. M. Sukuroglu *et al.*, [53] synthesized a series of 4,6-disubstituted-3(2*H*)-pyridazinone-acetohydrazide derivatives and evaluated their antibacterial activity. Compound **60** revealed the highest activity (MIC = 8µg/ML) against Gram positive *E. faecalis* compared to ampicillin (MIC = 2µg/ML) and more potent than gentamycin (MIC = 16µg/Ml). M.A. EL-Hashash *et al.*, [54] synthesized a series pyridazinone derivatives and tested their antibacterial activity. Compound **61** containing diazepine moiety revealed the strongest activity against *E. Coli*, *P. aeruginosa*, *S.aureus* and *B. subtilis*. D.S. Dogruer *et al.*, [55] synthesized a series of pyridazinone derivatives and evaluated their antibacterial activity. Compound **62** exhibited the strongest activity with MIC 15.62 µg /mL against *B. subtilis* more potent than sulfamethoxazole (MIC = 31.25 µg /ML) and comparable to ampicillin (MIC = 0.48 µg /ML). Moreover, J. Lee *et al.*, [56] synthesized a series of pyridazinone derivatives and evaluated their antibacterial activity against *K. pneumonia* and *S. Enterica* using ampicillin as standard drugs. The synthesized compounds showed moderate antibacterial activity against *S. Enterica* while exhibited good activity against *K. pneumonia* where MIC was 2.0 µg /ML for compounds **63** which is comparable to that of ampicillin 0.25 µg /ML. **(Figure 12)**

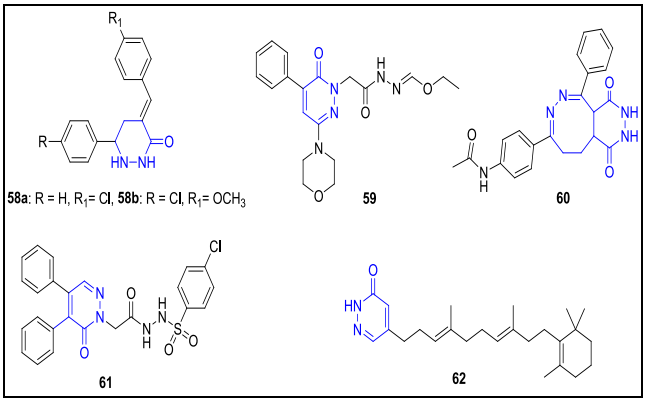

Figure 12: Pyridazinone derivatives with antibacterial activity.

3.9. Antifungal activity

X.J. Zou *et al.*, [57] synthesized a series of 5-[1-aryl-1,4-dihydro-6-methylpyridazin-4-one-3-yl]-2-arylamino-1,3,4-oxadiazoles with potent fungicidal activity. Compound **64** showed the best activity among this series. Also, some new metal complexes of 5-benzoyl-4-hydroxy-2-methyl-6-phenyl-2*H*-pyridazin-3-one were synthesized by M. Sonmez *et al.*, [58] and evaluated for their antifungal activity against *C. albicans* ATCC 27541 and *C. tropicalis*. Compounds **65** and **66** showed the strongest antifungal activity with MIC of 0.005 and 0.01µg/mL, respectively compared to fluconazole 0.005 µg/mL. **(Figure 13)**

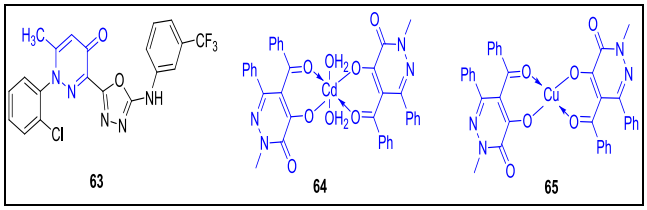

Figure 13: Pyridazinone derivatives with antifungal activity.

3.10. Antitubercular activity

A. Husain *et al.*, [59] synthesized two series of pyridazinone derivatives and evaluated for antitubercular activity against *Mycobacterium tuberculosis* H37Rv strain. The results indicated that compound **67** exhibited good antitubercular activity with MIC (12.5 µg/mL). Pyridazinones derived from 4-chloro-furanones were found to be more potent than those derived from 4-methylfuranones. The presence of nitro group in *para* position of benzyl group like compound **68** showed enhanced antitubercular activity. Additionally, A.A. Siddiqui *et al.*, [60] introduced a series of pyridazinones. The antitubercular activity of synthesized compounds was performed by adopting Alamar blue susceptibility test. Compound **69** emerged as highly active analogue of the series against *M. Tuberculosis* H37Rv.The antitubercular activity of a pyrdiazinone series introduced by S. Utku *et al.*, [61] was carried out using agar proportion method against *Mycobacterium tuberculosis* H37Rv. Compounds **70** and **71** showed the highest activity with MIC of 5 µg/mL compared to INH and EMB (MIC = 0.2 and 1.0 µg/mL), respectively**. (Figure 14)**

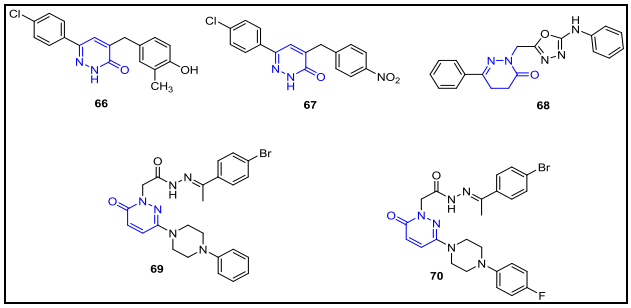

Figure 14: Pyridazinone derivatives with antitubercular activity.

3.11. Acetylcholinesterase inhibitor

T. Onkol *et al.*, [62] synthesized new group of *N*'-[(4-Substituephenyl)sulfonyl]-2-[4-(Substituephenyl)-piperazine]-3(2*H*)-pyridazinone-2-yl acetohydrazide derivatives as acetylcholinesterase inhibitors by Ellman's method. Compound **72** which possess CF_3 on four position of phenylsulfonyl ring have the highest activity with inhibition percentage of 95.39% against ACE which comparable to glantamine 97.20%. **(Figure 15)**

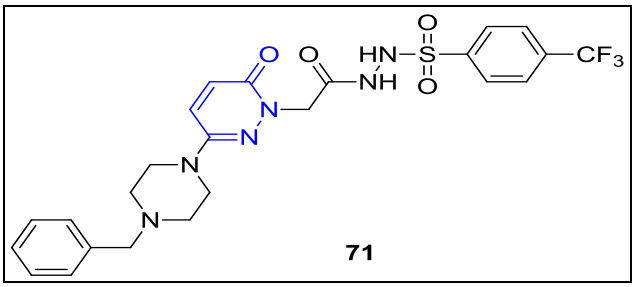

Figure 15: Pyridazinone derivatives with Acetylcholinesterase inhibitory activity.

3.12. Anticonvulsant activity

M. Asif *et al.*, [63] synthesized a series of 4-(benzylidene or substituted benzylidene)-6-(3-nitrophenyl)-4,5-dihydropyridazin-3(2*H*)-ones **73a-c**. The anticonvulsant activity of these compounds was evaluated using maximal electroshock (MES) induced seizure method. The synthesized compounds exhibited significant anticonvulsant activity against MES induced seizure in albino mice after administration of 50 mg/Kg. Additionally, P.S. Banerjee *et al.*, [64] synthesized a series of substituted 6-aryl-2,3,4,5-tetrahydro-3-pyridazinones and 6-aryl-2,3,4,5-tetrahydro-3-thiopyridazinones and evaluated as anticonvulsant agents using MES-induced seizure test. Compound **74** showed significant anticonvulsant activity. Similarly, K.C. Samanta *et al.*,[20] synthesized some pyridazinone derivatives and evaluated their anticonvulsant activity by MES method. Compound **75** revealed the highest activity with 100% recovery as phenytoin. S. Partap *et al.*, [65] synthesized a series of new hybrid benzimidazole containing pyridazinones derivatives that was evaluated as anticonvulsant using MES method and (scPTZ)-induced seizure. Compound **76** showed a significant anticonvulsant activity in both models with ED_{50} of 25.10 and 85.33 mg/kg in the MES and scPTZ methods, respectively which is compared to phenytoin with ED_{50} of 9.5 and >300 mg/kg, receptively in both models. Moreover, A. Husain *et al.*, [66] synthesized a series of pyridazinones and studied their effect as anticonvulsant agents through molecular docking. Compound **77** revealed the highest docking scores and concluded this compound may potentiate GABA mediated chlorine channel opening. M. Asif *et al.*, [67] introduced methylindole derivative of some 6-aryl-4,5-dihydropyridazin-3(2*H*)-ones. Compounds **78-80** gave the highest protection against MES, INH and scPTZ-induced convulsion models. **(Figure 16)**

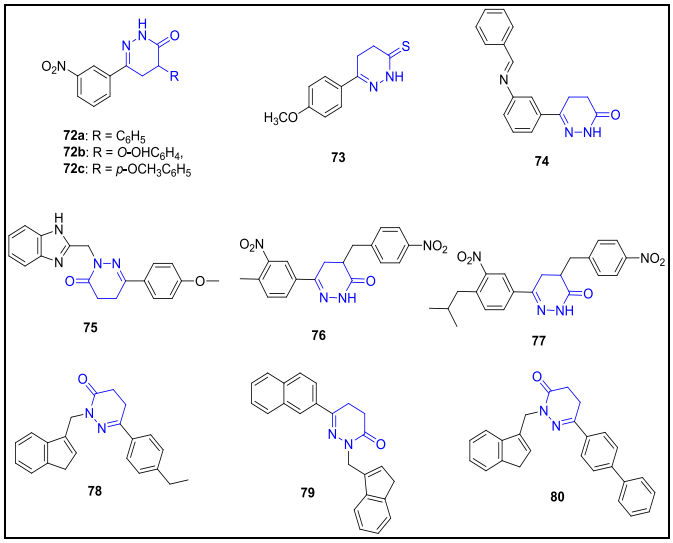

Figure 16: Pyridazinone derivatives with anticonvulsant activity.

4. Pyrrolones

Pyrrolones (pyrrolin-2-ones) are the five-membered heterocyclic ring can be synthesized by different methods which based on heterocyclization of various Schiff bases with maleic anhydride[68, 69] and reaction of furanone derivatives with amines[70, 71].

5. Biological activity of pyrrolones

Pyrrolone considered as an important nucleus with variable biological activities including antibacterial [72], anti-inflamatory [72], analgesic, antimycobacterial [73], antidepressant [74], antiviral [75] and antitumor activities[76]. **(Figure 17)**

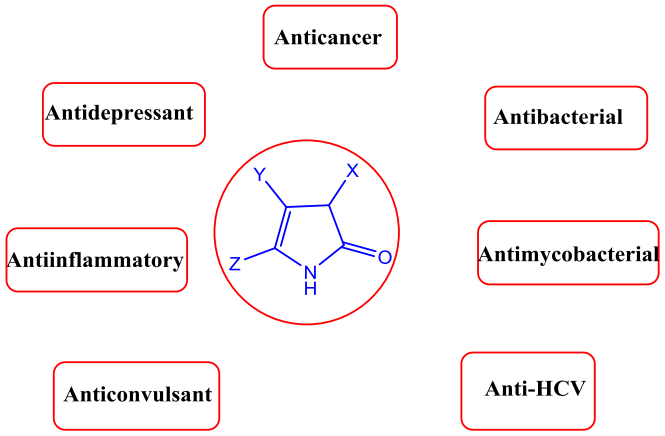

Figure 17: Biological activities of pyrrolones

5.1. Anti-inflammatory activity

A series of pyrrol-2-one was prepared by A. Husain *et al.*, [72], the anti-inflammatory activity results showed that compound **81**

has comparable activity to declofenac**.** S. Khokra *et al.*, [77] synthesized a series of quinolinyl-pyrrolone derivatives and tested as anti-inflammatory agents using carrageenan induced paw edema. Compounds **82** and **83** gave 53% and 63% inhibition, respectively. These results indicate that conversion of secondary -NH- group into tertiary moiety by benzyl amine increased the anti-inflammatory activity. Y. Ali et al., [78] synthesized a series of pyrrolone derivatives and tested their anti-inflammatory activity. Compounds **84** and **85** exhibited a comparable edema inhibition% to that of declofenac (71.47, 76.22 and 80.98%), respectively. Also, these compounds suppressed TNF-α level by 60.90 and 65.03%, respectively compared to indomethacin 68.40% inhibition. Moreover, M. Alam *et al*., [79] synthesized a series of 2(3*H*)-furanones and their corresponding 2(3*H*)-benzylpyrrolone derivatives. Compounds **86** and **87** showed a comparable anti-inflammatory activity to ibuprofen with inhibition % of 88.88, 89.50 and 89.50, respectively. Also, the two compounds revealed a superior gastric safety with protection % of 57.83 and 59.03 compared to ibuprofen (65.06%) and also, reduced lipid peroxidation more than the reference. Also, S. Khokra *et al*., [80] synthesized a series of pyrrolone derivatives, compounds **88** and **89** exhibited significant activity comparable to declofenac. Also, the two compounds revealed a higher safety profile twice than declofenac (1.3, 1.3 and 2.6), respectively. **(Figure 18)**

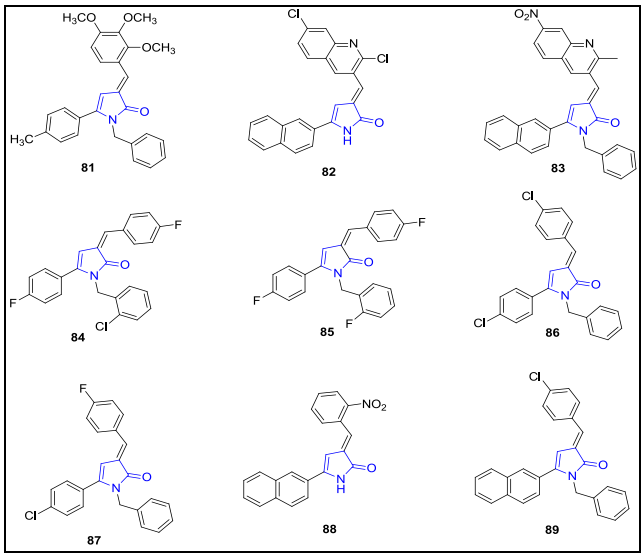

Figure 18: Pyrrolone derivatives with anti-inflammatory activity.

5.2. Antimicrobial activity

A. Husain *et al.*, [72] introduced a series of pyrrole-2-one derivatives, the pyrrole-2-one **90** showed significant activity against *S. aureus* with MIC (6.5 µg/mL) and good activity against *E.coli* with MIC (15 µg/mL. A novel 2(3*H*) pyrrolone derivatives were synthesized by A. Ahmad *et al*., [81] and evaluated as antibacterial agents. Compound **91** gave the strongest antibacterial activity against *S. aureus, E. coli* and *P. aeruginosa* which was equipotent to ciprofloxacin (MIC = 6.25µg/ML). Moreover, N.G. Kandile *et al*., [82] synthesized a series of indolyl-pyrrolones and tested their antibacterial activity. Compound **92** exhibited equipotent activity to chloramphenicol against *E. coli* with MIC of 2.5 µg/ML. **(Figure 19)**

A. Husain *et al*., [83] synthesized a series of pyrrolone and *N*-benzyl pyrrolone derivatives. The antibacterial evaluation exhibited that compound **93** was the strongest antibacterial with MIC of 6.25 µg/mL against *E.coli* and *P. aeruginosa* and 12.5 µg/mL against *S. aureus* comparable to ciprofloxacin (MIC = 6.5 µg/ML). Also, S. Khokra *et al*., [77] synthesized a series of quinolinyl-pyrrolone derivatives. Secreening results revealed that compound **94** has the highest antibacterial activity with MIC of 12.5 µg/mL against *E.coli* and *P. aeruginosa* and 6.25 µg/mL against *S. aureus* compared to ciprofloxacin (MIC = 6.5 µg/Ml). M.F. El-Shehry *et al*., [71] synthesized a series of pyrrolone derivatives and compound **95** exhibited remarkable antibacterial activity with inhibition zone diameter 5 and 7 mm against *S. aureus* and *E.coli*, respectively which more potent than Penicillin (32 and 15mm), respectively. In addition, A. Husain *et al*.,[84] synthesized a series of pyrrolone derivatives and tested as antimicrobial agents against *S. aureus* and *E. coli* and *C. albicans*. Compounds **96** and **97** revealed the strongest activity against *S. aureus* (MIC = 20 and 15 µg/mL), respectively and against *C. albicans* (MIC = 10 µg/mL). **(Figure 19)**

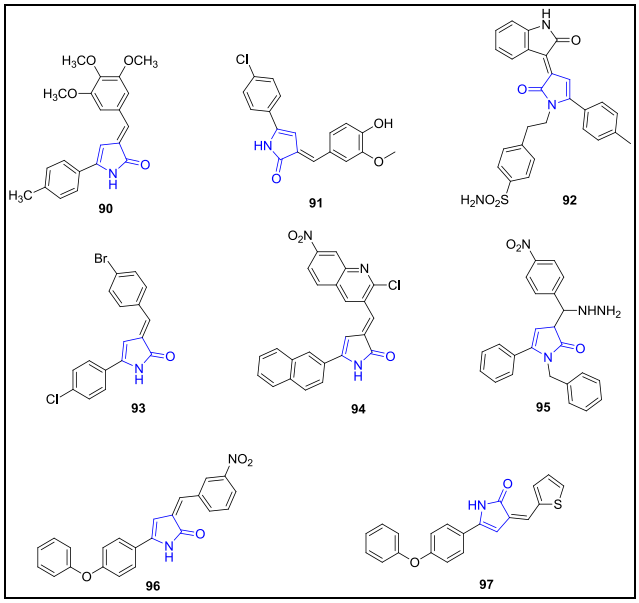

Figure 19: Pyrrolone derivatives with anti-microbial activity.

5.3. Anti-mycobacterial activity

A. Husain *et al.*,[85] synthesized a series of pyrrole-2-ones. Among these compounds, compound **98** showed the most promising antimycobacterial activity with IC_{50} of (11.34 µg/mL). **(Figure 20**)

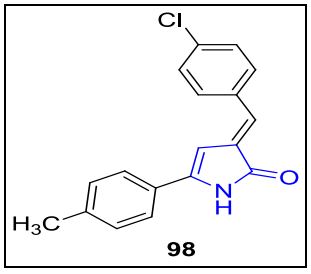

Figure 20: Pyrrolone derivatives with Anti-mycobacterial activity

5.4. Antidepressant activity

F. Micheli *et al*., [74] synthesized a series of pyrrolidinones and pyrrolones as 5-HT_{2C} inhibitors. Compound **99** exhibited significant potency, selectivity and pharmacokinetic profile; it showed nonmolar affainity to 5-HT_{2C} receptor. **(Figure 21)**

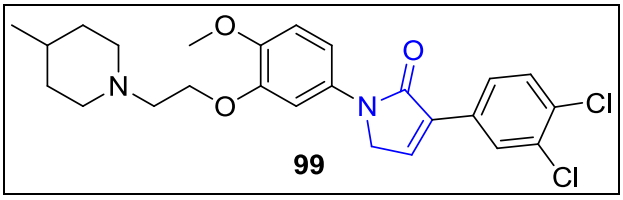

Figure 21: Pyrrolone derivatives with Antidepressant activity.

5.5. Anti-HCV

M. Bassetto *et al*.,[75] synthesized a series of pyrrolones and evaluated their antiviral activity against hepatitis C virus (HCV). Compound **100** showed moderate interference with the helicase unwinding activity with IC_{50} of 438 µM which is less potent than standard drug primuline (IC_{50} = 10 µM). Moreover, *N*. Kaushik-Basu *et al*.,[86] synthesizes a series of novel bicyclic octahydrocyclohepta[*b*]pyrrol-4(1*H*) one derivatives and tested their anti-hepatitis C viral activity. Compound **101** exhibited EC_{50} of 1.8 and 4.5 µM in genotype 1b and 2a, respectively. On the other hand, this compound did not affect HCV NS5B, IRES, NS3 helicase. **(Figure 22)**

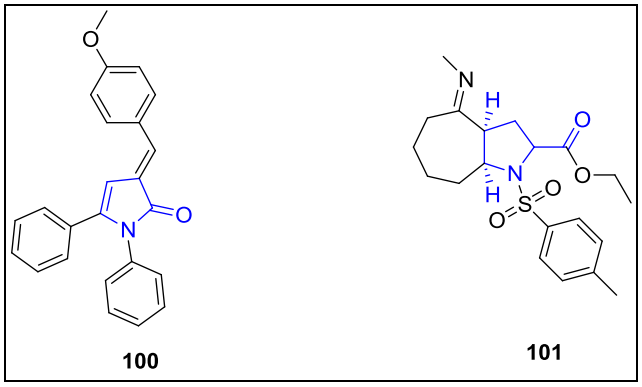

Figure 22: Pyrrolone derivatives with Anti-HCV activity.

5.6. Anticancer activity

V.Koz'minykh *et al.*,[87] synthesized 3-hydroxy-5-nitrophenyl-4-pivaloyl-2,5-dihydro-2-pyrrolone **102**. The results indicated that compound **102** exhibited antitumor activity against lung cancer with growth inhibition of 55% and CNS cancer with growth inhibition of 67%. Additionally, E. Lattmann *et al*.,[88] synthesized a series of 5-hydroxy-5-aryl-pyrrol-2-ones, compound **103** stopped growth of colon and pancreatic cancer models and act as Cholecystokinin-1 receptor antagonist with IC_{50} of 0.008 and 0.4 µM against CCK-A and CCK-B, respectively which are more potent than standard lorglumide (IC_{50} of 0.17 and >10 µM), respectively. Moreover, W.S. Abou-Elmagd *et al*.,[89] synthesized a group of pyrrolones and evaluated their anticancer activity against HePG 2, HCT116, and PC3 cancer cell lines. Compound **104** exhibited comparable activity to Doxorubicin against Hep-G2 cancer cell line with IC_{50} of 46.30 and 21.60 µM, respectively. S.H. Abbas *et al*.,[50] synthesized a series of pyrrolones and evaluated their cytotoxicity and tubulin polymeras inhibition. Compounds **105** and **106** showed good cytotoxic activity against Hep-G2 cancer cell line with IC_{50} of 11.47 and 7.11 µM, respectively comparable to Paclitaxel IC_{50} of 0.73 µM. Moreover, the two compounds gave a promising inhibition for tubulin polymerase enzyme. S. Olla *et al*.,[90] synthesized a series of indolyl-pyrrolone derivatives to evaluate them as pim1 kinase inhibitors and compound **107** gave the highest activity with ID_{50} of 4.5 µM. **(Figure 23).**

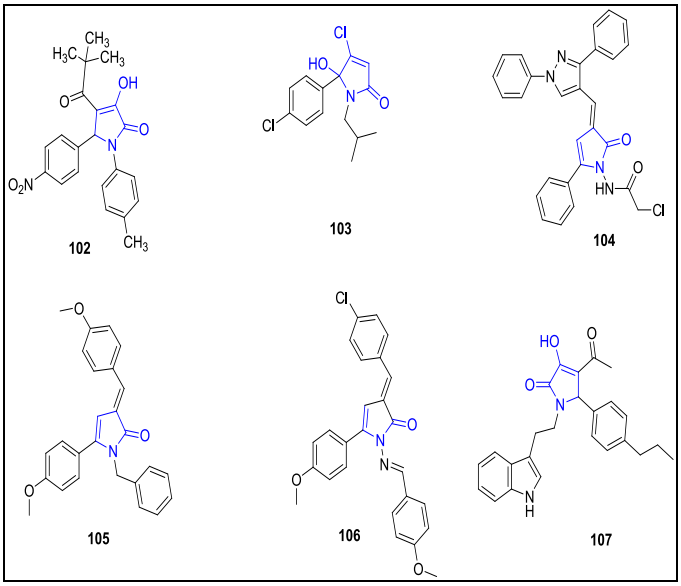

Figure 23: Pyrrolone derivatives with anticancer activity.

Conclusion

The importance of pyridazinone and pyrrolone derivatives arises from their variable biological activities such as antiinflammatory, antibacterial, cardiotonic, antimycobacterial, anticoagulant, antihypertensive, anti-mycobacterial, and most importantly their anticancer activities. It is obvious that medicinal chemists from research groups all over the world has synthesized different substituted pyridazinones and pyrrolones to explore their biological activity and sometimes their drug target. From this review article, an important conclusion could be identified; In spite of the known old anti-inflammatory activity of these scaffolds, there is a direction in the future towards utilization of these two nuclei in the design of anticancer molecules as tubulin polymerase or kinase inhibitors.

Conflict of Interest

There is no potential conflict of interest

References

[1] El-Shehry M. F., Abu-Zied K. M., Ewies E. F., Awad S. M., and Mohram M. E., Synthesis of some novel azaheterocycles utilizing 3-(4-nitrobenzylidene)-5-phenylfuran-2 (3h)-one with expected antimicrobial activity. *Der pharma chem***2013,** *5* (5), 318-326.

[2] Zarantonello P., Leslie C. P., Ferritto R., and Kazmierski W. M., Total synthesis and semi-synthetic approaches to analogues of antibacterial natural product althiomycin. *Bioorg Med Chem Lett* **2002,** *12* (4), 561-565.

[3] Böhm M., Morano I., Pieske B., Rüegg J., Wankerl M., Zimmermann R., and Erdmann E., Contribution of camp-phosphodiesterase inhibition and sensitization of the contractile proteins for calcium to the inotropic effect of pimobendan in the failing human myocardium. *Circ Res***1991,** *68* (3), 689-701.

[4] GÖKÇE M., DÜNDAR Y., and KÜPELİ E., Synthesis of (6-substituted-3 (2h)-pyridazinon-2-yl) acetic acid and (6-substituted-3 (2h)-pyridazinon-2-yl)

acetamide derivatives and investigation of their analgesic and anti-inflammatory activities. *FABAD J. Pharm. Sci* **2010,** *35*, 1-11.
[5] Kumar D., Carron R., La Calle C., Jindal D., and Bansal R., Synthesis and evaluation of 2-substituted-6-phenyl-4, 5-dihydropyridazin-3 (2h)-ones as potent inodilators. *Acta Pharm* **2008,** *58* (4), 393-405.
[6] Nieminen M., Fruhwald S., Heunks L., Suominen P., Gordon A., Kivikko M., and Pollesello P., Levosimendan: Current data, clinical use and future development. *Heart Lung Vessel* **2013,** *5* (4), 227.
[7] De Luca L., Colucci W. S., Nieminen M. S., Massie B. M., and Gheorghiade M., Evidence-based use of levosimendan in different clinical settings. *Eur Heart J* **2006,** *27* (16), 1908-1920.
[8] Endoh M., Changes in intracellular ca2+ mobilization and ca2+ sensitization as mechanisms of action of physiological interventions and inotropic agents in intact myocardial cells. *Jpn Heart J* **1998,** *39* (1), 1-44.
[9] J.Tjebbes, The heats of combustion and formation of the three diazines and their resonance energies. *Acta Chem. Scand* **1962,** *16*, 916-921.
[10] Youness Boukharsa Y. Z., Jamal Taoufik and M'hammed Ansar, Pyridazin-3 (2h)-ones: Synthesis, reactivity, applications in pharmacology and agriculture. *J. Chem. Pharm. Res* **2014,** *6*, 297-310.
[11] Li L.-S., Zhou Y., Zhao J., Dragovich P. S., Stankovic N., Bertolini T. M., Murphy D. E., Sun Z., Tran C. V., and Ayida B. K., Synthesis of new pyridazinone derivatives: 2, 6-disubstituted 5-hydroxy-3 (2h)-pyridazinone-4-carboxylic acid ethyl esters. *Synthesis* **2007,** *2007* (21), 3301-3308.
[12] Sotelo E., Fraiz N., Yáñez M., Terrades V., Laguna R., Cano E., and Raviña 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* (9), 2873-2882.
[13] Sotelo E., Coelho A., and Raviña E., Pyridazine derivatives 32: Stille-based approaches in the synthesis of 5-substituted-6-phenyl-3 (2h)-pyridazinones. *Chem. Pharm. Bull.* **2003,** *51* (4), 427-430.
[14] Bashir R., Yaseen S., Ovais S., Ahmad S., Hamid H., Alam M., Samim M., and Javed K., Synthesis and biological evaluation of some novel sulfamoylphenyl-pyridazinone as anti-inflammatory agents (part-ii). *J Enzyme Inhib Med Chem***2012,** *27* (1), 92-96.
[15] Asif M., Singh A., and Lakshmayya L., In-vivo anticonvulsant and in-vitro antimycobacterial activities of 6-aryl pyridazine-3 (2h)-one derivatives. *AJPS* **2014,** *2* (1), 1-6.
[16] Siddiqui A. A., Mishra R., Shaharyar M., Husain A., Rashid M., and Pal P., Triazole incorporated pyridazinones as a new class of antihypertensive agents: Design, synthesis and in vivo screening. *Bioorg Med Chem Lett* **2011,** *21* (3), 1023-1026.
[17] Thota S. and Bansal R., Synthesis of new pyridazinone derivatives as platelet aggregation inhibitors. *Med Chem Res***2010,** *19* (8), 808-816.
[18] Khaidem S., Sarveswari S., Gupta R., and Vijayakumar V., Synthesis and biological evaluation of some pyridazinone derivatives. *IJRPC* **2012,** *2* (2), 258-266.
[19] Asif M., General study of pyridazine compounds against cyclooxygenase enzyme and their relation with analgesic, anti-inflammatory and anti-arthritic activities. *CHRON. YOUNG SCI.* **2010,** *1* (3), 3.
[20] Samanta K. C., Asif M., Garg V., Sharma P., and Singh R., Synthesis of different substituted pyridazinone derivatives and their anticonvulsant activity. *Journal of Chemistry* **2011,** *8* (1), 245-251.
[21] El-Ghaffar N. A., Mohamed M. K., Kadah M. S., Radwan A. M., Said G. H., and Abd S. N., Synthesis and anti-tumor activities of some new pyridazinones containing the 2-phenyl-1h-indolyl moiety. *J Chem Pharm Res* **2011,** *3* (3), 248-259.
[22] Piaz V. D., Castellana M. C., Vergelli C., Giovannoni M. P., Gavaldà A., Segarra V., Beleta J., Ryder H., and Palacios J. M., Synthesis and evaluation of some pyrazolo [3, 4-d] pyridazinones and analogues as pde 5 inhibitors potentially useful as peripheral vasodilator agents. *J Enzyme Inhib Med Chem***2002,** *17* (4), 227-233.
[23] Abouzid K., Khalil N., Ahmed E., Esmat A., and Al-Abd A., Design, synthesis, and evaluation of anti-inflammatory and ulcerogenicity of novel pyridazinone derivatives. *Med Chem Res***2012,** *21* (11), 3581-3590.
[24] Bashir R., Yaseen S., Ovais S., Ahmad S., Hamid H., Alam M., Samim M., and Javed K., Synthesis and biological evaluation of some novel sulfamoylphenyl-pyridazinone as anti-inflammatory agents (part-ii*). *J Enzyme Inhib Med Chem***2012,** *27* (1), 92-96.
[25] Abouzid K. A., Khalil N. A., Ahmed E. M., El-Latif H. A. A., and El-Araby M. E., Structure-based molecular design, synthesis, and in vivo anti-inflammatory activity of pyridazinone derivatives as nonclassic cox-2 inhibitors. *Med Chem Res***2010,** *19* (7), 629-642.
[26] Abouzid K. and Bekhit S. A., Novel anti-inflammatory agents based on pyridazinone scaffold; design, synthesis and in vivo activity. *Bioorg Med Chem* **2008,** *16* (10), 5547-5556.
[27] DOĞRUER D. S., ŞAHİN M. F., Küpeli E., and YEŞİLADA E., Synthesis and analgesic and anti-inflammatory activity of new pyridazinones. *Turk J Chem* **2003,** *27* (6), 727-738.
[28] Ökçelik B., Ünlü S., Banoglu E., Küpeli E., Yeşilada E., and Şahin M. F., Investigations of new pyridazinone derivatives for the synthesis of potent analgesic and anti-inflammatory compounds with cyclooxygenase inhibitory activity. *Arch Pharm* **2003,** *336* (9), 406-412.
[29] Özdemir Z., Gökçe M., and Karakurt A., Synthesis and analgesic antiinflammatory and antimicrobial evaluation of 6 substituted 3 2h pyridazinone 2 acetyl 2 substituted benzal hydrazone derivatives. *FABAD J. Pharm. Sci* **2012,** *37*, 111-122.
[30] Şahina M., Badıcoglu B., Gökçe M., Küpeli E., and Yeşilada E., Synthesis and analgesic and antiinflammatory activity of methyl 6-substituted-3 (2h)-pyridazinone-2-ylacetate derivatives. *Arch Pharm* **2004,** *337* (8), 445-452.
[31] Saeed M. M., Khalil N. A., Ahmed E. M., and Eissa K. I., Synthesis and anti-inflammatory activity of novel pyridazine and pyridazinone derivatives as non-ulcerogenic agents. *Arch Pharm Res* **2012,** *35* (12), 2077-2092.
[32] Barberot C, Moniot A, Allart-Simon I, Malleret L, Yegorova T, Laronze-Cochard M, Bentaher A, Médebielle M, Bouillon J-P, Hénon E: Synthesis and biological evaluation of pyridazinone derivatives as potential anti-inflammatory agents. *Eur. J. Med. Chem.*2018, **146**:139-146.
[33] Asif M., Singh D., and Singh A., Analgesic activity of some 6-phenyl-4-substituted benzylidene tetrahydro pyridazin-3 (2h)-ones. *GJP* **2011,** *5* (1), 18-22.
[34] Biancalani C., Giovannoni M. P., Pieretti S., Cesari N., Graziano A., Vergelli C., Cilibrizzi A., Di Gianuario A., Colucci M., and Mangano G., Further studies on arylpiperazinyl alkyl pyridazinones: Discovery of an exceptionally potent, orally active, antinociceptive agent in thermally induced pain†. *J. Med. Chem.* **2009,** *52* (23), 7397-7409.
[35] Singh A. and Asif M., Analgesic and anti-inflammatory activities of several 4-substituted-6-(3'-nitrophenyl) pyridazin-(2h)-3-one derivatives.BJPS **2013,** *49* (4), 903-909.
[36] Süküroglu M., Ergün B. Ç., Sahin M. F., Küpeli E., Yesilada E., and Banoglu E., Synthesis, analgesic, and anti-inflammatory activities of [6-(3, 5-dimethyl-4-chloropyrazole-1-yl)-3 (2h)-pyridazinon-2-yl] acetamides. *Arch Pharm Res* **2005,** *28* (5), 509-517.
[37] Imran M. and Nayeem N., Synthesis and antihypertensive activity of some novel pyridazinones. *OJC* **2016,** *32* (1), 267-274.
[38] Mishra R., Siddiqui A. A., Husain A., Rashid M., Prakash A., Tailang M., Kumar M., and Srivastava N., Synthesis, characterization and antihypertensive activity of some new substituted pyridazine derivatives. *JCCS* **2011,** *56* (4), 856-859.
[39] Vikas Jakhmola S. J. a. R. M., Synthesis, characterization and antihypertensive activity of 4,5 dihydropyridazin-3(2h)-one derivatives. *Acta Scientific Pharmaceutical Sciences* **2018,** *2* (5), 2-7.
[40] Abouzid K., Abdel Hakeem M., Khalil O., and Maklad Y., Pyridazinone derivatives: Design, synthesis, and in vitro vasorelaxant activity. *Bioorg Med Chem* **2008,** *16* (1), 382-389.
[41] Bansal R., Kumar D., Sharma D., Calle C., and Carron R., Synthesis and pharmacological evaluation of 6-arylpyridazinones as potent vasorelaxants. *Drug Dev Res* **2013,** *74* (5), 296-305.
[42] Costas T., Besada P., Piras A., Acevedo L., Yañez M., Orallo F., Laguna R., and Terán C., New pyridazinone derivatives with vasorelaxant and platelet antiaggregatory activities. *Bioorg Med Chem Lett* **2010,** *20* (22), 6624-6627.
[43] Sotelo E., Fraiz N., Yáez M., Terrades V., Laguna R., Cano E., and Ravia 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* (9), 2873-2882.
[44]Laguna R., RODRIGUEZ-LINARED B., Cano E., ESTEVEZ I., RAVINA E., and SOTELO E., Pyridazines. Xiii. Synthesis of 6-aryl-5-oxygenated substituted-3 (2h)-pyridazinones and evaluation as platelet aggregation inhibitors. *Chem. Pharm. Bull.* **1997,** *45* (7), 1151-1155.
[45] Al-Tel T. H., Design and synthesis of novel tetrahydro-2h-pyrano [3, 2-c] pyridazin-3 (6h)-one derivatives as potential anticancer agents. *Eur. J. Med. Chem.* **2010,** *45* (12), 5724-5731.
[46] Pau A., Murineddu G., Asproni B., Murruzzu C., Grella G. E., Pinna G. A., Curzu M. M., Marchesi I., and Bagella L., Synthesis and cytotoxicity of novel hexahydrothienocycloheptapyridazinone derivatives. *Molecules* **2009,** *14* (9), 3494-3508.
[47] Selvakumar P., Thennarasu S., and Mandal A. B., Synthesis of novel pyridopyridazin-3 (2h)-one derivatives and evaluation of their cytotoxic activity against mcf-7 cells. *ISRN Org Chem* **2014,** *2014*, 1-7.
[48] Rathish I., Javed K., Ahmad S., Bano S., Alam M., Akhter M., Pillai K., Ovais S., and Samim M., Synthesis and evaluation of anticancer activity of some novel 6-aryl-2-(p-sulfamylphenyl)-pyridazin-3 (2h)-ones. *Eur. J. Med. Chem.* **2012,** *49*, 304-309.
[49] Liu Y., Jin S., Peng X., Lu D., Zeng L., Sun Y., Ai J., Geng M., and Hu Y., Pyridazinone derivatives displaying highly potent and selective inhibitory activities against c-met tyrosine kinase. *Eur. J. Med. Chem.* **2016,** *108*, 322-333.
[50] Abbas S. H., Abuo-Rahma G. E.-D. A., Abdel-Aziz M., Aly O. M., Beshr E. A., and Gamal-Eldeen A. M., Synthesis, cytotoxic activity, and tubulin polymerization inhibitory activity of new pyrrol-2 (3h)-ones and pyridazin-3 (2h)-ones. *Bioorg Chem* **2016,** *66*, 46-62.
[51] Kummari B, Ramesh P, Parsharamulu R, Allaka TR, Anantaraju H, Yogeeswari P, Balasubramanian S, Guggilapu SD, Babu BN, Anireddy JS: Design and Synthesis of New Etodolac-Pyridazinones as Potent Anticancer

Agents Using Pb (OAc) 4 to Assist N-N Bond Formation. *ChemistrySelect* 2018, **3**(18):5050-5054.

[52] Alang G., Kaur R., Singh A., Budhlakoti P., and Singh A., Synthesis, characterization and anti-bacterial activity of certain 2, 3, 4, 5-tetrahydropyridazinone analogues. *Turkish Journal of Pharmaceutical Sciences* **2011,** *8* (1), 71-80.

[53] Sukuroglu M., Onkol T., Onurdağ F. K., Akalın G., and Şahin M. F., Synthesis and in vitro biological activity of new 4, 6-disubstituted 3 (2h)-pyridazinone-acetohydrazide derivatives. *Z. Naturforsch. C Bio. Sci.* **2012,** *67* (5-6), 257-265.

[54] EL-Hashash M. A., Essawy A., and Sobhy Fawzy A., Synthesis and antimicrobial activity of some novel heterocyclic candidates via michael addition involving 4-(4-acetamidophenyl)-4-oxobut-2-enoic acid. *Advances in chemistry* **2014,** *2014*, 1-10.

[55] Doğruer D. S., Önkol T., Özkan S., Oezgen S., and ŞAHİN M. F., Synthesis and antimicrobial activity of some 3 (2h)-pyridazinone and 1 (2h)-phthalazinone derivatives. *Turk J Chem* **2008,** *32* (4), 469-479.

[56] Lee J., Shin A. Y., and Lee H. S., Isolation and synthesis of luffariellolide derivatives and evaluation of antibacterial activities against gram-negative bacteria. *Bull Korean Chem Soc* **2017,** *38* (7), 804-807.

[57] Zou X. J., Lai L. H., Jin G. Y., and Zhang Z. X., Synthesis, fungicidal activity, and 3d-qsar of pyridazinone-substituted 1,3,4-oxadiazoles and 1,3,4-thiadiazoles. *J Agric Food Chem* **2002,** *50* (13), 3757-3760.

[58] Sönmez M., Berber İ., and Akbaş E., Synthesis, antibacterial and antifungal activity of some new pyridazinone metal complexes. *Eur. J. Med. Chem.* **2006,** *41* (1), 101-105.

[59] Husain A., Ahmad A., Bhandari A., and Ram V., Synthesis and antitubercular activity of pyridazinone derivatives. *JCCS* **2011,** *56* (3), 778-780.

[60] Siddiqui A. A., Islam M., and Kumar S., Synthesis and antituberculostic activity of 5-{3'-oxo-6'-(substituted phenyl)-2', 3', 4', 5'-tetrahydropyridazin-2'-yl} methyl-2-substituted 1, 3, 4-oxadiazole. *Pharm Lett* **2010,** *2*, 319.

[61] Utku S., GÖKÇE M., ASLAN G., BAYRAM G., ÜLGER M., EMEKDAŞ G., and ŞAHİN M. F., Synthesis and in vitro antimycobacterial activities of novel 6-substituted-3 (2h)-pyridazinone-2-acetyl-2-(substituted/nonsubstituted acetophenone) hydrazone. *Turk J Chem* **2011,** *35* (2), 331-339.

[62] Önkol T., Gökçe M., Orhan İ., and Kaynak F., Design, synthesis and evaluation of some novel 3 (2h)-pyridazinone-2-yl acetohydrazides as acetylcholinesterase and butyrylcholnesterase inhibitors. *Organic Communications* **2013,** *6* (1), 55.

[63] Asif M. and Anita S., Anticonvulsant activity of 4-(substituted benzylidene)-6-(3-nitrophenyl)-4, 5-dihydro pyridazin-3 (2h)-ones against maximal electro shock induced seizure. *Middle-East J Sci Res* **2011,** *9* (4), 481-485.

[64] Banerjee P., Sharma P., and Nema R., Synthesis and anticonvulsant activity of pyridazinone derivatives. *Int. J. Chem. Tech. Res* **2009,** *1* (3), 522-525.

[65] Partap S., Yar M. S., Hassan M., Akhtar M., and Siddiqui A. A., Design, synthesis, and pharmacological screening of pyridazinone hybrids as anticonvulsant agents. *Arch Pharm* **2017,** *350* (10).

[66] Husain A., Khokra S., Thakur P., Choudhary D., Kohli S., Ahmad A., and Khan S., Molecular modeling and in silico evaluation of novel pyridazinones derivatives as anticonvulsant agents. *Journal of In Silico & In Vitro Pharmacology* **2015,** *1* (1).

[67] Asif M., Singh A., and Bilkanti L., In-vivo anticonvulsant and in-vitro antitubercular activity of methyl indole derivative of some 6-aryl-4, 5-dihydropyridazin-3 (2h)-ones and their expected anticonvulsant mechanisms. *Iran J Pharm Res* **2013,** *9* (1), 67-80.

[68] Kumar D., Singh A., and Walia Y. K., Synthesis and characterization of 2h-pyrrole-2-ones of (5-benzoyl-benzoimidazol-1-yl)-acetic acid hydrazide derivatives. *Asian J. of Adv. Basic Sci* **2014,** *2* (2), 40-46.

[69] Parmar K., Sutariya S., Shukla M., and Goswami K., Synthesis and antimicrobial activity of substituted 2h-pyrrole-2-ones derivatives based on 1-n-phenyl-3-phenyl-4-formyl pyrazole (pfp). *J Chem Pharm Res* **2012,** *4*, 3478-3482.

[70] Khan M., Husain A., and Sharma S., Studies on butenolides: 2-arylidene-4-(substituted aryl) but-3-en-4-olides—synthesis, reactions and biological activity. *IJC-B* **2002,** *41B*, 2160-2171.

[71] El-Shehry M. F., Abu-Zied K. M., Ewies E. F., Awad S. M., and Mohram M. E., Synthesis of some novel azaheterocycles utilizing 3-(4-nitrobenzylidene)-5-phenylfuran-2 (3h)-one with expected antimicrobial activity. *Der Pharma Chem*, **2013,** *5*, 318-326.

[72] Husain A., Alam M. M., and Siddiqui N., Synthesis, reactions and biological activity of 3-arylidene-5-(4-methylphenyl)-2 (3h)-furanones? *J. Serb.Chem. Soc.* **2009,** *74* (2), 103-115.

[73] Husain A., Alam M. M., Hasan S. M., and Yar M. S., 2 (3h)-furanones and 2 (3h)-pyrrolones: Synthesis and antimycobacterial evaluation. *Acta Pol Pharm* **2008,** *66* (2), 173-180.

[74] Micheli F., Pasquarello A., Tedesco G., Hamprecht D., Bonanomi G., Checchia A., Jaxa-Chamiec A., Damiani F., Davalli S., and Donati D., Diaryl substituted pyrrolidinones and pyrrolones as 5-ht 2c inhibitors: Synthesis and biological evaluation. *Bioorg Med Chem Lett* **2006,** *16* (15), 3906-3912.

[75] Bassetto M., Leyssen P., Neyts J., Yerukhimovich M. M., Frick D. N., and Brancale A., Shape-based virtual screening, synthesis and evaluation of novel pyrrolone derivatives as antiviral agents against hcv. *Bioorg Med Chem Lett* **2017,** *27* (4), 936-940.

[76] Ali Y., Alama M. S., Hamida H., and Hussain A., 2 (3h) pyrrolone–a biologically active scaffold (a review). *OJC* **2014,** *30* (1), 01-16.

[77] Khokra S. L., Kaushik P., Alam M., Zaman M., Ahmad A., Khan S. A., and Husain A., Quinoline based furanones and their nitrogen analogues: Docking, synthesis and biological evaluation.SPJ **2016,** *24* (6), 705-717.

[78] Ali Y., Alam M. S., Hamid H., Husain A., Shafi S., Dhulap A., Hussain F., Bano S., Kharbanda C., and Nazreen S., Design and synthesis of butenolide-based novel benzyl pyrrolones: Their tnf-α based molecular docking with in vivo and in vitro anti-inflammatory activity. *Chem Biol Drug Des***2015,** *86* (4), 619-625.

[79] Alam M., Husain A., Hasan S., and Anwer T., Synthesis and pharmacological evaluation of 2 (3h)-furanones and 2 (3h)-pyrrolones, combining analgesic and anti-inflammatory properties with reduced gastrointestinal toxicity and lipid peroxidation. *Eur. J. Med. Chem.* **2009,** *44* (6), 2636-2642.

[80] L Khokra S., A Khan S., Choudhary D., M Hasan S., Ahmad A., and Husain A., Rational design and synthesis of biologically active disubstituted 2 (3h) furanones and pyrrolone derivatives as potent and safer non steroidal anti-inflammatory agents. *Anti-Inflammatory & Anti-Allergy Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Inflammatory and Anti-Allergy Agents)* **2016,** *15* (1), 54-71.

[81] Ahmad A., Husain A., Khan S. A., Mujeeb M., and Bhandari A., Design, synthesis, molecular properties and antimicrobial activities of some novel 2 (3h) pyrrolone derivatives. *Journal of Saudi Chemical Society* **2015,** *19* (3), 340-346.

[82] Kandile N. G., Zaky H. T., Saleh Y. G., and Ahmed N. A., Synthesis of a new class of antimicrobial agents incorporating the indolin-2-one moiety. *J Enzyme Inhib Med Chem***2013,** *28* (4), 853-862.

[83] Husain A., Alam M. M., Shaharyar M., and Lal S., Antimicrobial activities of some synthetic butenolides and their pyrrolone derivatives. *J Enzyme Inhib Med Chem***2010,** *25* (1), 54-61.

[84] Asif Husain M. S. Y. K., S.M. Hasan , M.M. Alam 2-arylidene-4-(4-phenoxy-phenyl)but-3-en-4-olides:Synthesis, reactions and biological activity. *Eur. J. Med. Chem.* **2005,** *40*, 1394–1404.

[85] Husain A., Alam M. M., Hasan S. M., and Yar M. S., 2 (3h)-furanones and 2 (3h)-pyrrolones: Synthesis and antimycobacterial evaluation. *Acta Pol Pharm* **2009,** *66* (2), 173-180.

[86] Kaushik-Basu N., Ratmanova N. K., Manvar D., Belov D. S., Cevik O., Basu A., Yerukhimovich M. M., Lukyanenko E. R., Andreev I. A., and Belov G. M., Bicyclic octahydrocyclohepta [b] pyrrol-4 (1h) one derivatives as novel selective anti-hepatitis c virus agents. *Eur. J. Med. Chem.* **2016,** *122*, 319-325.

[87] Koz'minykh V., Igidov N., Zykova S., Kolla V., Shuklina N., and Odegova T., Synthesis and pharmacological activity of 3-hydroxy-1, 5-diaryl-4-pivaloyl-2, 5-dihydro-2-pyrrolones. *Pharml Chem J* **2002,** *36* (4), 188-191.

[88] Lattmann E., Russell S., Schwalbe C., Shortt A., Balaram P., Theochari E., Alharbi M., Narayanan R., and Lattmann P., Cholecystokinin-1 receptor antagonists: 5-hydroxy-5-aryl-pyrrol-2-ones as anticancer agents. *MedChemComm* **2016,** *7* (6), 1138-1145.

[89] Abou-Elmagd W. S., EL-Ziaty A. K., Elzahar M. I., Ramadan S. K., and Hashem A. I., Synthesis and antitumor activity evaluation of some n-heterocycles derived from pyrazolyl-substituted 2 (3 h)-furanone. *Synth. Commun.* **2016,** *46* (14), 1197-1208.

[90] Olla S., Manetti F., Crespan E., Maga G., Angelucci A., Schenone S., Bologna M., and Botta M., Indolyl-pyrrolone as a new scaffold for pim1 inhibitors. *Bioorg Med Chem Lett* **2009,** *19* (5), 1512-1516.