Chemistry International 5(3) (2019) 206-231

International Scientific Organization
http://iscientific.org/
Chemistry International
www.bosaljournals.com/chemint/

Diverse chemical and biological potentials of various pyridazine and pyridazinone derivatives

Mohammad Asif[1], Abida[2] and Md. Tauquir Alam[2]

[1]Department of Pharmacy, GRD (P.G) Institute of Management and Technology, Dehradun, 2480009, India
[2]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Northern Border University, Rafha 91911, PO Box 840, Saudi Arabia
*Corresponding author's E. mail: aasif321@gmail.com

A R T I C L E I N F O

Article type:
Review article
Article history:
Received January 2018
Accepted December 2018
July 2019 Issue
Keywords:
Pyridazine
Pyridazinone
Heterocyclic
Synthesis
Biological activities

A B S T R A C T

A series of heterocyclic compounds incorporating pyridazine moiety were for diverse biological activities. Pyridazines and pyridazinones derivatives showed wide spectrum of biological activities such as vasodialator, cardiotonic, anticonvulsant, antihypertensive, antimicrobial, anti-inflammatory, analgesic, anti-feedant, herbicidal, and various other biological, agrochemical and industrial chemical activities. The results illustrated that the synthesized pyridazine/pyridazine compounds have diverse and significant biological activities. Mechanistic insights into the biological properties of pyridazinone derivatives and various synthetic techniques used for their synthesis are also described.

Capsule Summary: The cardiotonic, anticonvulsant, antihypertensive, antimicrobial, anti-inflammatory, antileishmanial, anticancer, antiviral anti feedant, herbicidal, anti-nocieceptiv, PDE-inhibitors, antiplalets, COX-2 inhibitors, aldose reductase inhibitor; anti-diabetes, carbonic anhydrase inhibitors, anti-rheumatoid arthritis, tyrosine kinase inhibitor etc activities were reviewed in present study.

Cite This Article As: M. Asif, Abida and M. T. Alam. Diverse chemical and biological potentials of various pyridazine and pyridazinone derivatives. Chemistry International 5(3) (2019) 206-231. https://doi.org/10.5281/zenodo.2525555

INTRODUCTION

The synthesis of pyridazinone derivatives and investigation of their chemical and biological activities have gained more importance in recent years. Pyridazines and pyridazinones show wide spectrum of biological activities in the literature as potent inodilators (Kumar et al., 2010; Lee et al., 2010), vasorelaxants (Abouzid et al., 2010; Costas et al., 2010; Guerrero et al., 2008) and potent cardiotonic agents (Amin et al., 2008; Wang et al., 2009; Wang et al., 2008). They showed also anticonvulsant (Edith et al., 2009; Sivakumar et al., 2009; Siddiqui et al., 2006), vasodilatory (Demirayak et al., 2009; Bansal et al., 2009), antihypertensive (Siddiqui et al., 2002; Ogretir et al., 2002; Vergelli et al., 2007), antimicrobial (Sotelo et al., 2002; Sayed et al., 2002), anti-inflammatory (Gokce et al., 2001; Dogruer et al., 2003; Frolov et al., 2004; Banoglu et al., 2004), anti feedant (Cao et al., 2003), herbicidal (Han et al., 2002), anti-nocieceptiv (Barbaro et al., 2002) activities. They also possess phosphodiesterase (PDE) inhibitors, antiplalets, COX-2 inhibitors; LOX inhibitors; MAPK inhibitors; antileishmanial; antiviral; aldose reductase inhibitor; anti-diabetes; human carbonic anhydrase inhibitors; kinase inhibitor; c-Met inhibitor; anti-rheumatoid

arthritis; myocardial perfusion imaging; cytotoxicity; tyrosine kinase inhibitor; antiproliferative; anti-ulcerogenic activities. Some of 6-aryl-3(2H)pyridazinones are well known as potent analgesics (Okcelik et al., 2003), antiplatelet (Sotelo et al., 200; Coelho et al., 2004) and anticancer agents (Malinka et al., 2004) as well as other anticipated biological (Pattison at al., 2009; Li at al., 2009; Mantu at al., 2009; Youssef et al., 2005) and pharmacological activities. In view of the above mentioned findings, continuation of our efforts for the synthesis of new pyridazinne compounds that may be of value as active biological agent, we report here in some pyridazinone derivatives and their pharmacological acresidue (Helm at al., 2006; Abd El-Ghaffar et al., 2011; Qian at al., 2011; Soliman et al., 2016).

Biological activities

The pyridazine/pyridazinone derivatives having diverse chemical and biological activities, due to these properties pyridazine/pyridazinone have gained more importance. Finding new adenosine receptor (AR) ligands, a preliminary study focusing on the thieno[2,3-d]pyridazin-5(4H)-one (1) scaffold. The synthesized compounds were tested for their binding at hA_1, hA_{2A} and hA_3 ARs and efficacy at hA_{2B} subtype in order to determine the affinity at the human adenosine receptor subtypes. Small structural changes on this scaffold highly influenced affinity; compound, 5-ethyl-7-(thiazol-2-yl)thieno[2,3-d]pyridazin-4(5H)-one (2) emerged as the best of this series (Catarzi at al., 2018).

The cannabinoid type-2 receptors (CB_2R) have emerged as promising therapeutic targets in various diseases. Selective ligands of CB_2R are devoid of the psychoactive effects typically observed for CB_1 R ligands. Pyridazinone 4-carboxamides core were made to better investigate the structure-activity relationships (SAR) with the aim to develop potent CB_2 R ligands. In binding assays, two compounds 6-(3,4-dichlorophenyl)-2-(4-fluorobenzyl)-cis-N-(4-methyl-cyclohexyl)-3-oxo-2,3-dihydro-pyridazine-4-carboxamide (3) and 6-(4-chloro-3-methylphenyl)-cis-N-(4-methylcyclohexyl)-3-oxo-2-pentyl-2,3-dihydropyridazine-4-carboxamide (4) were showed high CB_2 R affinity, with K_i values of 2.1 and 1.6 nm, respectively. In addition, other active related derivatives revealed their pharmacological profiles as CB_2 R inverse agonists. Compound 3 displayed the highest CB_2 R selectivity and potency, favorable in silico pharmacokinetic profile (Ragusa at al., 2018). Pyridazine/pyridazinones were prepared as coagulation factor XIa inhibitors. Potent and selective inhibitors with single digit nanomolar affinity for factor XIa were discovered and selected inhibitors exhibitd moderate oral bioavailability (Hu at al., 2018). Cyclic nucleotide phosphodiesterase type-4 (PDE-4), that controls intracellular level of cyclic nucleotide cAMP, as a suitable target for anti-inflammatory therapy in respiratory diseases. Two families of pyridazinone derivatives act as potential PDE-4 inhibitors and used anti-inflammatory agents. Among these derivatives, 4,5-dihydropyridazinones possess promising activity, selectivity towards PDE-4 isoenzymes and are able to reduce IL-8 production by human primary polymorphonuclear cells (Barberot at al., 2018). Through cell-based screening models, compound IMB5043, a thio-phenylated pyridazinone, which exerted cytotoxicity against cancer cells and evaluated its antitumor efficacy and the possible mechanism. By MTT assay, IMB5043 inhibited the proliferation of various human cancer cells lines, especially hepatocarcinoma SMMC-7721 cells. IMB5043 blocked cell cycle with G2/M arrest, induced cell apoptosis, and inhibited the migration and invasion of SMMC-7721 cells. As verified by comet assay and γ-H2AX foci formation, IMB5043 caused DNA damage and activated ATM, Chk2 and p53 through phosphorylation. As shown by Gene microarray analysis, the differentially expressed genes in SMMC-7721 cells treated with IMB5043 were highly related to cell death and apoptosis. IMB5043 suppressed the growth of hepatocarcinoma SMMC-7721 xenograft in athymic mice. By histopathological study, no lesions were found in bone marrow and various organs of the treated mice. IMB5043 is as an active compound consisting of both pyridazinone and thiophene moieties exerts antitumor efficacy through activation of ATM-Chk2 pathway and may serve as a promising leading compound for the development of antitumor drugs (Gong at al., 2018).

A series of hybrid benzothiazole containing pyridazinones derivatives were synthesized and fulfilling all the pharmacophoric requirements essential for the anticonvulsant activity. The studies revealed that some of these hybrid derivatives demonstrated admirable GABA AT inhibitory activity. The GABA AT inhibition of the most potent compound is SPS-5F (IC_{50} 9.10 μM) through anticonvulsant test. Compound SPS-5F significantly increases the whole brain GABA level, might be through the inhibition of GABA AT enzyme (Partap at al., 2018).

A series of sulfenamide and sulfonamide derivatives were tested for the affinity at CB_1 and CB_2 receptors. The N-bornyl-S-(5,6-di-p-tolylpyridazin-3-yl)-sulfenamide (5), displayed good affinity and high selectivity for CB_1 receptors (K_i values=44.6 nM for CB_1 receptors and >40 μM for CB_2 receptors). The N-isopinocampheyl-sulfenamide and its sulfonamide analogue showed similar selectivity for CB_1 receptors with K_i values of 75.5 and 73.2 nM, respectively. These compounds behave as antagonists/inverse agonists at CB_1 receptor in the [^{35}S]-GTPγS binding assays, and none showed adequate predictive blood-brain barrier (BBB) permeation, exhibiting low estimated LD_{50}. However, N-isopinocampheyl-sulfenamide in a supraspinal analgesic test (hot-plate) revealed that it was as effective as the classic CB_1 receptor antagonist rimonabant, in reversing the analgesic effect of a cannabinoid agonist (Murineddu at al., 2018).

The PDE-3s belong to the PDEs family, where the PDE-3A isoform is the major subtype in platelets involved in the cAMP regulation pathway of platelet aggregation. PDE-3A inhibitors have been designed as potential antiplatelet agents. A homology model of PDE-3A was developed and used to obtain the binding modes of bicyclic heteroaromatic

pyridazinones. Besides, the SAR of the studied inhibitors was described by using a field-based 3D-QSAR method. Different structure alignment strategies were used, including template-based and docking-based alignments. Adequate correlation models were obtained according to internal and external validations. The QSAR models revealed that steric and hydrophobic fields describe the different inhibitory activities of the compounds, where the hydrogen bond donor and acceptor fields have minor contributions. It should be stressed that structural elements of PDE-3A inhibitors are reported here, through descriptions of their binding interactions and their differential affinities. The results could be useful in the future design of more specific and potent PDE-3A inhibitors that may be used for the treatment of cardiovascular diseases (Muñoz-Gutiérrez at al., 2017). Series of pyrrolo[2,3-b]pyridines and pyrrolo[2,3-d]pyrimidines bearing pyridazinone moiety were synthesized for the in vitro antitumor activity against four cancer cell lines (A549, HepG2, MCF-7 and PC-3). Some selected compounds were tested for the activity against c-Met kinase, and according to the results of kinase inhibitory activity, one compound was further tested for other four tyrosine kinases (Flt-3, VEGFR-2, c-Kit and EGFR) to test the enzyme-based selectivity and showed excellent activity than lead compound Foretinib against A549, HepG2, MCF-7 and PC-3 cell lines, with the IC_{50} values of 2.19 μM, 1.32 μM, 6.27 μM and 4.63μM. The SAR and docking studies indicated that the pyrrolo[2,3-b]pyridines bearing 4-oxo-pyridazinone moiety was superior to the pyrrolo[2,3-d]pyrimidines bearing 6-oxo-pyridazinone moiety. The target compounds modified were favorable to the activity and electron drawing groups of 4-Cl-3CF_3 on the aryl group show the best activity (Wang at al., 2017).

A series of hybrid benzimidazole containing pyridazinoness were synthesized in accordance with the pharmacophoric requirements essential for the anticonvulsant activity. These compounds were tested for anticonvulsant activity on mice by the maximal electroshock (MES) and subcutaneous pentylenetetrazole (scPTZ)-induced seizure models. Among the compounds tested, SS-4F showed significant anticonvulsant activity in both the screens with ED_{50} values of 25.10 and 85.33 mg/kg in the MES and scPTZ screens, respectively. Compound SS-4F emerged as safer and effective anticonvulsant due to its several-fold higher protective indices. Further, the gamma-aminobutyric acid (GABA) estimation result showed a marked increase in the GABA level (1.7-fold) as compared to the control, which was further confirmed by good binding properties with the $GABA_A$ receptor (Partap at al., 2017). Simultaneous blockade of more than one pathway is considered to be a promising approach to overcome the low efficacy and acquired resistance of cancer therapies. Thus, a series of c-Met/HDAC bifunctional inhibitors was synthesized by merging pharmacophores of c-Met and HDAC inhibitors. The most potent compound, inhibited c-Met kinase and HDAC1, with IC_{50} values of 0.71 and 38 nM, respectively, and showed efficient antiproliferative activities against both EBC-1 and HCT-116 cells with greater potency than the reference drug Chidamide. Western blot analysis revealed that this compound inhibited phosphorylation of c-Met and c-Met downstream signaling proteins and increased expression of Ac-H3 and p21 in EBC-1 cells in a dose-dependent manner. Compounds for the further exploration of dual c-Met/HDAC pathway inhibition achieved with a single molecule (Lu at al., 2017).

Photophysical properties of a biologically active 3(2H)-pyridazinone derivative 5-(4-chloro-2-hydoxy-phenyl)-2-phenyl-2H-pyridazin-3-one (6) [CHP] using solvatochromic approaches. Absorption and fluorescence spectra of CHP molecule have been measured at room temperature in various solvents of different polarities. The fluorescence quantum yield of CHP molecule is using Rhodamine B as a standard reference in different solvents (Desai at al., 2017a). The analysis of fluorescence quenching for biologically active 3(2H)-pyridazinone derivative 5-(5-bromo-2-hydroxy-phenyl)-2-phenyl-2H-pyridazin-3-one (7) [BHP] in five different solvents namely, methanol, ethanol, propan-2-ol, dimethylsulfoxide and ethyl acetate at room temperature. The fluorescence intensity of BHP molecule decrease with increasing in the aniline concentration and it is studied using the Stern-Volmer relation. The obtained Stern-Volmer plots were found to be linear in all the five solvents. Further, it is inferred that the fluorescence quenching reactions in BHP molecule are more significantly affected by activation energy processes (Desai at al., 2017b). Different 3-aroylpropionic acids and dihydropyrimidine hydrazine derivatives were condensed together to yield a series of dihydropyrimidine and pyridazinone hybrids to the development of therapeutic agents for the breast cancer with improved Cycloxygenase-2 (COX-2) selectivity. In-vitro anticancer test for these compounds was done against human breast cancer cell lines (MCF-7, MDA-MB-231) and normal human keratinocytes (HaCaT). One compound emerged as the most potent agent against both these cell lines with IC_{50} values of 3.43 and 2.56 μM respectively. These compounds were also tested for COX-2 selectivity(Akhtar at al., 2018).

Staphylococcus aureus is a leading cause of hospital-acquired infections and is a major health concern as methicillin-resistant *S. aureus* and other antibiotic-resistant strains are common. Compounds that inhibit the *S. aureus* sortase (SrtA) cysteine transpeptidase may function as potent anti-infective agents as this enzyme attaches virulence factors to the bacterial cell wall. While a variety of SrtA inhibitors have been discovered, the vast majority of these small molecules have not been optimized using structure-based approaches. The molecular basis through which pyridazinone-based small molecules inhibit SrtA. These inhibitors covalently modify the active cysteine thiol and partially mimic the natural substrate of SrtA by inducing the closure of an active site loop. Computational and synthetic chemistry methods led to second-generation analogues that are ~70-fold more potent than the lead molecule. These optimized molecules exhibit broad-spectrum activity against other types of class A sortases, have reduced

cytotoxicity, and impair SrtA-mediated protein exhibit on *S. aureus* cell surface. Pyridazinone analogues were attractive candidates for further development into anti-infective agents (Chan at al., 2017). Cannabinoid type-2 receptor (CB_2R) selective ligands have shown a great potential as therapeutic drugs in various diseases. Discovering new selective cannabinoid ligands, a series of pyridazinone-4-carboxamides were synthesized and tested for their affinity toward the hCB_1R and hCB_2R.

6-(4-chloro-3-methylphenyl)-2-(4-fluorobenzyl)-N-(cis-4-methylcyclohexyl)-3-oxo-2,3-dihydropyridazine-4-carboxamide (8) exhibited high CB_2-affinity (K_iCB_2 =2.0 nM) and a notable selectivity (K_iCB_1/K_iCB_2 > 2000). In addition, 9 and other active new synthesized entities have demonstrated to behave as CB_2R inverse agonists in [^{35}S]-GTPγS binding assay. ADME predictions of the newly synthesized CB_2R ligands suggest a favourable pharmacokinetic profile. Docking studies disclosed the specific pattern of interactions of these derivatives. Our results support that pyridazinone-4-carboxamides represent a new promising scaffold for the development of potent and selective CB_2R ligands (Ragusa at al., 2017).

The capsid of hepatitis B virus (HBV) plays a vital role in virus DNA replication. Targeting nucleocapsid function has been tested as an effective approach for anti-HBV drug development. A high-throughput screening and mechanism study revealed the hit compound 4a as an HBV assembly effector (AEf), which could inhibit HBV replication by inducing the formation of HBV DNA-free capsids. The subsequent SAR study and drug-like optimization resulted in the discovery of the lead candidate, with potent antiviral activity (IC_{50}=0.087 μM), low cytotoxicity (CC_{50}=90.6μM), sensitivity to nucleoside analogue-resistant HBV mutants, and synergistic effect with nucleoside analogues in HepG2.2.15 cells (Lu at al., 2017). In spite of the availability of a large number of anti-inflammatory and analgesic agents, fighting pain and inflammation remains a common problem. The need of new therapeutic targets for risk-free anti-inflammatory and analgesic therapy and some new agents in various stages of drug discovery are in pipeline (Singh at al., 2017). The K-Ras GTPase is a major target in anticancer drug discovery. However, direct interference with signaling by K-Ras has not led to clinically useful drugs yet. Correct localization and signaling by farnesylated K-Ras is regulated by the prenyl binding protein PDEδ. Interfering with binding of PDEδ to K-Ras by means of small molecules provides a new opportunity to suppress oncogenic signaling. The identification and structure-guided development of K-Ras-PDEδ inhibitor chemotypes based on pyrrolopyridazinones and pyrazolopyridazinones that bind to the farnesyl binding pocket of PDEδ with low nanomolar affinity. The SAR and in vivo pharmacokinetic (PK) and toxicokinetic (Tox) studies for pyrazolopyridazinone-based K-Ras-PDEδ inhibitors. These findings may inspire novel drug discovery efforts aimed at the development of drugs targeting oncogenic Ras (Murarka at al., 2017). Cyclic nucleotide cAMP is a ubiquitous secondary messenger involved in a plethora of cellular responses to biological agents involving activation of adenylyl cyclase. Its intracellular levels are tightly controlled by a family of cyclic nucleotide degrading enzymes, the PDEs. Cyclic nucleotide PDE-4 has aroused attention as a suitable target for anti-inflammatory therapy in respiratory diseases, particularly in the management of asthma and COPD. Through structure based design, with the inclusion of a variety of functional groups and physicochemical profiles in order to occupy the solvent-filled pocket of the PDE4 enzyme, modified the structure of oral PDE-4 inhibitors to reach compounds down to picomolar enzymatic potencies while at the same time tackling successfully an uncovered selectivity issue with the adenosine receptors (Gràcia at al., 2016).

A series of pyrazolo[3,4-d]pyridazin-7-one derivatives were tested for their in vitro antileishmanial activity against *Leishmania amazonensis* promastigote and axenic amastigote forms. The pyrazolo[3,4-d]-pyridazin-7-one-N-acylhydrazone-(bi)thiophene hybrids were exhibited antileishmanial activity with IC_{50} 3.63 μM, against the promastigote form and IC_{50} 2.32μM against the axenic amastigote form. The active compounds had their cytotoxicity tested against macrophages and fibroblast cells with a higher selectivity index than 10 for compounds. Molecular docking studies were performed for all active compounds using the enzyme trypanothione reductase (TR) to investigate a possible action mechanism. The active compounds had interactions with the residues of amino acids Gly 13, Thr 51, Thr 160, Gly 161, Tyr 198, Arg 287, Asp 327, Thr 335, which may inhibit the enzyme TR (Jacomini at al., 2016). Constant use of non-steroidal anti-inflammatory drugs is often accompanied by side effects such as bleeding, nephrotoxicity and gastrointestinal lesions. To minimise these side effects some of the pyridazinone derivatives are synthesised with an improved gastrointestinal tract and renal safety profile linked to other non-steroidal anti-inflammatory drugs. The pyridazinone nucleuses which are serve as therapeutic agents as nonsteroidal anti-inflammatory drugs. This nucleus has a wide spectrum in bioorganic and medicinal chemistry and application in drug discovery (Saini at al., 2016). The aryl-pyridazinone-substituted benzenesulphonylurea derivatives were tested for their anti-hyperglycaemic activity in glucose-fed hyperglycaemic normal rats. Most compounds were showed more or comparable area under the curve (AUC) reduction percentage (ranging from 21.9% to 35.5%) as compared to the standard drug gliclazide (22.0%). On the basis of docking results, 18 compounds were screened for their in vitro ability to inhibit rat lens aldose reductase. Few compounds were possessing significant dual action (anti-hyperglycaemic and aldose reductase inhibition) and may be used as lead compounds for developing new drugs (Yaseen at al., 2016a). A series of sulfonamide derivatives incorporating substituted pyridazinone moieties were tested for the inhibition of two human cytosolic carbonic anhydrase isoforms, hCA I and hCA II. All these compounds, together with the clinically used sulfonamide acetazolamide were tested as inhibitors of the physiologically relevant isozymes I

and II. These sulfonamides showed very strong inhibition against all these isoforms with K(I)'s in the range of 0.98-8.5 nM which makes such molecules possible to be used as leads for discovery of effective CA inhibitors (Yaseen at al., 2016b). A series of pyridazin-3-one substituted with morpholino-pyrimidine derivatives were tested as tyrosine kinase inhibitors against c-Met enzyme, and anti-proliferative activities of Hs746T human gastric cancer cell line. Most of compounds exhibited good biological activity, displayed excellent c-Met enzyme inhibitory activities and Hs746T cell-based activities (Kim at al., 2016). Over activation of c-Met tyrosine kinase is known to promote tumorigenesis and metastasis, as well as to cause therapeutic resistance. Biological activities of novel, ATP-competitive, c-Met tyrosine kinase inhibitors that are members of the 6-aryl-2-(3-(heteroaryl-amino) benzyl) pyridazinones (9), SAR study of these substances led to identification of pyridazinone as a highly selective and potent c-Met tyrosine inhibitor, which showed favorable pharmacokinetic properties in mice and significant antitumor activity against a c-Met driven EBC-1 tumor xenograft (Liu at al., 2016). A series of pyridazin-6-one-1-acetylhydrazone hybrids were rationally designed to inhibit PDE-4B. These compounds were tested for their in vitro ability to inhibit the PDE-4B enzyme; some of these compounds showed moderate activity compared to the reference drug, rolipram. Some compounds were emerged as the most potent inhibitors. The [3-(4-methoxyphenyl)-6-oxo-5,6-dihydro-4H-pyridazin-1-yl]acetic acid [1-(3,4,5-trimethoxy-phenyl)ethylidene]hydrazide (10) showed an IC_{50} value of 13 μM against PDE4B (Abdel-Rahman at al., 2016).

The BTK inhibitor GDC-0834 (1) was found to be rapidly metabolized in human studies, resulting in a suspension of clinical trials. The primary route of metabolism was through cleavage of the acyclic amide bond connecting the terminal tetrahydrobenzothiophene with the central linker aryl ring. SAR studies were focused on reducing metabolic cleavage of this amide, and resulted in the identification of several central aryl linker substituents that conferred improved stability. The most promising substituted aryl linkers were then incorporated into an optimized pyridazinone scaffold, resulting in the identification of lead a analog, possessing improved potency, metabolic stability and preclinical properties (Young at al., 2016). Pyridazinone derivative, compound 3711, as a nonnucleosidic hepatitis B virus (HBV) inhibitor in a cell model system, decreased extracellular HBV DNA levels by 50% (50% inhibitory concentration [IC_{50}]) at 1.5 μM and intracellular DNA levels at 1.9 μM, which exhibited antiviral activity. 3711 treatment induced the formation of genome-free capsids, a portion of which migrated faster on 1.8% native agarose gel. 3711 treatment decreased levels of HBV DNA contained in both secreted enveloped virion and naked virus particles in supernatant. 3711 could interfere with capsid formation of the core protein (Cp) assembly domain. A Cp V124W mutant, which strengthens capsid interdimer interactions, recapitulated the effect of 3711 on capsid assembly. Pyridazinone derivative 3711, a HBV inhibitor, may provide a new opportunity to combat chronic HBV infection (Wang at al., 2015). To make delivery improvements via delivery systems for 6-(4-morpholino-3-(trifluoromethyl)phenyl)pyridazin-3(2H)-one (11) a compound of hydrophobic antitumor candidate pyridazinone derivatives. Methoxy poly(ethylene glycol)-poly(D,L-lactide) (MPEG-PDLLA) micelle was used as a vector, and DZO was encapsulated in. The 11-loaded micelles were characterized its cytotoxicity, maximum tolerated dose (MTD) and pharmacokinetics were done. In vivo anticancer activity was studied through a subcutaneous 4T1 tumor model. Compared with free 11, the 11-loaded micelles possessed a sustained release property, an improved MTD, better pharmacokinetic parameters and an enhanced antitumor activity for subcutaneous 4T1 model in vivo. An effective injectable delivery system for 11 was developed successfully (Jin at al., 2015). The of 4-chloro-2-tert-butyl-5-[2-[[1-[2-[(18) F]fluroethyl]-1H-1,2,3-triazol-4-yl]methyl]-phenylmethoxy]-3(2H)-pyridazinone ([(18) F]Fmp2) for myocardial perfusion imaging (MPI). The tosylate precursor and non-radioactive compound [(19) F]Fmp2 were synthesized. The radiotracer [(18) F]Fmp2 was obtained by one-step nucleophilic substitution of tosyl with (18) F, and tested as an MPI agent in vitro and in vivo. Starting from [(18) F]KF/K222 solution, the typical decay-corrected radiochemical yield (RCY) was 38% with high radiochemical purity (>98%). In the mice biodistribution, [(18)F]Fmp2 showed very high initial heart uptake (53.35 %ID/g at 2 min after injection) and remarkable retention. The heart/liver, heart/lung, and heart/blood ratios were 7.98, 8.20, and 53.13, respectively at 2 min post-injection. The uptake value of the liver decreased modestly during the 2 h post-injection, while the heart uptake and heart/liver ratios continued to increase with time. [(18) F]Fmp2 exhibited good stability, high heart uptake and low lung uptake in mice and Chinese mini-swine. It may be worthy of further modification to improve liver clearance for MPI in the future (Mou at al., 2015). Test the analgesic as well as anti-inflammatory activities of the pyrrolo[3,4-d]pyridazinone derivatives, these compounds were highly active in the phenylbenzoquinone-induced 'writhing syndrome' test and had much lower activity in the hot plate, which indicates that mainly peripheral mechanisms of analgesia are involved in their effects. In these extended studies the analgesic activity of two tested compounds were confirmed in some animal models of pain. The compounds showed a significant and dose-related antinociceptive effect in the models of pain induced by formalin, capsaicin and glutamic acid. Both compounds decreased the edema formation and one of them attenuated mechanical hyperalgesia in carrageenan-induced paw inflammation in rats. Both compounds inhibited cell migration, plasma exudation and nociceptive reaction in zymosan A-induced mouse peritonitis. It was showed that analgesic and anti-inflammatory effects of the investigated structures are largely due to their competitive antagonism for histamine H1 receptor. The influence on the level of cAMP

in inflammatory cells and subsequent inhibition of cytokine (TNFα, IL-1β) release can also be one of the important mechanisms of their action. Moreover mechanisms may also be involved in the analgesic effect of pyrrolo[3,4-d]pyridazinone derivatives (Mogilski at al., 2015).

Trypanosomal PDEs B1 and B2 (TbrPDEB1 and TbrPDEB2) play an important role in the life cycle of *Trypanosoma brucei*, the causative parasite of human African trypanosomiasis (HAT), also known as African sleeping sickness. Knock down of both enzymes leads to cell cycle arrest and is lethal to the parasite. The phenylpyridazinone, NPD-001, with low nanomolar IC_{50} values on both TbrPDEB1 (IC_{50}: 4nM) and TbrPDEB2 (IC_{50}: 3nM). The SARs of phenylpyridazinone analogs are as TbrPDEB1 inhibitors. A selection of compounds was also shown to be anti-parasitic. A good correlation between TbrPDEB1 IC50 and EC50 against the whole parasite was observed. The SAR of selected compounds on TbrPDEB1 and human PDEs shows a large difference which shows the potential for obtaining parasite selective PDE inhibitors. The pharmacological validation of the Trypanosome PDEB family as new therapeutic approach for HAT and provide as well valuable information for the design of potent TbrPDEB1 inhibitors that could be used for the treatment of this disease (Veerman at al., 2016). A series of yridazin-3(2H)-ones 7a-f were synthesized and tested compounds revealed moderate activity against 60 cell lines. Furthermore, the in vitro cytotoxic activity against HepG2 and MCF-7 cell lines revealed that some compounds showed good cytotoxic activity against HepG2 with IC_{50} values of 14.80μM. Some compounds were showed a pronounced inhibitory effect against cellular localization of tubulin (Abuo-Rahma at al., 2016). A series of 2,6-disubstituted pyridazinone derivatives were tested for their c-Met inhibitory activity in enzyme and cellular assay. The SAR results arising from computer modeling analysis of members of the library led to the proposal that in order to obtain optimal inhibitory activity in cellular systems the lipophilic/hydrophilic properties of individual structural fragments in the inhibitors need to match those of corresponding binding pockets in the enzyme. Guided by this proposal, the quinoline-pyridazinone, containing hydrophobic 6-indolyl pyridazinone and quinoline moieties along with a hydrophilic morpholine terminal group, was designed. This substance showed that it is a selective c-Met inhibitor with both a high enzyme inhibition IC_{50} value of 4.2 nM and a high EBC-1 cell proliferation inhibition IC_{50} value of 17 nM (Xing at al., 2015).

A series of pyridazinone derivatives were synthesized, in which a suitable β(α)-substituted γ-hydroxybutenolide or a bicyclic lactone was the key intermediate. The synthesized compounds were tested in vitro as antiplatelet agents and some of them exhibited potent inhibitory effects on collagen-induced platelet aggregation with IC_{50} values in the low μM range. The most active compound of these series demonstrated its lack of activity as inhibitor of platelet aggregation induced by other agonists as thrombin, ionomycin or U-46619 suggesting a selective action on the biochemical mechanisms triggered by collagen in the platelets (Costas at al., 2015). In a high-throughput screening campaign for c-Met kinase inhibitors, a thiadiazinone derivative with a carbamate group was identified as a potent in vitro inhibitor. The thiadiazinone ring of the HTS hit was first replaced by a pyridazinone followed by an exchange of the carbamate hinge binder with a 1,5-disubstituted pyrimidine. Finally an optimized compound, 22 (MSC2156119), with excellent in vitro potency, high kinase selectivity, long half-life after oral administration and in vivo anti-tumor efficacy at low doses, was selected as a candidate for clinical development (Dorsch at al., 2015). Pyridazinone derivatives and their related analoges were introduced for gastric antiulcer and antisecretory activities. Some pyridazinone compounds are recently reported as H3R antagonists. Some amine analogs of pyridazinones, pyridazinone- phenethylamines and 4,5-fused pyridazinones showed histamine H3R antagonist activity with significant affinity for rat and human H3R. These pyridazinone analogs also showed excellent selectivity and metabolic stability, with adequatepharmacokinetics (Asif, 2015).

A series of pyridazinone-based PDE-10A (PDE10A) inhibitors were synthesized. The 1-[2-fluoro-4-(1H-pyrazol-1-yl)phenyl]-5-methoxy-3-(1-phenyl-1H-pyrazol-5-yl)pyridazin-4(1H)-one (12) has potent IC_{50}=0.inhibitory activity (30 nM), excellent selectivity (>15000-fold selectivity over other PDEs), and favorable pharmacokinetics, including high brain penetration, in mice. Oral use of compound to mice elevated striatal 3',5'-cyclic adenosine monophosphate (cAMP) and 3',5'-cyclic guanosine monophosphate (cGMP) levels at 0.3 mg/kg and showed potent suppression of phencyclidine (PCP)-induced hyperlocomotion at a minimum effective dose (MED) of 0.3 mg/kg. Compound 27h (TAK-063) is currently being evaluated in clinical trials for the treatment of schizophrenia (Kunitomo at al., 2014).

The ortho-selective diversification of a biologically active pyridazinone scaffold,series of pyridazinone analogues were synthesized conveniently as the synthetic precursors of potential sortase A (SrtA) inhibitors (Li at al., 2015). A series of phenyl substituted pyridazin-3-ones substituted with morpholino-pyrimidines, SAR of the phenyl was explored and their c-Met kinase and cell-based inhibitory activity toward c-Met driven cell lines were tested. Described herein is a potent c-Met inhibitor by structural modification of the parent morpholino-pyridazinone scaffold, with particular focus on the phenyl and pyrimidine substituents (Kang at al., 2014, 2017). A series of 4-phenoxyquinoline derivatives containing pyridazinone moiety were evaluated for their in vitro cytotoxic activity against five cancer cell lines (HT-29, H460, A549, MKN-45, and U87MG). Most of the compounds exhibited moderate-to-significant cytotoxicity and high selectivity against one or more cell lines. Some compounds were further examined for their inhibitory activity against c-Met kinase. The most promising compound (c-Met half-maximal inhibitory concentration [IC_{50}] = 2.15 nM) showed remarkable cytotoxicity against HT-29, H460, and A549 cell

lines with IC_{50} values of 0.10 μM, 0.13 μM, and 0.05 μM, respectively, and thus it was 1.5- to 2.3-fold more potent than foretinib. Their preliminary SARs studies indicate that electron-withdrawing groups on the terminal phenyl rings are beneficial for improving the antitumor activity (Zhou at al., 2014). Vascular adhesion protein-1 (VAP-1) is a primary amine oxidase and a drug target for inflammatory and vascular diseases. Despite extensive attempts to develop potent, specific, and reversible inhibitors of its enzyme activity, the task has proven challenging. Here we report the synthesis, inhibitory activity, and molecular binding mode of pyridazinone inhibitors, which show specificity for VAP-1 over monoamine and diamine oxidases. These compounds bind reversibly into a unique binding site in the active site channel. Although they are good inhibitors of human VAP-1, they do not inhibit rodent VAP-1 well. The potency and specificity of these new inhibitors and the detailed characterization of their binding mode is of importance for further development of VAP-1 inhibitors (Bligt-Lindén at al., 2013). There is widespread interest in the application, optimization, and evolution of the transition-metal-catalyzed arylation of N-heteroarenes to discover full-color tunable fluorescent core frameworks. Inspired by the versatile roles of pyridazinone in organic synthesis and medicinal chemistry, A simple and efficient copper-catalyzed cross-coupling reaction for the N-functionalization of pyridazinones in neat water has been reported. To achieve the efficient conversion of pyridazinones and organic halides in aqueous phase, a series of copper-salen complexes composed of different Schiff base ligands were investigated by rational design. A final choice of fine-tuned hydrophilicity balanced with lipophilicity among the candidates was confirmed, which affords excellent activity towards the reaction of a wide range of pyridazinones and organic halides. More importantly, the products as N-substituted pyridazinones were synthesized. The N2 position of pyridazinones was modified by different aryl group such as benzothiazole, N,N-dimethylaniline, 3-quinoline, 4-isoquinoline and 2-thiophene, resulting in a series of full-color tunable fluorescent reagents. Meanwhile, the effects of electron-donating and electron-withdrawing groups of the 6-substituted phenyl ring have also been tested to optimize the fluorescent properties (Liangat al., 2013).

Various 6-aryl-2-(p-(methanesulfonyl)phenyl)-4,5-dihydropyridazi-3(2H)-ones (13) were tested for in vitro anticancer and in vivo anti-inflammatory activities. Some compounds were tested for their antiproliferative activity towards 60 human cancer cell lines. One compound showed remarkable activity with GI_{50} less than 1 μM on 36 human tumor cell lines and another compound was also displayed promising antiproliferative activity against 20 different cell lines with GI_{50} less than 1 μM. Some compounds were found to have a comparable anti-inflammatory activity to that of standard drug etoricoxib (Ovais at al., 2013).

Despite significant progresses in antimicrobial therapy, infectious diseases caused by bacteria and fungi remain a major worldwide health problem because of the rapid development of resistance to existing antimicrobial drugs. Therefore, there is a constant need for new antimicrobial agents. There are a large number of heterocyclic derivatives containing nitrogen atoms that possess a broad spectrum of biological activities including pyridazine, which is the important heterocycles in medicinal chemistry. The pyridazinones were formed from the arylazo moiety was phenyl or phenyl substituted with an electron-donating group. Most of the synthesized compounds were evaluated as antimicrobial agents and the results indicated that many of the compounds exhibited high antimicrobial activity comparable to ampicillin. Synthesis of pyridazinone was established using 3-oxo-2-aryl-hydrazono-propanal as a precursor. Most of the synthesized compounds were found to exhibit strong inhibitory effects on the growth of Gram-positive bacteria especially Bacillus subtilis (Ibrahim at al., 2013). Disubstituted pyridazinone was identified by HTS as a acetylcholinesterase (AChE) inhibitor. Under SAR development, one compound stood out as displaying high AChE inhibitory activity and AChE/butyrylcholinesterase (BuChE) selectivity in vitro (Xing at al., 2013). The syntheses of pyridazinone and phthalazinone derivatives were tested to evaluate their activity and potential selectivity on four cancer cell lines to examine cytotoxic effects. The compounds inhibited DYRK1A and GSK3 with different activity. Findings suggest that pyridazinone and phthalazinone scaffolds are interesting starting points for design of potent GSK3 and DYRK1A inhibitors (Elagawany at al., 2013). Pharmacological properties of several series of pyridazine and pyridazinone derivatives were tested, in vivo, for their anti-inflammatory and ulcerogenic properties against indomethacin. Some compounds have shown a potent anti-inflammatory activity more than indomethacin with rapid onset of action and safe gastric profile. In the MTT assay in vitro, both compounds were identified as potent and selective COX-2 inhibitors (Saeed at al., 2012). The 3(2H)-pyridazinone derivatives containing a N'-benzyliden-acetohydrazide moiety at position 2 were tested for their antibacterial, antifungal, antimycobacterial, and cytotoxic activities. The compounds 2-[4-(4-chlorophenyl)-6-(morpholin-4-yl)-3-oxo-(2H)-pyridazin-2-yl]-N'-(4-tert-butylbenzyliden)acetohydrazide (14) and 2-[4-(4-chlorophenyl)-6-(morpholin-4-yl)-3-oxo-(2H)-pyridazin-2-yl]-N'-(4-chlorobenzyliden) aceto-hydrazide (15) exhibited activity against both Gram-positive and Gram-negative bacteria. Most of the compounds were active against E. coli ATCC 35218. The results showed that some target compounds exhibited promising antimicrobial activities (Sukuroglu at al., 2012).

A series of pyridazine-based small molecule glucan synthase inhibitors is described. The optimization of the PK profile of this series led to the discovery of a compound, which shwed in vivo potency ip in a lethal fungal infection model (Kuang at al., 2012). The SAR studies of a sulfonylurea series of piperazine pyridazine-based small molecule glucan synthase inhibitors are described. The optimization of PK profiles within the series led to the discovery of various

compounds with improved pharmacokinetic profiles which showed in vitro potency against clinically relevant strains. However, the advancement of compounds from this series into a non-lethal systemic fungal infection model failed to show in vivo efficacy (Zych at al., 2012). A series of pyridazinone-phenethylamine derivatives with moderate to low nanomolar affinity for rat and human H(3)R are described. These analogs exhibited excellent selectivity and metabolic stability, with acceptable rat pharmacokinetic properties. In vivo, some compound were exhibited potent H(3)R functional antagonism in the rat dipsogenia model and robust wake-promoting activity in the rat electroencephalogram/electromyography (EEG/EMG) model (Dandu at al., 2011). A series of N2-{2-[4-aryl(benzyl)-1-piperazinyl (piperidinyl)] ethyl} pyrrolo[3,4-d] pyridazinones (16) and related derivatives were synthesized as potential analgesic agents. Analgesic activity of the compounds was tested in the phenylbenzoquinone induced 'writhing' and 'hot plate' test in mice and at radio ligand binding assay. At 'writhing' test all compounds, were more active than aspirin with ED_{50} values ranging from 0.04 to 11 mg/kg (i.p.) (ED_{50} for Aspirin-39.15 mg/kg). Analgesic effect at the 'hot plate' test was observed for some compounds at the dose 3-5 times higher then that of morphine (ED_{50}-3.39 mg/kg). At radioligand binding assay of only a compound exhibited affinity for the μ-opioid receptors similar to that of Tramadol. The acute toxicity of the pyrrolopyridazinones were also studied and non-toxic effect was observed at the 2000 mg/kg (1420 mg/kg) i.p. dose level (Malinka at al., 2011).

Pyridazinone was reported as a potent H(3)R antagonist with good drug-like properties and in vivo activity. A series of constrained amine analogs of was synthesized to identify compounds with improved pharmacokinetic profiles. From these efforts, a class of (S)-2-pyrrolidin-1-ylmethyl-1-pyrrolidinyl amides was identified (Sundar at al., 2011). Some 6-aryl-2-(p-sulfamoylphenyl)-4,5-dihydropyridazin-3(2H)-ones (17) were tested for their anti-inflammatory activity. One compound was exhibited anti-inflammatory activity comparable to that of celecoxib. Two other compounds were showed promising anti-inflammatory activity (edema reduction more than 80% at 5 h). These compounds did not produce any ulceration in gastric region (Bashir at al., 2012). Ibudilast [1-(2-isopropylpyrazolo[1,5-a]pyridin-3-yl)-2-methylpropan-1-one] is a nonselective PDE inhibitor used to treat asthma. Efforts to selectively develop the PDE3- and PDE4-inhibitory activity of ibudilast led to replacement of the isopropyl ketone by a pyridazinone heterocycle. The SAR exploration in the resulting 6-(pyrazolo[1,5-a]pyridin-3-yl)pyridazin-3(2H)-ones (18) revealed that the pyridazinone lactam functionality is a critical determinant for PDE3-inhibitory activity, with the nitrogen preferably unsubstituted. The PDE-4 inhibition is strongly promoted by introduction of a hydrophobic substituent at the pyridazinone N(2) centre and a methoxy group at C-7' in the pyrazolopyridine. Migration of the pyridazinone ring connection from the pyrazolopyridine 3'-centre to C-4' strongly enhances PDE-4 inhibition. For development of potent PDE-4-selective and dual PDE-3/4-selective inhibitors derived from ibudilast (Allcock at al., 2011).

A series of pyridazinone analogs developed as potent β-1,3-glucan synthase inhibitors through SAR study of the lead 5-[4-(benzylsulfonyl)piperazin-1-yl]-4-morpholino-2-phenyl-pyridazin-3(2H)-one (19). Optimization of the sulfonamide moiety led to the identification of important compounds with much improved systematic exposure while retaining good antifungal activity against the fungal strains *Candida glabrata* and *C. albicans* (Zhouat al., 2011).

Various 6-substituted-3(2H)-pyridazinone-2-acetyl-2-(substituted/nonsubstituted benzal) hydrazone derivatives were synthesized as acetylcholinesterase and butyrylcholinesterase inhibitors. The acetylcholinesterase (AChE) and butyrylcholinesterase (BChe) inhibitory activities of these derivatives were measured using Ellman's method. While some of the 6-substituted-3(2H)-pyridazinone-2-propyl-3-(substituted/-nonsubstituted benzal)hydrazone derivatives were exhibited significant AChE inhibitory activity, none of the compounds showed BChE inhibitory activity. The one derivative was AChE inhibitors with AChE/ BChE selectivity (Utku at al., 2011). A series of pyridazinone derivatives were synthesized for safer anti-inflammatory agents. The compounds were tested for their anti-inflammatory, analgesic, ulcerogenic and lipid peroxidation (LPO) actions. Some compounds were exhibited good anti-inflammatory potential, comparable with that of ibuprofen (85.77%) within a range of 67.48-77.23%.

The 5-(4-fluoro-benzyl)-3-(4-chloro-phenyl)-1,6-dihydro-6-pyridazinone (20) and 5-(4-chloro-benzyl)-3-(4-chloro-phenyl)-1,6-dihydro-6-pyridazinone (21) were showed best anti-inflammatory activity. Furthermore, activity is more in case of chloro substitution as compared with methyl-substitution. The compounds synthesized were also tested for their ulcerogenic and LPO action and showed superior gastrointestinal safety profile along with reduction in LPO as compared with that of the ibuprofen (Husain at al., 2011).

The synthesis of three diverse libraries of pyridazin-3-ones incorporating α,β-unsaturated moieties at position 5 of the heterocyclic core has been developed using silica-supported aluminum trichloride as a heterogeneous and reusable catalyst. This robust procedure has facilitated the hit to lead process for these series of compounds and allowed the identification of potent derivatives that elicit antiplatelet activity in the low micromolar range (El Maatougui at al., 2011). The 6-substituted and 2,6-disubstituted pyridazinone derivatives were obtained starting from easily accessible alkyl furans by using oxidation with singlet oxygen to give 4-methoxy or 4-hydroxybutenolides. The pyridazinone derivatives have been tested as vasorelaxant and antiplatelet agents. Biological data revealed the silyl ethers and N,O-dibenzyl derivatives as the most active compounds (Costas at al., 2010). The synthesis of potent p38α MAP kinase inhibitors containing

a pyridazinone platform is described and evolution of the p38α selective pyridopyridazin-6-one series from the p38α/β dual inhibitor 2H-quinolizin-2-one series (Tynebor at al., 2011). Some ethyl-6-[(substituted-phenylpiperazine]-3(2H)-pyridazinone-2-yl propionate III and 6-[(substituted-phenylpiperazine]-3(2H)-pyridazinone-2-yl propionohydrazide IV derivatives were synthesized as acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) inhibitors. 6-Substituted-3(2H)-pyridazinone-2-yl propionates were showed significant inhibitory activity against AChE and BChE. 6-[4-(3-Trifluoromethylphenyl)piperazine]-3(2H)-pyridazinone-2-yl propionate has been found to be the most active compound in terms of inhibition of either AChE or BChE. Compound IIIe exhibited inhibitory activity close to that of galantamine (CAS 357-70-0) and did not show any selectivity between the two enzymes. All derivatives exhibited poor antibacterial activities but moderate antifungal activities (Ozçelik at al., 2010). The SAR and modeling of a series of 5-substituted-N-aryl pyridazinone based p38alpha inhibitors are described. In comparing the series to the similar N-aryl pyridinone series, it was found that the pyridazinones maintained a weaker interaction to the p38 enzyme, and therefore showed generally weaker binding than the pyridinones (Jerome at al., 2010).

Some 6-(substituted-phenyl)-2-(substitutedmethyl)-4,5-dihydropyridazin-3(2H)-one derivatives (22) were synthesized by reacting 6-substituted-phenyl-4,5-dihydropyridazin-3(2H)-one with cyclic secondary amine under Mannich reaction conditions. The final compounds were tested for antihypertensive activities by non-invasive method using Tail Cuff method. Some compounds were showed good antihypertensive activity (Siddiqui at al., 2010). Nonnucleoside reverse transcriptase inhibitors (NNRTIs) are allosteric inhibitors of the HIV-1 reverse transcriptase. A series of Triazolinone and Pyridazinone were reported as potent inhibitors of HIV-1 wild type reverse transcriptase. Docking and 3D-QSAR studies involving comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA) were performed on 31 molecules. The CoMFA model provides the most significant correlation of steric and electrostatic fields with biological activities. The CoMSIA model provides a correlation of steric, electrostatic, acceptor and hydrophobic fields with biological activities. The information rendered by 3D QSAR model initiated us to optimize the lead and design new potential inhibitors (Sivan at al., 2010). The SAR of a series of pyridazinone derived 5-HT(2C) agonists has been explored and resulted in identification of a compound with excellent levels of 5-HT(2C) functional agonism and selectivity over 5-HT(2A) and 5-HT(2B). This compound showed good in vivo efficacy in pre-clinical models of stress urinary incontinence, despite having physiochemical properties commensurate with impaired CNS penetration (Allerton at al., 2009). Synthesis and vasodilatory activity of some amide derivatives of 6-(4-carboxymethyloxyphenyl)-4,5-dihydro-3(2H)-pyridazinone (23) are reported. An effect of substitution at 2-position of pyridazinone ring on vasodilatory potential has also been explored. The most active compound 6-[4-(2-oxo-2-pyrrolidin-1-yl-ethoxy)phenyl]-2-(4-fluorophenyl)-4,5-dihydro-pyridazin-3-(2H)-one (24) exhibited vasodilating activity in nanomolar range (IC_{50}=0.051 microM) (Bansal at al., 2009).

The 6-substituted-3(2H)-pyridazinone-2-acetyl-2-(p-substituted benzal)hydrazone derivatives were synthesized as analgesic and anti-inflammatory agents. Some compounds were exhibited more potent analgesic activity than ASA. Also these derivatives exhibited anti-inflammatory activity as well as indomethacin. Side effects of the compounds were examined on gastric mucosa. None of the compounds showed gastric ulcerogenic effect compared with reference NSAIDs (Gökçe at al., 2009). Some pyridazinone substituted benzenesulfonylurea derivatives were synthesized from corresponding sulfonamides derivatives via novel carbamates. Blood sugar lowering effect of some sulfonylurea derivatives at the dose of 20 mg/kg (p.o.) were assessed using glucose tolerance test in normal and NIDDM (n2-STZ) rat models. All compounds except few almost completely prevented the rise of blood glucose of NIDDM rats as compared with NIDDM control. While two compounds showed more than 50% prevention in the rise of blood glucose levels. In glucose-fed normal rats these compounds at the same dose except one significantly prevented the rise of blood glucose (more than 50%) when compared with control of glucose-fed normal rats. From the results, new compounds exhibited considerably potent blood glucose lowering activity and may be used as lead compounds for developing new antidiabetic drugs. Some SAR was observed while varying nature of 'Ar' and 'R' (Rathish at al., 2009). A variety of 6-phenyl-4,5-dihydro-3(2H)-pyridazinone derivatives (25) were synthesized. The cardiotonic activities of these compounds were assessed by Straub's perfusion method and a clear cardiotonic effect was shown for compounds (2,3-dichloro-N-(4-(4-methyl-6-oxo-1,4,5,6-tetrahydro-pyridazin-3-yl)phenyl) benzamide) (26), (4-amino-3-methyl-N-(4-(4-methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl) phenyl)benzamide) (27), (3-methyl-4-nitro-N-(4-(6-oxo-1,4,5,6-tetrahydro-pyridazin-3-yl)phenyl)benzamide) (28) and (4-amino-3-methyl -N-(4-(6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)phenyl) benzamide) (29) when compared to another 3(2H)-pyridazinone derivative, levosimendan (CAS 141505-33-1). The SAR of the compounds were studied using the rough sets theory (Wang at al., 2008).

The pharmacological test of 2-substituted-6-(4-acylaminophenyl)-4,5-dihydro-pyridazin-3(2H)-ones as potent inodilating agents. The pyridazinone derivatives were tested 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). 6-(4-Methanesulfonamidophenyl)-2-phenyl-4,5-dihydropyridazin-3(2H)-one (30) exhibited significant inodilatory properties and showed vasorelaxant activity in a nanomolar range (IC_{50} = 0.08 mumol L-1) (Kumar at al.,

2008). A series of benzyl pyridazinones were tested as HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTIs). Various compounds of this series showed good activity against the wild-type virus and NNRTI-resistant viruses (Sweeney at al., 2008). The 5-Hydroxy-3(2H)-pyridazinone derivatives (31) were tested as inhibitors of genotype 1 HCV NS5B polymerase. Lead optimization led to the discovery of a compound, which exhibited potent inhibitory activities in biochemical and replicon assays, good stability toward human liver microsomes (t(1/2)>60 min), and high ratios of liver to plasma concentrations 12h after a single oral use to rats (Li at al., 2008). The interaction between a promising pyridazinone derivative (5-chloro-2-nitro-N-(4-(6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)phenyl)benzamide CNPB (32) and human serum albumin (HSA) under physiological conditions has been tested systematically. It was observed that CNPB had a strong ability to quench the intrinsic fluorescence of HSA through a static quenching procedure. The binding of CNPB to HSA was mainly of hydrophobic interaction, but the hydrogen bonding and electrostatic interaction could not be excluded. Furthermore, the study of molecular modeling also indicated that CNPB could strongly bind to the site I (subdomain IIA) of HSA mainly by hydrophobic interaction and there were hydrogen bond interactions between CNPB and the residue His242 (Wang at al., 2008).

The 4-phenyl-and 4-(2-chlorophenyl)-6-(5-chloro-2-oxo-3H-benzoxazol-7-yl)-3(2H)-pyridazinone derivatives (33a, 33b) tested for their testing as inhibitors of COX-1 and COX-2. These compounds were inhibited COX-1 (by 59-61 %) and COX-2 (by 37-28 %) at a concentration of 10 μM. The analgesic and anti-inflammatory activities of these compounds in vivo by using the p-benzoquinone-induced writhing test and the carrageenan-induced hind paw edema model, respectively. Some compounds were showed potent analgesic and anti-inflammatory activities without causing gastric lesions in the tested animals (Okçelik at al., 2003). A series of fluorinated pyridazinones with IC_{50} values ranging from 8 to 4000 nM for the mitochondrial complex 1 (MC1) have been prepared. The SAR assessment indicated preference of the fluorine label to be incorporated on an alkyl side chain rather than directly on the pyridazinone moiety. Tissue distribution studies of a series of analogues ([18F]22-28) in Sprague-Dawley (SD) rats identified [18F]27 as the most promising radiotracer with high uptake in cardiac tissue (3.41%ID/g; 30 min post injection) in addition to favorable heart to nontarget organ distribution ratios. MicroPET images of SD rats and nonhuman primates after [18F]27 use allowed easy assessment of the myocardium through 60 min with minimal lung or liver interference (Purohit at al., 2008). Various 6-substituted-3(2H)-pyridazinones and the corresponding methyl (6-substituted-3(2H)-pyridazinone-2-yl)acetate derivatives carrying the arylpiperazinyl present in potent antinociceptive agents were synthesized. A series of diverse arylpiperazine derivatives of ethyl (6-substituted-3(2H)-pyridazinone-2-yl)acetates (34) were tested for their in vivo analgesic and anti-inflammatory activity. Side effects of the compounds were examined on gastric mucosa. None of the compounds showed gastric ulcerogenic effect compared with reference NSAIDs. The SAR in the series of ethyl (6-substituted-3(2H)-pyridazinone-2-yl)acetates was also discussed. When compared to parent 6-substituted-3(2H)-pyridazinones, the ester derivatives, ethyl (6-4-[(2-fluoro)phenyl]piperazine-3(2H)-pyridazinone-2-yl)acetate exhibited better analgesic and anti-inflammatory activity and a lower ulcerogenic effect (Dündar at al., 2007).

Antioxidants are compounds that can delay, inhibit, or prevent the oxidation of materials that can be oxidized by scavenging free radicals and help in diminishing oxidative stress. They belong to different chemical classes. There are studies related to pyridazinone derivatives for their antioxidant activities. Since there are evidences implicates reactive oxygen species and nitric oxide as mediators of inflammation and/or tissue damage in inflammatory and arthritic disorders it was though that compounds that have both antioxidant and anti-inflammatory activities are essential for the inflammatory diseases. A series of 2H-pyridazine-3-one and 6-chloropyridazines that have anti-inflammatory activity was tested against α-tocopherol. Most of the compounds have strong inhibitory effect on superoxide anion (84-99%) at 10^{-3} M concentration. These compounds showed similar activity to α-tocopherol at 10^{-3} M concentrations (Caliskan-Ergün at al., 2008). The 5-Hydroxy-3(2H)-pyridazinone derivatives were tested as inhibitors of genotype 1 HCV NS5B polymerase. The synthesis, SAR, metabolic stability, and structure-based design approach for this class of compounds were discussed (Zhou at al., 2008). Structural modification and cellular adhesion inhibition activities of pyridazinone-substituted phenylalanine amide α4 integrin antagonists are described. Functionality requirements for the arylamide moiety and the carboxylic acid group were demonstrated. A selected compound showed effectiveness in a mouse leukocytosis study (Gong at al., 2008). The 5-Hydroxy-3(2H)-pyridazinone derivatives (35) were tested as inhibitors of genotype 1 HCV NS5B polymerase. The SAR associated with variation of the pyridazinone 2- and 6-substituents was discussed. The metabolic stability of this class of compounds are also described (Zhou at al., 2008).

The effect of oxadiazolyl 3(2H)-pyridazinone (ODP, 36), a insect growth regulator, on growth of larvae of the armyworm, *Pseudaletia separata* Walker (Lepidoptera: Noctuidae) was tested in comparison to the insecticide, toosendanin, a tetranortriterpenoid extracted from the bark of *Melia toosendan* that has multiple effects on insects. The digestive physiological properties of these compounds on insects were tested by feeding them maize leaves dipped in these compounds. The results showed that ODP inhibited the growth of *P. separata* significantly, causing a slowed development and a prolonged larval period, smaller body size and sluggish behavior, delayed pupation and a reduced eclosion rate of pupae and adults. Moreover, ODP strongly inhibited the activities of weak alkaline trypsin-like enzyme,

chymotrypsin-like enzyme and alpha amylase in the midguts of fifth instar P. separata larvae, in vivo, and inhibited the activity of alpha amylase, in vitro. The ODP has severe consequences on the larval carbohydrate assimilation and/or nutrient intake and thereby causes inhibition of larval growth. The regulatory action of ODP on larval growth development was similar to that of toosendanin; both could be used to decrease the growth of insect populations (Huang at al., 2008). A series of 6-phenyl-4,5-dihydro-3(2H)-pyridazinone (37) derivatives was tested for cardiotonic activity The cardiotonic activities of these compounds were studied on isolated perfused toad heart and compared with the activity of levosimendan (CAS 141505-33-1) (Wang at al., 2007). In an attempt to identify potential vasodilator-cardiotonic lead compounds, various pyridazinones were designed using 3-D pharmacophore developed with CATALYST software from a set of potent cyclic nucleotide PDE-III, cAMP PDEIII inhibitors. The features of the target compounds were based on the structures of many biologically active lead compounds with cAMP PDE-III inhibiting activity such as Milrinone and others. Compounds with higher fit scores to the developed pharmacophore were synthesized namely; 6-(3-ethoxycarbonyl-4-oxo-1,4-dihydroquinolin-6-yl)-4,5-dihydro-3(2H)-pyridazinones (38), 6-[4-(2,6-disubstituted-quinolin-4-ylamino)phenyl]-4,5-dihydro-pyridazin-3(2H)-ones (39), and 6-[3-(5-cyano-6-oxo-4-aryl-1,6-dihydro-2-pyridyl)-phenyl-amino]-3(2H)pyridazinone (40). The vasodilator activity of the synthesized compounds was examined on the isolated main pulmonary artery of the rabbit. Some of the tested compounds showed moderate vasorelaxant activity compared with standard drug, Milrinone (Abouzid at al., 2008).

A series of 6-morpholino-4-aryl-3(2H)-pyridazinone alkanoic acids (41), their ester and amide derivatives were tested for their in vivo analgesic activity by using the p-benzoquinone-induced writhing test. The analgesic activity of the compounds 6-morpholino-4-aryl-3(2H)-pyridazinone (42) were comparable but little lower than that of aspirin (CAS 50-78-2) as an analgesic agent. The 6-morpholino-4-aryl-3(2H)-pyridazinones having a propanoic acid, ester and amides as side chains at the position 2 of the pyridazinone ring showed higher activity than the reference drug without gastric ulceration forming potential. All other compounds generally showed higher activity but caused gastric ulceration in the animals (Süküroglu at al., 2006).

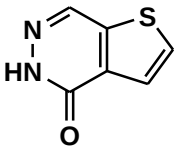
A series of pyridazinone-functionalized phenylalanine analogues was tested for inhibition of cellular adhesion mediated by α4β1/VCAM-1 and α4β7/MAdCAM-1 interactions. Potent dual antagonists of α4β1 and α4β7 were generated from an amide subseries; antagonists selective for α4β7 were identified from urea and carbamate-based subseries. The pharmacokinetic properties of selected members of the series demonstrate that the use of ester prodrugs and alterations to the amide linkage can lead to improved oral bioavailability in this series. An α4β7-selective member of the carbamate subseries, upon oral use, demonstrated in vivo efficacy in the mouse DSS colitis model (Gong at al., 2006). A series of α,α,α--trifluoro-m-tolyl pyridazinones were synthesised. Herbicidal activities of the two intermediate compounds and pyridazinones were tested through barnyardgrass and rape cup tests and Spirodela polyrrhiza (L.) Schleiden tests. Selected compounds were also tested under greenhouse conditions. Bleaching activities were observed at 10 μg/ml and some compounds exhibited herbicidal activities at a rate of 300 g/ha (Xu at al., 2006). The PC-09, a new pyridazinone derivative, has antiplatelet activity in vitro and further tested the possible mechanisms involved. Pretreatment with PC-09 resulted in an inhibition on rabbit platelet aggregation and ATP release induced by arachidonic acid, collagen or thrombin, with the IC_{50} values of 5.4 to 76.8 muM. The thromboxane B(2) formation caused by collagen or thrombin was markedly inhibited by PC-09, but there was no alteration in that caused by arachidonic acid (AA). The rise of platelet intracellular calcium level stimulated by aggregation agonists and collagen-induced platelet membrane surface glycoprotein IIb/IIIa expression was also reduced by PC-09. In addition, PC-09 itself significantly increased the cyclic AMP level through inhibiting cyclic AMP PDE activity. The PC-09 is an inhibitor of platelet aggregation, which may be associated with mechanisms including inhibition of thromboxane A(2) formation, intracellular calcium mobilization and platelet surface GPIIb/IIIa expression accompanied by increasing cAMP level (Cherng at al., 2006). The design of a class of piperazine-pyridazinone analogues, the arylpiperazine moiety, the length of the spacer, and the terminal molecular fragment were varied to test their influence in determining the affinity of the compounds toward the α1-AR, α2-AR, and the 5-HT1A serotoninergic receptor (5-HT1AR). Most of the compounds have α1-AR affinity in the nanomolar or subnanomolar range, while affinity toward the other two receptors was lower in most cases. However, several of the tested compounds also showed very good (in the nanomolar range) or moderate affinity toward the 5-HT1AR subtype (Betti at al., 2006). The sulfonyl-pyridazinone inhibitor in complex with aldose reductase, the pyridazinone head group of the inhibitor occupies the catalytic site, whereas the chloro-benzofuran moiety penetrates into the opened specificity pocket. The pyridazinone exhibits a binding affinity similar to those of tolrestat and sorbinil, and shows slightly reduced affinity compared to IDD 594. The binding mode and providing information about protonation states of protein side-chains involved in binding of this class of inhibitors establish the platform for further structure-based drug design (Steuber at al., 2006). Various metal complexes of 5-benzoyl-4-hydroxy-2-methyl-6-phenyl-2H-pyridazin-3-one (43) were tested for their antimicrobial activities against Gram-positive, Gram-negative bacteria and fungi using microdilution procedure. The Cd(II) and Ni(II) complexes exhibited selective and effective activities against one Gram-positive bacterium (*Staphylococcus aureus*), one Gram-negative bacterium *(Pseudomonas putida*) and against two

yeast (*Candida albicans* and *Candida tropicalis*) in contrast to poor activity observed other microorganisms (Sönmez at al., 2006).

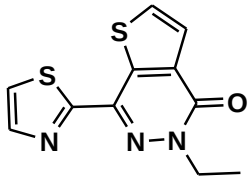
A series of structurally different amide derivatives of [6-(3,5-dimethylpyrazol-1-yl)-3(2H)-pyridazinone-2-yl]acetic acid (44)were tested for their analgesic and anti-inflammatory activity. The analgesic and anti-inflammatory activity of the some compounds were equipotent were more potent than aspirin (CAS 50-78-2) as an analgesic and indometacin (CAS 53-86-1) as an anti-inflammatory drug, respectively. The other amide derivatives and parent carboxylic acid molecule generally resulted in lower activity to reference drugs. Inhibitor activity of the active compounds on COX isoforms was also tested by using in vitro COX inhibitor screening assay and found that these derivatives did not exert their analgesic and anti-inflammatory activities through COX inhibition and that other mechanisms might be involved (Banoğlu at al., 2005). Despite the increasing implication of the permeability transition pore (PTP) in the pathophysiology of neurodegenerative diseases, few selective PTP inhibitors have been reported so far. The pharmacological properties of a PTP inhibitor, BBMP (5-(benzylsulfonyl)-4-bromo-2-methyl-3(2H)-pyridazinone) (45) was discovered from the screening of a compound library against the PTP using a functional assay with isolated mitochondria. Similarly to cyclosporin A, the drug prevented Ca^{2+}-induced permeability transition and mitochondrial depolarization. BBMP appeared more potent that minocycline in both swelling and membrane potential assays displaying pIC_{50} values of 5.5+/-0.1 and 5.6+/-0.0, respectively. Unlike minocycline, BBMP dose-dependently prevented DNA fragmentation induced by KCl 25/5 mM shift and serum deprivation in cerebellar granule neurons with a pIC_{50} of 5.7+/-0.6. The inhibition of PTP-mediated cytochrome c release observed in isolated mitochondria at 10 and 100 µM may explain its neuroprotective properties in vitro. The mitochondrial PTP is potentially involved in neuronal cell death and that PTP inhibitors, like BBMP, may possess a therapeutic potential in neurodegenerative disorders (Fuks at al., 2005). A series of 2-[[4-(substituted-phenyl/benzyl)-1-piperazinyllmethyl]-6-(4-methoxyphenyl)-3(2H)pyridazinones (46) was tested for analgesic and anti-inflammatory activities. The 2-[[4-(4-fluorophenyl)-1-piperazinyl]methyl]-6-(4-methoxyphenyl)-3(2H)pyridazinone (47) was found to be a most promising analgesic and anti-inflammatory agent. Some compound showed more potent analgesic activity than aspirin in the phenylbenzoquinone-induced writhing test and showed anti-inflammatory activity comparable to the indometacin. Side effects of the compounds were examined on gastric mucosa. None of the compounds showed a gastric ulcerogenic effect compared with reference NSAIDs. The SAR of the series of 2-[[4-(substituted-phenyl/benzyl)-1-piperazinyl] methyl]-6-(4-methoxyphenyl)-3(2H) pyridazinones is also discussed (Gökçe at al., 2005). The biological activity of a class of non-peptidyl, pyridazinone derived human melanocortin subtype-4 receptor agonists is disclosed (Ujjainwalla at al., 2005). A series of amide derivatives of [6-(3,5-dimethyl-4-chloro-pyrazole-1-yl)-3(2H)-pyridazinone-2-yl]acetic acid (48) were tested for their in vivo analgesic and anti-inflammatory activity. The analgesic and anti-inflammatory activity of the some compounds were found to be equipotent to aspirin (analgesic) and indometacin (anti-inflammatory) drug. The other amide derivatives generally resulted in lower activity on comparision with reference drugs (Sükürоglu at al., 2005). Various oxa(thia)diazolyl3(2H)-pyridazinone derivatives (49) were synthesized and some compounds showed good chronic growth activities against the armyworm, *Pseudaletia separata* (Walker). Their EC_{50} values were determined in vivo. Nineteen 2-tert-butyl-4-chloro-5-[5'-aryl-2'-(1',3',4'-oxadiazolyl)methoxy]-3(2H)-pyridazinones were QSAR procedure (Cao at al., 2005).

A 2-nonsubstituted/2-methyl-/2-(2-acetyloxyethyl)-6-[4-(substituted pyrrol-1-yl)phenyl]-4,5-dihydro-3(2H)-pyridazinones (50) and 2-nonsubstituted/2-methyl- 4-[4-(substituted pyrrol-1-yl)phenyl]-1(2H)-phthalazinones (51) were synthesised by reacting hexan-2,5-dion or 1-aryl-3-carbethoxypent-1,4-diones with corresponding 2-substituted/ nonsubstituted 6-(4'-aminophenyl)-4,5-dihydro-3(2H)-pyridazinone or 2-substituted/ nonsubstituted-4-(4'-aminophenyl)-(2H)-phthalazinone under Paal-Knorr pyrrole synthesis conditions. The antihypertensive activities of the compounds were tested both in vitro and in vivo. Some pyridazinone derivatives showed appreciable activity (Demirayak at al., 2004). A series of 6-substituted-3(2H)-pyridazinone derivatives were tested for analgesic and anti-inflammatory activities. Analgesic and anti-inflammatory activities of these compounds have been tested. Some compounds possessed significant analgesic effects. The most active derivatives were void of gastric ulcerogenic effect or acute toxicity at the maximal dose (200 mg/kg p.o.). Compound (6- [4- (2-fluorophenyl) piperazin-1-yl]-3(2H)-pyridazinone) (52) was showed anti-inflammatory activity similar to the standard drug indometacin (CAS 53-86-1). A significant dependence of the anti-inflammatory effect on the substituents was observed. These compounds confirms that modification of the chemical group at position 6 of the 3(2H)-pyridazinone ring influences analgesic and anti-inflammatory activities (Gökçe at al., 2004).

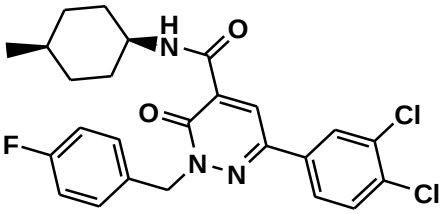
A series of methyl 6-substituted-3(2H)-pyridazinone-2-ylacetates (53) were tested for analgesic and anti-inflammatory effects. Side effects of the compounds were examined on gastric mucosa. None of the compounds showed gastric ulcerogenic effect compared with reference NSAIDs. Methyl 6-(4-(4-fluorophenyl)piperazine)-3(2H)-pyridazinone-2-ylacetate was found to be more active than aspirin (ASA) and has shown an anti-inflammatory activity as compared to the standard drug indometacin. These compounds confirms that modification of the chemical group at the position 6 of the 3(2H)-pyridazinone system influences analgesic and anti-inflammatory activities (Sahina at al., 2004). The NSAIDs are efficacious for the treatment of pain associated with inflammatory disease.



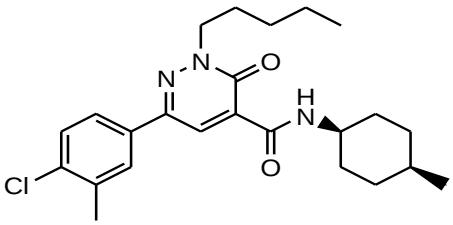
(1)



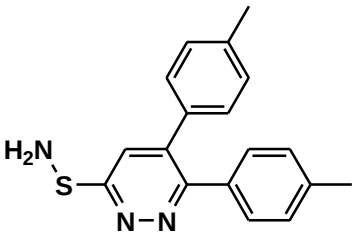
(2)



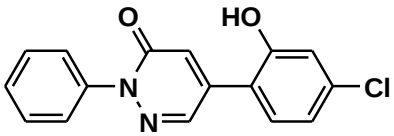
(3)



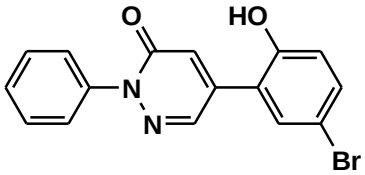
(4)



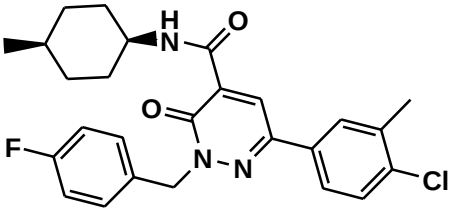
(5)



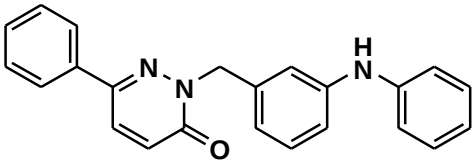
(6)



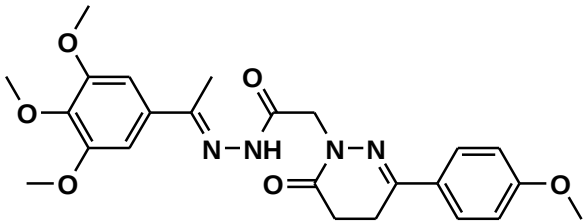
(7)



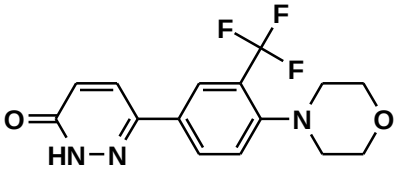
(8)



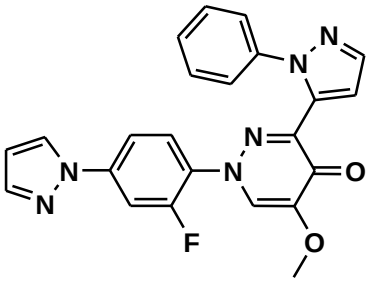
(9)



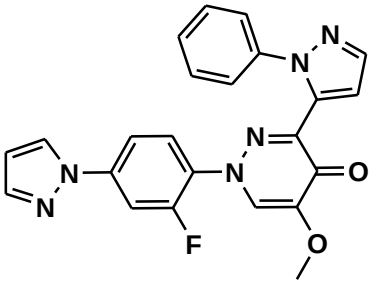
(10)



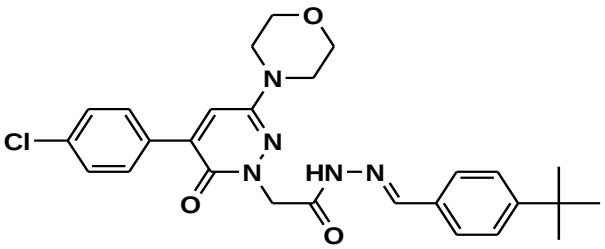
(11)



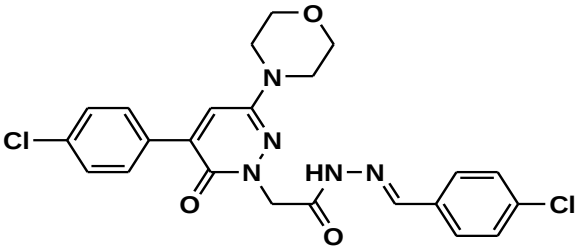
(12)



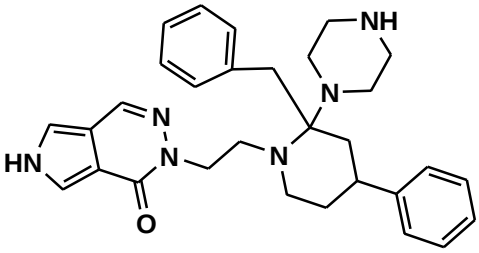
(13)



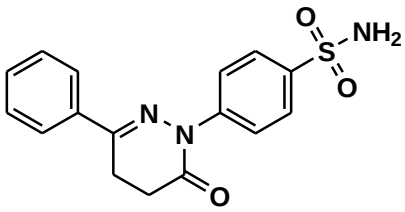
(14)



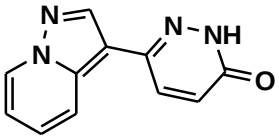
(15)



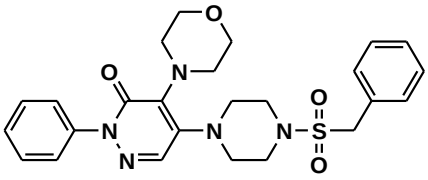
(16)



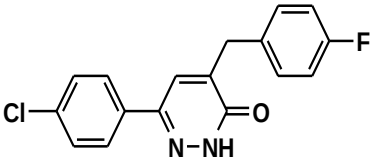
(17)



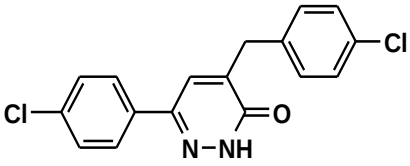
(18)



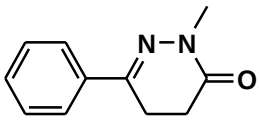
(19)



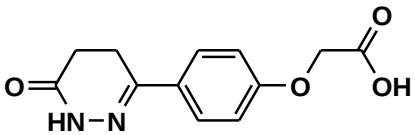
(20)



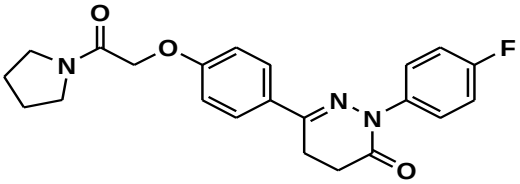
(21)



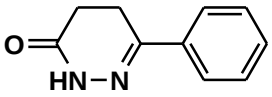
(22)



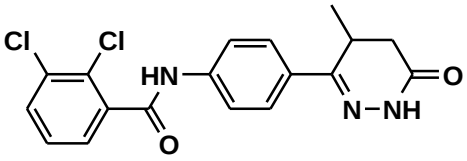
(23)



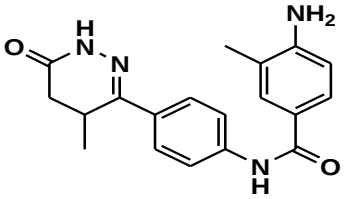
(24)



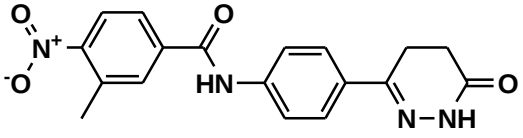
(25)



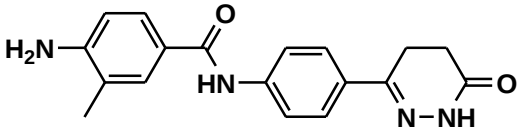
(26)



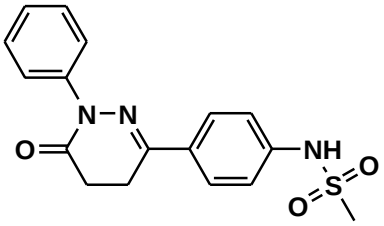
(27)



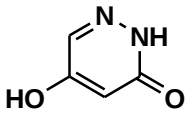
(28)



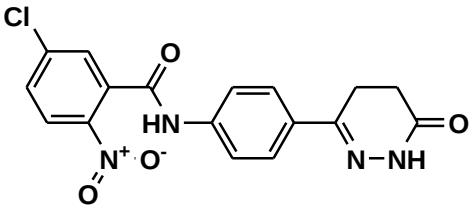
(29)



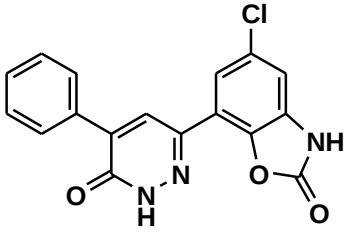
(30)



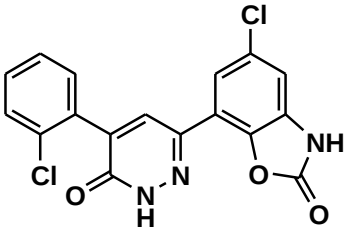
(31)



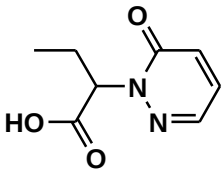
(32)



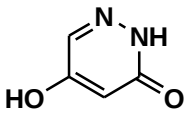
(33a)



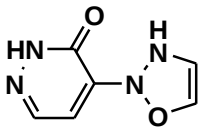
(33b)



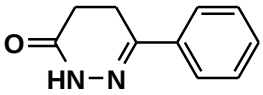
(34)



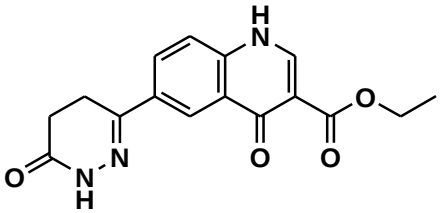
(35)



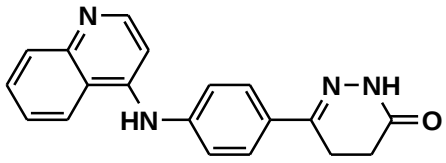
(36)



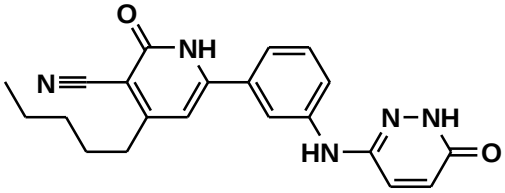
(37)



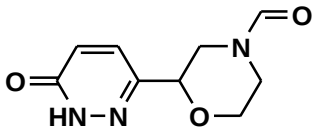
(38)



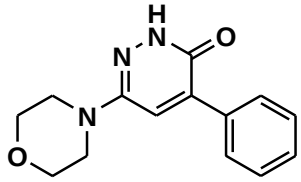
(39)



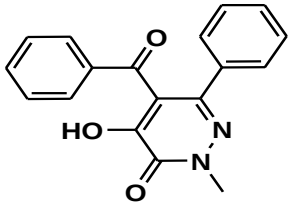
(40)



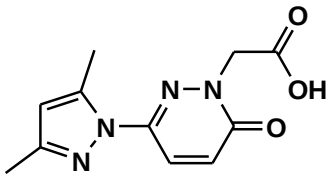
(41)



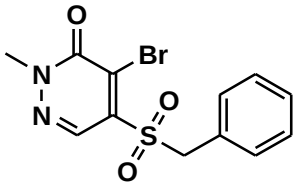
(42)



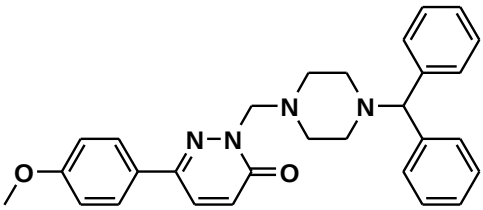
(43)



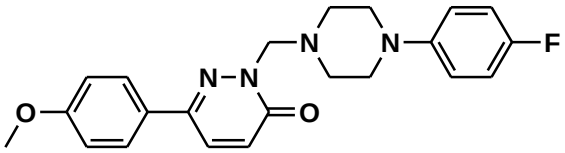
(44)

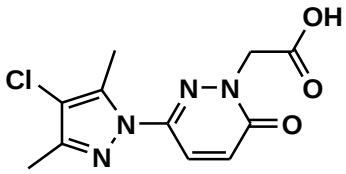


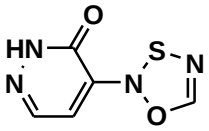
(45)

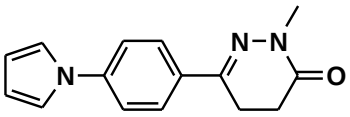


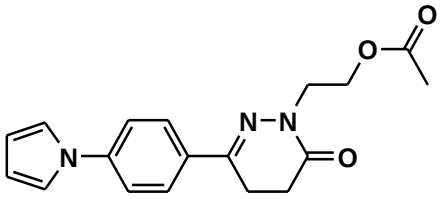
(46)

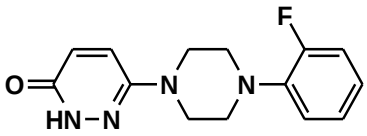

(47)

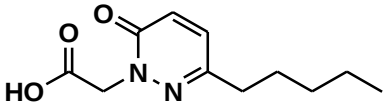

(48)

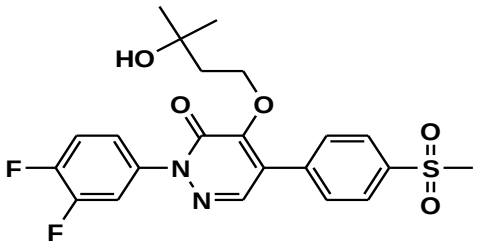

(49)

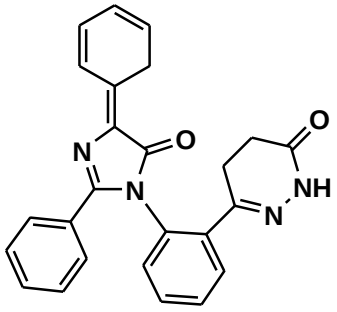

(50)

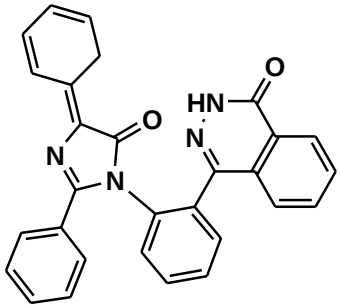

(51)

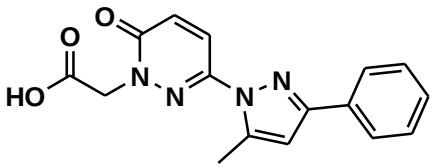

(52)

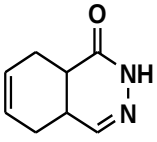

(53)

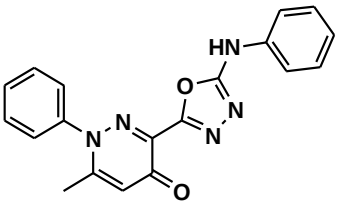

(54)

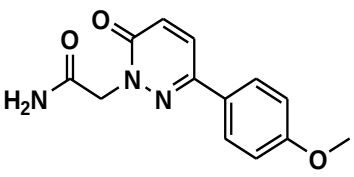

(55)

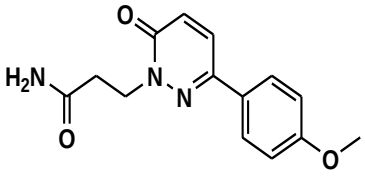

(56)


(57)


(58)


(59)


(60)


(61)

Clinical experience with marketed selective COX-2 inhibitors (celecoxib, rofecoxib, and valdecoxib) has confirmed the utility of these agents in the treatment of inflammatory pain with an improved gastrointestinal safety profile relative to NSAID comparators. These COX-2 inhibitors belong to the same structural class. Each contains a core heterocyclic ring with two appropriately substituted phenyl rings appended to adjacent atoms. The vicinally disubstituted pyridazinones as potent and selective COX-2 inhibitors, lead compound in the series, ABT-963 [2-(3,4-difluoro-phenyl)-4-(3-hydroxy-3-

methyl-butoxy)-5-(4-methanesulfonyl-phenyl)-2H-pyridazin-3-one] (54), has excellent selectivity (ratio of 276, COX-2/COX-1) in human whole blood, improved aqueous solubility compared with celecoxib and rofecoxib, high oral anti-inflammatory potency in vivo, and gastric safety in the animal studies. After oral use, ABT-963 reduced PG-E2 production in the rat carrageenan air pouch model (ED50 of 0.4 mg/kg) and reduced the edema in the carrageenan induced paw edema model with an ED30 of 1.9 mg/kg. ABT-963 dose dependently reduced nociception in the carrageenan hyperalgesia model (ED50 of 3.1 mg/kg). After 14 days of dosing in the adjuvant arthritis model, ABT-963 had an ED^{50} of 1.0 mg/kg in reducing the swelling of the hind paws. The ABT-963 significantly reduced bone loss and soft tissue destruction. ABT-963 is a highly selective COX-2 inhibitor that may have utility in the treatment of the pain and inflammation associated with arthritis (Harris at al., 2004).

Various derivatives of pyrrolo[3,4-d]pyridazinone modified at the pyrrole and pyridazine rings were synthesized and some of them were tested in vitro through anticancer screenings. None of the eight compounds assayed blocked the cell cycle regulating CDK1/cyclin B kinase, whereas two of the six compounds tested were active in anticancer screening at the cell experiments at a concentration of > or=10^{-5}M/l (Malinka at al., 2004). A conformationally constrained pyridazinone E(ag)-base PNA-monomer 2 capable of binding thymine in a triplex motif was synthesised. A bis-PNA with the E(ag)-base incorporated in the Hoogsteen strand was hybridised with a complementary DNA. Surprisingly, no significant difference was found in the thermodynamic parameters (DeltaH degrees, DeltaS degrees and DeltaG degrees) for PNA-DNA triplex formation involving 2 or the unconstrained analogue 1 (Olsen at al., 2004).

The6-[(4-arylidene-2-phenyl-5-oxoimidazolin-1-yl)phenyl]-4,5-dihydro-3(2H)-pyridazinone (55) and 4-[(4-arylidene-2-phenyl-5-oxoimidazolin-1-yl)phenyl]-1(2H)-phthalazinone derivatives (56) were synthesized by reacting 6-(4-aminophenyl)-4,5-dihydro-3(2H)-pyridazinone or 4-(4-amino-phenyl)-1(2H)-phthalazinone compound with different 4-arylidene-2-phenyl-5(4H)-oxazolone derivatives were tested for vasodilator activities both in vitro and in vivo. Some pyridazinone derivatives showed appreciable activity (Demirayak at al., 2004). Amide derivatives of [6-(5-methyl-3-phenyl-pyrazole-1-yl)-3(2H)-pyridazinone-2-yl]acetic acid (57) were tested for their in vivo analgesic and anti-inflammatory activity. Some compounds were more potent than that of aspirin as an analgesic and indomethacin as an anti-inflammatory drug, respectively. Inhibitor activity of the active compounds on COX isoforms was also tested and found that these derivatives did not exert their analgesic and anti-inflammatory activities through COX inhibition and other mechanisms might be involved (Banoglu at al., 2004).

The discovery and optimization of a class of non-peptidyl, pyridazinone derived melanocortin subtype-4 receptor agonists is disclosed (Ujjainwalla at al., 2003). Selective α1-AR antagonists, synthesized alkoxyarylpiperazinylalkylpyridazinone derivatives and were tested for their affinity toward α1- and α2-AR and toward the 5-HT_{1A} receptor. α1-AR affinity data are in the subnanomolar range, with 3 showing an affinity of 0.052 nM, about 5-fold higher than prazosin. None of the studied compounds was found to be α1/α2 selective, but 8 showed an interesting 5-HT_{1A}/α1 affinity ratio of 119 (Betti at al., 2003). The toxicities and anti-feedant activities of thirteen asymmetrical 1,3,4-oxadiazoles containing a 2H-pyridazin-3-one group were tested. The compounds were shown to possess considerable activity in retarding the development of larvae of a number of Lepidoptera, but they were all inactive against Homoptera, Diptera and Acarina. The compounds had powerful anti-feedant activity comparable with that of azadirachtin. The toxic symptoms of the poisoned larvae indicated that the compounds were novel insect growth regulators with a mode of action that might be similar to the chitin-synthesis inhibition of oxadiazole compounds and/or the juvenile hormone effect of pyridazinonecompounds (Huang at al., 2003). The synthesis and in vitro and in vivo pharmacological test of a series of phthalazinone/ pyridazinone hybrids with both PDE-3 and PDE-4 inhibitory activities are described. These compounds combine the pharmacophores of discovered 4a,5,8,8a-tetrahydro-2H-phthalazin-1-one (58) type inhibitors of PDE-4 and the well-known 2H-pyridazin-3-one-type PDE3 inhibitors such as the tetrahydrobenzimidazoles. Most of the compounds are pharmacologically spoken PDE-3/PDE-4 hybrids. All hybrids show potent PDE-4 inhibitory activity (pIC_{50}=7.0-8.7), whereas the pIC_{50} values for inhibition of PDE-3 vary from 5.4 to 7.5. In general, analogues with a 5-methyl-4,5-dihydropyridazinone moiety exhibit the highest PDE-3 inhibitory activities. The highest in vivo antiinflammatory activity is displayed by phthalazinones, at a dose of 30 μmol/kg po, 46% inhibition of AA induced mouse ear edema. No correlation was found between the in vitro PDE-3 and/or PDE-4 inhibitory activity and the in vivo antiinflammatory capacity after oral dosing (Van der Mey at al., 2003). Pyridazinone-arylpiperazine derivatives suggested some structural features that a compound should have to show high affinity and good selectivity for α1 adrenoceptors (AR) with respect to α2-AR. Two classes of alkoxyphenylpiperazinylheptylpyridazinones were test the effect of the alkoxy substituent on affinity and selectivity. As expected, affinity increased with larger alkoxy groups. Affinity values are all comparable with that of the reference drug prazosin, with the exception of a compound found 4.5-fold more active than prazosin (Betti at al., 2003).

A series of 5-[1-aryl-1,4-dihydro-6-methylpyridazin-4-one-3-yl] -2-arylamino-1,3,4-oxadiazoles (59), were synthesized based on bioisosterism and tested in vivo against wheat leaf rust, *Puccinia recondita*. These compounds were shown to be fungicidally active, and their activity was influenced by the nature of the substituents. By using the three-dimensional quantitative structure-activity relationships (3D-QSAR) method of comparative molecular

field analysis (CoMFA), we have studied the SAR of the compounds containing both pyridazinone-substituted 1,3,4-thiadiazoles and pyridazinone-substituted 1,3,4-oxadiazoles. The 3D-QSAR modes gave good correlation between the variations on percent inhibition and the steric-electrostatic properties. The results are consistent with a common mode of action for the pyridazinone-substituted 1,3,4-thiadiazoles and the pyridazinone-substituted 1,3,4-oxadiazoles, which further confirms that the 1,3,4-oxadiazole ring is a bioisosteric analogue of the 1,3,4-thiadiazole ring (Zou at al., 2002). The 3-O-substituted benzyl pyridazinone compounds were tested for their cyclooxygenase (COX) inhibitory activity and COX-2 selectivity. Among these compounds, some compounds have shown in vitro COX-2 selectivity. One compound showed 32% anti-inflammatory activity at 30 mg/kg dose (Chintakunta at al., 2002). A series of 3-pyridazinones carrying morpholino, arylpiperidino and arylpiperazino moiety in the position 6 were tested for antinociceptive activity. In the modified Koster test in mice 4-(4-fluorophenyl) piperazine was found the most active compound. Most of the compounds were more active than aspirin in the antinociceptive activity (Gokçe at al., 2001).

A series of pyridazin-3(2H)-one derivatives were tested for their in vitro affinity toward both α1- and α2-adrenoceptors by radio-ligand receptor binding assays. All target compounds were showed good affinities for the α1-adrenoceptor, with K(i) values in the low nanomolar range. The polymethylene chain constituting the spacer between the furoylpiperazinyl pyridazinone and the arylpiperazine moiety was shown to influence the affinity and selectivity of these compounds. A gradual increase in affinity was observed by lengthening the polymethylene chain up to a maximum of seven carbon atoms. In addition, a compound has a very interesting α1- adrenoceptors affinity (1.9 nM), was also shown to be a highly selective α1- adrenoceptor antagonist, the affinity ratio for α2- and α1-adrenoceptors being 274. To gain insight into the structural features required for α1 antagonist activity, the pyridazinone derivatives were submitted to a pharmacophore generation procedure using the program Catalyst (Barbaro at al., 2001). An optically pyridazinones were synthesized and identified as a nonprostanoid PGI2 agonist. It inhibited ADP-induced aggregation of human platelets with an IC_{50} value of 0.081 μM and has high oral bioavailability (56%) with a long half-life (4.3 h) in rats (Tsubaki at al., 2000). Various [6-(4-methoxyphenyl)-3(2H)-pyridazinone-2-yl]-acetamide (60) and 3-[6-(4-methoxyphenyl)-3(2H)-pyridazin-one-2-yl]propanamide (61) derivatives were synthesized. Antinociceptive activity of the compounds has been tested by modified Koster's Test in mice, using aspirin as a reference. All the compounds (at 100 mg/kg dose) except few were found more potent than aspirin. Compound in the group of acetamide derivatives and compound in the group of propanamides exhibited the highest antinociceptive activity. The propanamides have generally been found more potent than acetamides. The quantitative relationships between some structural parameters (like log P, parachor, molar refractivity, and molecular connectivity indices) and antinociceptive activity of the compounds have been tested (Dogruer at al., 2000).

Pyridazinones have drawn a substantial attention within the field of research analysis and development. The moiety is a subject matter of intensive research because of its wide spectrum of biological activities and therapeutic applications. The synthesis of pyridazinone and investigation of their chemical and biological activities have gained additional importance in recent years. In this review, we have compiled and discussed various biological and therapeutic potential of pyridazinone derivatives (Akhtar at al., 2016). Pyridazinone and its derivatives have various ranges of biological and pharmacological activities including anti-inflammatory, antifeedant, anticonvulsant, antidiabetic, herbicidal, anti-hypertensive, antiplatelet, antifungal, antibacterial, anticancer and antiviral activities. Pyridazinone magic moiety has allowed the generation of a huge number of structurally different derivatives. Most of the pyridazinone derivatives are derived from substitution of the pyridazinone oxygen, nitrogen and C4/C5/C6 carbon positions. Pyridazinone can be used for the synthesis of a large variety of heterocyclic compounds and as intermediate for a broad spectrum of drug synthesis (Abdelbaset et al., 2018; Ahmad et al., 2018; Barberot et al., 2018; Boukharsa et al., 2018; Çetin and Bildirici, 2018; Ewida et al., 2018; Hu et al., 2018; Ibrar et al., 2018; Murineddu et al., 2018; Wang et al., 2018).

CONCLUSIONS

The study reported the synthesis and biological activities of pyridazine/pyridazinone derivatives. Pyridazin-3(2H)-ones are nitrogen-rich heterocyclic compounds of considerable medicinal interest due to their diverse biological activities. The progressive development of this attractive scaffold is for the design and synthesis of new pyridazinone-based therapuic agents. The biological activities studies revealed that pyridazine/ pyridazinone derivatives were showed diverse biological activities against various diseases and infection caused by different pathogenic strains. The pyridazine/ pyridazinone derivatives were also exhibited large no of chemical and agrochemical activities.

REFERENCES

Abd El-Ghaffar, N.F., Mohamed, M.K., Kadah, M.S., Radwan, M.A., Sayed, G.H., Abdel, Al, S.N., 2011. Synthesis and anti-tumor activities of some new pyridazinones containing the 2-phenyl-1H-indolyl moiety. Journal of Chemical and Pharmaceutical Research 3(3), 248-259.

Abdelbaset, M.S., Abuo-Rahma, G.E.-D.A., Abdelrahman, M.H., Ramadan, M., Youssif, B.G.M., Bukhari, S.N.A., Mohamed, M.F.A., Abdel-Aziz, M., 2018. Novel pyrrol-2(3H)-ones and pyridazin-3(2H)-ones carrying quinoline scaffold as anti-proliferative tubulin polymerization inhibitors. Bioorganic Chemistry 80, 151-163.

Abdel-Rahman, H.M., Abdel-Aziz, M., Tinsley, H.N., Gary, B.D., Canzoneri, J.C., Piazza, G.A., 2016. Design and Synthesis of Substituted Pyridazinone-1-Acetylhydrazones as Novel Phosphodiesterase 4 Inhibitors. Archive der Pharmazei (Weinheim). 2016; 349(2), 104-111.

Abouzid, K., Hakeem, M.A., Khalil, O., Maklad, Y., 2008. Pyridazinone derivatives: Design, synthesis, and in vitro vasorelaxant activity. Bioorganic and Medicinal Chemistry 16, 382-389.

Ahmad, S., Alam, O., Naim, M.J., Shaquiquzzaman, M., Alam, M.M., Iqbal, M., 2018. Pyrrole: An insight into recent pharmacological advances with structure activity relationship. European Journal of Medicinal Chemistry 157, 527-561.

Akhtar, W., Verma, G., Khan, M.F., Shaquiquzzaman, M., Rana, A., Anwer, T., Akhter, M., Alam, M.M., 2018, Synthesis of Hybrids of Dihydropyrimidine and Pyridazinone as potential Anti-Breast Cancer Agents. Mini Review in Medicinal Chemistry18(4), 369-379.

Akhtar, W., Shaquiquzzaman, M., Akhter, M., Verma, G., Khan, M.F., Alam, M.M., 2016. The therapeutic journey of pyridazinone. European Journal of Medicinal Chemistry 123, 256-281.

Allcock, R.W., Blakli, H., Jiang, Z., Johnston, K.A., Morgan, K.M., Rosair, G.M., Iwase, K., Kohno, Y., Adams, D.R., 2011. Phosphodiesterase inhibitors. Part 1: Synthesis and structure-activity relationships of pyrazolopyridine-pyridazinone PDE inhibitors developed from ibudilast. Bioorganic and Medicinal Chemistry Letters 21(11), 3307-12.

Allerton, C.M., Andrews, M.D., Blagg, J., Ellis, D., Evrard, E., Green, M.P., Liu, K.K., McMurray, G., Ralph, M., Sanderson, V., Ward, R., Watson, L., 2009. Design and synthesis of pyridazinone-based 5-HT(2C) agonists. Bioorganic and Medicinal Chemistry Letters 19(19), 5791-5795.

Amin, E.N., Abdel-Alim, A.A., Abdel-Moty, S.G., El-Shorbagi, A.N., Abdel-Rahman, M. Sh., 2008. Synthesis of new 4,5-3(2H) pyridazinone derivatives and their cardiotonic, hypotensive, and platelet aggregation inhibition activities. Archives of Pharmeutical Research 33(1), 25-46.

Asif, M., 2015. A mini review on biological activities of pyridazinone derivatives as antiulcer, antisecretory, antihistamine and particularly against histamine H3R. Mini Review in Medicinal Chemistry 14(13), 1093-103.

Banoğlu, E., Akoğlu, C., Unlü, S., Ergün, B.C., Küpeli, E., Yeşilada, E., Sahin, M.F., 2005. Synthesis of amide derivatives of [6-(3,5-dimethylpyrazol-1-yl)-3(2H)-pyridazinone-2-yl] acetic acid and their analgesic and anti-inflammatory properties. Arzneimittelforschung 55(9), 520-7.

Banoglu, E., Akoğlu, C., Unlü, S., Küpeli, E., Yeşilada, E., Sahin, M.F., 2004. Amide derivatives of [6-(5-methyl-3-phenylpyrazole-1-yl)-3(2H)-pyridazinone-2-yl]acetic acids as potential analgesic and anti-inflammatory compounds. Archive der Pharmazei (Weinheim) 337(1), 7-14.

Bansal, R., Kumar, D., Carron, R., Calle, C. de la., 2009. Synthesis and vasodilatory activity of some amide derivatives of 6-(4-carboxymethyloxyphenyl)-4,5-dihydro-3(2H)-pyridazinone. European Journal of Medicinal Chemistry 44(11), 4441–4447.

Barbaro, R., Betti, L., Botta, M., Corelli, F., Giannaccini, G., Maccari, L., Manetti, F., Strappaghetti, G., Corsano, S., 2002. Synthesis and biological activity of new 1,4-benzodioxan-arylpiperazine derivatives. Further validation of apharmacophore model for alpha (1)-adrenoceptor antagonists. Bioorganic and Medicinal Chemistry 10(2), 361-9.

Barbaro, R., Betti, L., Botta, M., Corelli, F., Giannaccini, G., Maccari, L., Manetti, F., Strappaghetti, G., Corsano, S., 2001. Synthesis, biological evaluation, and pharmacophore generation of new pyridazinone derivatives with affinity toward alpha(1)- and alpha(2)-adrenoceptors. Journal of Medicinal Chemistry 44(13), 2118-32.

Barberot, C., Moniot, A., Allart-Simon, I., Malleret, L., Yegorova, T., Laronze-Cochard, M., Bentaher, A., Médebielle, M., Bouillon, J.-P., Hénon, E., Sapi, J., Velard, F., Gérard, S., 2018. Synthesis and biological evaluation of pyridazinone derivatives as potential anti-inflammatory agents. European Journal of Medicinal Chemistry 146, 139-146.

Barberot, C., Moniot,A., Allart-Simon, I., Malleret, L., Yegorova, T., Laronze-Cochard, M., Bentaher, A., Médebielle, M., Bouillon, J.P., Hénon, E., Sapi, J., Velard, F., Gérard, S., 2018. Synthesis and biological evaluation of pyridazinone derivatives as potential anti-inflammatory agents. European Journal of Medicinal Chemistry146, 139-146.

Bashir, R., Yaseen, S., Ovais, S., Ahmad, S., Hamid, H., Alam, M.S., Samim, M., Javed, K., 2012. Synthesis and biological evaluation of some novel sulfamoylphenyl-pyridazinone as anti-inflammatory agents (Part-II). Journal of Enzyme Inhibition and Medicinal Chemistry 27(1), 92-6.

Betti, L., Corelli, F., Floridi, M., Giannaccini, G., Maccari, L., Manetti, F., Strappaghetti, G., Botta, M., 2003, Alpha1-adrenoceptor antagonists. 6. Structural optimization of pyridazinone-arylpiperazines. Study of the influence on affinity and selectivity of cyclic substituents at the pyridazinone ring and alkoxy groups at the arylpiperazine moiety. Journal of Medicinal Chemistry 46(16), 3555-8.

Betti, L., Floridi, M., Giannaccini, G., Manetti, F., Strappaghetti, G., Tafi, A., Botta, M., 2003. alpha1-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. Bioorganic and Medicinal Chemistry Letters 13(2), 171-3.

Betti, L., Zanelli, M., Giannaccini, G., Manetti, F., Schenone, S., Strappaghetti, G., 2006. Synthesis of new piperazine-pyridazinone derivatives and their binding affinity toward alpha1-, alpha2-adrenergic and 5-HT1A serotoninergic receptors. Bioorganic and Medicinal Chemistry 14(8), 2828-36.

Bligt-Lindén, E., Pihlavisto, M., Szatmári, I., Otwinowski, Z., Smith, D.J., Lázár, L., Fülöp, F., Salminen, T.A., 2013. Novel pyridazinone inhibitors for vascular adhesion protein-1 (VAP-1): old target-new inhibition mode. Journal of Medicinal Chemistry 56(24), 9837-48.

Boukharsa, Y., Lakhlili, W., El harti, J., Meddah, B., Tiendrebeogo, R.Y., Taoufik, J., El Abbes Faouzi, M., Ibrahimi, A., Ansar, M.h., 2018. Synthesis, anti-inflammatory evaluation in vivo and docking studies of some new 5-(benzo[b]furan-2-ylmethyl)-6-methyl-pyridazin-3(2H)-one derivatives. Journal of Molecular Structure 1153, 119-127.

Caliskan-Ergün, B., Süküroğlu, M., Coban, T., Banoğlu, E., Suzen, S., 2008. Screening and evaluation of antioxidant activity of some pyridazine derivatives. Journal of Enzyme Inhibition and Medicinal Chemistry 23(2), 225-9.

Cao, S., Qian, X., Song, G., Chai, B., Jiang, Z., 2003. Synthesis and anti feedant activity of new oxadiazolyl 3(2H)-pyridazinones. Journal of Agriculture and Food Chemistry 51, 152-155.

Cao, S., Wei, N., Zhao, C., Li, L., Huang, Q., Qian, X., 2005. Syntheses, antifeedant activity, and QSAR analysis of new oxa(thia)diazolyl 3(2H)-pyridazinones. Journal of Agriculture and Food Chemistry 53(8), 3120-3125.

Catarzi, D., Varano, F., Falsini, M., Varani, K., Vincenzi, F., Pasquini, S., Dal Ben, D., Colotta, V., 2018. Development of novel pyridazinone-based adenosine receptor ligands. Bioorganic and Medicinal Chemistry Letters 28(9), 1484-1489.

Çetin, A., Bildirici, İ., 2018. A study on synthesis and antimicrobial activity of 4-acyl-pyrazoles. Journal of Saudi Chemical Society 22, 279-296.

Chan, A.H., Yi, S.W., Weiner, E.M., Amer, B.R., Sue, C.K., Wereszczynski, J., Dillen, C.A., Senese, S., Torres, J.Z., McCammon, J.A., Miller, L.S., Jung, M.E., Clubb, R.T., 2017. NMR structure-based optimization of Staphylococcus aureus sortase A pyridazinone inhibitors. Chemical Biology & Drug Design 90(3), 327-344.

Cherng, S.C., Huang, W.H., Shiau, C.Y., Lee, A.R., Chou, T.C., 2006. Mechanisms of antiplatelet activity of PC-09, a newly synthesized pyridazinone derivative. European Journal of Pharmacology 532(1-2), 32-37.

Chintakunta, V.K., Akella, V., Vedula, M.S., Mamnoor, P.K., Mishra, P., Casturi, S.R., Vangoori, A., Rajagopalan, R., 2002. 3-O-substituted benzyl pyridazinone derivatives as COX inhibitors. European Journal of Medicinal Chemistry 37(4), 339-347.

Coelho, A., Sotelo, E., Fraiz, N., Yanez, M., Laguna, R., Cano, E., Ravina, E., 2004. Pyridazines. Part 36: Synthesis and antiplatelet activity of 5-substituted-6-phenyl-3(2H)-pyridazinones. Bioorganic and Medicinal Chemistry Letters 4, 321-324.

Costas, T., Besada, P., Piras, A., Acevedo, L., Ya-ez, M., Orallo, F., Laguna, R., 2010. New pyridazinone derivatives with vasorelaxant and platelet anti aggregatory activities. Bioorganic and Medicinal Chemistry Letters 20(22), 6624-6627.

Costas, T., Costas-Lago, M.C., Vila, N., Besada, P., Cano, E., Terán, C., 2015. New platelet aggregation inhibitors based on pyridazinone moiety. European Journal of Medicinal Chemistry 94, 113-22.

Dandu, R.R., Gruner, J.A., Mathiasen, J.R., Aimone, L.D., Hostetler, G., Benfield, C., Bendesky, R.J., Marcy, V.R., Raddatz, R., Hudkins, R.L., 2011. Synthesis and evaluation of pyridazinone-phenethylamine derivatives as selective and orally bioavailable histamine H3 receptor antagonists with robust wake-promoting activity. Bioorganic and Medicinal Chemistry Letters 21(21), 6362-5.

Demirayak, S., Karaburun, A.C., Kayagil, I., Erol, K., Sirmagul, B., 2009. Some pyridazinone and phthalazinone derivatives and their vasodilator activities. Archives of Pharmaceutical Research 27(1), 13-8.

Demirayak, S., Karaburun, A.C., Beis, R., 2004. Some pyrrole substituted aryl pyridazinone and phthalazinone derivatives and their antihypertensive activities. European Journal of Medicinal Chemistry 39(12), 1089-95.

Demirayak, S., Karaburun, A.C., Kayagil, I., Erol, K., Sirmagul, B., 2004. Some pyridazinone and phthalazinone derivatives and their vasodilator activities. Archives of Pharmaeutical Research 27(1), 13-18.

Desai, V.R., Hunagund, S.M., Pujar, M.S., Basanagouda, M., Kadadevarmath, J.S., Sidarai, A.H., 2017. Photo-physical Properties of a Novel and Biologically Active 3(2H)-Pyridazinone Derivative Using Solvatochromic Approach. Journal of Fluorescence 27(5), 1793-1800.

Desai, V.R., Hunagund, S.M., Basanagouda, M., Kadadevarmath, J.S., Sidarai, A.H., 2017. Analysis of Fluorescence Quenching for Newly Synthesized Biologically Active 3(2H)-pyridazinone Derivative by Aniline. Journal of Fluorescence 27(5), 1839-1846.

Dogruer, D.S., Sahin, M.F., Kupeli, E., Yesilada, E., 2003. Synthesis and analgesic and anti-inflammatory activity of new pyridazinones. Turkey Journal of Chemistry 27, 727.

Dogruer, D.S., Sahin, M.F., Unlü, S., Ito, S., 2000. Studies on some 3(2H)-pyridazinone derivatives with antinociceptive activity. Archive der Pharmazei (Weinheim) 333(4), 79-86.

Dorsch, D., Schadt, O., Stieber, F., Meyring, M., Grädler, U., Bladt, F., Friese-Hamim, M., Knühl, C., Pehl, U., Blaukat, A., 2015. Identification and optimization of pyridazinones as potent and selective c-Met kinase inhibitors. Bioorganic and Medicinal Chemistry letters. 2015; 25(7), 1597-1602.

Dündar, Y., Gökçe, M., Küpeli, E., Sahin, M.F., 2007. Synthesis and analgesic and anti-inflammatory activity of ethyl (6-

substituted-3 (2H)-pyridazinone-2-yl)acetate derivatives. Arzneimittelforschung 57(12), 777-81.

Edith, G., Ales, K., Winfried, W., Marija, K., 2009. Synthesis and structure investigations of potential sedative and anticonvulsant Hydroxy- and Acetoxy-N-(3-oxobutyl)-pyrido [2,3-d]pyridazinones. Monatsheftefür Chemie 133, 1177-1185.

El Maatougui, A., Azuaje, J., Sotelo, E., Caamaño, O., Coelho, A., 2011. Silica-supported aluminum chloride-assisted solution phase synthesis of pyridazinone-based antiplatelet agents. ACS Combinatorial Science 13(1), 7-12.

Elagawany, M., Ibrahim, M.A., Ali Ahmed. H.E., El-Etrawy. A.S.H., Ghiaty, A., Abdel-Samii, Z.K., El-Feky, S.A., Bajorath, J., 2013. Design, synthesis, and molecular modelling of pyridazinone and phthalazinone derivatives as protein kinases inhibitors. Bioorganic and Medicinal Chemistry Letters 23(7), 2007-13.

Ewida, M.A., Abou El Ella, D.A., Lasheen, D.S., Ewida, H.A., El-Gazzar, Y.I., El-Subbagh, H.I., 2018. Imidazo[2′,1′:2,3]thiazolo[4,5-d]pyridazinone as a new scaffold of DHFR inhibitors: Synthesis, biological evaluation and molecular modeling study. Bioorganic Chemistry 80, 11-23.

Frolov, E.B., Lakner, F.J., Khvat, A.V., VIvachtchenko, A., 2004. An efficient synthesis of novel 1,3-oxazolo[4,5-d]pyridazinones. Tetrahedron Letters 45, 4693-4696.

Fuks, B., Talaga, P., Huart, C., Hénichart, J.P., Bertrand, K., Grimée, R., Lorent, G., 2005. In vitro properties of 5-(benzylsulfonyl)-4-bromo-2-methyl-3(2H)-pyridazinone: a novel permeability transition pore inhibitor. European Journal of Pharmacology 519(1-2), 24-30.

Gokce, M., Dogruer, D., Sahin, M.F., 2001. Synthesis and antinociceptive activity of 6- substituted-3-pyridazinone derivatives. Farmaco II 56, 233.

Gökçe, M., Bakir, G., Sahin, M.F., Küpeli, E., Yeşilada, E., 2005. Synthesis of new Mannich bases of aryl-pyridazinones as analgesic and anti-inflammatory agents. Arzneimittelforschung 55(6), 318-325.

Gokçe, M., Dogruer, D., Sahin, M.F., 2001, Synthesis and antinociceptive activity of 6-substituted-3-pyridazinone derivatives. Farmaco Il 56(3), 233-237.

Gökçe, M., Sahin, M.F., Küpeli, E., Yeşilada, E., 2004. Synthesis and evaluation of the analgesic and anti-inflammatory activity of new 3(2H)-pyridazinone derivatives. Arzneimittelforschung 54(7), 396-401.

Gökçe, M., Utku, S., Küpeli, E., 2009. Synthesis and analgesic and anti-inflammatory activities 6-substituted-3(2H)-pyridazinone-2-acetyl-2-(p-substituted/nonsubstituted benzal)hydrazone derivatives. European Journal of Medicinal Chemistry 44(9), 3760-3764.

Gong, J., Zheng, Y., Wang, Y., Sheng, W., Li, Y., Liu, X., Si, S., Shao, R., Zhen, Y., 2018. A new compound of thiophenylated pyridazinone IMB5043 showing potent antitumor efficacy through ATM-Chk2 pathway. PLoS One 13(2), e0191984.

Gong, Y., Kent Barbay, J., Kimball, E.S., Santulli, R.J, Carolyn Fisher, M., Dyatkin, A.B., Miskowski, T.A, Hornby, P.J., He, W., 2008. Synthesis and SAR of pyridazinone-substituted phenylalanine amide alpha4 integrin antagonists. Bioorganic and Medicinal Chemistry Letters 18(4), 1331-1335.

Gong. Y., Barbay. J.K., Dyatkin, A.B., Miskowski, T.A., Kimball, E.S., Prouty, S.M., Fisher, M.C., Santulli, R.J., Schneider, C.R., Wallace, N.H., Ballentine, S.A., Hageman, W.E., Masucci, J.A., Maryanoff., B.E., Damiano, B.P., Andrade-Gordon, P., Hlasta, D.J., Hornby, P.J., He, W., 2006. Synthesis and biological evaluation of novel pyridazinone-based alpha4 integrin receptor antagonists. Journal of Medicinal Chemistry 49(11), 3402-3411.

Gràcia, J., Buil, M.A., Castro, J., Eichhorn, P., Ferrer, M., Gavaldà, A., Hernández, B., Segarra, V., Lehner, M.D., Moreno, I., Pagès, L., Roberts, R.S., Serrat, J, Sevilla, S., Taltavull, J., Andrés, M., Cabedo, J., Vilella, D., Calama, E., Carcasona, C., Miralpeix, M., 2016. Biphenyl Pyridazinone Derivatives as Inhaled PDE4 Inhibitors: Structural Biology and Structure-Activity Relationships. Journal of Medicinal Chemistry 59(23), 10479-10497.

Guerrero, M., Puebla, P., Carrón, R., Martín, M. L, Román, L.S., 2008. Assessment of the antihypertensive and vasodilator effects of ethanolic extracts of some Colombian medicinal plants. Journal of Ethnopharmacoly 94, 185–198.

Han, X., Hong, H.X., Quan, Z.Y., Mao, Z.X., Zhong, H.F., Zheng, Y.H., 2002. Synthesis and herbicidal activities of novel 4-(3-trifluoromethylphenyl)-2H-pyridazin-3-one derivatives. Science China Chemistry 53(1), 157-166.

Harris, R.R., Black, L., Surapaneni, S., Kolasa, T., Majest, S., Namovic, M.T., Grayson, G., Komater, V., Wilcox, D., King, L., Marsh, K., Jarvis, M.F., Nuss, M., Nellans, H., Pruesser, L., Reinhart, G.A,, Cox, B., Jacobson, P., Stewart, A., Coghlan, M., Carter, G., Bell, R.L., 2004. ABT-963 [2-(3,4-di-fluoro-phenyl)-4-(3-hydroxy-3-methyl-butoxy)-5-(4-methanesulfonyl-phenyl)-2H-pyrida-zin-3-one], a highly potent and selective disubstituted pyridazinone cyclooxgenase-2 inhibitor. Journal of Pharmacology and Experimental Therapy 311(3), 904-12.

Helm, M.D, Plant, A, Harrity, JP. 2006. A novel approach to functionalised pyridazinone arrays.Organic Biomolecular Chemistry 4(23), 4278-80.

Hu, Z., Wang, C., Han, W., Rossi, K.A., Bozarth, J.M., Wu, Y., Sheriff, S., Myers, J.E., Luettgen, J.M., Seiffert, D.A., Wexler, R.R., Quan, M.L., 2018. Pyridazine and pyridazinone derivatives as potent and selective factor XIa inhibitors. Bioorganic and Medicinal Chemistry Letters 28, 987-992.

Hu, Z., Wang. C, Han. W, Rossi. KA, Bozarth. JM, Wu. Y, Sheriff. S, Myers. JE Jr., Luettgen, JM, Seiffert, DA, Wexler, RR, Quan, ML., 2018. Pyridazine and pyridazinone derivatives as potent and selective

factor XIa inhibitors. Bioorganic and Medicinal Chemistry Letters 28(6), 987-992.

Huang, Q, Kong, Y, Liu, M, Feng, J, Liu, Y., 2008. Effect of oxadiazolyl 3(2H)-pyridazinone on the larval growth and digestive physiology of the armyworm, Pseudaletia separata. Journal of Insect Sciences 8, 19.

Huang, Q, Qian, X, Song, G, Cao, S., 2003. The toxic and anti-feedant activity of 2H-pyridazin-3-one-substituted 1,3,4-oxadiazoles against the armyworm Pseudaletia separata (Walker) and other insects and mites. Pest Managagement Sciences 59(8), 933-9.

Husain, A., Drabu, S, Kumar, N, Alam, MM, Ahmad, A., 2011. Synthesis and biological evaluation of some new pyridazinone derivatives. Journal of Enzyme Inhibition and Medicinal Chemistry 26(5), 742-8.

Ibrahim, HM, Behbehani, H, Elnagdi, MH., 2013. Approaches towards the synthesis of a novel class of 2-amino-5-arylazonicotinate, pyridazinoneand pyrido[2,3-d]pyrimidine derivatives as potent antimicrobial agents. Chemistry Central Journal 7(1),123.

Ibrar, A., Shehzadi, S.A., Saeed, F., Khan, I., 2018. Developing hybrid molecule therapeutics for diverse enzyme inhibitory action: Active role of coumarin-based structural leads in drug discovery. Bioorganic and Medicinal Chemistry 26, 3731-3762.

Jacomini, AP, Silva, MJV, Silva, RGM, Gonçalves, DS, Volpato, H, Basso, EA, Paula, FR, Nakamura, CV, Sarragiotto, MH, Rosa, FA., 2016. Synthesis and evaluation against Leishmania amazonensis of novel pyrazolo[3,4-d]pyridazinone-N-acylhydrazone-(bi)thiophene hybrids. European Journal of Medicinal Chemistry 124, 340-349.

Jerome, KD, Hepperle, ME, Walker, JK, Xing, L, Devraj, RV, Benson, AG, Baldus, JE, Selness, SR.,2010. Discovery of 5-substituted-N-arylpyridazinones as inhibitors of p38 MAP kinase. Bioorganic and Medicinal Chemistry Letters 20(10), 3146-3149.

Jin, X, Wang, Y, Tan, L, He, Y, Peng, J, Hai, L, Wu, Y, Qian, Z., 2015. An efficient injectable formulation with block copolymer micelles for hydrophobic antitumor candidate-pyridazinone derivatives. Nanomedicine (Lond) 10(14), 2153-2165.

Kang, ST, Kim, EY, Achary, R, Jung, H, Park, CH, Yun, CS, Hwang, JY, Choi, SU, Chae, C, Lee, CO, Kim, HR, Ha, JD, Ryu, D, Cho, SY., 2014. Discovery of substituted 6-pheny-3H-pyridazin-3-one derivatives as novel c-Met kinase inhibitors. Bioorganic and Medicinal Chemistry letters 24(21), 5093-7. Erratum in Corrigendum to "Discovery of substituted 6-pheny-3H-pyridazin-3-one derivatives as novel c-Met kinase inhibitors. Bioorganic and Medicinal Chemistry Letters 24, 5093-5097.

Kim, EY, Kang, ST, Jung, H, Park, CH, Yun, CS, Hwang, JY, Byun, BJ, Lee, CO, Kim, HR, Ha, JD, Ryu, DH, Cho, SY., 2016. Discovery of substituted pyrazol-4-yl pyridazinone derivatives as novel c-Met kinase inhibitors. Archives of Pharmaceutical Research 39(4), 453-64.

Kuang, R, Wu, H, Ting, PC, Aslanian, RG, Cao, J, Kim, DW, Lee, JF, Schwerdt, J, Zhou, G, Herr, RJ, Zych, AJ, Yang, J, Lam, SQ, Jenkins, DM, Sakwa, SA, Wainhaus, S, Black, TA, Cacciapuoti, A, McNicholas, PM, Xu, Y, Walker, SS., 2012. optimization of pyridazinone series of glucan synthase inhibitors. Bioorganic and Medicinal Chemistry letters 22(16), 5268-5271.

Kumar, D, Carron, R, La Calle, CD, DP, ndal, JI, Bansal, R., 2010. Synthesis and evaluation of 2- substituted-6-phenyl-4,5-dihydropyridazin-3(2H)-ones as potent inodilators. Acta Pharmaceutica 58(4), 393-405.

Kumar, D., Carron, R., La Calle, C.D., Jindal, D.P., Bansal, R., 2008. Synthesis and evaluation of 2-substituted-6-phenyl-4,5-dihydropyridazin-3(2H)-ones as potent inodilators. Acta Pharmaceutica 58(4), 393-405.

Kunitomo, J., Yoshikawa, M., Fushimi, M., Kawada, A., Quinn, J.F., Oki, H., Kokubo, H., Kondo, M., Nakashima, K., Kamiguchi, N., Suzuki, K., Kimura, H., Taniguchi, T., 2014. Discovery of 1-[2-fluoro-4-(1H-pyrazol-1-yl)phenyl]-5-methoxy-3-(1-phenyl-1H-pyrazol-5-yl)pyridazin-4(1H)-one (TAK-063), a highly potent, selective, and orally active phosphodiesterase 10A (PDE10A) inhibitor. Journal of Medicinal Chemistry 57(22), 9627-43.

Lee, S.G., Kim, J.J., Kweon, D.H., Kang. Y.J., Cho. S.D., Kim. S.K., Yoon, Y.J., 2010. Recent progress in pyridazin-3(2H)-ones Chemistry. Current Medicinal Chemistry 8,1463-1480.

Li, L.S., Zhou, Y., Murphy, D.E., Stankovic, N., Zhao, J., Dragovich, P.S., Bertolini, T., Sun, Z., Ayida, B., Tran, C.V., Ruebsam, F., Webber, S.E., Shah, A.M., Tsan, M., Showalter, R.E., Patel, R., Lebrun, L.A., Bartkowski, D.M., Nolan, T.G., Norris, D.A., Kamran, R., Brooks, J., Sergeeva, M.V., Kirkovsky, L., Zhao, Q., Kissinger, C.R., 2008. Novel HCV NS5B polymerase inhibitors derived from 4-(1',1'-dioxo-1',4'-dihydro-1'lambda(6)-benzo[1',2',4']thiadiazin-3'-yl)-5-hydroxy-2H-pyridazin-3-ones. Part 3: Further optimization of the 2-, 6-, and 7'-substituents and initial pharmacokinetic assessments. Bioorganic and Medicinal Chemistry Letters 18(11), 3446-3455.

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)-pyridazinonewith trifluoroethylation agents. Molecules 14(2), 777-784.

Li, W., Fan, Z., Geng, K., Xu, Y., Zhang, A., 2015. Late-stage diversification of biologically active pyridazinones via a direct C-H functionalization strategy. Organic Biomolecular Chemistry 13(2), 539-548.

Liang, L., Wang, W., Wu, J., Xu, F., Niu, Y., Xu, B., Xu, P., 2013. Rational design, green synthesis, and initial evaluation of a series of full-color tunable fluorescent dyes enabled by the copper-catalyzed N-arylation of 6-phenyl pyridazinones and their application in cell imaging. Chemistry 19(41), 13774-13782.

Liu, Y., Jin, S., Peng, X., Lu, D., Zeng, L., Sun, Y., Ai, J., Geng, M., Hu, Y., 2016. Pyridazinone derivatives displaying highly potent and selective inhibitory activities against c-

Met tyrosine kinase. European Journal of Medicinal Chemistry108, 322-333.

Lu, D., Yan, J., Wang, L., Liu, H., Zeng, L., Zhang, M., Duan, W, Ji, Y., Cao, J., Geng, M., Shen, A., Hu, Y., 2017. Design, Synthesis, and Biological Evaluation of the First c-Met/HDAC Inhibitors Based on Pyridazinone Derivatives. ACS Medicinal Chemistry Letters 8(8), 830-834.

Lu, D., Liu, F., Xing, W., Tong, X., Wang, L., Wang, Y., Zeng, L., Feng, C., Yang, L., Zuo, J., Hu, Y., 2017. Optimization and Synthesis of Pyridazinone Derivatives as Novel Inhibitors of Hepatitis B Virus by Inducing Genome-free Capsid Formation. ACS Infectious Diseases 3(3), 199-205.

Malinka, W, Redzicka, A, Jastrzębska-Więsek, M, Filipek, B, Dybała, M, Karczmarzyk, Z, Urbańczyk-Lipkowska, Z, Kalicki, P., 2011. Derivatives of pyrrolo[3,4-d]pyridazinone, a new class of analgesic agents. European Journal of Medicinal Chemistry 46(10), 4992-4999.

Malinka, W, Redzicka, A, Lozach, O., 2004. New derivatives of pyrrolo[3,4-d]pyridazinone and their anticancer effects. Farmaco Il 59(6), 457-462.

Malinka, W., Redzicka, A., Lozach, O., 2004. New derivatives of pyrrolo[3,4-d]pyridazinone and their anticancer effects. Farmaco II 59, 457-462.

Mantu, D, Moldoveanu, C,, Nicolescu, A,, Deleanu, C, Mangalagiu, II., 2009. A facile synthesis of pyridazinone derivatives under ultrasonic irradiation. Ultrasonic Sonochemistry 16(4), 452-454.

Mogilski, S, Kubacka, M, Redzicka, A, Kazek, G, Dudek, M, Malinka, W, Filipek, B., 2015. Antinociceptive, anti-inflammatory and smooth muscle relaxant activities of the pyrrolo[3,4-d]pyridazinone derivatives: Possible mechanisms of action. Pharmacological and Biochemical Behavior 133, 99-110.

Mou, T, Zhao, Z, You, L, Wang, Q, Fang, W, Lu, J, Peng, C, Zhang, X.,2015. Synthesis and bioevaluation of 4-chloro-2-tert-butyl-5-[2-[[1-[2-[(18)F]fluroethyl]-1H-1,2,3-triazol-4-yl]methyl] phenyl-methoxy]-3(2H)-pyridazinone as potential myocardial perfusion imaging agent with PET. Journal of Labelled Compounds and Radiopharmaceuticals 58(8), 349-354.

Muñoz-Gutiérrez, C, Cáceres-Rojas, D, Adasme-Carreño, F, Palomo, I, Fuentes, E, Caballero, J., 2017. Docking and quantitative structure-activity relationship of bi-cyclic hetero-aromatic pyridazinoneand pyrazolone derivatives as phosphodiesterase 3A (PDE3A) inhibitors. PLoS One 12(12), e0189213.

Murarka, S., Martín-Gago. P., Schultz-Fademrecht. C., Al Saabi. A., Baumann, M, Fansa. EK, Ismail. S, Nussbaumer, P, Wittinghofer, A, Waldmann, H., 2017. Development of Pyridazinone Chemotypes Targeting the PDEδ Prenyl Binding Site. Chemistry 23(25), 6083-6093.

Murineddu, G, Deligia, F, Ragusa, G, García-Toscano, L, Gómez-Cañas, M, Asproni, B, Satta V, Cichero, E, Pazos, R, Fossa, P, Loriga, G, Fernández-Ruiz, J, Pinna, GA., 2018. Novel sulfenamides and sulfonamides based on pyridazinone and pyridazine scaffolds as CB_1receptor ligand antagonists. Bioorganic and Medicinal Chemistry 26(1), 295-307.

Murineddu, G., Deligia, F., Ragusa, G., García-Toscano, L., Gómez-Cañas, M., Asproni, B., Satta, V., Cichero, E., Pazos, R., Fossa, P., Loriga, G., Fernández-Ruiz, J., Pinna, G.A., 2018. Novel sulfenamides and sulfonamides based on pyridazinone and pyridazine scaffolds as CB1 receptor ligand antagonists. Bioorganic and Medicinal Chemistry 26, 295-307.

Ogretir, C., Yarligan, S., Demirayak, S., 2002. Spectroscopic determination of acid dissociation constants of some imidazole derivatives. Journal of Chemical Engineering Data 47, 1396–1400.

Okçelik, B., Unlü, S., Banoglu, E., Küpeli, E., Yeşilada, E., Sahin, M.F., 2003, Investigations of new pyridazinone derivatives for the synthesis of potent analgesic and anti-inflammatory compounds with cyclooxygenase inhibitory activity. Archive der Pharmazei (Weinheim) 336(9), 406-412.

Olsen, A.G., Dahl, O., Nielsen, P.E., 2004. Synthesis and evaluation of a conformationally constrained pyridazinone PNA-monomer for recognition of thymine in triple-helix structures. Bioorganic and Medicinal Chemistry Letters, 14(6), 1551-1554.

Ovais, S., Javed, K., Yaseen, S., Bashir, R., Rathore, P., Yaseen, R., Hameed, A.D., Samim, M., 2013. Synthesis, antiproliferative and anti-inflammatory activities of some novel 6-aryl-2-(p-(methane-sulfonyl)phenyl)-4,5-dihydropyridazi-3(2H)-ones. European Journal of Medicinal Chemistry 67, 352-358.

Ozçelik, A.B., Gökçe, M., Orhan, I., Kaynak, F., Sahin, M.F., 2010. Synthesis and antimicrobial, acetylcholinesterase and butyrylcholinesterase inhibitory activities of novel ester and hydrazide derivatives of 3(2H)-pyridazinone. Arzneimittelforschung 60(7), 452-458.

Partap, S., Akhtar, M.J., Yar, M.S., Hassan, M.Z., Siddiqui, A.A.,2018. Pyridazinone hybrids: Design, synthesis and evaluation as potential anticonvulsant agents. Bioorganic Chemistry 77, 74-83.

Partap, S., Yar, M.S., Hassan, M.Z., Akhtar, M.J., Siddiqui, A.A., 2017. Design, Synthesis, and Pharmacological Screening of Pyridazinone Hybrids as Anticonvulsant Agents. Archive der Pharmazei (Weinheim). 350(10), doi: 10.1002/ardp.201700135.

Pattison, G., Sandford, G., Yufit, D.S., Howard, J.A., Christopher, J.A., Miller, D.D., 2009. Polysubstituted pyridazinones from sequential nucleophilic substitution reactions of tetrafluoropyridazine. Journal of Organic Chemistry 74(15), 5533-5540.

Purohit, A., Radeke, H., Azure, M., Hanson, K., Benetti, R., Su, F., Yalamanchili, P., Yu, M., Hayes, M., Guaraldi, M., Kagan, M., Robinson, S., Casebier, D., 2008. Synthesis and biological evaluation of pyridazinone analogues as potential cardiac positron emission tomography tracers. Jounal of Medicinal Chemistry 51(10), 2954-2970.

Qian, W., Winternheimer, D., Allen, J., 2011. A "click and activate" approach in one-pot synthesis of a triazolyl-pyridazinone library. Organic Letters 13(7), 1682-1685.

Ragusa, G., Bencivenni, S., Morales, P., Callaway, T., Hurst, D.P., Asproni, B., Merighi, S., Loriga, G., Pinna, G.A., Reggio, P.H., Gessi, S., Murineddu, G., 2018. Synthesis, Pharmacological Evaluation, and Docking Studies of Novel Pyridazinone-Based Cannabinoid Receptor Type 2 Ligands. ChemMedChem doi: 10.1002/cmdc.201800152.

Ragusa, G., Gómez-Cañas, M., Morales, P., Rodríguez-Cueto, C., Pazos, M.R., Asproni, B., Cichero, E., Fossa, P., Pinna, G.A., Jagerovic, N., Fernández-Ruiz, J., Murineddu, G., 2017. New pyridazinone-4-carboxamides as new cannabinoid receptor type-2 inverse agonists: Synthesis, pharmacological data and molecular docking. European Journal of Medicinal Chemistry127, 398-412.

Rathish, I.G., Javed, K., Bano, S., Ahmad, S., Alam, M.S., Pillai, K.K., 2009. Synthesis and blood glucose lowering effect of novel pyridazinone substituted benzenesulfonylurea derivatives. European Journal of Medicinal Chemistry 44(6), 2673-8.

Saeed, M.M., Khalil, N.A., Ahmed, E.M., Eissa, K.I., 2012. Synthesis and anti-inflammatory activity of novel pyridazine and pyridazinone derivatives as non-ulcerogenic agents. Archives of Pharmacal Research 35(12), 2077-2092.

Sahina, M.F., Badiçoglu, B., Gökçe, M., Küpeli, E., Yeşilada, E., 2004. Synthesis and analgesic and antiinflammatory activity of methyl 6-substituted-3(2h)-pyridazinone-2-ylacetate derivatives. Archive der Pharmazei (Weinheim) 337(8), 445-52.

Saini, M., Mehta, D.K., Das, R., Saini, G., 2016. Recent Advances in anti-inflammatory potential of Pyridazinone Derivatives. Mini Review in Medicinal Chemistry 16(12), 996-1012.

Sayed, G.H., Sayed, M.A., Mahmoud, M.R., Shaaban, S.S., 2002. Synthesis and reactions of new pyridazinone derivatives of expected antimicrobial activities. Egyptian Journal of Chemistry 45, 767.

Siddiqui, A.A., Abdullah, M.M., Arora, M., Islam, M., Ahmad, S.R., 2006. Synthesis of novel pyridazinones possessing anticonvulsant activity. Indian Drugs 43(10), 790-794.

Siddiqui, A.A., Mishra, R., Shaharyar, M., 2002. Synthesis and pharmacological characterization of a novel nitric oxidereleasing diclofenac derivative containing a benzofuroxan moiety. European Journal of Medicinal Chemistry 45, 2283-2290.

Siddiqui, A.A., Mishra, R., Shaharyar, M., 2010. Synthesis, characterization and antihypertensive activity of pyridazinone derivatives. European Journal of Medicinal Chemistry 45(6), 2283-2290.

Singh, J., Sharma, D., Bansal, R., 2017. Pyridazinone: an attractive lead for anti-inflammatory and analgesic drug discovery. Future Medicinal Chemistry 9(1), 95-127.

Sivakumar, R., Anbalagan, N., Gunasekaran, V., Leonard, J.T., 2009. Synthesis and anticonvulsant activity of novel 1-substituted-1,2-dihydro-pyridazine-3,6-diones. Biological & Pharmaceutical Bulletin 26(10), 1407-1411.

Sivan, S.K., Manga, V., 2010. Molecular docking and 3D-QSAR studies on triazolinone and pyridazinone, non-nucleoside inhibitor of HIV-1 reverse transcriptase. Journal of Molecular Modelling 16(6), 1169-1178.

Soliman, F.M.A., Dawoud, N.T.A., Abdel-Ghaffar, N.F., El-Guindy, M.I., Naguib, H., 2016. Synthesis, Characterization and Antimicrobial Activity of Some New Heterocyclic Compounds Incorporating Pyridazine Moiety. American Chemical Sciences Journal 13(1), 1-14.

Sönmez, M., Berber, I., Akbaş, E., 2006. Synthesis, antibacterial and antifungal activity of some new pyridazinone metal complexes. European Journal of Medicinal Chemistry41(1), 101-105.

Sotelo, E., Fraiz, N., Yanez, M., Terrades, V., Laguna, R., Cano, E., Ravina, E., 2003. Pyridazines. Part XXIX: synthesis and platelet aggregation inhibition activity of 5-substituted-6-phenyl-3(2H)-pyridazinones. Novel aspects of their biological actions. Bioorganic and Medicinal Chemistry 10, 2873- 2882.

Sotelo, S., Centeno, N.B., Rodrigo, J., Ravina, E., 2002. Pyridazine derivatives 32: Stille-based approaches in the synthesis of 5-substituted-6-phenyl-3(2H)-pyridazinones. Tetrahedron Letters 58, 2389.

Steuber, H., Zentgraf, M., Podjarny, A., Heine, A., Klebe, G., 2006. High-resolution crystal structure of aldose reductase complexed with the novel sulfonyl-pyridazinone inhibitor exhibiting an alternative active site anchoring group. Journal of Molecular Biology 356(1), 45-56.

Süküroglu, M., Caliskan Ergün, B., Unlü, S., Sahin, M.F., Küpeli, E., Yesilada, E., Banoglu, E., 2005. Synthesis, analgesic, and anti-inflammatory activities of [6-(3,5-dimethyl-4-chloropyrazole-1-yl)-3(2H)-pyridazinon-2 yl]acetamides. Archives of Pharmacal Research 28(5), 509-517.

Süküroglu, M., Küpeli, E., Banoğlu, E., Unlü, S., Yeşilada, E., Sahin, M.F., 2006. Synthesis and analgesic activity of some 4,6-disubstituted-3(2H)-pyridazinone derivatives. Arzneimittelforschung 56(5), 337-345.

Sukuroglu, M., Onkol, T., Onurdağ, F.K., Akalin, G., Sahin, M.F., 2012. Synthesis and in vitro biological activity of new 4,6-disubstituted 3(2H)-pyridazinone-acetohydrazide derivatives. Zeitschrift für Naturforschung C 67(5-6), 257-265.

Sundar, B.G., Bailey, T., Bacon, E., Aimone, L., Huang, Z., Lyons, J., Raddatz, R., Hudkins, R., 2011. Amine-constrained pyridazinone histamine H_3 receptor antagonists. Bioorganic and Medicinal Chemistry Letters 21(18), 5543-5546.

Sweeney, Z.K., Dunn, J.P., Li, Y., Heilek, G., Dunten, P., Elworthy, T.R., Han, X., Harris, S.F., Hirschfeld, D.R., Hogg, J.H., Huber, W., Kaiser, A.C., Kertesz, D.J., Kim, W., Mirzadegan, T., Roepel, M.G., Saito, Y.D., Silva, T.M., Swallow, S., Tracy, J.L., Villasenor, A., Vora, H., Zhou, A.S., Klumpp, K., 2008. Discovery and optimization of pyridazinone non-nucleoside inhibitors of HIV-1

reverse transcriptase. Bioorganic and Medicinal Chemistry Letters 18(15), 4352-4354.

Tsubaki, K., Taniguchi, K., Tabuchi, S., Okitsu, O., Hattori, K., Seki, J., Sakane, K., Tanaka, H., 2000. A novel pyridazinone derivative as a nonprostanoid PGI2 agonist. Bioorganic and Medicinal Chemistry Letters 10(24), 2787-2790.

Tynebor, R.M., Chen, M.H., Natarajan, S.R., O'Neill, E.A., Thompson, J.E., Fitzgerald, C.E., O'Keefe, S.J., Doherty, J.B., 2011. Synthesis and biological activity of pyridopyridazin-6-one p38 MAP kinase inhibitors. Part 1. Bioorganic and Medicinal Chemistry Letters 21(1), 411-416.

Ujjainwalla, F., Warner, D., Snedden, C., Grisson, R.D., Walsh, T.F., Wyvratt, M.J., Kalyani, R.N., Macneil, T., Tang, R., Weinberg, D.H., Van der Ploeg, L., Goulet, M.T., 2005. Design and syntheses of melanocortin subtype-4 receptor agonists. Part 2: discovery of the dihydropyridazinone motif. Bioorganic and Medicinal Chemistry Letters 15(18), 4023-4028.

Ujjainwalla, F., Warner, D., Walsh, T.F., Wyvratt, M.J., Zhou, C., Yang, L., Kalyani, R.N., MacNeil, T., Van der Ploeg, L.H., Rosenblum, C.I., Tang, R., Vongs, A., Weinberg, D.H., Goulet M.T., 2003. Design and syntheses of melanocortin subtype-4 receptor agonists: evolution of the pyridazinone archetype. Bioorganic and Medicinal Chemistry Letters 13(24), 4431-4435.

Utku, S., Gökçe, M., Orhan, I., Sahin, M.F., 2011. Synthesis of novel 6-substituted-3(2H)-pyridazinone-2-acetyl-2-(substituted/-nonsubstituted benzal)-hydrazone derivatives and acetylcholinesterase and butyryl-cholinesterase inhibitory activities in vitro. Arzneimittelforschung 61(1), 1-7.

Van der Mey, M., Bommelé, K.M., Boss, H., Hatzelmann, A., Van Slingerland, M., Sterk, G.J., Timmerman, H., 2003. Synthesis and structure-activity relationships of cis-tetrahydrophthalazinone/pyridazinonehybrids: a novel series of potent dual PDE3/PDE4 inhibitory agents. Journal of Medicinal Chemistry 46(10), 2008-2016.

Veerman, J., van den Bergh, T., Orrling, K.M., Jansen, C., Cos, P., Maes, L., Chatelain, E., Ioset, J.R., Edink, E.E., Tenor, H., Seebeck, T., de Esch, I., Leurs, R., Sterk, G.J., 2016. Synthesis and evaluation of analogs of the phenylpyridazinone NPD-001 as potent trypanosomal TbrPDEB1 phosphodiesterase inhibitors and in vitro trypanocidals. Bioorganic and Medicinal Chemistry 24(7), 1573-1581.

Vergelli, C., Giovannoni, M.P., Pieretti, S., Giannuario, A. Di., Dal Piaz, V., Biagini, P., Biancalani, C., Graziano, A., Cesari, N., 2007. 4-Amino-5-vinyl-3(2H)-pyridazinones and analogues as potent antinociceptive agents: Synthesis, SARs, and preliminary studies on the mechanism of action. Bioorganic and Medicinal Chemistry 15, 5563-5575.

Wang, L., Xu, S., Chen, X., Liu, X., Duan, Y., Kong, D., Zhao, D., Zheng, P., Tang, Q., Zhu, W., 2018. Synthesis and bioevaluation study of novel N-methylpicolinamide and thienopyrimidine derivatives as selectivity c-Met kinase inhibitors. Bioorganic and Medicinal Chemistry 26, 245-256.

Wang, L.X., Liu, X., Xu, S., Tang, Q., Duan, Y., Xiao, Z., Zhi, J., Jiang, L., Zheng, P., Zhu, W., 2017. Discovery of novel pyrrolo-pyridine/pyrimidine derivatives bearing pyridazinone moiety as c-Met kinase inhibitors. European Journal of Medicinal Chemistry, 141, 538-551.

Wang, T., Dong, Y., Wang, L.C., Chen, Z., 2009. Synthesis and bioactivity of 6-phenyl-4,5-dihydro-3(2H)-pyridazinone derivatives. Arzneimittelforschung 57, 641-647.

Wang, T., Dong, Y., Wang, L.C., Xiang, B.R., Chen, Z., Qu, L.P., 2008. Design, synthesis and structure-activity relationship studies of 6-phenyl-4,5-dihydro-3(2H)-pyridazinone derivatives as cardiotonic agents. Arzneimittelforschung 58(11), 569-573.

Wang, T., Dong, Y., Wang, L.C., Chen, Z., 2007. Synthesis and bioactivity of 6-phenyl-4,5-dihydro-3(2H)-pyridazinone derivatives. Arzneimittelforschung 57(10), 641-646.

Wang, T., Xiang, B., Wang, Y., Chen, C., Dong, Y., Fang, H., Wang, M., 2008. Spectroscopic investigation on the binding of bioactive pyridazinone derivative to human serum albumin and molecular modeling. Colloids and Surfaces B: Biointerfaces 65(1), 113-119.

Wang, Y.J., Lu, D., Xu, Y.B., Xing, W.Q., Tong, X.K., Wang, G.F., Feng, C.L., He, P.L., Yang, L., Tang, W., Hu, Y.H., Zuo, J.P., 2015. A novel pyridazinone derivative inhibits hepatitis B virus replication by inducing genome-free capsid formation. Antimicrobial Agents and Chemotherapy 59(11), 7061-7072.

Xing, W., Ai, J., Jin, S., Shi, Z., Peng, X., Wang, L., Ji, Y., Lu, D., Liu, Y., Geng, M., Hu, Y., 2015. Enhancing the cellular anti-proliferation activity of pyridazinones as c-met inhibitors using docking analysis. European Journal of Medicinal Chemistry 95, 302-312.

Xing, W., Fu, Y., Shi, Z., Lu, D., Zhang, H., Hu, Y., 2013. Discovery of novel 2,6-disubstituted pyridazinone derivatives as acetyl-cholinesterase inhibitors. European Journal of Medicinal Chemistry 63, 95-103.

Xu, H., Zou, X.M., Zhu, Y.Q., Liu, B., Tao, H.L., Hu, X.H., Song, H.B., Hu, F.Z., Wang, Y., Yang, H.Z., 2006. Synthesis and herbicidal activity of novel alpha,alpha,alpha-trifluoro-m-tolyl pyridazinone derivatives. Pest Management Science 62(6), 522-530.

Yaseen, R., Ekinci, D., Senturk, M., Hameed, A.D., Ovais, S., Rathore, P., Samim, M., Javed, K., Supuran, C.T., 2016. Pyridazinone substituted benzenesulfonamides as potent carbonic anhydrase inhibitors. Bioorganic and Medicinal Chemistry Letters 26(4), 1337-41.

Yaseen, R., Pushpalatha, H., Reddy, G.B., Ismael, A., Ahmed, A., Dheyaa, A., Ovais, S., Rathore, P., Samim, M., Akthar, M., Sharma, K., Shafi, S., Singh, S., Javed, K., 2016. Design and synthesis of pyridazinone-substituted benzenesulphonylurea derivatives as anti-hyperglycaemic agents and inhibitors of aldose reductase

-an enzyme embroiled in diabetic complications. Journal of Enzyme Inhibition and Medicinal Chemistry 31(6), 1415-1427.

Young, W.B., Barbosa, J., Blomgren, P., Bremer, M.C., Crawford, J.J., Dambach, D., Eigenbrot, C., Gallion, S., Johnson, A.R., Kropf, J.E., Lee, S.H., Liu, L., Lubach, J.W., Macaluso, J., Maciejewski, P., Mitchell, S.A., Ortwine, D.F., Di Paolo, J., Reif, K., Scheerens, H., Schmitt, A., Wang, X., Wong, H., Xiong, J.M., Xu, J., Yu, C., Zhao, Z., Currie, K.S., 2016. Discovery of highly potent and selective Bruton's tyrosine kinase inhibitors: Pyridazinone analogs with improved metabolic stability. Bioorganic and Medicinal Chemistry Letters 26(2), 575-579.

Youssef, A.S., Marzouk. M.I., Madkour, H.M.F., El-Soll, A.M., El-Hashash, M.A., 2005. Synthesis of some heterocyclic systems of anticipated biological activities via 6-aryl-4-pyrazol-1-yl-pyridazin-3-one. Canadian Journal of Chemistry 83, 251-259.

Zhou, G., Ting, P.C., Aslanian, R., Cao, J., Kim, D.W., Kuang, R., Lee, J.F., Schwerdt, J., Wu, H., Herr, R.J., Zych, A.J., Yang, J., Lam, S., Wainhaus, S., Black, T.A., McNicholas, P.M., Xu, Y., Walker, S.S., 2011. SAR studies of pyridazinone derivatives as novel glucan synthase inhibitors. Bioorganic and Medicinal Chemistry Letters 21(10), 2890-2893.

Zhou, S., Liao, H., He, C., Dou, Y., Jiang, M., Ren, L., Zhao, Y., Gong, P., 2014. Design, synthesis and structure-activity relationships of novel 4-phenoxyquinoline derivatives containing pyridazinone moiety as potential antitumor agents. European Journal of Medicinal Chemistry 83, 581-593.

Zhou, Y., Li, L.S., Dragovich, P.S., Murphy, D.E., Tran, C.V., Ruebsam, F., Webber, S.E., Shah, A.M., Tsan, M., Averill, A., Showalter, R.E., Patel, R., Han, Q., Zhao, Q., Hermann, T., Kissinger, C.R., Lebrun, L., Sergeeva, M.V., 2008. Novel HCV NS5B polymerase inhibitors derived from 4-(1',1'-dioxo-1',4'-dihydro-1'lambda(6)-benzo[1',2',4']thiadiazin-3'-yl)-5-hydroxy-2H-pyridazin-3-ones. Part 2: Variation of the 2- and 6-pyridazinone substituents. Bioorganic and Medicinal Chemistry Letters 18(4), 1419-1424.

Zhou, Y., Webber, S.E., Murphy, D.E., Li, L.S., Dragovich, P.S., Tran, C.V., Sun, Z., Ruebsam, F., Shah, A.M., Tsan, M., Showalter, R.E., Patel, R., Li, B., Zhao, Q., Han, Q., Hermann, T., Kissinger, C.R., Lebrun, L., Sergeeva, M.V., Kirkovsky, L., 2008. Novel HCV NS5B polymerase inhibitors derived from 4-(1',1'-dioxo-1',4'-dihydro-1'lambda6-benzo [1',2',4'] thiadiazin-3'-yl)-5-hydroxy-2H-pyridazin-3-ones. Part 1: exploration of 7'-substitution of benzothiadiazine. Bioorganic and Medicinal Chemistry Letters 18(4), 1413-1418.

Zou, X,J., Lai, L.H., Jin, G.Y., Zhang, Z.X., 2002. Synthesis, fungicidal activity, and 3D-QSAR of pyridazinone-substituted 1,3,4-oxadiazoles and 1,3,4-thiadiazoles. Journal of Agricuture and Food Chemistry 50(13), 3757-60.

Zych, A.J., Lam, S.Q., Jenkins, D.M., Herr, R.J., Ting, P.C., Lee, J.F., Kuang, R., Wu, H., Kim, D.W., Aslanian, R.G., Wainhaus, S., Black, T.A., Cacciapuoti, A., McNicholas, P.M., Xu, Y., Walker, S.S., 2012. Lead optimization of a sulfonylurea-based piperazine pyridazinone series of glucan synthase inhibitors. Bioorganic and Medicinal Chemistry Letters 22(14), 4896-4899.