Asian Journal of Chemistry and Pharmaceutical Sciences, *Vol 1(1), 2016, 29-35*

Biological Potential and Chemical Properties of Pyridine and Piperidine Fused Pyridazine Compounds: Pyridopyridazine a Versatile Nucleus

Mohammad Asif*

Department of Pharmacy, GRD (PG) IMT, Dehradun - 248009, Uttarakhand, India; aasif321@gmail.com

Abstract

Pyridopyridazine compounds are important nitrogen atom containing heterocyclic compounds due to their pharmacological versatility. This heterocycle system characterized a structural feature for different types of bioactive compounds that exhibiting various types of biological activities which make it an attractive scaffold for the design and development of new drug molecules. This article provided information about the pharmacological properties of pyridopyridazines derivatives.

Keywords: Pharmacological Properties, Pyridopyridazine, Pyridopyridazinone

1. Introduction

Heterocyclic compounds are playing key role in the drug discovery and design because of their different types of biological properties. Several heterocyclic compounds are vital for life of plants and animals. Medicinal Chemistry point of view, the aza-heterocycles are more interesting because it may modify the electron distribution inside the scaffold leading to an alteration of the physical and chemical properties of the compounds. In addition to modification of the scaffold reactivity towards metabolic pathways, along with is its capacity to cross biological barriers[1]. Among the nitrogen containing six-member heterocylic compounds, the pyridine or piperidine structural is often found in naturally occurring bioactive compounds such as alkaloids[2]. Piperidinone derivatives are used as precursors for the synthesis of anti-malarial, febrifugine, and isofebrifugine[3]. Piperidinones display varied and potent biological properties like antiviral, antitumour, analgesic, local anaesthetic, antimicrobial, fungicidal, herbicidal, insecticidal, antihistaminic, anti-inflammatory, anticancer, CNS stimulant, and depressant properties[4–6]. Compounds containing the piperidin-4-one moiety elicit excellent biological activities when aromatic substitutions are present at 2 and/or 6 positions[7]. Pharmacologically important of pyridazin-3(2H)-one has been found to inhibit the activities of cGMP-phosphodiesterase (PDE-3) and cAMP-PDE-4 enzymes[8]. Pyridazine formally derived from benzene by the replacement of two of the ring carbon atom by nitrogen (diazines). Pyridazine is the important class of compounds due to their diverse pharmacological activities. This privileged structure attracts the interest of medicinal chemists as a nucleus of potential therapeutic utility[9–11]. The easy functionalization at various ring positions makes them an attractive synthetic building block for designing and synthesis of new drugs. Pyridazines are widely recognized as versatile scaffolds with a diverse set of biological activities[12–15]. Among pyridazine derivatives, pyridazinones is an important class of compounds mainly due to their diverse biological activities like analgesic, anti-inflammatory, antibacterial, herbicidal, antifungal, antituberculotic, anti-AIDs, antitumour, antihypertensive, anticonvulsant, anticancer, and antiviral activities[16–20]. In pyridazinones the amine group (NH) is suitably placed with the carbonyl group and most of the pyridazinones exhibit tautomerism. Pyridazinones exist mainly in the oxo form. Pyridazinones are also important class

* *Author for correspondence*

of heterocycles that are encountered in various natural products. Some pyridazinone containing drugs are Chloridazon, Emorfazone, Zardaverine, Pyridaphenthion, Dimidazon etc. Pyridopyridazines are structurally related to phthalazines and extensively described in the medicinal chemistry as an interesting scaffold. The introduction of a nitrogen atom into the benzo ring of phthalazines leads to pyridopyridazines. This scaffold can be easily functionalized at different ring positions, which makes it attractive compound for designing and development of the new pyridopyridazine drugs[21,22]. The pyridopyridazine ring attracted many pharmaceutical industries for their sensible biological activities. Clinically used antihypertensive drugs Endralazine Mesylate as active ingredient with pyridopyridazine core moiety[23,24]. Great work on pyridopyridazine nucleus in CNS related diseases[25]. Some pyridopyridazines have antihistaminic activities[26]. Some pyrido[2,3-d]- and pyrido[3,4-d]pyridazines are protein kinase, mainly p38 kinase inhibitors for treating inflammation and related states including rheumatoid arthritis, psoriasis, and other inflammation disorders[27,28]. Various pyridopyridazinones have been examined as potential analgesic agents[29]. Some pyridopyridazine derivatives were exhibited antitumor activities[30]. Pyridopyridazine nucleus showed antiasthmatic[31], antidiabetic[32], antituberculosis[33] and antimicrobial activities[34].

2. Pharmacological Activities

The wide spectrum of biological activities for pyridine/piperidine and pyridazine/pyridazinone moieties, the combination of these two different moieties into a single structural scaffold would confer synergistic activities on the molecule. Increasing attention in the synthesis and activities of pyridazines, pyridazinones, pyridopyridazines, and pyridopyridazinones has been observed. Pyridopyridazines and pyridopyridazinones showed wide spectrum of biological activities. Recently the pyridazinone ring has been extensively studied in the search for new and selective drug molecules[27–32]. In contrast to the phthalazinones, their aza derivatives, pyridopyridazinones are relatively little studied. The reasons for this are the complication related with the formation of pyridine starting materials which can easily be transformed into pyridopyridazinones[35]. In spite of various pyridopyridazinones attached to thiazole, oxadiazole, thiadiazole and triazole moieties having been prepared and studied. However, pyridopyridazine is a versatile scaffold which provides derivatives able to interact with different types of biological targets and divers activities. This review summarizes the current information about the pharmacological activites of pyridopyridazine derivatives.

2.1 Anti-Inflammatory and Analgesic Activity

Protein kinases are a family of enzymes, which trigger the phosphorylation of target protein substrates. Among these kinases, P38 kinase which is mediated in the regulation of Interleukin-I (IL-1) and Tumor Necrosis factor α (TNF-α) as pro-inflammatory cytokines secreted by macrophage and monocytes in response of inflammatory stimuli as Lipo Poly Saccharide (LPS). High expression of TNF-α is concerned in triggering various diseases like Rheumatoid Arthritis (RA), inflammatory bowel disease and osteoarthritis[27]. Some pyrido[2,3-d]pyridazine-2(1H)-ones are useful in prophylaxis and management of protein kinase mediated inflammation and related diseases like rheumatoid arthritis, pulmonary diseases and pain. Compounds 1a, 1b and 2 were showed the most potent activity in management of P38-kinase mediated diseases[27]. A class of p38α selective pyridopyridazin-6-ones from the p38 α/β dual inhibitor with high selectivity, potency and suppressing Lipo-Poly Saccharide (LPS) induced TNF-α production (pro-inflammatory cytokines) which resulting in efficient treatment response against autoimmune driven diseases (like RA). Compound 3 is a most active in suppressing TNF-α levels in LPS[28]. The compound 4 has subnanomolar p38α activity with moderate p38β isoform selectivity[36] (Figure 1). Pain is an unpleasant sensory and emotional incident connected with tissue damage[37]. Pain differentiated a major symptom of many pathological conditions and use analgesics to treat pain. The 4-aminosubstituted-2,6,7-trimethyl-1,5-dioxo-1,2,5,6-tetrahydropyrido[3,4-d]pyridazines were significantly inhibit the locomotors activity and decrease the excitatory activity of amphetamine and exhibited analgesic effects. Compounds 5a-c was showed strong analgesic effects. While compounds 5a and 5b was suppressed locomotors activity[38]. The N-(dimethylamino) ethylpyridopyridazinones have analgesic effect. Among

them, compounds 6a and 6b were exhibited potent analgesic activity[29]. Compound 7 was showed potent analgesic and anti-inflammatory activity[39] (Figure 2).

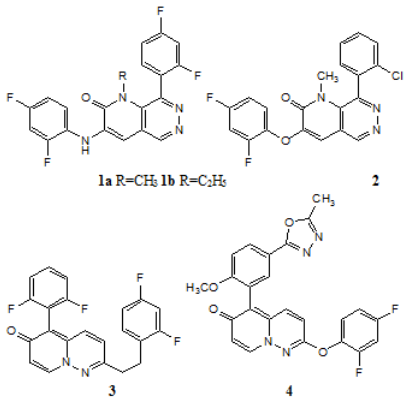


Figure 1. Pyridopyridazine derivatives as anti-inflammatory agents.

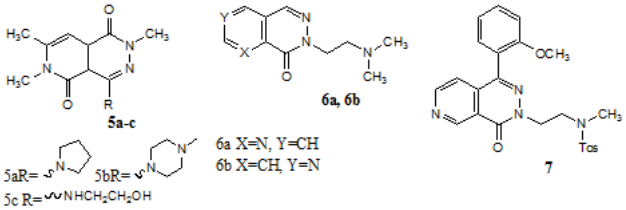


Figure 2. Pyridopyridazine derivatives as analgesic agents.

2.2 Antihypertensive Activity

Hypertension is a main factor for cardiovascular disorders like coronary disease, Myocardial Infarction (MI) or stroke as well as to Congestive Heart Failure (CHF) and renal insufficiency. The antihypertensive drugs are critical importance in order to control of Blood Pressure (B.P). A series of substituted-pyridopyridazines, some compounds have excellent diuretic activity and different characters from known diuretics like thiazides, carbonic anhydrase inhibitors or furosemide. Among these compounds, compound **8** was showed an outstanding diuretic activity[40]. Endralazine (**9**) is direct acting vasodilator which resembles Hydralazine. Endralazine is about five times more potent than Hydralazine and that allowing lower dosage usage. Thus, less immunological response would be achieved.[23,24] (Figure 3).

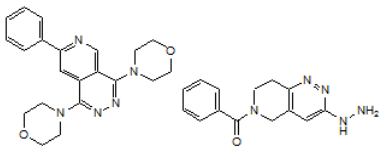


Figure 3. Pyridopyridazine derivatives as antihypertensive agents.

2.3 Central Nervous System Activities

A series of pyrido[2,3-d]pyridazines were a selective ligands for GABA-A receptors and they are used in treatment a various central nervous system (CNS) disorders like, anxiety, panic, phobia, psychoses (schizophrenia). Compound 10 was showed the highest activity[5]. A class of substituted pyrido[2,3-c] pyridazines were useful in the treatment of neorolgical disorders. A series of pyrido[2,3-c]pyridazine, compound 11[41], and 2,3,8-trisubstituted pyrido[2,3-d]pyridazine, compounds 10 and 12 revealed high affinity ligands for the GABAA receptor benzodiazepine binding sit[42] (Figure 4).

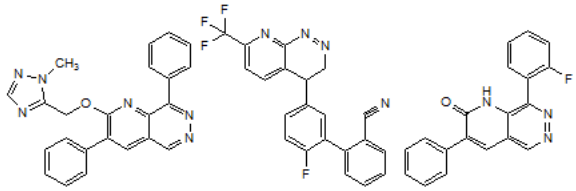


Figure 4. Pyridopyridazine derivatives useful in treatment of neurological disorders.

2.4 Antihistaminic Activity

Allergic rhinitis is mediated by histamine (intracellular chemical messenger) which is released from several cells and particularly by mast cells. Some substituted pyrido[3,4-d]pyridazines 13a-c were found to have antihistaminic action and could be useful in treatment of allergic and inflammatory diseases of the respiratory tract like asthma, bronchitis, allergic rhinitis, chronic Obstructive Pulmonary Disease (OPD). Compound 13a was showed a potent H_1 receptor antagonist. It exhibited a longer duration of action than Azelastine[26] (Figure 5).

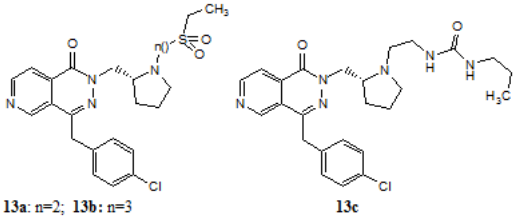


Figure 5. Pyridopyridazine derivatives as antihistaminic agents.

2.5 Antiasthmatic Activity

Bronchial asthma is a lung disease described by airway obstruction, inflammation and hyper responsiveness[43]. The pyrido-[2,3-d]pyridazinones were act as potent and selective Type-IV Phosphodiesterase (PDE) Inhibitors

(14a-c). These PDE-inhibitors are promising drugs in the management of asthma and inflammation[31]. Heterocyclic-fused pyridazinones were act as selective PDE-IV inhibitors, among these, compound 15, pyrido[2,3-d]pyridazinone was exhibited a good potency and selectivity versus PDE IV and it showed an affinity for Rolipram binding site by 2 orders of magnitude lower than Rolipram[44] (Figure 6).

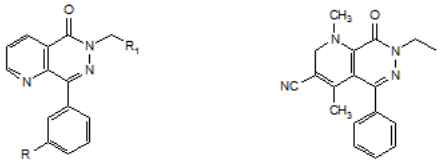


Figure 6. Pyridopyridazine derivatives as antiasthmatic agents.

2.6 Antidiabetic Activity

Diabetes Mellitus (DM) is a chronic multifactorial disease differentiated by a high blood glucose level. Diabetes is resulting from insulin deficiency (type-I diabetes) or insulin resistance (type-II diabetes), disturbs the metabolism giving rise to not only acute but also long term complications. More than 90% of diabetic patients suffer from type-II diabetes[45]. Increased glucose flux through the sorbitol pathway, which is mediated by the enzyme aldose reductase, has been concerned in the pathogenesis of diabetic complications. So, the developments of Aldose Reductase Inhibitors (ARIs) act as potential agents for reducing these complications. The pyrido[2,3-d] pyridazin-5-yl)acetic acids, its esters 16a-c and 17a,b were tested for their activity for inhibition of aldose reductase. Compound 16b was showed potent aldose reductase inhibitory activity[32] (Figure 7).

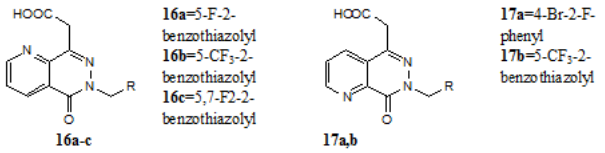


Figure 7. Pyridopyridazine derivatives as antidiabetic agents.

2.7 Antituberculosis

Tuberculosis (TB) is an infectious disease that chiefly affects lungs. Some pyrido[2,3-d]pyridazines have potent anti-TB. A compound 18 was showed the best activity against *M. tuberculosis* bacilli than other aza-phthlazine derivatives[46]. Other pyrido[3,4-d] pyridazines have anti-TB activity. Compound 19 was showed the strongest anti-TB activity[33] (Figure 8).

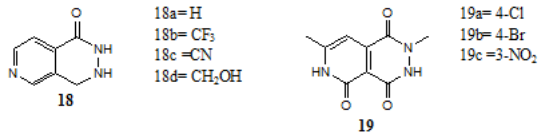


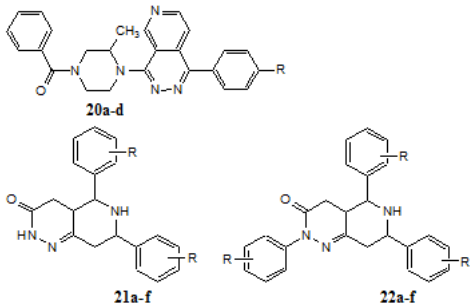
Figure 8. Pyridopyridazine derivatives as antituberculosis agents.

2.8 Anticancer Activity

Cancer in an uncontrolled proliferation of abnormal cells. These mutated cells attack adjoining tissues and sometimes transfer through the blood or lymph distribution to other body organs causing metastases, which are the main cause of death from cancer. A considerable fraction of cancers can be cured by surgery combined with radiotherapy or chemotherapy, particularly if they are detected early[26]. Some pyrido-pyridazines were showed anticancer activity. The pyridopyridazine derivatives inhibited cascade of signals which regulate proliferation. Inhibition of proliferation could be achieved by inhibition of cyclin-dependent kinases. Huge majority of kinase inhibitor scaffolds consist of heterocycles, compounds 20a-d were showed strong anticancer activity[30].

The 4, 4a, 5, 6, 7, 8 - Hexahydro-5, 7 -diphenylpyrido[4, 3-c]pyridazin-3(2H)-ones (21a–f) and 2-Phenyl-5,7-diarylpyrido[4,3-c]pyridazin-3(2H)-ones (22a–f) were tested for anticancer activity in-vitro against MCF-7 breast cancer cells. The MTT assay showed that pyridopyridazin-3(2H)-one derivatives 21a–f and 22a–f were possessed moderate cytotoxic activity. Compounds 22e (~810 μM) and 22f (~473 μM) was exhibited weak activity against the cancer cell line. The anticancer activities of 21a–f and 22a–f revealed that only the three compounds 21d–f bearing electron withdrawing substituent in the aromatic ring showed the maximum activity. The hydrazine incorporated derivatives 21d–f and not phenylhydrazine incorporated compounds 22d–f were showed the high activity against MCF-7 breast cancer cell line. The aryl ring at position 3 appears unimportant and reduces the activity against MCF-7 cells. The inhibitory activity of compounds against MCF-7 human breast adenocarcinoma cells, the importance of

functional groups for the higher levels of activity shown by 21d, 21e and 21f[48]. This elaborated potential anticancer agents against breast cancer (Figure 9).



Compounds	R	CF-7 IC50 a (?M)	Compounds	R	CF-7 IC50 a (?M)
21a	H	145 ± 8.5	22a	H	102.4± 5.9
21b	CH_3	166± 10.05	22b	CH_3	8.9.6 ± 4.58
21c	OCH_3	125.6 ± 21.7	22c	OCH_3	109.45 ± 7.63
21d	Cl	22.9 ± 2.5	22d	Cl	163.51 ± 9.1
21e	Br	36.3 ± 6.8	22e	Br	435± 19.29
21f	3-NO_2	55.7 ± 8.9	22f	3-NO_2	223.12 ± 12.38
			Doxorubicinb	----------	1.0907 ± 0.03

Figure 9. Pyridopyridazine derivatives as anticancer agents.

2.9 Antimicrobial Activities

Infectious diseases caused by microbes like bacteria, fungi and viruses. The purpose of microorganisms is to survive and many of them have determinants of resistance[49]. The anti-microbial effects of some fused pyridazine derivatives, compound 22 showed potential antimicrobial activity[34] (Figure 10).

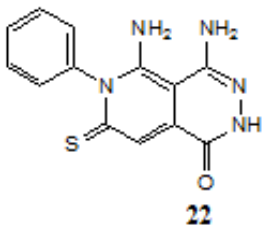


Figure 10. Pyridopyridazine derivatives as antimicrobial agent.

3. Discussion

In the search for new biologically active compounds, extensive research is based on the synthesis of heterocyclic molecules. The privileged scaffolds, which can interact with high affinity to broad range of receptors, provide new insights and hope for the formation of new biological active compounds. They are able to orient various substituents in these scaffolds. Because these moieties provides divers activities towards different receptors and considered as excellent lead molecule. Increasing the chemical diversity is a great interest for the medicinal chemistry industries. The pyridazine moiety is a versatile scaffold to develop new biological active compounds with wide varieties of biological activities and also be used to link other pharmacophoric groups. Pyridazine derivatives have various biological properties like anti-viral, anti-cancer, anti-hypertensive, anti-inflammatory, anti-microbial, anti-depressant, anti-HIV and other biological activities[50–56]. The polyfunctional 2H-pyrano[3,2-c]pyridazin-3(6H)-ones were exhibited potent anticancer agents[20]. The 3-Arylpyrimido[4,5-*c*] pyridazine-5,7(6*H*,8*H*)-diones possess Monoamine Oxidase (MAO) inhibitory activity and used for the treatment of depression and Alzheimer disease[57–59]

4. Conclusion

Increasing interest in the pyridazines, pyridazinones, pyridopyridazines, and pyridopyridazinones has been observed. These pyridazinne derivatives are showing wide spectrum of biological activities. Recently the pyridazinone moiety has been comprehensively studied in the search for novel and selective drugs. Several biological activities of pyridopyridazines derivatives and may act as important biological active pharmacophores in medicinal chemistry. This moiety may help in exploring new pathways to discover new drugs of potential therapeutic value.

5. References

1. Sainsbury M. Heterocyclic chemistry, basic concepts in chemistry. Bristol: Wiley Interscience and Royal Society of Chemistry; 2002.
2. Taniguchi T, Ogasawara K. A diastereo controlled synthesis of (+)-febrifugine: A potent antimalarial piperidine alkaloid. Organic Letters. 2000; 2(20):3193–5.
3. Takeuchi Y, Azuma K, Takakura K, Abe H, Harayama T. Asymmetric synthesis of febrifugine and isofebrifugine using yeast reduction. Chemical Commun. 2000; 17:1643–4.
4. El-Subbagh HI, Abu-Zaid SM, Mahran MA, Badria FA, Al-Obaid AM. Synthesis and biological evaluation of certain α,-unsaturated ketones and their corresponding fused pyridines as antiviral and cytotoxic agents. J Med Chem. 2000; 43(15):2915–21.
5. Perumal RV, Adiraj M, Pandiyan PS. Synthesis, analgesic and anti inflammatory evaluation of substituted 4-piperidones. Indian Drugs. 2001; 38(3):156–9.

6. Katritzky AR, Fan W-Q. A novel and versatile synthesis of 1-alkyl-, 1-aryl-, 1-(alkylamino)-, or 1-amido-substituted and of 1,2,6-trisubstituted piperidines from glutaraldehyde and primary amines or monosubstituted hydrazines. The J Org Chem. 1990; 55(10):3205–9.
7. Aridoss G, Amirthaganesan S, Ashok Kumar N, et al. A facile synthesis, antibacterial, and antitubercular studies of some piperidin-4-one and tetrahydropyridine derivatives. Bioorg and Med Chem Lett. 2008; 18(24):6542–8.
8. Margaretha VM, Armin H, Ivonne JL, et al. Novel selective PDE4 inhibitors. 1. Synthesis, structure-activity relationships, and molecular modeling of 4-(3,4-dimethoxyphenyl)-2H-phthalazin-1-ones and analogues. J Med Chem. 2001; 44(16):2511–22.
9. Eicher T, Hauptmann S. The Chemistry of Heterocycles: Structure, reactions, syntheses, and applications. 2nd ed. Wiley-VCH; 2003.
10. Asif M, Singh A, Lakshmayya. The development of structurally different new antitubercular molecules containing pyridazine ring system. Chronicle of Young Scientist. 2013; 4(1):1–8.
11. Asif M, Anita Singh A, Siddiqui AA. The effect of pyridazine compounds on the cardio-vascular system. Med Chem Res. 2012; 21:3336–46.
12. Asif M, Singh A, Ratnakar L. Antimicrobial Agents: Brief study of pyridazine Derivatives against some phathogenic microrganisms. J Pharm Res. 2011; 4(3):664–7.
13. Asif M, Singh A. Exploring potential, synthetic methods and general chemistry of pyridazine and pyridazinone: A brief introduction. Inter J Chem Tech and Res. 2010; 2(2):1112–28.
14. Asif M. Antifeedant, herbicidal and molluscicidal activities of pyridazinone compounds. Mini Rev in Org Chem. 2013; 10(2):113–22.
15. Asif M. The study of pyridazine compounds on prostanoids: Inhibitors of COX, cAMP phosphodiesterase, and TXA2 Synthase. J Chem. 2014. Available from: http://dx.doi.org/10.1155/2014/703238
16. Abubshait SA. An efficient synthesis and reactions of novel indolylpyridazinone derivatives with expected biological activity. Molecules. 2007; 12(1):25–42.
17. Youssef ASA, Marzouk MI, Madkour HMF, El-Soll AMA, El-Hashash MA. Synthesis of some heterocyclic systems of anticipated biological activities via 6-aryl-4-pyrazol-1-yl-pyridazin-3-one. Canadian J Chem. 2005; 83(3): 251–9.
18. Cherng S-C, Huang W-H, Shiau C-Y, Lee A-R, Chou T-C. Mechanisms of antiplatelet activity of PC-09, a newly synthesized pyridazinone derivative. Eur J Pharmacol. 2006; 532(1-2):32–7.
19. Dogruer DS, Onkol T, Ozkan S, Ozgen S, Sahin MF. Synthesis and antimicrobial activity of some 3(2H)-pyridazinone and 1(2H)-phthalazinone derivatives. Turkish J Chem. 2008; 32(4):469–79.
20. Taleb HA. Design and synthesis of novel tetrahydro-2HPyrano[3,2-c]Pyridazin-3(6H)-one derivatives as potential anticancer agents. Eur J Med Chem. 2010; 45(12):5724–31.
21. Ibrahim MA, Elmenoufy AH, Elagawany M, Ghoneim, MM, Moawad A. "Pyridopyridazine": A Versatile Nucleus in Pharmaceutical Field. J Biosci and Med, 2015; 3:59–66.
22. Brown DJ. 10. Halogenophthalazines (H 178; E 514). Cinnolines and Phthalazines. The Chemistry of Heterocyclic Compounds Series. Hoboken, NJ: John Wiley and Sons, Inc; 2005. p. 203.
23. Hoffmann J, Thien, T, van'Laar A. Effects of intravenous endralazine in essential hypertension. British J Clin Pharmacol. 1983; 16:39–44.
24. Meredith PA, Elliott H, McSharry DR, Kelman AW, Reid JL. The pharmacokinetics of endralazine in essential hypertensives and in normotensive subjects. British J Clin Pharmacol. 1983; 16:27–32.
25. Carling WR, Castro PJL, Mitchinson A, Street LJ. Pyrido-pyridazine derivatives as ligands for gaba receptors. Pyrido-pyridazine derivatives as ligands for gaba receptors. Google Patents; 2001.
26. Gore PM, Looker BE, Procopiou PA, Vile S. Phthalazine and pyrido[3, 4-D]pyridazine compounds as H1 receptor antagonists. Google Patents; 2008.
27. Pettus LH, Tasker A, Wu B. Pyrido[3,2-d]pyridazine-2(1H)-one compounds as p38 modulators and methods of use thereof. Google Patents; 2013.
28. Tynebor RM, Chen M-H, Natarajan SR, O'Neill EA, Thompson JE, Fitzgerald CE, et al. Synthesis and biological activity of pyridopyridazin-6-one p38 MAP kinase inhibitors. Part 1. Bioorg and Med Chem Lett. 2011; 21:411–6.
29. Pakulska W, Malinowski, Z Szczesniak, AK, Czarnecka E, Epsztajn J. Synthesis and pharmacological evaluation of N-(Dimethylamino)ethyl derivatives of benzo- and pyridopyridazinones. Archiv der Pharmazie. 2009; 342:41–7.
30. Kaizerman J, Lucas B, Mcminn DL, Zamboni R. Annelated pyridazines for the treatment of tumors driven by inappropriate hedgehog signalling. Google Patents; 2010.
31. Whilhelm R, Loe B, Alvarez R, Devens B, Fong A. pyrido-[2,3-d]pyridazinones as potent and selective type IV phosphodiesterase inhibitors. 8th RSC-SCI Medicinal Chemistry Symposium; Cambridge, UK. 1995. p. 32.
32. Mylari BL, Zembrowski WJ, Beyer TA, Aldinger CE, Siegel TW. Orally active aldose reductase inhibitors: Indazoleacetic, oxopyridazineacetic, and oxopyridopyridazineacetic acid derivatives. J Med Chem, 1992; 35:2155–62.
33. Stanasiuk J. Investigation on the synthesis and properties of 2-(alkyl, aryl)-1,4,5-trioxo-1,2,3,4,5,6-hexahydropyrido[3,4-d]pyridazine, derivatives with potential biological activity. Acta Pol Pharm. 2005; 63:420–1.
34. Elassar A-ZA. Synthesis and antimicrobial activity of new polyfunctionally substituted pyridines and their fused derivatives. Indian J Chem. 2004; 43:1314–9.

35. Matyus P. 3(2H)-pyridazinones: Some recent aspects of synthetic and medicinal chemistry. J Heterocycl Chem. 1998; 35:1075–89.
36. Tynebor RM, Chen M-H, Natarajan SR, O'Neill EA, Thompson JE, Fitzgerald CE, et al. Synthesis and biological activity of pyridopyridazin-6-One p38α MAP kinase inhibitors. Part 2. Bioorg and Med Chem Lett. 2012; 22:5979–83.
37. Bishnoi M, Premkumar LS. Changes in TRP channels expression in painful conditions. The Open Pain J. 2013; 6:10–22.
38. Śladowska H, Stanasiuk J, Sieklucka-Dziuba M, Saran T, Kleinrok Z. Investigations on the synthesis and properties of 4-aminosubstituted 2,6,7-trimethyl-1,5-dioxo-1,2,5,6-tetrahydropyrido[3,4-d]pyridazines. Il Farmaco. 1998; 53:475–9.
39. Epsztajn J, Czarnecka E, Szczesniak A, Pakulska W, Malinowski Z. Benzo- and pyrido-pyridazinones with analgesic and anti inflammatory activity. Google Patents; 2009.
40. Nishikawa K, Shimkawa H, Inada Y, Shibouta Y, Kikuchi S, Yurugi S, Oka Y. Structure-activity relationships of the diuretic activity of triaza- and tetraaza-naphthalene compounds. Chem and Pharm Bull. 1976; 24:2057–77.
41. Goodacre SC, Hallett DJ. Substituted pyrido-pyridazine derivatives which enhance cognition via the GABA-A Receptors. Google Patents; 2006.
42. Mitchinson A, Blackaby WP, Bourrain S, Carling RW, Lewis RT. Synthesis of pyrido [2,3-d]pyridazines and pyrazino[2,3-d]-pyridazines- novel classes of GABA receptor benzodiazepine binding site ligands. Tetrahedron Lett. 2006; 47:2257–60.
43. Kurosawa M. Role of thromboxane a2 synthase inhibitors in the treatment of patients with bronchial asthma. Clin Ther. 1995; 17:2–10.
44. Dal PV, Giovannoni MP, Castellana C, Palacios JM, Beleta J, Domenech T, et al. Novel heterocyclic-fused pyridazinones as potent and selective phosphodiesterase IV inhibitors. J Med Chem. 1997; 40:1417–21.
45. Zimmet P, Alberti K, Shaw J. Global and societal implications of the diabetes epidemic. Nature. 2001; 13:782–7.
46. Kakimoto S, Tonooka S. Antituberculous compounds. XXV. Some Derivatives of Pyrido [2,3-d] Pyridazine. Bull Chem Soc Japan. 1967; 40:153–9.
47. Cancer. Available: http://www.who.int/cancer/en/
48. Selvakumar P, Thennarasu S, Mandal AB. Synthesis of novel pyridopyridazin-3(2h)-one derivatives and evaluation of their cytotoxic activity against MCF-7 cells. Inter Scholarly Res Notices; 2014. Article ID: 410716.
49. Rennie RP. Current and future challenges in the development of antimicrobial agents. In: Coates, ARM, Ed. Antibiotics Resistance, Handbook of Experimental Pharmacology. Springer-Verlag, Berlin; 2012. p. 45–65.
50. Biancanali C, Giovannoni MP, Pieretti S, Cesari N, Graciano A, Vergelli C, Cilibrizzi A, di Gianuario A, Colucci M, Mangano G, Garrone B, Polenzani, L, dal Piaz V. Further studies on arylpiperazinyl alkyl pyridazinones: discovery of an exceptionally potent, orally active, antinociceptive agent in thermally induced pain. J Med Chem. 2009; 52:7397–409.
51. Rodrguez-Ciria M, Sanz AM, Yunta MJR, Gomez-Contreras F, Navarro P, Fernandez I, Pardo M, Cano C. Synthesis and cytotoxic activity of N,N-bis-{3-[N-(4- Chlorobenzo[g]-phthalazin-1-yl)]aminopropyl}-N-methylamine: A new potential DNA bisintercalator. Bioorg Med Chem. 2003; 11:2143–8.
52. Lee SG, Kim JJ, Kim KH, Kweon DH, Kang YJ, Cho SD, Kim SK, Yoon Y. Recent progress in pyridazin-3(2h)-ones chemistry. J Curr Org Chem. 2004; 8:1463–80.
53. Orru RVA, de Greaf M. Recent advances in solution-phase multicomponent methodology for the synthesis of heterocyclic compounds. Synthesis. 2003; 10:1471–99.
54. Butnariu R, Caprosu M, Bejan V, Ungureanu M, Poiata A, Tuchilus C, Florescu M, Mangalagiu I I. Pyridazine and Phthalazine Derivatives with 1149 Potential Antimicrobial Activity. J Het Chem. 2007; 44:1149–55.
55. Coelho A, Sotelo E, Ravina E. Pyridazine derivatives. Part 33: Sonogashira approaches in the synthesis of 5-substituted-6-phenyl-3(2H)-pyridazinones. Tetrahedron, 2003; 59:2477–88.
56. Rathish IG, Kalim J, Shamim A, et al. Synthesis and evaluation of anticancer activity of some novel 6-aryl-2-(psulfamylphenyl)-pyridazin-3(2H)-ones. Eur J Med Chem. 2012; 49:304–9.
57. Livermone DGH, Bethell RC, Cammack N, Hancock AP, Hann MM, Green DVS, Lamont RB, Noble SA, Orr DC, Payne JJ, Ramsay MVJ, Shingler AH, Smith AH, Storer R, Williamson C, Willson T. Synthesis and anti-HIV-1 Activity of a series of imidazo[1,5-b]pyridazines. J Med Chem. 1993; 36:3784–94.
58. Altomare C, Cellamare S, Summo L, Catto M, Carotti A. Inhibition of monoamine oxidase-b by condensed pyridazines and pyrimidines: effects of lipophilicity and structure-activity relationships. J Med Chem. 1998; 41:3812–20.
59. Patil PO, Bari SB, Firke SD, Deshmukh PK, Donda ST, Patil DA. A comprehensive review on synthesis and designing aspects of coumarin derivatives as monoamine oxidase inhibitors for depression and Alzheimer's disease. Bioorg Med Chem. 2013; 21:2434–50.