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Review Article

Study of Various Fused Heterocyclic Pyridazine Derivatives as Potent Anticancer Agents: A Brief Overview

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Abstract

Pyridazine is a compound that belongs to the heterocyclic class of diazines. Pyridazine derivatives show a wide range of pharmacological activities such as antihypertensive, antidepressant, hepatoprotective, anti-viral, anticancer, antimicrobial, cardiotonic, vasodilation, analgesic, anti-inflammatory etc. In addition, Pyridazine derivatives have remarkable activity against various types of cancers. In this review article we are discusses some various pyridazine derivatives as an effective anticancer agents.

Keywords: Biological Activities; Anticancer; Heterocyclic; Pyridazine; Pyridazinone

Introduction

A well-organized analysis of heterocyclic lead exposed that these compounds are pharmacologically active agents and play essential role in medicinal chemistry. The nitrogen atom containing heterocyclic compounds such as substituted pyridazine derivatives have an important position in discovery and development of useful synthetic drugs and their biological processes. Heterocyclic compounds are used in all types of diseases or disorders such as anti-inflammatory, antioxidant, ACE inhibition, antitumor, antitubercular, antiviral, antidepressant, anticonvulsant, antifungal, antibacterial, anticancer, antileukemic, antitumor, antiproliferative, anti-angiogenic, DNA interacting, proapoptotic, autophagy, antitubulin and other activities. Moreover these heterocyclic compounds are capable to exert notable effects in the course of inhibition of different types of enzymes, proteins and receptors which take part in important role for normal body functions [1-5].

This encouraged us to study the substituted pyridazine derivatives hoping to get more perceptive and information about pyridazine derivatives as anticancer agents [5]. Pyridazine hold two adjoining nitrogen atoms (1,2-diazine) in the ring structure (Figure 1).

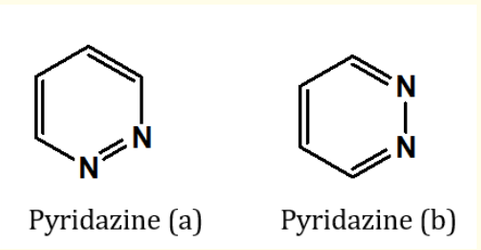

Figure 1

Biological activities

Pyridazine ring is a part of various drugs available in the market such as hydralazine, minaprine, cefozopran, and pipofezine. Various pyridazines derivatives have been reported to possess wide range of pharmacological activities such as antimicrobial, analgesic, anticancer, antifeedant, antitubercular, antidiabetic, antihypertensive, antiplatelet, anticonvulsant, antiasthma, anti-inflammatory, phosphodiesterase (PDE) inhibitors, cyclooxygenase (COX) inhibitors, antipyretic, insecticidal, neurological activity like anti anxiety and depressant, and intermediates for drugs synthesis, agrochemicals and other anticipated biological properties [6-15].

Anticancer activity

Various pharmacological activities of pyrido-pyridazine derivatives (Figure 2) which includes anticancer, antimicrobial, analgesics, anti-asthmatics, anti-inflammatory, anti tuberculosis, antihistaminic. These properties made them as an essential scaffold for the progress of novel drugs [16].

The anticancer activities of various pyridazines **(2)** and their related derivatives were showed significant action against leukemia, colon cancer, lung cancer, central nervous system (CNS) can-

Figure 2

melanoma, ovarian and breast cancer cell lines [5]. Some pyridazine derivatives **(3)** were tested for antitumor activity. Result showed that the *in-vitro* cytotoxicity activity was tested against liver HEPG2 cancer cell lines in comparison to the reference anticancer drugs, 5-Flurouracil (5-FU) and Doxorubicin (DOX) using SRB assay. The cytotoxic and growth inhibitory action of the one compound (IC_{50}: 3.92 µg/mL) was found very close to the 5-FU (IC_{50}: 5 µg/mL) against liver carcinoma cell line (HEPG2) [17].

A series of 2-acylamino-6-phenoxy-imidaz[1,2- b]pyridazine derivatives were tested as anticancer agents. Among these compounds, N-[5-({2-[(cyclopropylcarbonyl)amino] imidazo[1,2-b] pyridazine-6yl}oxy)-2-methylphenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (TAK-593) **(4)** was found highly potent VEGFR2 kinase (PDB Code: 3VO3) inhibitor (IC_{50} value=0.95 Nm). This compound also shows inhibition of platelet-derived growth factor receptor kinases as well as VEGF receptor kinases in kinase selectivity profile [18]. Two series of imidazo[1,2-b]pyridazine **(5)** and imidazo[1,2-a]pyridine derivatives act as dual c-Met and VEGFR2 kinase inhibitors. One compound was exhibited antitumor action *in-vivo* in MKN45 and COLO205 mouse xenograft models [19].

Anticancer activity of some 6-aryl-2-(p-sulfamylphenyl)-pyridazin-3(2H)-one **(6)** derivatives, among these derivatives, one compound has been selected as lead compound for development of new anticancer agents [20]. The imidazo[1,2-b]pyridazine derivatives having a benzamide ring were tested for its VEGFR2 kinase inhibition activity. Most of the tested compounds were exhibited antitumor action. In which, a strong inhibitory activity was exhibited by N-[3- (imidazo[1,2-b]pyridazin-6-yloxy)phenyl]-3-(trifluoromethyl) benzamide **(7)** against VEGFR2 (IC_{50} value = 7.1Nm) [21].

Some cinnoline derivatives were tested for its activities like anti-hypertensive, antithrombotic, antihistaminic, antileukemic, CNS activity, anti tumor, antibacterial and anti secretory etc. Halogen substituted cinnoline-imidazole compounds **(8),** mainly chloro substituted compound were showed potent antibacterial, anti-inflammatory and anti-fungal activity than other compounds. However methyl substituted compound were showed more potent antimicrobial and anti-inflammatory activity [22]. A series of 6-substituted-4-methyl-3-(4-aryl piperazin-1-yl)cinnoline **(9)** derivatives were exhibited the antitumour, antibacterial and antifungal activity [23]

A series of pyrido[2,3-*c*]pyridazine derivatives (**10**) were tested for antitumor activity. Amongst them some compounds were exhibited promising cytotoxicity along with good safety index and can be utilize for the designing of novel anti-cancer agents [24]. The 3-Amido-4-anilinocinnolines (**12**) have been identified as potent and highly selective inhibitors of CSF-1R [25].

The polyamine derivatives containing dimeric quinoline, cinnoline (**12**) and phthalimide moieties were tested *in-vitro* against in a highly aggressive melanoma cell line A375. Polyamine diimides containing phthalimide moieties showed no inhibitory effects against melanoma cells. Quinoline diamide derivatives were more proficient than cinnoline derivatives. Mainly cytostatic activity used as changed cell cycle profiles was observed. Based on their structure and biological activities, assume that some of these compounds may act as DNA bisintercalators. This study can be helpful for advance design and developing potent anticancer drugs [26].

A series of pyrazolo[1,5-b]pyridazine (**13**) derivatives as cyclin dependant kinase inhibitors effectively useful for the treatment of solid tumours. Modification of the hinge-binding amine or the C (2) and C (6) substitutions on the pyrazolo-pyridazine core provided effective inhibitors of CDK4 and showed enzyme selectivity against VEGFR-2 and GSK3β [27]. The Pyrazolo-pyridazine (**14**) in a high-throughput test, it act as a potent inhibitor of CDK1/cyclin B and shown to have selectivity for the CDK family. Analogues of the lead compound were tested for antitumor activities and a molecular model of the complex between the lead compound and the CDK2 ATP binding site has built for a combination of conformational search and automated docking techniques studied [28]. The pyrimido[5,4-c]cinnoline (**15**) and pyrimido[5,4-c]quinoline derivatives were used to determined its cytotoxicity on the two human leukemia cell lines, the promyelocytic HL-60 and the lymphoblastic NALM-6. The continous exposed cell viability was found out by the tryptan-blue exclusion assay. IC_{50} value recommended that the HL-60 leukemia cells are more resistant to toxic action of tested the compounds. All the compounds were exerted moderate cytotoxic action [29].

Several substituted dibenzo[c,h]cinnoline (**16**) derivatives were tested to target the topoisomerase-I and their relative cytotoxicity activity as in anticancer agents. The topoisomerase-I targeting activity and cytotoxicity of 2,3-Dimethoxy-8,9-methylene-dioxybenzo[i]phenanthridine was one of the more effective benzo[i]-phenanthridine derivative. The results showed that substituted dibenzo[c,h]cinnolines can exhibited potent topoisomerase I targeting action and were capable of defeat the multi-drug resistance (MDR) related with this efflux transporter [30]. The *in-vitro* cytotoxicity action of Pyrrole[2,3-d]pyridazine-4-one (**17**) derivatives against 60 human tumor cell lines derived from nine cancer cell types. Among them, the most potent compound was showed the significant cell line cytotoxicity, mainly against the renal cancer subpanel and exhibited significant activity against MOLT-4, SR (leukemia), NCI-H460 (non-small cell lung), HCT-116 (colon), and SF-295 (CNS) cancer cells [31].

Discussion

Pyridazine derivatives have been reported to possess various pharmacological activities including antibacterial, antifungal, anti-tubercular, anticonvulsant, antihypertensive, analgesic, anti-inflammatory and various other biological activities [34,35]. These explanation place new importance on the necessary of as well as explore for alternative novel and more efficient anticancer agents with a wide range of activity. In view of the anticancer activities exhibited by nitrogen containing heterocyclic such as pyridazines, it was consideration valuable to study their fused derivatives having heterocyclic ring and pyridazine in the same structure as probable anticancer agents. Some previously reported study the anticancer activity of some substituted pyridazine derivatives possessing a heterocyclic group that respectively adjacent to pyridazine moiety of the fused bicyclic ring system. Therefore, we thought to discuss of pyridazine derivatives bearing different substituents on their rings in order to study the anticancer activity against various types of cancers.

Conclusion

In conclusion, various heterocyclic containing substituted-pyridazine were successfully synthesized through multistep synthesis. From the anticancer data, it could be concluded that various fused heterocyclic pyridazine derivatives were exhibited potent anticancer activities against various types of cancer cells. These compounds could be further derivatized to get even better anticancer agents.

Conflict of Interest

Authors declare no conflict of interest.

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