DESIGN STRATEGIES OF NITROGEN-CONTAINING HETEROCYCLIC MOIETIES FOR THEIR ANTICANCER ACTIVITIES

Kamalesh Digambar Kulkarni

Research Scholar, Department of Chemistry,Sri Satya Sai University of Technology & Medical Sciences, Sehore, M.P., India.

Dr. Neelu Jain

Research Guide, Department of Chemistry, Sri Satya Sai University of Technology & Medical Sciences, Sehore, M.P., India

ABSTRACT

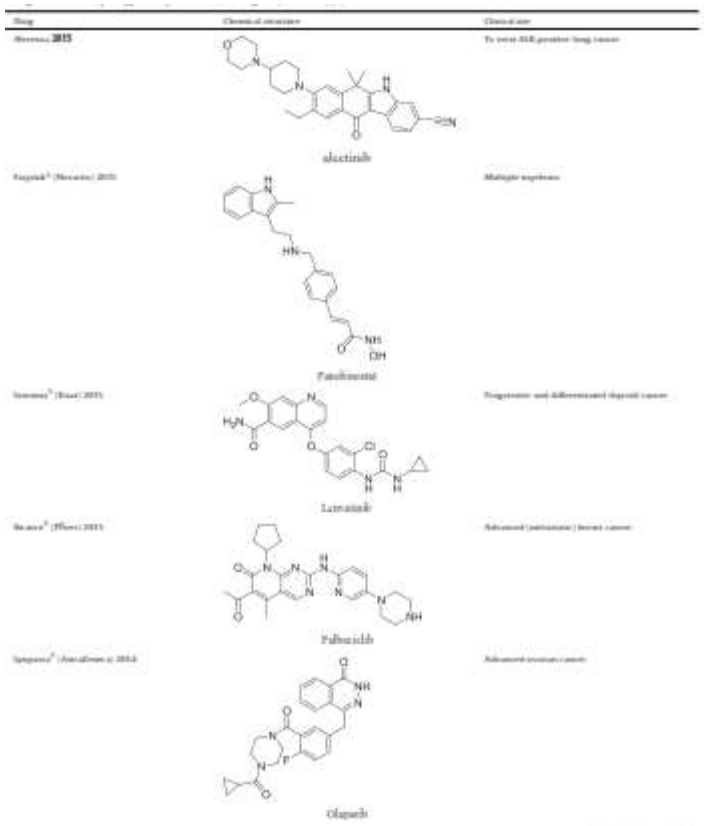
The design strategies employed for the synthesis of nitrogen-containing anticancer agents. The results of different studies describe the N-heterocyclic ring system is a core structure in many synthetic compounds exhibiting a broad range of biological activities. Benzimidazole, benzothiazole, indole, acridine, oxadiazole, imidazole, isoxazole, pyrazole, triazoles, quinolines and quinazolines including others drugs containing pyridazine, pyridine and pyrimidines are covered. The following studies of these compounds suggested that these compounds showed their antitumor activities through multiple mechanisms including inhibiting protein kinase (CDK, MK-2, PLK1, kinesin-like protein Eg5 and IKK), topoisomerase I and II, microtubule inhibition, and many others. Our concise representation exploits the design and anticancer potency of these compounds. The direct comparison of anticancer activities with the standard enables a systematic analysis of the structure activity relationship among the series

KEYWORD: Nitrogen-Containing, Anticancer Activities, Heterocyclic Moieties.

INTRODUCTION

Cancer, the uncontrolled, rapid and pathological proliferation of abnormal cells, is one of the most formidable afflictions in the world [1]. Cancer causes about 550,000 deaths a year and is second leading cause of death in the nation next to heart diseases [2]. Current therapy suffers from the major limitation of

side effect and drug resistance, so continued search for newer and safer anticancer drugs remains critically important. The compounds which bear heteroatoms such as nitrogen, sulfur and oxygen increase the strength of the complex by forming hydrogen bonds with DNA. The force of interaction between compound and DNA usually correlates with the anticancer activity. Besides, when one or more nitrogen heteroatoms exist on the chemical structure, intercalating chromophore possesses a polarized character and optimal interaction occurs [3]. N-heterocycles occurs in pharmaceuticals, natural products, dyes, organic materials, and particularly in biologically active molecules [4]. Over the past few years, there is a considerable interest in the development and pharmacology of heteroaromatic organic compounds, such as benzimidazoles, benzothiazoles, indole, acridine, oxadiazole, imidazole, isoxazole, pyrazole, triazoles, quinolines and quinazolines for their diverse activities. These N-heterocyclic produces anticancer effects in different types of cancer through inhibiting cell growth and induction of cell differentiation and apoptosis. Some of the N-heterocycles compounds approved by the US FDA are shown in Table. However, despite their wide range of biological activities along with their anticancer activity still there is a need for the development of novel, practical, and efficient methods for nitrogen-containing heterocyclic synthesis which nowadays becomes an important goal in modern organic synthesis. We represent here the overview in the synthesis of N-Heterocyclic compounds, their anticancer potency and some in silico modeling studies reported by various co-workers.



DESIGN STRATEGIES AND STRUCTURE-ACTIVITY RELATIONSHIP

Benzimidazole

Benzimidazole is a very important class of heterocyclic compounds in the area of drug design, the synthesis of benzimidazoles has received considerable attention in the past few decades [6]. Apart from the clinically approved benzimidazole derivatives albendazole, mebendazole, thiabendazole (anthelmintics); omeprazole, lansoprazole, pantoprazole (proton pump inhibitors); astemizole (antihistaminic); enviradine (antiviral); candesartan and telmisartan (antihypertensives), benzimidazole nucleus is also part of many antineoplastic derivatives [10]. Novel benzimidazole derivatives were designed, synthesized as potential SIRT1 and SIRT2 inhibitory activity by Yoon et al. in 2014. When tested compound 1 displayed the best inhibitory activity for SIRT1 (IC50 ¼ 54.21 mM) as well as for SIRT2 (IC50 ¼ 26.85 mM). Cell proliferation assay results also showed that compound 1 possessed good antitumor activity against three different types of cancer cells i.e. colon (HCT-116), breast (MDA-MB-468) and blood-leukemia (CCRF-CEM) with cell viability of 40.0%, 53.2% and 27.2% respectively at 50 mM. Docking studies of compound 1 into SIRT2 (PDB: 3ZGV)

revealed that the interaction with receptor was primarily due to hydrogen bonding and π-π stacking interactions [6]. Kamal et al. in 2015 reported a series of twenty aryl pyrazole linked benzimidazole conjugates as a microtubule destabilizing agents. The design makes the joining of aryl pyrazole to the benzimidazole moiety resulted in a four ring (A, B, C and D) with the polar heterocyclic rings in the middle and substituted aryl rings placed in the opposite directions attached with rotatable bonds. The synthesized compounds were evaluated against sixty cancer cell line panel of the NCI. Among the synthesized compounds 3 with methoxy group on D-ring expressed appreciable cytotoxic potential. A549 cells treated with 2, 3 and 4 arrested cells at G2/M phase apart from activating cyclin-B1 protein levels and disrupting microtubule network. These compounds effectively inhibited tubulin polymerization with IC50 values of 1.3e3.8 mM. Furthermore, a competitive colchicine binding assay and molecular modeling analysis suggest that these conjugates bind to the tubulin successfully at the colchicine binding site [7]. Novel benzimidazole acridine derivatives were designed and synthesized keeping in context that acridines can intercalate into DNA and benzimidazoles have the ability to bind in the DNA minor groove by Gao et al. in 2015. MTT assay indicated that most of the synthesized compounds displayed good antiproliferative activity, among which compound 5 demonstrated the highest activity against both K562 and HepG2 cells. Compound 5 could induce apoptosis in K562 cell lines and also displayed good DNA-binding capability and inhibited topoisomerase I activity [8]. New hybrid quinazoline and benzimidazole regioisomeric molecules were synthesized and evaluated against 60 cancer cell line panel by Paul et al. Compound 6, 7 showed the anticancer activity with GI50 value of 1.64 mM and 0.81. In vitro evaluation of compound 7 exhibited remarkable anticancer activity towards colon cancer cell lines and prostate cancer cell lines at five dose concentrations with GI50 values of 0.34 and 0.31 mM, respectively [9]

Indole

Indole ring is one of the widely distributed heterocycles in nature. Indole core forms the key components in naturally occurring plant hormone e.g. auxins while tryptophan, serotonin or 5- hydroxytryptamine (5-HT) and melatonin play an important role in physiological and biochemical process in animals [13]. Indole ring system has been becoming an important structural component in many pharmaceutical agents, such as

antidepressant, anticonvulsant, antifungal, antiviral and anti-inflammatory, particularly in the discovery of new antitumor agents [12]. Oxindole structure such as SU4984 and intedanib as RTK inhibitors led the synthesis of two series of new heterocyclic compounds containing oxindole scaffold and evaluated against the proliferation of nine cancer cell lines by Chen et al. in 2014. Among them, compounds 57 and 58 displayed the strongest anti-proliferative activity with the IC50 below 10 mM. Flow cytometric analysis showed that the compounds 57 and 58 dose-dependently arrested the cell cycle at G0/G1 phase. Molecular docking studies in the ATP-binding site demonstrated that 57 and 58 are potent inhibitors of the c-Kit kinase (PDB: 3G0E). These compounds are worthy of further evaluation as anticancer agents [11].

Acridine

In 1920s acridine and its derivatives (planar tricyclic aromatic molecules) were reported with anticancer potential [14]. Acridine analogs have been used for the treatment of inflammation and cancer for many years because of its unique planar ring structure which makes its strong interaction with DNA base pairs [15]. Azab et al. in 2013 synthesized new bis(acridine-9-carboxylate)-nitroeuropium(III) dihydrate complex 86 and highlight in-vivo antiangiogenic activities against Ehrlich ascites carcinoma (EAC) cells. The newly synthesized complex showed inhibition of proliferation of EAC cells and ascites formation through anti-angiogenic activity by the reduction of microvessel density in EAC solid tumors. The anti-angiogenic effect is mediated through down-regulation of VEGF receptor type-2 (Flk-1). Further, the complex exhibited antiangiogenic, apoptotic activity in vivo. It was also found that interaction between the europium(III)-acridine and DNA was via intercalation. Fluorescence technique was used to study the interaction of calf thymus DNA (ct-DNA) with bis(acridine-9-carboxylate)- nitro-europium(III) dihydrate complex 86. New acridine-based derivatives were synthesized and Li et al. reported their antiproliferative activity against K562 and HepG-2 cell lines in 2014. Compound 87 with pyridin-2-yl-methanamino group substituted at the C9 position of acridine showed good antitumor activity against both cell lines [16].

Oxadiazole

oxadiazole is a versatile lead molecule for designing potential bioactive agent [17]. 1,3,4-oxadiazoles are thermally stable and neutral heteroaromatic molecules and associated with potent pharmacological activity due to the presence of toxophoric eN¼CO- linkage [18]. 1,3,4-Oxadiazole derivatives have attracted significant attention because of their diverse pharmacological activities, including antibacterial, anti-inflammatory, antihypertension, muscle relaxing and anticancer activities [70]. Novel hybrid molecules containing 1,3,4-oxadiazole and 1,3,4-thiadiazole bearing Schiff base moiety were designed, synthesized. In vitro antitumor activities against SMMC- 7721, MCF-7 and A549 human tumor cell lines by CCK-8 assay were performed by Zhang et al. 2014. Compound 104 showed the best inhibitory effect against SMMC7721 cells; with an IC50 value of 2.84 mM. Compounds 105 and 106 displayed highly effective antitumor activities against MCF-7 cells, with IC50 values of 4.56 and 4.25 mM. Compounds 103 and 106 exhibited significant antiproliferative activity against A549 cells, with IC50 values of 4.11 and 4.13 mM, respectively [17].

Isoxazoles

Isoxazole and some naturally occurring isoxazole derivatives have attracted considerable attention from organic and medicinal chemists due to their significant biological activities [20]. Ibotenic acid from the Amanita muscaria mushroom is a potent neurotoxin. Similarly, muscimol, produced naturally in the Amanita muscaria, is an agonist of g-aminobutyric acid a receptor (GABAAR) which plays a role in regulating neuronal excitability in the central nervous system [19]. Shakeel-u-Rehman et al., in 2014 showed the anticancer activity against a panel of five different human cancer cell lines viz. prostate (PC-3), colon (HCT-116 and Colo-205), leukemia (HL-60) and lung (A-549) using MTT assay from the newly synthesized diverse isoxazoles and triazoles linked 6- hydroxycoumarin. Synthesized isoxazoles, compounds 148 and 149 showed the best activity with IC50 of 8.2 and 13.6 mM against PC-3 cancer cell line, while as, among the triazoles, compounds 150 and 151 were the most active with the IC50 of 10.2 and 12.6 mM against A-549 cancer cell line. Das et al. in 2015 introduced a series of 4-bromo spiro-isoxazolines possessing a variety of aromatic and aliphatic substituents at the 3 position, and screened it for in vitro anticancer activity

against two breast cancer cell lines (MCF-7 and MDA-MB-231) and two prostate cancer cell lines (PC-3 and DU-145) using the MTT viability assay by. Spiro-isoxazoline derivatives bearing a p-chloro or an o-dichloro aromatic substituent at the 3-position of the isoxazoline (152, 153) showed considerable antitumor activities in all four cell lines with IC50 values ranging from 43 mM to 56 mM.

CONCLUSION

The feature of the fusion of pharmacophoric subunits to generate more potent compounds. Some derivatives of Novel isosteviol-fused pyrazoline, ursolic acid linked triazole or D-ribose linked triazole exhibiting anticancer activity at nanomolar range. Various heterocyclic rings in particularly with benzimidazole have also shown to possess significant antitumor properties. Furthermore, the structureactivity relationships clearly indicate in the success of these hybridization techniques in reducing side effects and increase the selectivity. The successful synthesis and antitumor activity of these reviewed nitrogen-containing heterocyclic moieties in past few years are certainly a bright spot. However it has fallen short in treating cancer, thus lacks in the meeting our expectation and needs. A strong improvement is possible in coming years but that is dependent on the specific design of molecules targetting a single receptors/enzyme/protein, particularly keeping in mind to lessen side effects and toxicity. Synthesizing more such heterocyclic compounds targeting enzymes in modulating disease condition is the need of the hour.

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