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A THERAPEUTIC JOURNEY OF SULFONAMIDE DERIVATIVES AS POTENT ANTI-CANCER AGENTS: A REVIEW

Ali Irfan[1]*, Fozia Batool[1], Shamsha Irum[1], Sami Ullah[1], Muhammad Umer[1], Rabia Shaheen[1] and Amar Jeet Chand[1]

[1]Department of Chemistry, the University of Lahore, Sargodha Campus, Pakistan.

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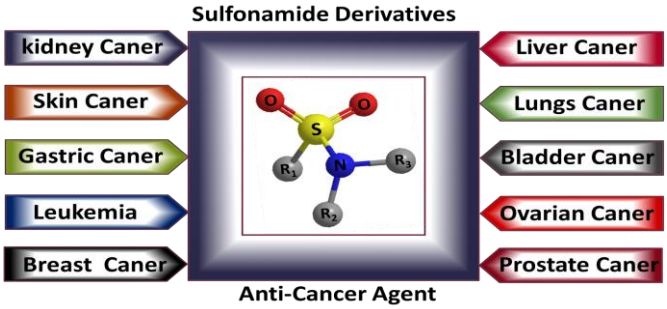
***Corresponding Author**
Ali Irfan
Department of Chemistry,
the University of Lahore,
Sargodha Campus, Pakistan.

ABSTRACT

Sulfonamide moiety is a core part of many clinical drugs which have broad spectrum applications in the fields of medicine, pharmacology and pharmaceutics such as antibacterial, antiviral, antifungal, anti-inflammatory, anti-carbonic anhydrase, diuretic, protease inhibitor, anti-diabetic, anti-cancer, anti-epileptic drug, cyclooxygenase-2-inhibitor, anticonvulsant, receptor tyrosine kinase inhibitors, anti-tumor and antipsychotic sulpiride etc. This review article focuses on the role of different sulfonamide scaffolds in the treatment of lethal cancer disease on the basis of structure-activity relationship (SAR). The analogs, scaffolds and combinatorial libraries of sulfonamide mentioned in this plethora of research is very helpful for drug discovery and development of novel anticancer therapeutic agents.

KEYWORDS: Sulfonamide derivatives, Anti-cancer, anti-tumor, Pyrimidine, Pyridin, Thiazole, Carbazole.

Graphical Abstract



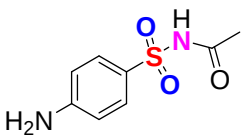
INTRODUCTION

The sulfonamide is an organic compound in which sulfonyl group attached to amine group. The general formula of sulfonamide is RSO_2NH_2.[1] The sulfonamide functional group is present in different medicines. The general sulfonamide functional group is given below.[2]

1

Figure 1.0: The structure of sulfonamide functional group.

The sulfonamides (sulfa drugs) are large group of antibiotics which are also used widely in different clinical purposes.[3] The prontosil was first sulfa antibiotic which was synthesized in laboratories of Bayer AG in 1932.[4] Sulfonamide is a base for different drugs such as sulfacetamide, sulfadiazine, acetohexamide, carbutamide, and acetazolamide.[5]



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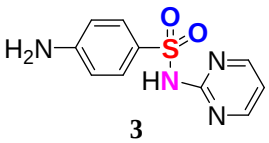
Sulfacetamide



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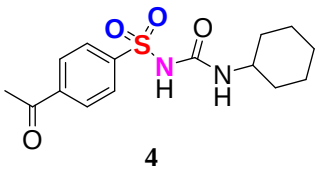
Sulfadiazine



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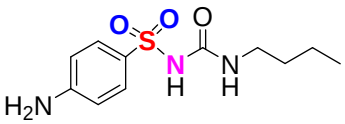
Acetohexamide



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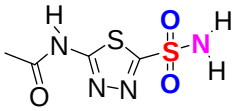
Carbutamide



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Acetazolamide

Figure 1.1: Different structures of sulfonamide drugs.

Sulfonamide based scaffolds are an important therapeutic agents which exhibited various biological activities. The sulfonamide derivatives demonstrated different antibacterial, anti-inflammatory, antimicrobial, antifungal, anti-malarial, antitumor, anti-diabetic, anti-viral[4] and anti-convulsant[5] activities.

Sulfonamide based drugs are clinically used in the cure and treatment of various types of cancer cells of different body parts. Cancer is a disease which deals with the growth of abnormal cells that quickly proliferative to other body parts. There are different types of cancers such as lung cancer, liver cancer, prostate cancer, breast cancer, pancreatic cancer, skin cancer, and lymphoma.[6] Each type of cancer has different symptoms. Cancer is a

worldwide health problem and the most fatal disease in humans. The causes of cancer are environmental pollution, poor food quality, unawareness in public and different sources of carcinogens. Cancer is increasing regularly day by day due to increase of these factors. Cancer can be treated via radiotherapy, surgery and chemotherapy.[7]

The literature survey of last decade mentioned in this review article provide a comprehensive insight that the heterocyclic moieties substituted with the sulfonamide core have effect on the therapeutic potential of sulfonamide derivatives against different types of cancer cell lines. The present study shows that the synthesized anti-cancer sulfonamide combinatorial libraries, analogs and scaffolds can be helpful for the development of new drugs design and future drugs discovery in pharmaceutics and medicine praxis.

Ghorab et al in 2014 synthesized sulfonamide derivatives having antitumor activity against Michigan Cancer Foundation-7 (MCF-7) cell line. The thiophene based thiazole sulfonamide scaffold 7, thiophene based pyrazole sulfonamide derivative 8 and thiophene based pyrimidin sulfonamide derivative 9 exhibited best activity against MCF-7 cell line from all the synthesized derivatives with IC_{50} values 10.25, 9.70 and 9.55 µmol L^{-1} respectively as compared with reference doxorubicin.[8]

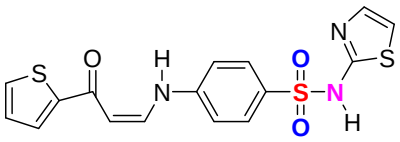

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Figure. 1.2: Thiophene based thiazole sulfonamide derivative

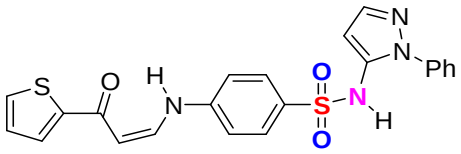

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Figure. 1.3: Thiophene based pyrazole sulfonamide derivative

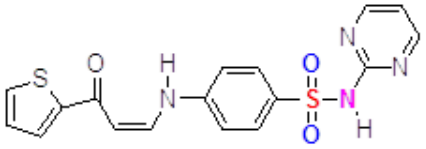

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Figure. 1.4: Thiophene based pyrimidine sulfonamide derivative

Bonakdar et al in 2017 screened chalcone based sulfonamide derivatives as anticancer agents against MCF-7 (Breast cancer) cell line. Among all these derivatives, the substituted acryloyl sulfonamide 10 scaffold showed potent anti-cancer activity as compared to the reference compound Tamoxifen with IC_{50} value 2.5 µM.[9]

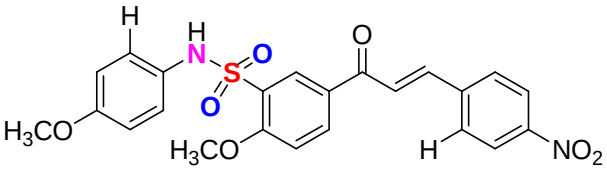

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Figure. 1.5: Substituted acryloyl sulfonamide derivatives

Reddy et al in 2016 prepared cinnamyl sulfonamide hydroxamate derivatives as anticancer activity against breast ER^+ adenocarcinoma (MCF-7), breast epithelial (MCF-10A), ER^- adenocarcinoma (MDA-MB-231), and lung cancer (A549). Among these derivatives, the NMJ-2 (cinnamyl sulfonamide hydroxamate derivative) 11 showed potent antitumor activity with the IC_{50} value 5.5 ± 0.43, 8.9 ± 0.80, 5.8 ± 0.27 and 6.5 ± 0.87 and for the MCF-7, MCF-10A, MDA-MB-231and A549 respectively.[10]

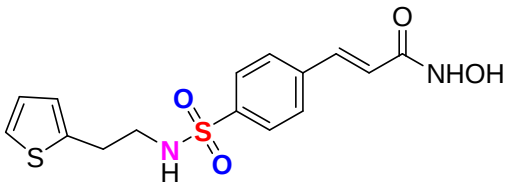

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Figure. 1.6: Cinnamyl sulfonamide hydroxamate derivative

Stawinski et al in 2013 synthesized heterocyclic substituted pyridine sulfonamide derivatives and studied their anticancer activity against 26 cell lines. Among these derivatives, the piperazine based pyridine sulfonamide 12 scaffold showed best antitumor activity against of melanoma (SK-MEL-5), breast cancer (T-47D), ovarian cancer (OVCAR-4) and leukemia (K-562) cell lines with the IGP 89%, 72 %, 65 % and 65 % respectively.[11]

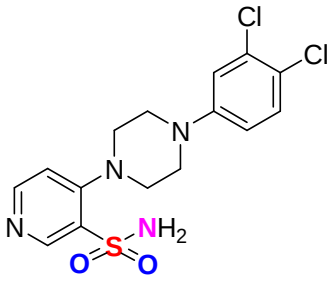

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Figure. 1.7: Piperazine based pyridine sulfonamide derivative

Ghorab et al afforded sulfonamide derivatives as anticancer activity against liver cancer cell line (HEPG2) and MCF-7 (breast cancer) cell line. Among all synthesized derivatives, pyrimidine based thiazole sulfonamide scaffold 13 showed significant antitumor activity against liver cell with the IC_{50} value 3.12 µM and pyrimidine based pyridine sulfonamide derivatives 14 against breast cancer cell with the IC_{50} value 3.15 µM.[12]

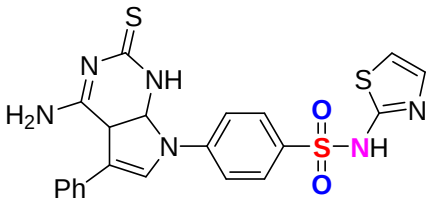

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Figure. 1.8: Pyrimidine based thiazole sulfonamide derivative

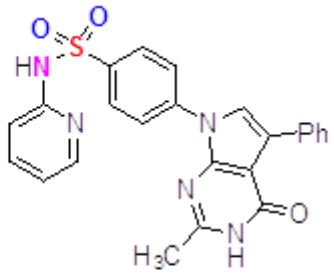

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Figure. 1.9: Pyrimidine based pyridine sulfonamide derivative

Luo et al in 2011 afforded cinnamic acyl sulfonamide derivatives as anticancer agent. The substituted acryl sulfonamide derivative 15 showed best antitumor activity against B16-F10 cell line (melanoma) having IC_{50} value 0.8µg/ml.[13]

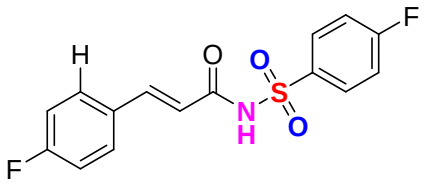

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Figure. 1.10: Substituted acryl sulfonamide derivative

Zayed et al afforded quinazolinone sulfonamide derivatives and evaluated their anticancer activities. The pyrimidine based quinazolin sulfonamide derivative 16 showed best antitumor activity against NCI (National Cancer Institute) lung cancer cell line with the IC_{50} value 2.51 ± 0.48 µM. The methotrexate used as reference drug with the IC_{50} value 2.4 ± 0.23 µM.[14]

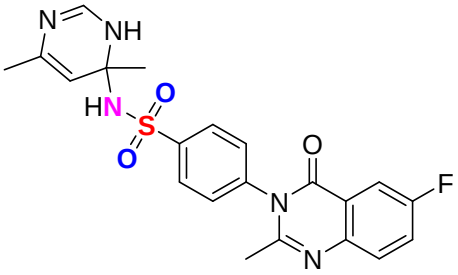

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Figure. 1.11: Pyrimidine based quinazolin sulfonamide derivative

Lu et al in 2011 synthesized pyridine acyl sulfonamide derivatives tested for anticancer therapeutic potential against different cancer cell lines. Among the series of derivatives, pyridine based sulfonamide scaffold 17 demonstrated best antitumor activity against MCF-7 and HepG2 cell line having IC_{50} value 1.8 and 1.2µM.[15]

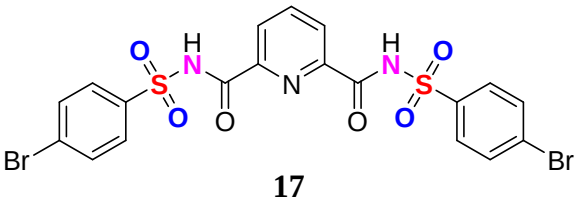

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Figure. 1.12: Pyridine based sulfonamide derivavtive

Ghorab et al in 2015 afforded sulfonamide derivatives and demonstrated their anti-tumor activities. The substituted hydrazinyl sulfonamide scaffold 18 showed highest anticancer activity against HEPG-2 cell line (liver cancer) having IC_{50} value 11.0 µM and doxorubicin used as the reference drug.[16]

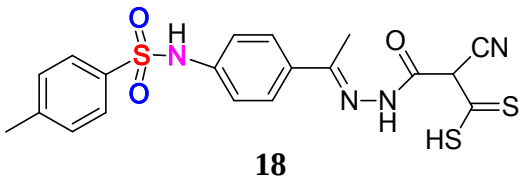

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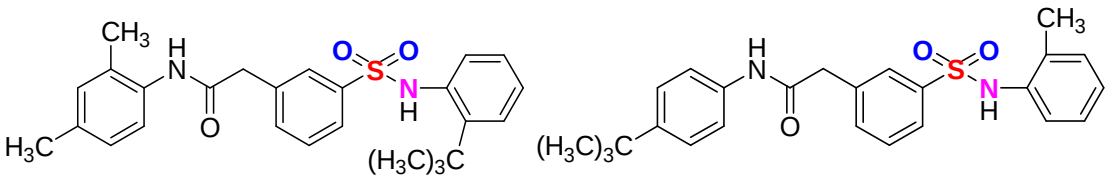
Figure. 1.13: Substituted hydrazinyl sulfonamide derivative

Pawar et al synthesized *N*-(substituted phenyl)-2-(3-substitued)sulfamoyl) phenyl) acetamide derivatives having antitumor activities. The derivative 19, 20 and 21 exhibited highest anti-tumor activity against MCF-7, cervical (HeLa 31), prostate cancer (Du-145) and lung cancer (A549) cell lines. The derivative 19 showed IC $_{50}$ ± SD values 2.36 ± 0.12, 1.99 ± 0.22, 2.52 ± 0.11 and 1.82 ± 0.11 µM for MCF-7, HeLa 31, Du-145 and A549 respectively. The scaffold 20 have IC $_{50}$ ± SD values 2.52 ± 0.16 for MCF-7, 2.52 ± 0.16 for HeLa 31, 2.12 ± 0.08, for Du-145 and 2.06 ± 0.12 for A549. The IC $_{50}$ ± SD values for compound 21 were 2.12 ± 0.08, 2.12 ± 0.08, 2.32 ± 0.11 and 2.02 ± 0.11for MCF-7, cervical cancer, prostate cancer and lung cancer cell lines respectively.[17]



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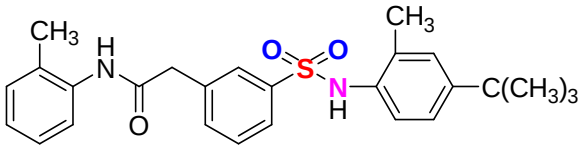

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Figure 1.14: *N*-(substituted phenyl)-2-(3-substitued) sulfamoyl) phenyl) acetamide derivatives.

Kamel et al in 2010 afforded sulfonamide shiff's base derivatives and evaluated their anticancer activity against cervix carnomia HeLa cell line and MCF-7 cell line. In these derivatives, substituted pyridine sulfonamide scaffold 22 showed best antitumor activity against MCF-7 with the IC_{50} value 0.74 m/mL and thiazine based pyridine sulfonamide derivative 23 showed highest antitumor activity against HeLa having IC_{50} value 1.48 mg/ mL. The compounds 5-flurouracil and doxorubincin are used as reference drugs.[18]

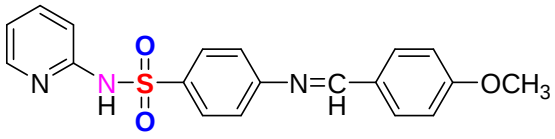

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Figure. 1.15: Substituted pyridine sulfonamide derivative

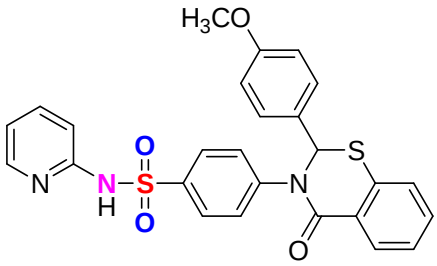

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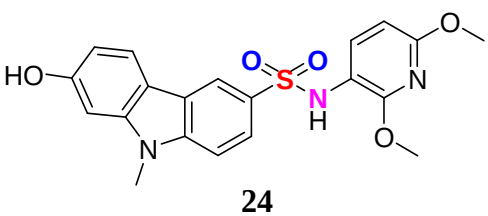
Figure. 1.16: Thiazine based pyridine sulfonamide derivative

Sun et al in 2016 synthesized carbazole sulfonamide derivatives and studied their anti-tumor activity against hepatoma cancer (HepG2), MCF-7, pancreatic cancer (MIA PaCa-2) and liver cancer (Bel-7402). The substituted carbazole sulfonamide derivatives 24 and 25 showed potent antitumor activities. The IC_{50} values of the scaffold 24 were 0.012, 0.051, 0.014 and 0.056 µM for HepG2, MIA PaCa-2, MIA PaCa-2, and Bel-7402 cell lines respectively. The compound 25 have IC_{50} value 0.071 µM for HepG2, 0.092 µM for MIA PaCa-2, 0.036 µM for MIA PaCa-2, and 0.18 µM for Bel-7402 cell line.[19]



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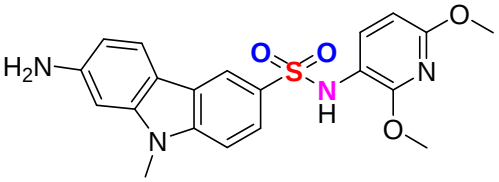

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Figure. 1.17: Substituted carbazole sulfonamide derivatives

A series of quinoline sulfonamide combinatorial libraries were afforded by Ghorab et al in 2009. They studied their antitumor activity against MCF-7 cell line. In the series of these derivatives, quinolone based pyrimidine sulfonamide derivative 26 showed potent anticancer activity with the IC_{50} value 2.37 µM and doxorubicin was used as reference compound.[20]

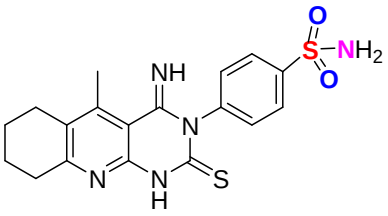

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Figure. 1.18: Quinoline based pyrimidine sulfonamide derivative

Zaib et al in 2015 afforded tosyl sulfonamide derivatives and evaluated their anticancer activity. The Zn(II) complex based tosyl sulfonamide derivative 27 evaluated as best anticancer activity against H-157 (lung carcinoma cancer cell line), BHK-21 (kidney fibroblast cell line), and vero cell line with IC_{50} ± SEM value 1.82 ± 0.11 µM, 2.19 ± 0.15 µM and 13.7 ± 1.8 % when compared with vincristine.[4]

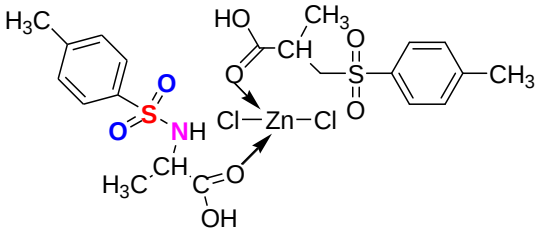

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Figure. 1.19: Zn(II) complex of tosyl sulfonamide derivative

Ghorab et al in 2011 synthesized a series of sulfonamide derivatives and tested these derivatives as potential anti-tumor agents. The pyran moiety containing thiazole sulfonamide scaffold 28 showed best antitumor activity against MCF-7 cell line with the IC_{50} value 34.64 µM when compared to doxorubicin as reference.[21]

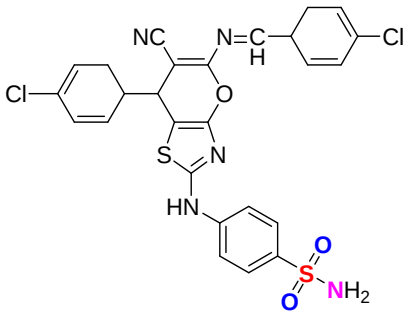

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Figure. 1.20: Pyran based thiazole sulfonamide derivative

Sayed et al in 2011 synthesized thiadiazolo based pyrimidine sulfonamide derivatives as anti-cancer activity. Among all these derivatives, substituted thiadiazolo based pyrimidine sulfonamide scaffolds 29, 30, and 31 showed potent antitumor activity in mice against Ehrlich ascites carcinoma (EAC) and increase the lifespan of the mice.[22]

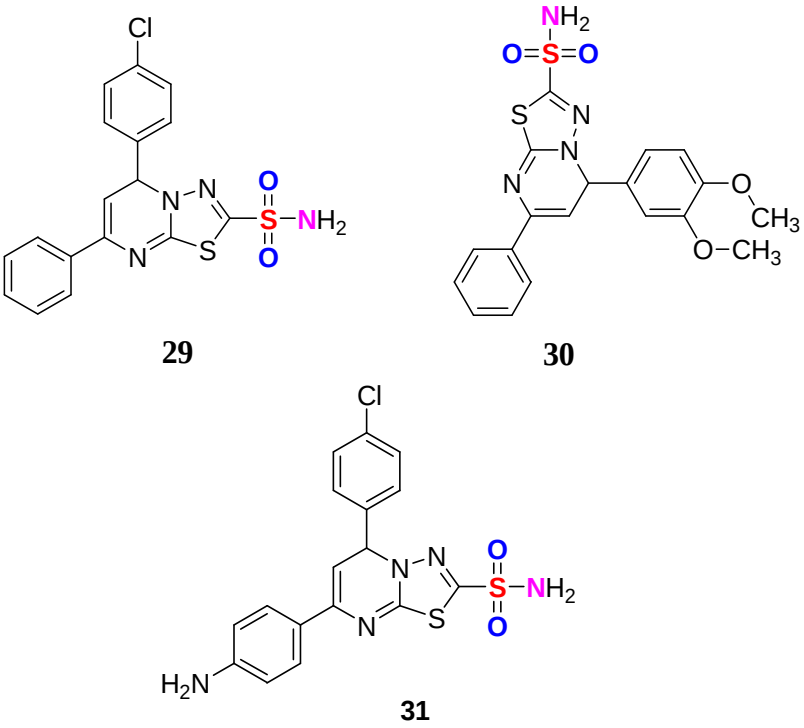

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Figure. 1.21: Substitued thiadiazolo based pyrimidine sulfonamide derivatives

Wang et al in 2014 afforded metronidazole sulfonamide derivatives evaluated their anticancer activities. The scaffold pyrimidine based imidazole sulfonamide 32 and thiazole based imidazole sulfonamide 33 showed highest antitumor activity against MCF-7 and B16-F10 (mouse melanoma cells) with the IC_{50} value 6.5 nM for MCF-7 and 150 nM for B16-F10 cell lines respectively when compared with semaxanib and doxorubicin as reference drugs.[23]

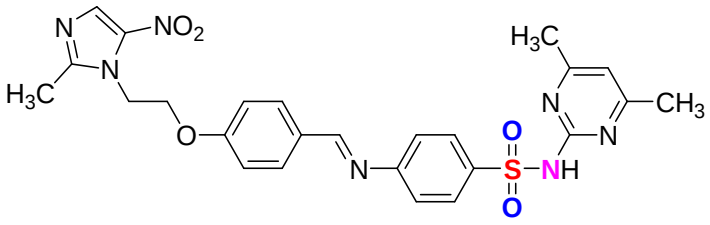

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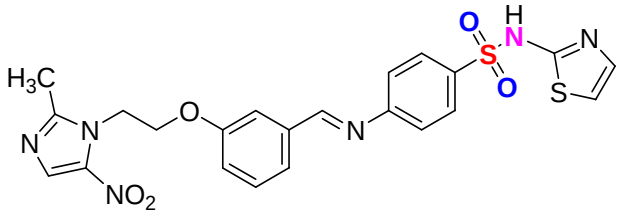
Figure. 1.22: Pyrimidine based imidazole sulfonamide derivatve



33

Figure. 1.23: Thiazole based imidazole sulfonamide derivative

Bavadi et al in 2017 synthesized pyrrole sulfonamide derivatives as anticancer activity against MCF-7, acute lymphoblastic leukemia (MOLT-4) and promyelocytic leukemia cell (HL-60). The substituted pyrimidine based pyrrole sulfonamide derivative 34 showed potent antitumor activity with the IC_{50} value 39.0 ± 4.5 µM for the MCF-7, 25.5 ± 1.1 µM for MOLT-4 and 30.6 ± 3.6 µM for HL-60 cell lines when compared with cisplatin reference drug.[24]

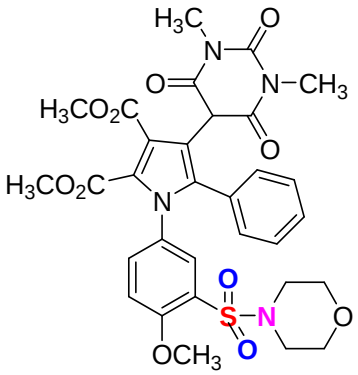


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Figure. 1.124: Substituted pyrimidine based pyrrole sulfonamide derivative

CONCLUSION

Sulfonamide scaffolds and analogs have broad spectrum applications in the fields of medicine, pharmaceutics and pharmacology such as anti-cancer, anti-tubercular, anti-leishmanial antimicrobial, anti-inflammatory, anti-diabetic, anti-convulsant and anti-depressant etc. Although the sulfonamide derivatives have significant and vast applications in the fields of medicine, pharmaceutical and pharmacological, the anticancer role of sulfonamide derivatives have been the main focus of this review article. This review article reveals that some sulfonamide derivatives have higher potency and better therapeutic index than the reference drugs. Sulfonamide derivatives demonstrated excellent and promising activities against different types of cancer cell lines such as breast cancer, lung cancer, liver

cancer, gastric cancer, kidney cancer, bladder cancer, skin cancer, leukemia, ovarian cancer and prostate cancer etc. Some of sulfonamide derivatives mentioned in the this review are of biological and pharmacological interest due to high potency and efficacy which will be helpful for researcher in the future drug discovery and drug design for the safer treatment of cancer disease.

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