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Quinazolinone Derivatives: Recent Structures with Potent Cytotoxic Activity

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ABSTRACT

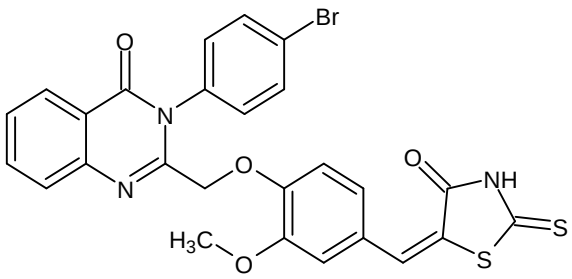
In medical chemistry, heterocyclic molecules are extremely important. Quinazolinone is a heterocycle with antibacterial, antifungal, anticonvulsant, anti-inflammatory, anti-HIV, anticancer, and analgesic characteristics, making it one of the most important heterocycles in medicinal chemistry. This skeleton is a privileged structure and an important pharmacophore.The latest breakthroughs in the synthesis of quinazolinone derivatives with significant cytotoxic properties are highlighted in this study.

1 Introduction

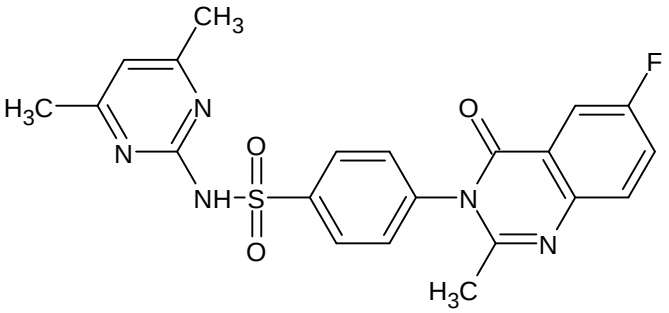
In medicinal chemistry, quinazolinones are noteworthy due to their wide range of biological activities such as anticonvulsants,(1),(2) anti-inflammatory, antibacterial,(3) anti-diabetic,(4) antifungal,(5) anticancer,(6) anthelmintics,(7) and antiviral(8). Quinazolinone derivatives produce their anticancer activity by potent inhibition of different enzymes, such asepidermal growth factor receptor tyrosine kinase, dihydrofolate reductase, folate thymidylate synthase, tyrosine kinase, aldose reductase, cyclic GMP phosphodiesterase and DNA repairing enzymes(6).There are several approved drugs with quinazolinone structure in the market such as, gefitinib and erlotinib.This review mainly focuses on recent quinazolinones structures with potent cytotoxic activity.The most recent references have been taken into account.

2 Review of literature

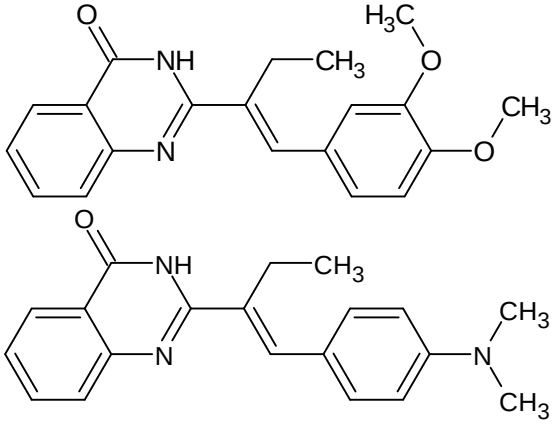
A variety of compounds containing quinazolinone-based rhodanines were synthesized by sayed *et al*and his colleagues and were found to be effective against leukemia cell lines, exhibiting in vitro cytotoxic activity in the micromolar scale.The significant activity against the leukemia cell lines was shown by four compounds.Among them one molecule showed IC50 values of 1.2 and 1.5µM.(9)



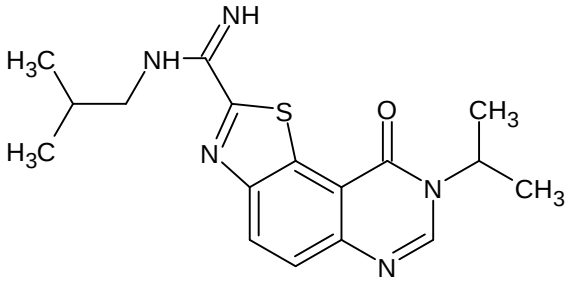
Zayed *et al*and his coworkers synthesized eight novel fluorinated quinazolinone sulphonamide derivatives and tested them for their cytotoxic activity in vitro. All newly synthesized compounds had substantial activity. Among them,4,6-dimethylpyrimidine-2-yl derivative compounds displayed promising activity and were considered to be safe because they were able to kill cancerous cells more competitive than non-cancerous cells(10).



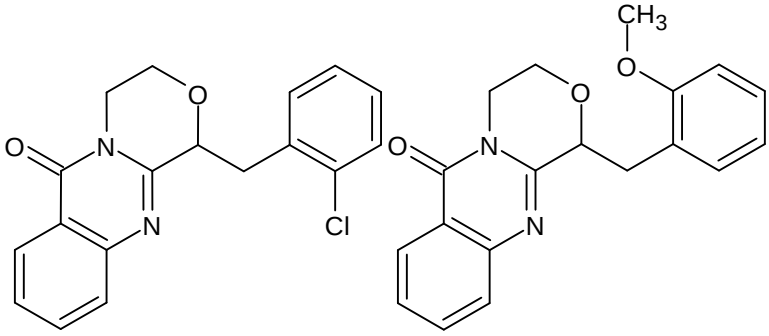
A sequence of 2,3-disubstituted-4-(3*H*)-quinazolinones were obtained from reactions of 3-aminoquinazolin-4(3*H*)-one derivative with other carbon electrophiles, such as chloracetamide, acetate anhydride, phenyl isocyanate and ethyl chloroacetate, and have been synthesized by hashash *et al* and his coworkers.The newly synthesized compounds have been evaluated against breast cancer, hepatocellular carcinoma, cervical cancer and human promyeolytic leukemia cell lines for their in vitro cytotoxic activity. All the compounds tested showed activity against cancer.(11)



In an attempt to identify a potent and selective GSK-3 inhibitors loge *et al* and his coworkers have synthesized2,8-disubstituted-9-oxo-thiazoloquinazoline-2-carbonitrile bearing an nisopropyl side chain on the N-8 nitrogen and an amidine functional group with a bulky N,N-dimethylethylenediamine group of the C-2 position of the thiazole moiety. This compound exihibited submicromolar IC50 against GSK-3 and moderate activity against CDKs(12)



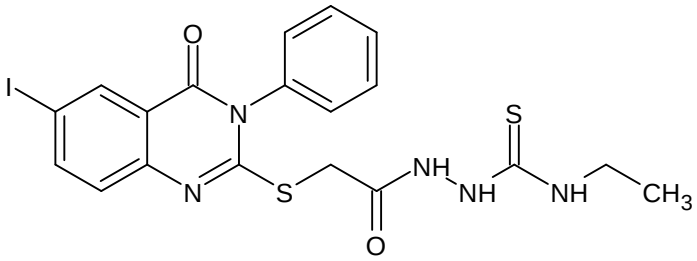
orfi *et al* synthesized 1-benzylidine and 1-phenyl hyrazone derivatives of 3,4-dihydro-1H,2H-(1,4) oxazino (3,4-b) quinazolin-6-one.. Using a cell homogenate of SW 620 human colon carcinoma cell lines as enzyme preparation, these compounds were tested for tyrosine kinase inhibitor activity. These compounds were evaluated against a synthetic peptide substrate originating from the *src* oncoprotein *pp6Osrc* autophosphorylation site, called EllG1. Two compounds from the screened compounds demonstrated strong inhibitory activity of protein kinase with an IC50 valu e ranging between 70-100 μm(13)



Khalil *et al*. investigated a new sequence of 2-substituted mercapto-3H-quinazolinone carrying 6-iodine and 2-heteroarylthio functions for their in vitro antitumor activity. The 2-SH feature of the quinazoline ring was connected to a variety of heterocycles via -CH2- or -CH2CO- bridges or directly

hooked to the sulfur atom to generate the target thioethers. Thioether functional group known to enhance the antitumor activity. N'-[(3Benzyl-4-oxo-6-iodo-3H-quinazoline-2-yl)-thioacetyl]-N3ethylthiosemicarbazide (a), N-benzoyl-N'-[2-(3-benzyl-4-oxo-6iodo-3H-quinozolin-2-yl)thioacetyl]hydrazine (d), 2-[(3,6-dioxopyridazin-4-yl)thio]-3-benzyl-4-oxo-6-iodo-3H-quinazoline (c) proved to be the most active members. They depicted MG-MID, GI50 values of 12.8, 11.3, and 13.8 μM, respectively .(14)

(a)



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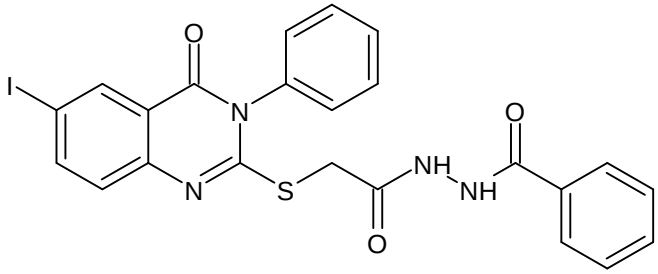
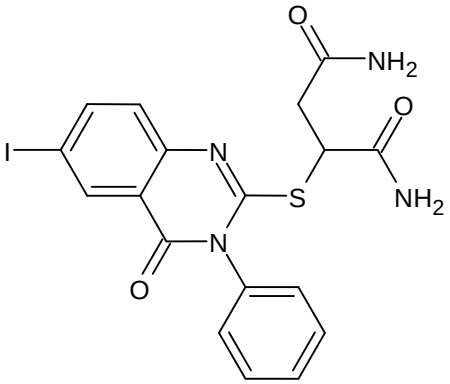
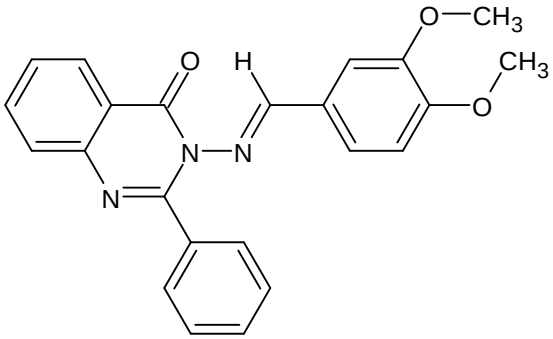


(c)

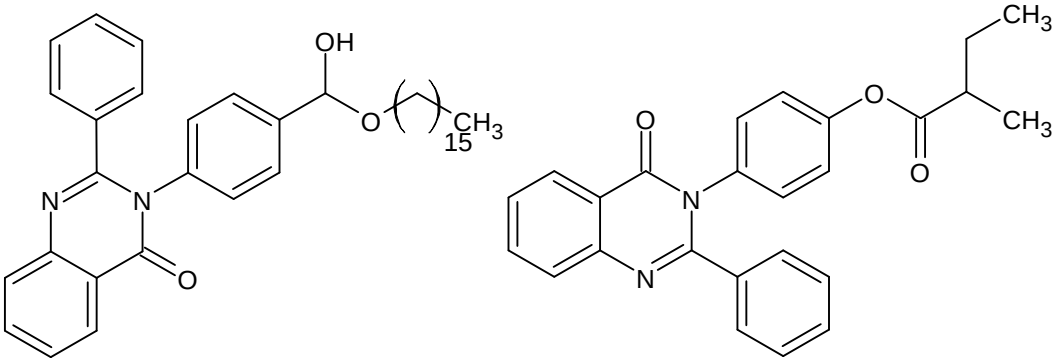


Nerkar *et al*. designed and in silico screened Schiff's bases of quinazolinones and pyridine carbohydrazide , among which the best fit molecules were selected for synthesis and in vitro anticancer evaluation against five human cancer cell lines for anticancer cytotoxicity assay. Methotrexate (MTX) was used as a monitor in this study to ensure that DHFR inhibition prevented cell proliferation in a similar way. As standards, paclitaxel, adriamycin, and 5fluoro-uracil were used. The Schiff's base derivative of pyridine carbohydrazide (4-(N, N dimethyl-amino)-phenyl), 32 Schiff's base derivative of pyridine carbohydrazide with G-Score -8.10 (approximately equivalent for all the compounds in this series) was found to be active among the pyridine carbohydrazide Schiff's bases.(15)

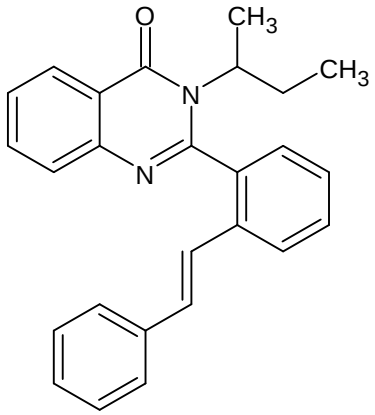


A series of novel quinazolinone derivatives were synthesized by noser *et al* and have examined for their cytotoxicity. among these derivatives compound (4 and 9) exihibited significant cytotoxic activity against caco-2, hepG2 and MCF-2 cancer cells. Compound 4 inhibited Caco-2, HepG2, and MCF7 cell lines more effectively than compound 9, with IC50 values of 23.31 0.09, 53.29 0.25, and 72.22 0.14M, respectively. The results

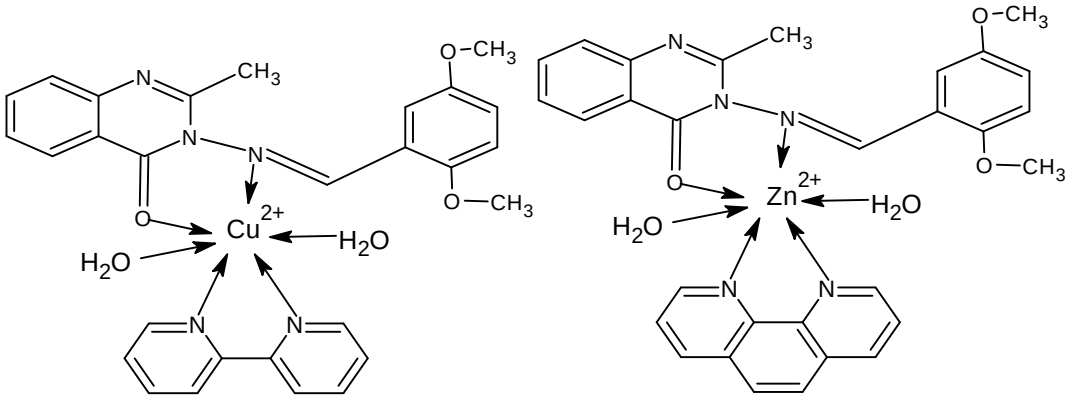
suggested that compounds 4 and 9 could be used as drug candidates for cancer therapy via its potential inhibition of AKT1 as described by docking study.(16)



A novel sequence of 2-arylquinazolinones 7a-o with a trans-stilbene moiety was synthesised and tested by M. Mahdavi *et al.* against human breast cancer cell lines, including MCF-7 and MOA-MO-231) and human ductal breast epithelial tumour (T-47D). The sec-butyl derivative had the best profile of operation (IC 50 5 micro) against all cell lines of the compounds tested.(17)



Ashok *et al* and his coworkers had synthesized three metal complexes,[Cu(DMPAQ)(Phen)].2H2O, [Zn(DMPAQ)(Phen)].2H2O, [Cd(DMPAQ)(Phen)].2H2O using a novel Schiff base ligand, [(E)-(2,5-dimethoxyphenyl)methylidene]amino-2-methylquinazolin-4(3H)-one (DMPAQ) .The synthesized DMPAQ ligand and complexes were screened for their *in vitro* anticancer activity against the human breast adenocarcinoma cell line, MCF-7. among the sythesized molecules two complexs displayed significant anticancer activity against MCF-7 cells with GI50 value (GI50=0.016µM).(18)



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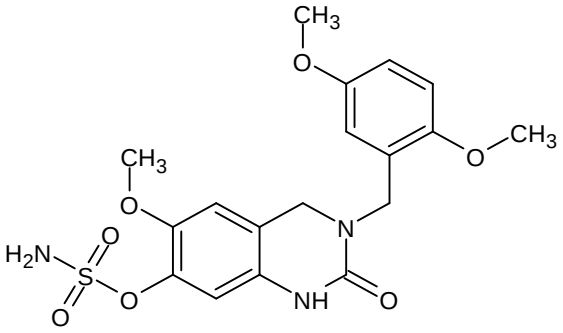
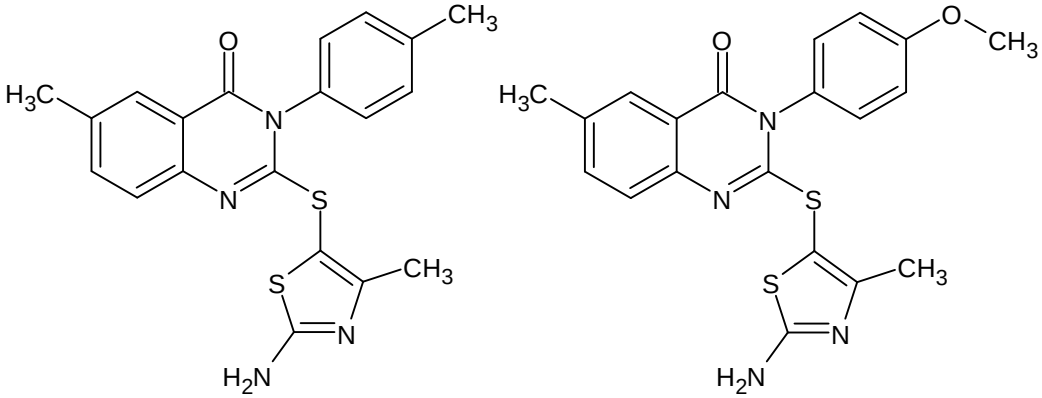
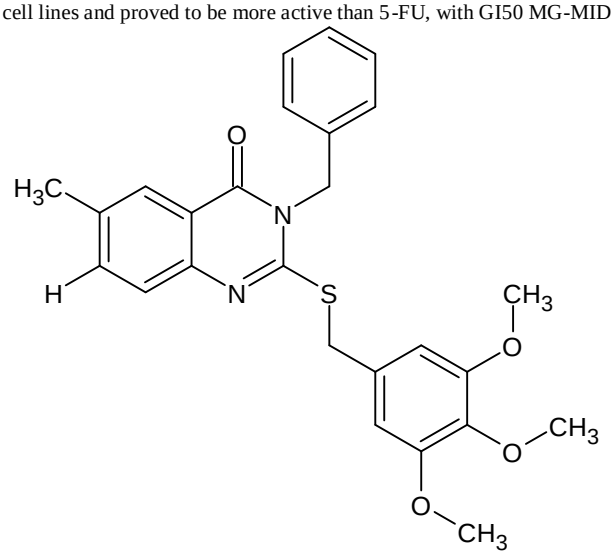
Quinazolinone-based anti-cancer agents were designed by integrating the aryl sulfamate motif of steroid sulfatase inhibitors and decorated with functional groups from a 2 methoxyestradiol-based microtubule disruptor sequence by W.Dohle *et al* and his coworkers. These compounds were evaluated against breast and prostate tumor cell lines .Among themone molecule showed anti-proliferative activity in the 50 nM range, inhibits tubulin assembly, and efficiently interferes with the colchicine site.(19)



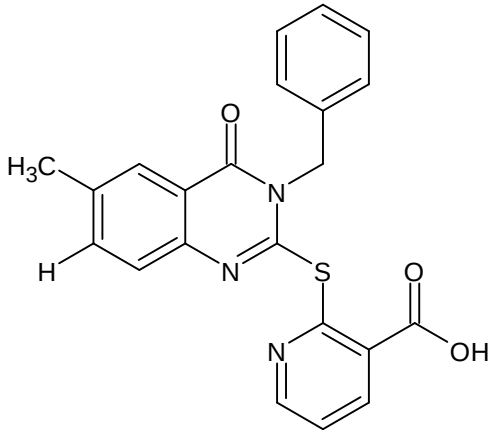
A new series of 2-(1,3,4-thiadiazolyl)thio-6-substituted-quinazolin- 4-one analogues were engineered, synthesized and tested for their in vitro for DHFR inhibition, antimicrobial, and antitumor activity by Rashood et al and his coworkers. Among the tested compounds 2 molecules showed broad spectrum antitumor activity with GI values ranges of 10.1-100% .(20)



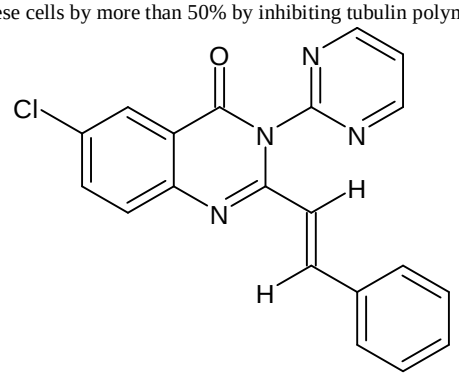
A new series of 2,3,6-substituted-quinazolin-4-ones was engineered, synthesized, and evaluated for their in vitro DHFR inhibition, antimicrobial, and antitumor activity by El-Messery *et al* and his coworkers . Among these synthesized compounds one compounds showed comprehensive spectrum antitumor activity toward diverse tumor cell lines and proved to be more active than 5-FU, with GI50 MG-MID values of 2.2 and 2.4 µM.(21)



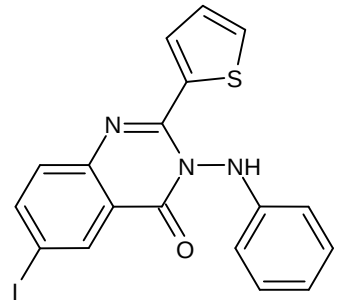
A new series of 2-heteroarylthio-6-substituted-quinazolin-4-one analogs was engineered, synthesized and evaluated for there in vitro DHFR inhibition, antimicrobial, and antitumor activities by Al-omary *et al* , Among the synthesized compounds one compound showed broad spectrum antitumor activity towards various cell lines with GI values range of 25.8-41.2.(22)



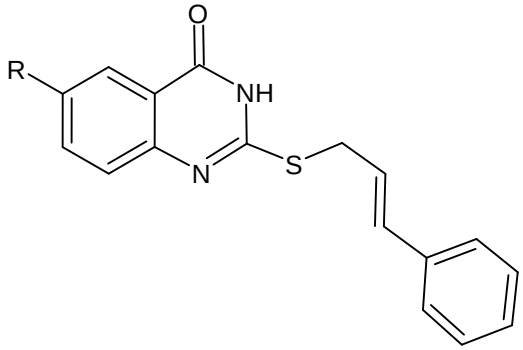
D.Raffa *et al* and his coworkers have synthesized a new series of 6-chloro-2-methyl-3-(heteroaryl)-4(3H)-quinazolinones. These compounds had some cytotoxic activity against the leukaemia cell lines LI210 and K562. One of the synthesised compounds, with an IC50 value of 5.8versus 3.2µM for colchicine, inhibited the growth of these cells by more than 50% by inhibiting tubulin polymerization.(23)



Al-obaid*et al* and coworkers synthesized 2-(2-thieno)-6-iodo-3-phenylamino-3,4-dihydro-quin-zolin-4-one. This compounds were most active member for inhibition ofepidermal growth factor receptor.(24)

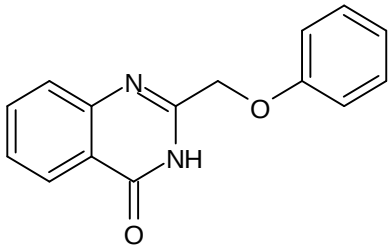


Dihydrofolate reductase (DHFR) which catalyzes the reduction of folate or 7,8-dihydrofolate to tetrahydrofolate and intimately couples with thymidylate synthase (TS) is a target for developing new cytotoxic quinazolinones. Inhibition of DHFR or TS activity, leads to 'thymineless cell death'. Al-Omary *et al*and colleagues designed and evaluated 3-benzyl-2-cinnamylthio-6-(methyl or nitro)-quinazolin-4(3H)-ones as active DHFR inhibitors.(25)

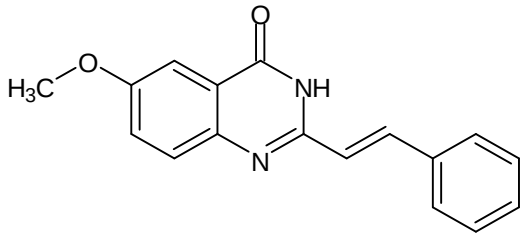


R = methyl and nitro group

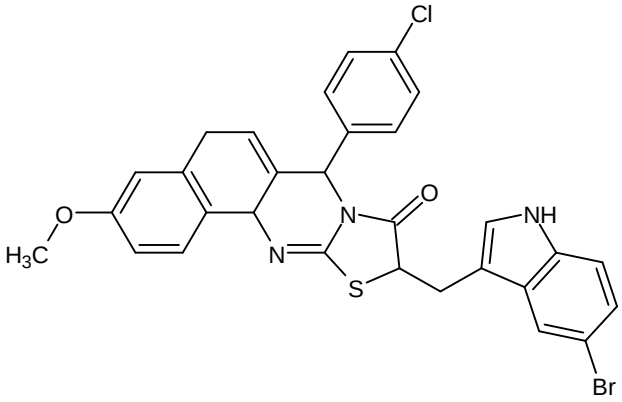
Cipak *et al*. investigated the antitumor efficacy of 2-phenoxymethyl-3H-quinazolin-4-one (PMQ) in human HL-60 leukaemia cells. The findings of this investigation clearly revealed that PMQ can be a promising anticancer drug with cytostatic and apoptotic effects mediated mostly through the mitochondrial or caspase-9 pathway.(26)



Jiang *et al*. developed 2-styrylquinazolin-4(3H)- derivatives that reduced tubulin polymerization and L1210 murine leukaemia cell proliferation. one lead chemical with promising anticancer efficacy in both murine solid tumours and human tumour xenografts.(27)



A series of novel10-((1H-indol-3-yl)methylene)-7-aryl-7 and 10-dihydro-5H-benzo[h]thiazolo[2,3-b]quinazolin-9(6H)-ones have been synthesized by Gali *et al* and his coworkers. Spectral analyses were used to identify all of the produced compounds, and they were then tested for anticancer and antibacterial activity in vitro.Among the synthesized compound one compound displayed magnificent activity against MCF-7 (breast cancer cell line) than the standard drug Doxorubicin.(28)



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