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UNLOCKING ANTICANCER POTENTIALS: RECENT ADVANCES IN EVALUATION OF CHEMICAL COMPOUNDS VIA *IN VITRO* AND *IN SILICO* STUDIES

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ABSTRACT:
Cancer is a worldwide health concern that lowers life expectancy and has a number of negative side effects from therapy. Finding new anticancer medications has become necessary as a result of cancer cells resistance to current treatments. The need for the development of innovative anticancer medications is considerable due to the rising morbidity and high death rate associated with cancer. Despite this optimism, the study points out the difficulties associated with drug resistance mechanisms and the complicated nature of pharmacokinetics, providing a foundation for further research. This study acts as a guide for researchers navigating the changing field of anticancer therapies by capturing the spirit of innovation and the essence of individuality. This review is expected to serve as useful valuable conceptual overview and encourage the upcoming generation to devise innovative approaches for the production of diverse scaffolds having anticancer properties.

KEY WORDS: Anticancer drugs, Heterocyclic compounds, Cell lines, Cell proliferation, Cytotoxicity, Computational approaches

INTRODUCTION:

Millions of dollars have been spent on research studies to try and figure out the exact processes underlying the many forms of cancer, yet the illness still has unmet medical needs. A number of small compounds that were shown to be effective in showing the disease's course have advanced to clinical usage[i]. The market is filled with both synthetic and natural anticancer medications, but they are almost invariably linked to severe adverse effects[ii]. Nowadays, the primary methods of treating cancer include surgery, radiation and chemotherapy. New alternatives for treating cancer have become available due to the recent

growth in immunotherapy[iii]. Thus far, several preclinical and clinical investigations have demonstrated increased treatment of effectiveness[iv].

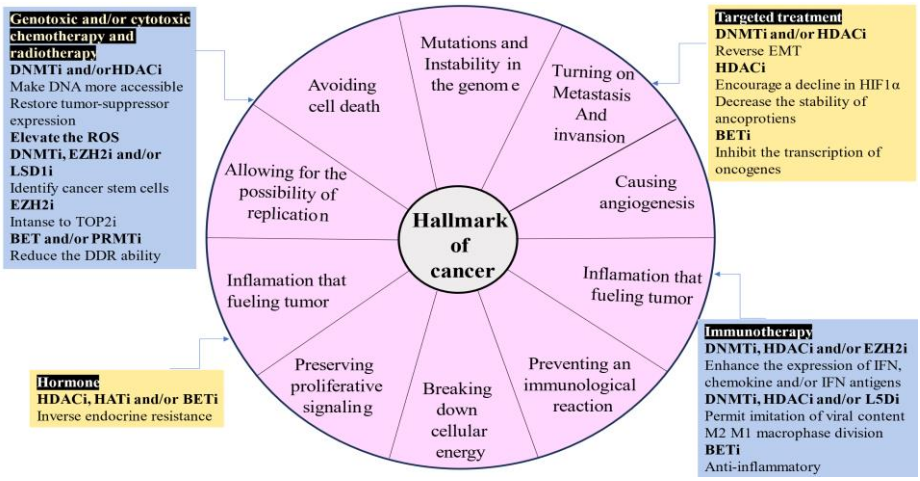
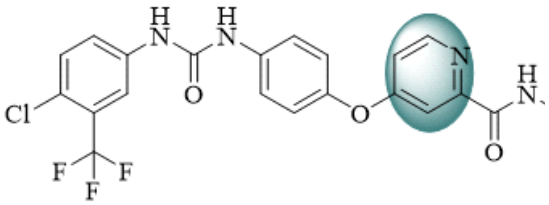
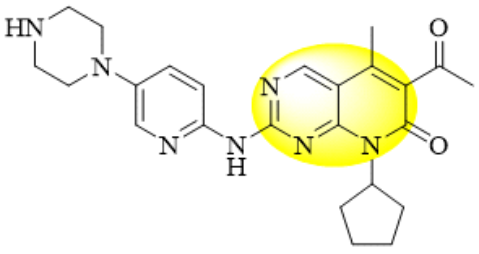
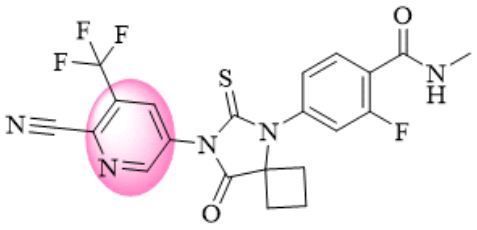
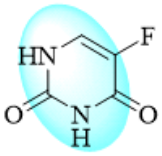
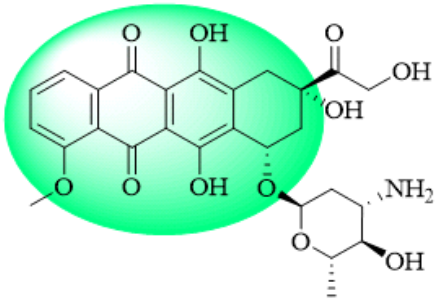
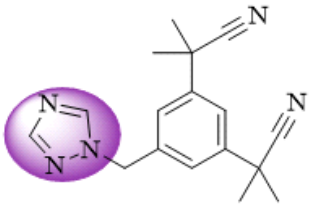
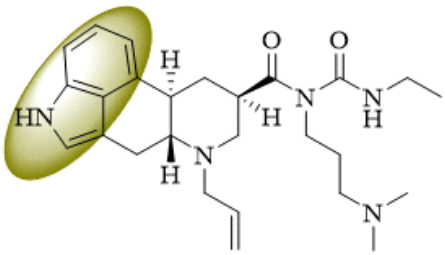
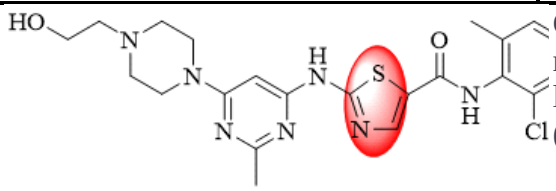
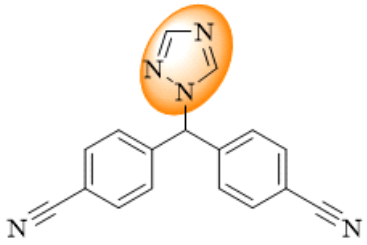
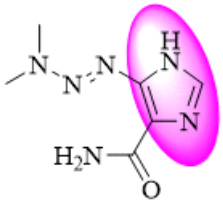
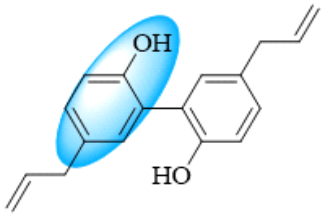
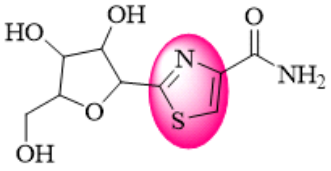
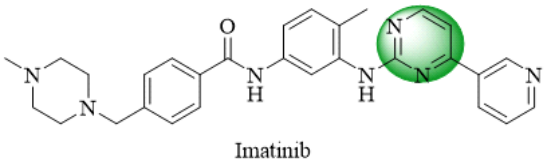
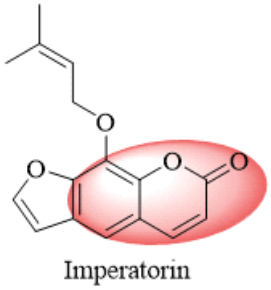


Fig.1: Popular anticancer treatments available today have inhibitory effects against a number of cancer diagnostic markers. (Explained by daphne morel and co-workers in 2020), as seen by the colored arcs encircling the cancer hallmarks wheel. The top green arc represents cytotoxic and/or genotoxic chemotherapy and radiation, the bottom yellow arc represents hormone treatment, the top yellow arc represents targeted treatment, and bottom green arc represents immunotherapy[v].

S.no.	Drug	Indication	Mechanism	Reference
1	 Sorafenib	Cancer	Inhibition of KIT, FLT-3, VEGFR-2, VEGFR-3, PDGFR-β, BRAF, and mutant BRAF	vi
2	 Palbociclib	Breast cancer	Cyclin dependent kinase (CDK) 4/6 inhibitor	vii

3	 Apalutamide	Prostate cancer	Androgen receptor inhibitor	viii
4	 5-Fluorouracil	Breast cancer, Stomach cancer, and pancreas cancer	Thymidylate synthase, disrupting DNA and RNA synthesis in cancer cells	ix
5	 Doxorubicin	Breast cancer, lung cancer, and ovarian cancer	Interact with DNA and inhibit cancer cell proliferation	x
6	 Anastrozole	Breast cancer	Blocking the enzyme that converts androgens into estrogen	xi
7	 Cabergoline	Neuro endocrine tumors, pituitary tumors	Dopamine receptor D1 (DRD1)	xii
8	 Dasatinib	Chronic myeloid leukemia (CML)	Bcr-Abl tyrosine kinase inhibitor	xiii

9	 Letrozole	Breast cancer	Blocking the enzyme aromatase, reducing estrogen levels	xiv
10	 Dacarbazine	Melanoma skin cancer, soft tissue sarcoma, Hodgkin lymphoma	Disrupting the DNA synthesis in cancer cells, inhibiting their growth	xv
11	 Magnolol	Breast, colon, esophagus, liver, lung, thyroid, prostate, and ovarian cancers	Modulates Bcl-2 family proteins, Down-regulates cyclins & CDKs, Inhibits VEGF expression	xvi
12	 Tiazofurin	AML, solid tumors, hemato-logic malignancies	IMP dihydro-genase inhibitor(IMPDH), Depletion of GTP	xvii
13	 Imatinib	CML, GIST	BCR-ABL Tyrosine kinase inhibitor	xviii
14	 Imperatorin	Gastric cancer, ovarian cancer, liver cancer, Leukemia	Apoptosis (Program-med cell death) induction, Cell cycle arrest	xix

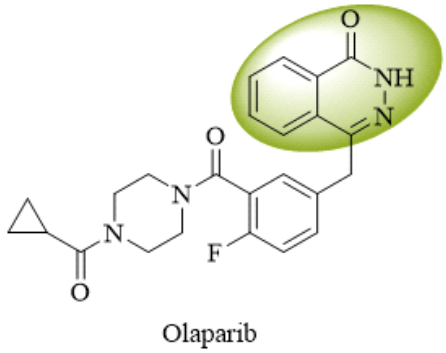
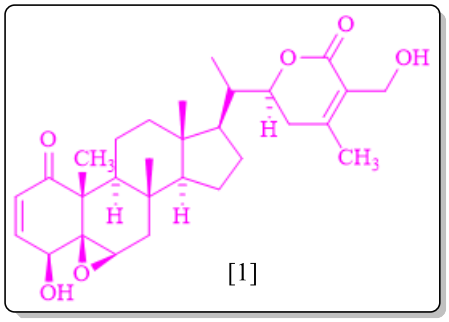
15	 Olaparib	ovarian cancer	PARP inhibitor	xx

Fig.2: Some clinically used anticancer drugs

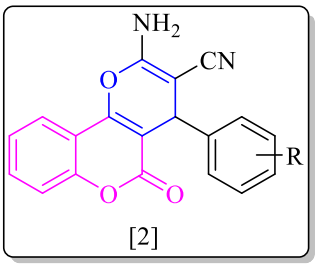
EVIDENCE FROM CHEMICAL STUDIES:

Sivasankarapillai et al. found that WA is capable of stopping both the G2 and M phases of the cell cycle. When WA is applied to MDA-MB-231 (oestrogen-independent) and MCF-7 (oestrogen-responsive) cell lines, G2-M increases in a concentration and time dependent manner. This dependence results in a decrease in the levels of Cdc25C, Cdk1, and/or Cdc25B proteins, which ultimately leads to an accumulation of tyrosine-15 phosphorylated (inactive) Cdk1. In MDA-MB-231 cells, ectopic expression of Cdc25C showed protective effective effect against cell cycle arrest in the G2-M phase, with WA mediating. In addition, WA treated MDA-MB-231/MCF-7 cells showed signs of mitotic arrest, which was attributed to elevated anaphase-promoting complex/cyclosome ensuring levels[xxi].



Structure of withaferin

El-Agrody et al. showed a sophisticated synthesis protocol of the halogenated 2-amino-4-aryl-5-oxo-4,5- dihydropyrano[3,2-*c*]chromene-3-carbonitriles (2a-m). All of the produced substances were evaluated for their *in vitro* anticancer activity against mammary gland breast cancer cell line (MCF-7), human colon cancer (HCT-116), and liver cancer (HepG-2) by using sulphorhodamine B assay (SRB) method, with doxorubicin utilized as standard reference drug. The cancer cells were treated with the synthesized compounds at differentiable dosages, and cell viability was determined. The cell cycle arrest behaviour of compounds 2e, 2f, and 2m was investigated. Compounds 2e, 2f and 2m showed excellent antitumor activity versus all cancer cell lines with IC_{50} values ranging from 0.2 to 1.7 M[xxii].

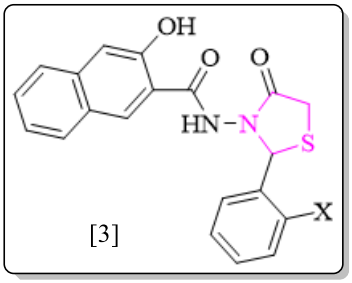


[2]

2a, R = 4-F	2h, R = 2,3-Cl
2b, R = 2-Cl	2i, R = 2,4-Cl_2
2c, R = 3-Cl	2j, R = 2,5-Cl_2
2d, R = 4-Cl	2k, R = 2,6-Cl_2
2e, R = 4-Br	2l, R = 3,4-Cl_2
2f, R = 2,4-F_2	2m, R = 2,3,4,5,6-F_5
2g, R = 2,6-F_2	

2-amino-4-aryl-5-oxo-4,5- dihydropyrano[3,2-*c*]chromene-3-carbonitriles(2a-m)

Sahiba et al. reported a range of innovative thiazolidinones 3-hydroxy-2-naphthoic motif were synthesised and subjected to *in vitro* cytotoxicity testing against HepG2 and human renal cell adenocarcinoma (769-P). The preparation of 1,3- Thiazolidin-4-one derivatives (3a-c) involved the reaction of 3-hydroxy-2-naphthoic acid hydrazide with aldehydes, which was then followed by cyclization with thioglycolic acid in dioxane. Rat cardiac myoblasts (H9c2) and GMK were employed as reference cell lines. At the IC_{25} concentration, compound c exhibited the highest potency and selectivity against 769-P cell lines. The results of the in vivo investigation indicated that compounds (a-c), which had the highest biological activity, were harmless to the swiss mice's CNS. Compound c, on the other had significant anodyne activity because it stimulated apoptosis and blocked the cell cycle during the G2/M phase. The cyclooxygenase-2 (COX-2) enzyme, which is connected to apoptosis, angiogenesis, and metastatic effects in reference cell lines, was thought to be involved in the investigation of chemicals (3a-c) as an anticancer medication. These findings confirmed the compounds significant anticancer efficacy (3a-c)[xxiii].

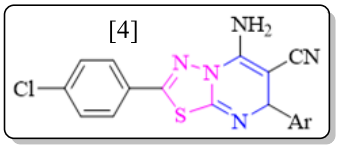


[3]

Compounds no.	3a	3b	3c
X	Cl	Br	F

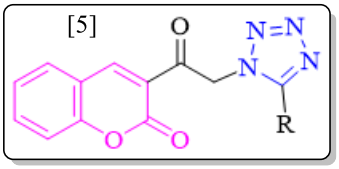
1,3-Thiazolidin-4-one derivatives(3a-c)

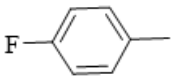
Insuasty et al. reported the synthesis of thiadiazolo[3,2-a]pyrimidine-6-carbonitriles via sonication. The advantages of ultrasonic irradiation over conventional heating for the identical transformation were revealed by comparative research comparing yields and reaction durations. Using fluorouracil as a positive control, the produced compounds were assessed for their *in vitro* anticancer activity against MCF-7, K562, Hela and PC-3 cancer cell lines. Based on the results of anticancer activity, compound (Ar = 3-OH-4-MeOC_6H_3) had the highest G150 values for the MCF-7, Hela, K562, and PC-3 cancer cell lines respectively at 32.7, 34.3, 55.3, and 28.9 M. Good binding mode was found in the active site of the enzyme thymidylate synthase, according to a docking investigation of the produced molecules[xxiv].

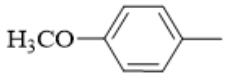
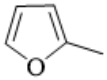


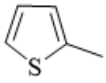
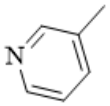
Thiadiazolo[3,2-a]pyrimidine-6-carbonitriles

Attia et al. synthesized (1*H*-tetrazol-5-yl)-coumarin hybrid and evaluate their *in vitro* anticancer activity for compounds a-f opposed to several cancer cell lines. The human normal lung cell line (Wi38) was assessed along with MCF-7, HepG2 and A549. Doxorubicin, the reference medication was also examined as a positive control. The tetrazole compounds were dissolved in dimethyl sulphoxide (DMSO), which was employed as the cancer cells negative control. In the culture system, the cancer cells grew normally and there was no discernible impact of DMSO on cellular proliferation. Comparing compounds 5a, 5b, 5d and 5e to MCF-7, HepG2 and A549 cell lines, they shown moderate to poor anticancer activity[xxv].



5a : R =  (As model target compound), 5b : R =  (92%)

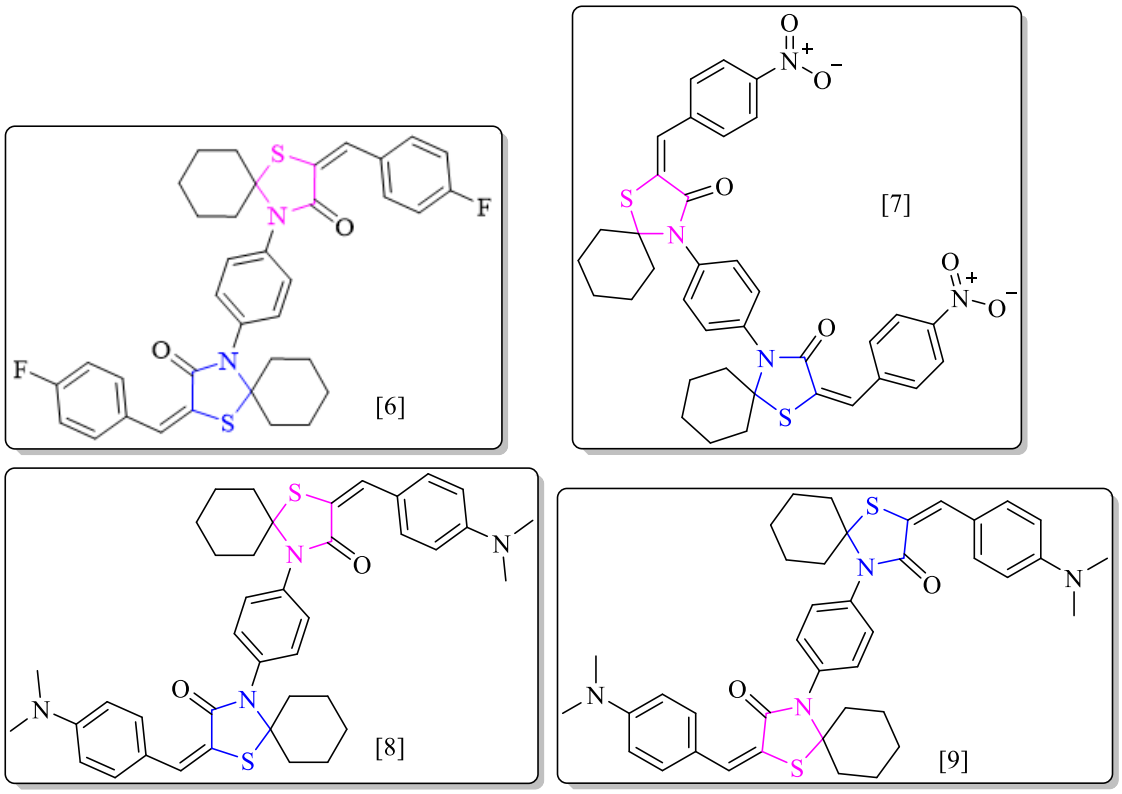
5c : R =  (94%), 5d : R =  (90%)

5e : R =  (93%), 5f : R =  (96%)

(1*H*-tetrazol-5-yl)-coumarin hybrid (5a-f)

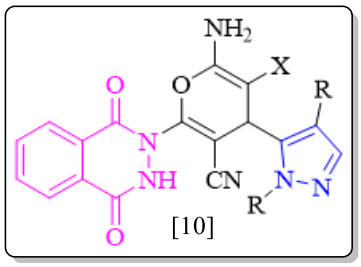
Dhadda et al. reported the arylidene end products of the new bis spiro thiazolidine ring system were developed and their *in vitro* anticancer activity. The newly synthesized compounds were evaluated *in vitro* against human normal retina pigmented epithelium (RPE-1) and HepG-2 (Liver Cancer) cell lines using the lactate dehydrogenase (LDH) assay to identify significant irreversible cell damage and permeabilization of the cellular membrane. The results showed that four compounds 4,4′-(1,4-phenylene)bis(2-(4 fluorobenzylidene)-1-thia-4-azaspiro [4.5]decan-3-one) (6), 4,4′ (1,4-phenylene)bis(2-(4-nitrobenzylidene)-1-thia-4-azaspiro [4.5] decan-3-one) (7), 4,4′-(1,4-phenylene)bis(2-(4(dimethylamino) benzylidene)-1-thia-4-azaspiro[4.5]decan-3-one) (8), and 4,4′ (1,4-phenylene)bis(2-(4(dimethylamino)benzylidene)-1-thia-4 azaspiro [4.5]decan-3-one) (9) had considerably

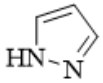
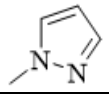
higher anti-cancer efficiency than the positive control doxorubicin in the case of HepG-2 cancer[xxvi].

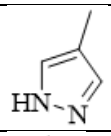
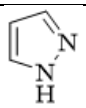
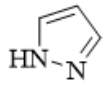
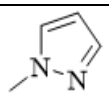
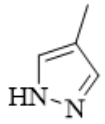
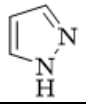


Bis spirothiazolidines with anticancer activity

Malik et al. have synthesized novel pyran-linked phthalazinone-pyrazole hybrids (10a-h) against human cervival cancer cells (HeLa) and human lung carcinoma cells (A549) by using MTT test. With IC_{50} values ranging from 9.8 to 41.6 µM against HeLa cells, all tested hybrids demonstrated moderate-to-good activity. Compound 10c, with an IC_{50} value of 9.8 µM, had substantial activity against A549 cells, making it the most promising hybrid in the series, according to the data. It demonstrated comparable efficacy with an IC_{50} value of 10.1µM in the case of HeLa cancer cell lines. IC_{50} values of 14.1, 10.6, 16.4, and higher were demonstrated by the additional hybrids 10a, 10b, 10f, and 10g against A549 cells[xxvii].

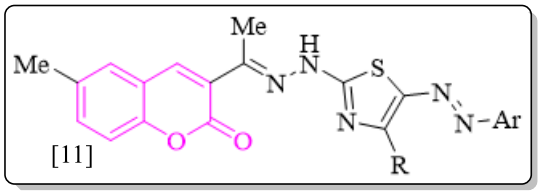


Compounds no.	X	
10a	CN	
10b	CN	

10c	CN	
10d	CN	
10e	COOEt	
10f	COOEt	
10g	COOEt	
10h	COOEt	

Pyran-linked phthalazinone-pyrazole hybrids (10a-h)

Alshabanah et al. have generated novel 3-azolyl-coumarins(11a-i) using ultrasonic irradiation. Elemental and spectral analysis data clarified the defined structure for each freshly produced molecule. Furthermore, the MTT viability assay was used to evaluate the novel compounds against the HEPG2-1 cell line *in vitro*. Comparing compounds 11b, 11d, and 11e to the reference medication doxorubicin (IC50 value of 0.31 ± 0.48 μM), the compounds exhibit promising activity (IC_{50} values of 0.43 ± 0.66, 0.29 ± 0.45, and 0.49 ± 0.38 μM, respectively)[xxviii].

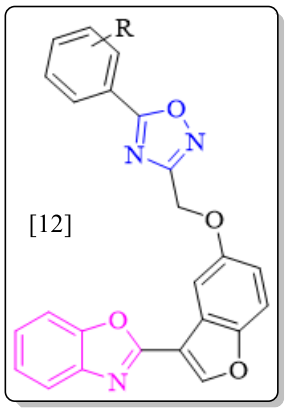


[11]

R/Ar	
11a, Me/C_6H_5	11f, Me/4-BrC_6H_4
11b, Me/4-MeC_6H_4	11g, Me/4-O_2NC_6H_4
11c, Me/3-MeC_6H_4	11h, Me/2,4-$Cl_2C_6H_3$
11d, Me/4-MeOC_6H_4	11i, 2-thienyl/C_6H_5
11e, Me/4-ClC_6H_4	

3-azolyl-coumarins(11a-i)

Goshal et al. have reported that minimal procedures and high yields were required to synthesize benzoxazole fused with benzofuran and 1,2,4-oxadiazole, and combretastatin-A4 was used as a positive control to test the compounds cytotoxicity against human cell lines, including MCF-7, A549, A375, HT-29, and lung. Comparing compound 12b, 12c, 12d, 12g, 12h, and 12i, higher potency activity was observed[xxix].

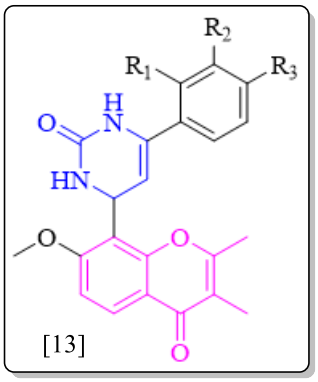


[12]

12a, R = H	12f, R = 4-Fluoro
12b, R = 3,4,5 trimethoxy	12g, R = Nitro
12c, R = 4-Methoxy	12h, R = Cyano
12d, R = 4-Chloro	12i, R = 4-methyl
12e, R = 4-Bromo	12j, R = 4-triflouromethyl

Benzoxazole-1,2,4 oxadiazole derivatives 12(a-j)

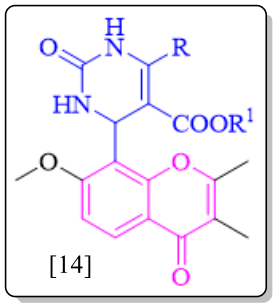
Kantankar et al. have synthesized novel series of chromone-8-dihydropyrimidinones (13a-j) and chromone-8-tetrahydropyrimidine-5-carboxylates (14a-e) using facile multi-component modified Biginelli reaction. These hybrids have been evaluated for their anti cancer activity against three selected human cancer cell lines namely lung A549, human cervical HeLa, myelogenous leukaemia K562 and normal cell line HEK-293(derived from human kidney) as the selectivity reference. All the newly synthesized compounds have exhibited predominant anti cancer activity with micromolar(μM) IC_{50} values. One of them, tetrahydropyrimidine hybrids (14a-e) showed remarkable specific anti-cancer activity selectively against K562 with IC_{50} values ranging from 7.19 to 13.10 μM, where as compounds 6a-6j showed non selective anti cancer activity. Particularly compounds 13a, 13b, 13c and 13f showed potential anti-cancer activity, specifically against the cell lines A549 and HeLa with IC 50 values < 8 μM. All the newly synthesized compounds were relatively nontoxic towards normal cell lines with higher IC_{50} values ranging from 54.92 to 128.56 μM and among them, compounds 13a, 13b, 13c, 13f, 14b and 14e have shown SI value > 10. The selectivity of compounds 14a-14e compared to 13a-13j towards K562 (CML) cell line supported by molecular docking study which provided plausible interactions of the newly synthesized chromone derivatives with the catalytic site of BCR-ABL Tyrosine kinase using genetic algorithm program (GOLD 3.0.1)[xxx].



[13]

Entry	R_1	R_2	R_3
13a	H	H	F
13b	F	H	H
13c	H	H	OCH_3
13d	H	H	H
13e	H	OCH_3	OCH_3
13f	H	H	OCF_3
13g	H	H	CH_3
13h	H	Br	H
13i	H	H	Br
13j	H	H	Cl

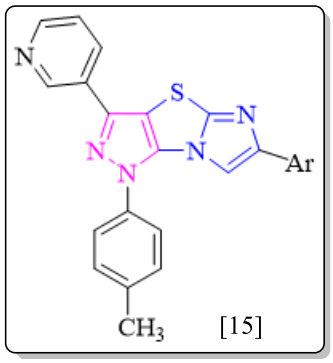
Chromone-8-dihydropyrimidinones hybrids (13a-j)



Entry	R	R_1
14a	$-CH_2OCH_3$	$-CH_3$
14b	$-CH_3$	$-C_2H_5$
14c	$-C_2H_5$	$-CH_3$
14d	i-C_3H_7	$-C_2H_5$
14e	$-CH_3$	$-CH_2$-Ph

Chromone-8-tetrahydropyrimidine-5-carboxylates (14a-e)

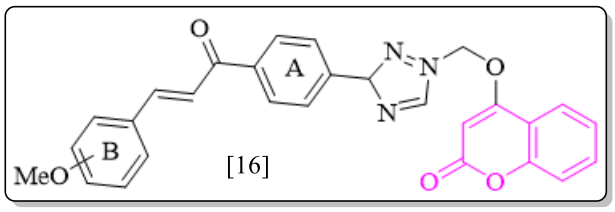
Rizk et al. have synthesized pyrazolothiazolimidazole derivatives (15a-c) using microwave irradiation as an eco-friendly technique besides the conventional heating. The newly synthesized compounds were selected to be evaluated for their *in vitro* anticancer effect using the standard MTT assay against a panel of two human tumor cell lines, namely liver cancer (hepatocellular carcinoma, HepG-2) and breast cancer (MCF-7) using doxorubicin as reference drug. MTT assay is a standard colorimetric assay for measuring cell growth. It is used to determine cytotoxicity of potential possible pharmaceuticals and other toxic materials. The compounds 15a–c were found to have almost identical antitumor activity, with IC_{50} ranging from 8.95 to 41.95 µg/mL(in MCF-7 cell line) and 10.14 to 35.06 µg/mL(in HepG-2 cell line) , respectively[xxxi].



15a: Ar = 4-Cl-C_6H_4
15b: Ar = 4-CH_3-C_6H_4
15c: Ar = C_6H_5

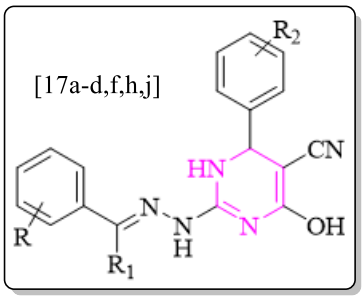
pyrazolothiazolimidazole derivatives (15a-c)

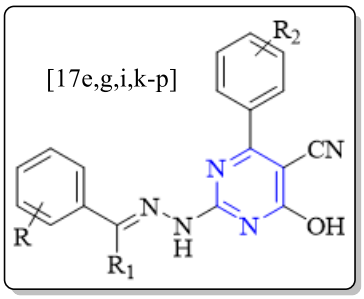
Konidala et al. reported the anticancer potential of chalcone-coumarin hybrids (16) against HuCCA-1, HepG2, A549, and MOLT-3. The triazole-containing hybrids exhibit strong antitumor activity against HuCCA-1 and MOLT-3. Tri-substituted methoxy group hybrid hybrid (16) selectively inhibits MOLT-3. 2,3-dimetoxy group hybrids have strong anti-A549 action. The inhibitory efficacy of hybrids with 2,3-dimethoxy groups on ring "B" and 3-substituted coumarinyl ring is higher than that of comparable 3,4-dimethoxy substitution on chalcone's ring "B"[xxxii].



Chalcone-coumarin hybrids (16)

Çağlar Yavuz et al. have synthesized pyrimidine derivatives (17a-p). These substances were evaluated *in vitro* against two different cancer cell lines: the human breast cancer cell line (MDA-MB-231) and the human colon cancer cell line (DLD-1). Based on the acquired data, almost all of the compounds exhibit cytotoxic action against the cell lines used for testing. Compounds 17j, 17k, and 17n in particular showed a strong impact against DLD-1. Additionally, when compared to other produced compounds against MDA-MB-231, compounds 17g, 17m, and 17o showed fewer IC_{50} values. To theoretically investigate the binding manner and location of pyrimidine compounds with the highest activity, molecular docking was carried out in accordance with both topoisomerase I and N-acetyltransferase 1 proteins[xxxiii].



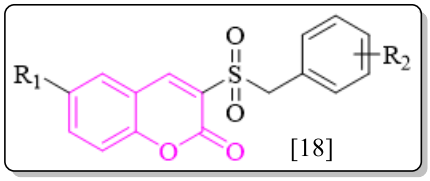


17a	4-Me	H	H
17b	4-MeO	H	H
17c	H	H	H
17d	4-EtO	H	H
17e	4-$(CH_3)_2CH$	H	H
17f	2-Cl	H	H
17g	2-Cl-6-F	H	H
17h	4-NO_2	H	H
17i	4-$(CH_3)_2N$	H	H
17j	2,4-diMeO	H	H
17k	H	Me	H
17l	4-Me	Me	H
17m	4-CH_3CONH	H	H
17n	4-MeO	Me	H
17o	4-Me	H	4-Me
17p	4-MeO	H	4-Me

Pyrimidine derivatives (17a-p)

Song et al. described the coumarin–benzylsulfone hybrid 18 (IC_{50}:18.3–83.9μM; MTT assay) showed a significant amount of activity against cancer cell lines HeLa, HepG2, H1299, HCT-116, and MCF-7, but it was far less potent than the reference rigosertib (IC_{50}: 0.01–2.36μM).

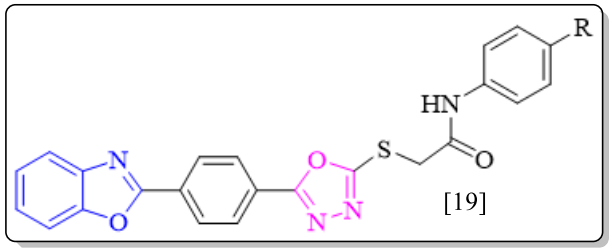
Among the derivatives, hybrid 18a (IC_{50}:18.12–32.60µM) showed the most potent activity against the mentioned cancer cell lines, followed by compound 18b (IC_{50}: 29.30–42.14µM). Furthermore, these two hybrids also evidently inhibited HeLa cell migration *in vitro*, and both of them might be strong PI3K inhibitors, specifically targeting PI3Kα and PI3Kβ[xxxiv].



18a: $R_1 = NO_2$; R_2 = 4-F
18b: R_1 = Br; R_2 = 4-F

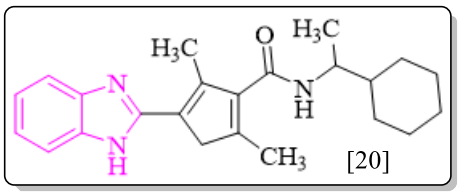
Coumarin–benzylsulfone hybrid (18a&b)

Vaghani et al. explored the novel series of amide 1, 3, 4–oxadiazole-linked benzoxazole derivatives(19a&b) and spectral data was used to support their structures. Synthesized compounds were examined against four human cancer cell lines, including A549, MCF7, A375, and HT-29 using Combretastatin-A4 as a reference drug. Compounds N1-(4-Methoxyphenyl)-2-{5-[4-(1,3-benzoxazol-2- yl)phenyl]-1,3,4-oxadiazol-2-ylsulfanyl}acetamide (a) and N1-(4-Nitrophenyl)-2-{5- [4- (1, 3-benzoxazol2- yl)- phenyl]-1, 3, 4-oxadiazol- 2- ylsulfanyl} acetamide (b) displayed higher anticancer activity than the standard drug, against HT29 cancer cell line with IC_{50} values of 0.018 and 0.093 µM[xxxv.]



Amide 1, 3, 4–oxadiazole-linked benzoxazole derivatives(19a&b)

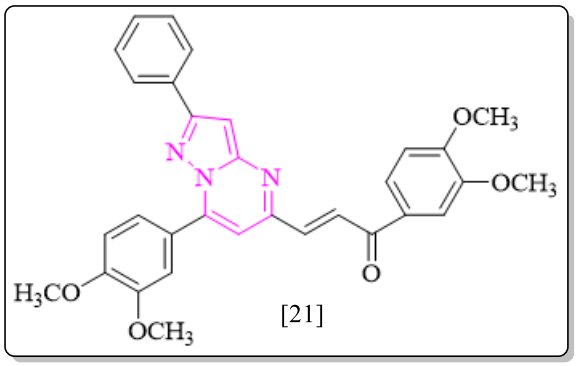
Satija et al. proposed a novel array of 2,4-dimethyl-1*H*-pyrrole-3-carboxamide hybrids (20) containing 1*H*-benzimidazole moiety using molecular hybridization technique and evaluated them for their *in vitro* antitumor action against different human cancer cell lines at 10 µM concentration. Some of them showed active anti proliferative activity via acting as VGEF inhibitor even at slight doses whereas, compound 20 that is, (5-(1H-benzo [d]imidazol-2-yl)-N-(1-cyclohexylethyl)-2,4-dimethyl-1H pyrrole-3-carboxamide) showed significant anti-cancer activity especially via acting as a PGDF inhibitor against MDA-MB-435 (62.46% growth inhibition) and MDA-MB 468 (40.24% growth inhibition). SAR studies mentioned that anticancer activity of the compounds was affected by change in the substituent at amide linkage, that is, anti-cancer activity was increased when benzene ring was replaced with an alicyclic moiety[xxxvi].



2,4-dimethyl-1*H*-pyrrole-3-carboxamide hybrids containing 1H-benzimidazole moiety(20)

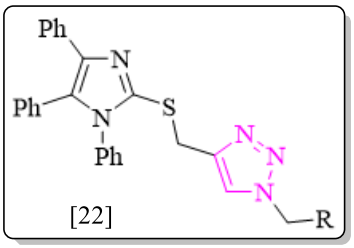
Mahapatra et al. explored the chalcone-linked pyrazolo [1, 5-a] pyrimidines. It has been reported that pyrimidines have anticancer properties. As shown by the MTT experiment, compound 21 (IC_{50} = 2.6 µM) had the highest potency against the MDA-MB231 cancer cell

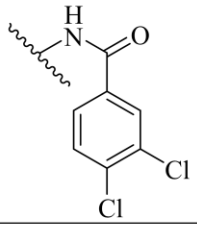
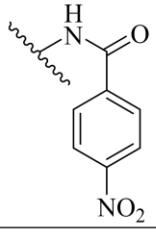
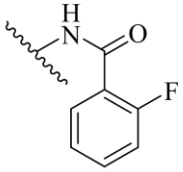
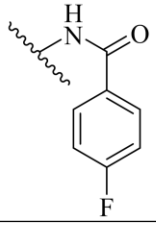
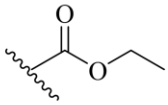
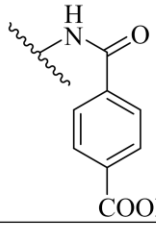
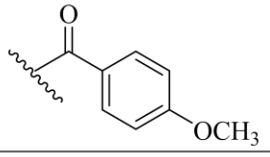
line. The substance stopped the cell cycle in sub G1 phase and increased the expression of proteins that induce apoptosis, such as p53, p21, and Bax, and lowered the production of proapoptotic proteins, such as Bcl-2 and procaspase-9. The primary causes of the activity were C-7 phenyl ring and C-5 substitution phenylprop-2-en-1-one[xxxvii].



Chalcone-linked pyrazolo [1, 5-a] pyrimidines(21)

Al-blewi et al. have designed and synthesized novel imidazole-1,2,3-triazole hybrids using copper(I) catalyzed click reaction carrying different un/functionalized alkyl/aryl side chains (22a-k). Using the MTT test, the resultant adducts were examined for their anticancer activity against four cancer cell lines (Caco-2, HCT-116, HeLa, and MCF-7) and shown moderate to considerable activity. Among these, compound 4k exhibited strong cytotoxic effects on cancer cell lines, particularly MCF-7, with an IC_{50} of 0.38 M. The majority of the synthesized compounds were found to be CYP2C19 and CYP3A4 inhibitors based on an analysis of their pharmacokinetic properties. It was discovered that none of the synthetic chemicals were carcinogenic. GSK-3 was identified as a potential cancer target receptor and used in an *in silico* molecular docking study. The outcomes of the *in vitro* experiments and the *in silico* research coincided. Molecular hybridization of 1,2,3-triazole to biologically interesting imidazole scaffolds with diverse aromatic substituents was a fascinating protocol for producing new anticancer agents targeting the GSK3 enzyme for the treatment of breast cancer, as demonstrated by the study's overall results[xxxviii].

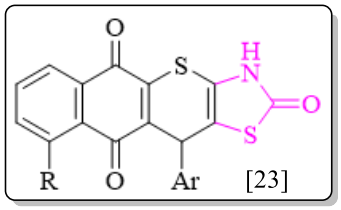


22a		22g	
22b		22h	
22c		22i	
22d		22j	
22e		22k	
22f			

Imidazole-1,2,3-triazole hybrids (22a-k)

I. Ivasechko et al. have designed a series of 11-substituted 9-hydroxy-3,5,10,11-tetrahydro-2*H*-benzo[6,7]thiochromeno[2,3-*d*][1,3]thiazole2,5,10-triones (23a-m) were synthesized via hetero-Diels-Alder reaction. The produced compounds were evaluated in a panel of peripheral human blood lymphocytes, normal and pseudo normal cells, and cell lines representing various cancer types. The most potent derivative was discovered to be compound 23j, which showed cytotoxic effects comparable to those of doxorubicin (IC_{50} varied from 0.6 to 5.98 μM) but less harmful to normal and pseudo normal cells. All of the synthesized substances had DNA interaction capabilities; however, the strength of the compounds' anticancer effects was not correlated with their DNA interaction potency. In colorectal cancer cells, the activity of the produced derivatives 23a, 23g, and 23j was

associated with the p53 status. In contrast to the well-known anticancer medication doxorubicin, which was utilized as a positive control, Compound 23j did not have an immediate harmful effect on the body of C57BL/6 mice. In contrast to doxorubicin, which resulted in anemia and leukopenia, 23j (20 mg/kg) injection did not affect the levels of hemoglobin, erythrocytes, platelets, or leukocytes in the mice's blood. This suggests that 23j is bio-tolerant *in vivo*[xxxix].

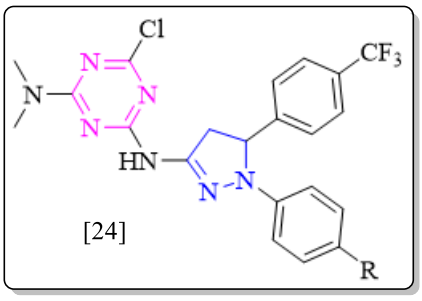


[23]

23a: Ar = 2-OH-5-Cl-C_6H_3, R = OH	23h: Ar = C_6H_4-CH=CCH_3, R = OH
23b: Ar = 4-Br-C_6H_4, R = OH	23i: Ar = Thiophen-2-yl, R = OH
23c: Ar = 4-Cl-C_6H_4, R = OH	23j: Ar = Furan-2-yl , R = OH
23d: Ar =4-OMe-C_6H_4 , R = OH	23k: Ar = Furan-2-yl , R = H
23e: Ar = 4-NMe_2-C_6H_4, R = OH	23l: Ar = $(Me)_2$, R = OH
23f: Ar = C_6H_4-CH=CH , R = OH	23m: Ar = C_6H_5- CH_2, R = OH
23g: Ar = 2-NO_2-C_6H_3-CH=CH, R = OH	

9-hydroxy-3,5,10,11-tetrahydro-2H-benzo[6,7]thiochromeno[2,3-*d*][1,3]thiazole2,5,10-triones (23a-m)

Raghu et al. have synthesized novel 1,3,5-triazine-based pyrazole derivatives (24a–i) with anticancer activity targeting the epidermal growth factor (EGFR) tyrosine kinase. Compound 24i shown poor activity against the MCF-7 (human breast), HepG2 (human liver), HCT116 (human colorectal), PC-3 (human prostate), LoVo (human colon) and LoVo/DX (doxorubicin-resistant) cancer cell lines. All other compounds showed moderate to good anticancer activity against these cancer cell lines. The anticancer activity of compounds 24f, 24g, and 24h was more promising; the data were reported as IC_{50} values in nM. These compounds exhibited significant inhibitory activity against EGFR-tyrosine kinase, with IC_{50} values of 395.1, 286.9, and 229.4 nM, respectively, compared to the standard drug erlotinib. The compounds demonstrated a strong affinity for the target EGFR kinase (PDB ID: 6V6O) as demonstrated by the multiple H-bonds that the compounds formed with amino acids. The more active compounds (24f, 24g, and 24h) were found to exhibit a consistent pattern of binding to Ct-DNA through spectroscopic, viscometric, electrochemical, and docking techniques; these findings confirmed the groove mode of interaction between the compounds and DNA. Additionally, the *in vitro* ADME properties were assessed, enabling the identification of optimized compounds as potentially effective anticancer agents[xl].

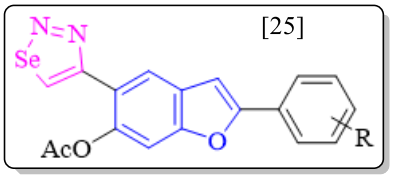


[24]

Compound	24a	24b	24c	24d	24e	24f	24 g	24h	24i
R	-H	-OH	$-NH_2$	$-OCH_3$	-F	-Cl	-Br	$-CF_3$	$-N(CH_3)_2$

1,3,5-triazine-based pyrazole derivatives (24a–i)

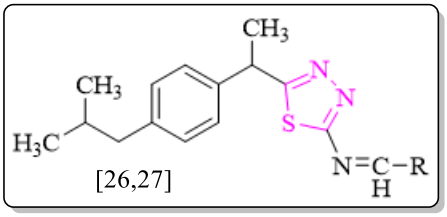
Abbas et al. reported that compounds containing selenium show a wide range of biological properties, such as anticancer activity. Benzofuran compounds (25a–f) based on 1,2,3-selenadiazole were made and tested for against proliferation activity against human embryonic kidney derived (HEK-293-T) and breast cancer (MCF-7) cell lines as determined by the MTT test. Compound 25f had good antigrowth effect against MCF-7 cells with an IC_{50} of 2.6 mM, in comparison to doxorubicin's IC_{50} of 0.8 mM. The majority of derivatives (25a–f)shown mild to moderate inhibition. For the normal cell line, compound 25f exhibited comparatively lower cytotoxicity (IC_{50} = 1.2 mM). However, compound 25a showed little effect (IC_{50} = 7.1 mM) against the MCF-7 cell line. However, when it came to the Hek293-T cell line (IC_{50} = 3.5 mM), compound 25a was comparatively more cytotoxic than doxorubicin (IC_{50} = 1.2 mM)[xli].



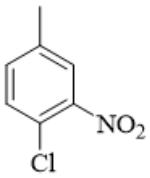
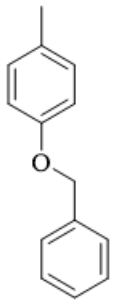
25a: R= H	25d: R= 3-Cl
25b: R= 3-F	25e: R=4-Me
25c: R= 4-F	25f: R=4-MeO

1,2,3-selenadiazole based benzofuran derivatives(25a-f)

S. I. Farooqi et al. synthesized two new aryl Schiff bases [(E)-N-(4-(benzyloxy)-3-methoxybenzylidene)-5-(1-(4-isobutylphenyl)ethyl)-1,3,4-thiadiazol-2-amine] (ASB-1)(26) and [(E)-N-(4-(benzyloxy)- benzylidene)-5-(1-(4-isobutylphenyl)ethyl)-1,3,4-thiadiazol-2-amine] (ASB-2)(27). These substances were examined for DNA binding after being explained using various analytical methods. Further research with these chemicals was conducted with the Huh-7 cancer cell line, a model used to study hepatocellular carcinoma. A considerable and spontaneous binding of both ASB-1 and ASB-2 with the DNA was shown by the evaluation of the binding constant, free energy change, and binding site size, or Kb, DG, and n. Data, however, showed that ASB-1 bound to DNA comparatively more strongly. There was mutual support between the voltammetric and spectral data. Measurements of viscosity and binding site sizes supported the mixed binding style of interactions—intercalation with groove binding—that was seen in molecular docking studies. In vitro experiments on the Huh-7 cell line and regular HEK-293 cell lines showed a strong correlation with the results of DNA binding investigations. Compared to ASB-2, the chemical ASB-1 had a lower IC_{50} value and a larger anticancer efficacy in addition to a higher binding affinity toward DNA[xlii].

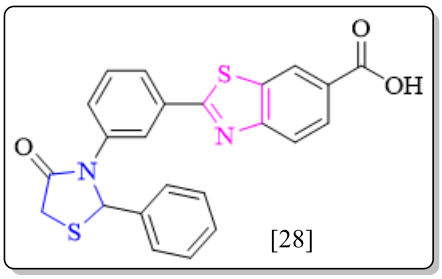


[26,27]

R		
	 ASB-1	 ASB-2

N-(substituted-benzylidene)-5-(1-(4-isobutylphenyl) ethyl)-1,3,4-thiadiazol-2-amine ASB-1(26) and ASB-2(27).

S. Hosseininezhad and A. Ramazani. stated and assessed the in vitro anticancer activity of a new 8 derivatives comprising thiazole scaffold 28(a-h) against the HeLa human cervical cancer cell line, using cisplatin as the standard medication. Structure 28b showed greater activity. The anticancer activity of structure 28b was often greater than that of structures 28e, 28g, and 28h. Additionally, there was reduced anticancer activity shown by Structures 28d, 28c, 28f, and 28a[xliii].



[28]

28a: R= H
28b: R= p-Cl
28c: R= m-F
28d: R= p-NO_2
28e: R = p-OMe
28f: R= p-F, m-OMe
28g: R= p-Me
28h: R= p-OH

Thiazolidinone substituted benzothiazole-6-carboxylic derivatives(28a-h)

CONCLUSION AND PERSPECTIVE:

Every person's health in our world is continuously and repeatedly threatened by cancer. To discover a more effective solution to this issue, several researchers from all across the world are doing research in this area. Cancer treatment research gets considerably more difficult, especially because molecular pharmacology is still largely unknown. Because of this, finding and developing new medications is thought to be exceedingly costly and time-consuming. In this regard, a variety of activities, such as virtual screening, drug-target prediction, binding site prediction, and study of protein interaction networks, might benefit from the use of computational approaches. These cutting-edge techniques might all greatly aid in the search for anti-cancer drugs. More complex techniques, such as drug scaffold development, retro-synthetic routine plan, and drug binding affinity predictions, have been created recently with the advancement of AI. When paired with experimental validations, the valuable predictions produced by computational models have the potential to expedite the discovery of anti-cancer drugs.

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REFERENCES:

i. Oyedele A. S.; Bogan D. N.; & Okoro C. O.; Synthesis, biological evaluation and virtual screening of some acridone derivatives as potential anticancer agents; Bioorganic & Medicinal Chemistry; 2020, **28**(9), 115426.

ii. Brandao P.; Marques C.; Burke A. J.; & Pineiro M.; The application of isatin-based multicomponent-reactions in the quest for new bioactive and druglike molecules; European journal of medicinal chemistry; 2021, **211**, 113102.

iii. Jia Y.; Wang X.; Deng Y.; Li S.; Xu X.; Qin Y.; & Peng L.; Pyroptosis provides new strategies for the treatment of cancer; Journal of Cancer; 2023, **14**(1), 140.

iv. Zhang M.; Chen X.; & Radacsi N.; New tricks of old drugs: Repurposing non-chemo drugs and dietary phytochemicals as adjuvants in anti-tumor therapies; Journal of Controlled Release; 2021, **329**, 96-120.

v. Morel D.; Jeffery D.; Aspeslagh S.; Almouzni G.; & Postel-Vinay S.; Combining epigenetic drugs with other therapies for solid tumours—past lessons and future promise. Nature Reviews Clinical Oncology; 2020, **17**(2), 91-107.

vi. Beigh S.; Saleem R. M.; Maghrabi A. H. A.; Khalifa E. H.; Mushtaq S.; Rehman M. U.; & Wali A. F.; Journal of Pharmaceutical Research and Development; 2023, **4**(1), 1-13.

vii. Venturini Filho E.; Pinheiro E. M.; Pinheiro S.; & Greco S. J.; Aminopyrimidines: Recent synthetic procedures and anticancer activities; Tetrahedron, 2021, **92**, 132256.

viii. Cui W.; Aouidate A.; Wang S.; Yu Q.; Li Y.; & Yuan S.; Discovering anti-cancer drugs via computational methods; Frontiers in pharmacology, 2020, **11**, 733.

ix. Ciaffaglione V.; Modica M. N.; Pittalà V.; Romeo G.; Salerno L.; & Intagliata S.; Mutual Prodrugs of 5-Fluorouracil: From a Classic Chemotherapeutic Agent to Novel Potential Anticancer Drugs; ChemMedChem, 2021, **16**(23), 3496-3512.

x. Sobczak M.; & Kędra K.; Biomedical polyurethanes for anti-cancer drug delivery systems: A brief, comprehensive review; International Journal of Molecular Sciences, 2022, **23**(15), 8181.

xi. Alia A. H.; & Slaihimb M. M.; Design, Synthesis, And Characterization Of New Schiff Bases For 3-Amino-1, 2, 4-Triazole-5-Thiolate Salt, Bearing Morpholine Ring And Biological Evaluation As Antibacterial Agents; Journal of Angiotherpay, 2023, **7**(1), 1-9.

xii. Usman S.; Khawer M.; Rafique S.; Naz Z.; & Saleem K.; The current status of anti-GPCR drugs against different cancers; Journal of Pharmaceutical Analysis, 2020, **10**(6), 517-521.

xiii. Belete T. M.; Recent updates on the development of deuterium-containing drugs for the treatment of cancer; Drug design, development and therapy,

2022, **16**, 3465-3472.

xiv. Dixit D.; Verma P. K.; & Marwaha R. K.; A review on 'triazoles': Their chemistry, synthesis and pharmacological potentials; Journal of the Iranian Chemical Society, 2021, **18**(10), 2535-2565.

xv. Anand U.; Dey A.; Chandel A. K. S.; Sanyal R.; Mishra A.; Pandey D. K.; ... & de la Lastra J. M. P.; Cancer chemotherapy and beyond: Current status, drug candidates, associated risks and progress in targeted therapeutics; Genes & Diseases, 2022, **10**(4), 1367-1401.

xvi. Mottaghi S.; & Abbaszadeh H.; Natural lignans honokiol and magnolol as potential anticarcinogenic and anticancer agents. A comprehensive mechanistic review. Nutrition and Cancer, 2022, **74**(3), 761-778.

xvii. Mamidala S.; Aravilli R. K.; Ramesh G.; Khajavali S.; Chedupaka R.; Manga V.; & Vedula R. R.; A facile one-pot, three-component synthesis of a new series of thiazolyl pyrazole carbaldehydes: *In vitro* anticancer evaluation, in silico ADME/T, and molecular docking studies; Journal of Molecular Structure, 2021, **1236**, 130356.

xviii. Abduelkarem A. R.; Anbar H. S.; Zaraei S. O.; Alfar A. A.; Al-Zoubi O. S.; Abdelkarem E. G.; & El-Gamal M. I.; (2020). Diarylamides in anticancer drug discovery: A review of pre-clinical and clinical investigations; European Journal of Medicinal Chemistry, 2020, **188**, 112029.

xix. Venugopala K. N.; Rashmi V.; & Odhav B.; Review on natural coumarin lead compounds for their pharmacological activity; BioMed research international, **2013**, 963248.

xx. He Z. X.; Gong Y. P.; Zhang X.; Ma L. Y.; & Zhao W.; Pyridazine as a privileged structure: An updated review on anticancer activity of pyridazine containing bioactive molecules; European journal of medicinal chemistry, 2021, **209**, 112946.

xxi. Sivasankarapillai V. S.; Madhu Kumar Nair R.; Rahdar A.; Bungau S.; Zaha D. C.; Aleya L.; & Tit D. M; Overview of the anticancer activity of withaferin A, an active constituent of the Indian ginseng Withania somnifera; Environmental Science and Pollution Research, 2020, **27**, 26025-26035.

xxii. El-Agrody A. M.; Fouda A. M.; Assiri M. A.; Mora A.; Ali T. E.; Alam M. M.; & Alfaifi M. Y.; *In vitro* anticancer activity of pyrano [3, 2-*c*] chromene derivatives with both cell cycle arrest and apoptosis induction; Medicinal Chemistry Research, 2020, **29**, 617-629.

xxiii. Sahiba N.; Sethiya A.; Soni J.; Agarwal D. K.; & Agarwal S.; Saturated five-membered thiazolidines and their derivatives: from synthesis to biological applications; Topics in Current Chemistry, 2020, **378**(2), 34.

xxiv. Insuasty D.; Castillo J.; Becerra D.; Rojas H.; & Abonia R.; Synthesis of biologically active molecules through multicomponent reactions; Molecules, 2020, **25**(3), 505.

xxv. Attia Y. A.; Mohamed Y. M.; Awad M. M.; & Alexeree S.; Ag doped ZnO nanorods catalyzed photo-triggered synthesis of some novel (1*H*-tetrazol-5-yl)-coumarin hybrids; Journal of Organometallic Chemistry, 2020, **919**, 121320.

xxvi. Dhadda S.; Sharma S.; Jakhar P.; & Sharma H.; Contemporary progress in the green synthesis of spiro-thiazolidines and their medicinal significance: a review; RSC advances, 2023, **13**(6), 3723-3742.

xxvii. Malik M. S.; Asghar B. H.; Syed R.; Alsantali R. I.; Morad M.; Altass H. M.; ... & Ahmed S. A.; Novel pyran-linked phthalazinone-pyrazole hybrids: synthesis, cytotoxicity evaluation, molecular modeling, and descriptor studies; Frontiers in Chemistry, 2021, **9**, 666573.

xxviii. Al-Blewi F.; Shaikh S. A.; Naqvi A.; Aljohani F.; Aouad M. R.; Ihmaid S.; & Rezki N.; Design and synthesis of novel imidazole derivatives possessing triazole pharmacophore with potent anticancer activity, and in silico ADMET with GSK-3β molecular docking investigations; International journal of molecular sciences, 2021, **22**(3), 1162.

xxix. Ghoshal T.; & Patel T. M.; Anticancer activity of benzoxazole derivative (2015 onwards): a review; Future Journal of Pharmaceutical Sciences, 2020, **6**, 1-24.

xxx. Kantankar A.; Rao Y. J.; Mallikarjun G.; Hemasri Y.; & Kethiri R. R.; Rational design, synthesis, biological evaluation and molecular docking studies of chromone-pyrimidine derivatives as potent anti-cancer agents; Journal of Molecular Structure, 2021, **1239**, 130502.

xxxi. Rizk H. F.; El-Borai M. A.; Ragab A.; & Ibrahim S. A.; Design, synthesis, biological evaluation and molecular docking study based on novel fused pyrazolothiazole scaffold; Journal of the Iranian Chemical Society, 2020, **17**, 2493-2505.

xxxii. Konidala S.; Chimakurthy J.; & Kotra V.; RECENT STRATEGIES FOR EFFICIENT SYNTHESIS AND BIOLOGICAL ACTIVITIES OF COUMARIN-CHALCONE DERIVATIVES; Asian journal of pharmaceutical and clinical research, 2020, **13**(5), 28-37.

xxxiii. Çağlar Yavuz S.; Akkoç S.; Türkmenoğlu B.; & Sarıpınar E.; Synthesis of novel heterocyclic compounds containing pyrimidine nucleus using the Biginelli reaction: Antiproliferative activity and docking studies; Journal of Heterocyclic Chemistry, 2020, **57**(6), 2615-2627.

xxxiv. Song X. F.; Fan J.; Liu L.; Liu X. F.; & Gao F.; Coumarin derivatives with anticancer activities: An update; Archiv der Pharmazie, 2020, **353**(8), 2000025.

xxxv. Vaghani H.; Patel S.; & Patel S.; 1, 3, 4-OXADIAZOLE AND ITS POTENCY: A REVIEW; IJPSR, 2021, **12**(10), 5292-5299.

xxxvi. Satija G.; Sharma B.; Madan A.; Iqubal A.; Shaquiquzzaman M.; Akhter M.; ... & Alam M. M.; Benzimidazole based derivatives as anticancer agents: Structure activity relationship analysis for various targets; Journal of Heterocyclic Chemistry, 2022, **59**(1), 22-66.

xxxvii. Mahapatra A.; Prasad T.; & Sharma T.; Pyrimidine: a review on anticancer activity with key emphasis on SAR; Future journal of pharmaceutical Sciences, 2021, **7**(1), 123.

xxxviii. Al-Blewi F.; Shaikh S. A.; Naqvi A.; Aljohani F.; Aouad M. R.; Ihmaid S.; & Rezki N.; Design and synthesis of novel imidazole derivatives possessing triazole pharmacophore with potent anticancer activity, and in silico ADMET with GSK-3β molecular docking investigations; International journal of molecular sciences, 2021, **22**(3), 1162.

xxxix. Ivasechko I.; Lozynskyi A.; Senkiv J.; Roszczenko P.; Kozak Y.; Finiuk N.; ... & Lesyk R.; Molecular design, synthesis and anticancer activity of new thiopyrano [2, 3-*d*] thiazoles based on 5-hydroxy-1, 4-naphthoquinone (juglone); European journal of medicinal chemistry, 2023, **252**, 115304.

xl. Raghu M. S.; Kumar C. P.; Prashanth M. K.; Kumar K. Y.; Prathibh B. S.; Kanthimathi G.; ... & Osman S. M.; Novel 1, 3, 5-triazine-based pyrazole derivatives as potential antitumor agents and EFGR kinase inhibitors: Synthesis, cytotoxicity, DNA binding, molecular docking and DFT studies; New Journal of Chemistry, 2021, **45**(31), 13909-13924.

xli. Abbas A. A.; & Dawood K. M.; Anticancer therapeutic potential of benzofuran scaffolds; RSC advances, 2023, **13**(16), 11096-11120.

xlii. Farooqi S. I.; Arshad N.; Channar P. A.; Perveen F.; Saeed A.; Larik F. A.; ... & Yamin M.; New aryl Schiff bases of thiadiazole derivative of ibuprofen as DNA binders and potential anticancer drug candidates; Journal of Biomolecular Structure and Dynamics, 22021, **39**(10), 3548-3564.

xliii. Hosseininezhad S.; & Ramazani A.; Thiazole Ring-The Antimicrobial, Anti-Inflammatory, and Anticancer Active Scaffold; Arabian Journal of Chemistry, 2023, **16**, 105234.

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