Frontiers in Scientific Research and Technology

Online ISSN: 2682-2970
Print ISSN: 2682-2962
http://fsrt.journals.ekb.eg

FSRT J 10 (2025) 66 – 78 10.21608/fsrt.2024.346199.1145

Thiazolidines: Synthesis and Anticancer Activity

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ARTICLE INFO

Article history:
Submitted 20 December 2024
Received in revised form 28 December 2024
Accepted 28 December 2024
Available online 2 January 2025

Keywords
Thiazolidine;
Anticancer;
Thiazolidinone;
Synthesis;
Derivatives

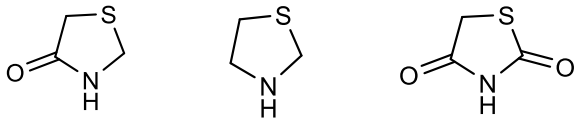
ABSTRACT

Thiazolidine (TZD) is often utilized in modern medicine due to its organic features. TZD derivatives and their complexes were characterized using various spectroscopic approaches, including infrared, and ultraviolet-visible measurements. This review discusses the synthesis and anticancer properties and molecular mechanisms of TZD in recent years. TZD derivatives are created when their molecular composition is modified, increasing the probability that they will bind to proteins. With great therapeutic results, it has been employed to treat a wide range of disorders. Therefore, it is a promising drug with a lot of scope for study.

1. Introduction

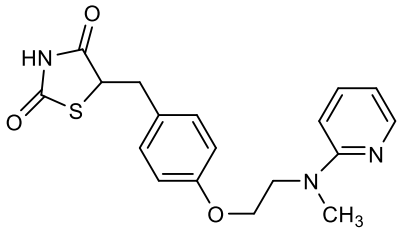
Numerous biologically active compounds containing sulfur, nitrogen, and oxygen have long attracted researchers, owing to their biological relevance. Thiazolidinones contain a sulfur atom at position 1, a carbonyl group at positions 2–5, and a nitrogen atom at position 3. Nevertheless, its derivatives matched to the highest often researched moieties, and its inclusion in penicillin was the first confirmation of its existence in nature [1].

Thiazolidine-2,4-diones are deemed essential medically-active compounds among this class and have many potential biological effects as anti-tubercular, anti-microbial, anti-diabetic (such as Pioglitazone and Rosiglitazone), antifungal, antioxidant, anti-inflammatory, anticonvulsant, and anti-cancer, etc. [2].

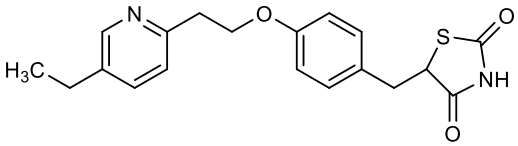


Thiazolidinone Thiazolidine Thiazolidinedione

Fig. (1): Structures of TZD Derivatives



Rosiglitazone
(Antidiabetic agent)



Pioglitazone
(Antidiabetic agent)

Fig. (2): Marketed drugs having thiazolidinedione moiety.

2. Tautomerism of Thiazolidinone

The 4-thiazolidinone ring shows tautomerism, as illustrated in the scheme below. The presence of a certain tautomeric form is dependent on the basic and acidic circumstances, as well as the general structure of the ring system [3].

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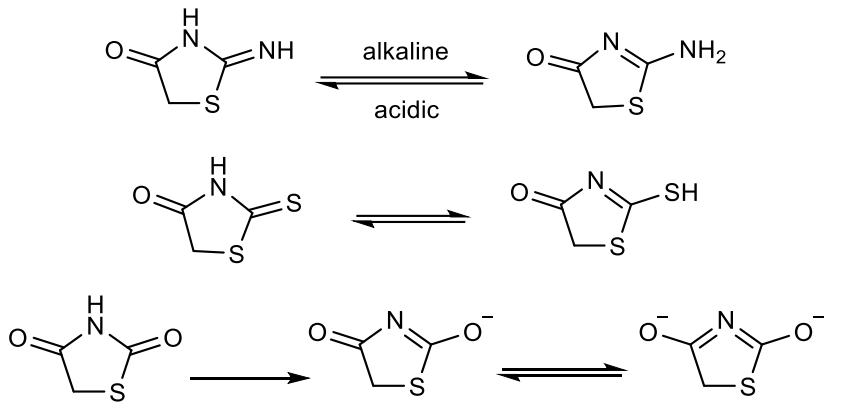
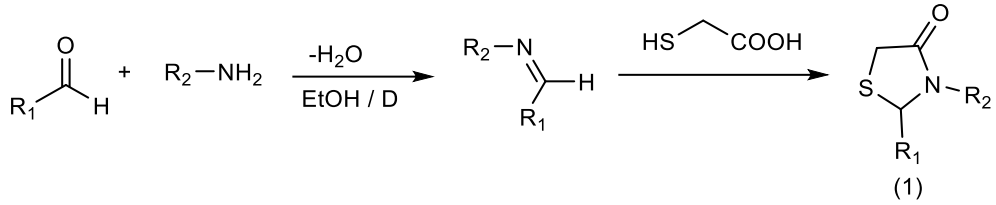


3. Thiazolidine synthesis

3.1. From mercapto-acetic acid

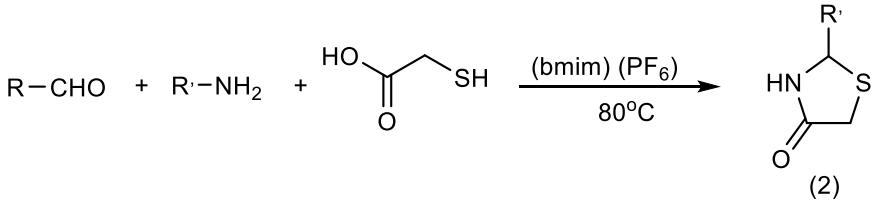
3.1.1. Reaction with amine

The primary synthesis methods to 1,3-thiazolidin-4-ones (**1**) have 3 compartments: an amine, a carbonyl molecule, and a mercapto-acid. The synthesizing disclosed could be done in one pot with 3 components or in 2 steps (**Scheme 1**). The processes start with the creation of an imine, that follows assault by the produced S nucleophile, then proceed to intrinsic cyclization on removal of water, EtOH/Δ [1].



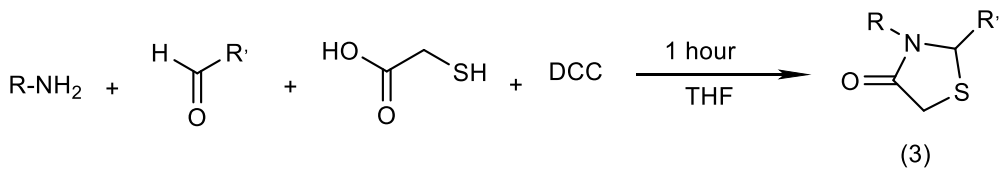
Scheme (1): Synthesis of 1,3-thiazolidin-4-ones

Several amine substrates and aldehyde interacted well with mercapto-acetic acid (MCA) in the presence of [bmim (1-butyl-3-methylimidazolium hexafluorophosphate)] [PF_6], as shown in (**Scheme 2**), yielding the compatible 2,3-disubstituted-1,3-thiazolidin-4-ones (**2**) with moderate to high yields [4].



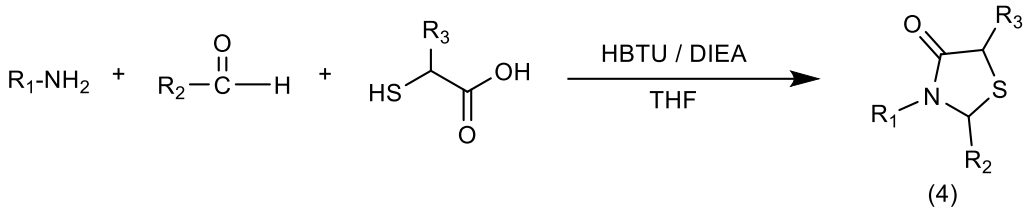
Scheme (2): Synthesis of 2,3-disubstituted-1,3-thiazolidin-4-ones using bmim/ PF_6 mixture

The reaction between amine, thioglycolic acid, and aldehyde in the presence of DCC (N,N′-Dicyclohexylcarbodiimide) in THF for 5 minutes at 0-5◦C then stirring for 50 minutes at room temperature yielded the respective 4-thiazolidinone compound (**3**) (**Scheme 3**) [5].



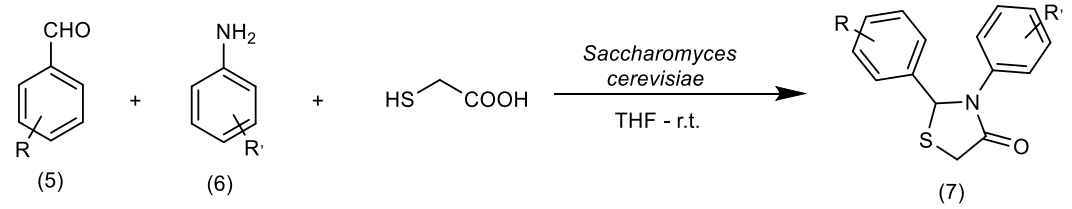
Scheme (3): DCC synthesis of 4-thiazolidinones

At room temperature, HBTU (Hexafluorophosphate Benzotriazole Tetramethyl Uronium) catalyzed a three-component compartment reaction of aldehyde, amine, and mercapto-acid derivatives to produce 4-thiazolidinones (**4**). The resulting substances are formed in 30 minutes in high yields (**Scheme 4**) [6].



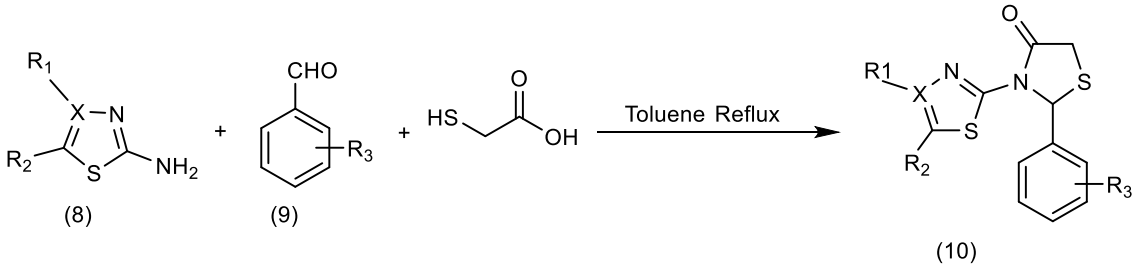
Scheme (4): HBTU catalyzed Synthesis of 4-thiazolidinones

Three-compartments one-pot aryl aldehydes (**5**), amines (**6**), and thioglycolic acid cyclocondensation results in 4-thiazolidinones (**7**), with *S. cerevisiae* acting as biocatalyst at room temperature in an organic medium. The yeast has enhanced catalytic activity in watery media. Nevertheless, organic substrates are not compatible and insoluble in water. Consequently, the cyclocondensation occurred in an organic media using *S. cerevisiae* [7].



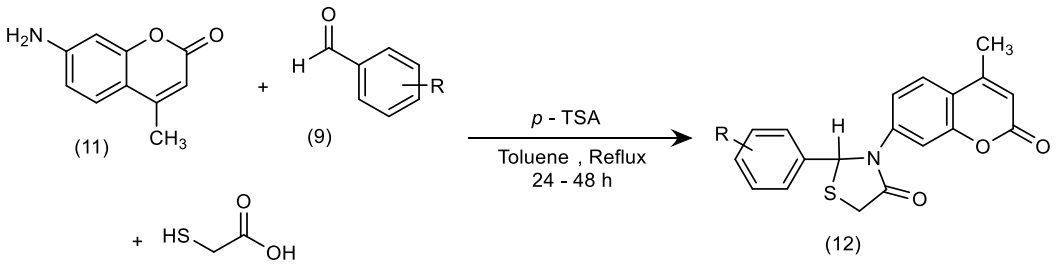
Scheme (5): *S. cerevisiae* promoted the one-pot three-compartment formation of 4-thiazolidinones

The 2,3-diaryl-1,3-thiazolidin-4-ones (**10**) were synthesized using the previously described procedure, which involved the refluxing of an appropriate heteroaromatic amine (**8**) with a comparable quantity of 2,6-dihalo-benzaldehyde (**9**) in excess of MCA in toluene (**Scheme 6**). The necessary compounds have been produced in good to exceptional purity and yield after 24 hours [8].



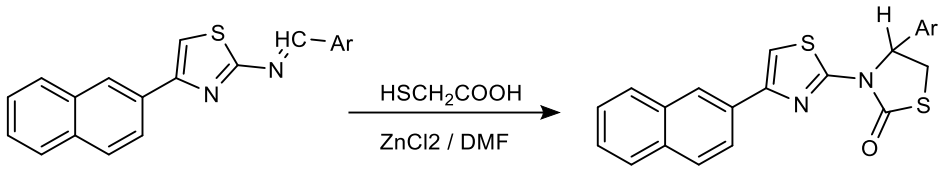
Scheme (6): Synthesis of 2,3-diaryl-1,3-thiazolidin-4-ones

Several of 2-(substituted phenyl)-3-(4-methyl-2-oxo-2*H*-chromen-7-yl)-thiazolidin-4-one derivatives (**12**) were produced by reacting 7-amino-4-methyl-benzopyran-2-one (**11**) with a diversity of aromatic aldehydes (**9**) and thioglycolic acid (**Scheme 7**). The structure of the synthesized compounds was confirmed using spectroscopic procedures and analysis of elements, as well as TLC was used to verify the purity [9].



Scheme (7): synthesis of 2-(substituted phenyl)-3-(4-methyl-2-oxo-2*H*-chromen-7-yl)-thiazolidin-4-ones

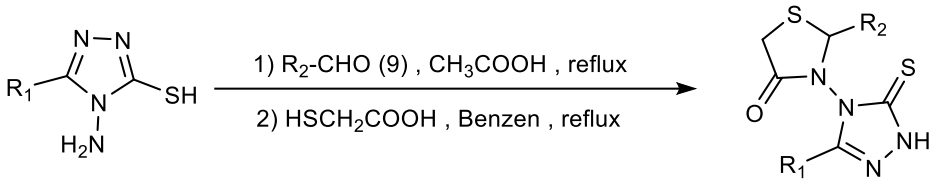
Schiff's base (**13**), which is formed by reacting of 2-amino-4-(2-naphthalenyl) thiazole with aromatic aldehydes, on cyclocondensation with thioglycolic acid afford 2-thiazolidinones (**14**) (**Scheme 8**) [10].



(13) (14)

Scheme (8): Synthesis of 4-Ar-3-(4-napthalen-2yl)thiazolidine-2-one

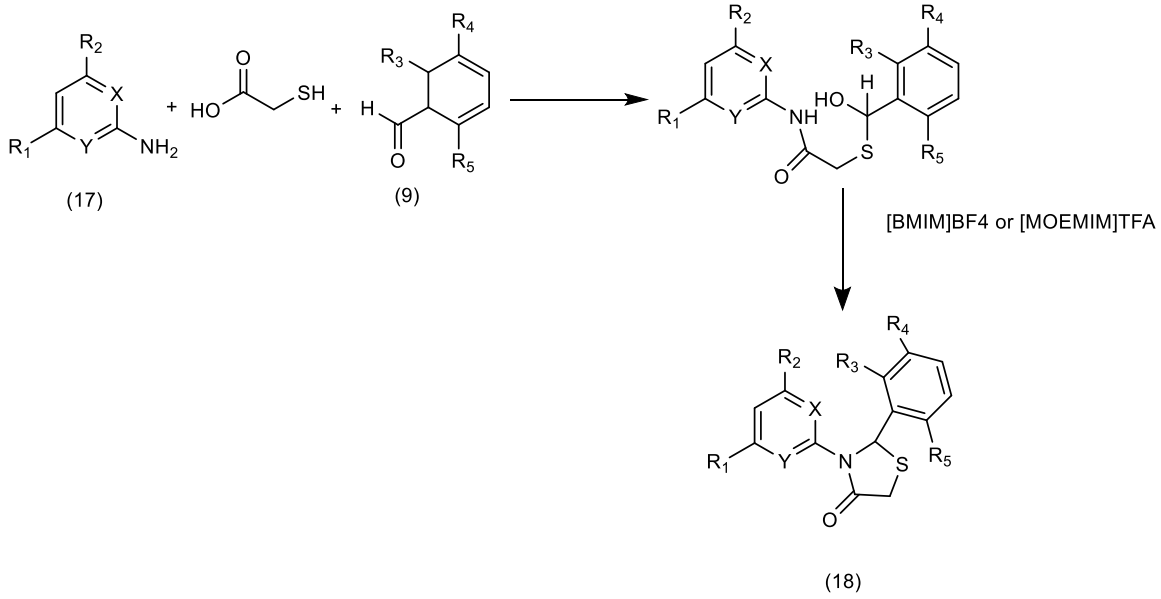
The Schiff's base was formed by the reaction of (**15**) with aromatic aldehydes and glacial acetic acid (GAA), which was subsequently cyclized by refluxing with thioglycolic acid in dry benzene for 6-8 hours to produce the targeted product of thiazolidenone (**16**) (**Scheme 9**) [11].



(15) (16)

Scheme (9): Synthesis of 2-substituted-3-(3-substituted-5-sulfanylidene-1,2,4-triazolin-4-yl)1,3-thiazolidin-4-one

An efficient one-step formation of 2,3-diaryl/2-aryl-3-heteroaryl-1,3-thiazolidin-4-ones (**18**) was achieved by condensing aromatic/hetero amine (**17**), 2-MCA, and aromatic aldehyde (9) in ionic liquids, specifically 1-methoxyethyl-3-methylimidazolium trifluoroacetate [MOEMIM]TFA and 1-butyl-3-methyl-imidazolium tetrafluoroborate [BMIM]BF4 (**Scheme 10**). A microwave-induced production of the exact chemical using toluene as a solvent was described. Except for the ionic liquid-assisted synthesis reported here, the majority of synthesizing techniques are linked with harsh reaction circumstances, low yields, and environmentally hazardous solvents [12].



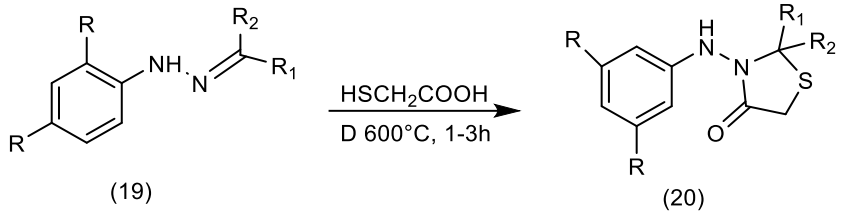
(17) (9) (18)

X, Y= C or N; R_1= H, Me, OMe, Cl, Br; R_2= H, Me; R_3= H, Cl; R_4= H, Me; R_5= Cl, F

Scheme (10): One-step formation of 2,3-diaryl/2-aryl-3-heteroaryl-1,3-thiazolidin-4-ones

3.1.2 Reaction with Hydrazone

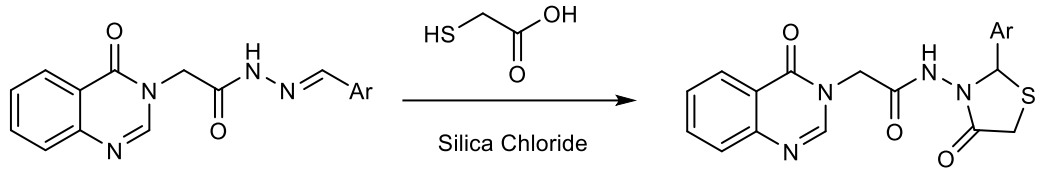
Neuenfeldt et al. [13] reported that 3-(N-phenyl)-1,3-thiazolidin-4-ones (**20**) was synthesized by an effective solvent-free technique from the reaction of MCA, ketones (cyclopentanone and cyclohexanone), or aldehydes (benzaldehyde and valeraldehyde) and hydrazines (phenylhydrazine and 2,4-dinitrophenylhydrazine) (19) (**Scheme 11**).



(19) (20)

Scheme (11): Potential solvent-free formation of 4-thiazolidinones

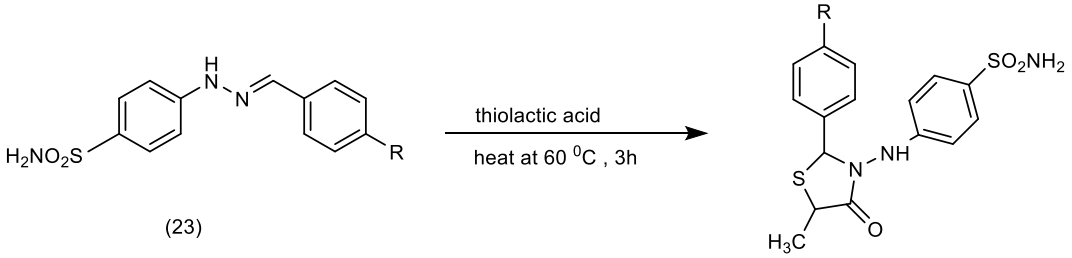
Various quinazolinyl azomethines (**21**) were treated with MCA with the inclusion of $SiCl_4$, which was utilized as a heterogeneous promotor for speeding the intrinsic cyclocondensation through solvent-free conditions, yielding 4-thiazolidinones (**22**) (**Scheme 12**) [14].



(21) (22)

Scheme (12): Solvent-free synthesis of 4-thiazolidinones using Silica chloride

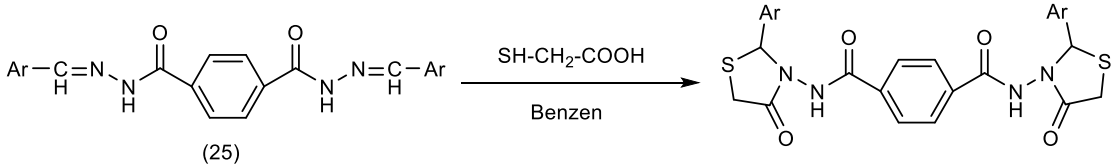
A novel approach permits the formation of 4-thiazolidinones produced from phenyl hydrazine, even when the phenyl ring contains electron-removing groups. As a result, the hydrazones (**23**) were formed in high yields by heating 4-substituted aldehydes with 4-hydrazinobenzene sulfonamide hydrochloride in the sodium acetate in ethanol. In solvent-free conditions, heating the formed hydrazones with excess thiolactic acid to 60°C yielded (35–60%) of 4-thiazolidinone derivatives (**24**) (**Scheme 13**) [15].



(23) (24)

Scheme (13): Solvent-free formation of 4-thiazolidinones using excess thiolactic acid

Another series of 4-thiazolidinone (**26**) was synthesized by cyclocondensation of certain altered hydrazones (**25**) and thioglycolic acid in benzene (**Scheme 14**) [16].

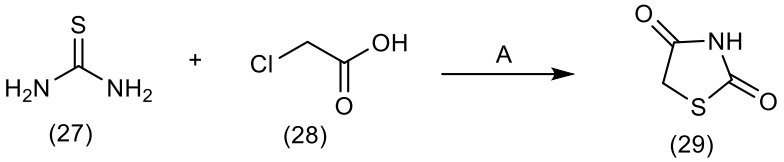


(25) (26)

Scheme (14): Formation of 4-thiazolidinone by cyclocondensation

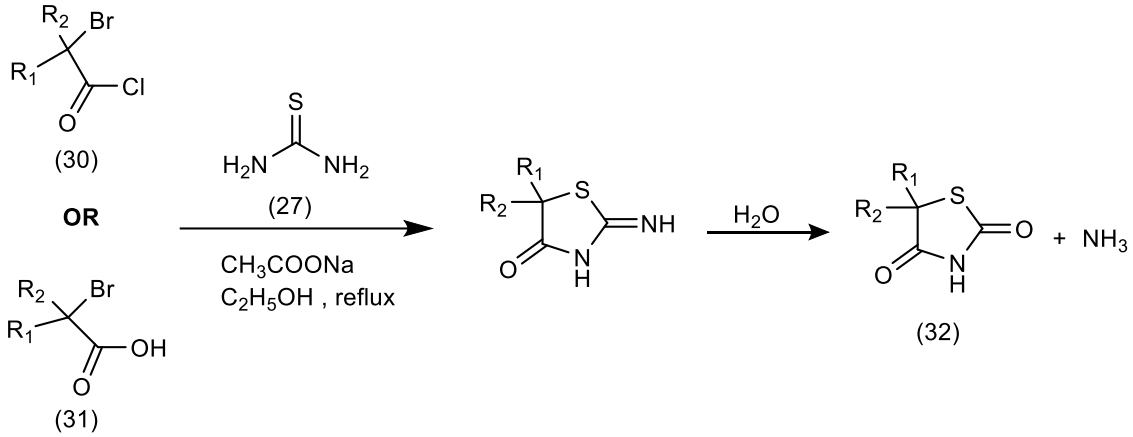
3.2. From Thiourea derivatives and Thiosemicarbazones

Thiazolidine-2,4-dione (**29**) can be produced by refluxing of thiourea (**27**), $ClCH_2COOH$ (**28**), or bromoacetic acid in concentrated HCl in the presence of GAA, for 12-24 hours (**Scheme 15**) [17].



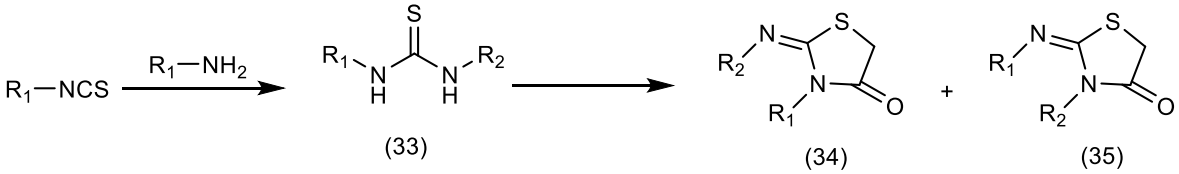
Scheme (15): Synthesis of Thiazolidine-2,4-dione utilizing thiourea and chloroacetic acid

Alternatively, dialkyl-substituted bromoacetic acid (**31**) or bromoacetyl chloride (**30**) can be used to yield 5-dialkyl-substituted thiazolidinones (**32**) by refluxing with thiourea (**27**) in ethanol in the presence of sodium acetate, then on hydrolysis the formed intermediate gave 5,5-dialkyl-thiazolidin-2,4-dione (**Scheme 16**) [18].



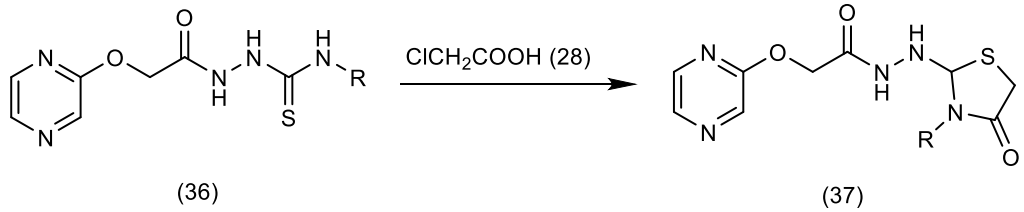
Scheme (16): Formation of 5,5-dialkyl-thiazolidin-2,4-dione

The two isomeric 2-imino-thiazolidin-4-ones (**34**) and (**35**) were obtained by immediately cyclizing the thiourea derivative (**33**), which was produced by reacting alkyl or aryl isothiocyanate with a 1º amine, using halo acetic acid (**Scheme 17**) [19]. Commercial availability of a great variety of aryl and alkyl isothiocyanates gives easy access to thiourea. It therefore makes the pathway very attractive for a rapid assembly of substituted 2-imino-thiazolidin-4-one scaffolds. Thus, reacting an aryl or alkyl isothiocyanate with a primary amine furnished the corresponding thiourea derivative, which was directly cyclized to the iminothiazolidinone by treating this intermediate with a bromoacetic acid ester in the presence of pyridine. It is known that this synthetic route usually gives a mixture of the two isomeric 2-imino-thiazolidin-4-ones of the general structures (**34**) and (**35**)



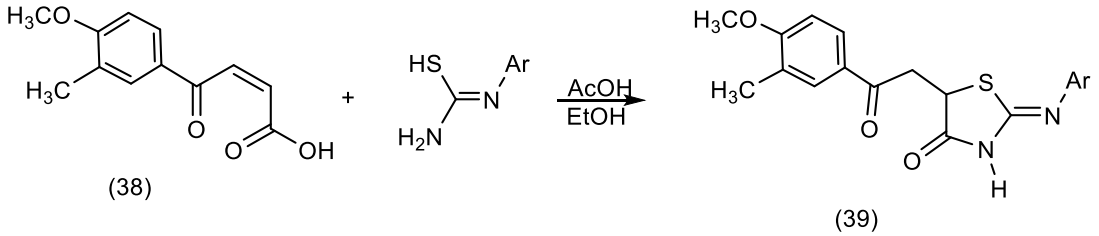
Scheme (17): Formation of two isomers of 2-imino-thiazolidin-4-one

The interaction of (**36**) with chloroacetic acid (**28**) in heating ethanol in the presence of CH_3COONa yielded the equivalent N`-[(2Z)-3-(4-substituted)-4-oxo-1,3-thiazolidin-2-ylidene]-2-[(pyrazin-2-yl)oxy]acetohydrazide (**37**) (**Scheme 18**) [20].



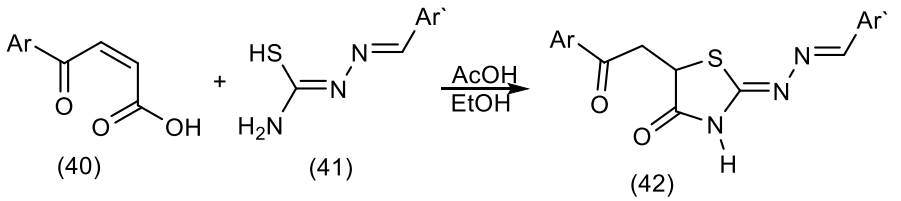
Scheme (18): Synthesis of N`-[(2Z)-3-(4-substituted)-4-oxo-1,3-thiazolidin-2-ylidene]-2-[(pyrazin-2-yl)oxy]acetohydrazide

When 4-(3-methyl-4-methoxyphenyl)-4-oxobutenoic acids (**38**) were permitted to interact with thiourea derivatives in EtOH in CH_3COOH afforded the corresponding arylimino-thiazolidine derivatives (**39**) (**Scheme 19**) [21].



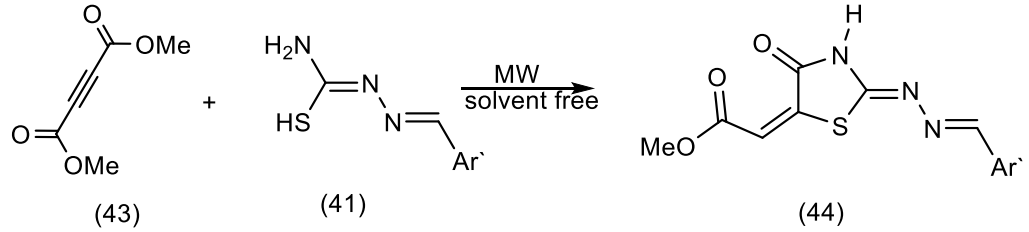
Scheme (19): Synthesis of arylimino-thiazolidine derivatives

Similarly, 2-((arylidene)hydrazono)-5-(2-aryl-2-oxoethyl)thiazolidin-4-one derivatives (**42**) were obtained from the reaction of 4-aryl-4-oxobutenoic acid (40**)** with arylthiosemicarbazone (**41**) in CH_3COOH in GAA (**Scheme 20**) [22].



Scheme (20): Synthesis of 2-((arylidene)hydrazono)-5-(2-aryl-2-oxoethyl)thiazolidin-4-one derivatives

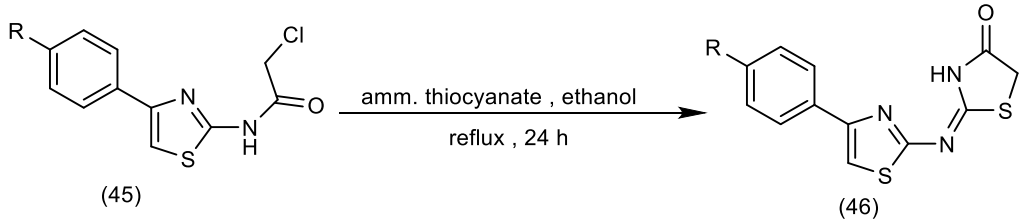
Furthermore, the cyclocondensation of thiosemicarbazones (**41**) with dimethyl but-2-yne-dioate (DMAD) (**43**) under solvent-free conditions provided the corresponding methyl [2-(arylmethylene-hydrazono)-4-oxo-thiazolidin-5-ylidene] acetate derivatives (**44**) in good yields (**Scheme 21**) [23].



Scheme (21): Synthesis of methyl [2-(arylmethylene-hydrazono)-4-oxo-thiazolidin-5-ylidene] acetate derivatives

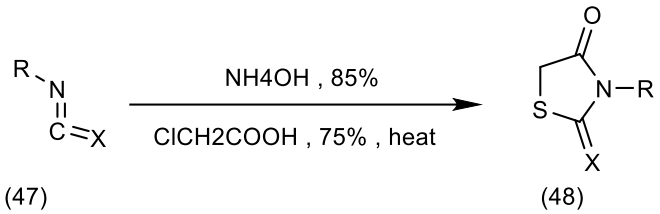
3.3. From Isothiocyanate

Cyclization of acetamide derivatives (**45**) with ammonium thiocyanate in ethanol produced thiazolidinone compounds (**46**) in good yield (40-50%) **(Scheme 22**) [15].



Scheme (22): Synthesis of 1,3-thiazolidin-4-one derivatives

Many thiazolidinones (**48**) are readily accessible or accessible be produced in 2 steps from methyl isothiocyanate (**47**) (**Scheme 23**) [24].

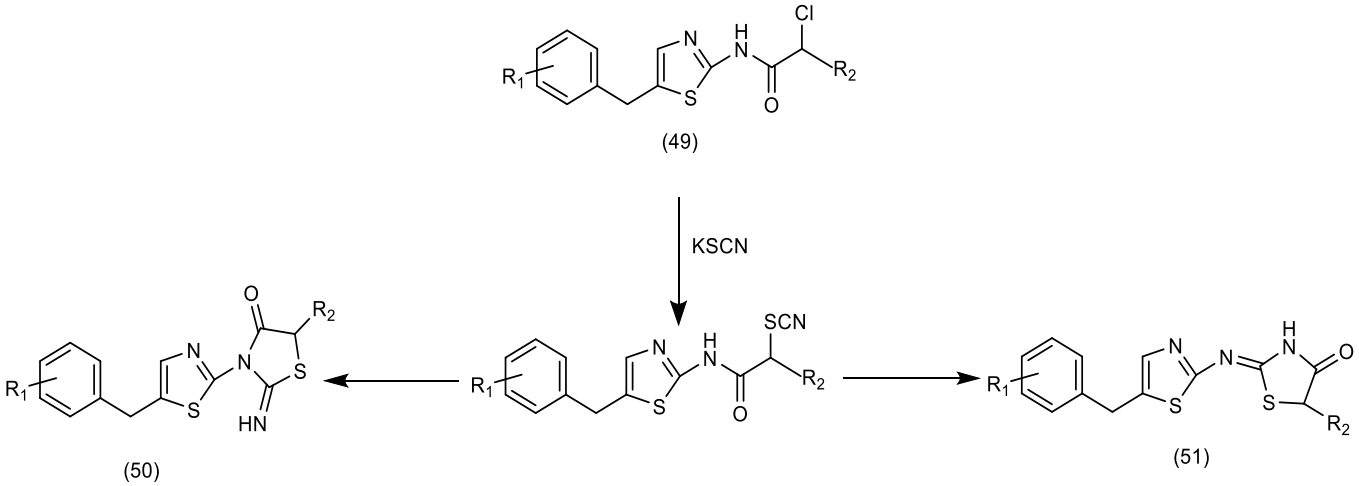


(47) (48)

X= S , NH , R= H , Me

Scheme (23): Synthesis of 3-substituted-1,3-thiazolidin-4-one

Via transformation, 2-[(5-Benzyl-1,3-thiazol-2-yl)-imine].-1,3-thiazolidin-4-ones (**50**), (**51**) were produced by the reaction of 2-chloro-acetamido/ chloropropioamido-5-benzylthiazole (**49**) with KSCN (**Scheme 24**) [25].



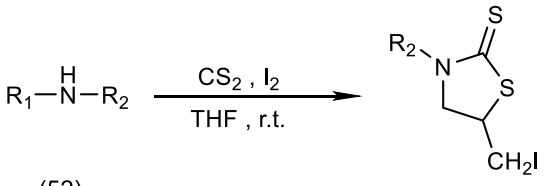
(49) (50) (51)

Scheme (24): Formation of 2-[(5-Benzyl-1,3-thiazol-2-yl)-imine]-1,3-thiazolidin-4-ones

3.4. Other methods

3.4.1. From carbon disulfide

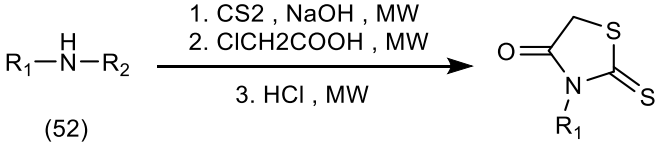
Three distinct materials were combined in a single pot to create the 5-iodomethyl thiazolidine-2-thiones. Thus by region-specific iodocyclization of an allyl amine (**52**), iodine, and CS_2 at room temperature to produce 5-iodomethyl thiazolidine-2-thiones (**53**) (**Scheme 25**) [26].



(52) (53)

Scheme (25): Synthesis of 5-iodomethyl thiazolidine-2-thiones

Additionally, some one-pot microwave assistance methods are disclosed to produce 3-substituted thiazolidine-2-thione (**54**). It is possible to convert alkyl and benzylamines (**52**) into the proper [9-(2-carboxyphenyl)-6-diethylamino-3-xanthenylidine]. In a microwave, diethylamine hydrochloride reacts quickly with chloroacetic acid and carbon disulfide (**Scheme 26**) [27].

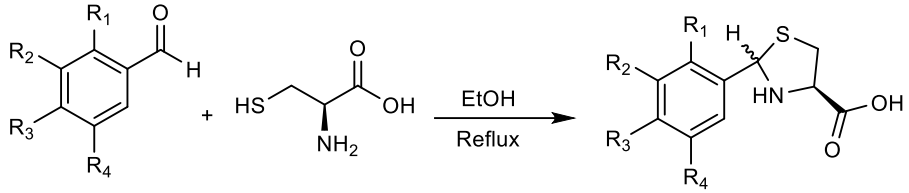


(52) (54)

Scheme (26): One-pot microwave assistance to produce 3-substituted thiazolidine-2-thione

3.4.2 From L-Cystine

Substituted benzaldehyde (**55**) and L-cysteine (**56**) were reacted in ethanol under reflux for 1.5–48 hours to create substituted phenyl thiazolidine-4-carboxylic acid derivatives (**57**) (**Scheme 27**) [28].



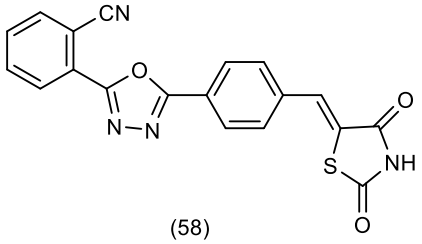
(55) (56) (57)

Scheme (27): Synthesis of substituted phenyl thiazolidine-4-carboxylic acid derivatives

4. Thiazolidine derivatives antitumor/anticancer activity

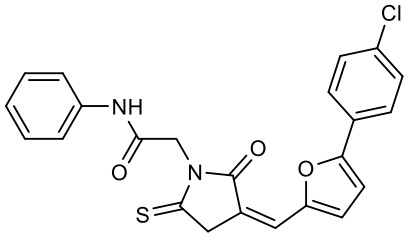
Globally, cancer ranks as the 2nd most common cause of death. 1 out of 5 individuals will suffer from cancer throughout life, and 1 out of 12 females and 1 out of 9 males will die as a consequence of cancer. As a result, cancer is a severe condition that has an impact on everyone's life. Regretfully, it is a tissue-level disorder, and this type makes it difficult to diagnose specifically and determine whether therapy is effective [29]. Chemotherapy is an important part of cancer treatment. Many novel chemotherapy drugs have recently been employed to treat various cancer types [30,31].

Asati et al. [32] developed and formed numerous novel TZD-2,4-dione derivatives and tested them for anti-tumor potency through the MCF-7 using the sulforhodamine B assay, with adriamycin serving as a reference medication. Compound (**58**), with a cyano group at position-2 of the phenyl ring and oxadiazole of the TZD-2,4-dione scaffold, demonstrated substantial antitumor potential. The SAR research revealed that substituting a phenyl ring with electron-acceptor groups on the TZD scaffold increased the effectiveness against cancer. Docking analyses were conducted with PIM-1 kinase, and substance (**58**) displayed decent binding energy of -6.68. The oxygen atom of TZD-2,4-dione forms H-bonds with amino acids, Lys 67 and Asp 186, that is critical for its effectiveness against cancer.



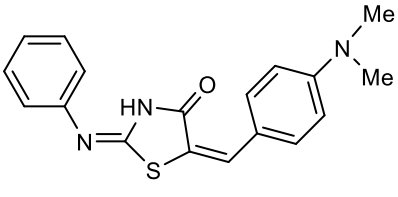
(58)

Chandrappa et al. [33] synthesized 2-(5-((5-(4-chlorophenyl)furan-2-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl) acetic acid derivatives and tested their cellular toxicity properties. It was discovered that molecules with electron donors at the C-terminal of the phenyl ring increased activity by promoting apoptosis, but substances with electron acceptors (CN, F, CF3) reduced activity. Compound (**59**) was the most effective because it exhibited the highest cytotoxic effect, which may be attributable to its electron donor methoxy group. Compound (**59**) also demonstrated fragmentation of DNA at 50 lM.



(59)

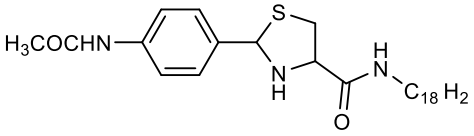
Zhou et al. [34] detailed the design, synthesis, viability, SAR correlations, and pharmacophore of thiazolidinone derivatives in their search for a more potent anticancer medication. A concentration of 10 lM was used for the initial screening against the cell panel. After 24 and 48 hours, 96-well plates showed changes in both cell population and shape. For the secondary verification tests, compounds that were toxic to cancerous cells but safe to normal ones were chosen. The concentration (used in the initial screening) was tested three times in a secondary assessment. Consequently, 11 compounds were detected as substantial cellular toxic materials. There was no cytoselective toxicity when a nitrogen atom was substituted in the thiazolidinone ring or the NMe2 group at position-4 of the phenyl ring. The compound 5-(4-(dimethylamino) benzylidene)-2-(phenylimino)TZD (2E,5E)-4-one (**60**) showed IC_{50} against H460 and H460taxR of 0.50 and 0.21 lM.



(60)

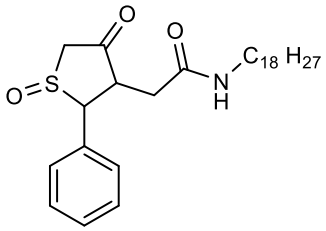
The investigation for possible cellular toxicity effects in prostate carcinoma assessed several 2-arylthiazolidine-4-carboxylic acid amides. With an IC_{50} of 0.55 lM and a 38-fold effect in PPC-1 cells, compound (**61**) was shown to have the highest cellular toxicity. Increasing the alkyl chain

by 1 C unit led to a substantial decline of activity, consequently, the alkyl chain with the C18 unit was convenient for the usefulness of TZD analogues, according to the SAR analysis, which also showed that potency increased as chain length elevated from C7 to C18. While substituting an cyclohexyl or alkyl group for the phenyl ring reduced its efficacy, substituting a derivative of the furanyl ring showed similar cytotoxicity [35].



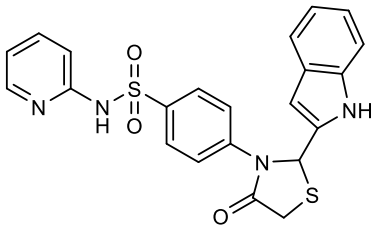
(61)

The same group of researchers created a second series of 2-aryl-4-oxo-thiazolidin-3-yl amides (62), and all the chemicals they made were evaluated on 5 human prostate cancer cell lines. They found that while adding an aryl group to the alkyl chain reduced the biological activity, expanding the alkyl chain increased the anticancer impact [36].



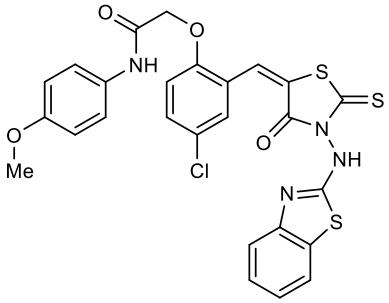
(62)

The IC_{50} values of compound (**63**) against MCF7 and HELA were 1.07 and 1.97 lg/mL, respectively. The thiazolidin-4-one ring connected to the pharmacophoric moiety had a limited effect on the efficacy, which was primarily dependent on the 4-[(pyridin-2-ylamino) sulfonyl]benzene pharmacophoric moiety. The molecule in question had the least binding energy (DGb: -9.07 kcal/mol), 1 H-bond with Thr670, and an RMSD of 0.99 A, according to docking research [37].



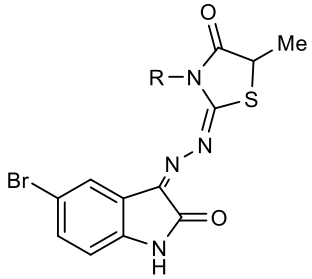
(63)

Havrylyuk et al. [38] revealed that the most active candidate was found to be 4-chlorophenoxy-N-(4-methoxyphenyl)-acetamide (**64**), the SAR analysis showed that compound 64's antitumor potential was influenced by the type of replacement in position 5 of the 4-thiazolidinone cycle, and that performance was increased by adding a 4-chlorophenoxy-N-(4-methoxyphenyl)-acetamide group in position 5 of the 4-thiazolidinone core.



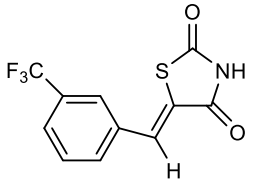
(64)

5-Bromo-3-[(3-substituted-5-methyl-4-thiazolidinone-2-ylidene)hydrazone]-1*H*-2-indolinones (**65**) were studied for the basic cellular toxicity potential against MCF7, NCI-H460, and SF-268. Indolinones thiosemicarbazone derivatives demonstrated remarkable cellular toxic action [39].



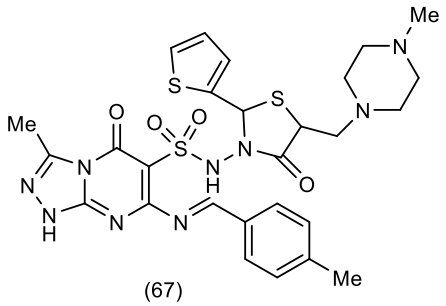
(65)

Cyclooxygenase (COX) is responsible for prostaglandin synthesis. COX-2 is elevated in various human malignancies, and the formation of E-series prostaglandins increases dramatically in cancer tissue during colorectal cancer progression [40]. Compound (**66**) did not interfere with the COX enzyme and reduced the viability of the HT29 that downregulated COX-2, reaching activity values with IC_{50} range of 38.8-59.7 lM [41].



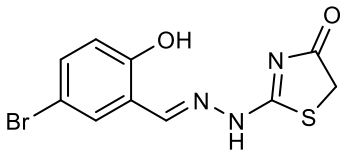
(66)

Hafez et al. [42] developed a group of substituted triazolo[4,3-a]pyrimidin-6-sulfonamides with a thiazolidinone moiety and investigated their anticancer efficacy. The main part of the produced substances was moderately active, and compound (**67**) had notably lowered proliferative activity on all 60 cell lines examined, with IC_{50} values ranging from 5.89 to 37.1 x 10-6 lM. The thienyl group at C-2 of thiazolidinone and morpholine/4-methylpiprazin presence on C-5 seem to be very important for its anticancer activities.



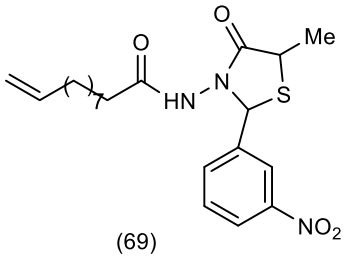
(67)

2-(2-(5-Bromo-2-hydroxybenzylidene)hydrazinyl)thiazol-4(5*H*)-one (**68**) showed that the HER-2 and EGFR kinase inhibitors had IC_{50} values of 0.42 and 0.09 lM, respectively. The inhibitory action of compounds with aromatic rings was superior to that of compounds substituted with aliphatic rings [43].



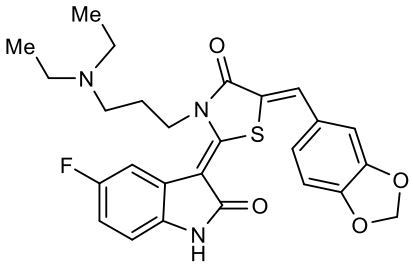
(68)

Compound (**69**) was assessed against 9 cancer cell lines and exhibited considerable cytotoxic action in cases of melanoma, lung, and kidney cancers, where the decrease in proliferation was reported to be 97, 75, and 84%, respectively, [44].

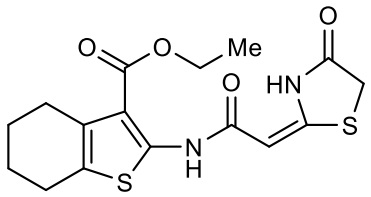


(69)

Compound (**70**) was tested against HT-29, MDA-MB-231, and H460 using MTT assay and showed IC_{50} values of 0.025, 0.77, and 0.075 lM, respectively. The SAR investigation revealed that replacement with a smaller electron-drawing fluorine atom had an advantageous effect on improving antitumor potential [45]. Gouda et al. [46] demonstrated that thiazolidinone compounds can degrade DNA (**71**). Only a few of the produced compounds demonstrated full destruction of calf thymus DNA.

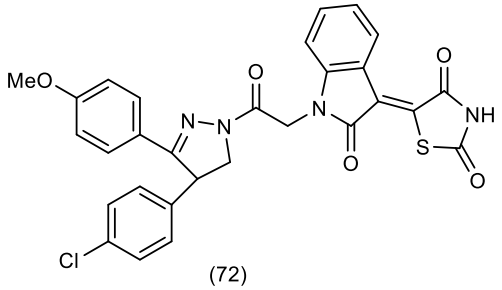


(70)



(71)

Numerous isatin-based thiazolidine conjugates (**72**) have been reported for their potential antitumor effects; their specificity for tyrosine kinase indicates that they may be employed as innovative anticancer therapies. Compared to 1,3-dihydroindol-2-one bounds with 3,5-diaryl-4,5-dihydropyrazolyne derivatives, none of the thiazolidinone bounds exhibited remarkable activity [38].



(72)

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