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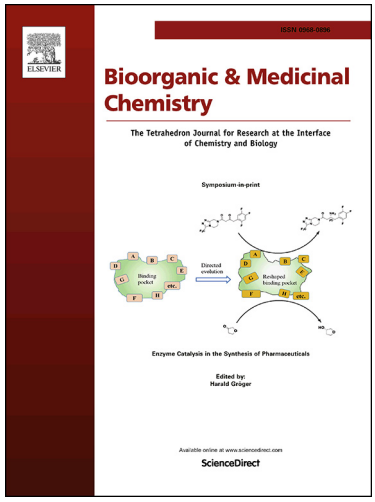

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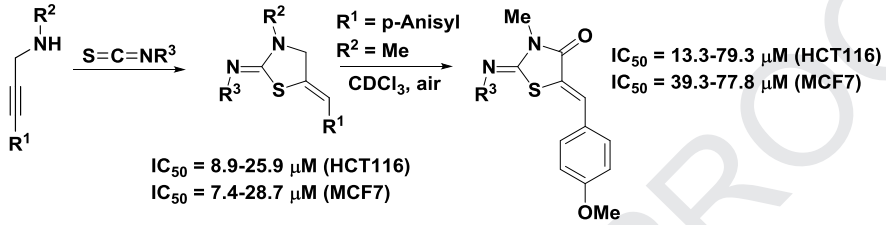

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Novel thiazolidines: Synthesis, antiproliferative properties and 2D-QSAR studies

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ABSTRACT

A series of (*Z*)-2-imino-(5*Z*)-ylidene-N-substituted thiazolidines/thiazolidin-4-ones were synthesized and their antiproliferative activities against colon (HCT-116) and breast (MCF7) cancer cell lines were evaluated utilizing an MTT growth assay. A 2D-QSAR investigation was conducted to probe and validate the obtained antiproliferative properties for the thiazolidine derivatives. The majority of the thiazolidines exhibit higher potency against a colon cancer cell line relative to the standard reference. The *p*-halophenylimino *p*-anisylidene derivatives exhibited the highest anti-proliferative activity against HCT116 relative to control (IC_{50} = 8.9-10.0 μM compared to 20.4 μM observed for 5-fluorouracil as positive control). An X-ray study confirmed the *Z, Z`*-configurations for two examples of the synthesized compounds.

1. Introduction

Cancer and cardiovascular diseases are the largest contributors to global mortality rates; out of these two, cancer is predicted to be the single controlling factor for life expectancy worldwide in the 21st century. Globally, approximately 18.1 million new cancer cases were predicted to be diagnosed in 2018 in addition to 9.6 million deaths attributable to the disease.[1] Contributing to these statistical data, there are an estimated 4700 diagnosed cancer cases per day in the United States, which is equivalent to approximately 1.7 million cases and 609,640 cancer deaths in 2018. Lung, prostate, colorectal, and breast cancers are the four most common malignancies leading to death, accounting for 45% of the total number of cancer mortalities.[2] Based on the GLOBOCAN database published in September 2018, colorectal cancer (CRC) is the third most common malignancy and the second leading cause of death from cancer. It was estimated that more than 1.8 million new CRC cases will occur in 2018 that relates to 881,000 deaths.[1]

Accordingly, the discovery of novel small molecules as potential antitumor drugs against colon and breast cancer continues to demand the attention of several research groups worldwide. Candidate structures containing a thiazolidine framework have engendered significant attention from many researchers due to the diversity of their biological activities, the generally short synthetic sequences required for their construction and the potential for rapid acquisition of diverse substitution patterns.[10] Specifically, for example, diverse biological/pharmacological activities including antibacterial and antifungal,[11] antihypertensive,[12] antidiabetic,[13] antidepressant, anticonvulsant,[14] anti-inflammatory, analgesic,[13, 15] and antitumor properties have been described for synthetic 2-imino-5-arylidine-thiazolidin-4-ones.[16]

Recently, special interest has been directed towards 2-imino-5-arylidine-thiazolidines due to the antimitotic activity revealed against various cancer cells.[10b] Teraishi *et al*. have explored the apoptotic activity of a series of 2-imino(amino)-5-ylidene-4-thiazolidinones against various drug resistant human cancer cell lines.[16d, 16e] Among these compounds, MMPT (**1**) and DBPT (**2**) induce cell death in drug resistant colon and lung cancer cells (Fig. 1). These two thiazolidinones induce apoptosis by causing G2/M-phase arrest in p53-deficient H1299 (lung cancer) and HCT116 (colon cancer) cells.[16d] Ottanà *et al*. have demonstrated that 2-phenylimino-5-(3-methoxyphenyl-methylidene)-3-propyl-4-thiazolidindione (**3**) (Fig. 1) inhibits the growth of HT-29 colon cancer cell lines with high COX-2 expression.[16b] Also, 2-{[4-(4-chlorophenyl)-1,3-thiazol-2-yl]imino}-5-(4-methoxybenzyl-idene)-1,3-thiazolidin-4-one (**4**) (Fig. 1) was reported to exhibit antimitotic activity against colon and breast cancers.[16c] Peroxisome proliferator activated receptors (PPARs) are overexpressed in various tumors including colon, breast, prostate, lung, pituitary, and thyroid cancers. HL005 (**5**) (Fig. 1) is reported to be a PPARγ antagonist especially for breast cancer. Specifically, it antagonizes the rosiglitazone stimulated PPARγ/CBP interaction with an IC_{50} = 7.97 μM, and also inhibits the proliferation of MCF7 cells by inducing apoptosis at G2/M phase (IC_{50} = 108 μM).[16a] It is interesting to note that most of the active 2-imino-5-arylidene-thiazolidines described in the literature contain the 4-thiazolidinone scaffold; this may be a reflection of the paucity of available synthetic approaches for 2-imino-5-arylidene-thiazolidine compounds.

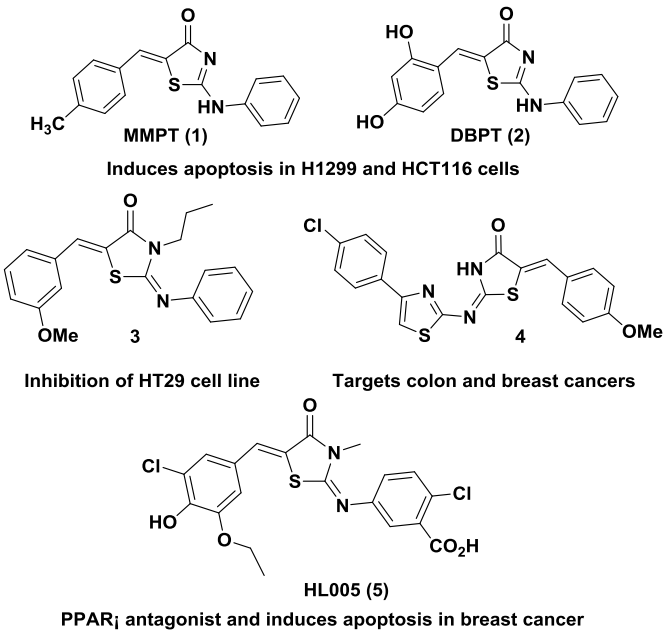


Figure 1. Structures of some known anti-proliferative thiazolidinones.

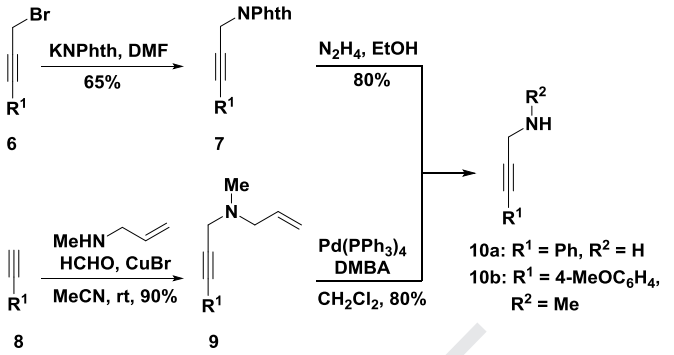
In this present study, we describe th synthesis of 2-imino-5-ylidine-thiazolidines and derived thiazolidinones through application of a new synthetic method developed by our research group,[19] and an investigation of their antiproliferative properties against HCT-116 (colon) and MCF7 (breast) cancer cell lines using an MTT growth assay.

2. Results and discussion

2.1. Chemistry

Synthetic methods for the construction of thiazolidinones abound in the literature, but the synthesis of the corresponding thiazolidines has received significantly less attention. Several synthetic protocols for the preparation of substituted thiazolidin-2-imines have been reported recently.[17] For example, Dethe and co-workers have described a method to synthesize thiazolidin-2-ylideneamine derivatives via thiol–yne coupling of propargylamine with isothiocyanate under metal- and solvent-free conditions, although there are some limitations in terms of substrate scope.[18] Herein, we report the preparation of a variety of thiazolidines in good to excellent yields via our recently discovered silica gel-promoted tandem thioacylation-hydrosulfenylation of propargylamines **10a-d** with thiocyanates.[19]

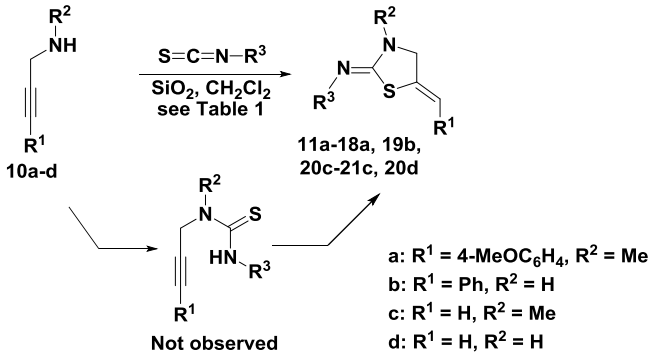
The two terminal alkynes **10c** and **10d** (R^1 = H, R^2 = Me; R^1 = R^2 = H) used in this study were commercially available whereas the internal alkynes required synthesis. The primary propargylamine **10a** (R^1 = Ph, R^2 = H) was synthesized from the corresponding bromide via Gabriel chemistry using previously described procedures.[20] The secondary propargylamine substrate **10b** (R^1 = 4-$MeOC_6H_4$, R^2 = Me) was synthesized using chemistry described previously by Looper and coworkers (Scheme 1).[21] Specifically, a copper-mediated, three-component coupling reaction of 4-ethynylanisole **8** with formaldehyde and the N-allyl amine was carried out to produce tertiary amine **9**. Pd-Catalyzed deallylation was employed to yield the requisite amine **10b**.



Scheme 1. Synthesis of 3-(substituted)-prop-2-yn-1-amines **10a-b**.

The (Z)-2-imino-5-(Z)-alkylidenethiazolidines **11a-18a**, **19b**, **20c-21c**, **20d** were readily synthesized by application of a recently described method utilizing silica gel-mediated tandem thio-acylation and subsequent anti-hydrosulfenylation of the alkyne. Propargyl amines **10a-d** were reacted on silica gel with several different isothiocyanates to afford the corresponding targeted thiazolidines in good yields (Scheme 2 and Table 1) via the intermediacy of the corresponding thiourea. The spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR, and mass spectrometry) and X-ray crystallography corroborate the structures of **11a-18a**, **19b**, **20c-21c**, and **20d**. For example, the ^{1}H NMR spectrum of compound **15a** shows the diagnostic vinylic and methylene protons at δ_H = 6.46 (triplet) and δ_H = 4.40 (doublet) ppm respectively, with a small long-range coupling of J = 1.9 Hz. An X-ray crystal structure analysis of compound **15a** (for more details, see below) confirms the geometry of the two exocyclic double bonds at C2 and C5 as possessing *Z*, *Z*`-configurations (Fig. 2).

4-Thiazolidinones, have been known for a long time to possess a wide range of biological activities. Out of all types of thiazolidinones, 4-thiazolidinones and 2-imino-4-thiazolidinones are exceedingly common.[22] There are several methods known for the synthesis of 2-imino-4-thiazolidinones from the corresponding thioureas.[23] However, in this context, we observed the formation of thiazolidinones from the corresponding thiazolidines via auto-oxidation. Interestingly, only the thiazolidine compounds which contained a 4-methoxybenzylidine moiety underwent air oxidation to the corresponding (Z)-2-imino substituted-5-((Z)-alkylidene)-thiazolidin-4-ones **28-38** upon standing at room temperature and open to the atmosphere for few days either neat or in solution (Scheme 3). The NMR spectra readily confirm the thiazolidin-4-one structures by, for example, disappearance of the C4-methylene protons in the ^{1}H NMR spectrum in addition to the ^{13}C NMR data, which now exhibit an absorption due to the C4 carbonyl; for example, compound **22** exhibits a resonance at $\delta_{C=O}$ = 167.1 ppm. Also, the IR spectra show a carbonyl stretching vibration band for each member of the thiazolidinone family, Furthermore, a single crystal X-ray study confirms the structure of **31** (an example of the synthesized thiazolidinones) as shown in Fig. 2.



Scheme 2. Synthesis of (*Z*)-2-imino-5-(*Z*)ylidene-*N*-substituted thiazolidines **11a-18a**, **19b**, **20c-21c**, and **20d**.

Table 1. Synthesis of (*Z*)-2-imino-(5*Z*)-ylidene-N-substituted thiazolidines **11a-18a**, **19b**, **20c-21c**, and **20d**.[a]

Entry	Cpd.	R^1	R^2	R^3	Yield (%)[b]
1	**11a**	4-$MeOC_6H_4$	Me	4-MeC_6H_4	97
2	**12a**	4-$MeOC_6H_4$	Me	4-FC_6H_4	99
3	**13a**	4-$MeOC_6H_4$	Me	4-$NO_2C_6H_4$	93
4	**14a**	4-$MeOC_6H_4$	Me	4-$CF_3C_6H_4$	94
5	**15a**	4-$MeOC_6H_4$	Me	4-$CH_3OC_6H_4$	99
6	**16a**	4-$MeOC_6H_4$	Me	4-BrC_6H_4	99
7	**17a**	4-$MeOC_6H_4$	Me	4-ClC_6H_4	99
8	**18a**	4-$MeOC_6H_4$	Me	4-*t*-BuC_6H_4	95
9	**19b**	C_6H_5	H	3,5-$(CF_3)_2C_6H_3$	75
10	**20c**	H	H	C_6H_5	80
11	**21c**	H	H	Allyl	67
12	**20d**	H	Me	C_6H_5	78
13	**22**	C_6H_5	PhNHC=S	C_6H_5	9[c]

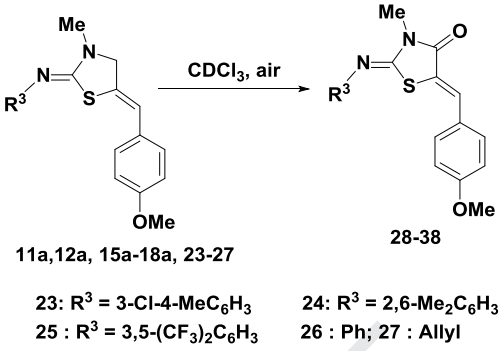
[a] Reaction was performed with 200 mg of **10a-d** in CH_2Cl_2 (0.2 mL/mmol) and isothiocyanate (1 equiv) on silica gel (1.75 g/mmol) for 2 h.

[b] Isolated yields after purification by column chromatography.

[c] Isolated as a minor byproduct.

2.2. Single crystal X-ray studies

Analysis of compounds **15a** and **31** has been undertaken by single crystal X-ray diffraction to confirm the composition and connectivity of these analogs. These results are consistent with crystallographic analysis of related congeners prepared in our lab.[19] Thiazolidine **15a** crystallizes in a monoclinic space group P21/c with one molecule per asymmetric unit cell and 4 molecules per unit cell whereas compound **31** crystallizes in a triclinic space group P-1 with one molecule per asymmetric unit cell and 2 molecules per unit cell. Molecules of compound **15a** are arranged in a zig-zag orientation and connected to each other through weak H-bonding stabilizing the crystallographic structure and forming a three-dimensional supramolecular arrangement. Similarly, molecules of compound **31** are arranged in a zig-zag shape linked with weak H bonds as well as Br...H bonds stabilizing the extended arrangement of the crystal structure. For molecule **31**, the 4-bromophenyl fragment is found to have two statistically different orientations. Therefore, the atoms sites (C10/C13), (C11/C14), (C15/C17) and (C16/C18) are all half occupied. Fig. 2 illustrates the independent molecules of compounds **15a** and **31** as refined.



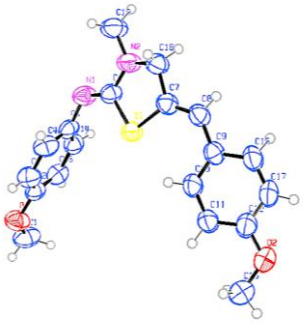
Scheme 3. Synthesis of (Z)-2-substituted imino-5-((Z)-ylidene)-thiazolidin-4-ones **28-38**.

Table 2. Synthesis of (*Z*)-2-substituted imino-5-((*Z*)-ylidene)-thiazolidin-4-ones **28-38**[a] via air oxidation.

Entry	Cpd.	R^1	R^2	R^3	Yield (%)[b]
1	**28**	4-$MeOC_6H_4$	Me	4-$CH_3C_6H_4$	23
2	**29**	4-$MeOC_6H_4$	Me	4-FC_6H_4	26
3	**30**	4-$MeOC_6H_4$	Me	4-$MeOC_6H_4$	22
4	**31**	4-$MeOC_6H_4$	Me	4-BrC_6H_4	17
5	**32**	4-$MeOC_6H_4$	Me	4-ClC_6H_4	16
6	**33**	4-$MeOC_6H_4$	Me	4-^{t}BuC_6H_4	18
7	**34**	4-$MeOC_6H_4$	Me	3-Cl-4-MeC_6H_3	22
8	**35**	4-$MeOC_6H_4$	Me	2,6-$Me_2C_6H_3$	20
9	**36**	4-$MeOC_6H_4$	Me	3,5-$(CF_3)_2C_6H_3$	17
10	**37**	4-$MeOC_6H_4$	Me	C_6H_5	17
11	**38**	4-$MeOC_6H_4$	Me	Allyl	14

[a] Reaction was done with 100 mg of corresponding thiazolidine in $CDCl_3$ (1 mL) open to the atmosphere for 1-3 days.

[b] Isolated yields after purification by column chromatography (40-50% of the starting thiazolidine was also recovered).



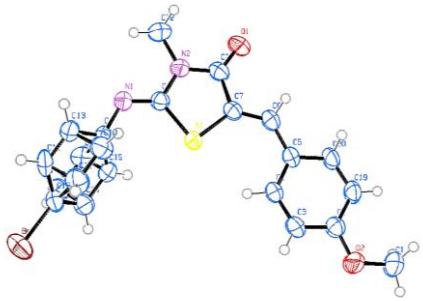


Figure 2. ORTEP views of compounds **15a** (top) and **31** (bottom) showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii. Blue, red, yellow, purple and brown spheres refer to carbon, oxygen, sulfur, nitrogen and bromide atoms, respectively.

2.3. Antiproliferative properties

An MTT growth assay[24] was utilized for evaluation of the antiproliferative activities of the synthetic 2-imino-5-alkylidine-thiazolidines/thiazolidinones (Table 1 and 2) against HCT-116 (colon), and MCF7 (breast) carcinoma cell lines using 5-fluorouracil as a positive control (approved drug against colon, breast and skin cancers).[25] It is observed from the data shown in Table 3 that several of the synthetic thiazolidine derivatives exhibit higher potency against colon cancer relative to the standard reference (Supplementary Figs. S1-S3).

Eleven analogs (**11a-13a**, **15a-17a**, **19b**, **29**, **31**, **32**, and **34**) out of the synthesized compounds are potentially promising antiproliferative hits, especially against colon cancer. All 11 of these compounds have higher antiproliferative activity than 5-fluorouracil with variable potency (IC_{50} values). It is noteworthy that most of these compounds belong to the thiazolidine library, while only four thiazolidinone-containing compounds display higher activity than standard reference. Compounds **16a, 17a, 12a, 13a,** and **32** exhibit the highest antiproliferative activity among this library against HCT116 relative to 5-fluorouracil (IC_{50} = 8.9, 9.8, 10.0, 10.2, and 10.4 μM respectively in comparison to the corresponding 20.4 μM observed for 5-fluorouracil). Compounds **11a**, **29**, **34**, **15a**, **19b**, and **31** display higher activities with mild potencies than that of 5-fluorouracil (IC_{50} = 11.1, 13.3, 14.1, 15.9, 16.1, 17.0 μM respectively, and 20.4 μM corresponding to 5-fluorouracil).

In comparison, the antiproliferative activities of the synthetic derivatives against MCF7 cell line (breast cancer) did not exhibit improved cytotoxicities over the standard reference used; however, they were still in low micromolar range. For example, the IC_{50} values of **11a-13a** and **15a-17a** are 7.4-9.8 μM, whereas the 5-fluorouracil reference value is 3.15 μM. An analysis of the structure activity relationship (SAR) suggests the substituent attached to the exocyclic 2-imino group of the thiazolidines and thiazolidin-4-ones (mostly aryl groups) contribute to the factors controlling the antiproliferative properties. The antiproliferative activities of the synthetic thiazolidine derivatives against HCT116 are enhanced by the presence of an electron-deficient aryl system attached to the exocyclic amine rather than an electron-rich aryl group. Therefore, it was observed that the activity of compound **19b** possessing a (3,5-bis(trifluoromethyl)phenyl moiety exhibits twice the activity of compound **7** (4-trifluoromethylphenyl) against HCT116 (IC_{50} = 16.1, 34.3 μM for **19b** and **14a** respectively). Of particular note is that thiazolidines containing phenyl rings substituted with halogens display the highest potency among all the synthesized compounds, exhibiting essentially identical IC_{50} values (8.9, 9.8, and 10.0 μM for **16a, 17a,** and **12a** respectively).

A comparable SAR analysis for the synthetic thiazolidinones against HCT116 reveals similar observations. Derivatives in which the exocyclic amine contains an electron deficient aryl moiety are much more active than those with electron rich systems. The effect of electron withdrawing groups is exemplified in compounds **32** (4-chloro) and **29** (4-fluoro) which exhibit higher activities than 5-fluorouracil (IC_{50} = 10.4 and 13.3 μM, respectively), while the impact of electron donating is shown in compounds **28** (*p*-tolyl) and **33** (4-(*t*-butyl)phenyl), significantly reducing the activity to >100 μM for both analogs. Additionally, an N-allyl amine group attached at C2 and methylene at C5 of thiazolidines and thiazolidinones attenuates the activity significantly such as observed for **38** and (**20c, 21c,** and **20d**) (IC_{50} = 79.3 and >100 μM, respectively).

Broadly similar SAR correlations for these derivatives in their antiproliferative activities against MCF7 cell line can be observed. The thiazolidines derivatives are more active than the corresponding thiazolidinone analogues but both groups exhibit attenuated activity in comparison to the positive control (IC_{50} = 3.15 μM for 5-fluorouracil). Also, a similar overall impact of electronegative substituents was noted along with within group trends. Bromine substitution on the iminophenyl ring results in the highest activity among the electronegative groups (IC_{50} = 7.4, 8.0 and 28.7 μM for **16a, 12a,** and **18a** respectively).

All the synthesized thiazolidines/thiazolidinones were tested against a normal (non-cancer) cell line (RPE1, retinal pigment epithelial). The observed data can explain and support the safety profile against normal cells. From the results observed, it has been noticed that most of the effective antiproliferative agents synthesized reveal safe cytotoxicity profile against normal cell line tested (high IC_{50} values relative to that of the cancer cell lines tested).

2.4. 2D-QSAR study

Application of 2D-QSAR (quantitative structure-activity relationship) permits the expression of biological properties in mathematical equations in terms of descriptor values (physico-chemical parameters). This analysis can provide some insight into the parameters controlling activity and simultaneously validates the observed data. In other words, the 2D-QSAR descriptors can unpack hidden features of SAR in terms of thermodynamic, quantum, topological, etc. features. Additionally, QSAR equations when optimized can determine/calculate the difference due to experimental and theoretical values quantitatively that should be within the acceptable statistical range (validation protocol).[26] Fourteen of the synthetic thiazolidines/thiazolidinones possessing variable antiproliferative properties against the HCT116 (colon) carcinoma cell line (**11a-18a**, **19b**, **29**, **31**, **32**, **34**, and **38**) were subjected to 2D-QSAR modeling by CODESSA-Pro software employing the standard technique.[26b] A robust two-descriptor QSAR model was obtained through this analysis [R^2 (correlation coefficient) = 0.941] (Supplementary Table S1). A more detailed explanation of the QSAR descriptors[27] is provided in the supplementary file. The major conclusion from this QSAR study reveals that the constitutional descriptor is the most important parameter controlling the biological properties. This is observed in many of the tested analogues and is exemplified by pair **17a** and **38** which is attributed to the presence of *p*-chlorophenylimino and allylimino residue, respectively. In summary the QSAR model mentioned can assist in developing of effective hits through manipulating the substituents/functions of

the targeted agents, calculating the descriptor values (mainly constitutional parameter) and assigning the predicted property prior for preparation in a future study.

Table 3. Antiproliferative properties of the synthesized thiazoline-containing compounds and 5-fluorouracil (standard reference).

Entry	Cpd	R^1	R^2	R^3	IC_{50},[a] (μM) ± SD		
					HCT116	MCF7	RPE1
1	**11a**	4-$CH_3OC_6H_4$	Me	4-$CH_3C_6H_4$	11.1 ± 1.07	7.6 ± 0.36	65.7 0.22
2	**12a**	4-$CH_3OC_6H_4$	Me	4-FC_6H_4	10.0 ± 0.98	8.0 ± 0.17	42.8 ± 0.84
3	**13a**	4-$CH_3OC_6H_4$	Me	4-$NO_2C_6H_4$	10.2 ± 1.11	9.8 ± 0.09	>100.0 ± 1.25
4	**14a**	4-$CH_3OC_6H_4$	Me	4-$CF_3C_6H_4$	34.3 ± 1.60	24.1 ± 0.37	72.0 ± 1.16
5	**15a**	4-$CH_3OC_6H_4$	Me	4-$CH_3OC_6H_4$	15.9 ± 0.85	8.7 ± 0.52	65.9 ± 1.14
6	**16a**	4-$CH_3OC_6H_4$	Me	4-BrC_6H_4	8.9 ± 0.74	7.4 ± 0.47	61.3 ± 0.79
7	**17a**	4-$CH_3OC_6H_4$	Me	4-ClC_6H_4	9.8 ± 0.54	7.6 ± 0.09	39.6 ± 0.99
8	**18a**	4-$CH_3OC_6H_4$	Me	4-$Bu^tC_6H_4$	25.9 ± 1.68	28.7 ± 1.03	23.5 ± 0.69
9	**19b**	C_6H_5	H	3, 5-$(CF_3)_2C_6H_3$	16.1 ± 1.50	13.5 ± 0.99	32.8 ± 0.85
10	**20c**	H	H	C_6H_5	>100.0 ± 2.02	>100.0 ± 1.92	>100.0 ± 1.85
11	**21c**	H	H	Allyl	>100.0 ± 0.67	>100.0 ± 1.27	>100.0 ± 1.54
12	**20d**	H	Me	C_6H_5	>100.0 ± 1.18	>100.0 ± 1.25	>100.0 ± 1.49
13	**22**	C_6H_5	Ph-NH-C=S	C_6H_5	>100.0 ± 1.95	>100.0 ± 0.87	>100.0 ± 1.36
14	**28**	4-$CH_3OC_6H_4$	Me	4-$CH_3C_6H_4$	>100.0 ± 1.67	>100.0 ± 0.88	>100.0 ± 1.44
15	**29**	4-$CH_3OC_6H_4$	Me	4-FC_6H_4	13.3 ± 0.45	66.5 ± 1.16	>100.0 ± 1.26
16	**30**	4-$CH_3OC_6H_4$	Me	4-$CH_3OC_6H_4$	>100.0 ± 0.98	>100.0 ± 1.35	>100.0 ± 1.94
17	**31**	4-$CH_3OC_6H_4$	Me	4-BrC_6H_4	17.0 ± 1.54	>100.0 ± 1.22	>100.0 ± 1.46
18	**32**	4-$CH_3OC_6H_4$	Me	4-ClC_6H_4	10.4 ± 0.48	39.3 ± 0.87	>100.0 ± 1.37
19	**33**	4-$CH_3OC_6H_4$	Me	4-$Bu^tC_6H_4$	>100.0 ± 1.67	>100.0 ± 0.96	46.7 ± 1.01
20	**34**	4-$CH_3OC_6H_4$	Me	3-Cl,4-$CH_3C_6H_3$	14.1 ± 1.00	>100.0 ± 1.66	23.0 ± 1.00
21	**35**	4-$CH_3OC_6H_4$	Me	2,6-$(CH_3)_2C_6H_3$	>100.0 ± 1.95	>100.0 ± 1.29	>100.0 ± 0.89
22	**36**	4-$CH_3OC_6H_4$	Me	3,5-$(CF_3)_2C_6H_3$	>100.0 ± 1.34	77.8 ± 1.24	>100.0 ± 0.69
23	**37**	4-$CH_3OC_6H_4$	Me	C_6H_5	>100.0 ± 0.59	>100.0 ± 1.69	>100.0 ± 1.37
24	**38**	4-$CH_3OC_6H_4$	Me	Allyl	79.3 ± 0.32	>100.0 ± 0.86	>100.0 ± 1.27
25	5-Fluorouracil	-	-	-	20.4 ± 0.22	3.2 ± 0.21	-

[a] IC_{50} is the concentration required to produce 50% inhibition of cell growth compared to the control ± SD (standard division).

3. Conclusion

In summary, antiproliferative thiazolidine derivatives have been readily synthesized in good to excellent yields (67–99%) through a one-pot thio-acylation/anti-hydrosulfenylation of propargylamines and isothiocyanates mediated by silica gel. The reaction is tolerant of the amine and the isothiocyanate thus offering a facile method for the construction of diversely substituted examples of this important heterocycle. In addition, the 4-methoxybenzylidene-substituted analogs undergo slow autoxidation at room temperature yielding the corresponding 4-thiazolidinones **28-38**. An X-ray study of two examples, **15a** and **31**, confirmed both the constitution and the *Z, Z*`-configurations for the synthesized compounds.(ref) Some of the synthetic derivatives reveal promising antiproliferative properties through in vitro growth inhibition against HCT-116 (colon) and MCF7 (breast) cancer cell lines exhibiting higher potency higher than 5-fluorouracil (positive control) in an MTT assay but were non-toxic in a normal cell line. The thiazolidines exhibited higher activity than the corresponding thiazolidinone analogues against colon cancer. Statistically significant 2D-QSAR using a two-descriptor model describes the antiproliferative properties against HCT-116. 2D-QSAR results show that the estimated properties are also correlated to the experimental values. We are continuing to explore this framework both in synthetic and medicinal chemistry contexts and will publish these data elsewhere.

4. Experimental

4.1 Thiazolidine Synthesis

All the starting materials were synthesized and characterized according to the reported procedures.[21] Thiazolidines (**19b**, **20c**, **21c**, **20d**, and **22**) and thiazolidinones **35-38** were prepared and characterized previously by our research group.[19]

4.1.1 General procedure (A) for the synthesis of (*Z*)-2-imino-(5*Z*)-ylidene-N-substituted thiazolidines **11a-18a**, **19b**, **20c**, **21c**, **20d**, and **22**.

To vigorously stirred silica gel (1.75g/mmol), a solution of propargyl amine (200 mg, 1.14 mmol) in CH_2Cl_2 (0.2 mL) and isothiocyanate (1.14 mmol) was added dropwise. The resulting slurry was stirred at rt for 2 h. The resulting slurry was placed directly on a column of silica gel and the crude reaction mixture was purified by flash chromatography to afford the thiazolidine.

4.1.2 General procedure (B) for the synthesis of (Z)-2-substituted imino-5-((Z)-ylidene)- thiazolidin-4-ones **28-38**.

The thiazoline (100 mg) was dissolved in $CDCl_3$ (1 mL) and left open to the atmosphere for 1-3 days. The resulting mixture was concentrated and purified by column chromatography to afford a yellow solid. The obtained solid was triturated with a mixture of diethyl ether: hexanes (1:10, 1 mL) and filtered to obtain the oxidized product.

(*Z*)-N-Tolyl-5-((*Z*)-4-methoxybenzylidene)-3-methylthiazolidin-2-imine (11a): Synthesized following general procedure A, (200 mg, 1.14 mmol), purified by column chromatography (ethyl acetate:hexanes = 1:4) to afford compound **11a** (362 mg, 97%) as a light-yellow solid. m.p. 88-92 °C. ^{1}H NMR: δ 7.20 (d, *J* = 8.8 Hz, 2H), 7.11 (d, *J* = 8.2 Hz, 2H), 6.89 (d, *J* = 8.2 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.46 (t, *J* = 1.9 Hz, 1H), 4.43 – 4.34 (d, *J* = 1.9 Hz, 2H), 3.77 (s, 3H), 3.10 (s, 3H), 2.34 (s, 3H). ^{13}C NMR: δ 158.6, 156.4, 149.1, 132.7, 129.7, 129.3, 128.7, 126.6, 122.1, 119.5, 114.1, 59.5, 55.4, 33.1, 21.1. FT-IR (neat, cm^{-1}): 2950, 2920, 2832, 1647, 1602, 1505, 1286, 1246, 1175, 1026, 957, 821. HR-MS (*m/z*): calc for $[M+H]^+$ $C_{19}H_{20}N_2OS$, 325.1369, found: 325.1374.

(*Z*)-N-(4-Fluorophenyl)-5-((*Z*)-4-methoxybenzylidene)-3-methylthiazolidin-2-imine (12a): Synthesized following general procedure A, (200 mg, 1.14 mmol), purified by column chromatography (ethyl acetate:hexanes = 1:4) to afford compound **12a** (375 mg, 99%) as a colorless solid. m.p. 112-116 °C. ^{1}H NMR: δ 7.19 (d, *J* = 8.8 Hz, 2H), 6.98 (t, *J* = 8.9 Hz, 2H), 6.91 (dd, *J* = 8.9, 5.0 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.47 (t, *J* = 2.0 Hz, 1H), 4.41 (d, *J* = 2.0 Hz, 2H), 3.77 (s, 3H), 3.09 (s, 3H). ^{13}C NMR δ 160.4, 158.7, 157.1, 147.8, 129.3, 127.4 (d, *J* = 306 Hz), 123.5 (d, *J* = 7.5 Hz), 119.8, 115.6 (d, *J* = 22.5 Hz), 114.2, 59.5, 55.4, 33.0. FT-IR (neat, cm^{-1}): 3016, 2965, 2930, 2901, 2837, 1643, 1605, 1496, 1249, 1176, 1027, 959, 839. HR-MS (*m/z*): calc for $[M+H]^+$ $C_{18}H_{17}N_2OFS$, 329.1118, found: 329.1122.

(*Z*)-N-(4-Nitrophenyl)-5-((*Z*)-4-methoxybenzylidene)-3-methylthiazolidin-2-imine (13a): Synthesized following general procedure A, (200 mg, 1.14 mmol), purified by column chromatography (ethyl acetate:hexanes = 1:4) to afford compound **13a** (380 mg, 93%) as a yellow solid. m.p. 160-164 °C. ^{1}H NMR: δ 8.16 (d, *J* = 9.0 Hz, 2H), 7.17 (d, *J* = 8.7 Hz, 2H), 7.03 (d, *J* = 9.0 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.53 (t, *J* = 2.0 Hz, 1H), 4.50 (d, *J* = 2.0 Hz, 2H), 3.78 (s, 3H), 3.14 (s, 3H). ^{13}C NMR: δ 158.9, 157.8, 157.1, 129.2 128.2, 125.2, 122.7, 120.6, 114.2, 59.4, 55.4, 33.0. FT-IR (neat, cm^{-1}): 3019, 2921, 2834, 1638, 1567, 1493, 1318, 1248, 1174, 1105, 1030, 843. HR-MS (m/z): calc for $[M+H]^+$ $C_{18}H_{17}N_3O_3S$, 356.1063, found: 356.1062.

(*Z*)-N-(4-Trifluromethylphenyl)-5-((*Z*)-4-methoxybenzyl-idene)-3-methylthiazolidin-2-imine (14a): Synthesized following general procedure A, (200 mg, 1.14 mmol), purified by column chromatography (ethyl acetate:hexanes = 1:4) to afford compound **14a** (406 mg, 94%) as a colorless solid. m.p. 148-151 °C. ^{1}H NMR: δ 7.53 (d, *J* = 8.2 Hz, 2H), 7.19 (d, *J* = 8.7 Hz, 2H), 7.03 (d, *J* = 8.2 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.50 (t, *J* = 2.0 Hz, 1H), 4.46 (d, *J* = 2.0 Hz, 2H), 3.78 (s, 3H), 3.12 (s, 3H). ^{13}C NMR δ 158.8, 156.9, 154.7, 129.3, 128.4, 126.3 (q, *J* = 3.8 Hz), 125.0 (q, *J* = 31.3 Hz), 124.8 (q, *J* = 269 Hz), 122.5, 120.2, 114.2, 59.4, 55.4, 33.0. FT-IR (neat, cm^{-1}): 3130, 2954, 2925, 2834, 1647, 1508, 1421, 1322, 1255, 1099, 848. HR-MS (*m/z*): calc for $[M+H]^+$ $C_{19}H_{17}N_2OF_3S$, 379.1086, found: 379.1092.

(*Z*)-N-(4-Methoxyphenyl)-5-((*Z*)-4-methoxybenzylidene)-3-methylthiazolidin-2-imine (15a): Synthesized following general procedure A, (200 mg, 1.14 mmol), purified by column chromatography (ethyl acetate:hexanes = 1:4) to afford compound **15a** (389 mg, 99%) as a colorless solid. m.p. 132-136 °C. ^{1}H NMR: δ 7.19 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 6.87 – 6.81 (m, 4H), 6.46 (t, *J* = 1.9 Hz, 1H), 4.40 (d, *J* = 1.9 Hz, 2H), 3.80 (s, 3H), 3.78 (s, 3H), 3.10 (s, 3H). ^{13}C NMR: δ 158.6, 156.8, 155.9, 145.1, 129.3, 128.7, 126.6, 123.2, 119.5, 114.3, 114.1, 59.5, 55.5, 55.4, 33.1. FT-IR (neat, cm^{-1}): 3131, 2958, 2929, 2832, 1643, 1497, 1456, 1254, 1183, 1027, 835. HR-MS (*m/z*): calc for $[M+H]^+$ $C_{19}H_{20}N_2O_2S$, 341.1318, found: 341.1320.

(*Z*)-N-(4-Bromophenyl)-5-((*Z*)-4-methoxybenzylidene)-3-methylthiazolidin-2-imine (16a): Synthesized following general procedure A, (200 mg, 1.14 mmol), purified by column chromatography (ethyl acetate:hexanes = 1:4) to afford compound **16a** (442 mg, 99%) as a colorless solid. m.p. 130-134 °C. ^{1}H NMR δ 7.39 (d, *J* = 8.7 Hz, 2H), 7.18 (d, *J* = 8.7 Hz, 2H), 6.85 (dd, *J* = 10.0, 8.8 Hz, 4H), 6.47 (t, *J* = 2.0 Hz, 1H), 4.41 (d, *J* = 2.0 Hz, 2H), 3.78 (s, 3H), 3.09 (s, 3H). ^{13}C NMR: δ 158.8, 156.9, 150.7, 132.0, 129.3, 128.5, 125.9, 124.2, 120.0, 116.2, 114.2, 59.5, 55.4, 33.0. FT-IR (neat, cm^{-1}): 3046, 2919, 2840, 1642, 1575, 1481, 1250, 1178, 953, 840. HR-MS (*m/z*): calc for $[M+H]^+$ $C_{18}H_{17}N_2OSBr$, 389.0318, found: 389.0321.

(*Z*)-N-(4-Chlorophenyl)-5-((*Z*)-4-methoxybenzylidene)-3-methylthiazolidin-2-imine (17a): Synthesized following general procedure A, (200 mg, 1.14 mmol), purified by column chromatography (ethyl acetate:hexanes = 1:4) to afford compound **17a** (390 mg, 99%) as a colorless solid. m.p. 116-118 °C. ^{1}H NMR δ 7.24 (d, *J* = 8.7 Hz, 2H), 7.19 (d, *J* = 8.7 Hz, 2H), 6.88 (dd, *J* = 15.8, 8.7 Hz, 4H), 6.48 (t, *J* = 1.9 Hz, 1H), 4.42 (d, *J* = 2.0 Hz, 2H), 3.78 (s, 3H), 3.09 (s, 3H). ^{13}C NMR: δ 158.8 157.0, 150.3, 129.3, 129.1, 128.5, 128.4, 125.9, 123.7, 120.0, 114.2, 59.5, 55.4, 33.0. FT-IR (neat, cm^{-1}): 3046, 2919, 2841, 1642, 1583, 1484, 1251, 1178, 1082, 841. HR-MS (*m/z*): calc for $[M+H]^+$ $C_{18}H_{17}N_2OSCl$, 345.0823, found: 345.0816.

(*Z*)-N-(4-tert-Butylphenyl)-5-((*Z*)-4-methoxybenzylidene)-3-methylthiazolidin-2-imine (18a): Synthesized following general procedure A, (200 mg, 1.14 mmol), purified by column chromatography (ethyl acetate:hexanes = 1:4) to afford compound **18a** (400 mg, 95%) as a colorless solid. m.p. 146-149 °C. ^{1}H NMR: δ 7.30 (d, *J* = 8.6 Hz, 2H), 7.21 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.50 – 6.45 (t, *J* = 2.0 Hz, 1H), 4.41 (d, *J* = 2.0 Hz, 2H), 3.78 (s, 3H), 3.11 (s, 3H), 1.33 (s, 9H). ^{13}C NMR δ 158.6, 156.0, 148.7, 145.9, 129.7, 128.8, 126.8, 125.9, 121.7, 119.5, 114.1, 59.4, 55.4, 34.4, 33.1, 31.6. FT-IR (neat, cm^{-1}): 3046, 2959, 2841, 1638, 1597, 1507, 1250, 1177, 1035, 857, 816, 530. HR-MS (*m/z*): calc for $[M+H]^+$ $C_{22}H_{26}N_2OS$, 367.1839, found: 367.1831.

(*Z*)-2-((4-Methylphenyl)imino)-5-((*Z*)-4-methoxybenzylidene)-3-methylthiazolidin-4-one (28): Synthesized following general procedure B, (100 mg, 0.31 mmol), purified by column chromatography (ethyl acetate:hexanes = 1:9) to afford compound **28** (24 mg, 23%) as a light yellow solid. m.p. 152-154 °C. ^{1}H NMR: δ 7.70 (s, 1H), 7.40 (d, *J* = 8.7 Hz, 2H), 7.19 (d, *J* = 7.9 Hz, 2H), 6.92 (m, 2H),

6.91 (m, 2H), 3.82 (s, 3H), 3.44 (s, 3H), 2.37 (s, 3H). ^{13}C NMR: δ 167.3, 160.9, 151.1, 145.8, 134.5, 132.0, 130.6, 130.1, 126.6, 121.2, 119.0, 114.6, 55.5, 29.7, 21.1. FT-IR (neat, cm^{-1}): 3097, 3056, 2915, 2836, 1697, 1629, 1591, 1504, 1256, 1181, 1025, 818. HR-MS (*m/z*): calc for $[M+H]^+$ $C_{19}H_{18}N_2O_2S$, 339.1162, found: 339.1162.

(*Z*)-2-((4-Fluorophenyl)imino)-5-((*Z*)-4-methoxybenzylidene)-3-methylthiazolidin-4-one (29): Synthesized following general procedure B, (100 mg, 0.30 mmol), purified by column chromatography (ethyl acetate:hexanes = 1:9) to afford compound **29** (27 mg, 26%) as a light yellow solid. m.p. 160-162 °C. ^{1}H NMR: δ 7.72 (s, 1H), 7.40 (d, *J* = 8.8 Hz, 2H), 7.08 (t, *J* = 8.8 Hz, 2H), 6.98 (dd, *J* = 8.9, 4.9 Hz, 2H), 6.93 (d, *J* = 8.9 Hz, 2H), 3.82 (s, 3H), 3.43 (s, 3H). ^{13}C NMR: δ 167.2, 160.20 (d, *J* = 241 Hz), 160.0, 152.1, 144.5, 132.0, 131.1, 126.4, 122.7 (d, *J* = 7.5 Hz), 118.6, 116.2 (d, *J* = 22.5 Hz), 114.7, 55.5, 29.7. FT-IR (neat, cm^{-1}): 3052, 3035, 2959, 2841, 1705, 1633, 1595, 1506, 1258, 1182, 1026, 821. HR-MS (*m/z*): calc for $[M+H]^+$ $C_{18}H_{15}N_2O_2FS$, 343.0911, found: 343.0914.

(*Z*)-2-((4-Methoxyphenyl)imino)-5-((*Z*)-4-methoxybenzyl-idene)-3-methylthiazolidin-4-one (30): Synthesized following general procedure B, (100 mg, 0.29 mmol), purified by column chromatography (ethyl acetate:hexanes = 1:9) to afford compound **30** (23 mg, 22%) as a light yellow solid. m.p. 157-160 °C. ^{1}H NMR: δ 7.70 (s, 1H), 7.41 (d, *J* = 8.8 Hz, 2H), 6.97 (d, *J* = 9.0 Hz, 2H), 6.92 (dd, *J* = 9.0, 2.6 Hz, 4H), 3.83 (s, 3H), 3.82 (s, 3H), 3.44 (s, 3H). ^{13}C NMR: δ 167.3, 160.9, 157.0, 151.2, 141.6, 131.9, 130.6, 126.6, 122.4, 119.0, 114.7, 55.6, 29.7. FT-IR (neat, cm^{-1}): 3100, 3073, 3033, 2929, 2836, 1701, 1627, 1596, 1502, 1237, 1173, 1021, 824. HR-MS (*m/z*): calc for $[M+H]^+$ $C_{19}H_{18}N_2O_3S$, 355.1111, found: 355.1108.

(*Z*)-2-((4-Bromophenyl)imino)-5-((*Z*)-4-methoxybenzylidene)-3-methylthiazolidin-4-one (31): Synthesized following general procedure B, (100 mg, 0.25 mmol), purified by column chromatography (ethyl acetate:hexanes = 1:9) to afford compound **31** (18 mg, 17%) as a light yellow solid. m.p. 174-176 °C. ^{1}H NMR: δ 7.72 (s, 1H), 7.49 (d, *J* = 8.7 Hz, 2H), 7.40 (d, *J* = 8.7 Hz, 2H), 6.93 (d, *J* = 8.9 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 3.83 (s, 3H), 3.43 (s, 3H). ^{13}C NMR: δ 167.1, 161.1, 152.1, 147.5, 132.5, 132.0, 131.3, 126.4, 123.2, 118.4, 118.0, 114.7, 55.5, 29.7. FT-IR (neat, cm^{-1}): 3050, 3015, 2922, 2839, 1703, 1596, 1510, 1258, 1180, 1099, 819. HR-MS (*m/z*): calc for $[M+H]^+$ $C_{18}H_{15}N_2O_2SBr$, 403.0110, found: 403.0103.

(*Z*)-2-((4-Chlorophenyl)imino)-5-((*Z*)-4-methoxybenzylidene)-3-methylthiazolidin-4-one (32): Synthesized following general procedure B, (100 mg, 0.29 mmol), purified by column chromatography (ethyl acetate:hexanes = 1:9) to afford compound **32** (17 mg, 16%) as a light yellow solid. m.p. 160-162 °C. ^{1}H NMR: δ 7.72 (s, 1H), 7.40 (d, *J* = 8.7 Hz, 2H), 7.35 (d, *J* = 8.7 Hz, 2H), 6.94 (dd, *J* = 11.2, 8.7 Hz, 4H), 3.83 (s, 3H), 3.43 (s, 3H). ^{13}C NMR: δ 167.1, 161.1, 152.2, 147.0, 132.0, 131.2, 130.3, 129.6, 126.4, 122.8, 118.5, 114.7, 55.5, 29.7. FT-IR (neat, cm^{-1}): 3049, 3015, 2922, 2839, 1703, 1596, 1510, 1258, 1180, 1099, 819. HR-MS (*m/z*): calc for $[M+H]^+$ $C_{18}H_{15}N_2O_2SCl$, 359.0616, found: 359.0632.

(*Z*)-2-((4-tert-Butyl)phenyl)imino)-5-((*Z*)-4-methoxybenzyl-idene)-3-methylthiazolidin-4-one (33): Synthesized following general procedure B, (100 mg, 0.27 mmol), purified by column chromatography (ethyl acetate:hexanes = 1:9) to afford compound **33** (19 mg, 18%) as a light yellow solid. m.p. 206-208 °C. ^{1}H NMR δ 7.71 (s, 1H), 7.42 (d, *J* = 8.7 Hz, 2H), 7.39 (d, *J* = 8.6 Hz, 2H), 6.96 (d, *J* = 8.6 Hz, 2H), 6.93 (d, *J* = 8.7 Hz, 2H), 3.82 (s, 3H), 3.44 (s, 3H), 1.35 (s, 9H). ^{13}C NMR: δ 167.3, 160.9, 150.6, 147.8, 145.5, 131.9, 130.6, 126.6, 120.8, 119.1, 114.6, 55.5, 34.6, 31.6, 29.7. FT-IR (neat, cm^{-1}): 3075, 3050, 2968, 2837, 1697, 1638, 1597, 1508, 1257, 1177, 1034, 822. HR-MS (*m/z*): calc for $[M+H]^+$ $C_{22}H_{24}N_2O_2S$, 381.1631, found: 381.1633.

(*Z*)-2-((3-Chloro-4-methylphenyl)imino)-5-((*Z*)-4-methoxy-benzylidene)-3-methylthiazolidin-4-one (34): Synthesized following general procedure B, (100 mg, 0.28 mmol), purified by column chromatography (ethyl acetate:hexanes = 1:9) to afford compound **34** (23 mg, 22%) as a light yellow solid. m.p. 178-181 °C. ^{1}H NMR: δ 7.72 (s, 1H), 7.41 (d, *J* = 8.8 Hz, 2H), 7.23 (d, *J* = 8.1 Hz, 1H), 7.03 (d, *J* = 2.2 Hz, 1H), 6.93 (d, *J* = 8.8 Hz, 2H), 6.82 (dd, *J* = 8.1, 2.2 Hz, 1H), 3.83 (s, 3H), 3.42 (s, 3H), 2.38 (s, 3H). ^{13}C NMR: δ 167.2, 161.0, 152.1, 147.2, 134.9, 132.4, 132.0, 131.6, 131.2, 126.4, 122.0, 119.7, 118.6, 114.7, 55.5, 29.7, 19.7. FT-IR (neat, cm^{-1}): 3052, 3007, 2947, 2922, 2843, 1703, 1631, 1595, 1510, 1413, 1367, 1246, 1104, 1024, 821. HR-MS (*m/z*): calc for $[M+H]^+$ $C_{19}H_{17}N_2O_2SCl$, 373.0772, found: 373.0776.

4.2. *Single Crystal X-ray Diffraction Studies*

Single-Crystal X-Ray diffraction data were collected on a Bruker Apex diffractometer at 295(2) K using monochromated Mo-K radiation (λ=0.71073 Å) and a detector-to-crystal distance of 5.990 cm. Data were collected in a hemisphere or full sphere of reciprocal space with 0.3° scans in ω for an exposure time of 60 s per frame up to a maximum 2θ value of 56.55°. The measured intensities were corrected for Lorenz and polarization effects and were further corrected for absorption using the multi-scan method SADABS.[28] Based on the data, structural model was obtained by direct method using the SHELXTL-PLUS program.[29] The refinement was performed via full-matrix least-squares on F2 by using the JANA2006 software package.[30] Final atomic structures and data associated with the refinements were deposited with the Cambridge Crystallographic Data Centre under deposition numbers CCDC-1873910 (compound **15a**) and CCDC-1873911 (compound **31**).

4.3. *Antiproliferative properties*

Method(s) used for antiproliferative properties determination are described in the supplementary information.

4.4.*2D-QSAR study*

Experimental details for the 2D-QSAR study are described in the supplementary information.

Conflict of interest

The authors declare no competing financial interest

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