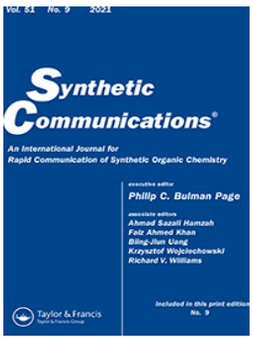

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Synthesis of thiazole linked chalcones and their pyrimidine analogues as anticancer agents

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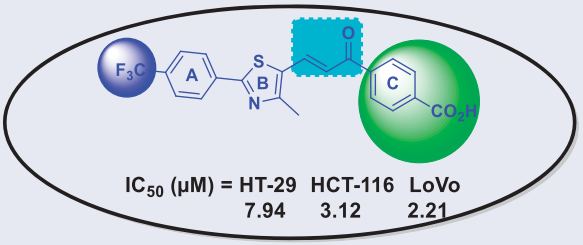
ABSTRACT

A series of nine novel thiazole linked chalcones, (E)-3-(4-methyl-2-(4(trifluoromethyl)phenyl)thiazol-5-yl)-1-phenylprop-2-en-1-one derivatives **7–15** were synthesized. To establish the structure–activity relationship (SAR), furthermore, the corresponding, ring-closed pyrimidine analogs **17–23** were synthesized. The derivatives thus obtained were evaluated for their anti-cancer activity against three genetically different colorectal cancer (CRC) cell lines. Thiazole derivatives **7, 9,** and**10** showed anti-cancer activity with GI50 values ranging from 0.19 to 100 μM. Importantly, compounds **7** and **10** outperformed the standard drug cisplatin in the tested cell lines and thus show promise for further optimization. Some of pyrimidine derivatives retain activity comparable to cisplatin in the HT-29 cell line, e.g. compounds **17** and **18** with IC50 of 25 μM, however, none of these compounds demonstrated improved antiproliferative activity as compared with the starting thiazole, thus the enone linker was critical for obtaining more active compounds in this series.

GRAPHICAL ABSTRACT



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Introduction

Globally, colorectal cancer (CRC) ranks third in terms of incidence but second in terms of mortality. Over 1.8 million new CRC cases and 881,000 deaths are estimated to occur in 2018, accounting for about 10% of all cancer incidents and deaths.[1] Generally, most

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Supplemental data for this article can be accessed on the publisher's website.

Table 1.

Cell line	MSI status	KRAS	TP53	CIMP	CIN	Localization	Primary tumor/metastasis	Patient stage
HT29	MSI	**Wt**	R273H	+	+	Colon	Primary tumor	Dukes' C
HCT-116	MSI	G13D	Wt	+	−	Colon ascendens	Primary tumor	Dukes' C
LoVo	MSI	G13D A14V	Wt	−	−	Colon	Primary tumor	Dukes' C

MSI: microsatellite instability; CIMP: CpG island methylator phenotype; CIN: chromosomal instability

cytotoxic treatments of cancer are not efficient.[2] Presently, metastatic CRC (mCRC) patients are treated with combinations of only three cytotoxic drugs (5-Fluorouracil (5-FU), oxaliplatin, and irinotecan) and commonly co-administration of leucovorin (folinic acid) potentiating the effect of 5-fluorouracil. The combinations mostly applied are the FOLFOX regimen (leucovorin, 5-FU, and oxaliplatin) or the FOLFIRI regimen (leucovorin, 5-FU, and irinotecan). These regimens have significantly increased the response rates and survival of mCRC patients.[3] However, the major problem is that only 30–50% of the patients show an objective, response to either FOLFOX or FOLFIRI regimens, and progression of the cancer is a common outcome.[4] These low response rates clearly reveals the serious problem of insufficient efficiency of drugs and this emphasizes the need for investigations in novel anti-cancer drugs in CRC.

CRC is a genetically heterogeneous disease, which may contribute to differences in response to drug treatment. CRC cells display genetic instability caused by chromosomal instability (CIN), microsatellite instability (MSI), and the CpG island methylator phenotype (CIMP), which result in activation of proto-oncogenes such as KRAS and inactivation of tumor suppressor genes such as TP53 (p53).[5] Furthermore, mutations in KRAS and TP53 are often observed. The presence or absence of certain genetic alterations may determine the response to treatment and therefore it is important to study CRC cell lines that harbor different combinations of the genetic alterations described above. Importantly, CRC cell lines have been found to represent the main molecular subtypes of primary cancers.[6] Therefore, we chose three genetically different CRC cell lines in this study (HT29, HCT116, and LoVo) (Table 1).

Chalcone derivatives (1,3-diphenyl-2-propen-1-ones) are open-chain flavonoids found in nature as secondary plant metabolites. These compounds show a broad spectrum of biological activities including anticancer,[7] antibacterial,[8] antifungal,[9] anti-diabetic,[10] anti-infective, and anti-inflammatory activities,[11] acting through multiple mechanisms. Chalcone derivatives are reported to exhibit anticancer activity in several types of cancer cells with different origin, such as breast, lung, prostate, ovarian and colon cancer cells.[12–14] Structural modifications of both aryl rings in chalcone, such as replacement of aryl rings with heteroaryl moieties, have provided enhancement of the anticancer activity.[15–18] Accordingly, the preparation of novel heterocycle-based chalcones is a promising path for improved compounds. A 1,3-thiazole ring has been used extensively as a scaffold in the identification of new lead compounds in drug discoverywithin an extremely broad set of diseases includinginfection,[19] inflammation,[20] and cancer.[21] In relation to the present investigation, this heterocycle has been used as a bioisostere replacing one of the aromatic rings in chalcone (Fig. 1).[22–24]

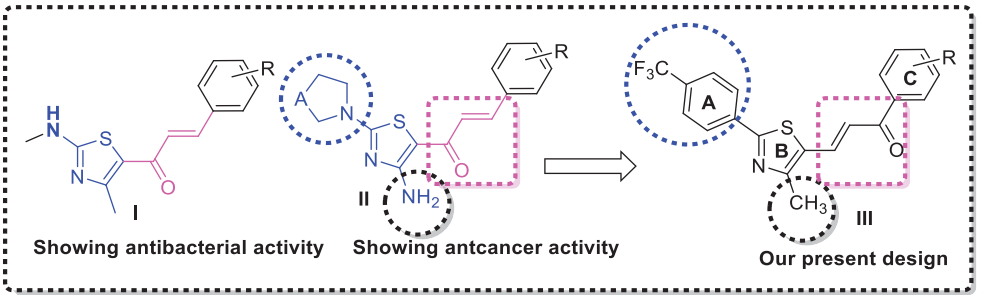


Figure 1. Design of thiazole-based chalcones by hybridization of reported anticancer agent compound II.

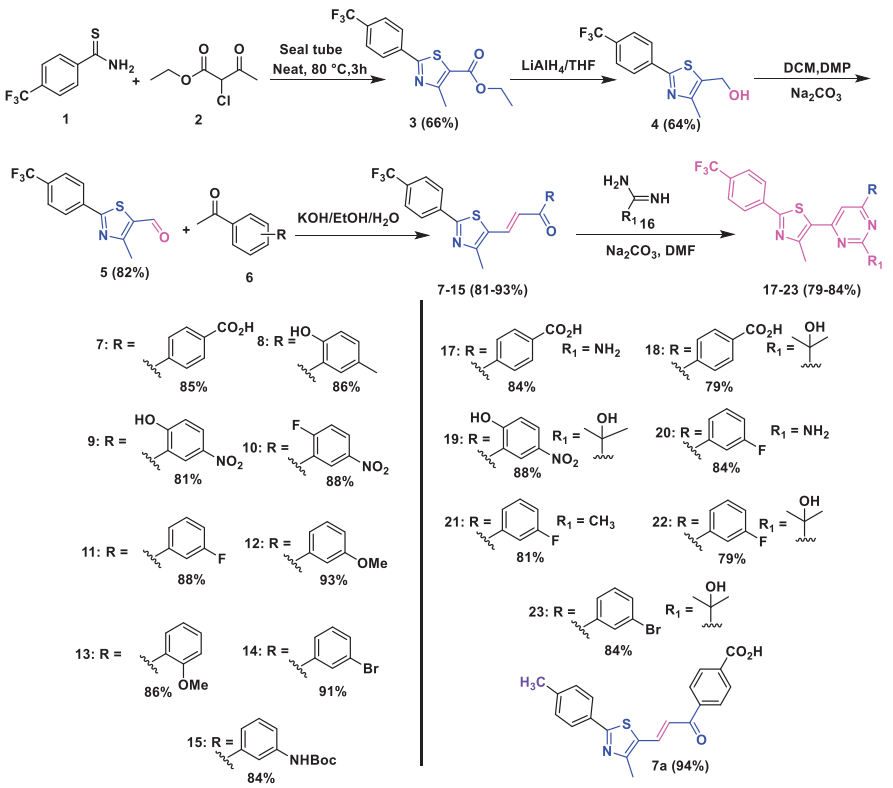
Results and discussion

Thus, a series of 4-amino-5-cinnamoylthiazoles have recently been prepared and evaluated for anticancer activity (Fig. 1, comp. **II**).[25] The cytotoxicity was determined in three different cancer cell lines (breast carcinoma MCF-7, human liver cancer HepG2, and human colon adenocarcinoma SW480). (*E*)-1-(4-Amino-2-(pyrrolidin-1-yl)thiazol-5-yl)-3-(2,4-dichlorophenyl)prop-2-en-1-one was the most potent compound found during the *in vitro* structure–activity relationship (SAR) study.[25] Inspired by this, we describe herein the synthesis and anticancer activity of a novel series of structurally analogs (*E*)-3-(4-methyl-2-(4-(trifluoromethyl)phenyl)thiazol-5-yl)-1-phenyl prop-2-en-1-one derivatives (Fig. 1, comp. **III**), as a continuation of our ongoing effort on the synthesis of anticancer agents.[25–30]

4-Methyl-2-(4-(trifluoromethyl)phenyl)thiazole-5-carbaldehyde (**5**) was a key intermediate for the preparation of the new thiazole derivatives. The thiazole building block **5** was synthesized in 3 steps (Scheme 1). First, the thiazole ring was formed reacting 4-(trifluoro)thiobenzamide (**1**) with ethyl 2-chloroacetate (**2**) to get ethyl 4-methyl-2-(4-(trifluoromethyl)phenyl)thiazole-5-carboxylate (**3**). Ester **3** was reduced by $LiAlH_4$ to obtain the corresponding alcohol **4**, followed by Dess–Martin oxidation to furnish target aldehyde intermediate **5** (Scheme 1). With the building block **5** in hand, the thiazole derivatives **7–15** were prepared in high yield by Claisen–Schmidt condensation using a diverse set of substituted acetophenones (Scheme 1). The SARs were further explored by masking the enone system as pyrimidine derivatives (**17–23).** Four of the active compounds **7**, **10**, **11**, **14** were conveniently transformed into pyrimidines using selected guanidines (**16**, Scheme 1). In our new series, the A ring is substituted by a CF_3 group in the para-position (Fig. 1). To assess the influence of this electron-withdrawing substitution the corresponding methyl derivative was prepared (**7a**) using the same synthetic method. All the new synthesized compounds were characterized using NMR, and mass spectrometry (Supporting Information).

Biological studies: anticancer activity

The antiproliferative activity of the **17** novel thiazole derivatives (**7–15** and **17–23**) was assessed in three genetically different CRC cell lines as described above, HT29, HCT116,



Scheme 1. Synthesis thiazole linked chalcone derivatives 7–15 and their pyrimidines derivatives 17–23.

and LoVo using a standard MTT assay. Initially, a broad concentration ranges from 12.5 to 50 μM was chosen to identify active thiazole derivatives.

Compounds **7, 9,** and **10** showed dose-dependent activity in all three cancer cell lines (Fig. 2A–C). Furthermore, **14** and **7a** showed antiproliferative activity at the highest concentration (50 μM). Cisplatin was active in all three cancer cell lines and thus used as a positive antiproliferative control. Based on these results, IC_{50} values for inhibition was determined for the active compounds **7, 9, 10, 14, 7a,** and cisplatin (Fig. 3A–C). The same activity was presented as best fit sigmoidal curves for all the active compounds (see the Supporting Information Figs. S1–S3).

As observed from the IC_{50} values, the antiproliferative activity of the individual compounds varied among the cancer cell lines, as was also the case for cisplatin. Two compounds **7** and **10** were found more potent than reference compound cisplatin in all three cell lines, thus, showed a good activity in cell lines of different genetic background (Table 2).

Structure–activity relationship (SAR) studies

The presence of an electron-withdrawing group in C ring of the thiazole (Fig. 1) such as COOH (**7**), NO_2 (**9, 10**) provided active compounds whereas introduction of the electron-donating groups in the C ring such as CH_3 (**8**), F (**11**) OMe (**12**, **13**) Br (**14**),

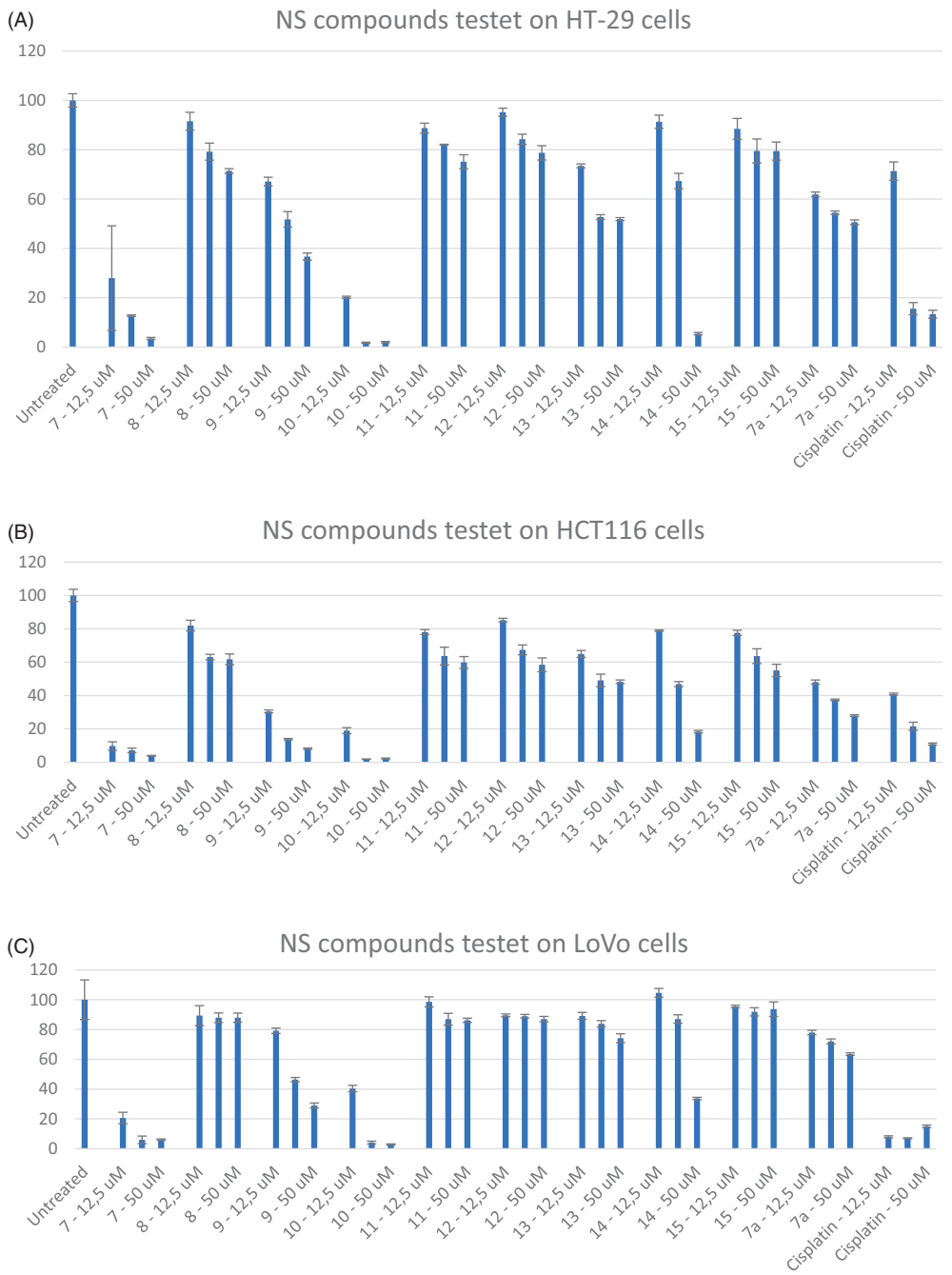


Figure 2. (A–C) Dose dependent antiproliferative activity of all the synthesized chalcones. The three columns for each compound represent concentrations of 12.5, 25, and 50 μM, respectively.

and NHBoc (**15**) gave compounds with less or no activity (Table 2). In addition, when we replace the CF_3 substituent in A ring with CH_3 in our most active compounds **7** we observed reduced activity **7a**, thus, an electron-withdrawing group in A ring seems to promote activity. In comparison with chalcone and previously published anticancer

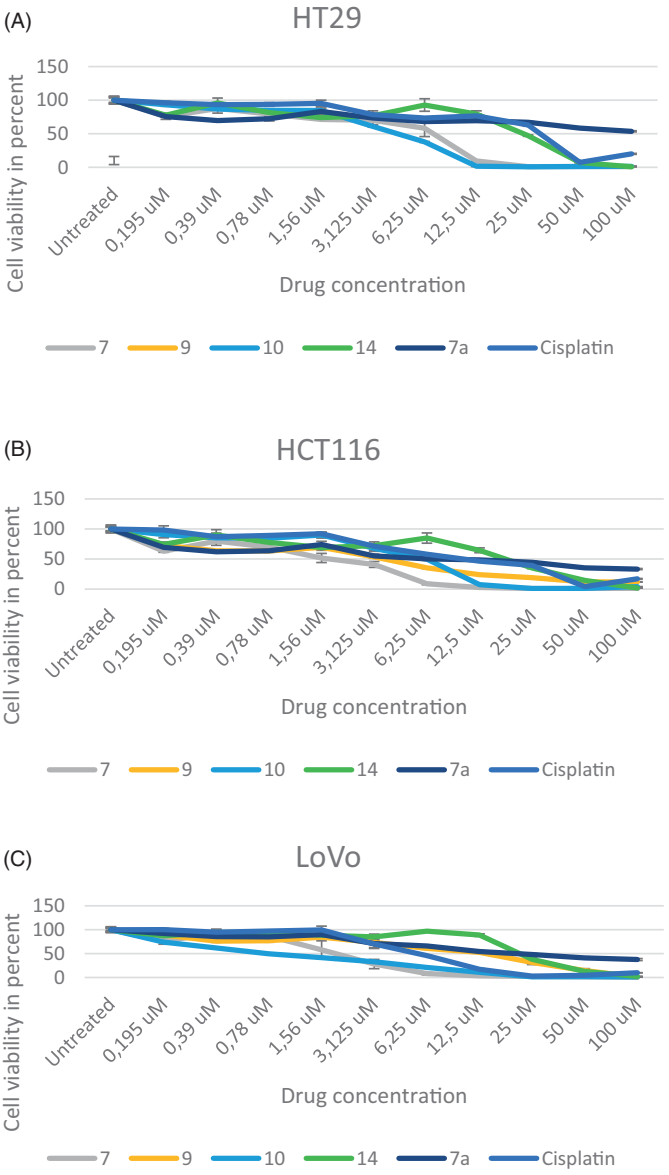


Figure 3. Dose dependent antiproliferative activity of most potent compounds 7, 9, 10, 14, 7a, and cisplatin with increased concentration range (from 0.195 to 100 μM).

thiazoles based on this scaffold, the reversal of the direction of the enone linker did not affect the activity negatively. As an alternative method to explore the importance of the enone structural fragment, we converted some of the active thiazole derivatives to the corresponding pyrimidine analogs (**17–23**). Even though some of these derivatives retain activity comparable to cisplatin in the HT-29 cell line, e.g. compounds **17** and **18** which are derivatives of compound **7** (Table 2), none of these compounds demonstrated improved antiproliferative activity, as compared with the starting thiazole, in any of the cancer cell lines used (Table 2). Thus, we concluded that the structural change imposed

Table 2. IC_{50} values of most activity compounds and comparisons with Cisplatin.

		IC50 value (μM)		
S.No	Compound	HT-29	HCT-116	LoVo
1	7	7.94	3.12	2.21
2	9	36.82	5.49	23.96
3	10	4.89	6.28	1.17
4	14	26.62	23.25	22.72
5	7a	51.78	10.54	7.12
6	17	24.91	23.86	23.71
7	18	25.33	23.34	23.10
8	19	44.06	30.22	29.93
9	20	46.58	31.37	28.43
10	21	31.44	37.57	65.86
11	22	N.A.	28.16	44.48
12	23	41.64	53.93	38.92
13	Cisplatin	25.76	10.55	5.19

N.A.: not analyzed

by the ring-formation provides a sterically more demanding structure, which is not favorable, and the somewhat more flexible enone linker was critical for obtaining more active compounds in this series.

Materials and methods

Cell lines

The cell lines HCT116 and HT29 were obtained from the NCI/Development Therapeutics Program, while LoVo was obtained from the American Tissue Culture Collection. Cells were maintained at 37 C, 5% CO_2 in RPMI 1640 + Glutamax growth medium (Invitrogen, Naerum, Denmark) supplemented with 10% fetal calf serum (Invitrogen).

The cell line identities of the cell lines were confirmed using short tandem repeat DNA analysis (IdentiCell-Cell Line Authentication Service, Aarhus University Hospital, Aarhus, Denmark) (Jensen et al. PMID: 25759163). In addition, all cell lines were recurrently tested, and determined to be mycoplasma-free (Mycoplasma PCR Detection Kit, Minerva Biolabs, Berlin, Germany).

Compound sensitivity analysis and MTT assay

Compounds were diluted in growth medium at appropriate concentrations immediately prior to use. *In vitro* compound sensitivity was determined using the methylthiazolyldiphenyl-tetrazolium bromide (MTT) (Sigma-Aldrich, St. Louis, MO, USA) assay. Cells were seeded in 96-well plates, and a range of compound concentrations was added the following day. Following 48 h of compound exposure, the medium was discarded, and the plates were incubated with medium containing MTT (0.5 mg/ml) for 3 h. Acidified (0.02 M HCl) sodium dodecyl sulfate (20%, Sigma-Aldrich) was added to dissolve the formed formazan. Optical density at 570 and 670 nm for background was measured, and the cell viability was calculated in percent compared to untreated cells. Experiments were repeated at least three times and the mean IC50-value ± standard deviation was determined.

Experimental

General

All commercially available starting materials and reagents were used without further purification. The solvents were dried and deoxygenated by refluxing and storing them over sodium. Chemical reactions were monitored with thin-layer chromatography using pre-coated silica gel 60 (0.25 mm thickness) plates. Flash column chromatography was performed on silica gel 60 (0.040–0.063 mm). ^{1}H and ^{13}C spectra were recorded with a 400 MHz instrument at 298 K in DMSO and $CDCl_3$, using the residual signals from DMSO (^{1}H: $\delta = 2.50$ ppm; ^{13}C: $\delta = 39.52$ ppm) $CHCl_3$ (^{1}H: $\delta = 7.26$ ppm; ^{13}C: $\delta = 77.2$ ppm) as internal standard.

General procedures for the synthesis of chalcones derivatives (7–15)

To the stirred solution of aryl methyl ketone (1.0 eq.) and aldehyde (1.0 eq.) in ethanol, was added KOH (1.0 eq.) solution drop wise at 0 °C and the reaction mixture was stirred for 1 h at same temperature, the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was filtered and washed with water 2–3 times, collect the solid, and dried under vacuum to get yellow solid compounds. The above solid was recrystallized with ethanol to get pure yellow solid compounds with good purity.

Spectral data of the compounds 7 and 8

(E)-4-(3-(4-methyl-2-(4-(trifluoromethyl)phenyl)thiazol-5-yl)acryloyl)benzoic acid (7)

Yellow solid: Yield = 85%: ^{1}H NMR (400 MHz, DMSO): δ 8.19 − 8.05 (m, 6H), 7.96 − 7.86 (m, 3H), 7.55 (d, $J = 15.1$ Hz, 1H), 2.61 (s, 3H): ^{13}C NMR (101 MHz, DMSO) δ 187.95, 164.87, 158.28, 139.36, 135.85, 133.08, 130.47, 129.52, 128.28, 127.06, 126.38, 126.35, 125.24, 123.57, 15.66. LC-HRMS: *m/z* calcd for $[C_{21}H_{14}F_3NO_3S + H]^+$ 418.0644, Found: 418.0639.

(E)-1-(2-hydroxy-5-methylphenyl)-3-(4-methyl-2-(4-(trifluoromethyl)phenyl)thiazol-5-yl)prop-2-en-1-one (8)

Pale-yellow solid: Yield = 86%; ^{1}H NMR (400 MHz, DMSO) δ 12.07 (s, 1H), 8.18 (d, $J = 8.1$ Hz, 2H), 8.02 − 7.88 (m, 4H), 7.67 (d, $J = 15.0$ Hz, 1H), 7.38 (dd, $J = 8.3$, 2.1 Hz, 1H), 6.91 (d, $J = 8.4$ Hz, 1H), 2.63 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 191.28, 158.81, 157.79, 136.51, 135.22, 132.29, 129.85, 129.59, 127.43, 126.44, 126.04, 125.75, 123.16, 119.91, 117.16, 116.90, 19.26, 15.03. LC-HRMS: *m/z* calcd for $[C_{21}H_{16}F_3NO_2S + H]^+$ 404.0921, Found: 404.0916.

Conclusions

In summary, we synthesized and evaluated a novel series of thiazole linked chalcone analogs as anticancer agents. Many of these thiazole analogs showed significant antiproliferative activity in CRC cell lines HT29, HCT-116, and Lovo. Out of all the thiazole

analogs three compounds **7, 9,** and **10** were active in all three cancer cell lines and showed increased potency as compared with the control drug cisplatin. To further modify the structure of the new thiazole analogs, we prepared the corresponding cyclic pyrimidine derivatives shielding the enone fragment in the structure, however, none of these derivatives showed improved activity. Collectively, the SAR investigation performed provides guidance for further improvement of this compound class.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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