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Short communication

Cytotoxic activity of 3-(5-phenyl-3*H*-[1,2,4]dithiazol-3-yl)chromen-4-ones and 4-oxo-4*H*-chromene-3-carbothioic acid *N*-phenylamides

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ABSTRACT

6/6,7-Substituted-3-formylchromones (**8a**–**g**) were reacted with 2 equivalents thiobenzamide (**9**) in refluxing toluene to furnish substituted-3-(5-phenyl-3*H*-[1,2,4]dithiazol-3-yl)chromen-4-ones (**10a**–**g**) in high yields. Similarly, when substituted-2-anilino-3-formylchromones (**8a**–**d**) were reacted with thiobenzamide (**9**, 2 equivalents) in refluxing xylene, 4-oxo-4H-chromene-3-carbothioic acid *N*-phenylamides (**11a**–**d**) were obtained in high yields. All the compounds (**10a**–**g**) and (**11a**–**d**) display significant cytotoxic activity against a number of human cancer cell lines. Among these compounds **10e** (IC_{50} = 10 μM), **10b** (IC_{50} = 14.6 μM) and **10a** (IC_{50} = 10.5 μM) showed maximum cytotoxic activity on neuroblastoma. Also, the compound **10c** (IC_{50} = 10.5 μM) showed maximum cytotoxic activity on ovarian cancer cell line.

1. Introduction

Design, synthesis and evaluation of anticancer agents continues to be a major area of activity, because, despite the progress made in chemotherapy of cancer, complete control of malignancies is still a distinct dream [1–5]. Major efforts are directed towards evaluation of small molecules with minimal toxicity to normal cells [6–9] and heterocyclic compounds have emerged as important candidates in the treatment of cancers [10–13]. The known anticancer five membered heterocycles (Fig. 1) include triazole derivative, 3-arylamine-5-(hetro)aryl-1,2,4-triazole (**1**), which acts as tubulin polymerization inhibitor by binding to the colchicines binding site on tubulin [14], 3-*S*-alkylated-5-(hetero)aryl-1,2,4-triazole (**2**), a somatostatin, sst2/sst5 binding agonist [15,16], 2-amino-1,3,4-thiadiazole derivative, 2-(4-flurophenylamino)-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazole (**3**), involved with apoptotic mechanisms and angiogenesis [17–24], and dithiazole derivatives, 4-chloro-5-heteroimmino-1,2,3-dithiazoles (**4a**–**e**) [25].

On the other hand, chromone and xanthone derivatives (Fig. 2) also display high anticancer activity [26] with novel mechanisms, such as carcinogens inactivation, antiproliferation, cell cycle arrest, induction of apoptosis and differentiation, inhibition of angiogenesis, antioxidation and reversal of multidrug resistance [27]. For example, psorospermin (**5**) a natural antitumor antibiotic [28], which is apparently an alkylating agent resembling pluramycin A (**6**), has been shown to intercalate with DNA and its alkylating potential is significantly increased in the presence of topoisomerase-II [29,30] and recently, chloro/flurochromones (**7**) have been designed as potential topoisomerase inhibitors, which exhibit high anticancer activity against Ehrlich ascites cancer cells, *in vitro*, as well as EAC implanted mice [31].

Taking cognizance of high anticancer activity of both five membered heterocycles, in particular, dithiazoles, and chromones derivatives, it was decided to synthesize substituted-3-(5-phenyl-3*H*-[1,2,4]dithiazol-3-yl)chromen-4-ones (**10a**–**g**), possessing both dithiazole and chromone moieties, and substituted-4-oxo-4H-chromene-3-carbothioic acid *N*-phenylthioamide (**11a**–**d**) according to the earlier reported procedure [32,33] and evaluate their cytotoxic activity against number of human cancer cell line.

2. Results and Discussion

2.1. Chemistry

2.1.1. Synthesis of chromanyl-1,2,4-dithiazoles and N-phenylthioamides

The substituted-3-(5-phenyl-3*H*-[1,2,4]dithiazol-3-yl)chromen-4-ones (**10a**–**g**) were obtained in high yield when substituted-3-

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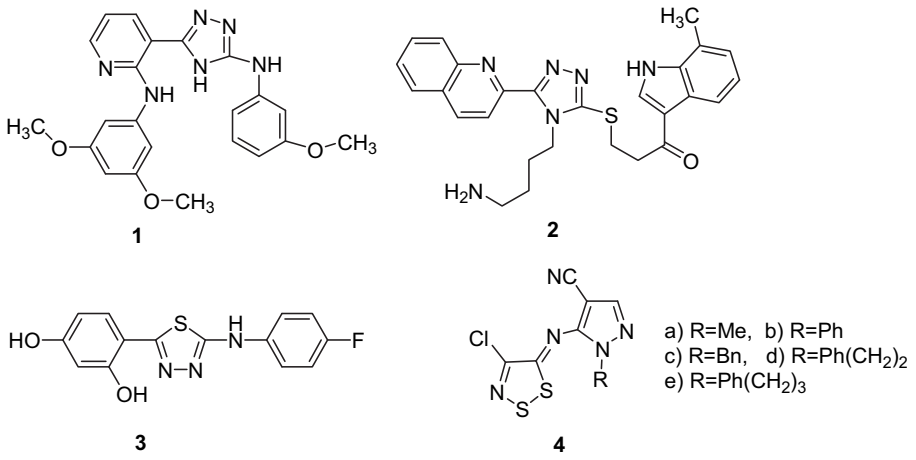


Fig. 1. Some five membered heterocycles as anticancer agents.

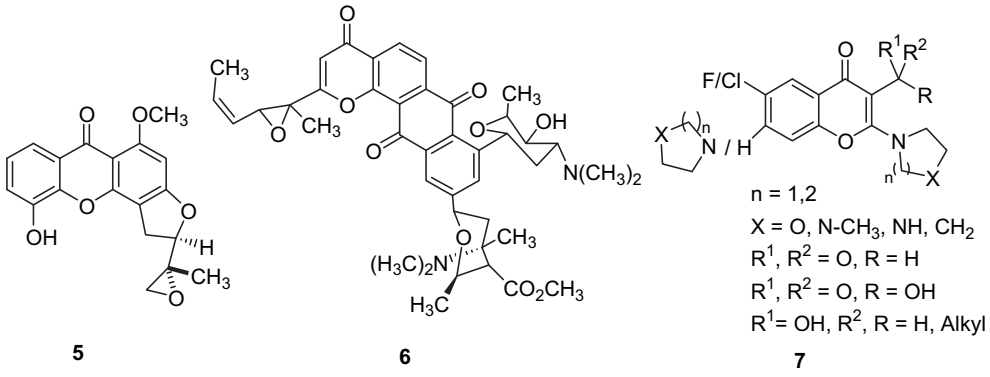
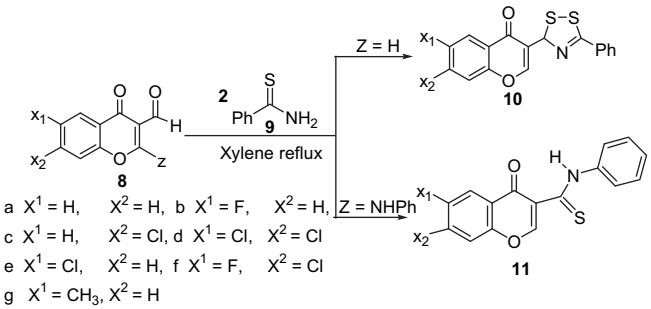


Fig. 2. Some chromone based anticancer agents.

formylchromones (**8a–g**, $Z = H$) were reacted with two equivalents of thiobenzamide (**9**) in refluxing toluene. The-oxo-4*H*-chromene-3-carbothioic acid *N*-phenylamides (**11a–d**) were synthesized by the reaction of substituted-2-anilino-3-formylchromones (**8a–d**, Z = NHPh) with 2 equivalents of thiobenzamide (**9**) in refluxing xylene. All the compounds were purified by column chromatography (Scheme 1, Table 1) using neutral (pH ~ 7) silica 60–120 mesh (Loba Cheme, 30 g, packed in hexane) and eluted with 1–5% ethylacetate in hexane. All the compounds have been characterized by detailed spectroscopic (IR, ^{1}H and ^{13}C NMR, mass) and elemental analysis. Structures of compounds **10a** and **11c** were further confirmed by X-ray crystallography (CCDC-286229 for **10a** and 702090 for **11c**) [32,33].



Scheme 1. Synthesis of chromanyl-1,2,4-dithiazoles and N-phenylthioamides..

2.2. Pharmacology

In vitro cytotoxic studies of dithiazoles (**10a–g**) and (**11a–d**) were carried out on different cancer cell lines according to the protocol of Skehan et al. [34–36]. The cytotoxic effects of chromanyldithiazoles and *N*-phenylthioamides were observed on colon (COLO-205), prostrate (PC-3), ovary (OVCAR-5), lungs (A-549), liver (HEP-2) and neuroblastoma (IMR-32) cancer cell lines. The cytotoxic effects are reported in terms of % age inhibitory concentration (Table 2) and IC_{50} Values (μM), which is the concentration required to inhibit cancer cell proliferation by 50% after exposure of cells to test compounds, have also been determined (Table 3).

In the case of colon cell line (COLO-205) the maximum inhibition 71% (100 μM) was observed for **11a** with $IC_{50} = 72.6$ followed by 57% ($IC_{50} = 76.7$) for **10c** at same concentration. In the case of

Table 1
Reaction yield (%) of the products **10** and **11**.

Entry	Chromones	Reaction time (h)	Yield of **10** (%) Z = H	Yield of **11** (%) Z = NHPh
1	**8a**	**5**	70	70
2	**8b**	**6**	70	75
3	**8c**	**6**	73	60
4	**8d**	**6**	70	78
5	**8e**	**7**	74	–
6	**8f**	**7**	72	–
7	**8g**	**7**	73	–

Table 2
In vitro cytotoxicity of compounds (**10a–g**) and (**11a–d**) against different human cancer cell lines.

Compounds/ standard drugs	Conc. (μM)	% Growth inhibition against human cancer cell lines[a]					
		COLO-205 Colon	PC-3 Prostate	OVCAR-5 Ovary	A-549 Lung	HEP-2 Liver	IMR-32 Neuroblastoma
10a	100	18	23	11	42	48	82
10b	100	37	32	27	55	51	75
10c	100	57	81	91	76	31	53
10d	100	50	70	68	52	51	77
10e	100	12	62	71	73	69	92
10f	100	45	76	75	57	52	80
10g	100	32	40	54	67	43	53
11a	100	71	63	58	79	32	53
11b	100	26	45	49	70	32	59
11c	100	38	55	47	66	41	56
11d	100	16	16	2	3	4	18
5-Fu	20	12	20	26	–	–	–
Mito-C	10	44	41	65	–	–	–
Paclitaxel	10	–	–	–	67	55	45
Adriamycin	01	–	–	–	93	57	55

[a] %age growth inhibition, %age inhibition caused by the compounds and standard drugs at various concentrations.

prostrate cancer cell line (PC-3) the maximum inhibition 81% at 100 μM was shown by **10c** with IC_{50} = 38.4, followed by 76% (IC_{50} = 56.9) for **10f**. For ovarian cancer cell line (OVCAR-5) the maximum inhibition 91% (100 μM) was observed for **10c** (IC_{50} = 10.5), followed by 75% at the same concentration for **10f** (IC_{50} = 61.7). In the case of the lung cancer cell line (A-549) the maximum inhibition 79% at 100 μM was observed for **11a** with IC_{50} = 52.8, followed by 76% for **10c** with IC_{50} = 57.5 at same concentration. In the case of liver cell line (HEP-2) the maximum inhibition observed was 69% (IC_{50} = 74.9) for **10e**.The inhibitory effect on CNS was also evaluated using (IMR-32) cell lines in the latter case maximum inhibition observed was 92% (IC_{50} = 10) for **10e**, followed by 82% (IC_{50} = 16.5) and 75% (IC_{50} = 14.6) at 100 μM concentration for **10a** and **10b**, respectively. The results indicate that some of the dithiazoles such as (**10b**,**e**) are active on neuroblastoma, while the compound (**10c**) is active against ovarian cancer cells. It is pertinent to mention here that compounds **10a**,**b**,**e** have IC_{50} value of 16.5, 14.6 and 10.0, respectively, against neuroblastoma (IMR-32 cells). Adriamycin is a DNA alkylating agent and topoisomerase-II inhibitor, and is known to be active on the neuroblastoma (IC_{50} = 1.7). Also, recently, Ishar et al. reported the design, synthesis and evaluation of chromone based molecules as potential topoisomerase inhibitor anticancer agents [31]; plausibly presently investigated molecules may be having similar mode of action.

Table 3
IC_{50} value for compounds (**10a–g**) and (**11a–d**) against different human cancer cell lines.

Compounds	IC_{50}(μM)[a]					
	COLO-205 Colon	PC-3 Prostate	OVCAR-5 Ovary	A-549 Lung	HEP-2 Liver	IMR-32 Neuroblastoma
10a	>100	>100	>100	>100	>100	16.5
10b	>100	>100	>100	91.1	98.6	14.6
10c	76.7	38.4	10.5	57.5	>100	95.1
10d	>100	60.0	65.2	95.0	98.0	58.0
10e	>100	52.7	66.5	71.3	74.9	10
10f	>100	56.9	61.7	93.5	97.6	56.8
10g	>100	>100	93.7	66.5	>100	70.7
11a	72.6	60.6	86.4	52.8	>100	95.8
11b	>100	>100	>100	71.9	>100	89.8
11c	>100	90.8	>100	63.6	>100	92.7
11d	>100	95.4	>100	71.2	>100	89.9
5-Flurouracil	21	–	–	–	–	–
Mito-C	–	1.5	–	–	1.5	–
Paclitaxel	–	–	2.7	2.7	–	–
Adriamycin	–	–	–	–	–	1.7

[a] IC_{50}, 50% inhibitory concentration represents the mean from dose response curves of number of experiments.

2.3. Structure activity relationship

Though systematic establishment of SAR has not been taken up, however, apparently compounds (**10b**,**e** Fig. 3) bearing electron withdrawing groups at the positions C6 are found to be more active, whereas, the compounds **10a**,**c** bearing electron withdrawing groups at position C7 or unsubstituted at C6 and C7 position are relatively less active. The compound bearing electron releasing groups at C6 position have low activity. In the case of *N*-phenylthioamides **11a**, derivatives unsubstituted at C6 or C7 are found to be highly active, whereas compound **11b** bearing electron withdrawing group at C6 showed moderate activity.

3. Conclusions

Chromanyl-1,2,4-dithiazole(**10a–g**) and *N*-Phenylthioamides (**11a–d**) were synthesized and evaluated for cytotoxic activity against human cancer cell lines. The results of investigations indicate that in most of the experimental observations, maximum activity was observed when chromone ring either bears electron withdrawing groups at C6 and C7 position (**10e**,**c**,**f**) or unsubstituted (**10a**). The compounds **10e**,**b**,**a** are active on neuroblastoma, **10c** on ovary, **10c**,**d**,**e**,**f** on prostrate and **10c** and **11a** on lung cancer cell lines; no significant activity was observed on liver and colon cancer cell lines. These molecules shall serve as useful 'Lead' for further development.

4. Experimental protocols

Starting materials, reagents and solvents were purchased from commercial suppliers and purified/distilled/crystallized before use. JEOL AL-300FT (300 MHz) NMR spectrometer was used to record ^1H and ^{13}C NMR (75 MHz) spectra. Chemical shifts (δ) are reported as downfield displacements from TMS used as internal standard and coupling constants (J) are reported in Hz. IR spectra were recorded with Shimadzu FT-IR-8400S spectrophotometer on KBr pellets. Mass spectra, ESI-method, were recorded on Bruker Daltonics Esquire 300 mass spectrometer. Elemental Analyses were

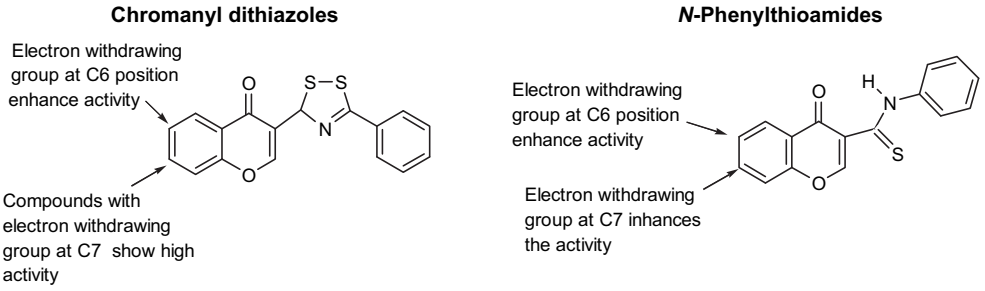


Fig. 3. Structure activity relationship.

carried out on a Thermoelectron EA-112 elemental analyzer and are reported in percent atomic abundance. All melting points are uncorrected and measured in open glass-capillaries on a Veego (make) MP-D digital melting point apparatus. X-ray analysis was recorded at Bruker SMART APEX diffractometer equipped with low-temperature device and the structure was solved by direct methods using SHELXS 97 software (Sheldrick, 1997).

4.1. Synthesis

4.1.1. Synthesis of 1,2,4-dithiazoles (**10c**,**d**)

Synthesis of 3-(5-phenyl-3*H*-[1,2,4]dithiazol-3-yl)chromen-4-ones and 4-oxo-4H-chromene-3-carbothioic acid *N*-phenyl-amides had been earlier [31,32]. Two new compounds **10c**,**d** bearing electron withdrawing groups (Cl) at C6 and C7 position were synthesized by the same procedure and characterized detailed spectroscopic analysis.

*4.1.1.1. 7-Chloro-3-(5-phenyl-3H-[1,2,4]dithiazol-3-yl)-chromen-4-one (**10c**).* Yield: 89%; Light orange crystalline solid, mp 140–143 °C (chloroform: hexane, 1:1); UV (MeOH): 307, 247 nm; IR (KBr): ν_{max} 1645, 1517, 1220 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 8.15$ (d, 1H, $J = 1.8$ Hz ArH), 7.95 (dd, 2H, $J = 7.5$ and 1.6 Hz, ArH), 7.73 (s, 1H, C_2H), 7.58–7.08(m, 6H, 5-Ar H and $C_{5'}$ H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 175.2$ (C_4), 170.7 ($C_{3'}$), 156.4 (q), 152.7 (C_2), 132.4 (q), 131.4 (C_7), 129.2 (CH), 128.9 (C_5), 127.2 (CH), 126.4 (CH), 126.3 (q), 124.6 (C_6), 122.4 (C_8), 118.2 (C_3), 82.7 ($C_{5'}$); MS (ESI): m/z 359 ($M + Na^+$); Anal. calcd. For $C_{17}H_{10}ClNO_2S_2$: C, 56.74; H, 2.80; N, 3.89; Found C, 56.62; H, 2.67 and N, 3.76%.

*4.1.1.2. 6,7-Dichloro-3-(5-phenyl-3H-[1,2,4] dithiazol-3-yl)-chromen-4-one (**10d**).* Yield: 73%; solid, Light orange crystalline solid, mp 183–186 °C (chloroform: hexane, 1:1); UV (MeOH): 306, 253, 248 nm; IR (KBr): ν_{max} 1600, 1521, 1245 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.01$ (s, 1H, ArH), 7.98(dd, 2H, $J = 7.2$ and 1.5 Hz, ArH), 7.80 (d, 1H, $J = 0.9$ Hz, C_2H), 7.67–7.47 (m, 6H, 5-Ar H and $C_{5'}$H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 186.0$ (C_4), 171.7 ($C_{3'}$), 151.1 (C_2), 132.3 (q), 131.2 (C_7), 131.8 (CH), 129.5 (C_5), 129.3 (CH), 129.2 (CH), 128.1 (q), 128.7 (q), 128.2 (C_8), 122.5 (q), 120.4 (C_3), 82.4 ($C_{5'}$); MS (ESI): m/z 394 (M); Anal. calcd. For $C_{17}H_9Cl_2NO_2S_2$: C, 51.78; H, 2.30; N, 3.55%; Found C, 51.67; H, 2.27; N, 3.43%.

4.2. Pharmacology

4.2.1. Cytotoxic analysis

All the compounds (**10a**–**g**) and (**11a**–**d**), were dissolved in DMSO and stock solution of 2×10^4 μM was prepared. Stock solutions were further diluted with complete growth medium supplemented with 50 μg/ml gentamycin to obtain test concentration of 100 μM. Adriamycin and paclitaxel were dissolved in DMSO and stock solution of 2×10^{-3} μM was prepared. 5-Flurouracil and Mitomycin-C were dissolved in double distilled water and stock solution of 2×10^3 μM was prepared. Stock solutions were further diluted with complete growth medium supplemented with 50 μg/ml gentamycin to obtain desired concentration. All the cells were maintained in RPMI-1640 medium, supplemented with fetal bovine serum (10%), 100 units/ml penicillin and 100 μg/ml streptomycin (complete medium). The cells were seeded into 96 well cell culture plates (1×10^4 cells/100 μl/well) and incubated in CO_2 incubator (37 °C, 5% CO_2, 95% relative humidity) for 24 h. After 24 h, compounds **10a**–**g**, **11a**–**d** and positive controls (100 μl/well) were added in quadruplets and the plates were further incubated in CO_2 incubator for 48 h. Suitable controls were also included in each experiment. After 48 h chilled trichloro acetic acid (50% w/v, 50 μl) was laid gently on top of the medium in all the wells. The plates were incubated at 4 °C for one hour to fix the cells. All the contents of the wells were gently pipetted out and discarded. The plates were washed five times with distilled water to remove trichloro acetic acid, growth medium, low molecular weight metabolites and serum proteins etc. The plates were air-dried. Sulphorhodamine-B (0.4% SRB in 1% acetic acid, 100 μl/well) was added to each well of the 96 well plates for 30 min. Excess of the dye was washed off using 1% acetic acid and the plates were air-dried. Tris buffer (10 mM, pH 10.5, 100 μl/well) was added to each well and plates were shaken on a mechanical stirrer for 10 min and O. D. was recorded on ELISA reader at 540 nm. Viability of cells was evaluated by trypan blue exclusion method immediately before setting up the experiment for cytotoxicity determination. Cells with >98% viability were used in the assay [37].

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