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Original Article

In-vitro Antioxidant and Antitumor Activity of Dihydropyrimidine-2(1-*H*)-thione Derivatives with Carbazole Moiety

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ABSTRACT

Aim: Prepared a series of molecules called Dihydropyrimidine-2(1-*H*)-thione of carbazole to evaluate antioxidant and antitumor activity. **Materials and Methods:** Compounds from DTP-1 to DTP-11 were prepared and subjected for Spectral analysis like infrared, ^{1}H NMR, and Mass spectroscopy. Further evaluated antioxidant property of molecules using DPPH free radical scavenging method and analyzed the antitumor activity by MTT assay. **Results:** The molecule DTP-4 (4-(9*H*-carbazol-9-yl)-6-(3-hydroxyphenyl)-5,6-dihydropyrimidine-2(1*H*)-thione) exhibit the spectral values i.e, Mass, m/z: 371.08, 166.45; IR (KBr) ν_{max}, cm^{-1}: 3420 (NH Str), 3567(O-H); ^{1}H NMR (MHz, δ): (15H, Ar-H) 8.003-7.019, (1H, N-H) 11.129, (1H, O-H) 10.03 and DTP-6: 4-(9*H*-carbazol-9-yl)-6-(4-Dimethylamino-phenyl)-5,6-dihydropyrimidine-2(1*H*)-thione Mass value of m/z: 398.03, 166.09; IR $(KBr)_{vmax}$, cm^{-1}: 3419 (NH Str), (Ar C=S); ^{1}H NMR (MHz, δ): (15H, Ar-H) 8.128-7.121, (1H, N-H) 11.290, (6H, -N-$(CH_3)_2$)3.491-2.791. **Conclusion:** Among all of those prepared molecules, DTP-4, which includes the functional group (3-OH) ortho-hydroxy, has an IC_{50} value of 2.32 µm against the Jurkat T cell line while compound DTP-06, which contains the functional group 4-dimethylamino, exhibits an IC_{50} value of 05.39 µm against the HeLa cell line.

Keywords: Carbazole, Antioxidant activity, *In-vitro* method, DPPH Method, Dihydropyrimidin-thiones.

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INTRODUCTION

According to a World Health Organization report from 2018, cancer is the biggest cause of mortality worldwide, with an estimated 9.6 million deaths that year. Lung cancer (1.76 million deaths), colorectal cancer (862000 deaths), stomach cancer (783000 deaths), liver cancer (782000 deaths), and breast cancer are the most frequent types of cancer (627000 deaths).[1]

The term "cancer" refers to a group of diseases marked by abnormal cell growth that have the possibility of spreading to other connected body parts and other organs, ultimately resulting in death. External factors, such as physical carcinogens, chemical carcinogens, food contaminants, and biological carcinogens, such as infections from specific bacteria, parasites, and viruses, can mutate the DNA in normal cells, leading to the growth of cancer. Internal factors, such as immune conditions, hormones, mutations, and mutations occurring in regular metabolisms, can also cause cancer. We can obtain the highest success rates in cancer treatments by combining a variety of techniques, include early detection, diagnosis through screening, clinical evaluation, treatment, and palliative care.[2]

Natural or synthetic antioxidants may protect our cells from the damaging effects of free radicals, which can cause diseases like cancer and heart disease. Free radicals are molecules that are produced by the body as a result of food digestion, radiation exposure, or inhaling tobacco smoke.[3,4]

The anticancer activity of synthetic compounds may be related to the antioxidant characteristics based on the association between anticancer activity on U87 and A549 cell lines and antioxidant activity.[5]

Chalcones are an important class of natural yields, and many heterocyclic compounds, like dihydropyrimidine-2(1-*H*)-thione of carbazole, are hetero-arylated from their chalcone intermediates.[6] Numerous carbazole derivatives exhibit a wide range of biological actions, including antimicrobial,[7] anticancer,[8-14] anti-inflammatory,[16] anti-HIV, anti-tubercular,[15] anti-cancer, anti-cancer, anti-cancer, anti-cancer, anti-cancer, anti-cancer, and anti-fungal drugs.[17]

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Experimental Part

The Dihydropyrimidine-2(1-*H*)-thione of carbazole compounds were synthesized by us before at the Department of Pharmaceutical Chemistry, Sri Adichunchanagiri College of Pharmacy and recrystallization was performed for purification purpose. All the chemicals and reagents used in this research were obtained from departmental store of the college with the verified Certificate of Analysis.

Scheme

ACD Lab/ChemSketch and Chem Draw were used to draw the synthetic route which are utilized to design and the synthesis of Dihydropyrimidine-2(1H)-thione of carbazole derivatives as mentioned in the scheme (Figure 1).

Step 1: Procedure for the synthesis of (2E)-1-(9H-carbazol-9-yl)-3 -phenylprop-2-en-1-one derivatives

A solution of NaOH 50% (14 mL) is treated with an equimolar mixture of n-Acetylcarbazole (0.01mole) and different aldehydes (0.01 mole) in 10 mL of ethanol 95%; the addition is performed under stirring condition at room temperature.

The reaction is kept for stirring overnight, placed in cool condition for five hours and diluted with water followed by acidification with the help of dilute hydrochloric acid; the precipitate is separated by filtration and dried. Recrystallization was performed by suitable solvent.[6]

Step-2: Procedure for the synthesis of various derivatives of Dihydropyrimidine-2(1H)-thione of carbazole [DTP-1 to DTP-11]

(2E)-1-(9H-carbazol-9-yl)-3-phenylprop-2-en-1-one (1.00 mmol), Thiourea (1mmol), and 15% NaOH (2mmol) were combined with ethanol (12 mL) and refluxed for 4-5 hr. Using a water condenser. Afterward cooling the reaction mixture, the mixture was completely poured into ice-cold water and further acidified with dilute hydrochloric acid, filtered and washed through ice cold water and dried with hot air oven. The product was recrystallized from ethanol to give the desired analogue.[18]

Determination of Antioxidant Activity

DPPH free radical scavenging assay

The prepared synthetic compounds were subjected to screen DPPH radical scavenging activity using the experimental procedure mentioned before by Purushotham KN *et al.* (2014) briefly 1mL of DPPH reagent was added to 1 mL of the DTP with the concentration range of 50-100 µg/mL. Related amount of DPPH reagent was transferred to 1 mL of different concentrations of Ascorbic acid (1-10 µg/mL) Additionally, this solution was incubated at ambient temperature (25 +/-1°C) in the dark for 30 min. Using a UV-visible spectrophotometer, the decrease in absorbance (intensity of purple blue) was observed at 517 nm. 1 mL of methanol and 1 mL of DPPH solution serve as the control. The percentage of inhibition was calculated based on this measurement. Higher the percentage of inhibition, better the free radical scavenging activity and all the measurements were done in triplicates.[4]

Formula for the calculation of percentage inhibition:

$$\text{Percentage of inhibition} = \frac{Ao - Ai}{Ao} X100$$

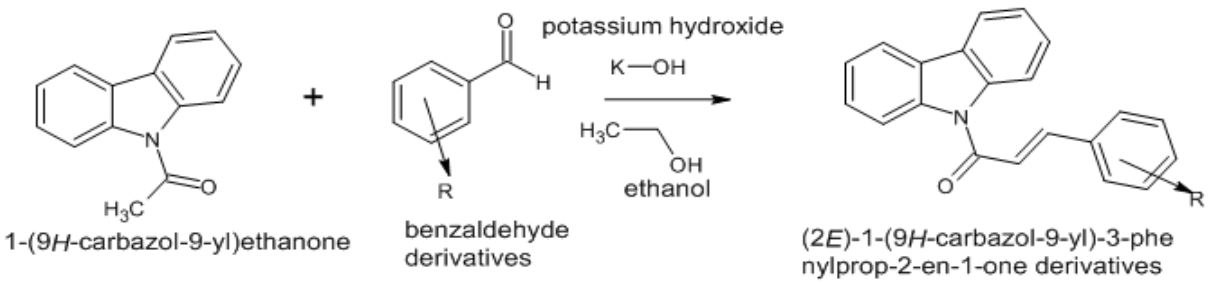
Whereas,

Ao = absorbance of the control

Ai = absorbance of samples.

Cytotoxicity

Using the MTT assay, the effects of dihydropyrimidine-2(1H)-thione of carbazole [DTP-1 to DTP-11] on the proliferation of Jurkat T leukaemia cells and HeLa cells were examined. The cell lines were subsequently cultured in 96-well plates with 100 µL of medium. The experimental fluids containing various concentrations of dihydropyrimidine-2(1H)-thione of carbazole were added on the next day, followed by a 48-hr incubation period. 50µL of MTT solution (2 mg/mL in PBS) was added to each well of 96-well plates and incubated for 4 hr. After separating the medium carefully, 150µL of DMSO was added to each well. After shaking, the absorbance was determined with an ELISA microplate reader at a wavelength of 570 nm.



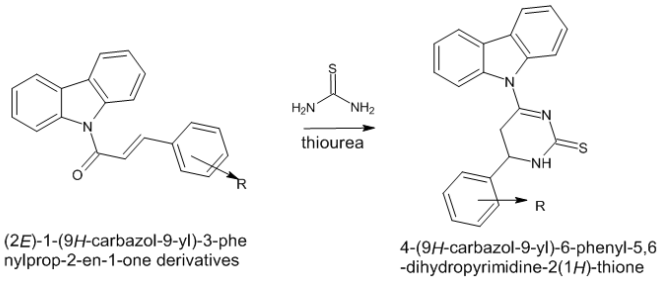
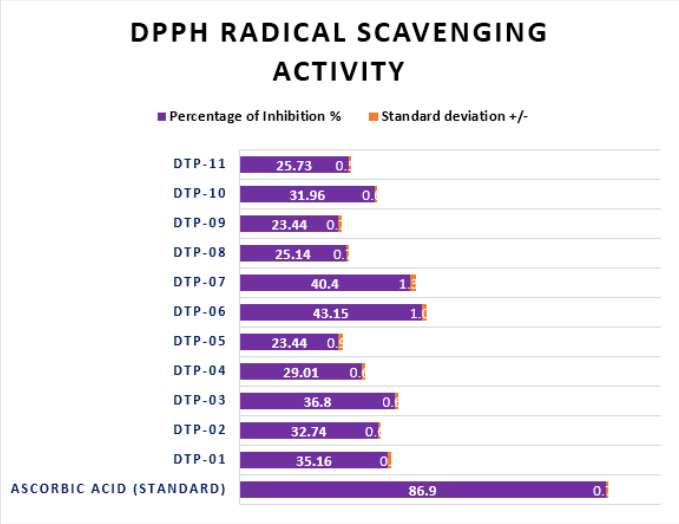
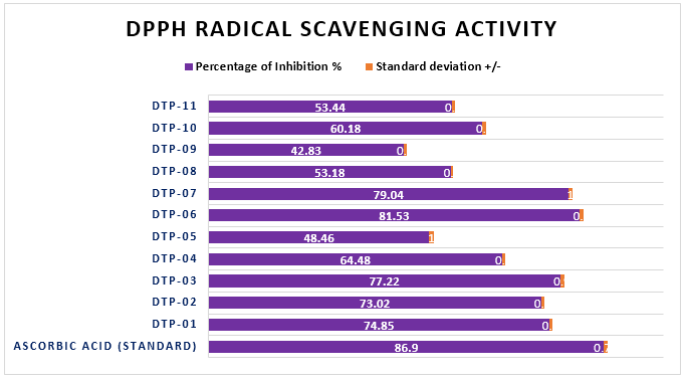


Figure 1: Synthesis of Dihydropyrimidine-2(1-H)-thione of carbazole derivatives.



Horizontal bar diagram for the percentage inhibition of samples for 50µg/mL with standard.



Horizontal bar diagram for the percentage inhibition of samples for 100µg/mL with standard.

RESULTS

Experimental data of Synthesized Compounds

DTP-1: 4-(9H-carbazol-9-yl)-6-(4-nitrophenyl)-5,6-dihydropyrimidine-2(1H)-thione

Yield: 92%; m.p. 222–226°C; MS, m/z: 399.90, 354.10; IR (KBr) νmax, cm^{-1}: 3421 (NH Str), 1450 (Ar-C=C), 1204(C-N), 3050 (Ar C-H), 1238(C=S), 1493(Ar NO_2); ^{1}H NMR (DMSO-d6, 400 MHz, δ): (16H, Ar-H) 8.116 – 7.153, (1H, N-H) 11.261.

DTP-2: 4-(9H-carbazol-9-yl)-6-(3-nitrophenyl)-5,6-dihydropyrimidine-2(1H)-thione

Yield: 89%; m.p. 233–235°C; MS, m/z: 399.98, 166.08; IR (KBr) νmax, cm^{-1}: 3419 (NH Str), 1450 (Ar-C=C), 1204(C-N), 3050.98 (Ar C-H), 1335(C=S), 1490(Ar NO_2): ^{1}H NMR (DMSO-d6, 400 MHz, δ): (16H, Ar-H) 8.120-7.102, (1H, N-H) 11.251.

DTP-3: 4-(9H-carbazol-9-yl)-6-(4-hydroxyphenyl)-5,6-dihydropyrimidine-2(1H)-thione

Yield: 83%; m.p. 220–222°C; MS, m/z: 370.98, 166.06; IR (KBr) ν_{max}, cm^{-1}: 3421 (NH Str), 1453 (Ar-C=C), 1204(C-N), 3056 (Ar C-H), 1204(C=S), 3331(O-H); ^{1}H NMR (DMSO-d6, 400 MHz, δ): (15H, Ar-H) 8.103–7.100, (1H, N-H) 11.309, (1H, O-H) 9.571.

DTP-4:4-(9H-carbazol-9-yl)-6-(3-hydroxyphenyl)-5,6-dihydropyrimidine-2(1H)-thione

Yield: 82%; m.p. 174–178°C; MS, m/z: 371.08, 166.45; IR (KBr) ν_{max}, cm^{-1}: 3420 (NH Str), 1450 (Ar-C=C), 1204(C-N), 3049 (Ar C-H), 1204(Ar C=S), 3567(O-H); ^{1}H NMR (DMSO-d6, 400 MHz, δ): (15H, Ar-H) 8.003-7.019, (1H, N-H) 11.129, (1H, O-H) 10.03.

DTP-5: 4-(9H-carbazol-9-yl)-6-phenyl-5,6-dihydropyrimidine-2(1H)-thione

Yield: 32%; m.p. 98-103°C; MS, m/z:355.09, 166.05; IR (KBr) ν_{max}, cm^{-1}: 3419 (NH Str), 1601 (Ar-C=C), 1450(C-N), 3051 (Ar C-H), 1140(Ar C=S); ^{1}H NMR (DMSO-d6, 400 MHz, δ): (16H, Ar-H) 8.129-7.003, (1H, N-H) 11.210.

DTP-6:4-(9H-carbazol-9-yl)-6-(4-Dimethylamino-phenyl)-5,6-dihydropyrimidine-2(1H)-thione

Yield: 63%; m.p. 118–121°C; MS, m/z: 398.03, 166.09; IR (KBr) ν_{max}, cm^{-1}: 3419 (NH Str), 1601 (Ar-C=C), 1451(C-N), 3050 (Ar C-H), 1167(Ar C=S); ^{1}H NMR (DMSO-d6, 400 MHz, δ): (15H, Ar-H) 8.128-7.121, (1H, N-H) 11.290, (6H, -N-$(CH3)_2$)3.491-2.791.

DTP-7: 4-(9H-carbazol-9-yl)-6-(4-chlorophenyl)-5,6-dihydropyrimidine-2(1H)-thione

Yield: 65%; m.p. 105–108°C; MS, m/z: 389.40, 232.09; IR (KBr) ν_{max}, cm^{-1}: 3418 (NH Str), 1699 (Ar-C=C), 1452(C-N), 1238(Ar C=S), 724(C-Cl); ^{1}H NMR (DMSO-d6, 400 MHz, δ): (15H, Ar-H) 8.103-7.123, (1H, N-H) 10.321.

DTP-8: 6-(4-bromophenyl)-4-(9H-carbazol-9-yl)-5,6-dihydropyrimidine-2(1H)-thione

Yield: 62%; m.p. 116–119°C; MS, m/z: 434.35, 265.09; IR (KBr) ν_{max}, cm^{-1}: 3420 (NH Str), 1679 (Ar-C=C), 1452(C-N), 1239(Ar C=S), 856(C-Br); ^{1}H NMR (DMSO-d6, 400 MHz, δ): (15H, Ar-H) 8.193-7.009, (1H, N-H) 9.410.

Various derivatives of Dihydropyrimidine - 2(1 - *H*)-thione of carbazole with compound code (DTP - 1 to DTP - 11), substituent type, IUPAC Name, molecular formula and predicted molecular weight.

Compounds Code	Substituent type (-R)	IUPAC Name	Molecular Formula	Molecular Weight gm/mol
DTP-1	4-NO_2	4-(9H-carbazol-9-yl)-6-(4-nitrophenyl)-5,6-dihydropyrimidine-2(1H)-thione	$C_{22}H_{16}N_4O_2S$	400.45
DTP-2	3-NO_2	4-(9H-carbazol-9-yl)-6-(3-nitrophenyl)-5,6-dihydropyrimidine-2(1H)-thione	$C_{22}H_{16}N_4O_2S$	400.45
DTP-3	4-OH	4-(9H-carbazol-9-yl)-6-(4-hydroxyphenyl)-5,6-dihydropyrimidine-2(1H)-thione	$C_{22}H_{17}N_3OS$	371.45
DTP-4	3-OH	4-(9H-carbazol-9-yl)-6-(3-hydroxyphenyl)-5,6-dihydropyrimidine-2(1H)-thione	$C_{22}H_{17}N_3OS$	371.45
DTP-5	H	4-(9H-carbazol-9-yl)-6-phenyl-5,6-dihydropyrimidine-2(1H)-thione	$C_{22}H_{17}N_3S$	355.45
DTP-6	4-$N(CH_3)_2$	4-(9H-carbazol-9-yl)-6-(4-Dimethylamino-phenyl)-5,6-dihydropyrimidine-2(1H)-thione	$C_{24}H_{22}N_4S$	398.52
DTP-7	4-Cl	4-(9H-carbazol-9-yl)-6-(4-chlorophenyl)-5,6-dihydropyrimidine-2(1H)-thione	$C_{22}H_{16}ClN_3S$	389.90
DTP-8	4-Br	6-(4-bromophenyl)-4-(9H-carbazol-9-yl)-5,6-dihydropyrimidine-2(1H)-thione	$C_{22}H_{16}BrN_3S$	434.35
DTP-9	4-F	4-(9H-carbazol-9-yl)-6-(4-fluorophenyl)-5,6-dihydropyrimidine-2(1H)-thione	$C_{22}H_{16}FN_3S$	373.44
DTP-10	3,4,5-3(O-CH_3)	4-(9H-carbazol-9-yl)-6-(3,4,5-trimethoxyphenyl)-5,6-dihydropyrimidine-2(1H)-thione	$C_{25}H_{23}N_3O_3S$	445.53
DTP-11	4-O-CH_3	4-(9H-carbazol-9-yl)-6-(4-methoxyphenyl)-5,6-dihydropyrimidine-2(1H)-thione	$C_{23}H_{19}N_3OS$	385.48

Percentage inhibition of various derivatives at the concentration of 50µg/mL along with its standard deviation.

Sample	Concentration µg/mL	Percentage of Inhibition %	Standard deviation +/-
Ascorbic acid (standard)	10	86.9	0.74
DTP-01	50	34.83	0.60
DTP-02	50	33.59	0.85
DTP-03	50	34.25	0.49
DTP-04	50	33.26	0.30
DTP-05	50	34.70	0.30
DTP-06	50	32.28	0.49
DTP-07	50	39.75	1.00
DTP-08	50	44.20	1.09
DTP-09	50	33.98	0.98
DTP-10	50	32.61	0.85
DTP-11	50	36.41	0.60

Percentage inhibition of various derivatives at the concentration of 100µg/mL along with its standard deviation.

Sample	Concentration µg/mL	Percentage of Inhibition %	Standard deviation +/-
Ascorbic acid (standard)	10	86.9	0.74
DTP-01	100	74.85	0.6
DTP-02	100	73.02	0.8
DTP-03	100	77.22	0.9
DTP-04	100	64.48	0.7
DTP-05	100	48.46	1
DTP-06	100	81.53	0.9
DTP-07	100	79.04	1
DTP-08	100	53.18	0.6
DTP-09	100	42.83	0.7
DTP-10	100	60.18	0.9
DTP-11	100	53.44	0.7

The *in - vitro* anti - proliferative activities (IC_{50} µm) of compounds DTP - 01 to DTP - 11 against human cancer cell lines.

Code	DTP-1	DTP-2	DTP-3	DTP-4	DTP-5	DTP-6	DTP-7	DTP-8	DTP-9	DTP-10	DTP-11
HeLa cell line	72.71 +/- 4.11	21.86 +/- 2.56	3.123 +/- 1.34	2.32 +/- 0.84	13.85 +/- 2.35	15.87 +/- 2.65	55.08 +/- 3.90	70.09 +/- 2.11	14.00 +/- 1.31	12.03 +/- 0.84	16.53 +/- 0.84
Jurkat T cell line	21.03 +/- 2.93	20.63 +/- 1.01	31.93 +/- 1.40	21.23 +/- 1.01	6.16 +/- 1.03	05.39 +/- 1.03	29.07 +/- 0.19	16.01 +/- 0.50	73.01 +/- 0.13	34.05 +/- 1.04	62.40 +/- 1.03

DTP-9: 4-(9H-carbazol-9-yl)-6-(4-fluorophenyl)-5,6-dihydropyrimidine-2(1H)-thione

Yield: 57%; m.p. 146–149°C; MS, m/z:373.04, 207.03; IR (KBr) ν_{max}, cm^{-1}: 3418 (NH Str), 1626 (Ar-C=C), 1450(C-N), 1205(Ar C=S), 890(C-F); ^1H NMR (DMSO-d6, 400 MHz, δ): (15H, Ar-H) 8.399 – 7.041, (1H, N-H) 9.980.

DTP-10:4-(9H-carbazol-9-yl)-6-(3,4,5-trimethoxyphenyl)-5,6-dihydropyrimidine-2(1H)-thione

Yield: 78%; m.p. 206–210°C; MS, m/z: 445.04, 165.04; IR (KBr) ν_{max}, cm^{-1}: 3420 (NH Str), 1625 (Ar-C=C), 1450.98(C-N), 1239(Ar C=S), 2853(Ar O-CH_3); ^1H NMR (DMSO-d6, 400 MHz, δ): (13H, Ar-H) 8.193-7.382, (1H, N-H) 11.119, (9H, (-O-CH_3)$_3$) 4.38-4.347.

DTP-11: 4-(9H-carbazol-9-yl)-6-(4-methoxyphenyl)-5,6-dihydropyrimidine-2(1H)-thione

Yield: 70%; m.p. 231–234°C; MS, m/z: 385.01, 165.09; IR (KBr) ν_{max}, cm^{-1}: 3420.32 (NH Str), 1679 (Ar-C=C), 1450.98(C-N), 1205(Ar C=S), 3050(Ar O-CH_3); ^1H NMR (DMSO-d6, 400 MHz, δ): (15H, Ar-H) 8.196-7.030, (1H, N-H) 11.119, (3H, O-CH_3) 3.850-3.609.

CONCLUSION

According to the methods described above, we have prepared a molecule series of Dihydropyrimidine-2(1H)-thione of carbazole [DTP-1 to DTP-11] as anticancer agents. All these compounds were characterized by spectral methods such as Infra-red, ^1H and Mass Spectroscopy. Evaluation an *in-vitro* antioxidant activity reports that compound DTP-06 shows the percentage of free radical inhibition of 43.15% and 81.53% for 50µg/mL and 100µg/mL respectively against the standard ascorbic acid 86.9% at the strength of 10µg/mL. The DTP-06 molecule is showing the increment in the activity when the concentration increases, we can say that compound is having dose dependent property in antioxidant activity. All of the synthetic compounds *in-vitro* anticancer activity was assessed using the MTT test against the two human cancer cell lines HeLa cell line and Jurkat T cell line. Among these, compounds DTP-4, DTP-3, DTP-6 and DTP-5 with Dihydropyrimidine-2(1H)-thione of carbazole ring's in different location of functional groups revealed high cytotoxicity. Among which DTP-4 with the functional group of (3-OH) Ortho-hydroxy shows the IC_{50} Value of 2.32 µm against the human cancer cell line that is HeLa cell line and compound DTP-06 which contains 4-dimethylamino with the IC_{50} value of 05.39 µm against Jurkat T cell line.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

MTT: 3-(4, 5-dimethylthiazolyl-2)-2, 5-diphenyltetrazolium bromide; **µg/mL:** Microgram per milliliter; **%:** Percentage; **M/Z:** Mass divided by charge number; **H NMR:** Proton nuclear magnetic resonance; **MHz:** Megahertz; **IR:** Infrared radiation; **cm^{-1}:** Reciprocal centimeter.

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