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Free Radical Scavenging and Cytotoxic Activities of Substituted Pyrimidines

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Abstract

A library of substituted pyrimidines was synthesized and evaluated for free radical scavenging, and in vitro cytotoxic activity in 3T3 cells. All compounds showed good free radical scavenging activity with IC50 values in the range of 42.9 ± 0.31 to 438.3 ± 3.3 µM as compared to the standard butylated hydroxytoluene having IC50 value of 128.83 ± 2. 1 µM. The structure activity-relationship was also established. Selected analogues 1, 2, 3, 5, 6, 7, 8, 9, 10, 12, 13, 15, 19, 20, 21, 24, 25, 26 and 28 were tested for cytotoxicity in mouse fibroblast 3T3 cell line using MTT assay, and most of the analogues showed cytotoxicity. This study has identified a number of cytotoxic novel substituted pyrimidines having free radical scavenging activities that can be used as inhibitory compounds for those cancer cells whose growth is mediated by reactive oxygen species.

Keywords: Pyrimidine nucleotide, Synthesis, Free radical scavenging, SAR, Cytotoxicity

Abbreviations: MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide

Introduction

Scavenging of free radicals by antioxidant compounds is an important biological function that may maintain in the body a low oxidative damage [1-3]. Antioxidant compounds of different synthetic, and natural sources can scavenge these free radicals with the formation of less reactive species, and thus diminish the radical induced oxidative damage that is possibly associated with many diseases, including cancers [2-5]. Numerous classes of synthetic compounds have been screened to reveal their free radical scavenging ability, including synthetically obtained deoxyribonucleic acids (DNA) and nucleotide analogues like pyrimidine derivatives [6,7].

These pyrimidines, present in numerous pharmaceutically important compounds, have been known to prevent cancer cell proliferation. Substituted pyrimidines primarily display their anticancer activity through intercalating with DNA nucleotide bases. However, they may prevent ROS induced DNA mutations in a way similar to other anticancer and antiviral molecules [8-11]. In recent years, anticancer drugs already being used in medical practice or being tested in clinical studies have been often based on pyrimidine skeleton, and new pyrimidine derivatives continue to show promising activities [12-15]. However, synthesis of antioxidant molecules can be a new approach to prevent proliferation of tumors whose growth is mediated by oxygen species [16].

Besides their anti-tumor action, pyrimidine derivatives have also been found to possess additional biological activities including antibacterial, anti-folate, antibiotic, anti-HIV, anti-fungal, anti-mycobacterial, anti-leishmanial were also found to inhibit tumor necrotic factor alpha (TNF-α) production and as potent inhibitors of urease enzyme [17-21]. Herein, we report the free radical scavenging activities of a new library of pyrimidine derivatives to evaluate their potential against free radical sustained cancer cell proliferation. IN the past, a number of pyrimidines were also found to inhibit enzymes such as tyrosine kinases, urease, β-glucuronidase, and cholinesterase [22-25]. Furthermore, many pyrimidine analogues were found to exhibit inhibitory or modulatory activities in a number of biological situations [26,27]. Therefore, we screen these synthetic pyrimidine derivatives for their in vitro free radical scavenging activity as well as to establish their cytotoxicity in a 3T3 mouse fibroblast cell line (Figure 1).

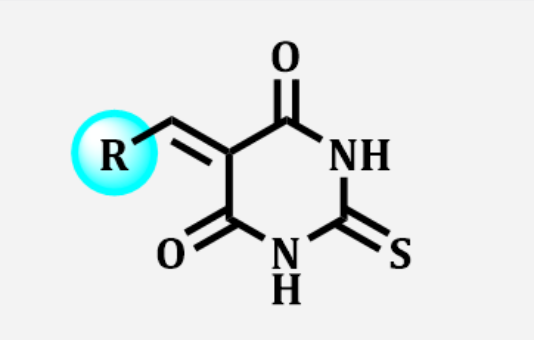

Figure 1: Basic Skeleton of Pyrimidines.

Material and Methods

All substituted pyrimidines were obtained from the in-house Molecular Bank facility of the Dr. Panjwani Center for Molecular Medicine and Drug Research, International Center for Chemical and Biological Sciences, University of Karachi, Pakistan. DPPH was purchased from Sigma Aldrich (Germany). Ethanol and dimethyl sulfoxide (DMSO) (reagent grade) were purchased from Sigma Aldrich (USA). Standard compounds, i.e., butylated hydroxytoluene was purchased from Sigma Aldrich (Germany).

DPPH Radical Scavenging Assay

The Kumari Madhu method of DPPH (2,2-diphenyl-1-picryl-hydrazyl) assay [28] was used to measure the free radical scavenging activity with small variations. This assay is based on the reduction of DPPH radical (violet colour) by free radical scavenger with a change of colour to pale yellow. The intensity of colour conversion is directly related to the potency of free radical scavenging compounds, and to the extent of reduction in absorbance. In the visible region, absorbance reduction can be measure at 517 nm. Compounds solutions of (0.5 mM) in DMSO were prepared. Two-fold dilution method was used to dilute compounds solutions to different concentrations. 5 µ*l* sample of each concentration was transferred to 96 wells plate in triplet, at 517 nm pre read was recorded. 95 µl of 0.3 mM freshly prepared ethanolic solution of DPPH was added in each of the 96 wells. A final absorbance reading was taken at 517 nm. DMSO was used as negative control and butylated hydroxytoluene was used as the positive control. The radical scavenging activities were calculated by the following equation:

% Radical scavenging activity of DPPH

= [A0-A1/A0] ×100

Where:

A0: The absorbance of all reagents without the tested compounds.

A1: The absorbance in the presence of test compounds.

MTT Assay

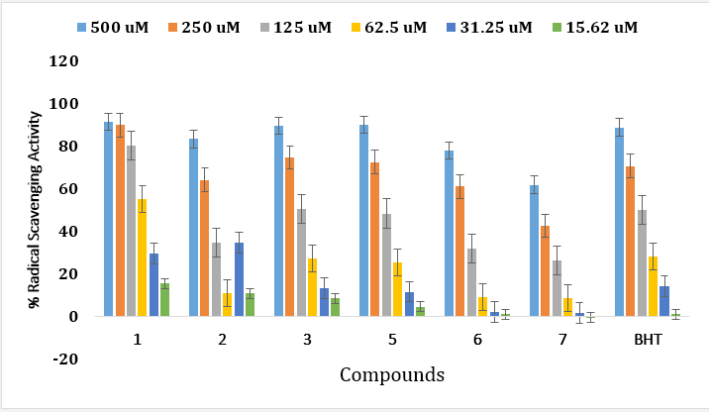

Figure 2: Concentrations dependent changes in free radical scavenging activities of pyrimidine derivatives [1–7].

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The pyrimidine derivatives were tested by the method previously described by Dimas *et al*. to establish their cytotoxicities in a normal cell line [29]. In 96-well plate, mouse fibroblast 3T3- cells (2 ×10^5 cells/ mL) were grown over night in DMEM medium along with 10% FBS, pen/ strep (100 units/ mL), supplemented with 5% CO_2 at 37 °C. After 24 h, the old media was discarded, cells were treated with different concentrations of the tested compound, and further incubated for 24 h. After 24 h, cells were washed, and the plate was again incubated with MTT solution for 4 h after which dimethyl sulfoxide 100uL added for 15 min to dissolved formazan crystals at room temperature. Finally, a micro plate reader (SpectraMax Plus-384) was used to record the absorbance at 540 nm. The IC_{50} was calculated and defined as the drug concentration (µM) causing cytotoxicity in 50%. Cells (Figure 2).

Results and Discussion

Free Radical Scavenging Activity

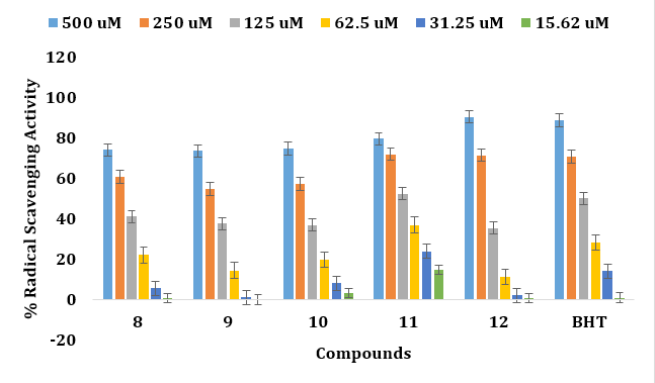

Figure 3: Concentrations dependent changes in free radical scavenging activities of pyrimidine derivatives [8–12].

The synthetic pyrimidine derivatives 1-28 were tested for their free radical scavenging, and cell cytotoxic potential. All compounds showed various degrees of radical scavenging activity in DPPH radical scavenging assay, and their IC_{50} values ranged between 42.9 ± 0.31 to 438.3 ± 3.3 µM. Derivatives **1**, **3**, **11**, **13**, **18**, **26**, and **28** with IC_{50} values of 55.6 ± 2.1, 122.4 ± 1. 9, 107.65 ± 1.3, 108.4 ± 2.8, 113.4 ± 1.3, 42.9 ± 0.31, and 65.7± 1.80 µM, respectively, showed free radical inhibitory activity that is many folds better than the standard butylated hydroxytoluene with IC_{50} value of 128.83 ± 2.1 µM, as depicted in Figures 2-5, and Table- Compounds **2**, **5**, **8**, **12**, **19**, and **27** showed good to moderate activities (Figures 2-5 & Table 1). The remaining derivatives, including **6**, **7**, **9**,**10**, **15**, **21**, **22**, **23**, and **24** showed weak inhibitory activities (Figures 2-5 & Table 1). Derivatives **4**, **14**, **16**, **17**, **20**, **25** were declared as inactive derivatives of this series.

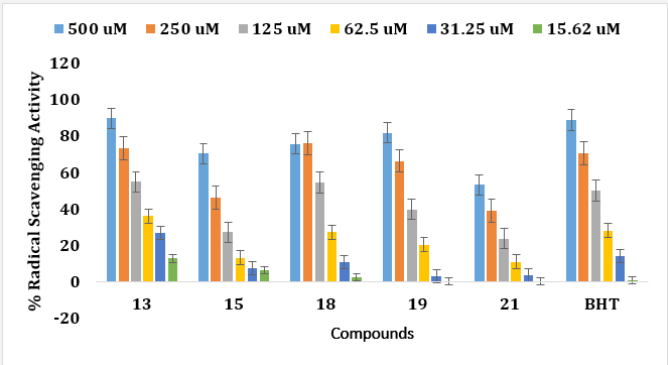

Figure 4: Concentrations dependent changes in free radical scavenging activities of pyrimidine derivatives [13–21].

Structure- Activity Relationship

A structure-activity relationship established for all compounds that confirmed substitution of various functionalities at the aromatic ring confers free radical scavenging activity to each particular pyrimidine analogue. Analogue **26**, a 3,4-dihydroxybenzylidene was found to be the most active pyrimidine among the series, with an IC_{50} value of 42.9 ± 0.31 µM,

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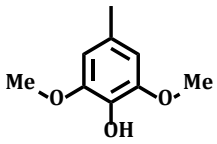
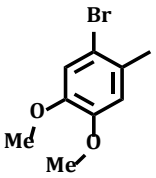
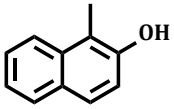
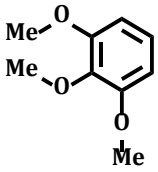
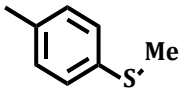
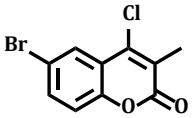
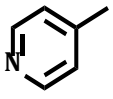
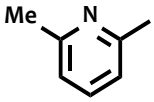
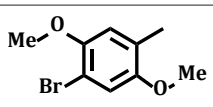
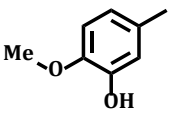
corresponding to 84.07% radical scavenging activity that is as good as 85.87% radical scavenging activity of the standard drug (Tables 1 & 2). The high activity shown by analogue **26** is due to the positional change of dihydroxyl groups present an aromatic moiety (Table 1). Literature reports have also shown that the phenolic hydroxyl group is responsible for the antioxidant function [21,24] (Figure 3).

Table 1: Free radical scavenging activity of compounds [1–28].

Compounds	IUPC Names	R	IC_{50} ± SEM[a] (μM)
1	5-(4-Hydroxy-3,5-dimethoxybenzylidene)-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione		55.6 ± 2.1
2	5-(2-Bromo-4,5-dimethoxybenzylidene)-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione		198.2 ± 4.5
3	5-((2-Hydroxynaphthalen-1-yl) methylene)-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione		122.4 ± 1.9
4	5-(Thiophen-2-ylmethylene)-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione		NA
5	2-Thioxo-5-(3,4,5-trimethoxybenzylidene) dihydropyrimidine-4,6(1*H*,5*H*)-dione		132.6 ± 1.2
6	5-(4-(Methylthio)benzylidene)-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione		209 ± 4.4
7	5-((6-Bromo-4-chloro-2-oxo-2*H*-chromen-3-yl)methylene)-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione		322.4 ± 1.9
8	5-(Pyridin-4-ylmethylene)-2-thioxodihydropyrimidine-4,6 (1*H*,5*H*)-dione		179.7 ± 6.2
9	5-((6-Methylpyridin-2-yl)methylene)-2-thioxodihydropyrimidine-4,6 (1*H*,5*H*)-dione		211.2 ± 4.6
10	5-(4-Bromo-2,5-dimethoxybenzylidene)-2-thioxodihydropyrimidine-4,6 (1*H*,5*H*)-dione		204.5 ± 3.5
11	5-(3-Hydroxy-4-methoxybenzylidene)-2-thioxodihydropyrimidine-4,6 (1*H*,5*H*)-dione		107.65 ± 1.3

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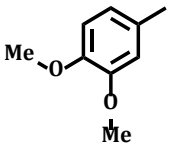
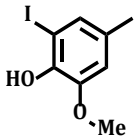
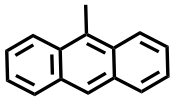
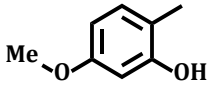
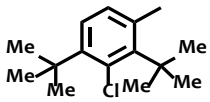
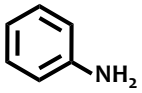
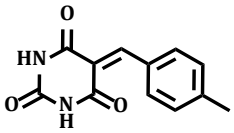
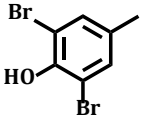
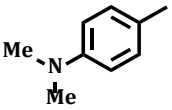
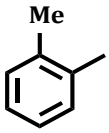
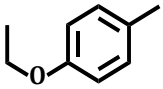
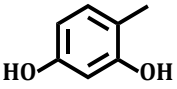
12	5-(3,4-Dimethoxybenzylidene)-2-thioxodihydropyrimidine-4,6 (1*H*,5*H*)-dione		170.4 ± 2.5
13	5-(4-Hydroxy-3-iodo-5-methoxybenzylidene)-2-thioxodihydropyrimidine-4,6 (1*H*,5*H*)-dione		108.4 ± 2.8
14	5-(Anthracen-9-ylmethylene)-2-thioxodihydropyrimidine-4,6 (1*H*,5*H*)-dione		NA
15	5-(2-Hydroxy-4-methoxybenzylidene)-2-thioxodihydropyrimidine-4,6 (1*H*,5*H*)-dione		284.2 ± 5.9
16	5-(2,4-Di-tert-butyl-3-chlorobenzylidene)-2-thioxodihydropyrimidine-4,6 (1*H*,5*H*)-dione		NA
17	5-(2-Aminobenzylidene)-2-thioxodihydropyrimidine-4,6 (1*H*,5*H*)-dione		NA
18	5,5'-(1,4-Phenylenebis(methanylylidene)) bis(2-thioxodihydropyrimidine-4,6 (1*H*,5*H*)-dione)		113.45 ± 1.130
19	5-(3,5-Dibromo-4-hydroxybenzylidene)-2-thioxodihydropyrimidine-4,6 (1*H*,5*H*)-dione		170.87 ± 1.34
20	5-(4-(Dimethylamino)benzylidene)-2-thioxodihydropyrimidine-4,6 (1*H*,5*H*)-dione		NA
21	5-(2-Methylbenzylidene)-2-thioxodihydropyrimidine-4,6 (1*H*,5*H*)-dione		438.3 ± 3.3
22	5-(4-Ethoxybenzylidene)-2-thioxodihydropyrimidine-4,6 (1*H*,5*H*)-dione		230.7 ± 2.6
23	5-(2,4-Dihydroxybenzylidene)-2-thioxodihydropyrimidine-4,6 (1*H*,5*H*)-dione		231.9 ± 6.9

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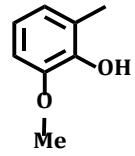
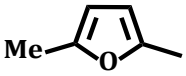
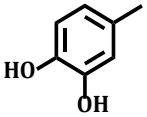
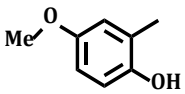
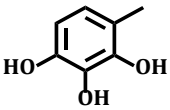
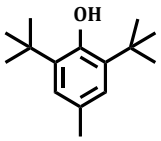
24	5-(2-Hydroxy-3-methoxybenzylidene)-2-thioxodihydropyrimidine-4,6 (1*H*,5*H*)-dione		200.6 ± 1.8
25	5-((5-Methylfuran-2-yl)methylene)-2-thioxodihydropyrimidine-4,6 (1*H*,5*H*)-dione		NA
26	5-(3,4-Dihydroxybenzylidene)-2-thioxodihydropyrimidine-4,6 (1*H*,5*H*)-dione		42.9 ± 3.605
27	5-(2-Hydroxy-5-methoxybenzylidene)-2-thioxodihydropyrimidine-4,6 (1*H*,5*H*)-dione		177.1 ± 3.6
28	2-Thioxo-5-(2,3,4-trihydroxybenzylidene) dihydropyrimidine-4,6(1*H*,5*H*)-dione		65.7 ± 1.80
BHT[b]	2,6-Di-tert-butyl-4-methylphenol		128.83 ± 2.1

[a]SEM is the standard error of the mean, BHT[b]: Butylated hydroxytoulene

Table 2: % Free radical scavenging activities of selected pyrimidine derivative.

Compounds	% Radical Scavenging Activity	Compounds	% Radical Scavenging Activity
1	91.58	15	70.64
2	89.25	16	2.61
3	89.85	17	1.52
4	13.45	18	75.84
5	90.43	19	81.95
6	78.00	20	19.29
7	62.01	21	53.44
8	74.35	22	70.78
9	73.81	23	81.96
10	75.00	24	81.72
11	79.85	25	15.54
12	90.76	26	84.07
13	89.95	27	81.36
14	34.92	28	74.69

% RSA: % Radical Scavenging Activity, Butylated hydroxytoulene (BHT) % RSA: 85.87.

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Compound **1** is the second most potent derivative among the series, containing 4-hydroxy-3,5-dimethoxy groups with IC_{50} of value 55.6 ± 2.1 µM, with corresponding 91.58% radical scavenging activity (Tables 1 & 2). With 74.69% radical scavenging activity derivative **28** with three hydroxyl groups at 2,3, and 4-positions, was found to be the third most effective derivative of the series (Tables 1 & 3). The lesser activity shown by analogue **28** as compared to compound **26** might be due to the extra hydroxyl group which creates some steric hindrance (Tables 1 & 2). In this study, we observed that all other hydroxyl group containing derivatives, such as **3**, **11**, **13**, **15**, **19**, **23** and **27,** also showed antioxidant activity. The lesser activity shown by analogue **28** as compared to compound **26** might be due to the extra hydroxyl group which creates some steric hindrance (Tables 1 & 2).

In this study, we observed that all other hydroxyl group containing derivatives, such as **3**, **11**, **13**, **15**, **19**, **23** and **27,** also showed antioxidant activity. The difference in their activity seems to be either due to the number, position, and presence of other substituents along with the hydroxyl group (Table 1). Compound **8,** and **12** have almost identical free radical scavenging activity with 74.3%, and 90.76 % (Table 2) (Figure 4). The moderate activity of compound 8 may be due to the lone pair of electrons on the pyridine nitrogen while in derivative **12,** due to the presence of two methoxy groups (Table 1). Compound **7**, and with (6-bromo-4-chloro-2-oxo-2*H*-chromen-3-yl) and (6-bromo-4-chloro-2-oxo-2 -chromen-3-yl) substitutions were found to be the least active of the series (Tables 1 & 2).

The anthranyl analogue **14**, di *tert*-butyl compound **16**, derivative **17** having aminobenzylidene, derivative **20** with dimethylamino group, methylfuryl molecule **25**, and thiophenyl derivative **4** did not show any antioxidant activity 4-Bromo-2,5-dimethoxy compound **10** and 2-bromo-4,5-dimethoxy analogue **2** have the same substituents but their positions are different, providing little difference in their activities (Table-1) (Figure 5). By changing the substituent from *p*-thiomethyl, as in analogue **6**, to an amino groups such as *N*, *N*-dimethyl amino derivative **19** and methyl-2-pyridinyl molecule **9**, it was observed the amino analogues showed greater radical scavenging activity than the one with *p*-thiomethyl and *N*, *N*-dimethyl amino functionalities. This might be due to the better ability of the former to provide free electrons (Tables-1, and 2).

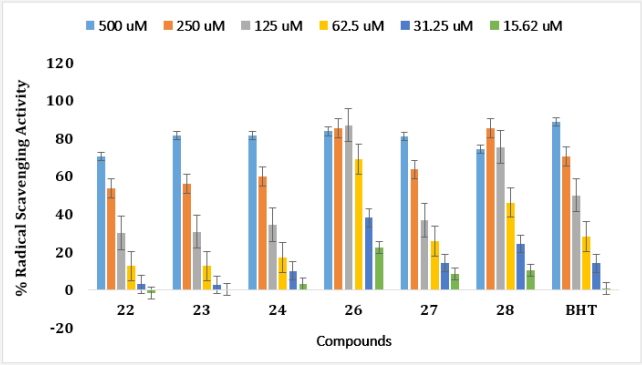

Figure 5: Concentrations dependent changes in free radical scavenging activities of pyrimidine derivatives [22–28].

Cell Cytotoxic Activity

Cytotoxicity of compounds **1**, **2**, **3**, **5**, **6**, **7**, **8**, **9**, **10**, **12**, **13**, **15**, **19**, **20**, **21**, **24**, **25**, **26** and **28** was carried out by using mouse fibroblast 3T3 cell line. Derivatives **1**, **3**, **5**, **6**, **8**, **9**, **12**, **13**, **15**, **19**, **21**, **24**, **25**, **26** and **28** exhibited non-cytotoxicity in mouse fibroblast 3T3 cell line (Table 3). Derivatives **7** and **20** were found to have weak cytotoxic effect with IC_{50} values of 27.038 ± 0.26, and 22.4 ± 0.76, µM, respectively. However, compound **2** was found to be moderately cytotoxic with IC_{50} value of 19.482 ± 0.406 µM, and only compound **10** was found to be cytotoxic with IC_{50} value of 7.038 ± 0.26 µM.

Table 3: Cytotoxicity studies of selected pyrimidine derivatives.

Compounds	Cell Cytotoxicity (3T3 cell line) IC_{50} (µM)± SEM	Compounds	Cell Cytotoxicity (3T3 cell line)IC_{50} (µM) ± SEM
1	>30	**12**	>30
2	19.482 ± 0.40	**13**	>30
3	>30	**15**	>30
5	>30	**19**	>30
6	>30	**20**	22.4 ± 0.768

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7	27.038 ± 0.26	**21**	>30
8	>30	**24**	>30
9	>30	**25**	>30
10	7.038 ± 0.26	**26**	>30
Cycloheximide	0.26 ± 0.1	**28**	>30

SEM: Standard Error Mean, Cycloheximide Standard Drug

Conclusion

The present study identifies new series of pyrimidines as potential radical scavengers. All analogues were found to display diverse free radical scavenging potential when compared with the standard butylated hydroxytoluene. Compounds **1**, **3**, **11**, **13**, **17**, **25**, and **27**, with IC_{50} values of 55.6 ± 2.1, 122.4 ± 1.9, 107.65 ±1.3, 108.4 ± 2.8, 113.4 ±1.3, 42. 9± 0.31, and 65.7 ± 1.80 µM, respectively, showed good free radical scavenging potential better than the standard butylated hydroxytoluene having IC_{50} value of 128.83 ± 2.1µM. Cytotoxic evaluation of selected derivatives further support our study. Compound **1**, **13**, and **25** were identified as non-cytotoxic against 3T3 cells; therefore, these can serve as lead compounds for further development as potential drug candidates to scavenge reactive oxygen species.

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