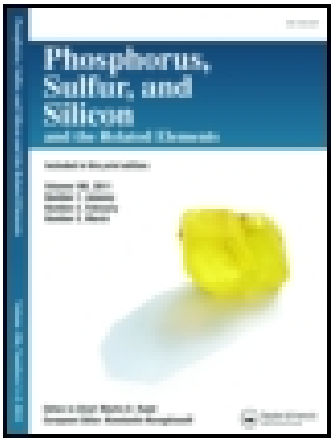

Phosphorus, Sulfur, and Silicon and the Related Elements

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Synthesis of Novel 4H-Chromenes Containing a Pyrimidine-2-Thione Function in the Presence of Fe_3O_4 Magnetic Nanoparticles and Study of Their Antioxidant Activity

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SYNTHESIS OF NOVEL 4*H*-CHROMENES CONTAINING A PYRIMIDINE-2-THIONE FUNCTION IN THE PRESENCE OF Fe_3O_4 MAGNETIC NANOPARTICLES AND STUDY OF THEIR ANTIOXIDANT ACTIVITY

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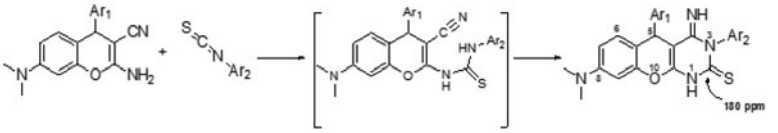
GRAPHICAL ABSTRACT



Abstract *The aim of the present work was to search for identification of novel reactive oxygen species (ROS) scavengers by testing new fused chromenopyrimidinethiones, which was synthesized using Fe_3O_4 nanoparticles. The new compounds were also tested for their cytotoxic activity. The obtained results showed that the incorporated pyrimidinethione moiety significantly increase antioxidant activity. In conclusion, the study of the pharmacological properties of the new chromenopyrimidinethiones allowed establishing new structure–activity relationships for splitting antioxidant and cytotoxic activity of these compounds.*

Keywords Fe_3O_4 nanoparticles; antioxidant; synthesis; cytotoxic activity; chromenopyrimidinethiones

INTRODUCTION

Nanotechnology has been one of the most active research areas in recent years.[1] The reactivity of catalytic nanoparticles is largely determined by the energy of surface

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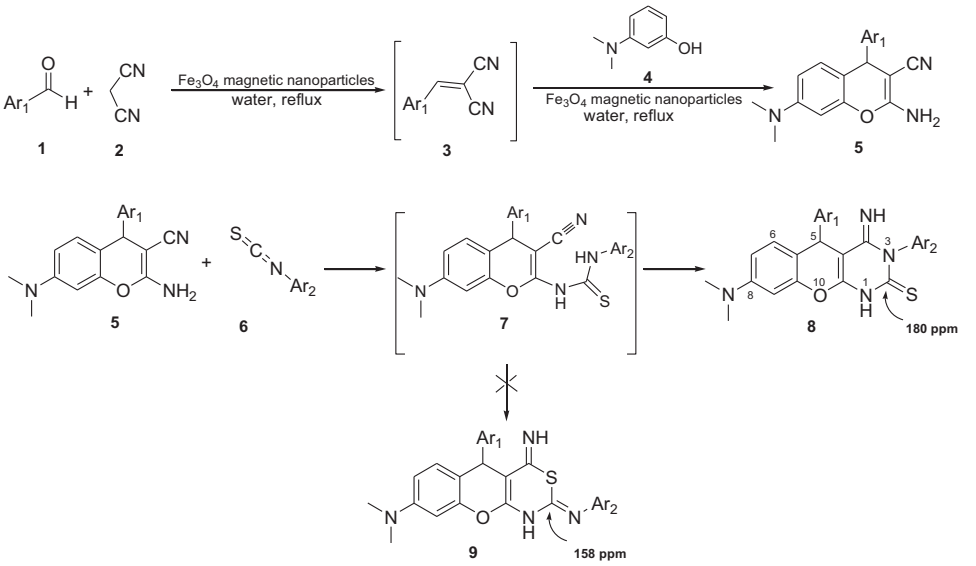
atoms, which can be easily gauged by the number of neighboring atoms and by the bonding modes and accompanying energies of small molecules to be transformed on the surfaces of nanoparticles.[1,2] Magnetic nanoparticles are a class of nanostructured materials of current interest, due to the largely advanced technology and medical applications, envisioned or realized. Among the various magnetic nanoparticles under investigation, Fe_3O_4 nanoparticles (Fe_3O_4 NPs) are arguably the most extensively studied.[3] The main characteristic of these nanoparticles is the simple and convenient separation from a reaction media by magnetic separation.[4,5] Recently, magnetite nanoparticles were used as an efficient catalyst in many organic transformations.[6–8]

Various reactive oxygen species (ROS), such as the hydroxyl radical and superoxide anion radical, have been known to induce lipid peroxidation as well as to damage membranes, proteins, and DNA. Enzymatic and nonenzymatic antioxidative defense systems can remove ROS under normal conditions. Oxidative stress, however, occurring when antioxidant systems are inadequate and/or active oxygen species are overproduced can damage the tissues and DNA, thus resulting in a progression of a number of human diseases such as atherosclerosis,[9] diabetes, inflammation, Alzheimer's disease, and senescence. Hence, antioxidants may stop the free-radical formation, or interrupt an oxidizing chain reaction.[10] This had attracted a great deal of research interest in therapeutic antioxidant-based drugs formulations. The development of synthetic compounds, capable of scavenging free radicals, has been a great success.[11]

The chromene (or benzopyran) moiety often appears as an important structural component in both biologically active and natural compounds. Chromene fragments occur in alkaloids, flavonoids, tocopherols, and anthocyanins.[12] Moreover, functionally substituted chromenes have played increasing roles in synthetic approaches to promising compounds in the field of biomedicinal chemistry. The current interest in 4*H*-chromene derivatives bearing a nitrile functionality arises from their potential application as antimicrobial,[13] antiviral,[14] antitumor[15] agents and in the treatment of human inflammatory TNF α-medicated diseases, such as rheumatoid and psoriatic arthritis and of cancer therapy.[16]

Previous studies showed that 2-amino-4*H*-chromene derivatives exert cytotoxic activity through the apoptosis induction mechanism.[17,18] Another study demonstrated the antioxidant activity of pyrimidine thione derivatives.[19] Thus, in continuation of a research program to find a novel anticancer drug,[20,21] in the present study we incorporate the pyrimidinethione moiety into 2-amino-4*H*-chromene scaffold in order to achieve new 4*H*-chromenes containing a pyrimidine-2-thione function and evaluation of their cytotoxic and antioxidant activities.

Development of clean technologies to replace hazardous materials in reaction media with environmentally friendly substances is an increasing interest in "green chemistry." Water is an obviously benign and inexpensive solvent to reduce pollution, cost, and tedious work-ups in synthetic methodologies. Bearing in mind the usefulness and efficiency of Fe_3O_4 NPs in organic reactions[22] and in connection with our previous works on evaluation of biological active compounds,[23,24] we decided to explore an application of Fe_3O_4 NPs for the preparation of 2-amino-4-aryl-4*H*-chromene-3-carbonitrile derivatives **5** with using multicomponent reaction[25] of **1**, **2**, and **4** (Scheme 1). Also, a novel series of chromenopyrimidinethione derivatives **8** were synthesized in order to develop novel antioxidant agents with low cytotoxicity activity.



Scheme 1 Synthetic method for the synthesis and atom numbering of chromenopyrimidinethiones **8**.

RESULTS AND DISCUSSION

Chemistry

As outlined in Scheme 1, compounds **8** could be easily prepared by a rather convenience one-pot, three-component reaction of an aromatic aldehyde **1**, malononitrile **2**, and 3-(dimethylamino)phenol **4** to afford the corresponding 2-amino-4-aryl-4*H*-chromene-3-carbonitrile **5** in high yields. The reaction was carried out in aqueous media under reflux condition using catalytic amounts of Fe_3O_4 magnetic nanoparticles (Fe_3O_4 MNPs) as a green, high-efficient and recoverable magnetic nanocatalyst for very short reaction time. This "one-pot" reaction protocol proceeds through formation of arylidenemalononitrile intermediate **3**. The catalytic performances of Fe_3O_4 MNPs were screened in aqueous media and solvent-free conditions. The results show that without the catalyst, 21% yields could be obtained after 10 h and water is a suitable accelerator of the reaction. A viscous mixture was obtained under solvent-free media, which cause to difficult dispersion and magnetic separation of the catalyst. Also, we noticed that reducing in the amount of the catalyst (5 mg) decreased the yield of the reaction and no significant improvement was obtained when the catalyst increased (see Table S1, Supplemental Materials). In the next step, the chromene **5** was treated with isothiocyanates **6** in various solvent and catalyst. Unfortunately, a mixture of product was obtained in the presence of DBU or DABCO as catalyst in several solvents, as well as separation and purification of the target product **8** was difficult (Table S1). Only in the presence of pyridine as solvent and catalyst under reflux condition, the target product was obtained without any byproduct, easily separated by simple filtration and purified from crystallization. All of products were appropriately characterized by spectral data. For example, compound **8c** was fully characterized by IR, ^{1}H, and ^{13}C NMR spectra and MS. The mass spectrum of **8c** displayed a molecular ion signal at *m/z* 486 and an ion signal at *m/z* 393 indicating the loss of the aniline group. In

the ^{1}H NMR spectrum of compound **8c**, in addition to the aromatic protons of chromene ring and those assigned to the phenyl rings (δ = 8.40–6.46 ppm), a sharp singlet due to hydrogen in the chromene moiety on 5 position (5.10 ppm) were observed. Also three singlets at 3.71, 3.67, and 2.89 ppm due to the two methoxy and dimethylamino groups were assigned, respectively. The most important absorption band of **8c** in the IR spectrum was detected at 3384 cm^{-1} and attributed to the N−H group stretching frequency. Absorption band at 1570 cm^{-1} was associated with the C=N stretching frequency. The ^{1}H decoupled ^{13}C NMR spectrum of **8c** showed 23 distinct signals. In this spectrum, the methine of the chromene moiety on 5 position resonated at δ = 87 and the signal for the C=S was observed at δ = 178 ppm, respectively. As indicated in Scheme 1, the corresponding chromenothiazine derivatives **9** could be achieved in the aqueous reaction media. These structures of compounds **8** and **9** can be easily distinguished by their ^{13}C NMR spectra. In compound **8**, C=S appeared around 180 ppm, while in compound **9**, C=N on 2 position should resonate around 158 ppm. Since in the product, no signal was detected around 180 ppm, compound **9** was consequently ruled out (see Scheme 1 and Table 1).

Biology

The antioxidant activities of the synthesized chromenopyrimidinethiones **(8a-l)** were evaluated by two in vitro methods in order to compare the results and to establish some structure antioxidant activity relationships for each method. The evaluation study was carried out at various concentrations and in comparison with the standard antioxidants. The DPPH radical scavenging activity assay is a simple method for measuring the antioxidant ability to trap free radicals. The scavenging effects of chromenopyrimidinethiones (**8a-l**)

Table 1 Synthesis of 2-amino-4-aryl-4H-chromene-3-carbonitrile derivatives **5** and chromenopyrimidinethiones **8**

Compounds	Ar_1	Ar_2	Yield (%)[a]	Time	mp	Ref.
5a	2,5-dimethoxyphenyl	—	78	30 min	126–128	26
5b	3,4-dimethoxyphenyl	—	73	35 min	159–161	26
5c	2,3-dimethoxyphenyl	—	80	45 min	107–109	26
5d	3,4,5-trimethoxyphenyl	—	71	30 min	182–184	26
5e	2-bromophenyl	—	68	50 min	199–201	26
5f	3- bromophenyl	—	73	45 min	177–179	26
5g	2,3-dichlorophenyl	—	77	50 min	207–208	26
8a	2,5-dimethoxyphenyl	2-bromophenyl	58	24 h	291–293	—
8b	2,5-dimethoxyphenyl	2-chlorophenyl	66	24 h	272–274	—
8c	3,4-dimethoxyphenyl	Ph	48	24 h	>300	—
8d	3,4-dimethoxyphenyl	2-chlorophenyl	59	24 h	288–290	—
8e	3,4-dimethoxyphenyl	2-bromophenyl	62	24 h	277–279	—
8f	3,4-dimethoxyphenyl	2-fluorophenyl	68	24 h	273–275	—
8g	2,3-dimethoxyphenyl	2-chlorophenyl	63	24 h	267–269	—
8h	2,3-dimethoxyphenyl	2-bromophenyl	54	24 h	224–226	—
8i	3,4,5-trimethoxyphenyl	2-fluorophenyl	71	24 h	280–282	—
8j	3,4,5-trimethoxyphenyl	2-bromophenyl	61	24 h	290–292	—
8k	3,4,5-trimethoxyphenyl	2-chlorophenyl	64	24 h	>300	—
8l	3,4,5-trimethoxyphenyl	Phenyl	72	24 h	>300	—

[a]Isolated yield.

are shown in Table S3 (Supplemental Materials). Two controls, ascorbic acid and trolox, are included. As shown in Table S3, all pyrimidinethione derivatives **8a-l** exhibited significant DPPH radical scavenging activity against their precursors with IC_{50} values less than 42 μg/mL. For example, a nine-fold enhancement in the radical scavenging activity of compound **5d** was observed by the addition of pyrimidinethione moiety to chromene scaffold in **8l**.

The ABTS assay is a widely used method for measuring the antioxidant ability to trap free radicals. The ABTS radical cation scavenging capacity of chromenopyrimidinethiones (**8a-l**) demonstrated all compounds have good antioxidant ability to trap free radicals. The IC_{50} values of synthesized compounds were in the range of 21.28–72.98 μg/mL. Among the chromenopyrimidinethiones, compound **8l** exhibited the most potent antioxidant activity in both DPPH and ABTS methods. Although compounds **8l** was not as potent as reference drug Trolox, but its antioxidant activity could be considered as attendant property of the title compound.

The IC_{50} values of target compounds **8** against PC3 and HepG2 cells in Table S3 revealed that all compounds showed no growth inhibitory activity ($IC_{50} > 100$ μg/mL) against two tested cell lines.

CONCLUSION

New chromene derivatives incorporating the pyrimidine thione moiety were synthesized. The new compounds were evaluated for the antioxidant and cytotoxic activity. The results showed that most of the chromenopyrimidinethiones had a high degree of potency in scavenging activity against the DPPH and ABTS radicals and showed no cytotoxic activity against cancer cell lines.

MATERIALS AND METHODS

Experimental

All commercially available reagents were used without further purification. Column chromatography was carried out on silica gel (70–230 mesh). TLC was conducted on silica gel 250 micron, F254 plates. Melting points were measured on a Kofler hot-stage apparatus and are uncorrected. The IR spectra were taken using Nicolet FTIR Magna 550 spectrographs (KBr disks). The morphological analysis by X-ray diffraction was performed on XPert MPD advanced diffractometer using Cu (K_α) radiation (wavelength: 1.5406 A°) at room temperature in the range of 2θ from 1 to 10° with a scanning rate of $0.02^\circ.S^{-1}$. The magnetic properties of samples were detected at room temperature using vibrating sample magnet—ometer (VSM, Lake Shore 7410). The particle size and morphology of the surfaces of Fe_3O_4 NPs[27] were analyzed by a scanning electron microscopy (VEGAII TESCAN) with an acceleration voltage of 15 kV. The disc was pasted with copper tape, and the sample was dispersed over the tape. The disc was coated with gold in an ionization chamber. ^{1}H NMR spectra were recorded on a Bruker 400 or 500 MHz NMR instruments. The chemical shifts (δ) and coupling constants (J) are expressed in parts per million and hertz, respectively. Mass spectra of the products were obtained with a HP (Agilent technologies) 5937 Mass Selective Detector. Elemental analyses were carried out by a CHN-Rapid Heraeus elemental analyzer. The results of elemental analyses (C, H, N) were within $\pm$0.4% of the calculated values.

Preparation of Fe_3O_4 Magnetic Nanoparticles. The coprecipitation method was used to prepare the Fe_3O_4 NPs:[28] $FeCl_3{\cdot}6H_2O$ (13.0 g) and $FeCl_2{\cdot}4H_2O$ (4.8 g) in a 1:2 molar ratio were dissolved in distilled water (200 mL) under nitrogen atmosphere with vigorous stirring. As the solution was heated to 70°C, $NH_3{\cdot}H_2O$ (28 wt%, 25 mL) was added dropwise to the solution under vigorous stirring and the reaction was allowed to proceed for 5 h at 70°C, and then the temperature was increased to 85°C to vapor the residual NH_3. A more complete characterization is presented in the Supplemental Materials (Figures S1–S4).

General Procedure for the Preparation of 2-Amino-4-aryl-4H-chromene-3-carbonitrile Derivatives 5. A mixture of an aromatic aldehyde **1** (1.0 mmol), malononitrile **2** (1.2 mmol), Fe_3O_4 MNPs (10.0 mg), and water (5 mL) was heated under reflux conditions for a few minutes to afford the corresponding intermediate **3**. To this stirred mixture, 3-(dimethylamino)phenol **4** (1.0 mmol) was added and the reaction mixture was refluxed for the length of time as indicated in Table S1 (Supplemental Materials). The progress of the reaction was monitored by TLC. After completion of the reaction, ethyl acetate was added and the catalyst was easily separated from the reaction mixture with an external magnet and washed twice with ethyl acetate. The combined organic layers were concentrated in vacuum and the resulting residue was purified by recrystallization from ethanol. Selected spectra for **8b** and **8g** are presented in the Supplemental Materials (Figures S5–S9).

General Procedure for the Preparation of Compounds 8. A mixture of appropriate *2-amino-4-aryl-4H-chromene-3-carbonitrile* ***5*** (1.0 mmol) and aryl isothiocyanate (12.0 mmol) in dry pyridine (15 mL) was refluxed for 24 h. The progress of reaction was followed by TLC. After completion of the reaction, the mixture was allowed to cool, washed twice with *n*-hexane and finally the resulting residue was purified by recrystallization from ethanol.

3-(2-Bromophenyl)-5-(2,5-dimethoxyphenyl)-8-(dimethylamino)-4-imino-3,4-dihydro-1H-chromeno[2,3-d]pyrimidine-2(5H)-thione (8a). White solid, Yield (52%), mp = 291–293°C; IR (KBr) (ν_{max}, cm^{-1}): 3372 (NH) and 1627 (C=N). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.88 (s, 6H, $N(Me)_2$), 3.62 (s, 6H, 2OMe), 5.21 (s, H_4 chromene), 6.44–6.87 (m, 6H, 3H chromene, and 3H phenyl), 7.38–7.68 (m, 4H, N-Ph). Anal. Calcd. for $C_{27}H_{25}BrN_4O_3S$ (565): C, 57.35; H, 4.46; N, 9.91. Found: C, 57.42; H, 4.10; N, 9.52%.

3-(2-Chlorophenyl)-5-(2,5-dimethoxyphenyl)-8-(dimethylamino)-4-imino-3,4-dihydro-1H-chromeno[2,3-d]pyrimidine-2(5H)-thione (8b). White solid, Yield (59%), mp = 272–274°C; IR (KBr) (ν_{max}, cm^{-1}): 3371 (NH) and 1630 (C=N). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.86 (s, 6H, $N(Me)_2$), 3.63 (s, 6H, 2OMe), 5.22 (s, H_4 chromene), 6.45–6.87 (m, 6H, 3H chromene, and 3H phenyl), 7.27–7.64 (m, 4H, N-Ph). ^{13}C NMR (125 MHz, $CDCl_3$): δ 55.2, 56.3, 56.5, 87.0, 99.2, 109.2, 109.9, 112.0, 113.3, 113.4, 115.4, 115.8, 129.0, 129.1, 130.7, 131.1, 133.1, 133.3, 135.7, 150.1, 150.3, 150.6, 153.2, 153.4, 160.6, 177.8. Anal. Calcd. for $C_{27}H_{25}ClN_4O_3S$ (521): C, 62.24; H, 4.84; N, 10.75. Found: C, 62.41; H, 5.02; N, 10.68%.

5-(3,4-Dimethoxyphenyl)-8-(dimethylamino)-4-imino-3-phenyl-3,4-dihydro-1H-chromeno[2,3-d]pyrimidine-2(5H)-thione (8c). White solid, Yield (40%), mp > 300°C; IR (KBr) (ν_{max}, cm^{-1}): 3384 (NH) and 1616 (C=N). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.86 (s, 6H, $N(Me)_2$), 3.63 (s, 6H, 2OMe), 5.22 (s, H_4 chromene), 6.46 (s, 1H, H_8 chromene), 6.51 (d, 1H, $J = 7.6$ Hz H_6 chromene), 6.74 (d, 1H, $J = 7.6$ Hz,

H_5 phenyl), 6.84 (d, 1H, $J = 7.6$ Hz, H_6 phenyl), 6.99 (s, 1H, H_2 phenyl), 7.00 (d, 1H, $J =$ 7.6 Hz, H_5 chromene), 7.03–8.40 (m, 5H, N-Ph). MS (EI, 70 eV): *m/z* (%) = 486 (100), 426 (35), 393 (41), 363 (52), 349 (58), 335 (23), 290 (76), 256 (73), 214 (64), 135 (20), 93 (29), 77 (23). Anal. Calcd. for $C_{27}H_{26}N_4O_3S$ (486): C, 66.65; H, 5.39; N, 11.51. Found: C, 66.42; H, 5.12; N, 11.68%.

3-(2-Chlorophenyl)-5-(3,4-dimethoxyphenyl)-8-(dimethylamino)-4-imino-3,4-dihydro-1H-chromeno[2,3-d]pyrimidine-2(5H)-thione (8d). White solid, Yield (52%), mp = 288–290°C; IR (KBr) (ν_{max}, cm^{-1}): 3372 (NH) and 1619 (C=N). ^1H NMR (500 MHz, $CDCl_3$): δ 3.13 (s, 6H, $N(Me)_2$), 3.67 (s, 6H, 2OMe), 5.13 (s, H_4 chromene), 6.45–6.98 (m, 6H, 3H chromene, and 3H phenyl), 7.29–7.64 (m, 4H, N-Ph). Anal. Calcd. for $C_{27}H_{25}ClN_4O_3S$ (521): C, 62.24; H, 4.84; N, 10.75. Found: C, 62.12; H, 4.73; N, 10.68%.

3-(2-Bromophenyl)-5-(3,4-dimethoxyphenyl)-8-(dimethylamino)-4-imino-3,4-dihydro-1H-chromeno[2,3-d]pyrimidine-2(5H)-thione (8e). White solid, Yield (57%), mp = 277–279°C; IR (KBr) (ν_{max}, cm^{-1}): 3373 (NH) and 1619 (C=N). ^1H NMR (500 MHz, $CDCl_3$): δ 2.88 (s, 6H, $N(Me)_2$), 3.66 (s, 6H, 2OMe), 5.14 (s, H_4 chromene), 6.46–6.99 (m, 6H, 3H chromene, and 3H phenyl), 7.39–7.78 (m, 4H, N-Ph). Anal. Calcd. for $C_{27}H_{25}BrN_4O_3S$ (565): C, 57.35; H, 4.46; N, 9.91. Found: C, 57.42; H, 4.42; N, 9.68%.

3-(2-Fluorophenyl)-5-(3,4-dimethoxyphenyl)-8-(dimethylamino)-4-imino-3,4-dihydro-1H-chromeno[2,3-d]pyrimidine-2(5H)-thione (8f). White solid, Yield (65%), mp = 273–275°C; IR (KBr) (ν_{max}, cm^{-1}): 3398 (NH) and 1617 (C=N). ^1H NMR (500 MHz, $CDCl_3$): δ 2.89 (s, 6H, $N(Me)_2$), 3.67 (s, 3H, OMe), 3.71 (s, 3H, OMe), 5.14 (s, H_4 chromene), 6.45–7.12 (m, 6H, 3H chromene, and 3H phenyl), 7.24–7.53 (m, 4H, N-Ph). Anal. Calcd. for $C_{27}H_{25}FN_4O_3S$ (504): C, 64.27; H, 4.99; N, 11.10. Found: C, 64.42; H, 5.02; N, 11.18%.

3-(2-Chlorophenyl)-5-(2,3-dimethoxyphenyl)-8-(dimethylamino)-4-imino-3,4-dihydro-1H-chromeno[2,3-d]pyrimidine-2(5H)-thione (8g). White solid, Yield (55%), mp = 267–269°C; IR (KBr) (ν_{max}, cm^{-1}): 3372 (NH) and 1627 (C=N). ^1H NMR (500 MHz, $CDCl_3$): δ 2.89 (s, 6H, $N(Me)_2$), 3.64 (s, 3H, OMe), 3.74 (s, 3H, OMe), 5.25 (s, H_4 chromene), 6.46–6.97 (m, 6H, 3H chromene, and 3H phenyl), 7.24–7.63 (m, 4H, N-Ph). Anal. Calcd. for $C_{27}H_{25}ClN_4O_3S$ (521): C, 62.24; H, 4.84; N, 10.75. Found: C, 62.42; H, 5.02; N, 10GPSS-2013-0279.68%.

3-(2-Bromophenyl)-5-(2,3-dimethoxyphenyl)-8-(dimethylamino)-4-imino-3,4-dihydro-1H-chromeno[2,3-d]pyrimidine-2(5H)-thione (8h). White solid, Yield (49%), mp = 224–226°C; IR (KBr) (ν_{max}, cm^{-1}): 3395 (NH) and 1615 (C=N). ^1H NMR (500 MHz, $CDCl_3$): δ 2.89 (s, 6H, $N(Me)_2$), 3.63 (s, 3H, OMe), 3.74 (s, 3H, OMe), 5.25 (s, H_4 chromene), 6.47–6.98 (m, 6H, 3H chromene and 3H phenyl), 7.24–7.78 (m, 4H, N-Ph). Anal. Calcd. for $C_{27}H_{25}BrN_4O_3S$ (565): C, 57.35; H, 4.46; N, 9.91. Found: C, 57.42; H, 4.42; N, 9.68%.

3-(2-Fluorophenyl)-5-(3,4,5-trimethoxyphenyl)-8-(dimethylamino)-4-imino-3,4-dihydro-1H-chromeno[2,3-d]pyrimidine-2(5H)-thione (8i). White solid, Yield (68%), mp = 280–282°C; IR (KBr) (ν_{max}, cm^{-1}): 3398 (NH) and 1617 (C=N). ^1H NMR (500 MHz, $CDCl_3$): δ 2.88 (s, 6H, $N(Me)_2$), 3.57 (s, 3H, OMe), 3.70 (s, 6H, 2OMe), 5.12 (s, H_4 chromene), 6.50–7.12 (m, 5H, 3H chromene and 2H phenyl), 7.30–7.52 (m, 4H, N-Ph). Anal. Calcd. for $C_{28}H_{27}FN_4O_4S$ (534): C, 62.91; H, 5.09; N, 10.48. Found: C, 62.42; H, 5.12; N, 10.68%.

3-(2-Bromophenyl)-5-(3,4,5-trimethoxyphenyl)-8-(dimethylamino)-4-imino-3,4-dihydro-1H-chromeno[2,3-d]pyrimidine-2(5H)-thione (8j). White solid, Yield (59%), mp = 290–292°C; IR (KBr) (ν_{max}, cm^{-1}): 3390 (NH) and 1616 (C=N). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.88 (s, 6H, $N(Me)_2$), 3.57 (s, 3H, OMe), 3.69 (s, 6H, 2OMe), 5.13 (s, H_4 chromene), 6.51–7.03 (m, 5H, 3H chromene, and 2H phenyl), 7.39–7.74 (m, 4H, N-Ph). Anal. Calcd. for $C_{28}H_{27}BrN_4O_4S$ (595): C, 56.47; H, 4.57; N, 9.41. Found: C, 56.42; H, 4.52; N, 9.61%.

3-(2-Chlorophenyl)-5-(3,4,5-trimethoxyphenyl)-8-(dimethylamino)-4-imino-3,4-dihydro-1H-chromeno[2,3-d]pyrimidine-2(5H)-thione (8k). White solid, Yield (61%), mp > 300°C; IR (KBr) (ν_{max}, cm^{-1}): 3389 (NH) and 1616 (C=N). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.88 (s, 6H, $N(Me)_2$), 3.57 (s, 3H, OMe), 3.70 (s, 6H, 2OMe), 5.13 (s, H_4 chromene), 6.46–7.13 (m, 5H, 3H chromene, and 2H phenyl), 7.34–7.64 (m, 4H, N-Ph). Anal. Calcd. for $C_{28}H_{27}ClN_4O_4S$ (551): C, 61.03; H, 4.94; N, 10.17. Found: C, 60.92; H, 5.02; N, 10.28%.

5-(3,4,5-Trimethoxyphenyl)-8-(dimethylamino)-4-imino-3-phenyl-3,4-dihydro-1H-chromeno[2,3-d]pyrimidine-2(5H)-thione (8l). White solid, Yield (42%), mp > 300°C; IR (KBr) (ν_{max}, cm^{-1}): 3390 (NH) and 1615 (C=N). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.88 (s, 6H, $N(Me)_2$), 3.58 (s, 3H, OMe), 3.71 (s, 6H, 2OMe), 5.12 (s, H_4 chromene), 6.46–7.03 (m, 5H, 3H chromene, and 2H phenyl), 7.12–7.54 (m, 5H, N-Ph). Anal. Calcd. for $C_{28}H_{28}N_4O_4S$ (516): C, 65.10; H, 5.46; N, 10.85. Found: C, 65.42; H, 5.32; N, 10.68%.

Biological Evaluation

Antioxidant Activity. *$ABTS^{\cdot+}$ radical scavenging assay*

ABTS radical scavenging activity was measured using the method of Pennycooke et al. with some modifications.[29] ABTS stock solution was prepared by reacting 7 mM 2,2′-azinobis(3-ethylbenzothiazoline-6-sulphonic acid) (ABTS) with 2.45 mM ammonium persulfate in dark at room temperature for 12–16 h.

DPPH radical scavenging assay

The DPPH free-radical scavenging activity of the synthetic compounds was assayed on the basis of Brand-William et al. with some modifications.[30]

Cytotoxicity Study. The in vitro anti-cancer activity of target compounds **8a-l** was determined against PC3 (prostate cancer cell lines) and HepG2 (human liver carcinoma) cells using MTT (3-(4,5- dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide method.[31] Additional details are provided in the Supplemental Materials.

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SUPPLEMENTAL MATERIAL

Supplementary data for this article can be accessed on the publisher's website, www.tandfonline.com/gpss

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