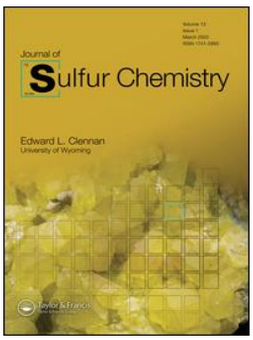

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Synthesis and antiproliferative assessments of new derivatives of isothiazolo[3,4-*d*]pyrimidine

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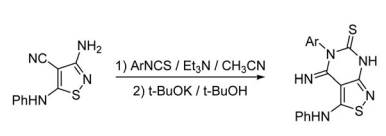
ABSTRACT

Various derivatives of 5-aryl-4-imino-3-(phenylamino)-4,5-dihydroi sothiazolo[3,4-*d*]pyrimidines (3a-f) were synthesized. The synthesis has been done through treatment of 3-amino-4-cyano-5-(phenyla mino)isothiazole with various aryl isothiocyanates. The isothiazole skeleton was obtained by the reaction of malononitrile and phenyl isothiocyanate followed by chloramine treatment. Some of the synthesized dihydroisothiazolo[3,4-*d*]pyrimidines were tested against different cancer cell lines, including ACHN, HeLa, HL-60, MCF-7, and PC3. Malignant cells were cultured in RPMI medium and incubated with different concentrations of the mentioned compounds. Cell viability was assessed using the MTS assay. The cytotoxicities of the synthesized compounds are not significant and are probably safe for other biological use.



Ar:	Yield
C_6H_5-	68%
3-Cl-C_6H_4-	54%
4-Cl-C_6H_4-	62%
4-Br-C_6H_4-	64%
4-F-C_6H_4-	43%
4-NO_2-C_6H_4-	67%

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KEYWORDS
Isothiazolo[4,3-*d*]pyrimidine; heterocyclization; aryl isothiocyanate; cytotoxicity; MTS assay

Introduction

Pyrimidines and isothiazolopyrimidines are two promising compounds that have been used for the synthesis of various compounds with a broad spectrum of biological activities [1,2]. Various synthetic methods for these compounds have been reported in the literature for use in studying such biological properties. For example, the condensation of aroyl halides with malononitrile yields an intermediate which is converted to isothiazolopyrimidine via treatment with PCl_5, diethyl dithiophosphate, and H_2O_2, respectively

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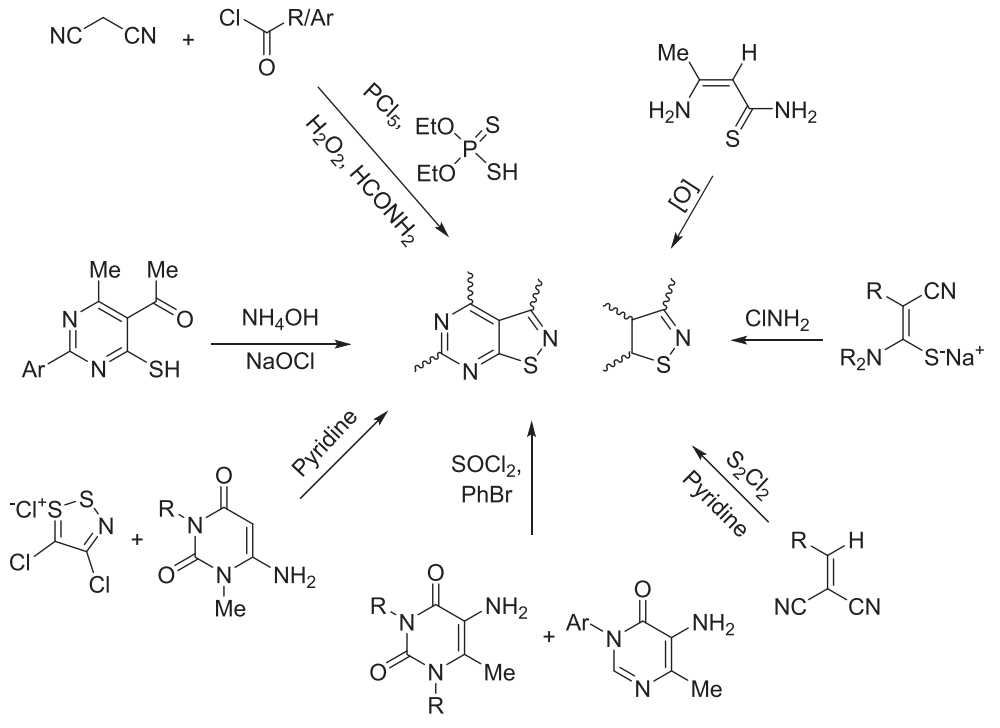
This paper is dedicated to Prof. Mehdi Bakavoli, who passed away in 2018.

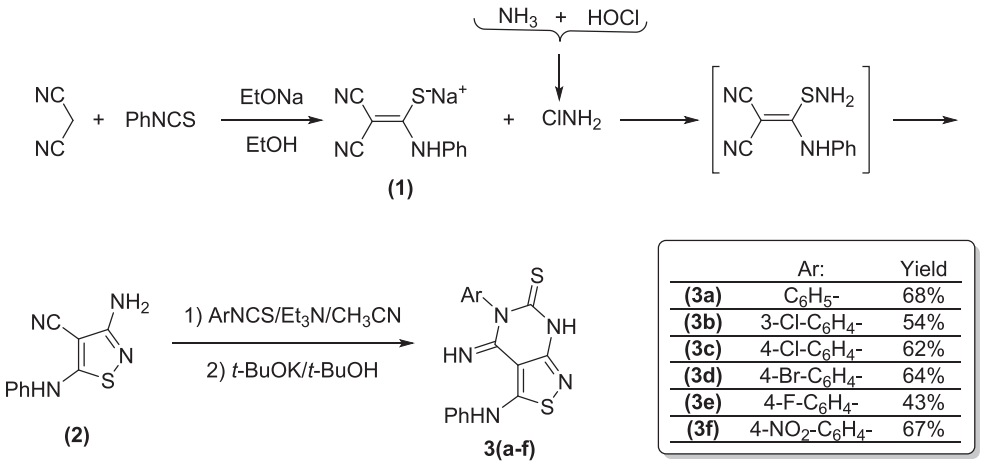


Scheme 1. Common synthetic routes to Isothiazolines and Isothiazolopyrimidines.

[3]. Other examples are the sulfonation and intramolecular cyclization of 4-mercapto-5-acetylpyrimidine derivatives[4], cyclization of 3-amino-3-mercaptoacrylonitriles [5], oxidative cyclization of β-aminothioamide [6], self-condensation reaction of 1,3-disubstituted 5-amino-6-methyluracil in bromobenzene [7], treatment of 6-amino-1,3-dialkyluracils with 4,5-dichloro-5*H*-1,2,3-dithiazolium chloride [8], and cyclization of arylmethylene-malononitriles with thionyl chloride in pyridine [9] (Scheme 1).

Biological applications of fused isothiazolopyrimidine are reported in the literature. For instance, they have been shown to have antimicrobial [10] and anti-HIV activity [11], and used as a tyrosine kinase receptor [3], and PDE7 inhibitors [12]. Such characteristics are well-known for pyrimidines and fused-pyrimidines [13–19]. It is noteworthy that isothiazole chemistry also has interesting biological implications [20] and new rational synthesis routes for the production of isothiazolopyrmidine moieties can are needed.

In continuation of our interests in the synthesis of potentially biological active heterocyclic compounds derived from pyrimidine and isothiazole scaffolds [21–24] we report in this study an efficient protocol for the synthesis of some new isothiazolo[3,4-*d*]pyrimidine derivatives. We also investigated the reaction with various aryl isothiocyanates. This report further describes an investigation of the possible cytotoxic effects of some of the synthesized isothiazoloprymidine moieties on five different malignant cancer cell lines including human breast cancer (MCF-7), human epithelial (HeLa), human prostatic cancer (PC3), human promyelocytic leukaemia (HL-60), and human kidney adenocarcinoma cell line (ACHN).



	Ar:	Yield
(3a)	C_6H_5-	68%
(3b)	3-Cl-C_6H_4-	54%
(3c)	4-Cl-C_6H_4-	62%
(3d)	4-Br-C_6H_4-	64%
(3e)	4-F-C_6H_4-	43%
(3f)	4-NO_2-C_6H_4-	67%

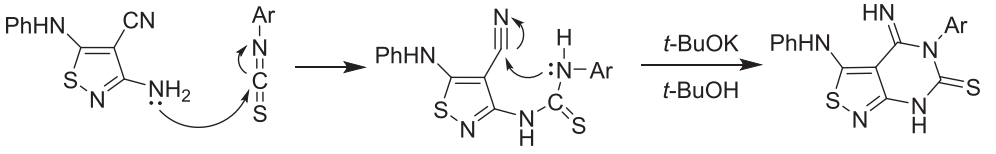
Scheme 2. Synthesis of 5-aryl-4-imino-3-(phenylamino)-4,5-dihydroisothiazolo[3,4-*d*]pyrimidine-6(7*H*)-thiones.

Results and discussion

Chemistry

The general synthetic strategy for the preparation of isothiazolopyrimidines is described in Scheme 2. The condensation of phenylisothiocyanate with malononitrile in the presence of EtONa/EtOH led to the formation of sodium 2,2-dicyano-1-(phenylamino)ethene-1-thiolate (1). Treatment of compound (1) with the mixture of NH_3 and HOCl (Chloramine) subsequently converted it to 3-amino-4-cyano-5-(phenylamino)isothiazole (2) [5]. The reaction of compound (2) with various aryl isothiocyanates in the presence of Et_3N and subsequent refluxing in *t*-BuOK/*t*-BuOH yielded the desired compounds (3a-f) (Scheme 2).

The proposed heterocyclization mechanism of the aryl isothiocyanates and 3-amino-4-cyano-5-(phenylamino)isothiazole (2) is shown in Scheme 3. The reaction starts with nucleophilic attack of NH_2 moiety of 3-amino-4-cyano-5-(phenylamino)isothiazole to arylisothiocyanate, followed by a proton exchange. Further cyclization completes via nucleophilic attack of NHAr to the nitrile substitution of isothiazole precursor. The structures of isothiazolo[3,4-*d*]pyrimidine 3(a-f) were confirmed from their spectral and microanalytical data. For example, the ^{1}H NMR spectrum of compound (3d) did not show the signal at $\delta = 5.82$ and 9.51 ppm, belonging to NH_2 and NH moiety of the precursor (2), respectively, but instead showed three singlet peaks at $\delta = 10.66$ (the NHPh group attached to isothiazole), 10.75 (the NH of imine group attached to pyrimidine ring), and 12.86 ppm (the NH of thioamide moiety on pyrimidine ring) in compound (3d) which disappeared when adding D_2O. Furthermore, the spectrum also showed the peaks in the aromatic region, confirming the presence of phenyl and *p*-Br-phenyl rings and the occurrence of heterocyclization. The aromatic proton nuclei of (3d) can be classified into two groups for each existing aromatic ring. The protons of phenyl group showed two multiplet signals at δ 7.03–7.25 ppm. The other two signals at δ 7.49 and 7.54 ppm with coupling constants of $J = 6.3$ Hz could be observed in the ^{1}H NMR spectrum for *p*-bromophenyl moiety. The



Scheme 3. The proposed mechanism of the synthesis of 5-aryl-4-imino-3-(phenylamino)-4,5-dihydroisothiazolo[3,4-*d*]pyrimidine-6(7*H*)-thiones.

IR spectrum was also devoid of the stretching vibration bands at 3446 and 3349 cm^{-1}, for the NH_2 moiety of the precursor. Instead, it converted to one band at 3394 cm^{-1} for the NH moiety. The molecular ion peaks of compound (3d) were observed at 429 (M^+) and 431 ($M^+ + 2$) corresponding to the molecular formula of $C_{17}H_{12}BrN_5S_2$.

Cell culture and cytotoxic assessments

ACHN, HL-60, MCF-7, and PC3 cancer cell lines were obtained from Pasteur Institute (Tehran, Iran) and maintained at 37°C in a humidified atmosphere (90%) containing 5% CO_2. All cell lines were cultured in Roswell Park Memorial Institute medium (RPMI) except ACHN which were cultured in Dulbecco's modified Eagle's medium (DMEM) with 5% (v/v) Fetal Calf Serum (FCS), 100 units/mL penicillin, and 100 μM streptomycin.

The protocol was the same as previously reported [25]. 5,000 cell/well (MCF-7, Hela, PC3, HL-60, and ACHN) were seeded in each well of 96-microwell plates overnight and then treated for 48 h with various concentrations (60, 125, and 250 µM) of some of the synthesized isothiazoloprymidine compounds. There was a control sample for each concentration and time course study, which remained untreated and received an equal volume of the medium. After incubation for 48 h, the MTS assay for cell viability measurement was done. Cell Titer 96® Aqueous One Solution Reagent (Promega, Madison, WI, USA), which is composed of the novel tetrazolium compound MTS and an electron coupling reagent phenazine methosulfate (PES, a redox intermediary) was added to each well according to the manufacturer's instructions. After two hours, cell viability was determined by measuring the absorbance at 490 nm using an ELISA microplate reader (Awareness, Palm City, FL, USA).

The results are presented in Table 1. Compounds (3a) and (3f) were insoluble in the medium. Hence, their antiproliferative characteristic measurement was difficult. The antiproliferative assessment of the other compounds, namely (3c), (3d), and (3e), demonstrated that the presence of halogens on the phenyl group has moderate effects on the toxicity of the mentioned compounds. The cytotoxic effects of the newly synthesized compounds on cell lines were not statistically significant. It could be because of their low solubility in the medium or low cytotoxic effect of the compounds.

Conclusion

This study reports a simple and efficient protocol for the synthesis of new derivatives of isothiazolo[3,4-d]pyrimidine through the intermediates formed by the reaction of 3-amino-4-cyano-5-(phenylamino)isothiazole (2) with various aryl isothiocyanates. The

Table 1. The dose-dependent growth inhibition of ACHN, PC3, MCF-7, and HL-60 cells by compounds (3c), (3d), and (3e) with various concentrations (60–250 µM) after 48 h. Viability was quantified by MTS assay. Results are mean ± SEM. Values are from at least three independent experiments, each in triplicates.[a]

		Concentration (µM)			
Cell line	Compound	C	60	125	250
ACHN	3c	100.0 ± 0.88	90.89 ± 1.27	92.78 ± 3.38	87.12 ± 1.49
	3d	100.0 ± 0.88	89.78 ± 3.82	82.90 ± 0.11	83.40 ± 0.55
	3e	100.0 ± 0.88	78.91 ± 4.66	76.80 ± 6.32	78.80 ± 3.32
pC3	3c	100.0 ± 2.038	110.67 ± 1.74	106.84 ± 1.60	96.99 ± 0.97
	3d	100.0 ± 2.038	110.97 ± 4.36	104.85 ± 6.01	95.92 ± 4.75
	3e	100.0 ± 2.038	98.68 ± 9.75	88.39 ± 1.31	79.22 ± 3.10
MCF7	3c	100 ± 0.26	104.92 ± 6.71	98.21 ± 3.56	102.88 ± 6.33
	3d	100 ± 0.26	105.38 ± 5.57	97.68 ± 2.27	97.15 ± 3.03
	3e	100 ± 0.26	96.81 ± 5.57	118.01 ± 3.33	109.36 ± 4.17
HL60	3c	100 ± 0.71	96.24 ± 3.04	101.5 ± 5.53	120.31 ± 4.189
	3d	100 ± 0.71	111.30 ± 4.26	109.44 ± 0.59	126.20 ± 3.28
	3e	100 ± 0.71	94.07 ± 6.56	107.53 ± 3.91	113.5 ± 3.63

[a]Bonferroni's Multiple comparisons.

results demonstrate that the cytotoxicity of newly synthesized halogenated compounds (3c), (3d), and (3e) on MCF-7, HeLa, PC3, HL-60, and ACHN cancer cell lines were moderate and these results can be of value for researchers who screen chemicals for potential cytotoxic activities or even other biological effects due to its low cytotoxicity.

Experimental

Instrumental

Melting points were measured by an Electrothermal type-9100 melting point apartus (Staffordshire, U.K.). The FT-IR spectra was recorded with Avatar 370 FT-IR Thermo Nicolet (Madison, WI) and only well-known absorptions were highlighted. ^{1}H-NMR (400 MHz) and ^{13}C-NMR (100 MHz) spectra obtained via Bruker Avance DRX-400 Fourier transformer spectrometer (Rheinstetten, Germany) and reported as downfield of tetramethylsilane internal reference with parts per million units. Varian Mat CH-7 (Palo Alto, CA) and Thermo Finnigan Flash EA microanalyzer (Milan, Italy) were utilized respectively to scanning mass spectra and elemental analysis.

Synthesis of 3-amino-4-cyano-5-(phenylamino)isothiazole (2)

Malononitrile (25 mmol, 1.65 g) was added to a stirred solution of (0.6 g Na in 25 ml absolute ethanol) and then placed in an ice bath. The solution was stirred for 10 min. Then, phenylisothiocyanate (25 mmol, 2.98 g) was added and stirred for 12 h at room temperature. Then, a solution of $ClNH_2$, which was prepared from the dropwise addition of NaOCl(aq) (2%, 300 ml) to NH_3 (25%, 50 ml) was added gradually and stirred at room temperature for 24 h. The mixture was neutralized by 10% HCl solution, and the resulting solid was filtered off and recrystallized in EtOH. The spectral data of the product was in accordance with the product which was prepared with a little modification following the previously published method [5].

General procedure for the synthesis of isothiazolo[3,4-d]pyrimidine (3a-f)

The appropriate isothiocyanate (1 mmol) was added to a stirred solution of compound (2) (1 mmol, 0.216 g) and Et_3N (1.5 mmol, 0.15 g) in CH_3CN (10 ml). The solution then refluxed for 12 h. The progress of the reaction was monitored by TLC using $CHCl_3$: MeOH (15:1). The solvent was evaporated under reduced pressure with a rotary evaporator and the resulting solid was filtered off, washed with water, and dried. The resulting solid was dissolved in a solution of potassium (1.5 mmol, 0.058 g) in t-BuOH (20 ml) and refluxed for 12 h. The solvent was removed under reduced pressure and neutralized with 10% HCl solution. The resulting solid was filtered off and recrystallized in DMF-water.

4,5-Dihydro-4-imino-5-phenyl-3-(phenylamino)isothiazolo[3,4-d]pyrimidine-6(7H) -thione (3a)

Yield = 68% (0.238 g, insoluble in water and chloroform, soluble in DMSO), mp = 308–310°C (decomposed), ^{1}H NMR (DMSO-d_6, ppm): δ 7.02–7.43 (m, 5H, PhH), 7.36–7.75 (m, 5H, PhH), 7.53 (br s, 1H, NHPh, D_2O exchangeable), 9.71 (br s, 1H, NH(thiouracil, HN=C−N), D_2O exchangeable), 13.35 (br s, 1H, NH(thiouracil, HN−C=S), D_2O exchangeable); ^{13}C NMR (DMSO-d_6, ppm): δ 177.5, 155.3, 157.2, 147.6, 136.9, 135.5, 128.5, 129.2, 128.7, 127.4, 123.4, 122.2, 117.4; IR (KBr disc) ν 3392 (N-H stretching), 3174 (N-H stretching), 3112, 1638 (C=N stretching), 1455, 1266 cm^{-1}; MS: *m/z*: 351 [M^+], 274 [M^+ - (C_6H_5)], 260 [M^+ - NHPh]. *Anal.* Calcd. for $C_{17}H_{13}N_5S_2$ (%): C, 58.10; H, 3.73; N,19.93; S, 18.25. Found: C, 58.01; H, 3.81; N.19.89; S, 18.47.

5-(3-Chlorophenyl)-4-imino-3-(phenylamino)-4,5-dihydroisothiazolo [3,4-d]pyrimidine-6(7H)-thione (3b)

Yield = 54% (0.208 g, insoluble in water and chloroform, soluble in DMSO), mp = 297–299°C (decomposed), ^{1}H NMR (DMSO-d_6, ppm) δ 7.03–7.44 (m, 5H, PhH), 7.19–7.68 (m, 4H, ArH), 10.70 (br s, 2H, NHPh and NH(thiouracil, HN=C−N), D_2O exchangeable), 12.89 (br s, 1H, NH(thiouracil, HN−C=S), D_2O exchangeable); ^{13}C NMR (DMSO-d_6, ppm): δ 179.6, 157.0, 156.2, 147.8, 139.9, 138.1, 135.3, 134.6, 131.1, 130.4, 129.5, 128.3, 123.4, 122.4, 117.8; IR (KBr disc) ν 3378 (N-H stretching), 3182 (N-H stretching), 3108, 1640 (C=N stretching), 1457, 1268 cm^{-1}; MS: *m/z*: 385 [M^+], 387 [$M^+ + 2$], 294 [M^+ - NHPh], 274 [M^+ - (3-Cl-C_6H_4)]. *Anal.* Calcd. For $C_{17}H_{12}ClN_5S_2$ (%) C, 52.91; H, 3.13; N, 18.15; S, 16.62. Found: C, 52.88; H, 3.10; N, 18.11; S, 16.59.

5-(4-Chlorophenyl)-4-imino-3-(phenylamino)-4,5-dihydroisothiazolo [3,4-d]pyrimidine-6(7H)-thione (3c)

Yield = 62% (0.239 g, insoluble in water and chloroform, soluble in DMSO), mp = 303–305°C (decomposed), ^{1}H NMR (DMSO-d_6, ppm) δ 7.02–7.44 (m, 5H, PhH), 7.24 (d, 2H, J = 6.7 Hz, ArH), 7.63 (d, 2H, J = 6.7 Hz, ArH), 10.71 (br s, 2H, NHPh and NH(thiouracil, HN=C−N), D_2O exchangeable), 12.88 (br s, 1H, NH(thiouracil, HN−C=S), D_2O exchangeable); ^{13}C NMR (DMSO-d_6, ppm): δ 176.3, 167.2, 154.5, 146.0, 140.2, 132.5, 130.1, 124.3, 123.8, 123.0, 122.2, 118.1, 116.2; IR (KBr disc) ν 3394 (N-H stretching), 3186

(N-H stretching), 3100, 1627 (C=N stretching), 1457, 1267 cm^{-1}; MS: *m/z*: 385 [M^+], 387 [$M^+ + 2$], 294 [M^+ - NHPh], 274 [M^+ - (4-Cl-C_6H_4)]. *Anal.* Calcd. For $C_{17}H_{12}ClN_5S_2$ (%) C, 52.91; H, 3.13; N, 18.15; S, 16.62. Found: C, 52.85; H, 3.10; N, 18.15; S, 16.60.

5-(4-Bromophenyl)-4-imino-3-(phenylamino)-4,5-dihydroisothiazolo [3,4-d]pyrimidine-6(7H)-thione (3d)

Yield = 64% (0.275 g, insoluble in water and chloroform, soluble in DMSO), mp = 309–311°C (decomposed), ^{1}H NMR (DMSO-d_6, ppm) δ 7.03–7.42 (m, 5H, PhH), 7.22 (d, 2H, J = 6.3 Hz, ArH), 7.63 (d, 2H, J = 6.3 Hz, ArH), 10.66 (br s, 1H, NHPh, D_2O exchangeable), 10.75 (br s, 1H, NH(thiouracil, HN=C−N), D_2O exchangeable), 12.86 (br s, 1H, NH(thiouracil, HN−C=S), D_2O exchangeable); ^{13}C NMR (DMSO-d_6, ppm): δ 176.6, 167.6, 153.9, 146.3, 139.7, 132.5, 130.4, 124.9, 124.6, 123.4, 122.7, 118.5, 116.3; IR (KBr disc) ν 3394 (N-H stretching), 3182 (N-H stretching), 3108, 1630 (C=N stretching), 1457, 1266 cm^{-1}; MS: *m/z*: 429 [M^+], 431 [$M^+ + 2$], 338 [M^+ - NHPh], 274 [M^+ - (4-Br-C_6H_4)]. *Anal.* Calcd. For $C_{17}H_{12}BrN_5S_2$ (%) C, 47.45; H, 2.81; N, 16.27; S, 14.90. Found: C, 47.55; H, 2.86; N, 16.66; S, 14.96.

5-(4-Fluorophenyl)-4-imino-3-(phenylamino)-4,5-dihydroisothiazolo [3,4-d]pyrimidine-6(7H)-thione (3e)

Yield = 43% (0.159 g, insoluble in water and chloroform, soluble in DMSO), mp = 311–313°C (decomposed), ^{1}H NMR (DMSO-d_6, ppm) δ 6.97–7.39 (m, 5H, PhH), 7.26–7.58 (m, 4H, ArH), 9.35 (br s, 1H, NHPh, D_2O exchangeable), 10.22 (br s, 1H, NH(thiouracil, HN=C−N), D_2O exchangeable), 12.88 (br s, NH(thiouracil, HN−C=S), D_2O exchangeable); ^{13}C NMR (DMSO-d_6, ppm): δ 175.6, 161.3, 157.0, 156.0, 147.7, 139.2, 136.0, 130.3, 129.3, 129.1, 123.5, 122.6, 117.7, 116.8; IR (KBr disc) ν 3390 (N-H stretching), 3186 (N-H stretching), 3112, 1640 (C=N stretching), 1489, 1266 cm^{-1}; MS: *m/z*: 369 [M^+], 278 [M^+ - NHPh], 274 [M^+ - (4-F-C_6H_4)]. *Anal.* Calcd. For $C_{17}H_{12}FN_5S_2$ (%) C, 55.27; H, 3.27; N, 18.96; S, 17.36. Found: C, 55.14; H, 3.24; N, 18.93; S, 17.36.

4,5-Dihydro-4-imino-5-(4-nitrophenyl)-3-(phenylamino)isothiazolo [3,4-d]pyrimidine-6(7H)-thione (3f)

Yield = 67% (0.266 g, insoluble in water and chloroform, soluble in DMSO), mp = 310–312°C (decomposed), ^{1}H NMR (DMSO-d_6, ppm) δ 7.10–7.59 (m, 5H, PhH), 8.14 (d, 2H, J = 8.2 Hz, ArH), 8.33 (d, 2H, J = 8.2 Hz, ArH), 10.65 (br s, 1H, NHPh, D_2O exchangeable), 11.02 (br s, 1H, NH(thiouracil, HN=C−N), D_2O exchangeable), 12.92 (br s, NH(thiouracil, HN−C=S), D_2O exchangeable); ^{13}C NMR (DMSO-d_6, ppm): δ 177.6, 168.6, 154.9, 147.3, 139.7, 133.5, 131.4, 125.9, 126.6, 124.4, 123.7, 119.5, 117.3; IR (KBr disc) ν 3390 (N-H stretching), 3178 (N-H stretching), 3105, 1637 (C=N stretching), 1335 cm^{-1}; MS: *m/z*: 396 [M^+], 305 [M^+ - NHPh], 274 [M^+ - (4-NO_2-C_6H_4)]. *Anal.* Calcd. For $C_{17}H_{12}N_6S_2O_2$ (%) C, 51.50; H, 3.05; N, 21.20; S, 16.18. Found: C, 51.29; H, 3.00; N, 20.93; S, 15.87.

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Disclosure statement

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

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