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# Synthesis, Reactions and Antioxidant Activity of 4,6-dimethyl-2-Substituted-nicotinonitrile Derivatives.

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**ABSTRACT**

A new derivatives of functionally 4,6-dimethyl-2-substituted-nicotinonitrile derivatives **4**, **6**, **7**, **8** and **9** were synthesized through condensation reaction of the key compound 2-((4-acetylphenyl)amino)-4,6-dimethylnicotinonitrile **(3)** with thiosemicarbazide followed by cyclization of the produced thiosemicarbazone with various α-halogenated carbonyl reagents. The structures of the newly synthesized compounds were confirmed by IR, $^{1}$H NMR, MS and elemental analyses. They were evaluated for their potential antioxidant activity by using ABTS Radical Cation Decolorization Assay. Among the tested compounds, **4** and **7** exhibited promising antioxidant activity against ABTS free radical.

**Keywords**: Nicotinonitrile, 4-aminoacetophenone, thiosemicarbazone, thiazole, thiazolidine-4-one, antioxidant activity.

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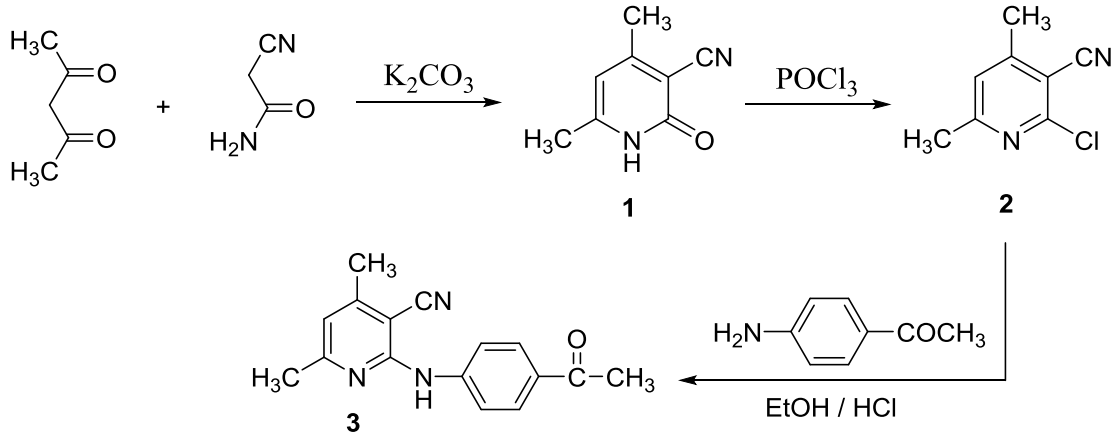
## INTRODUCTION

Due to their therapeutic and pharmacological properties [1–3], synthesis of pyridine ring system and its derivatives play an important place in organic synthesis. Also the pyridine ring is an integral part of anticancer and anti-inflammatory agents [4, 5]. On the other hand, pyridine-carbonitrile derivatives have promising antimicrobial [6] and anticancer activities [7]. The interest in nicotinonitrile and their derivatives is due to their wide range of practical uses as medicinal compounds. Recently, new pyridine-carbonitriles were reported as anti-inflammatory agents [8] and pyrazolopyridine derivatives have been recently reported as antitumor agents [9].

## RESULTS AND DISCUTION

In the present study, as shown in scheme (1), the target compound 2-chloro-4,6-dimethyl-nicotinonitrile **(2)** was prepared by treating the corresponding 3-cyano-4,6-dimethyl-2-pyridone **(1)** with phosphorous oxychloride according the previously reported method [10]. Halogenated heteroaromatic nitriles were available to nucleophilic aromatic substitution reactions ($S_N$-Ar). Amino-3-cyanopyridine derivatives were used as inhibitors for treating TNFα- mediated diseases in particular inflammations such as arthritis [11]. Therefore, the reaction of 2-chloro-4,6-dimethyl-nicotinonitrile **(2)** with 4-aminoacetophenone as amine was investigated. Refluxing of 2-chloro-4,6-dimethyl-nicotinonitrile **(2)** with 4-aminoacetophenone in ethanol containing few drops of concentrated HCl gave the corresponding 2-(*p*-acetylphenyl)amino-nicotinonitrile derivative **3**. This reaction was expected to introduce aminoaryl substituent at 2-position of pyridine ring as shown in scheme (1). The spectral data of the isolated product are in agreement with the assigned structure. For example, the $^1$H NMR spectrum of the isolated compound showed singlet signal at 9.32 ppm (NH), doublet signal at 7.89 ppm (2H, Ar-H), doublet signal at 7.74 ppm (2H, Ar-H), singlet signal at 6.88 ppm ($C_5$-H pyridine ring), two singlet signals at 2.51 and 2.37 ppm corresponding to $C_6$-$CH_3$ and $C_4$-$CH_3$ of pyridine ring, in addition to singlet signal at 2.37 ppm ($COCH_3$).




**Scheme 1**

The thiosemicarbazones comprise a class of molecules known for their diverse biological activities such as antimicrobial [12], antitumor [13-15], antileishmanial [16] and antiplasmodic [17] properties. In view of these observations and as a part of our ongoing search devoted to the synthesis of biologically active heterocycles we report herein synthesis of new thiosemicarbazone and its cyclized products as useful leads towards the development of potent antioxidant agents. Therefore, as shown in scheme (2), reaction of 2-((4-acetylphenyl)amino)-4,6-dimethylnicotinonitrile **(3)** with thiosemicarbazide in refluxing ethanol led to formation of the corresponding thiosemicarbazone derivative **4**. IR spectrum of compound **4** showed an absorption band at 2209 $cm^{-1}$ due to presence of cyano group (C≡N) with the absence of carbonyl group (C=O) absorption band. The mass spectrum of **4** showed a molecular ion peak at m/z = 338 (17.51 %) corresponding to the molecular weight of the molecular formula $C_{17}H_{18}N_6S$.

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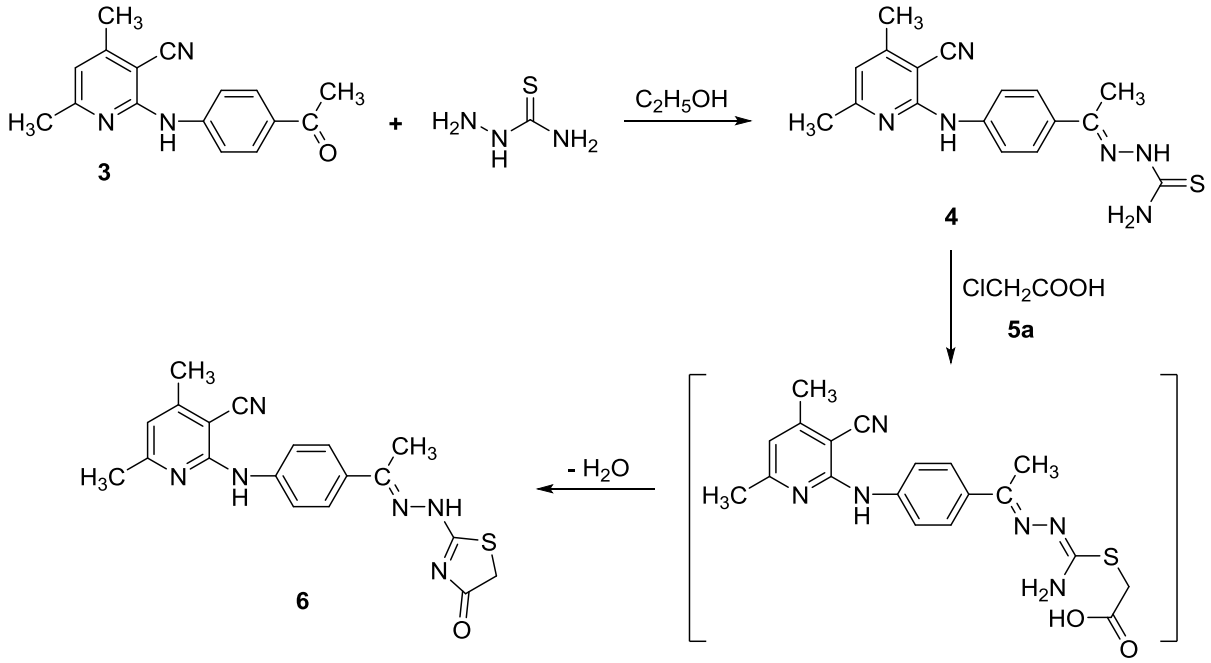
Previous studies have shown that the use of thiazole-based compounds as starting materials in organic synthesis led to the formation of several thiazole-derivatives with a wide spectrum of biological activities [18,19] such as antifungal [20,21], antimicrobial [22-24], antimalarial [25] and anticancer [26-32]. Furthermore, 4-thiazolidinones and their derivatives are an important class of compounds in organic and medicinal chemistry. The 4-thiazolidinone ring system is a core structure in various synthetic pharmaceutical agents, displaying a broad spectrum of biological activities [33] such as anti-tubercular [34] anti-convulsant [35] anti-cancer [36] anti-fungal [37] anti-inflammatory, and analgesic [38]. These observations have encouraged us to synthesis some new products containing the above-mentioned heterocyclic moiety hoping to obtain new biologically active compounds.

Next, we investigated the reactivity of thiosemicarbazone **4**, as it contains thiourea residue as a substituent, with different α-halogenated reagents. Thiosemicarbazone derivative **4** was utilized in the synthesis of poly functionally substituted thiazolidin-4-one or substituted-thiazole derivatives via cyclization with alkylating reagents. Thus, thiosemicarbazone **4** was cyclized with alkylating reagents **5a-d** (namely, chloroacetic acid **5a**, chloroacetone **5b**, phenacyl chloride **5c** and hydrazonoyl chloride **5d**) to form the non-isolable *S*-alkyalted intermediate via nucleophilic substitution followed by intramolecular cyclocondesation to give the corresponding polyfunctionally substituted thiazole derivatives **6-9** in good yield (Schemes 2 and 3).

Cyclization of thiosemicarbazone **4** with chloroacetic acid was achieved by reflux in acetic acid containing fused sodium acetate to furnish the corresponding thiazolidin-4-one derivative **6**. The suggested chemical structure of **6** elucidated on the basis of its correct elemental analysis and spectral data. The IR spectrum exhibited the absence of $NH_2$ band and displayed the characteristic absorption band at 1708 $cm^{-1}$ due to the carbonyl group of thiazolidine-4-one derivative **6**. The presence of methylene group of thiazolidine-4-one in compound **6** was demonstrated by $^1H$ NMR spectroscopy as a singlet signal at 3.85 ppm for two protons.




**Scheme 2**

In addition, heating of thiosemicarbazone **4** with α-chloroketone (namely, chloroacetone and phenacyl chloride) in ethanol containing drops of triethylamine afforded the corresponding 4-substituted-thiazole derivatives **7** and **8**. Spectroscopic data have been utilized to elucidate the chemical structure of such thiazole derivatives. The presence of $C_5$-H of thiazole ring in compound **7** was demonstrated by $^1H$ NMR spectroscopy which exhibited singlet signal at 6.56 ppm for one proton.

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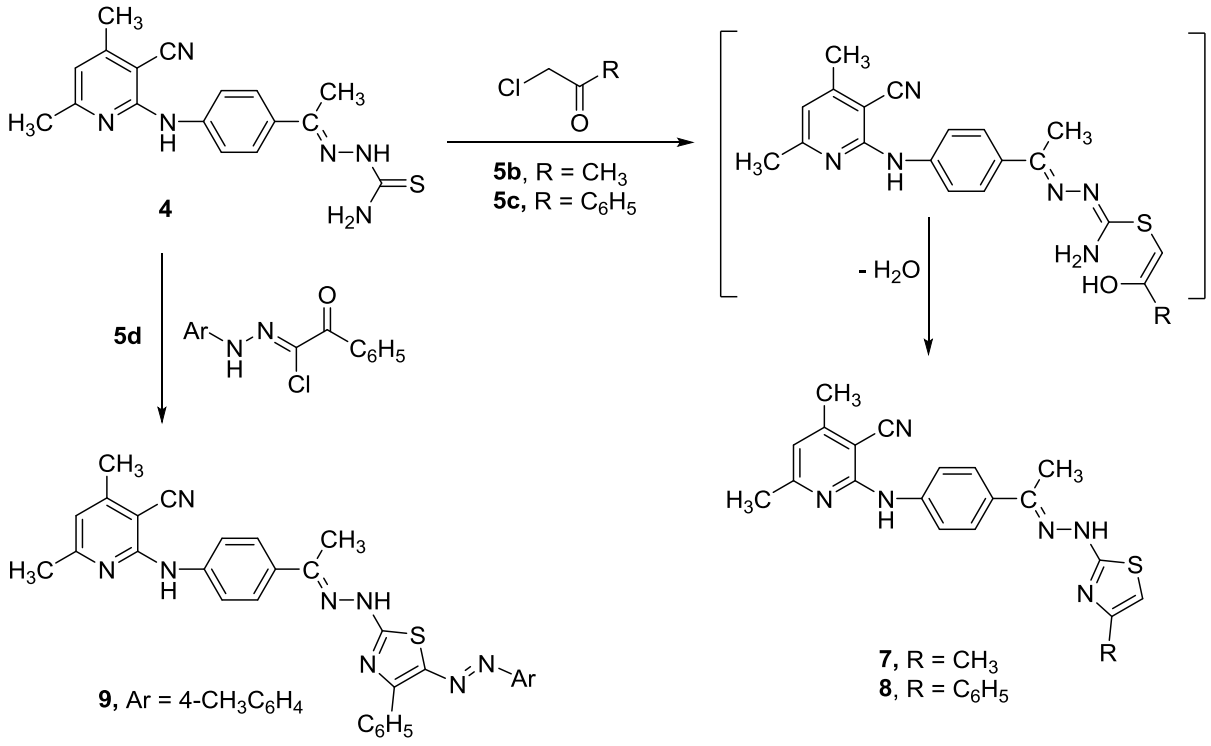
Finally, treatment of thiosemicarbazone **4** with 2-oxo-2-phenyl-*N*-(*p*-tolyl)-acetohydrazonoyl chloride **5d** in refluxing ethanol containing drops of triethylamine afforded the corresponding p-tolylazo-thiazole derivative **9** (Scheme 3). The assigned structure for the product was established as usual based on elemental and spectral (IR, $^1$H NMR, mass) data. The IR spectrum showed two absorption bands in the region 3347 and 3236 cm$^{-1}$ for two NH groups besides the cyano band at 2216 cm$^{-1}$. The $^1$H NMR spectrum revealed two singlet signals at 12.24 and 9.10 ppm due to the protons of two NH groups, multiplet in the region 8.03-7.24 ppm due to the aromatic protons, singlet at 6.88 ppm due to the proton of $C_5$-H pyridine-$C_5$ and four singlet signals at 2.54, 2.46, 2.38 and 2.32 ppm for the protons of four methyl groups.




**Scheme 3**

**Antioxidant Activity**

The newly synthesized nicotinonitrile derivatives **2, 3, 4, 6**, **7**, **8** and **9** were tested for their antioxidant activities by using ABTS Radical Cation Decolorization Assay [39,40]. The results (Table 1) indicated that most of the examined compounds exhibited weak to moderate antioxidant activity. Among the tested compounds, **4** and **7** displayed excellent antioxidant property (86.3%) and (80.0%) respectively. They were even very close to the standard inhibitor (L-Ascorbic acid 89.2%).

**Table 1: Antioxidant activity of the synthesized 4,6-dimethyl-2-substituted-nicotinonitriles**

| Method | ABTS<br>Abs(control)-Abs(test)/Abs(control)×100 | |
|---|---|---|
| **Compounds** | **Absorbance of samples** | **% Inhibition** |
| **Control of ABTS** | **0.510** | **0%** |
| **Ascorbic acid** | **0.055** | **89.2%** |
| **2** | 0.422 | 17.2% |
| **3** | 0.411 | 19.4% |
| **4** | 0.070 | 86.3% |
| **6** | 0.401 | 21.4% |
| **7** | 0.102 | 80.0% |
| **8** | 0.213 | 58.2% |
| **9** | 0.376 | 26.3% |

In conclusion, the current investigation has described the facile synthesis of antioxidant heterocyclic compounds containing sulphur and nitrogen and well characterized by spectroscopic methods such as IR, $^1$H NMR, mass spectra and elemental analyses. The results of the antioxidant activity of the newly synthesized compounds indicated that insertion of ring incorporated with the pyridine-3-carbonitrile moiety increasing the anti-oxidant activity (compound **7** is the best example).

## EXPERIMENTAL

All melting points were determined on Gallenkamp electric melting point apparatus and being incorrect. The IR spectra were recorded using FT-IR spectrometer (Thermo Scientific Nicolet iS 50) in KBr disks, microanalysis unit, Chemistry Department, Faculty of Science, Mansoura University. The $^1$H NMR spectra were measured on a Varian Spectrophotometer at 300 MHz, using TMS as an internal reference and $CDCl_3$ or DMSO-$d_6$ as solvent at the Chemistry Department, Faculty of Science, Cairo University. Elemental analyses were carried out at Microanalysis Center, Faculty of Science, Cairo University. All Reactions were monitored by thin layer chromatography (TLC) using silica gel (GF 254) coated plates with visualization by irradiation with ultraviolet lamp. Compounds **1** and **2** were prepared as previously reported [10], hydrazonoyl chloride **5d** was prepared as previously reported [41].

**Synthesis of 2-((4-acetylphenyl)amino)-4,6-dimethylnicotinonitrile (3):**

A mixture of 5 mmol (0.82 g) of compound **2** [10a] and 5 mmol (0.67 g) of 4-aminoacetophenone in ethanol (20 mL) and concentrated HCl (1 mL) was subjected to reflux during 6 h. The reaction progress was monitored by TLC. After complete reaction, the reaction mixture was allowed to cool and the formed solid precipitate was collected by filtration to give compound **3**.

Light brown powder; yield = 82%; m.p. = 160-162 °C. IR ($\bar{\nu}$ /cm$^{-1}$): 3320 (NH), 2210 (C≡N), 1667 (C=O). $^1$H NMR (DMSO-$d_6$): δ /ppm = 9.32 (s, 1H, NH), 7.89 (d, 2H, Ar-H), 7.74 (d, 2H, Ar-H), 6.88 (s, 1H, $C_5$-H pyridine), 2.51 (s, 3H, $CH_3$), 2.41 (s, 3H, $CH_3$), 2.37 (s, 3H, $CH_3$). MS (EI): m/z (%) = 265 ($M^+$, 55.87%), 250 ($M^+$ - $CH_3$, 100.0%), 222 ($M^+$ - $COCH_3$, 31.04%), 134 ($M^+$ - NH-$C_6H_4$-$COCH_3$, 4.10%). Anal. Calcd. for $C_{16}H_{15}N_3O$ (265.32): C, 72.43; H, 5.70; N, 15.84%; found: C, 72.63; H, 5.55; N, 15.94%.

**Synthesis of 2-(1-(4-((3-cyano-4,6-dimethylpyridin-2-yl)amino)phenyl)ethylidene)-hydrazine-1-carbothioamide (4):**

To a solution of substituted aminoacetophenone derivative **3** (2.65 g, 10 mmol) in absolute ethanol (20 mL), thiosemicarbazide (0.91 g, 10 mmol) was added. The reaction mixture was refluxed for 4 h and then cooled to room temperature. The solid precipitate was filtered and washed with ethanol to afford the target compound **4** in pure state.

Orange powder; yield = 65 %; m.p. = 241-242 °C. IR ($\bar{\nu}$ /cm$^{-1}$): 3383, 3261 ($NH_2$), 3168 (NH), 2209 (C≡N), 1600 (C=N), 1086 (C=S). MS (EI): m/z (%) = 338 ($M^+$, 17.51%), 321 ($M^+$ - $NH_2$, 62.75%), 278 ($M^+$ - $CSNH_2$, 11.32 %), 263 ($M^+$ - $NHCSNH_2$, 100 %), 248 ($M^+$ - $NNHCSNH_2$, 31.81 %). Anal. Calcd. for $C_{17}H_{18}N_6S$ (338.43): C, 60.33; H, 5.36; N, 24.83%; found: C, 60.12; H, 5.43; N, 24.61%.

**Synthesis of 4,6-dimethyl-2-((4-(1-(2-(4-oxo-4,5-dihydrothiazol-2-yl)hydrazono)ethyl)-phenyl)-amino)-nicotinonitrile (6):**

A mixture of thiosemicarbazone **4** (0.68 g, 2 mmol), chloroacetic acid (0.19 g, 2 mmol), fused sodium acetate (0.5 g) in 15 mL acetic acid was heated under reflux with stirring for 4 h. After cooling at room temperature, the reaction mixture was poured into ice-cooled water and the precipitate that formed was filtered off and purified by recrystallization from ethanol.

Yellow crystals; yield = 65 %; m.p. = 255-256 °C. IR ($\bar{\nu}$ /cm$^{-1}$): 3421 (NH), 3139 (NH), 2197 (C≡N), 1708 (C=O), 1612 (C=N). $^1$H NMR ($CDCl_3$): δ /ppm = 11.87 (s, 1H, NH), 9.08 (s, 1H, NH), 7.78 (d, 2H, Ar-H), 7.68 (d, 2H, Ar-H), 6.81 (s, 1H, $C_5$-H pyridine), 3.85 (s, 2H, $CH_2$ thiazolidine), 2.49 (s, 3H, $CH_3$), 2.40 (s, 3H, $CH_3$), 2.35 (s, 3H, $CH_3$). MS (EI): m/z (%) = 378 ($M^+$, 100.00%), 363 ($M^+$ - $CH_3$, 31.69%), 263 ($M^+$ – NH – thiazolidine, 34.33 %), 249 ($M^+$ - NNH - thiazolidine, 52.24%), 247 ($M^+$ - 4,6-dimethylpyridine-3-carbonitrile, 29.46), 223 ($M^+$ - NNH - thiazolidine

- CN, 25.73 %), 131 (4,6-dimethylpyridine-3-carbonitrile, 33.29). Anal. Calcd. for $C_{19}H_{18}N_6OS$ (378.45): C, 60.30; H, 4.79; N, 22.21%; found: C, 60.24; H, 4.72; N, 22.26%.

**Synthesis of 4-substituted-thiazole derivatives 7, 8 and 9:**

A mixture of thiosemicarbazone **4** (0.68 g, 2 mmol) and the corresponding α-chloroketone (namely: chloroacetone **5b**, phenacyl chloride **5c** or hydrazonoyl chloride **5d**) (2 mmol) was refluxed for 4 h in 25 mL ethanol containing five drops of triethylamine. After cooling the solution back to room temperature, the solid products were filtered off and purified by recrystallization from ethanol.

**4,6-Dimethyl-2-((4-(1-(2-(4-methylthiazol-2-yl)hydrazono)ethyl)phenyl)amino)-nicotinonitrile (7):**

Yellow crystals; yield = 62 %; m.p. = 260-261 °C. IR ($\bar{\nu}$ /cm$^{-1}$): 3338 (NH), 3214 (NH), 2210 (C≡N), 1614 (C=N). $^1$HNMR (DMSO-$d_6$): δ /ppm = 11.94 (s, 1H, NH), 9.08 (s, 1H, NH), 7.85 (d, 2H, Ar-H), 7.69 (d, 2H, Ar-H), 6.88 (s, 1H, $C_5$-H pyridine), 6.56 (s, 1H, $C_5$-H thiazole), 2.49 (s, 3H, $CH_3$), 2.40 (s, 3H, $CH_3$), 2.37 (s, 3H, $CH_3$), 2.14 (s, 3H, $CH_3$). MS (EI): m/z (%) = 375 ($M^+$ - 1, 22.13%), 361 ($M^+$ - $CH_3$, 31.69%), 263 ($M^+$ – NH–thiazole–$CH_3$, 100 %), 248 ($M^+$ - NH–thiazole – 2$CH_3$, 78.20%), 222 ($M^+$ - NH–thiazole – CN - 2$CH_3$, 89.80 %). Anal. Calcd. for $C_{20}H_{20}N_6S$ (376.48): C, 63.81; H, 5.35; N, 22.32%; found: C, 63.92; H, 5.39; N, 22.22%.

**4,6-Dimethyl-2-((4-(1-(2-(4-phenylthiazol-2-yl)hydrazono)ethyl)phenyl)amino)-nicotinonitrile (8):**

Orange crystals; yield = 65 %; m.p. = 286-287 °C. IR ($\bar{\nu}$ /cm$^{-1}$): 3319 (NH), 2209 (C≡N), 1615 (C=N). MS (EI): m/z (%) = 438 ($M^+$, 100.00%), 263 ($M^+$ – NH–thiazole–$C_6H_5$, 84.28 %), 248 ($M^+$ - NH–thiazole–$C_6H_5$ - $CH_3$, 50.41%), 222 ($M^+$ - NH–thiazole – CN - $C_6H_5$ - $CH_3$, 57.72 %), 189 (NNH–thiazole–$C_6H_5$, 46.38 %), 175 (NH–thiazole–$C_6H_5$, 56.98%). Anal. Calcd. for $C_{25}H_{22}N_6S$ (438.55): C, 68.47; H, 5.06; N, 19.16%; found: C, 68.62; H, 5.16; N, 19.22%.

**4,6-Dimethyl-2-((4-(-1-(2-(4-phenyl-5-(*p*-tolylazo)thiazol-2yl)hydrazono)ethyl)- phenyl)amino)-nicotinonitrile (9):**

Red powder; yield = 62 %; m.p. = 295-297 °C. IR ($\bar{\nu}$ /cm$^{-1}$): 3347, 3236 (2 NH), 2216 (C≡N), 1652 (C=N), 1536 (N=N). $^1$HNMR (DMSO-$d_6$): δ /ppm = 12.24 (s, 1H, NH), 9.10 (s, 1H, NH), 8.03-7.24 (m, 13H, Ar-H), 6.88 (s, 1H, $C_5$-H pyridine), 2.54 (s, 3H, $CH_3$), 2.46 (s, 3H, $CH_3$), 2.38 (s, 3H, $CH_3$), 2.32 (s, 3H, $CH_3$). Anal. Calcd. for $C_{32}H_{28}N_8S$ (556.69): C, 69.04; H, 5.07; N, 20.13%; found: C, 69.22 ; H, 5.15; N, 20.21%.

**Antioxidant Activity Screening Assay by the ABTS Method**

This assay employs the radical cation derived from 2,2'-azinobis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) as stable free radical. The advantage of ABTS-derived free radical method over other methods is that the produced color remains stable for more than 1 h and the reaction is stoichiometric [39,40]. By screening our reported compounds in this work for antioxidant activity by the latter method. For each of the investigated compounds (2 mL) of ABTS solution (60 µM) was added to 3 mL $MnO_2$ solution (25mg/mL), all prepared in (5 mL) aqueous phosphate buffer solution (pH 7, 0.1 M). The mixture was shaken, centrifuged, filtered and the absorbance of the resulting green blue solution (ABTS radical solution) at 734 nm was adjusted to approx. ca. 0.5. Then, 50 µl of (2 mM) solution of the tested compound in spectroscopic grade MeOH/phosphate buffer (1:1) was added. The absorbance was measured and the reduction in color intensity was expressed as inhibition percentage. L–Ascorbic acid was used as standard antioxidant (Positive control). Blank sample was run without ABTS and using MeOH/phosphate buffer (1:1) instead of tested compounds. Negative control was run with ABTS and MeOH/phosphate buffer (1:1) only [42,43].

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