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# Synthesis and Antioxidant activity of some novel pyridine derivatives.

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**Abstract** Synthesis of 2-amino-4-(furan-2-yl)-5,6-dimethylnicotinonitrile **4** was achieved from the mixture of malononitrile **1**, furan-2-carboxaldehyde **2,** butan-2-one **3** and ammonium acetate in ethanol. Compound **4** reacted with formamid , formic acid and acetic anhydride furnished pyrido[2,3-d]pyrimidine derivaive **5** , pyridine derivatives **6** and **7** ,respectively. Reaction of **6** with $P_2S_5$ afforded pyridine derivative **8**. Reaction of **4** with urea or with thioured afforded **9** and **10,** respectively. Refluxing of **4** with urea in glacial acetic acid and hydrochloric acid afforded the diaminopyrimidine derivative **11.** Reaction of **4** with butanone or with acetylacetone furnished 1,8-naphthyridine derivatives **12** and **13,** respectively. Fusion of **4** with cyanoacetamide afforded the 2-oxo-1,8-naphthyridine derivative **14.** Condensation of **4** with 5,5-dimethyl-1,3-cyclohexanedione or cyclohexanone in ethanol furnished the pyridine derivatives **16** and **17,** respectively **.** Refluxing of **4** with ethylene diamine , carbon disulfide and concentrated sulfuric acid afforded 4,5-dihydro-1H-imidazol-2-yl pyridine derivative **19**, **20** and **21,** respectively**.** The reaction of **4** with phenacylchloride or with ethylchloroacetate 1-phenyl3-(pipridin-1-yl)propan-1-one hydrochloride in glacial acetic acid afforded pyridine derivatives **22, 23** and **24,** respectively. The structure of synthesized compounds was characterized by spectral data and elemental analyses. The new compounds were screened for antioxidant activity, whereas, some of them exhibited promising activities.

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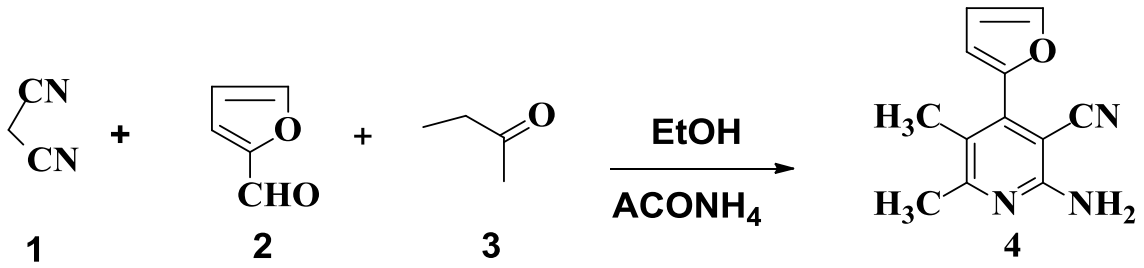
## Introduction

Pyridine derivatives have occupied a unique position in the field of medicinal chemistry. Many naturally occurring compounds having pyridine moiety show interesting biological and pharmacological activities (Purushothaman, *et. al.*, 2012). Pyridine derivatives have been used as herbicides(Temple, *et. al*,1992), for enrichment of cereals (Budgentt, *et. al*, 1947), for regulation of arterial pressure (Mericier, *et. al.*, 1963) and cholesterol levels in blood (Doner, *et. al.*,1961). Some of pyridines constitute an important class of antitumor compounds (Boger, *et. al.*, 1991) and (Boger, *et. al.*, 1989 and Zhang, *et. al*, 1995). 2-amino-3-cyanopyridines have been identified to possess anti bacterial (Konda, *et. al.*, 2010), anti-microbial (Mungra, *et. al*, 2009), (Altalbawy, 2013), antifungal (Makawana, *et. al.*, 2012), cardiotionic (Bekhit, *et. al.*, 2005), analgesic

(Murata, *et. al.*, 2003), anti-inflammatory (Al-Said, *et. al.*, 2011) and anti lung cancer (Shi, *et. al.*, 2005) activities. Pyridine derivatives have also been found to be selective IIK –β serin-threonine protein kinase inhibitors (Altundas, *et. al.*, 2011) . Recently , many synthetic methods have been used for the preparation of 2-amino-3-cyanopyridine derivatives (Davoodnni, *et, al.*, 2010), (Tavakoli-Hoseini, *et. al,* 2010) and (Gupta, *et. al,* 2010).

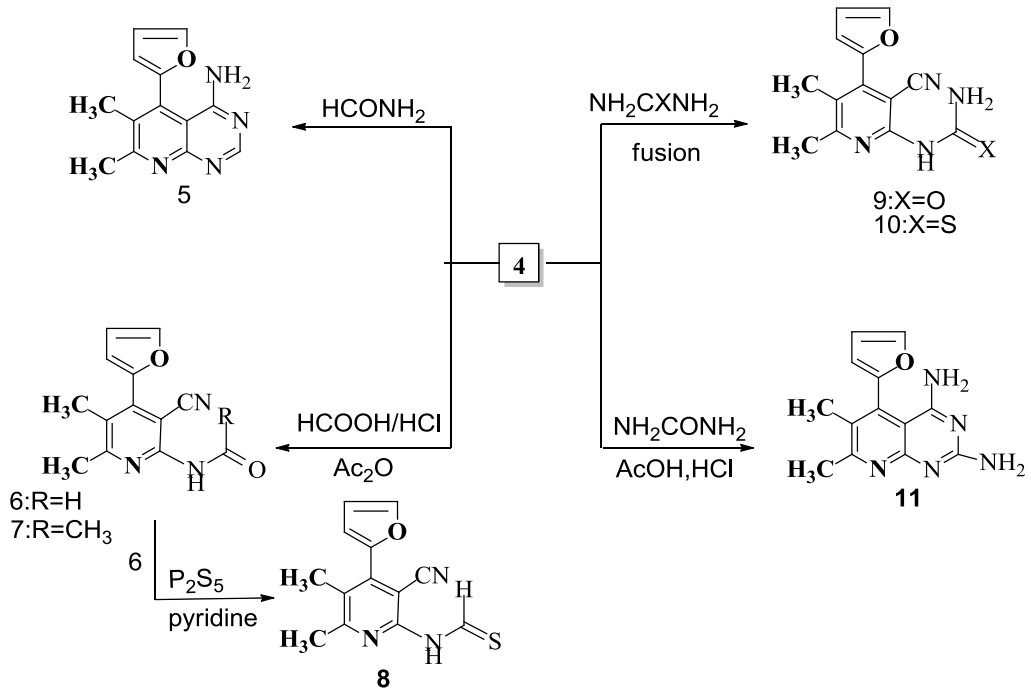
**Results and Discussion**

It has been reported that , 2-amino-4-(furan-2-yl)-5,6-dimethylnicotinonitrile **4** was obtained with high yield and purity *via* a One-pot condensation of malononitrile **1**, furan-2-carboxaldehyde **2,** butan-2-one **3,** and ammonium acetate in ethanol(Mahmoud. *et. al.*, 2013)**(Scheme1).** Furthermore, compound **4** was used as a key intermediate for the synthesis of pyrimidine, quinoline, imidazole and pyridine derivatives. We reported herein, the synthesis and antioxidant activity of some pyridine derivatives (**Scheme1-5**).




**Scheme1**

The pyrido[2,3-d]pyrimidine **5** was obtained by refluxing of **4** in formamide. Reaction of **4** with formic acid or with acetic anhydride afforded the corresponding amide derivatives **6** and **7,** respectively. Refluxing of **6** with $P_2S_5$ in pyridine afforded the thioanilide derivative **8.** Compound **4** was reacted with urea or thiourea to afford the ureado **9** and thioureado **10,** respectively. Whereas, refluxing of **4** with urea in a solution of glacial acetic acid and hydrochloric acid afforded the diaminopyrimidine derivative **11 (Scheme 2**).

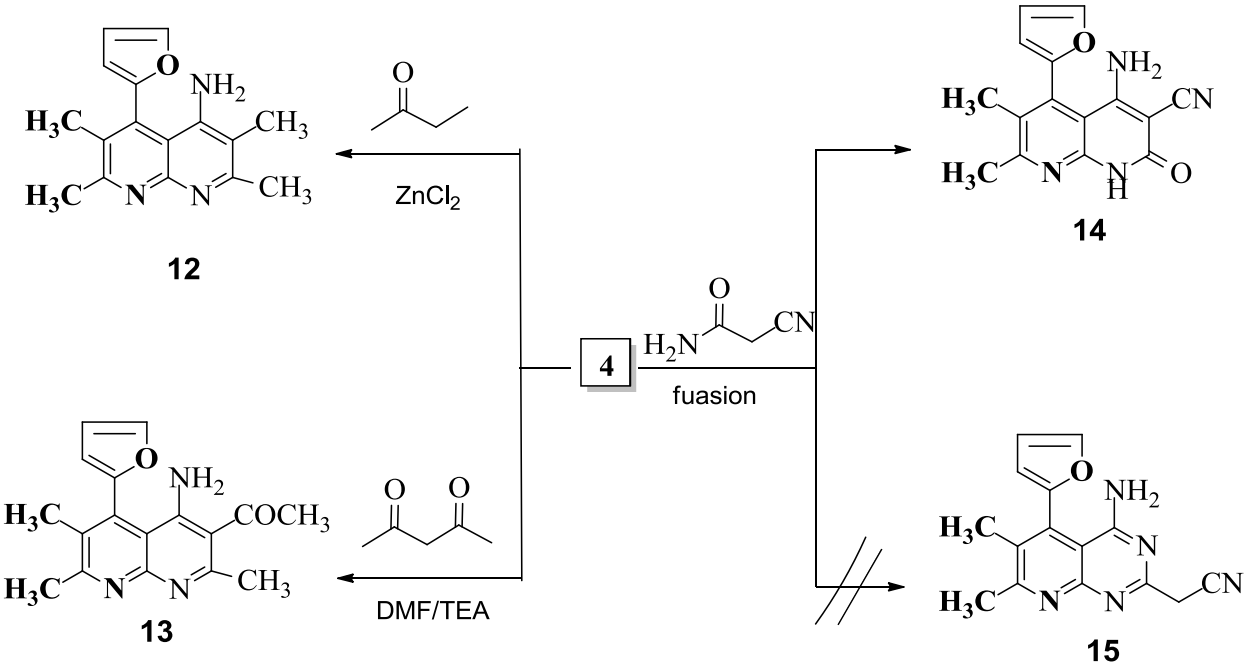



**Scheme2**

The structure of compound **5** was established through spectroscopic techniques, including IR, $^1$H-NMR and mass spectroscopy and satisfactorily elemental analysis. Whereas, its IR spectrum revealed appearance of absorption bands at $\upsilon$ = 3388 and 3305 cm$^{-1}$ due to the stretching vibrations of $NH_2$ group. The $^1$H-NMR of **5** showed singlet signal at δ 8.48 ppm which corresponds to the methine proton of the pyridine moiety.

Also, the structure of compounds **6-8** were confirmed by IR, $^1$H-NMR and mass spectra and satisfactorily elemental analysis. The IR spectrum of compounds **6** and **7** showed absorption bands at $\upsilon$ = 2208 and 2220 cm$^{-1}$ for the CN group, respectively. Absorption bands at $\upsilon$ = 1657 and 1640 cm$^{-1}$ are attributed to the amidic carbonyl groups of **6** and**7**, respectively. The IR spectrum of **8** showed a characteristic absorption bands at $\upsilon$ = 3247, 3137 and 2210 cm$^{-1}$ due to NH, CH and CN groups, respectively. Furthermore, the $^1$H-NMR spectrum of compound **6** exhibited singlet signal at δ 8.2 ppm due to the HC=O proton. The $^1$H-NMR spectrum of **7** displayed singlet signal at δ 1.9 ppm for an $COCH_3$ group. Finally, formation of **8** from its precursor 6 was confirmed by its mass spectrum which showed a molecular ion peak at m/z 257($M^+$) ( 0.2 %) corresponding to a molecular formula $C_{13}H_{11}N_3OS$.

The structures of compounds **9** and **10** were confirmed through spectroscopic techniques, including IR and mass spectroscopy and satisfactorily elemental analysis. The IR spectrum of **9** showed bands at $\upsilon$ =2207 and 1645 cm$^{-1}$ due to a CN and CO group, respectively. Moreover, the mass spectra of compounds **9** and **10** showed the molecular ion peaks at *m/z* 256($M^+$) (59.3%) and 272($M^+$) (13.5 %), respectively, which are in agreement with the molecular formula $C_{13}H_{12}N_4O_2$ and $C_{13}H_{12}N_4OS$, respectively.
The IR spectrum of compound **11** displayed broad bands at $\upsilon$ = 3406 cm$^{-1}$ corresponding to (2NH2) group. The $^1$H-NMR of **11** exhibited two singlet signals at δ 7.43 and 7.91 ppm, each of them is corresponding to two protons of an $NH_2$ group, respectively.
Reaction of compound **4** with butanone or acetylacetone furnished the corresponding 1,8-naphthyridine derivatives **12** and **13** respectively. On the other hand, Fusion of **4** with cyanoacetamide afforded the 2-oxo-1,8-naphthyridine derivative **14** instead of pyrido [2,3-d]pyrimidine derivative **15 (Scheme 3).**

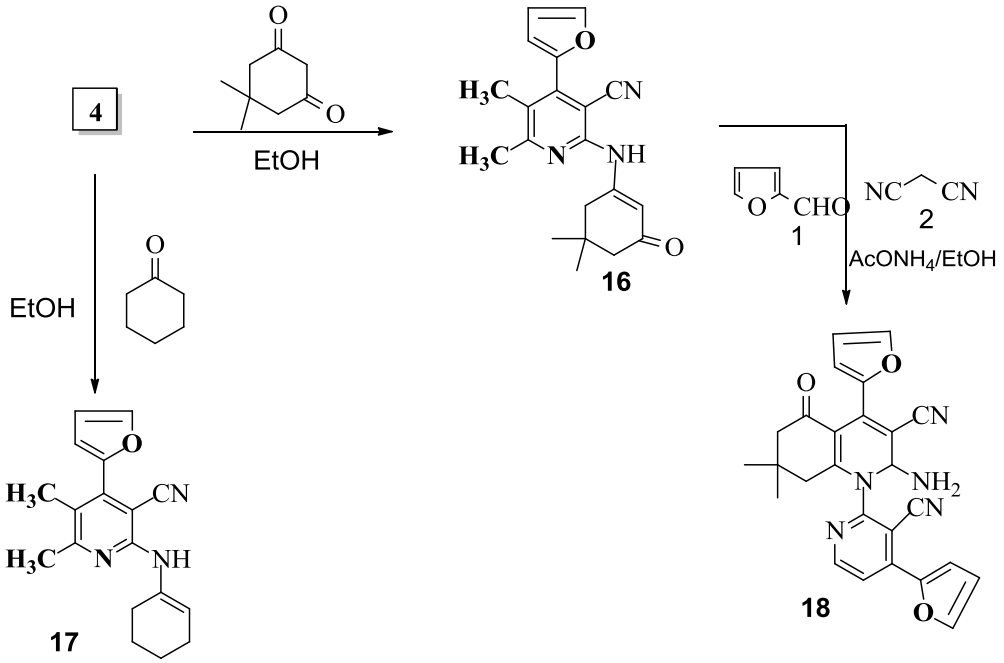



**Scheme3**

The structure of each **12- 14** was elucidated on the basis of spectral data and satisfactorily elemental analysis. The IR spectrum of compounds **12** and **13** showed absorption bands in the region of at $\upsilon$ = 3405-3330 cm$^{-1}$ due to stretching vibrations of the $NH_2$ groups.

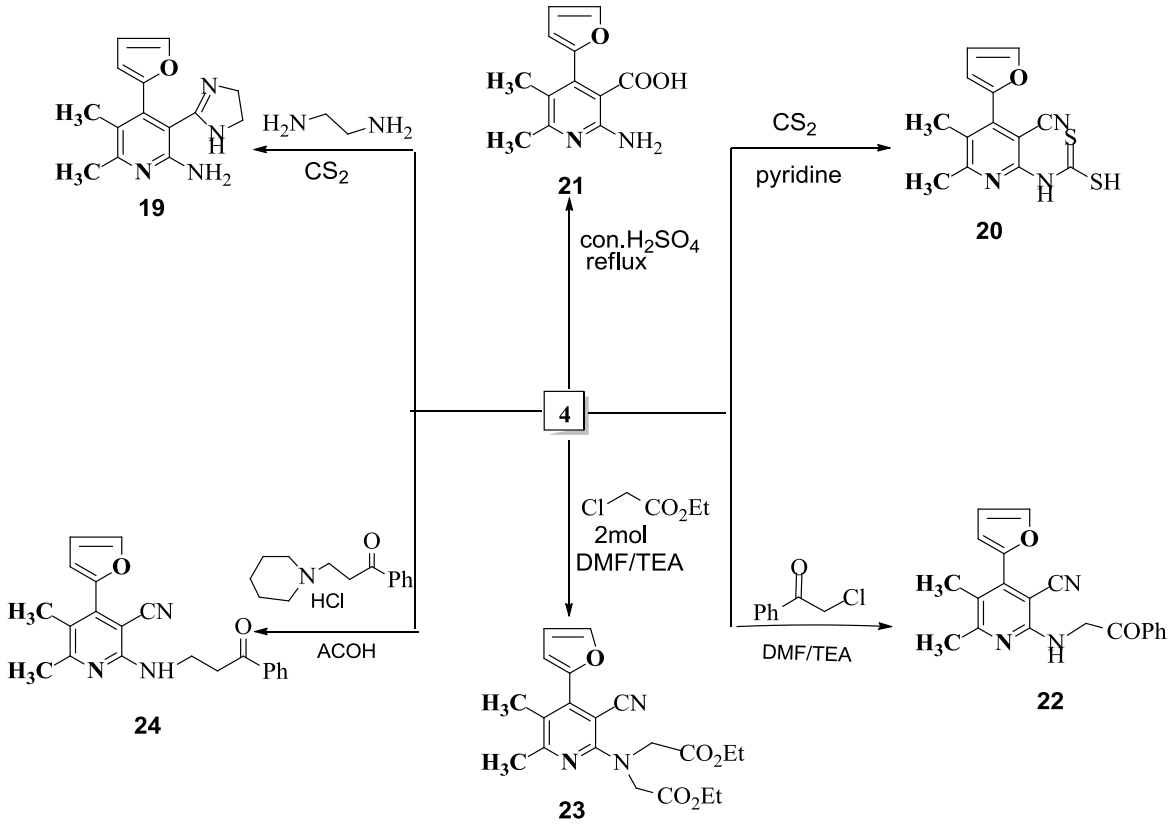
Furthermore, IR spectrum of compound **14** showed the appearance of characteristic absorption bands at $\upsilon$ =(3379, 3334 ,3243), 2211 and 1700 $cm^{-1}$ due to ($NH_2$, NH) ,CN and CO, respectively. Moreover, the $^1$H-NMR spectrum of **13** showed two singlet signals at δ 2.04 and 2.57 ppm attributed to methyl protons ( $CH_3CO$ and $CH_3$) at C-2 and C-3 of the constructed system. The $^1$H-NMR spectrum of **14** displayed a comp.pat. signal at δ 6.58-7.02 (m, 5H, furanyl, $NH_2$), 7.90 ppm (s,1H,NH).
The mass spectrum of **12** revealed molecular ion peak at m/z 267($M^+$)( 15.7%) corresponding to a molecular formula $C_{16}H_{17}N_3O$ Finally, the mass spectrum of **14** exhibited molecular ion peak at m/z 280($M^+$) corresponding to a molecular formula $C_{15}H_{12}N_4O_2$.

On the other hand, the condensation of **4** with 5,5-dimethyl-1,3-cyclohexanedione or cyclohexanone in ethanol furnished the pyridine derivatives **16** and **17,** respectively**.** Compound **16 was** reacted with malononitrile **1,** furan-2-carbaldehyde **2** and ammonium acetate in ethanol and afforded 5-oxoquinoline derivative **18 (Scheme 4).** Assignment of compound **16-18** were based IR, $^1$H-NMR and mass spectral data and satisfactorily elemental analysis. The IR spectrum of **16** showed absorption bands at $\upsilon$ = 3334, 3244, 2211 and 1650 $cm^{-1}$ due to NH, CN and CO groups, respectively. Moreover, the $^1$H-NMR spectrum of **16** exhibited singlet signals at δ 1.15, 2.04, 2.30 and 2.58 ppm for $2CH_3$, $2CH_2$ and $CH_2CO$ protons, respectively. Furthermore, the IR spectrum of **17** revealed absorption bands at $\upsilon$ = 3326 (NH), 2213 (CN) and 1648$cm^{-1}$ (C=N). The mass spectrum of **17** displayed molecular ion peak at m/z 293 ($M^+$) corresponding to a molecular formula $C_{18}H_{19}N_3O$. The IR spectrum of **18** revealed bands at ( 3405, 3334), 2206 and 1650 $cm^{-1}$ attributed to( $NH_2$), CN and CO, respectively. The mass spectrum of 18 showed an deprotonated molecular ion peak at m/z 478 ($\overline{M-1}^+$)( 33.1%), where **18** has a molecular formula $C_{28}H_{25}N_5O_3$.




**Scheme4**

Moreover, refluxing of **4** with ethylenediamine in carbon disulfide afforded 4,5-dihydro-1H-imidazol-2-ylpyridine derivative **19 (Scheme 5)**. Refluxing of **4** with carbon disulfide in pyridine; or with concentrated sulfuric acid furnished pyridine derivatives **20** and **21,** respectively**.** On the other hand, the reaction of **4** with phenacylchloride; or with ethylchloroacetate in *N*,*N*-dimethylformamide and catalytic amount of triethylamine afforded pyridine derivatives **22** and **23,** respectively. Furthermore, reaction of **4** with the mannish base 1-phenyl3-(pipridin-1-yl)propan-1-one hydrochloride in glacial acetic acid afforded phenylpropylaminopyridine derivative **24 (scheme 5).**




**Scheme5**

The Structure of each compounds **19-21** were confirmed on basis of their spectral data and satisfactorily elemental analysis. The IR spectrum of **19** was characterized by the absence of a CN group and the appearance of NH and $NH_2$ absorption bands at υ= 3477, 3381 and 3248 $cm^{-1}$, respectivily. Furthermore, the IR spectrum of **20** showed the presence of bands at υ= 3336(NH), 2211(CN) and 1256(CS) $cm^{-1}$. Moreover, the IR spectrum of **21** was characterized by the disappearance of CN group and the appearance of OH, $NH_2$ and CO bands at υ= 3413 and 1670 $cm^{-1}$, respectively.

The $^1$H-NMR spectrum of **19** revealed two characteristic singlet signals at δ 1.86 ppm corresponding to two $CH_2$ protons. Further, the $^1$H-NMR spectrum of **20** exhibited characteristic singlet signal at δ 8.60 ppm attributed to SH proton. Furthermore, the $^1$H-NMR spectrum of **21** displayed signal at δ10.4 ppm due to OH proton. The mass spectrum of **20** showed an ion peak /at m/z 288($^{M-1}$)$^+$(0.5%) derived from a molecular ion $M^+$ which is corresponding to a molecular formula $C_{13}H_{11}N_3OS_2$ and a base peak at m/z 186. Also, the mass spectrum of **21** revealed the presence of a molecular ion peak at m/z 232($M^+$)( 0.3 %) and the base peak at m/z 69( 100 %).

The structure of each of the products **22** and **23** was confirmed on basis of their spectral data satisfactorily elemental analysis. The IR spectrum of **22** displayed bands at υ= 3327, 2207 and 1656 $cm^{-1}$ corresponding to NH, CN, and CO groups, respectively. The IR spectrum of **23** characterized by appearance of absorption bands at υ= 2208, 1738 and 1657 $cm^{-1}$ due to stretching vibration of CN and (2CO) groups, respectively. The mass spectrum of **22** exhibited molecular ion peak at 331($M^+$) corresponding to a molecular formula $C_{20}H_{17}N_3O_2$. The mass spectrum of **23** showed molecular ion peak at 385($M^+$) (2.1%) corresponding to a molecular formula of $C_{20}H_{23}N_3O_5$ and a base peak at m/z 79.

Moreover, the IR spectrum of **24** revealed absorption bands at υ= 3328, 2207 and 1657 $cm^{-1}$ due to NH, CN and CO groups, respectively. In addition, the mass spectrum of **24** showed molecular ion peak at 345($M^+$) (51.2%) corresponding to molecular formula $C_{21}H_{19}N_3O_2$ and a base peak at m/z 79(100%).

*ABTS Antioxidant assay*

Antioxidant activity screening assay ABTS 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 perecentage. 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 (Lissi, *et. al.*,1999) ,(El-Gazar, *et. al.*, 2009) and (Aeschlach *et. al.*, 1994). Some of the tested compounds displayed antioxidant activity compared with L-ascorbic acid as shown in Table 1. Compounds **8, 19 a**nd **22** displayed high antioxidant potency, while compounds **5, 13** and **18** showed moderate antioxidant activity and the rest of the tested compounds showed weak antioxidant activity.

**Table 1**: ABTS Antioxidant activity assay of the new compounds

| Compound No | Absorbance of samples (λ) | % inhibition |
|---|---|---|
| Control of ABTS [a] | 0.525 | 0% |
| Ascorbic acid | 0.042 | 89.90% |
| 4 | 0.476 | 9.33% |
| 5 | 0.433 | 70.52% |
| 9 | 0.472 | 30.09% |
| 8 | 0.488 | 75.04% |
| 12 | 0.451 | 14.09% |
| 13 | 0.497 | 50.33% |
| 18 | 0.152 | 71.04% |
| 19 | 0.508 | 80.23% |
| 22 | 0.468 | 79.85% |

[a] ABTS: The method used for antioxidant activity

(%) Inhibition = [A (control) – A (test) /A (control)] x 100

*Bleomycin-dependent DNA damage assay*

The bleomycin are a family of glycopeptides antibiotics that are used routinely as antitumor agents. The bleomycin assay has been adopter for assessing the pro-oxidant of food antioxidants. The antitumor antibiotic bleomycin binds iron ions and DNA. The bleomycin – iron complex degrades DNA that, heating with thiobarbituric acid (TBA), yields a pink chromogen. Upon the addition of suitable reducing agents antioxidant compete with DNA and diminish formation (Gutteridge, *et. al.*, 1981).

*Bleomycin - dependent DNA damage assay*

To the reaction mixtures in a final volume of 1.0 ml, the following reagents at the final concentrations started were added: DNA (0.2 mg/m L), dependent (0.05 mg/mL), $FeCl_3$ (0.025 mM), magnesium chloride (5

mM), $KH_2PO_4$ – KOH buffer pH 7.0 (30 mM), and L- ascorbic acid (0.24 mM) or the test fractions diluted in MeOH to give a concentration of (0.1 mg/mL). The reaction mixtures were incubated in water – bath at 37$^o$ C for 1 h. At the end of the incubation period, 0.1 mL of ethylenediaminetetraacetic acid (EDTA) (0.1 M) was added to stop the reaction (the iron – EDTA complex is unreactive in the bleomycin assay). DNA damage was assessed by adding 1 mL 1% (w/v) thiobarbituric acid (TBA) and 1 ml of 25% (v/v) hydrochloric acid (HCl) following by heating in a water-bath maintained at 80C for 15 min. The chromogen formed was extracted into 1-butanol, and the absorbance was measured at 532 nm (Abdel-Wahab, *et. al.*, 2009) and (Badria, *et. al.*, 2007).

The protective activity against DNA damage induced by Bleomycine iron complex was examined in order to show the mechanism of action of the potent **5, 8,9,12,13,18,19** and **22** compounds. The results in Table 2 showed that compound **19** exhibited a high protection against DNA damage induced by the bleomycine iron complex, thus, diminishing chromogen formation between the damaged DNA and TBA molecules.

**Table 2:** Bleomycin dependent-DNA damageof the investigated compounds.

| Compound No | Absorbance of samples |
|---|---|
| Ascorbic acid | 0.083 |
| 4 | 0.168 |
| 5 | 0.119 |
| 8 | 0.192 |
| 9 | 0.134 |
| 12 | 0.128 |
| 13 | 0.237 |
| 18 | 0.085 |
| 19 | 0.253 |
| 22 | 0.144 |

**Experimental**

All the melting points are recorded on Gallenkamp electric melting point apparatus and are uncorrected. The IR spectra $\upsilon$ ($cm^{-1}$) (KBr) were recorded on a Perkin Elmer Infrared Spectrophotometer Model 157 at the Microanalytical Unit, Faculty of Science, Mansoura University. The $^1$H-NMR spectra spectra were obtained on a Varian Spectrophotometer at 300 MHz using tetramethylsilane (TMS) as an internal reference and DMSO-$d_6$ as solvent and were carried out at the Microanalytical Center, Cairo University. The mass spectra (EI) were recorded on 70 eV with Kratos MS equipment and/or a Varian MAT 331 A Spectrophotometer at the Micro analytical Center, Cairo University, Giza, Egypt. Elemental analyses (C, H and N) were carried out at the Micro analytical Center, Cairo University, Giza, Egypt. Biological activities were carried out at the Pharmacognosy Department, Faculty of Pharmacy, Mansoura University, Mansoura, Egypt.

**Synthesis of 2-amino-4-(furan-2-yl)-5,6-dimethyl pyridine-3-carbonitrile (4).**A mixture of furan-2-carboxaldehyde (0.48 g, 5mmol), 2-butanone (0.36 g, 5mmol), malononitrile (0.33g, 5mmol) and ammonium acetate (4.66gm, 40 mmol) in ethyl alcohol (10 ml) was heated under reflux for 12 hr. The reaction mixture was cooled and the formed precipitate was filtered, washed with water, dried and crystallized from methanol to give **4.**

Yellow crystals, yield, 50%, m.p:198 °C, IR (KBr): $\nu_{max}/cm^{-1}$: 3380, 3336; ($NH_2$); 2211 (CN), 1645 (C=N). $^1$H NMR (DMSO-$d_6$): $\delta$ 2.30 ( s,3H,$CH_3$) , 2.49 (s ,3H, $CH_3$), 6.57-7.19 (m, 3H ,furanyl-H), 7.90(s ,2H ,$NH_2$). MS: m/z (%) = 213 ($M^+$, 100), 197 (0.95), Anal. Calcd for $C_{12}H_{11}N_3O$ (213.09): C,

67.59; H, 5.20; N, 19.71.Found: C, 67.61; H, 5.23; N, 19.73%.

**Synthesis of 5-(furan-2-yl)-6,7-dimethylpyrido[2,3-d]pyrimidin-4-amine(5).**

A mixture of compound **4** (1.06g, 5mmol) and (10ml) of formamide was refluxed for 11hr. After cooling the precipitated crystals were filtered off, washed with ethanol and crystallized from DMF to give **5**.Green crystals, yield 30 %, m.p =170°C, IR(KBr)$\nu_{max}$/cm$^{-1}$ = 3388, 3305 ($NH_2$). $^1$H-NMR(DMSO-$d_6$) δ ppm =2.36 (s,3H,$CH_3$), 2.50 (s ,3H, $CH_3$) , 6.59-7.90 (m, 3H, furanyl-H) , 7.95(s ,2H ,$NH_2$) 8.48(s,1H ,=CH),, MS : m/z (%) :240 ($M^+$, 30.6) , 223(5.4), 213 (100) ,196(5.8), 184 (42.3), 171(4.6), 167(7.3), 143(81.7),132(2.3), 104(11.2), 115(78.9) , 93(2.6), 88(85.4) ,76(96.4). Anal. Calcd for $C_{13}H_{12}N_4O$ (240.26): C, 64.99; H, 5.03; N, 23.32.Found: C, 65.01; H, 5.06; N, 23.34%.

**Synthesis of *N*-(3-cyano-4-(furan-2yl)-5,6-dimethylpyridin-2-yl) formamide (6).**

A mixture of compound **4** (1.06g, 5mmol), formic acid (10ml) and concentrated hydrochloric acid (1ml) was heated under reflux for18hr. The reaction mixture was cooled, poured into cold water and neutralized with KOH to give **6**. Brown crystals, yield 56 % , m.p = 232°C. IR(KBr)$\nu_{max}$/cm$^{-1}$ = 3326 (NH) , 3162 (CH), 2208(CN), 1657 (CO). $^1$H-NMR (DMSO-$d_6$) δ ppm = 2.37 (s,3H,$CH_3$), 2.49 (s,3H,$CH_3$), 6.58-6.83(m,3H,furanyl), 7.91 (s,1H,NH), 8.20 (s,1H,HCO) .MS : *m/z* (%) :221 ($M^+$-20,7.2) ,221(7.2), 213 (56,4), 185 (11,9), 173(8.4), 156(10.3), 143 (20,9) ,128(8.7), 117(9.8), 103(7.5), 89(22.4), 77 (54,2) , 50 (100). Anal. Calcd for $C_{13}H_{11}N_3O_2$ (241.25): C, 64.72; H, 4.60; N, 17.42.Found: C, 64.76; H, 4.62; N, 17.44%.

**Synthesis of *N*-(3-cyano-4-(furan-2yl)-5,6-dimethylpyridin-2-yl)acetamide(7).**

A mixture of compound **4** (1.06g, 5mmol) and acetic anhydride (15ml) was heated under reflux for 24 hr. The reaction mixture was cooled and poured in ice cold water. The formed precipitate was collected by filtration and crystallized from ethanol to give **7**.Black crystals, yield 20 %, m.p= above 320 °C. IR(KBr)$\nu_{max}$/cm$^{-1}$ = 3350(NH), 2220(CN), 1640(CO).$^1$H-NMR(DMSO-$d_6$)δ ppm = 1.90 (s,3H,$COCH_3$), 2.36 (s,3H,$CH_3$), 2.54 (s,3H, $CH_3$), 6.60-7.20 (m,3H,furanyl), 7.90 (s,1H,NH) MS: *m/z* (%): 258($\overline{M+2}^+$ ,0.2) ,256 ($\overline{M+1}^+$ , 11.1) , 229 (31.1), 213 (71.7) , 205(1.8), 193(3.1), 184 (1.8) ,178(1.81), 165(1.9), 155(6.7), 141(6.8), 133(4.3), 123(2.16), 114(5.7) 78(76.1) , 63(100). Anal. Calcd for $C_{14}H_{13}N_3O_2$ (255.27): C, 65.87; H, 5.13; N, 16.46.Found: C, 65.89; H, 5.15; N, 16.48%.

***N*-(3-cyano-4-(furan-2yl)-5,6-dimethylpyridin-2-yl)methanethioamide(8).**

A mixture of compound **6** (1.2g ,5mmol)and phosphorous pentasulfide (1.1g , 5mmol) in pyridine (10ml) was refluxed for14 hr, the reaction mixture was cooled and then poured onto ice cold water , then acidified with diluted HCl. The obtained solid was crystallized from ethanol to give **8**.Black crystals, yield 30 %, m.p = above 320 °C IR(KBr)$\nu_{max}$/cm$^{-1}$ = 3240(NH), 3136(CH), 2210(CN).MS : *m/z* (%) : 259($\overline{M+2}^+$ , 0.13), 258($\overline{M+1}^+$ ,0.1), 257($M^+$ ,0.2) , 237 (2.3) ,227(0.2), 219(0.1), 213 (100) ,206(0.2), 198(3.1), 188(2.0), 171(5.4), 148(0.3), 125(0.3), 77 (18.9). Anal. Calcd for $C_{13}H_{11}N_3OS$ (257.31): C, 60.68; H, 4.31; N, 16.33.Found: C, 60.69; H, 4.33; N, 16.35%.

**Synthesis of 1-(3-cyano-4-(furan-2yl)-5,6-dimethylpyridin-2-yl)urea (9). Synthesis of 1-(3-cyano-4-(furan-2yl)-5,6-dimethylpyridin-2-yl)thiourea (10).**

A mixture of compound **4** (1.06g, 5mmol) and urea (0.3g,5mmol) or thiourea (0.38,5mmol) was heated at 180°C on a sand bath for 6hr. The mixture was solidified by cooling and addition of methanol (10ml), then filtered and recrystallized from DMF:EtOH to give **9 and 10,** respectively.

**Compound9**: Black crystals, yield 36 %, m.p =above300°C IR(KBr)$\nu_{max}$/cm$^{-1}$ =3444, 3330,3121 ($NH_2$ ,NH) ,2207 (CN),1645 (CO) . $^1$H-NMR(DMSO-$d_6$) δ ppm = 2.36 (s,3H,$CH_3$) , 2.41 (s,3H, $CH_3$), 6.38-6.89 (m, 3H, furanyl-H ) ,7.90 (s ,2H ,$NH_2$),11.09 (br,1H ,NH). MS : *m/z* (%): 257($\overline{M+1}^+$ ,62.8), 256( $M^+$, 59.3), 240(7.1),

234(3.3), 227(23.3), 213(100), 205(3.3), 199(14.3), 184(36.3) ,164(2.5), 144(22.3),129 (20.2) , 116(26.3) ,76(70.2). Anal. Calcd for $C_{13}H_{12}N_4O_2$ (256.1): C, 60.93; H, 4.72; N, 21.86.Found: C, 60.96; H, 4.75; N, 21.88%.

**Compound 10:** Black crystals, yield 34 %, m.p =above 300° C. IR(KBr)$\nu_{max}$/cm$^{-1}$ = 3404, 3327,3157($NH_2$ ,NH),2207(CN), . MS : *m/z* (%) :273($\overline{M+1}^+$ , 13.7), 272 ($M^+$, 13.5) , 263(5.2), 251(5.2), 245 (1.9) , 237(3.3), 225( 6.8), 213(44.6), 194(4.2) , 184(52.7) ,157 (47.2) ,133(13.06), 116 (100) , 64 (14.4). Anal. Calcd for $C_{13}H_{12}N_4OS$ (272.3): C, 57.34; H, 4.44; N, 20.57. Found: C, 57.36; H, 4.46; N, 20.59%.

**Synthesis of 5-furan-2-yl-6,7-dimethylpyrido [2,3-d]pyrimidine 2,4-diamine(11).**

A mixture of compound **4** (1.06g, 5mmol) and urea (0.3g ,5mmol ) was refluxed in glacial acetic acid and hydrochloric acid (3:1) for10hr . After cooling the formed precipitated was filtered off and crystallized from EtOH to give **11.** Brown crystals, yield 29%, m.p =above 320°C, IR (KBr)$\nu_{max}$/cm$^{-1}$ = 3406($2NH_2$ ). $^1$H-NMR(DMSO-$d_6$) δ ppm = 2.37 (s,3H,$CH_3$) , 2.50 (s,3H, $CH_3$) , 6.58-7.27 (m, 3H, furanyl-H ) ,7.43 (s ,2H ,$NH_2$) ,7.91 (s,2H ,$NH_2$ ). MS : *m/z* (%) :257 ($\overline{M+2}^+$ ,1.8),256 ($\overline{M+1}^+$ , 2.04), 255 ($M^+$, 1.9) , 244 (2.9) , 237(2.1), 220(2.0), 213(100) ,198(3.9), 184(34.3) ,170(1 0.6) ,167(3.1), 155(4.2), 128(2.9), 116(6.6) ,69(39.5). Anal. Calcd for $C_{13}H_{13}N_5O$ (255.28): C, 61.17; H, 5.13; N, 27.43.Found: C, 61.19; H, 5.15; N, 27.44%.

**Synthesis of 5-(furan-2-yl)-2, 3, 6, 7-tetramethyl-1,8-naphthyridin-4-amine(12).**

A mixture of compound **4** (1.06g, 5mmol), butanone (0.36g, 5mmol) and $ZnCl_2$ (0.68g, 5mmol) was heated at 120-130°C for 2-3hr. After cooling, the reaction mixture was stirred in ice and neutralized with aqueous NaOH solution. The separated solid was collected by filtration and crystallized from ethanol to give **12**.White crystals, yield 40%, m.p= 160°C. IR(KBr)$\nu_{max}$/cm$^{-1}$ = 3405($NH_2$) . $^1$H-NMR(DMSO-$d_6$) δ ppm = 2.34(s,3H, $CH_3$), 2.39( s,3H, $CH_3$ ), 2.43 (s,3H, $CH_3$), 2.57 (s,3H, $CH_3$), 6.58-7.20 (m,3H,furanyl), 7.91 (br,s,2H,$NH_2$ ). MS : *m/z*(%): 267 ($M^+$ ,15.7) ,255(17.5), 247(20.4) ,235(15.7), 213 (17.5) ,206(15.2), 192(18.2), 184(15.2), 177(16.9), 167(15.2), 140(15.2),117 (27.7) ,69(100). Anal. Calcd for $C_{16}H_{17}N_3O$ (267.14): C, 71.89; H, 6.41; N, 15.72.Found: C, 71.90; H, 6.42; N, 15.75%.

**Synthesis of 5-(furan-2-yl)-2,6,7-trimethyl-3-acetyl-1,8-naphthyridin-4-amine (13).**

A mixture of compound **4** (1.06gm ,5mmol) , acetylacetone (0.5g ,5mmol) , DMF(10ml) and triethylamine (5drops ) was refluxed for 15 hr . The reaction mixture was cooled, then poured onto cold water and neutralized with dil HCl . The separated solid was collected by filtration and crystallized from ethanol to give **13**.Black crystals, yield 35 % ,m.p= above 320 °C. IR(KBr)$\nu_{max}$/cm$^{-1}$ = 3380, 3343($NH_2$), 1649(CO).$^1$H-NMR(DMSO-$d_6$) δ ppm = 2.04(s,3H,$COCH_3$), 2.30(s,3H, $CH_3$), 2.36( s,3H, $CH_3$ ), 2.57 (s,3H, $CH_3$), 6.68-7.35(m,3H,furanyl), 7.95 (br,s,2H,$NH_2$ ). MS : *m/z*(%): 294 ($\overline{M-1}^+$ ,0.2), 287(0.2), 265(1.1), 253(0.3), 237 (48.7), 227(0.5), 216(0.3), 205(0.9), 186 (89.4), 155(2.0), 135(2.4),122(1.1), 97 (69.9) ,68(100). Anal. Calcd for $C_{17}H_{17}N_3O_2$(295.13): C, 69.14; H, 5.80; N, 14.23.Found: C, 69.15; H, 5.82; N, 14.25%.

**Synthesis of 4-amino-5(furan-2-yl)-1,2-dihydro-6,7-dimethyl-2-oxo-1,8-naphthyridine-3-carbonitrile(14).**

A mixture of compound **4** (1.06g ,5mmol) and cyanoacetamide (0.4g ,5mmol) was heated in a sand bath for 15hr .The mixture was solidified by cooling and addition of methanol (10ml),then filtered and crystallized from DMF:EtOH to give **14**.Black crystals , yield 45 % ,m.p= above 320 °C. IR(KBr)$\nu_{max}$/cm$^{-1}$ = 3379, 3334 ,3243($NH_2$ ,NH), 2211(CN), 1700(CO) . $^1$H-NMR (DMSO-$d_6$) δ ppm = 2.37 (s, 3H, CH3), 2.57 (s, 3H, CH3), 6.58-7.02 (m, 5H, furanyl, $NH_2$), 7.90 (s,1H,NH). MS: *m/z*(%): 280 ($M^+$,2.3), 267(3.2), 250(2.3), 248(3.1), 237(3.0), 222(2.3), 213(9.5), 192(2.8), 186(100), 162(2.4), 144(4.3), 128(3.0), 118(8.2), 105(9.5), 67(65.2). Anal. Calcd for $C_{15}H_{12}N_4O_2$

(280.1): C, 64.28; H, 4.32; N, 19.99.Found: C, 64.30; H, 4.33; N, 20.00%.

**Synthesis of 2-(3,3-dimethyl-5-oxocyclohexylideneamino)-4-(furan-2-yl)-5,6-dimethylpyridine-3-carbonitril(16).**
A mixture of a compound **4** (1.06g , 5mmol) , 5,5-dimethyl-1,3-cyclohexandione (0.7g ,5mmol) and ethanol (10ml) was heated under reflux for 6hr.The formed solid mass collected and crystallized from DMF: EtOH (2:1) to give **16**.Black crystals , yield 30 % m.p= 230 °C. IR(KBr)$\nu_{max}/cm^{-1}$ = 3334, 3244(NH), 2211(CN), 1650(CO). $^1$H-NMR(DMSO-$d_6$) δ ppm = 1.15 (br,s,6H,2$CH_3$), 2.04 (br,s,2H,$CH_2$), 2.36 (s,3H,$CH_3$), 2.49 (s,3H,$CH_3$), 2.58 (s,2H,$CH_2CO$), 6.58-7.20 (m,4H,3H-fyrany,CH=),7.90(s,1H,NH). MS: *m/z*(%): 321 ($M^+$-$CH_2$ ,9.8), 307(7.6), 298(10.5), 277(8.3), 256(8.7), 243(10.2), 236(7.1), 224(9.8) , 213(100), 204(7.1), 198(9.1), 186 (12.0), 162(7.8), 124(7.4) , 69(67.6). Anal. Calcd for $C_{20}H_{21}N_3O_2$ (335.16): C, 71.62; H, 6.31; N, 12.53.Found: C, 71.64; H, 6.33; N, 12.55%.

**Synthesis of 2-(cyclohexylideneamino)-4-(furan-2-yl)-5,6-dimethylnicotinonitrile(17).**
A mixture of compound **4** ( 1.06g ,5mmol) , cyclohexanone (0.5g,5mmol) and ethanol (10ml) was refluxed in for 5hr. The reaction mixture was allowed to cool to room temperature, then the deposited solid was filtered off, dried and crystallized by ethanol to give **17**.Brown crystals, yield 35 % ,m.p=239°C. IR(KBr)$\nu_{max}/cm^{-1}$ = 3326(NH) 2213 (CN), 1648(C=N) . MS: *m/z*(%):293 ($M^+$ ,0.2) ,288(0.2), 279(0.5), ,268(0.3), 255(1.2), 237 (12.8) , 213(7.3) , 205(0.6), 186 (100) ,173 (56.7), 158(3.1), 147(4.2), 126(2.6), 110(3.6), 68(8.4). Anal Calcd for $C_{18}H_{19}N_3O$ (293.15): C, 73.69; H, 6.53; N, 14.32. Found: C, 73.70; H,6.54 ; N, 14.33%.

**Synthesis of 2-amino-1-(3-cyano-4-(furan-2-yl)-5,6-dimethylpyridin-2-yl)-4-(furan-2-yl)-1,2,5,6,7,8-hexahydro-7,7-dimethyl-5-oxoquinoline-3-carbonitrile(18).**
A mixture of compound (1.6g, 5mmol), malononirile (0.33g,5mmol), furan-2-carbaldehyde (0.46g, 5mmol) in ethanol (10ml) containing triethylamine (3drops) was refluxed for 10hr . The reaction mixture was cooled and then poured onto cold water, the obtained solid was filtered off dried, then crystallized from methanol to give **18**.Browne crystals , yield 50 % ,m.p= 260 °C IR(KBr)$\nu_{max}/cm^{-1}$ = 3405, 3334($NH_2$), 2206(CN), 1650(CO) . MS:*m/z*(%):478($\overline{M-1}^+$, 33.1), 477($\overline{M-2}^+$,43.8), 440(33.6), 414(28.8), 405(39.1), 377(43.3), 340(32.1), 325(4.8), 387 (39.04), 261 (33.69) , 228 (39.57), 213(29.9), 197(31.0), 172 (59.36) , 69 (100). Anal. Calcd for $C_{28}H_{25}N_5O_3$ (479.2): C, 70.13; H, 5.25; N, 14.60.Found: C, 70.15; H,5.27; N, 14.62%.

**Synthesis of 4-(furan-2-yl)-3-(4,5-dihydro-1H-imidazol-2-yl)-5,6-dimethylpyridine-2-amine(19).**A mixture of compound **4** ( 1.06g ,5mmol) and ethylenediamine (0.3g,5mmol) was refluxed in carbon disulfide (2ml) for 6hr. The reaction mixture was allowed to cool to room temperature. The formed solid collected by filtration and crystallized by methanol to give **19**. Brown crystals, yield 55 % ,m.p= 150 °C. IR(KBr)$\nu_{max}/cm^{-1}$ = 3477, 3381,3248(NH,$NH_2$).$^1$H-NMR(DMSO-$d_6$) δppm= 1.86(br,4H,2$CH_2$), 2.36(s,3H,$CH_3$),2.57(s,3H,$CH_3$),6.57-7.19 (m,3H,furanyl) , 7.90-7.95 (m ,3H, NH, $NH_2$). MS: *m/z*(%): 256($M^+$,16.1 ) , 237(0.6), 226(0.6), 213 (74.6), 208(0.3), 192 (8.6) , 184 (48.3) ,174(0.2), 163(0.3), 146(2.1), 127(23.5), 101(100) , 88(18.2), 63(91.8). Anal. Calcd for $C_{14}H_{16}N_4O$ (256.13): C, 65.61; H, 6.29; N, 21.86. Found: C, 65.62; H,6.30 ; N, 21.87%.

**Synthesis of (3-cyano-4-(furan-2-yl)-5,6-dimethylpyridine-2-yl)carbomodithioic acid(20).**
A mixture of compound **4** (1.06g, 5mmol ) in pyridine (20ml) and carbon disulfide (0.76g ,10mmol ) was heated on water-bath (80°C) for 20hr. The reaction mixture was allowed to cool the precipitate was filtered off washed with ethanol and dried to give **20**.Black crystals, yield 50 % ,m.p= 286 °C. IR(KBr)$\nu_{max}/cm^{-1}$ = 3336 (NH), 2211(CN),

1256(CS). $^1$H -NMR(DMSO-$d_6$)δppm= 2.36 (s,3H,$CH_3$), 2.57 (s,3H,$CH_3$), 6.58-7.37 (m,3H,furanyl), 7.94 (s,1H,NH), 8.60(s,1H,SH). MS: *m/z*(%): 288($M-1]^+$,0.5) ,274(1.1), 260(1.5), 246(1.2), 236 (3.7), 223(2.1) , 213 (1.8) ,186 (100) ,173(71.0), 158 (32.9) ,134(18.7), 116(11.5), 80(6.8), 63(71.7). Anal. Calcd for $C_{13}H_{11}N_3OS_2$ (289.13): C, 53.96; H, 3.83; N, 14.52. Found: C, 53.98; H,3.85 ; N, 14.53%.

**Synthesis of 2-amino-4-(furan-2-yl)-5,6-dimethyl pyridine-3-carboxylic acid(21).**

A solution of **4** (1.06g, 5mmol), in conc. $H_2SO_4$ (10ml) was refluxed for 18hr**.** The reaction mixture was allowed to cool to room temperature and poured onto cooled water .The formed solidwas collected and treated with ethanol then filtered and crystallized by ethanol to give **21**.Black crystals, yield 15 % ,m.p= 230°C. IR(KBr)$\nu_{max}$/cm$^{-1}$ = 3413 (br$NH_2$ ,OH), 1670 (CO). $^1$H -NMR(DMSO-$d_6$) δ ppm = 2.4 (s,6H,2$CH_3$), 4.0(s,2H,$NH_2$), 6.9-7.4(m,3H,furanyl), 10.4(s,1H,OH). MS: *m/z*(%): 232 ($M^+$ ,0.3 ), 227(0.7), 213(1.3) ,209(0.3), 198(0.1), 175(1.5) ,162(0.7), 149 (7.6), 122(3.8), 118(0.5) ,110(4.6), 99(3.3), 69(100),56(7.7) . Anal Calcd for $C_{12}H_{12}N_2O_3$ (232.08): C, 62.06; H, 5.21; N, 12.06. Found: C, 62.08; H,5.22 ; N, 12.07%.

**Synthesis of 2-(2-oxo-2-phenylethylamino)-4-(furan-2-yl)-5,6-dimethyl pyridine-2-yl)-3-carbonitrile(22).**

A mixture of compound **4** (1.06g, 5mmol), phenacylchloride (0.77g, 5mmol), DMF (5ml) and TEA (0.3ml) was refluxed in for 7hr. The reaction mixture was allowed to cool to room temperature and poured onto cooled water .the formed solid was collected by filtration and crystallized by ethanol to give **22**.Brown crystals, yield 30 % ,m.p= 224 °C. IR(KBr)$\nu_{max}$/cm$^{-1}$ = 3327(NH) , 2207(CN) ,1656(CO) . MS: *m/z*(%):331($M^+$,1.8), 322(0.7), 314(0.5), 299(0.9), 275(11.6), 254(2.8), 238(0.3), 212(7.8) , 199(6.1), 162(16.6) ,140(1.6), 120(7.8), 102(1.8), 80(100). Anal Calcd for $C_{20}H_{17}N_3O_2$ (331.13): C, 72.49; H, 5.17; N, 12.68. Found: C, 72.50; H, 5.18 ; N, 12.88%.

**Synthesis of Bis-ethyl(-2-(3-cyano-4-(furan-2-yl)-5,6-dimethylpyridin-2-ylamino) acetate(23).**

A mixture of compound **4**(1.06g ,5mmol) , ethyl chloroacetate (1.2g,10mmol) in DMF (15ml) and potassium carbonate (1.2g ,5mmol) was refluxed for 20hr. The reaction mixture was allowed to cool to room temperature and poured onto cooled water. The formed solid was collected by filtration and crystallized by ethanol to give **23**. Brown crystals, yield 25 % ,m.p=above 300°C.IR(KBr)$\nu_{max}$/cm$^{-1}$ = 2208 (CN)1738, 1657 (2CO). MS: *m/z*(%): 385($M^+$,2.1) , 361(0.1), 337(0.7), 356(0.1) 314(0.3), 296 (0.2), 272(0.1), 257 (2.6), 220 (0.5), 198(0.8), 174(0.2), 124(3.1) , 110(3.3), 79(100) Anal. Calcd for $C_{20}H_{23}N_3O_5$ (385.16): C, 62.33; H, 6.01; N, 10.90. Found: C, 62.35; H,6.02 ; N, 10.11%.

**Synthesis of 2-(3-oxo-3-phenylpropylamino)-4-(furan-2-yl)-5,6-dimethyl pyridine-2-yl)-3-carbonitrile(24).**

A mixture of compound **4** (1.06g,5mmol), 1-phenyl-3-(pipridinyl)-propan-1-one hydrochloride (1.14g,5mmol), acetic acid (5ml) was refluxed for 10hr. The reaction mixture was allowed to cool to room temperature .The formed solid was collected by filtration and crystallized from ethanol to give **24.** Pale brown crystals, yield 10 %, m.p= 265 °C. IR(KBr)$\nu_{max}$/cm$^{-1}$ = 3328 (NH), 2207 (CN), 1657(CO). $^1$H- NMR (DMSO-$d_6$) δ ppm :2.37 (m,5H,$CH_3$,$CH_2$CO), 2.5 (m,5H,$CH_3$,$CH_2$), 6.58-6.83(m,8H,Ar-H) , 7.91 (s,1H,NH).MS: *m/z*(%):345 ($M^+$,51.2 ) ,334(37.8), 318(34.7), 307(42.6), 297 (59.1) , 274(35.5), 257(34.7), 223 (53.05), 213(51.22), 170 (44.5) , 133(51.2), 108(1.7), 69 (98.1) , 55(100). Anal Calcd for $C_{21}H_{19}N_3O_2$ (345.13): C, 73.03; H, 5.54; N, 12.17. Found: C, 73.05; H,5.55 ; N, 12.19%.

**Conclusion**

The objective of the present study was to synthesize and evaluate the antioxidant activity of some novel pyridine, imadazole and quinoline derivatives with the hope of discovering new structure serving as antioxidant gent. The data showed clearly that compounds **8, 12, 13, 19** and **22** displayed promising *in vitro* antioxidant activities using ABTS method. Compound **19** exhibited high protection against DNA damage induced by the bleomycine iron complex.

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# التشيد والنشاط المضاد اللاكسده لبعض مشتقات البريدين الجديده

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تحضير ٤ -امينو--فيروانبل-٥و٦-داى ميثيل نيكوتينونيتريل ٤ وتفاعله مع فورماميد والفورميك اسيد والاسيتك انهيدرايد لانتاج بيريدو بريميدين **٥و ٦ و٧** ثم تفاعل **٦**مع فوسفرس بينتاسلفيت واعطاء ٨. تفاعل **٤** مع يوريا والثيو يوريا الانتاج **٩ و١٠** تفاعل**٤** مع يوريا فى وجود حمض الخليك الثلجىوحمض الهيدروكلوريك يعطى**١١**.تفاعل **٤** مع البيتانون والاسيتيل اسيتون يعطى **١٢و١٣** .صهر **٤** مع سيانوايتاميد يعطى **١٤**.تفاعل**٤** مع٥ و٥-دامينيل-١و٣-سيكلوهيكسادايون وسيكلوهيكسانونيعطى **١٦و١٧**.تفاعل **٤** مع ايثيلين دامين وكاربوندسالفيد و حمض السافوريك اسد يعطى **١٩و ٢٠ و٢١**.اخيرا تفاعل **٤** مع فينسيل كلورو و ايسيل كلورو اسيتات و ١-فينيل-٣-(بيبيرديزيل-١-يل)بروبان-١-اون هيدروكلوريد يعطى **٢٢ و ٢٣ و٢٤**.