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**RESEARCH ARTICLE**

# One pot synthesis of pyridine, thiazolidine, pyrazole and 2, 3-dihydro-1, 3, 4-thiadiazole derivatives under solvent-free condition

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***Abstract***

Claisen condensation of 2-acetylbenzofuran and 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde **2** gave chalcone **3** which was exploited as a starting material for the syntheses of hitherto unknown different types of new heterocyclic compounds incorporating the benzofuran moiety via the reaction with various active methylene compounds. On the other hand, several new thiadiazolines, pyrazoles and pyrazolo[3,4-*d*]pyridazine were synthesized by the reaction of 3-(benzofuran-2-yl)-3-oxopropanenitrile **12** withα-halo ketone, α-halo ester and hydrazonoyl halides.



## 1. Introduction

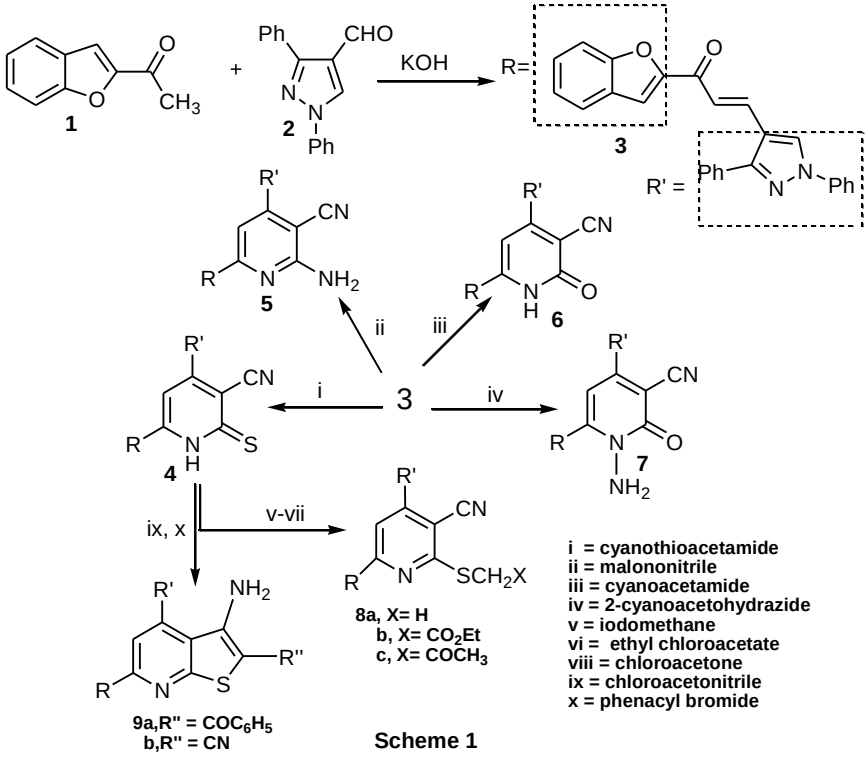
Many organic solvents are hazardous and can be deleterious to human health. They are volatile and cause an environmental threat by polluting the atmosphere [1,2]. The replacement of volatile organic solvents in organic reaction processes is an important green chemistry goal. Furthermore, the solvent-free or solid-state reactions have numerous advantages: reduced pollution, low costs, high yields and purities of products, simplicity in process and handling [3,4]. On the other hand, various benzofuran derivatives possess different pharmacological and biological activities, of which the most potent is anti-inflammatory [5], pesticidel& insecticidal [6], antihistaminic [7], anticonvulsant [8], antiallergic [9] and In-vitro anti-HIV-1, anticancer, anti-microbial activities [10, 11]. The antimicrobial activity of benzofuran derivative appears to be dependent on substitution at the heterocyclic furan ring than the aromatic moiety [12]. As a continuation of our program, we report a facial, eco-friendly approach with excellent yield for the synthesis of pyridine, pyrazole, thiazoline and 2,3-dihydro-1,3,4-thiadiazoles bearing benzofuran moiety by grinding method.

## 2. Result and Discussion

The starting compound **3** was synthesized *via* grinding method where 2-acetylbenzofuran (**1**), 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde (**2**) and moist potassium hydroxide were ground with a pestle in an open mortar (Scheme 1). Structure of the product **3** was confirmed on the basis of its correct elemental analysis, spectral data and chemical transportation. The IR spectrum of compound **3** revealed bands at 3064 *v*(CH-arom), 1660 *v*(CO), 1610 *v*(C=N), 1570 *v*(C=C). Its $^1$H NMR spectrum revealed signals at δ = 7.10-8.17 (m, ArH's and –CH=CH-). Thus, treatment of 1-(benzofuran-2-yl)-3-(1,3-diphenyl-1*H*-pyrazol-4-yl)prop-2-en-1-one (**3**) with 2-cyanoethanethiamide and ammonium acetate in acetic acid under reflux afforded the corresponding 2-mercapto-6-(benzofuran-2-yl)-4-(1,3-diphenyl-1*H*-pyrazol-5-yl)pyridine-2(1*H*)-thione (**4**).

Similarly, compound **3** reacted with each of malononitrile, 2-cyanoacetamide or 2-cyanoacetohydrazide yielded the corresponding pyridine derivatives **5-7 (**Scheme 1). The structures of **4-7** were confirmed on the basis of their elemental analysis, spectral data and alternative synthetic route. The IR spectrum of **4** revealed bands at 3340 *v*(NH), 3058 *v*(CH-aroma.), 2218 *v*(CN), 1604 *v*(C=N), 1234 *v*(C=S) and the IR spectrum of **5** showed the presence of 3266, 3200 *v*($NH_2$), 3062 *v*(CH-aroma.), 2206 *v*(CN), 1589 *v*(C=C).The structure of **5** was supported by its $^1$HNMR which showed signals at δ = 4.24 (s, 2H, $NH_2$), 7.20-7.85 (m, 17H, ArH's). Thus, one pot reaction of 2-acetylbenzofuran (**1**), 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde (**2**) and the appropriate of 2-cyanoethanethioamide,

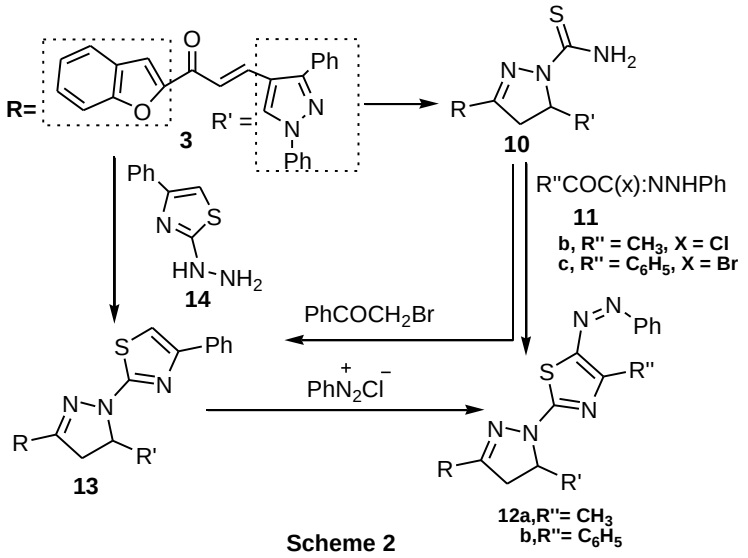
malononitrile, 2-cyanoacetamide or 2-cyanoacetohydrazide and excess ammonium acetate in n-butanolgave products identical in all aspects (mp., mixed mp. and spectra) with the corresponding compounds **4**-**7** (Scheme 1). Structure **4** was also confirmed by chemical transformation, where the appropriate of iodomethane, ethyl chloroacetate, chloroacetone, ω-bromoacetophenone and irtinotecaorolhcle were reacted with **4** by two different methods either with ethanolic triethylamine or (ethanolic potassium hydroxide) at room temperature *or via* grinding in which equimolar amounts of pyridine-2-thion **4**, potassium hydroxide and each of methyl iodide, ethyl chloroacetate, chloroacetone, ω-bromoacetophenone and chloroacetonitrile were mixed and ground in a mortar to give the corresponding product **8a-c** and **9a**,**b**, respectively (Scheme 1, Table 1).




**Scheme 1**

Structures of **8a-c**, **9a** and **9b** were elucidated on basis of analytical and spectral data. Thus, IR spectrum of **8b** showed the absence of SH band and the presence of bands at 3058 *v*(CH-aromatic), 2981, 2931 *v*(CH-aliphatic), 2214 *v*(CN), 1732 *v*(C=O), 1596 *v*(C=C). Its $^1$H NMR (DMSO-$d_6$) revealed signals at δ 1.20 (t, 3H, *J* = 7 Hz, $CH_2\mathbf{CH_3}$), 4.22 (q, 2H, *J* = 7 Hz, $\mathbf{CH_2}CH_3$), 4.70 (s, 2H, $SCH_2$), 7.22-8.10 (m, 17H, ArH's).

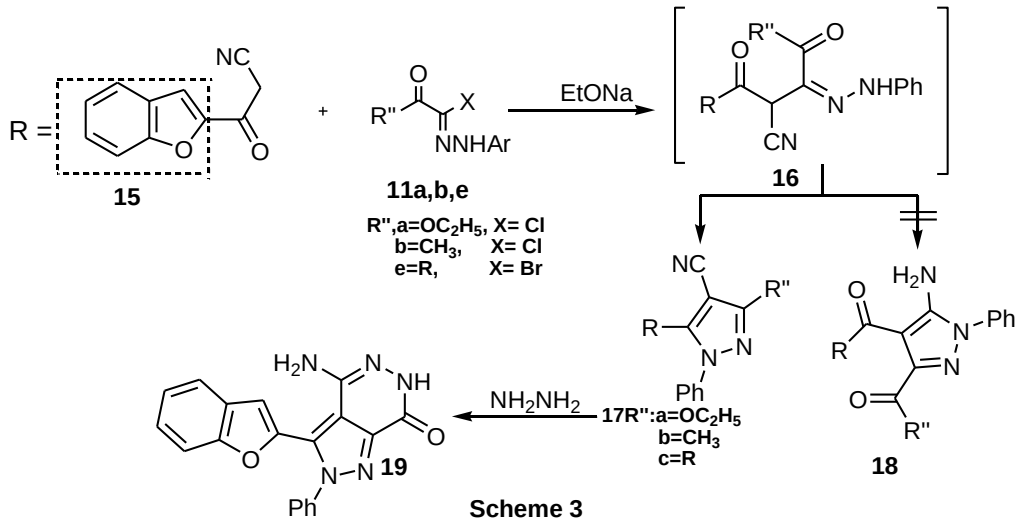
However, compound **3** was reacted with thiosemicarbazide afforded 5-(benzofuran-2-yl)-2',5'-diphenyl-3,4-dihydro-2*H*,2'*H*-[3,3'-bipyrazole]-2-carbothioamide (**10**).Structure **10** was elucidated *via* elemental analysis, spectral data and chemical transformation.




**Scheme 2**

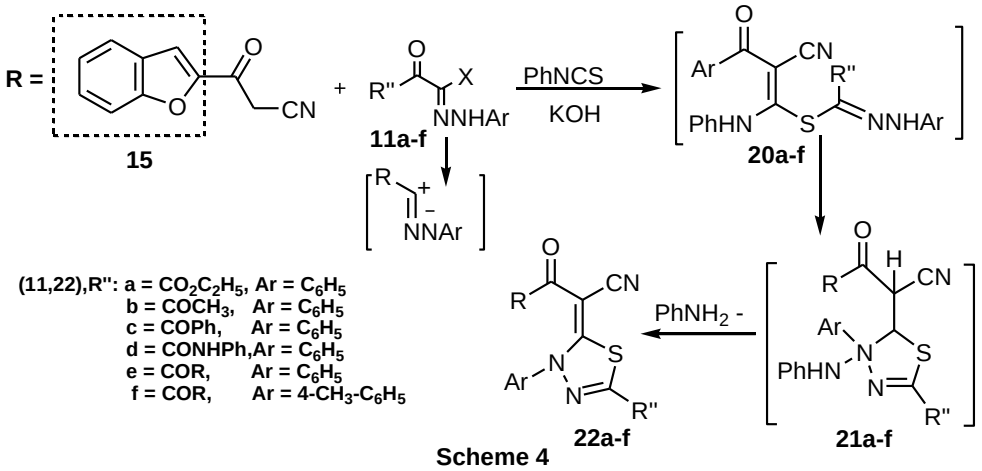
Thus, $^1$H NMR spectrum of **10** showed signals at δ = 3.66 (dd, 1H, *J* = 18.1, 5.8Hz, $CH_2$(pyraz), 4.01 (dd, 1H, *J* = 18.1, 12Hz, $CH_2$(pyraz), 5.33 (dd, *J* = 12.2 5.8 Hz, CH(pyraz), 5.98 (s, 1H, pyrazole H-5), 7.00–7.82 (m, 15H, ArH's and pyrazole H-5), 9.34 (s, br., 2H, $NH_2$). Compound **10** was reacted with the appropriate hydrazonoyl halides **11b,c** gave 2-(5-(benzofuran-2-yl)-3',5'-diphenyl-3,4-dihydro-1'*H*,2*H*-[3,4'-bipyrazol]-2-yl)-4-methyl-5-(phenyl-diazenyl)thiazole (**12a**), and 2-(5-(benzofuran-2-yl)-3',5'-diphenyl-3,4-dihydro-1'*H*,2*H*-[3,4'-bipyrazol]-2-yl)-4-phenyl-5-(phenyldiazenyl)thiazole (**12b**) (Scheme 2). Structures **12** were confirmed by elemental analyses, spectral data, and alternative synthetic routes. Thus, benzenediazonium chloride reacted with 2-(5-(benzofuran-2-yl)-2',5'-diphenyl-3,4-dihydro-2*H*,2'*H*-[3,3'-bipyrazol]-2-yl)-4-phenylthiazole (**13**), which prepared via reaction of **3** with **14** or **10** with ω-bromoacetophenone, in pyridine to give a product identical in all aspects (m.p., mixed m.p., and spectra) with **12b** (Scheme 2, Table 1).

On the other hand, the reactivity of compound **15** [13, 14] towards a variety of hydrazonoyl halides was also studied. Thus, treatment of compound **15** with the appropriate hydrazonoyl halides **11a,b** and **11e** in moist sodium carbonate furnished without solvents, in each case, one isolable product. The isolable products were assigned as 3-substituted 5-(benzofuran-2-yl)-4-cyano-1-phenyl-1*H*-pyrazole **17a-c** on the basis of their analytical and spectral data (Scheme 3, Table 1). The IR spectrum of **17a-c** revealed bands near 2229 *v*(CN), 1724-1693 *v*(C=O). The $^1$H NMR spectrum of **17a** in (DMSO-d6) revealed signals at δ1.33 (t, 3H, *J* = 7 Hz, $CH_2\mathbf{CH_3}$), 4.41 (q, 2H, *J* = 7 Hz, $\mathbf{CH_2}CH_3$), 6.93 (s, 1H, CH-furan) and 7.41-7.63 (m, 9H, ArH's). From the above data the structures **18** were ruled out (Scheme 3).




**Scheme 3**

Structure of **17a-c** can also be confirmed by alternative synthetic routes. Thus, compound **15** together with the appropriate **11a**, **b** and **11e** in ethanol in presence of sodium ethoxide gave product identical in all aspects (mp. mixed mp. and spectra) with **17**. The corresponding pyrazolopyridazine derivatives were obtained by the reaction of pyrazole**17a** with hydrazine hydrate under reflux in ethanol for 5 hrs. The lack of nitrile and carbonyl groups in the IR spectrum of the isolated product supported the formation of pyridazine **19** (Scheme 3).Finally, 2,3-dihydro 1,3,4-thiadiazoles **22a-f** were obtained by grinding (solvent-free conditions) of compound **15**, potassium hydroxide, phenyl isothiocyanate and hydrazonoyl halides (Scheme 4). Thus, $^1$H NMR spectrum of **22f** showed signal at δ 2.520 (s, 3H, $CH_3$), 6.90 (s, 1H, CH-furan) and 7.08-8.30 (m, 13H, ArH's).




**Scheme 4**

**Table1: Comparison between grinding and traditional method for synthesized compounds**

| Comp. No. | Grinding method | | Traditional method | |
|---|---|---|---|---|
| | Time | Yield % | Time | Yield % |
| **3** | 10 min. | 95 % | 2 hrs | 88 % |
| **4** | 10 min. | 92 % | 4 hrs | 85 % |
| **5** | 10 min. | 92 % | 4 hrs | 75 % |
| **6** | 10 min. | 92 % | 4 hrs | 80 % |
| **7** | 10 min. | 92 % | 4 hrs | 79 % |
| **8a** | 10 min. | 90 % | 2hrs | 75 % |
| **8b** | 10 min. | 90 % | 2hrs | 78 % |
| **8c** | 10 min. | 90 % | 2hrs | 75 % |
| **9a** | 10 min. | 92 % | 2hrs | 78 % |
| **9b** | 10 min. | 94 % | 2hrs | 82 % |
| **10** | 10 min. | 90 % | 6hrs | 74 % |
| **12a** | 10 min. | 91 % | 4hrs | 76 % |
| **12b** | 10 min. | 90 % | 4hrs | 75 % |
| **13** | 10 min. | 89 % | 6hrs | 74 % |
| **17a** | 10 min. | 92 % | 4hrs | 75 % |
| **17b** | 10 min. | 94 % | 4hrs | 75 % |
| **17c** | 10 min. | 90 % | 4hrs | 75 % |
| **19** | 10 min. | 90 % | 5hrs | 75 % |
| **22a** | 10 min. | 92 % | 4hrs | 70 % |
| **22b** | 10 min. | 93 % | 4hrs | 70 % |
| **22c** | 10 min. | 92 % | 4hrs | 80 % |
| **22d** | 10 min. | 90 % | 4hrs | 70 % |
| **22e** | 10 min. | 90 % | 4hrs | 70 % |
| **22f** | 10 min. | 93 % | 4hrs | 71 % |

### 3. Antimicrobial Activity

Some newly synthesized compounds were screened for in vitro antibacterial activity against the standard strains Gram- positive bacteria: *Staphylococcus aureus (ATCC 25923)* and *Bacillus subtilis (ATCC 6635)*, Gram-negative bacteria: *Escherichia coli (ATCC 25922)* and *Salmonela typhimurium (ATCC 14028*) by standardized disc – agar diffusion method at 1 and 0.5 mg/ml concentration. *N*,*N*-dimethylformamide was used as solvent control. The antibiotic chloramphenicol was used as standard reference in the case of Gram – negative bacteria; Cephalothin was used as standard reference in the case of Gram – positive bacteria and the results were summarized in Table 2.

The synthesized compounds were also tested for antifungal activity against fungal organisms *Aspergillus fumigatus* and one yeast fungus; *Candida albicans* by standardized disc – agar diffusion method at 1 and 0.5 mg/ml concentration. *N*,*N*-dimethylformamide was used as solvent control. Cycloheximide was used as standard reference in the case of yeasts and fungi. Zones of inhibition were determined for the tested compounds and the results were summarized in Table 2.

The in vitro study results demonstrated that for high and low concentrations, compounds **4a-c**, **12a** and **18b** were capable low inhibition against Gram-positive bacteria *Bacillus Subtilis* and compounds **10b** and **11a** were capable intermediate inhibition against Gram-negative bacteria *Escherichia coli* whereas compound **4a** show intermediate inhibition against Yeast and Fungi.

**Table 2: Antimicrobial activity data of tested compounds**

| **Organism** | **Mean* of zone diameter, nearest whole mm.** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Gram - positive bacteria** | | | | **Gram - negative bacteria** | | | | ****Yeast and Fungi** | | | |
| | ***S.aureus* (ATCC 25923)** | | ***B .subtilis* (ATCC 6635)** | | ***S typhimurium* (ATCC 14028)** | | ***E. coli* (ATCC 25922)** | | **C.Albicans (ATTCC 10231)** | | ***A.Fumigatus*** | |
| **Conc. Sample** | **1 mg/ ml** | **0.5 mg/ ml** | **1 mg/ ml** | **0.5 mg/ ml** | **1 mg/ ml** | **0.5 mg/ ml** | **1 mg/ ml** | **0.5 mg/ ml** | **1 mg/ ml** | **0.5 mg/ ml** | **1 mg/ ml** | **0.5 mg/ ml** |
| 4a | - | - | 11L | 7L | - | - | - | - | - | - | - | - |
| 4b | - | - | 13L | 7L | | | - | - | 13I | 10I | 12I | 8I |
| 4c | - | - | 10L | 8L | | | - | - | - | - | - | - |
| 10b | - | - | - | - | - | - | 12I | 7I | - | - | 11L | 7L |
| 10c | - | - | | | - | - | - | - | - | - | - | - |
| 11a | - | - | - | - | - | - | 14I | 11I | - | - | - | - |
| 11c | - | - | L | L | - | - | - | - | - | - | - | - |
| 12a | - | - | 11L | 8L | - | - | - | - | - | - | - | - |
| 12c | - | - | - | - | - | - | - | - | - | - | - | - |
| 18a | - | - | - | - | - | - | - | - | - | - | - | - |
| 18b | - | - | 10L | 7L | - | - | - | | 11L | 7L | - | - |
| Control # | 35 | 26 | 35 | 25 | 36 | 28 | 38 | 27 | 35 | 28 | 37 | 26 |

* = Calculate from 3 values, ** = identified on the basis of routine culture, morphological and microscopical characteristics. – = No effect. ,L: Low activity = Mean of zone diameter ≤ 1/3 of mean zone diameter of control. I: Intermediate activity = Mean of zone diameter ≤ 2/3 of mean zone diameter of control. H: High activity = Mean of zone diameter > 2/3 of mean zone diameter of control. #: Chloramphenicol in the case of Gram-positive bacteria, Cephalothin in the case of Gram-negative bacteria. . Cycloheximide was used as standard reference in the case of yeasts and fungi

## 4. Experimental

### *Instrumentation*

All melting points were determined on an electrothermal apparatus and are uncorrected. IR spectra were recorded (KBr discs) on a Shimadzu FT-IR 8201 PC spectrophotometer. $^1$H and $^{13}$C NMR spectra were recorded in $CDCl_3$ and $(CD_3)_2SO$ solutions on a Varian Gemini 300 MHz and JNM-LA 400 FT-NMR system spectrometer and chemical shifts are expressed in ppm units using TMS as an internal reference. Massspectra were recorded on a GC-MS QP1000 EX Shimadzu. Elemental analyses were carried out at the Microanalytical Center of Cairo University. Hydrazonoyl halides **11a-f**were prepared as previously reported [15-18].

***1-(Benzofuran-2-yl)-3-(1,3-diphenyl-1H-pyrazol-4-yl)prop-2-en-1-one (3).***

***Grinding method***:2-acetylbenzofuran (**1**) (1.6 g, 10mmol),1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde (**2**)(1.24 g, 10mmol), potassium hydroxide (0.56 g, 10 mmol) and few drops of water was ground with a pestle in an open mortar at room temperature for 2-3 min. until the mixture turned into a melt. The initial syrupy reaction mixture solidified within 3-5 min. Grinding was continued for 5-10 min while the reaction was monitored by TLC. The solid was washed with water and recrystallized from ethanol to give the corresponding **3**.

***Traditional method***:Potassium hydroxide (10 mL, 10%) was added dropwise to a mixtureof 2-acetylbenzofuran (**1**) and 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde (**2**)(10mmol each) in ethanol (20 mL) while stirring at 0-5°C. The stirring was continued for 2 hrs. Then the resulting solid was collected and recrystallized from ethanol to give **3**. White crystals from ethanol. mp.: 168-170°C; FT-IR (KBr, cm$^{-1}$): 3064 *v*(CH-aroma.), 1660 *v*(CO), 1610 *v*(C=N), 1570 *v*(C=C); $^1$H NMR (300 MHz, DMSO-$d_6$, δ, ppm): 7.10-8.17 (m, ArH's) and CH=CH). Anal.Calcd.for$C_{26}H_{18}N_2O_2$ (390.43):C, 79.98; H, 4.65; N, 7.17. Found: C, 79.94; H, 4.61; N, 7.13%.

***Synthesisofpyridine derivatives 4-7***

***Grinding Method***: Equimolar amounts of **1** (0.8 g, 5 mmol), **2** (5 mmol) and the appropriate cyanothioacetamide, malononitrile, cyanoacetamide, or cyanoacidhydrazide (5 mmol) and ammonium acetate (0.77 g, 10 mmol) was ground with a pestle in an open mortar at room temperature for 2-3 min. until the mixture turned into a melt. The initial syrupy reaction mixture solidified within 3-5 min. Grinding was continued for 5-10 min. while the reaction was monitored by TLC. The solid was washed with water and recrystallized from *N, N*-dimethylformamide to give the corresponding **4-7**, respectively.

***Traditional Method A***: A mixture of l-(benzofuran-2-yl)-3-(1,3-diphenyl-1*H*-pyrazol-4-yl)-prop-2-en-1-one **(3)** (5 mmol), the appropriate 2-cyanoethanethioamide,malononitrile, cyanoacetamide, ω-bromoacetophenone or cyanoacetohydrazide and ammonium acetate (5 mmol) was heated in acetic acid (10 mL) under reflux for 3 hrs. The reaction mixture was cooled; the separated solid was collected, filtered and crystallized from a proper solvent to give **4-7**.

***Traditional Method B***: A mixture of 2-acetylbenzofuran (**1**)(5 mmol), 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde (**2**) (5 mmol) and the appropriate 2-cyanoethanethioamide, malononitrile, cyanoacetamide, ω-bromoacetophenoneor cyanoacidhydrazide (5 mmol) and ammonium acetate (1.54 g, 20 mmol) was heated in n-butanol (10 mL) under reflux for 4 hrs. The excess solvent was evaporated and the residue was triturated with ethanol (10 mL). The solid formed was filtered off and crystallized from a proper solvent to give corresponding products which obtained in method A.

***6-(Benzofuran-2-yl)-2-mercapto-4-(1,3-diphenyl-1H-pyrazol-4-yl)pyridine-3-carbonitrile(4).*** Orange crystals from ethanol.mp.: 288-90°C; FT-IR (KBr, cm$^{-1}$): 3058 *v*(CH-aroma.), 2218 *v*(CN), 1604 *v*(C=N), 1234 *v*(SH). Anal.Calcd.for $C_{29}H_{18}N_4OS$ (470.54): C, 74.02; H, 3.86; N, 11.91; S, 6.81. Found: C, 74.06; H, 3.82; N, 11.96; S, 6.77. %.

***2-Amino-6-(benzofuran-2-yl))-4-(1,3-diphenyl-1H-pyrazol-4-yl)pyridin-3-carbonitrile (5).***Red crystals from ethanol.mp.: 89-90°C; FT-IR (KBr, cm$^{-1}$): 3288, 3200 *v*($NH_2$), 3062 *v*(CH-arom.), 2206 *v*(CN), 1589 *v*(C=C). $^1$H NMR (300 MHz, DMSO-$d_6$, δ,ppm):4.24 (s, 2H, $NH_2$), 7.20-7.85 (m, 17H, ArH's). Anal.Calcd.for $C_{29}H_{19}N_5O$ (453.49): C, 76.81; H, 4.22; N, 15.44. Found: 76.77; H, 4.26; N, 15.40%.

***1,2-Dihydro-6-(benzofuran-2-yl))-2-oxo-4(1,3-diphenyl-1H-pyrazol-4-yl)-pyridin-3-carbonitrile (6).*** Yellow crystals from ethanol.mp.: 128-130°C; FT-IR (KBr, $cm^{-1}$): 3340 *ν*(NH), 3066*ν*(CH-arom.), 2241 *ν*(CN), 1674 *ν*(CO), 1604 *ν*(C=N). $^1$H NMR (300 MHz, DMSO-$d_6$, δ, ppm): 7.22-7.81 (m, 17H, ArH's), 11.21 (s, H, NH). Anal.Calcd. For $C_{29}H_{18}N_4O_2$ (454.48): C, 76.64; H, 3.99; N, 12.33. Found: 76.68; H, 4.03; N, 12.37%.

***6-(benzofuran-2-yl)-2-hydrazinyl-4-(1,3-diphenyl-1H-pyrazol-4-yl)pyridine-3-carbonitrile (7).*** Yellow crystals from ethanol.m.p.: 220°C; FT-IR (KBr, $cm^{-1}$): 3290, 3200 *ν*($NH_2$), 3062 *ν*(CH-arom.), 2210 *ν*(CN), 1689 *ν*(C=O).Anal.Calcd. for $C_{29}H_{19}N_5O_2$(469.49):C, 74.19; H, 4.08; N, 14.92. Found: 74.15; H, 4.04; N, 14.97%.

***2-(Substituted) 6-(benzofuran-2-yl)-4-(1,3-diphenyl-1H-pyrazol-4-yl)-pyridine-3-carbonitrile 8a*-c.**

***Grinding Method***:Equimolar amounts of **4**(2.35 g, 5 mmol) and potassium hydroxide (0.28 g,5 mmol) was ground with a pestle in an open mortar followed by the appropriate iodomethane, ethyl chloroacetate or chloroacetone (5 mmol) at room temperature for 2-3 min. until the mixture turned into a melt. The initial syrupy reaction mixture solidified within 3-5 min. Grinding was continued for 5-10 min. while the reaction was monitored by TLC. The solid was washed with water and recrystallized from *N*,*N*-dimethylformamide to give the corresponding ***8a*-c**, respectively.

***Traditional Method***: A mixture of **4**(2.35 g, 5 mmol) and potassium hydroxide (0.28 g, 5 mmol) in *N*,*N*-dimethylformamide (10 mL) was stirred for 2 hrs at room temperature. The appropriate of iodomethane, ethyl chloroacetate or chloroacetone (5 mmol) was added while stirring. Stirring was continued for 2 hrs. The resulting solid was collected and crystallized from *N*,*N*-dimethylformamide to afford ***8a*-c**, respectively.

***6-(Benzofuran-2-yl))-2-(methylthio)-4-(1,3-diphenyl-1H-pyrazol-4-yl)-pyridin--3-carbonitrile (8a).***Yellow crystals from *N*, *N*-dimethylformamide. mp.: 234-36°C; FT-IR (KBr, $cm^{-1}$):3055 *ν*(CH-aroma.), 2923, 2854 *ν*(CH-aliph.), 2210 *ν*(CN), 1596 *ν*(C=C). $^1$H NMR (300 MHz, DMSO-$d_6$, δ, ppm): 2.77 (s, 3H, $SCH_3$), 7.27-8.49(m, 17H, ArH's). Anal.Calcd.for $C_{30}H_{20}N_4OS$ (484.57): C, 74.36; H, 4.16; N, 11.56; S, 6.62. Found: 74.40; H, 4.20; N, 11.60; S, 6.70 %.

***Ethyl 6-(benzofuran-2-yl))-4-(1,3-diphenyl-1H-pyrazol-4-yl)-pyridin-2-ylthio)acetate-3-carbonitrile (8b).***Yellow crystals from *N*, *N*-dimethylformamide. mp.: 200-02°C; FT-IR (KBr, $cm^{-1}$):3058 *ν*(CH-aroma.), 2981, 2931 *ν*(CH-aliph.), 2214 *ν*(CN), 1732 *ν*(C=O), 1596 *ν*(C=C)$^1$H NMR (300 MHz, DMSO-$d_6$, δ, ppm):1.20 (t, 3H, *J* = 7 Hz, $CH_2\mathbf{CH_3}$), 4.22 (q, 2H, *J* = 7 Hz, $\mathbf{CH_2}CH_3$), 4.70 (s, 2H, $SCH_2$), 7.22-810 (m, 17H, ArH's); MS (El, m/z (%): 557 (M+1, 25), 556(M+,33.3), 512 (33.3), 85 (29.2), 73(100). Anal.Calcd.for $C_{33}H_{24}N_4O_3S$ (556.63):C, 71.21; H, 4.35; N, 10.07; S, 5.76. Found: 71.29; H, 4.44; N, 10.13; S, 5.80 %.

***S-6-(benzofuran-2-yl)-3-cyano-4-(1,3-diphenyl-1H-pyrazol-4-yl)pyridin-2-yl-ethanethioate (8c).***Yellow crystals from *N*, *N*-dimethylformamide.mp.: 100-02°C; FT-IR (KBr, $cm^{-1}$):3062 *ν* (CH-aroma.), 2931, 29854 *ν* (CH-aliph.), 2194 *ν*(CN), 1666 *ν*(C=O), 1596 *ν*(C=C). $^1$H NMR (300 MHz, DMSO-$d_6$, δ, ppm):(s, 3H, $COCH_3$), 4.70 (s, 2H, $SCH_2$), 7.20-8.15 (m, 17H, ArH's). Anal.Calcd.for $C_{32}H_{22}N_4O_2S$ (526.61):C, 72.98; H, 4.21; N, 10.64; S, 6.09. Found: C, 72.94; H, 4.25; N, 10.60; S, 6.05 %.

***2-(Substituted-3-amino-6-(benzofuran-2-yl)-4-(1,3-diphenyl-1H-pyrazol-4-yl)thieno[2,3-b]pyridine (9a,b)***

***Grinding Method***: Equimolar amounts of **4**(2.35 g, 5 mmol) and potassium hydroxide (0.28 g, 5 mmol) was ground with a pestle in an open mortar followed by the appropriate phenacyl bromide or chloroacetonitrile (10mmol) at room temperature for 2-3 min. until the mixture turned into a melt. The initial syrupy reaction mixture solidified within 3-5 min. Grinding was continued for 5-10 min. while the reaction was monitored by TLC. The solid was washed with water and recrystallized from *N*, *N*-dimethylformamide to give the corresponding **9a**, **b**, respectively.

***Traditional Method***: A mixture of **4**(2.35 g, 5 mmol) and potassium hydroxide (0.28 g, 5 mmol) in *N*,*N*-dimethylformamide (10 mL) was stirred for 2 hrs at room temperature. The appropriate of phenacyl bromide or chloroacetonitrile (10mmol) was added while stirring. Stirring was continued for 2 hrs. The resulting solid was collected and crystallized from *N*, *N*-dimethylformamide to afford **9a**, **b** respectively.

***(3-amino-6-(benzofuran-2-yl)-4-(1,3-diphenyl-1H-pyrazol-4-yl)thieno[2,3-b]pyridin-2-yl)(phenyl)methanone(9a)***

Yellow crystals from ethanol. mp.: 199-200°C; FT-IR (KBr, $cm^{-1}$): 3370, 3286 *v*($NH_2$), 3058 *v* (CH-aroma.), 1666 *v*(C=O).$^1$H NMR (300 MHz, DMSO-$d_6$, δ, ppm): 6.24 (s, 2H, $NH_2$), 7.20-7.85 (m, 22H, ArH's). Anal.Calcd.for $C_{37}H_{24}N_4O_2S$(588.68): C,75.49; H, 4.11; N, 9.52; S, 5.45. Found: C, 75.45; H, 4.15; N, 9.56; S, 5.41%.

***3-amino-6-(benzofuran-2-yl)-4-(1,3-diphenyl-1H-pyrazol-4-yl)thieno[2,3-b]pyridine-2-carbonitrile (9b)***

Yellow crystals from DMF.mp.:>300°C; FT-IR (KBr, $cm^{-1}$): 3463, 3332 *v* ($NH_2$), 3058 *v* (CH-aroma.), 2202 *v* (CN), 1627 *v*(C=N). $^1$H NMR (300 MHz, DMSO-$d_6$, δ, ppm): 5.60 (s, 2H, $NH_2$), 7.20-7.85 (m, 17H, ArH's). Anal.Calcd.for$C_{31}H_{19}N_5OS$(509.58): C, 73.07; H, 3.76; N, 13.74; S, 6.29. Found:C, 73.10; H, 3.72; N, 13.70; S, 6.25%.

***3-(benzofuran-2-yl)-4,5-dihydro-5-(1,3-diphenyl-1H-pyrazol-4-yl)pyrazole-1-carboxamide(10)***

***Grinding method***: Chalcone **3** (1.95 g, 5mmol), thiosemicarbazide (0.485 g, 5mmol), sodium hydroxide (0.4 g, 10 mmol) and few drops of water was ground with a pestle in an open mortar at room temperature for 2-3 min. until the mixture turned into a melt. The initial syrupy reaction mixture solidified within 3-5 min. Grinding was continued for 5-10 min while the reaction was monitored by TLC. The solid was washed with water and recrystallized from ethanol to give the corresponding **10**.

***Traditional method***: A mixture of chalcone **3** (1.95 g, 5mmol)and thiosemicarbazide (0.485 g, 5 mmol) in acetic acid (20 mL) was heated under reflux for 6hrs. The resulting solid that obtained after cooling was collected and recrystallized from ethanol to give **10**.Page crystals from ethanol.mp.: 205-07°C; FT-IR (KBr, $cm^{-1}$):3417, 3367 *v* ($NH_2$), 3058 *v* (CH-aroma.), 1600 *v*(C=N; $^1$H NMR (300 MHz, DMSO-$d_6$, δ, ppm):3.66 (dd, 1H, *J* = 18.1, 5.8Hz, $CH_2$(pyraz), 4.01 (dd, 1H, *J* = 18.1, 12Hz, $CH_2$(pyraz), 5.33 (dd, *J* = 12.2 5.8 Hz, CH(pyraz), 5.98 (s, 1H, pyrazole H-5), 7.00–7.82 (m, 15H, ArH's and pyrazole H-5), 9.34 (s, br., 2H, $NH_2$).Anal. Calcd.for $C_{27}H_{21}N_5OS$ (463.55): C, 69.96; H, 4.57; N, 15.11; S, 6.92. Found: C, 69.91; H, 4.53; N, 15.15; S, 6.96%.

***1-(2-(3-(benzofuran-2-yl)-4,5-dihydro-5-(1,3-diphenyl-1H-pyrazol-4-yl)pyrazol-1-yl)-4-substituted 1,3-thiazol-5-yl)-2-phenyldiazene (12a,b)***

***Grinding method***:Carboxamide **10** (2.32 g, 5mmol), the appropriate hydrazonoyl halides **11b**,**c** (5 mmol), sodium carbonate (1g, 10 mmol) and few drops of water was ground with a pestle in an open mortar at room temperature for 2-3 min. until the mixture turned into a melt. The initial syrupy reaction mixture solidified within 3-5 min. Grinding was continued for 5-10 min while the reaction was monitored by TLC. The solid was washed with water and recrystallized from ethanol to give the corresponding **12a** and **12b**, respectively.

***Traditional method***: A mixture of **10** (2.32 g, 5mmol) and hydrazonoyl halides **11b**,**c** (5 mmol) in ethanol containing triethylamine was heated under reflux for 4hrs. The resulting solid that obtained after cooling was collected and recrystallized from ethanol to give **12a**,**b**, respectively.

***2-(5-(benzofuran-2-yl)-3',5'-diphenyl-3,4-dihydro-1'H,2H-[3,4'-bipyrazol]-2-yl)-4-methyl-5-(phenyldiazenyl)thiazole (12a)***

Red crystals from ethanol. mp.: 220°C; FT-IR (KBr, $cm^{-1}$):3062, 2927 *v*(CH),1608 *v*(C=N). $^1$H NMR (300 MHz, DMSO-$d_6$, δ,ppm):2.53(s, 3H, $CH_3$), 3.20 (dd, 1H, *J* = 18.1, 5.8Hz, $CH_2$(pyraz), 3.82 (dd, 1H, *J* = 18.1, 12.0 Hz, $CH_2$(pyraz), 5.23 (dd, 1H, *J* = 12.2, 5.8 Hz, CH(pyraz), 7.20-7.75 (m, 21H, ArH's).Anal.Calcd. for $C_{36}H_{27}N_7OS$ (605.71): C, 71.38; H, 4.49; N, 16.19; S, 5.29. Found: C, 71.34; H, 4.43; N, 16.15; S, 5.25%.

***2-(5-(benzofuran-2-yl)-3',5'-diphenyl-3,4-dihydro-1'H,2H-[3,4'-bipyrazol]-2-yl)-4-phenyl-5-(phenyldiazenyl)thiazole (12b)***

Red crystals from ethanol. mp.: 230°C; FT-IR (KBr, $cm^{-1}$):3058, 2927 *v*(CH),1600 *v*(C=N). Anal.Calcd.for $C_{41}H_{29}N_7OS$ (667.78):C, 73.74; H, 4.38; N, 14.68; S, 4.80. Found: C, 73.70; H, 4.34; N, 14.72; S, 4.84%.

***4-(3-(benzofuran-2-yl)-4,5-dihydro-1-(4-phenylthiazol-2-yl)-1H-pyrazol-5-yl)-1,3-diphenyl-1H-pyrazole (13)***

***Grinding method***: Chalcone **3** (1.95 g 5mmol), 1-(4-phenylthiazol-2-yl)hydrazine **(14)** (1.45 g, 5 mmol), sodium hydroxide (10 mmol) and few drops of water was ground with a pestle in an open mortar at room temperature for 2-3 min. until the mixture turned into a melt. The initial syrupy reaction mixture solidified within 3-5 min. Grinding was continued for 5-10 min while the reaction was monitored by TLC. The solid was washed with water and recrystallized from ethanol to give the corresponding **13**.

***Traditional method***: A mixture of chalcone **3**(1.95 g 5mmol)and 1-(4-phenylthiazol-2-yl) hydrazine **(14)** (1.45 g, 5 mmol) in acetic acid (20 mL) was heated under reflux for 6hrs. The resulting solid that obtained after cooling was collected and recrystallized from ethanol to give **13**.

***Alternative method***: A mixture of **10** (2.32 g, 5mmol)andω-bromoacetophenone (1 g, 5 mmol) in ethanol containing triethylamine was heated under reflux for 4 hrs. The resulting solid that obtained after cooling was collected and recrystallized from ethanol to give **13**.
Brown crystals from ethanol.mp.: 160°C; FT-IR (KBr, $cm^{-1}$): 3061, 2929 *v* (CH),1600 *v* (C=N). $^1$H NMR (300 MHz, DMSO-$d_6$, δ,ppm):3.23 (dd, 1H, *J* = 18.1, 5.8Hz, $CH_2$(pyraz), 3.95 (dd, 1H, *J* = 18.1, 12.0 Hz, $CH_2$(pyraz), 5.33 (dd, 1H, *J* = 12.2, 5.8 Hz, CH(pyraz)), 6.58 (s, 1H, thiazole H-5), 7.25-7.72 (m, 21H, ArH's).Anal.Calcd.for$C_{35}H_{25}N_5OS$(563.67): C, 74.58; H, 4.47; N, 12.42; S, 5.69. Found: C, 74.54; H, 4.43; N, 12.46; S, 5.65%.

***Synthesis of 3-substituted 5-(benzofuran-2-yl)4-cyano-1-phenyl-1H-pyrazole (17a-c).***

***Grinding Method***: A mixtureof **15** (0.925 g, 5 mmol),the appropriate hydrazonoyl halide **11a-c** (5 mmol), sodium carbonate (1 g, 10 mmol) and few drops of water was ground with a pestle in an open mortar at room temperature for 2-3 min. until the mixture turned into a melt. The initial syrupy reaction mixture solidified within 3-5 min. Grinding was continued for 5-10 min while the reaction was monitored by TLC. The solid was washed with water and recrystallized from the appropriate solvent to give the corresponding **17a-c**, respectively.

***Traditional Method***: Compound **15** (0.925 g, 5 mmols) was added to a stirred ethanolic sodium ethoxide solution (0.12 g sodium metal in absolute ethanol 20 mL). After 20 min., the appropriate hydrazonoyl halide **11a-c** (5 mmols) was added and the reaction mixture was stirred for 4 h. The resulting solid was collected by filtration, dried and recrystallized from a proper solvent to give **17a-c**, respectively.

***Ethyl 5-(benzofuran-2-yl)-4-cyano-1-phenyl-1H-pyrazole-3-carboxylate (17a).*** Yellow crystals from ethanol.mp.: 174°C. FT-IR (KBr, $cm^{-1}$):3066 *v*(CH-aroma.), 2985, 2912 *v*(CH-aliph.), 2229 *v*(CN), 1724 *v*(CO), 1596 *v*(C=C). $^1$H NMR (300 MHz, DMSO-$d_6$, δ, ppm):1.33 (t, 3H, *J* = 7 Hz, $CH_2\mathbf{CH_3}$), 4.41 (q, 2H, *J* = 7 Hz, $\mathbf{CH_2}CH_3$), 6.93 (s, 1H, CH-furan), 7.41-7.63 (m, 9H, ArH's). Anal.Calcd.for$C_{21}H_{15}N_3O_3$(357.36): C, 70.58; H, 4.23; N, 11.76. Found: 70.50; H, 4.27; N, 11.80%.

***3-Acetyl-5-(benzofuran-2-yl)-1-phenyl-1H-pyrazole-4-carbonitrile (17b)*** Yellow crystals from acetic acid. mp.: 220°C. FT-IR (KBr, $cm^{-1}$):3062 *v*(CH-arom.), 2237 *v*(CN), 1693 *v*(CO), 1604 *v*(C=N). $^1$H NMR (300 MHz, DMSO-$d_6$, δ, ppm):2.68 (s, 3H, $CH_3$), 7.05 (s, 1H, CH-furan), 7.25-7.61 (m, 9H, ArH's). Anal.Calcd.for $C_{20}H_{13}N_3O$ (327.34): C, 73.38; H, 4.00; N, 12.84. Found: C, 73.42; H, 4.04; N, 12.80%.

***3-(Benzofuran-2-yl-carbonyl)-5-(benzofuran-2-yl)-1-phenyl-1H-pyrazole-4-carbonitrile (17c).*** Red crystals from ethanol.Yield: 75%, mp.: 210-12°C.$^1$H NMR (300 MHz, DMSO-$d_6$, δ, ppm): 7.33-7.61 (m, 15H, ArH's). Anal.Calcd.for $C_{27}H_{15}N_3O_3$ (429.43): C, 75.52; H, 3.52; N, 9.79. Found: C, 75.48; H, 3.56; N, 9.75%.

***4-amino-3-(benzofuran-2-yl)-2-phenyl-2H-pyrazolo[3,4-d]pyridazin-7(6H)-one*(19)**

***Grinding method***: A mixture of **17a** (1.8 g, 5mmol) and hydrazine hydrate (0.5 g, 10mmol) was ground with a pestle in an open mortar at room temperature for 2-3 min. until the mixture turned into a melt. The initial syrupy reaction mixture solidified within 3-5 min. Grinding was continued for 5-10 min while the reaction was monitored by TLC. The solid was washed with water and recrystallized from ethanol to give the corresponding **19**.

***Traditional method***: A mixture of **17a** (1.8 g, 5mmol) and hydrazine hydrate (0.5 g, 10 mmol) in ethanol (20 mL) was heated under reflux for 5hrs. The resulting solid that obtained after cooling was collected and recrystallized from ethanol to give **19** as white crystals from ethanol. mp.: 273-74°C. $^1$H NMR (300 MHz, DMSO-$d_6$, δ, ppm): 6.32 (br, 2H, $NH_2$), 7.33-7.61 (m, 10H, ArH's), 9.50(s,1H, NH). Anal.Calcd.for$C_{19}H_{13}N_5O_2$(343.34): C, 66.47; H, 3.82; N, 20.40. Found: C, 66.43; H, 3.86; N, 20.45%.

***Synthesis of 2,3-dihydro 1,3,4-thiadiazoles 22a-f***

***Grinding Method***: 3-(benzofuran-2-yl)-3-oxopropanenitrile **15** (1.84 g, 10 mmol), phenyl isothiocyanate (1.37 g, 10 mmol) and potassium hydroxide (0.56 g, 10 mmol) was ground with a pestle in an open mortar followed by the appropriate hydrazonoyl halides **11a-f** (10 mmol) at room temperature for 2-3 min. until the mixture turned into a melt. The initial syrupy solidified within 3-5 min. Grinding was continued for 5-10 min. while the reaction was monitored by TLC. The solid was washed with ethanol-water and recrystallized froma proper solvent to afford **22a-f**, respectively.

***Traditional Method***: A mixture of Compound **15** (1.84 g, 10 mmol), phenyl isothiocyanate (1.37 g, 10 mmol) and potassium hydroxide (0.56 g, 10 mmol) in *N*, *N*-dimethylformamide (10 mL) was stirred for 2 hrs at room temperature. The appropriate hydrazonoyl halides **11a-f** (10mmol) was added while stirring. Stirring was continued for 2 hrs. The resulting solid was collected and crystallized from a proper solvent to afford **22a-f**,respectively.

***Ethyl-5-(2-(benzofuran-2-yl)-1-cyano-2-oxoethylidene)-4-phenyl-4,5-dihydro-1,3,4-thiadiazole-2-carboxylate (22a)***

Yellow crystals from ethanol.mp.: 210-12°C (lit mp. 210 [19]). FT-IR (KBr, cm$^{-1}$): 3062 *v*(CH-arom.), 2190 *v*(CN), 1720, 1680 *v*(CO). $^1$H NMR (300 MHz, DMSO-$d_6$, δ, ppm): 1.36 (t, 3H, *J* = 7.5 Hz, $CH_2\mathbf{CH_3}$), 4.2 (q, 2H, *J* = 7.5 Hz, $\mathbf{CH_2}CH_3$), 7.10 – 7.92 (m, 10H, ArH's). Anal.Calcd.for$C_{22}H_{15}N_3O_4S$ (417.44): C, 63.30; H, 3.62; N, 10.07; S, 7.68.Found: C, 63.15; H, 3.52; N, 10.21, S, 7.86 %

***2-(5-Acetyl-3-phenyl-1,3,4-thiadiazol-2(3H)-ylidene)-3-(benzofuran-2-yl)-3-oxopropanenitrile (22b)***

Red crystals from ethanol.mp.: 200-202 °C (lit mp. 200 [19]). FT-IR (KBr, cm$^{-1}$): 3062 *v*(CH-arom.), 2190 *v*(CN), 1665, 1655 *v*(CO). $^1$H NMR (300 MHz, DMSO-$d_6$, δ, ppm): 2.11 (s, 3H, $CH_3$), 7.10- 7.92 (m, 10H, ArH's). Anal.Calcd.for$C_{21}H_{13}N_3O_3S$ (387.41): C, 65.11; H, 3.38; N, 10.85; S, 8.28.Found: C, 65.00; H, 3.41; N, 10.99, S, 8.41%.

***3-(Benzofuran-2-yl)-2-(5-benzoyl-3-phenyl-1,3,4-thiadiazol-2(3H)-ylidene)-3-oxopropanenitrile (22c)***

Red crystals from ethanol.mp.: 181-82 °C (lit mp. 181 [19]). FT-IR (KBr, cm$^{-1}$): 3062 *v*(CH-arom.), 2190 *v*(CN), 1680, 1660 *v*(CO). $^1$H NMR (300 MHz, DMSO-$d_6$, δ, ppm): 7.10–7.92 (m,15H, ArH's). Anal.Calcd.for$C_{26}H_{15}N_3O_3S$ (449.48): C, 69.48; H, 3.36; N, 9.35; S, 7.13.Found: C, 69.51; H, 3.27; N, 9.53, S, 7.25%.

***2-(5-(Benzofuran-2-carbonyl)-3-phenyl-1,3,4-thiadiazol-2(3H)-ylidene)-3-(benzofuran-2-yl)-3-oxopropanenitrile (22d)***

Red crystals from ethanol.mp.: 220-22 °C (lit mp. 220 [19]). FT-IR (KBr, cm$^{-1}$): 3062 *v*(CH-arom.), 3220 *v*(NH), 2190 *v*(CN), 1680, 1665 *v*(CO). $^1$H NMR (300 MHz, DMSO-$d_6$, δ, ppm): 7.10 – 8.24 (m, 15H, ArH's). Anal.Calcd.for$C_{28}H_{15}N_3O_4S$ (489.50): C, 68.70; H, 3.09; N, 8.58; S, 6.55.Found: C, 68.64; H, 2.95; N, 8.47, S, 6.72%.

***5-(2-(Benzofuran-2-yl)-1-cyano-2-oxoethylidene)-N,4-diphenyl-4,5-dihydro-1,3,4-thiadiazole-2-carboxamide (22e)***

Yellow crystals from ethanol.mp.: 191-92 °C (lit mp. 192 [19]). FT-IR (KBr, cm$^{-1}$): 3062 *v*(CH-arom.), 3220 *v*(NH), 2190 *v*(CN), 1680, 1665 *v*(CO). $^1$H NMR (300 MHz, DMSO-$d_6$, δ, ppm): 7.10 – 7.92 (m, 15H, ArH's), 9.31 (s, br., 1H, NH). Anal.Calcd.for$C_{26}H_{16}N_4O_3S$ (464.50): C, 67.23; H, 3.47; N, 12.06; S, 6.90.Found: C, 67.42; H, 3.63; N, 11.89, S, 6.81 %.

***2-(5-(Benzofuran-2-yl-carbonyl)-3-p-tolyl-1,3,4-thiadiazol-2(3H)-ylidene)-3-(benzofuran-2-yl)-3-oxopropanenitrile (22f).***

Brown crystals from acetic acid.mp.: 220-22°C;$^1$H NMR (300 MHz, $CDCl_3$-$d_6$, δ, ppm): 2.520(s, 3H, $CH_3$), 6.90 (s, 1H, CH-furan) and 7.08-8.30 (m, 13H, ArH's).Anal.Calcd.for $C_{29}H_{17}N_3O_4S$ (503.53): C, 69.17; H, 3.40; N, 8.35; S, 6.37. Found: C, 69.14; H, 3.44; N, 8.39; S, 6.32%.

**Antimicrobial activity:**

Screening of antimicrobial activity was performed at a Microbiology Lab in Faculty of Agriculture, Al-Azhar University, Cairo, Egypt. Antimicrobial activity of the newly synthesized compounds was determined *in vitro* by standardized disc – agar diffusion method [20]. Cultures of two fungal species, namely, *Aspergillusfumigatus* and one yeast fungus; *Candida albicans*, as well as four bacterial species, namely, Gram- positive bacteria: *Staphylococcus aureus (ATCC 25923)* and *Bacillus subtilis (ATCC 6635)*, Gram-negative bacteria: *Escherichia coli (ATCC 25922)* and *Salmonela typhimurium (ATCC 14028)*, were used to investigate the antimicrobial activity of the newly synthesized compounds.

***Testing for anti-bacterial and yeasts activity*:**

Bacterial cultures were grown in nutrient broth medium at 30 °C. After 16 h of growth, each microorganism, at a concentration of $10^8$ cells/mL, was inoculated on the surface of Mueller-Hinton agar plates using sterile cotton swab. Subsequently, uniform size filter paper disks (6 mm in diameter) were impregnated by equal volume (10 µl) from the specific concentration of dissolved compounds and carefully placed on surface of each inoculated plate. The plates were incubated in the upright position at 36ºC for 24 hours. Three replicates were carried out for each extract against each of the test organism. Simultaneously, addition of the respective solvent instead of dissolved compound was carried out as negative controls. After incubation, the diameters of the growth inhibition zones formed around the disc were measured with transparent ruler in millimeter, averaged and the mean values were tabulated. The antibiotic chloramphencol was used as standard reference in the case of Gram – negative bacteria; Cephalothin was used as standard reference in the case of Gram – positive bacteria. The results are summarized in Table 2.

***Testing for anti-fungal activity*:**

Active inoculum for experiments were prepared by transferring many loopfuls of spores from the stock cultures to test tubes of sterile distilled water (SDW) that were agitated and diluted with sterile distilled water to achieve optical density corresponding to $2.0x10^5$ spore/ml. inoculum of 0.1 % suspension was swabbed uniformly and the inoculum was allowed to dry for 5 minutes then the same procedure was followed as described above. Cycloheximide was used as standard reference in the case of yeasts and fungi. Measurements were considered after 72 h for fungi and 24 h for bacteria. The results are summarized in Table 2.

## 5. Conclusion

A convenient, efficient and rapid method was developed for synthesis of pyridines, pyrazoles, thiadiazoline and 2,3-dihydro 1,3,4-thiadiazoles in a good to excellent yields by a grinding under catalyst- and solvent-free conditions. Comparison between the above twomethods showed that the solvent-free method (grinding method) was found to be better than the traditional method in terms of reaction time, yield, simplicity of the reaction procedure, ease of handling, low costs for performing the reaction and no solvents.

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