# Efficient and Expeditious Synthesis of Pyrano-pyrimidines, Multi-substituted γ-Pyrans, and Their Antioxidant Activity

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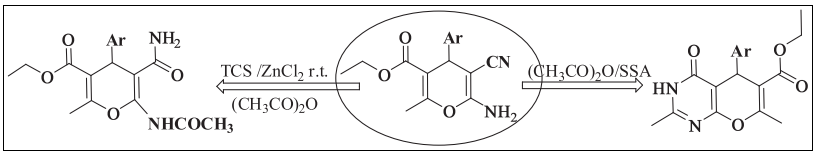


An efficient, expeditious catalytic route for the synthesis of ethyl 6-amino-5-cyano-2-methyl-4-aryl-4*H*-pyran-3-carboxylates **2** was achieved via a three-component, one-pot reaction of malononitrile, ethyl acetoacetate, and various aromatic aldehydes in water as a solvent at room temperature. The key advantages are excellent yield, reaction time, and inexpensive catalyst. Also, cyclization of 4*H*-pyrans **2** to the corresponding 4*H*-pyrano[2,3-*d*]pyrimidines **3** using silica sulfuric acid in the presence of acetic anhydride was described. Some synthesized compounds exhibited promising antioxidant activities.

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## INTRODUCTION

Multi-component reactions are processes in which three or more reactants combined in a single chemical step to produce products incorporating substantial portions of all the reactants. These reactions are known to be effective in building highly functionalized small organic molecules from readily available starting materials in a single step with inherent flexibility for creating molecular complexity and diversity coupled with minimization of time, labor, cost, and waste production [1].

Polyfunctionalized 4*H*-pyrans and their fused derivatives have received considerable attention over the past years because of their wide range of biological activity. Compounds with these ring systems have diverse pharmacological activity, such as antitumor [2], cardiotonic [3], hepatoprotective [4], antihypertensive, antibronchitic [5], as well antifungal activity [6].

Heterogeneous catalysts are advantageous over conventional homogeneous catalysts as they can easily recovered from the reaction mixture by simple filtration and can be reused after activation, thereby making the process economically viable. Catalysts based on silica are considered as one of the most significant types of heterogeneous catalysts because of their high surface areas and porosities, excellent stabilities (chemical and thermal), and facile functionalization with organic groups that can be robustly anchored to the surface [7–9].

So, the present work aimed to explore cyclization of some prepared ethyl 6-amino-5-cyano-2-methyl-4-aryl-4*H*-pyran-3-carboxylates to the related 5-substited-4,5-dihydro-3*H*-pyrano[2,3-*d*]pyrimidine-6-carboxylate using silica sulfuric acid (SSA) in the presence of acetic anhydride in an excellent yield, short reaction time, and inexpensive catalyst advantages.

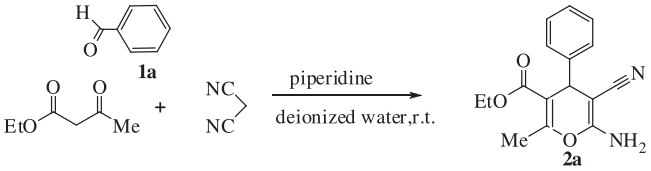
## RESULTS AND DISCUSSION

In continuation to our investigations for the synthesis of novel alicyclic and heterocyclic compounds for designing novel procedures in multi-component reactions, one-pot synthesis using tetrachlorosilane (TCS)/$ZnCl_2$ [10], we have developed in the present work an efficient and a rapid reaction for the synthesis of ethyl 6-amino-4-phenyl-5-cyano-2-methyl-4*H*-pyran-3-carboxylate **2a** in an excellent yield. This reaction was accomplished through three-component one-pot reaction of benzaldehyde **1a**, ethylacetoacetate, and malononitrile in the presence of piperidine, using deionized water as a solvent at room temperature (Scheme 1).

For optimization, some preliminary trials were investigated for the reaction conditions with regard to some catalysts (e.g., piperidine, SSA, $ZnCl_2$, TCS) and solvents. The reaction was carried out under various conditions in order to find out the best catalyst, solvent, time, and yield (Table 1).

From the primary optimization, the best reaction results were 1:1:1 ratio of aldehyde, malononitrile, and ethyl acetoacetate, respectively, in the presence of few drops of piperidine (0.5 mL) and deionized water (as a solvent) at room temperature (entry 1). These initial results prompted

**Scheme 1.** Synthesis of ethyl 6-amino-4-phenyl-5-cyano-2-methyl-4*H*-pyran-3-carboxylates **2a**.




us to explore the potential synthesis of functionalized 4*H*-pyrans (**2a–k**). Thus, when several examples of the aromatic aldehydes (**1a–k**), ethyl acetoacetate and malononitrile were left to react at room temperature in acetonitrile in the presence of few drops of piperidine, the pyran-3-carboxylates (**2a–k**) were afforded in good yield (Table 2). The obtained results are presented in Scheme 2. The IR spectra of the 4*H*-pyran-3-carboxylates **2** showed the characteristic bands for $NH_2$, CO, and C≡N. The NMR spectra revealed signals for three $CH_3$ proton signals at (δ: ppm) [1.20 (t, $CO_2CH_2CH_3$), 2.46 (s, $CH_3$) and 4.00 (q, $CO_2CH_2CH_3$)], for CH at 4.48 (s, CH) and for $NH_2$ at 4.62 (b, $NH_2$) together with the aromatic protons in 7.25–7.79 region (m, ArH). The mass spectra of **2i**, **k** revealed molecular ion peaks at $m/z = 288$ (12.12%) and 334.92 (24.12%), respectively.

Numerous pyrano [2,3-*d*]pyrimidines are considered as one of the most important derivatives of 4*H*-pyrans and well known to have diverse pharmacological activity. Several derivatives with such annulated uracils have antitumor [3], antibacterial [11], (antihypertensive, hepatoprotective, and cardiotonic) [4], vasodilator [12], bronchodilators [3], and antiallergic activities [13]. Some of these uracils exhibited antimalarial [14], antifungal [6], analgesics [15], and herbicidal [16] properties. As a continuation of the present investigation, a trial was attempted to synthesize pyrano[2,3-*d*]pyrimidine derivatives **3**. Thus, when selected examples of the pyran-3-carboxylates

**Table 1**

Effect of catalysts and solvent on the yield and time of the one-pot synthesis of ethyl 6-amino-4-phenyl-5-cyano-2-methyl-4*H*-pyran-3-carboxylate **2a**.

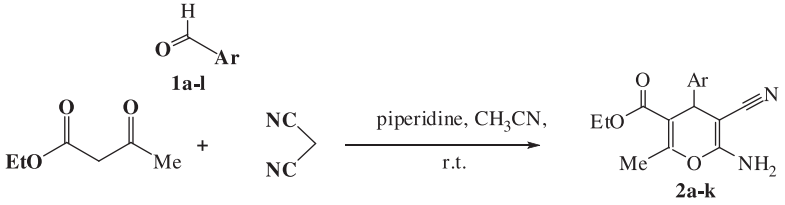
| Entry | Catalyst | Solvent | Time (min) | Yield (%) |
|---|---|---|---|---|
| 1 | Piperidine | $CH_3CN$ | 10 | 98 |
| 2 | Piperidine | Deionized water | 5 | 87 |
| 3 | Piperidine | $CH_2Cl_2$ | 20 | 65 |
| 4 | Silica sulfuric acid | $CH_3CN$ | 30 | 50 |
| 5 | $ZnCl_2$ | $CH_3CN$ | 30 | 25 |
| 6 | Tetrachloro silane | $CH_3CN$ | 30 | 20 |

**Table 2**

Multi-component synthesis of ethyl 6-amino-4-aryl-5-cyano-2-methyl-4*H*-pyran-3-carboxylate **2a–k**.

| **1**,**2** | Ar | Reaction time (min) | **2**: yield (%) | **1**,**2** | Ar | Reaction time (min) | **2**: yield (%) |
|---|---|---|---|---|---|---|---|
| (**a**) | $C_6H_5$ | 5 | 98 | (**g**) | 4-$NO_2C_6H_5$ | 25 | 80 |
| (**b**) | 4-F-$C_6H_4$ | 5 | 95 | (**h**) | 2-Furyl | 20 | 85 |
| (**c**) | 2-Cl-$C_6H_4$ | 20 | 90 | (**i**) | 5-Mefuryl | 10 | 90 |
| (**d**) | 3-Br-$C_6H_4$ | 15 | 90 | (**j**) | 2-Thienyl | 15 | 85 |
| (**e**) | 4-CN-$C_6H_4$ | 20 | 88 | (**k**) | 2-Naphthyl | 20 | 82 |
| (**f**) | 4-$MeOC_6H_5$ | 15 | 94 | | | | |

**Scheme 2.** Multi-component synthesis of ethyl 6-amino-4-aryl-5-cyano-2-methyl-4*H*-pyran-3-carboxylates **2a–k**.



(**2a–d**, **h**) were stirred at room temperature for 3 h, or heated in the presence of piperidine, a mixture of SSA and acetic anhydride (1:1 ratio: 0.5 mmol) for a short time (2–20 min) afforded smoothly the corresponding pyrano[2,3-*d*]pyrimidine derivative in a relatively high yield.

Upon heating 2-amino-pyran **2a** under reflux in excess acetic anhydride (excess) without any catalyst for 5–6 h, ethyl 2,7-dimethyl-4-oxo-5-phenyl-4,5-dihydro-3*H*-pyrano [2,3-*d*]pyrimidine-6-carboxylate **3a** was formed in low yield (25%). This reaction step can recommend the role of SSA presence in the reaction medium for obtaining products of type **3** in a relative good yield (62–85%) and in short reaction time (2–20 min). Presumably, this may be due to the presence of hetero-aryl moiety in their structure (Scheme 3 and Table 3).

Structure of the obtained pyrano[2,3-*d*]pyrimidines (**3a–h**) was confirmed by careful inspections of their spectroscopic data. The IR spectra of **3a** and **c** showed bands at υ = 3471, 1714, 1665, 1599 $cm^{-1}$ corresponding to NH, carbonyl of ($C_2H_5OCO$), carbonyl of (NHCO) and CN functional groups, respectively. The PMR spectra of **3a**, **c** displayed signals at (δ: ppm, 500 MHz, $CDCl_3$) 1.15 ($CH_3$), 2.33 ($CH_3$), 2.46 ($CH_3$), 4.05 ($CO_2CH_2CH_3$), 4.90–4.35 (CH), 13.30–13.21 (NH, $D_2O$-exchangeable).

The $^{13}C$ NMR of (**3c**) showed characteristic signals for ($CH_3CH_2$), (C7$CH_3$), (C2$CH_3$), ($CH_2O$), (C-7), (NHCO), and (CO-carboxylate) at (δ: ppm) 14.4, 18.90, 21.28, 61.60, 158.61, 160.6, and 166, respectively. Mass spectra of the pyrano[2,3-*d*]pyrimidines (**3a** and **d**) revealed molecular ion peaks at: *m/z* = 326 (43.46%) and 406 (15.55%), respectively (Experimental Part). Moreover, the reactivity of 4*H*-pyrans of type **2**, to our knowledge, is unknown towards TCS/$ZnCl_2$ as a binary catalytic reagent. Therefore, when 4*H*-pyrans (**2a–e** as selected examples) reacted with acetic anhydride and this binary catalytic reagent (1:3:3 ratio) for 30–45 min, hydrolysis of the CN to $CONH_2$ function occurred with simultaneous acetylating of $NH_2$ at 6 position; the corresponding 4-aryl-4*H*-pyran-3-carboxylates (**4a–e**) were afforded in good yield (62–83%), and no traces of the expected pyrano [2,3-*d*]pyrimidines of type (**3**) were detected.

The IR spectra of products (**4**) showed characteristic bands for $NH_2$ and NH, and CO at 3470–320 and 1710–1705, and 1670–1650 $cm^{-1}$ regions, respectively. The proton NMR spectra of these products revealed signals for $CH_3$, CH, ($NH_2$ and NH $D_2O$ exchangeable) beside the aromatic proton signals. Also, $^{13}C$ NMR spectrum of product **4c** confirmed its proposed structure (Scheme 4 and Table 4).

**Scheme 3.** Synthesis of ethyl 5-aryl-2,7-dimethyl-4-oxo-4,5-dihydro-4*H*pyrano[2,3-*d*]pyrimidine-6-carboxylates.

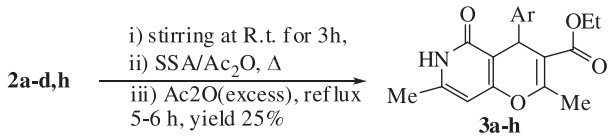



**Table 3**

Silica sulfuric acid/acetic anhydride catalyzed synthesis of ethyl 5-aryl-2,7-dimethyl-4-oxo-4,5-dihydro-4*H*-pyrano[2,3-*d*]pyrimidine-6-carboxylates **3a–h**.

| **3** | Ar | Reaction time (min) | Yield (%) | **3** | Ar | Reaction time (min) | Yield (%) |
|---|---|---|---|---|---|---|---|
| (**a**) | $C_6H_5$ | 2 | 85 | (**e**) | 4-$OMeC_6H_4$ | 15 | 84 |
| (**b**) | 4-F-$C_6H_4$ | 2 | 82 | (**f**) | 4-$NO_2C_6H_4$ | 20 | 62 |
| (**c**) | 2-Cl-$C_4H_4$ | 12 | 78 | (**g**) | 5-Me-Furyl | 10 | 75 |
| (**d**) | 3-Br-$C_6H_4$ | 12 | 78 | (**h**) | 2-Naphtyl | 15 | 65 |

**Scheme 4.** Synthesis of ethyl 6-acetamido-5-carbamoyl-2-methyl-4-aryl-4*H*-pyran-3-carboxylates **4a–e**.

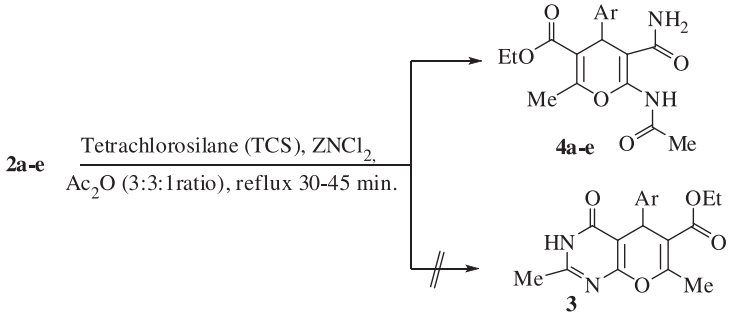


**Table 4**

Synthesis of ethyl 6-acetamido-5-carbamoyl-2-methyl-4-aryl-4*H*-pyran-3-carboxylates **4a–d**.

| Yield (%) | Reaction time (min) | Ar | 4 |
|---|---|---|---|
| 83 | 30 | $C_6H_5$ | (**a**) |
| 82 | 30 | 4-F-$C_6H_4$ | (**b**) |
| 75 | 45 | 2-Cl-$C_6H_4$ | (**c**) |
| 71 | 45 | 3-Br-$C_6H_4$ | (**d**) |
| 80 | 60 | 4-$NO_2C_6H_4$ | (**e**) |

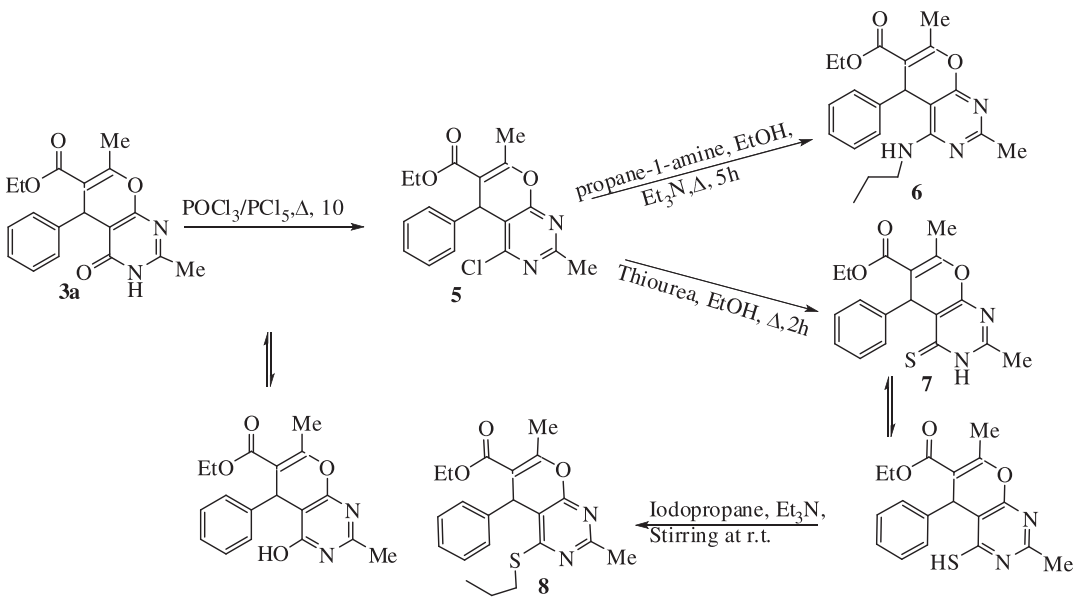
The present work was continued for exploring other related derivatives of 4*H*-pyrano[2,3-*d*] pyrimidines. Thus, when pyrano[2,3-*d*]pyrimidine-6-carboxylate (**3a**) was heated under reflux with $POCl_3/PCl_5$ in ethanol for ~10 h, it gave ethyl 4-chloro-2,7-dimethyl-5-phenyl-5*H*-pyrano [2,3-*d*]pyrimidine-6-carboxylate (**5**) in 81% yield. IR spectrum of the chloro compound (**5**) showed only one band due to CO (carboxylate) at 1714 $cm^{-1}$. Its mass spectrum revealed molecular ion peak $m/z = 344$ (4.3%). The latter chloro derivative afforded ethyl 2,7-dimethyl-5-phenyl-4-(propylamino)-5*H*-pyrano[2,3-*d*]pyrimidine-6-carboxylate (**6**) when reacted with propane-1-amine in absolute ethanol in the presence of $Et_3N$ (few drops). Also, the chloro pyrano[2,3-*d*]pyrimidine-6-carboxylate (**5**) on reaction with thiourea gave ethyl 2,7-dimethyl-5-phenyl-4-thioxo-4,5-dihydro-3*H*-pyrano[2,3-*d*]pyrimidine-6-carboxylate (**7**).

Previously, some thiopurine and pyrrolo[2,3-*d*]pyrimidine derivatives were obtained by treating chloro-purines with thiourea [17]. The thioxo-pyrano[2,3-*d*] pyrimidines (**7**) when left to react with iodopropane in ethanol in the presence of $Et_3N$ while stirring at room temperature produced ethyl 2,7-dimethyl-5-phenyl-4-(propylthio)-5*H*-pyrano[2,3-*d*]pyrimidine-6-carboxylate (**8**). Synthesis of such latter products can consider as another confirmation for the structures of the synthesized pyrano[2,3-*d*]pyrimidines of type (**3**). IR, NMR, and mass spectral determinations confirmed well the structures of the latter compounds. The IR spectrum of the thione product (**7**) showed characteristic bands due to CO (carboxylate) and CS vibrations at 174 and 1239 $cm^{-1}$, respectively. Mass spectrum revealed molecular ion peak at $m/z = 342$ (as base peak, 100%). PMR spectrum displayed signals (δ: ppm) for NH (broad band-$D_2O$ exchangeable) together with other signals for $CH_3$, $CH_2$ CH, and aromatic protons. The $^{13}C$ NMR spectrum (500 MHz, DMSO; δ: ppm) of product **8** displayed signals for $SCH_2$ (31.71) with other signals for $CH_3$, $CH_2$, C2 ($CH_3$), C5, C6, CS, C8a, and CO (carboxylate). Its mass spectrum showed molecular ion peak at $m/z = 384$ (49.78%) (Scheme 5 and Experimental part).

## EXPERIMENTAL

Melting points are uncorrected. Microanalyses were carried out by the Micro analytical Laboratory, National Research Center, Cairo, Egypt. Infrared spectra (KBr) were recorded using a Jasco FT/IR-300E spectrophotometer. $^1H$ and $^{13}C$ NMR spectra were measured in $CDCl_3$ using Varian Mercury 500 MHz spectrometers with chemical shifts using TMS as internal standard. Mass spectra were recorded on a GC/MS Finnigan SSQ 7000 spectrophotometer. All reactions were carried out under atmospheric conditions at room temperature. TCS, SSA, and anhydrous zinc chloride were obtained from commercial sources. Analytical TLC was performed with silica-gel $GF_{254}$ plates [petroleum ether/ethyl acetate (4:1 by volume)], and the products were visualized by UV detection. The

**Scheme 5.** Synthesis of 5-aryl-4*H*-pyrano[2,3-*d*]pyrimidines **5–8**.



antioxidant activity of the selected compound was assessed by measuring the ability of each compound to scavenge the free radical of 1,1-diphenyl-2-picrylhydrazyl (DPPH) using previously published methods [18,19] and modified one [20]. Test compounds were prepared in DMSO as 10× stocks from each test concentration (0.1–2.0 mM). The compounds were then tested to determine the $EC_{50}$ (effective concentration of the compound producing 50% scavenging of the stable free radical DPPH). Some known radical scavengers, quercetin, *t*-butyl hydroquinone, and gallic acid, were tested in the assay as positive controls. Briefly, each of compound stock solutions (15 μL/well) was pipetted onto 96-well plate. The assay was started with the addition of DPPH reagent (0.004% w/v in methanol, 135 μL/well). Appropriate negative controls were simultaneously run using methanol to serve as a correction for the optical density of colored compounds at 540 nm. The plate was immediately shaken for 30 s and incubated in the dark for 30 min at room temperature. The remaining DPPH was measured in a micro-plate reader (BMG Fluostar Optima, Germany) at 540 nm. The percentage of antioxidant activity (AA) was calculated using the following equation:

$$\%\ \text{Antioxidant activity (AA)} = 100 \times \left[\frac{\text{OD540 nm (blank)} - \text{OD540 nm (sample)}}{\text{OD540nm (blank)}}\right] \quad (1)$$

Regression analysis was used to determine the $EC_{50}$ values for each compound using the concentration–% AA relationship. All data were represented as the mean value of duplicate absorbance measurement.

**Synthesis of compounds 2a–k**. *General procedure*: To an aqueous mixture of aldehyde **1** (2 mmol), malononitrile (2 mmol), and ethylacetoacetate (2 mmol) was added piperidine (0.5 mL). The reaction mixture was stirred at room temperature for the specified time (Table 2). The precipitated product was filtered, washed with water, and then with a mixture of ethyl acetate/cyclohexane (20:80 v: v). The obtained solid product was crystallized from ethanol to give products **2a–k**.

***Ethyl 6-amino-5-cyano-2-methyl-4-phenyl-4H-pyran-3-carboxylate (2a)***. Yellow crystals, yield 98%, mp: 192–194°C (Ref. [21]); (EtOH). $R_f$ = 0.35. IR (potassium bromide): υ: $cm^{-1}$ = 3401, 3330 ($NH_2$), 2188 (C ≡ N), 1688 (CO) $cm^{-1}$. MS (EI) (*m/z*: %): 284 (68.24%). *Anal*. Calcd for $C_{16}H_{16}N_2O_3$; MW = (284.31): C, 67.59; H, 5.67; N, 9.85. Found: C, 67.56; H, 5.54; N, 9. 83%

***Ethyl 6-amino-5-cyano-4-(4-fluorophenyl)-2-methyl-4H-pyran-3-carboxylate (2b)***. Yellow crystals, yield: 95%, mp 158–160°C (Ref. [22]); (EtOH). $R_f$ = 0.33. IR (potassium bromide): (υ: $cm^{-1}$); 3406.64, 3333.36 ($NH_2$), 2193.63 (CN), 1688.37 (CO), 1610.27 (CC). $^1$H NMR (500 MHz, $CDCl_3$) δ = 1.09 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 2.35 (3H, s, $CH_3$), 4.02 (q, *J* = 7.2 Hz, 2H, $CO_2CH_2CH_3$), 4.24 (1H, s, CH), 4.51 (2H, s, $NH_2$, $D_2O$-exchangeable), 6.97–7.16 (4H, m, Ar-H). *Anal*. Calcd for $C_{16}H_{15}FN_2O_3$; MW = (302.30): C, 63.57; H, 5.00; N, 9.27. Found: C, 63.66; H, 4.98; N, 9.19%.

***Ethyl 6-amino-5-cyano-4-(4-chlorophenyl)-2-methyl-4H-pyran-3-carboxylate (2c)***. Yellow crystals, yield: 90%, mp 170–172°C (EtOH). $R_f$ = 0.33 IR (potassium bromide): (υ: $cm^{-1}$); 3408.64, 3333.36 ($NH_2$), 2193.63 (CN), 1688.37 (CO), 1610, 27 (CC). MS (*m/z*: %): 318.10 (19.30%). *Anal*. Calcd for $C_{16}H_{15}ClN_2O_3$; MW = (318.75): C, 60.29; H, 4.74; N, 8.79. Found: C, 60.27; H, 4.70; N, 8.76%.

***Ethyl 6-amino-4-(3-bromophenyl)-5-cyano-2-methyl-4H-pyran-3-carboxylate (2d)***. Yellow crystals, yield: 90%, mp 156–158°C (EtOH). $R_f$ = 0.35. IR (potassium bromide): υ: $cm^{-1}$ = 3396, 3329 ($NH_2$), 2191 (CN), 1685 (CO) $cm^{-1}$. MS (*m/z*: %): 362 (11.73%), 364 (10.50%). *Anal*. Calcd for $C_{16}H_{15}BrN_2O_3$; MW = (363.21): C, 52.91; H, 4.16; N, 7.71. Found: C, 53.09; H, 4.19; N, 7.80%.

***Ethyl 6-amino-5-cyano-4-(4-cyanophenyl)-2-methyl-4H-pyran-3-carboxylate (2e)***. Brown crystals, yield: 88% mp 156–158°C (EtOH). $R_f$ = 0.27. IR (potassium bromide): (υ: $cm^{-1}$); 3403.74, 3330.46 ($NH_2$), 2231.24, 2198.45 (CN), 1719.23 (CO), 1679.69 (C), 1602, 56 (CC). MS (*m/z*: %): 309.10 (9.73%). *Anal*. Calcd for $C_{17}H_{15}N_3O_3$; MW = (309.32): C, 66.01; H, 4.89; N, 13.58. Found: C, 65.98; H, 4.87; N, 13.56%.

***Ethyl 6-amino-5-cyano-4-(4-methoxyphenyl)-2-methyl-4H-pyran-3-carboxylate (2f)***. White crystals yield 94%, mp 138–140°C (Ref. [15]); (EtOH). $R_f$ = 0.30. IR (potassium bromide): υ: $cm^{-1}$ = 3401, 3330 ($NH_2$), 2190 (CN), 1686 (CO) $cm^{-1}$. MS (*m/z*: %): 314 (12.75%). *Anal.* Calcd for $C_{17}H_{18}N_2O_4$; MW = (314.34): C, 64.96; H, 5.77; N, 8.91. Found: C, 64.87; H, 5.76; N, 8.89%.

***Ethyl 6-amino-5-cyano-2-methyl-4-(4-nitrophenyl)-4H-pyran-3-carboxylate (2g).*** Brown crystals, yield: 80%, mp 176–178°C (EtOH). $R_f$ = 0.25. IR (potassium bromide): (υ: $cm^{-1}$); 3402.78, 3332.39 ($NH_2$), 2197.49 (CN), 1688.37 (CO), 1603, 52 (CC). MS (*m/z*: %): 329.05 (28.49%). *Anal*. Calcd for $C_{16}H_{15}N_3O_5$; MW (329.31): C, 58.36; H, 4.59; N, 12.76. Found: C, 58.40; H, 4.44; N, 12.78%.

***Ethyl 6-amino-5-cyano-4-(furan-2-yl)-2-methyl-4H-pyran-3-carboxylate (2h).*** Violet crystals yield 85%, mp 216–118°C (Ref. [23]); (EtOH). $R_f$ = 0.28. IR (potassium bromide): υ: $cm^{-1}$ = 3399, 3325 ($NH_2$), 2195 (CN), 1683 (CO) $cm^{-1}$. MS (*m/z*: %): 274 (6.12%). *Anal*. Calcd for $C_{14}H_{14}N_2O_4$; MW (274.27): C, 61.31; H, 5.41; N, 10.21%, Found: C, 61.26; H, 5.39; N; 10.17%.

***Ethyl 6-amino-5-cyano-2-methyl-4-(5-methylfuryl)-4H-pyran-3-carboxylate (2i).*** White crystals yield 90%, mp 196–198°C (EtOH). $R_f$ = 0.50. IR (potassium bromide): υ: $cm^{-1}$ = 3401, 3332 ($NH_2$), 2191 (CN), 1688 (CO) $cm^{-1}$. MS (*m/z*: %): 288 (12.12%).$^1$H NMR (500 MHz, $CDCl_3$): δ = 1.20 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 2.16 (3H,s, $CH_3$), 2.33 (3H,s, $CH_3$), 4.12 (q, *J* = 7.2 Hz, 2H, $CO_2CH_2CH_3$), 4.51 (1H, s, CH), 4.54 (2H, b, $NH_2$), 5.82 (1H, s, ArH), 5.94 (1H, s, ArH) ppm. $^{13}$ C NMR (500 MHz, DMSO-$d_6$): δ = 13.84 (Me-furyl), 14.32 ($CH_3CH_2$), 18.63 ($CH_3$-C2), 33.03 (C4), 54.75 (C5), 60.81 ($CH_2O$), 105.75, 106.64, 151.14, 154.72 (4 furyl carbon atoms), 106.94 (C3), 120.18 (CN), 160.03 (C6), 157.87 (C2), 165.09 (CO, carboxylate) ppm. *Anal*. Calcd for $C_{15}H_{16}N_2O_4$; MW (288.30): C, 62.49; H, 5.59; N, 9.72. Found: C, 62.42; H, 6.04; N, 9.80%.

***Ethyl 6-amino-5-cyano-2-methyl-4-(thiophen-2-yl)-4H-pyran-3-carboxylate (2j).*** Brown crystals yield 85%, mp 175–177°C (EtOH). $R_f$ = 0.33. IR (KBr): υ: $cm^{-1}$ = 3396, 3328 ($NH_2$), 2192 (CN), 1692 (CO) $cm^{-1}$. MS (*m/z*: %): 290 (12.12%). *Anal*. Calcd for $C_{14}H_{14}N_2O_3S$; MW = (290.34): C, 57.92; H, 4.86; N, 9.65; S, 11.04. Found: C, 57.87; H, 4.86; N, 9.58; S, 10.98%.

***Ethyl 6-amino-5-cyano-2-methyl-4-(naphthalen-2-yl)-4H-pyran-3-carboxylate (2k).*** White crystals yield 82%, mp 150–152°C (EtOH). $R_f$ = 0.63. IR (potassium bromide): υ: $cm^{-1}$ = 3402, 3331 ($NH_2$), 2192 (CN), 1691 (CO) $cm^{-1}$. MS (*m/z*: %): 288.95 (24.12%).$^1$H NMR (500 MHz, $CDCl_3$): δ = 1.05 (t, *J* = 7.0 Hz, 3H, $CO_2CH_2CH_3$), 2.46 (3H, s, $CH_3$), 4.00 (q, *J* = 7.0 Hz, 2H, $CO_2CH_2CH_3$), 4.48 (1H, s, CH), 4,62 (2H, b, $NH_2$), 7.25–7.79 (7H, m, ArH) ppm. $^{13}$ C NMR (500 MHz, DMSO-$d_6$): δ = 14.26

($CH_3$-$CH_2$), 18.76 ($CH_3$-C2), 39.89 (C4), 57.64(C5) 60.70 ($CH_2O$), 107.62 (C3), 126.22, 126.77, 128.03, 128.22, 128.81, 132.64, 133.41, 142.74 (10 aromatic carbon atoms), 120.28 (CN), 159.05 (C6), 157.21 (C2), 166.01 (CO, carboxylate) ppm. *Anal*. Calcd for $C_{20}H_{18}N_2O_3$; MW = (334.37): C, 71.84; H, 5.43; N, 8.38. Found: C, 71.90; H, 5.40; N, 8.50%.

**Synthesis of compounds (3a–h)**. ***General method A***: A mixture of pyran **2** (2.5 mmol), acetic anhydride (5 mL), and SSA (0.5 mmol) was stirred at room temperature for 3 h. The reaction mixture was poured on ice. The obtained solid was filtered off. To recover the catalyst; the crystalline residue was dissolved in dichloromethane (10 mL) and filtered. Evaporation of the filtrate gave products **3** as solid products.

***Method B***: A mixture of pyran **2a** (2.5 mmol) and acetic anhydride (5 mL) was heated under reflux for the specified time (Table 3). The reaction was monitored by TLC. After completion of the reaction, the mass was cooled. The reaction mixture was filtered and the obtained residue was washed with water (10 mL). To recover the catalyst; the crystalline residue was dissolved in dichloromethane (10 mL) and filtered. Evaporation of the filtrate gave products **3** as solid products. The products were further purified by crystallization from ethanol.

***Ethyl 2,7-dimethyl-4-oxo-5-phenyl-4,5-dihydro-3H-pyrano [2,3-d]pyrimidine-6-carboxylate (3a).*** White crystals; yield 85%, mp 256–258°C (Ref. [24]); (EtOH). $R_f$ = 0.08. IR (potassium bromide): υ: $cm^{-1}$ = 3417 (NH), 1714 (CO), 1665 (CO), 1599 (CN) $cm^{-1}$. MS (*m*/*z*: %): 326 (43.46%). $^1$H NMR (500 MHz, $CDCl_3$): δ = 1.13 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 2.30 (3H, s, $CH_3$), 2.49 (3H, s, $CH_3$), 4.04 (q, *J* = 7.2 Hz, 2H, $CO_2CH_2CH_3$), 4.91 (1H, s, CH), 7.18–7.29 (5H, m, ArH), 13.21 (1H, b, NH) ppm. *Anal*. Calcd for $C_{18}H_{18}N_2O_4$; MW = (326.35): C, 66.25; H, 5.56; N, 8.58. Found: C, 66.23; H, 5.54; N, 8.54%.

***Method B: Reaction of 5- amino-pyran (2a) with acetic anhydride without SSA catalyst.*** A mixture of pyran **2a** (2.5 mmol) and acetic anhydride (5 mL) was heated under refluxed for 5–6 h; the reaction was monitored by TLC. After completion of the reaction, the mixture was poured on ice water. The obtained solid was filtered off and crystallized from ethanol to give **3a**, yield 25%, (mp and mixed mp undepressed).

***Ethyl 5-(4-fluorophenyl)-2,7-dimethyl-4-oxo-3,5-dihydro-4H-pyrano[2,3d]pyri-midine-6-carboxylate (3b).*** White crystals, yield: 82%, mp 240–242°C (EtOH). $R_f$ = 0.10. IR (potassium bromide): (υ: $cm^{-1}$); 3414.35 (NH), 1715.37 (CO), 1666.2 (CO), 1599.7 (CN). MS (*m*/*z*%): 344.00 (63.39%) 344.95 (15.23%). $^1$H NMR (500 MHz, $CDCl_3$) δ = 1.20 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 2.37 (3H, s, $CH_3$), 2.52 (3H, s, $CH_3$), 4.07 (q, *J* = 7.2 Hz, 2H, $CO_2CH_2CH_3$), 4.91 (1H, s, CH), 6.88–7.29 (4H, m, Ar-H), 12.99 (1H, b, NH, $D_2O$-exchangeable). $^{13}$ C NMR (500 MHz, DMSO-$d_6$): δ = 14.33 ($CH_3CH_2$), 18.91 (C7-$CH_3$), 21.42 (C2-$CH_3$), 39.71 (C5), 60.72 ($CH_2O$), 100.96 (C4a), 108.19 (C6), 115.17,115.34, 130.40, 140.80, 159.27 (6 aromatic carbon atoms), 158.85 (C7), 160.33 (CO), 159.27 (C8a), 162.44 (C2), 166.04 (CO, carboxylate) ppm. *Anal*. Calcd for $C_{18}H_{17}FN_2O_4$; MW = (344.34): C, 62.79; H, 4.98; N, 8.14. Found: C, 63.33; H, 5.02; N, 8.08%.

***Ethyl 5-(2-chlorophenyl)-2,7-dimethyl-4-oxo-3,5-dihydro-4H-pyrano[2,3-d]pyri-midine-6-carboxylate (3c).*** White crystals yield 78%, mp 240–242°C (Ref. [24]); (EtOH). 0.07. IR (potassium bromide): υ: $cm^{-1}$ = 3417 (NH), 1714 (CO), 1665 (CO), 1599 (CN) $cm^{-1}$. MS (*m*/*z*: %): 360 (5.29%) 360.95. $^1$H NMR (500 MHz, $CDCl_3$): δ = 1.13 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 2.33 (3H,s,$CH_3$), 2.46 (3H, s, $CH_3$), 4.06 (q, *J* = 7.2 Hz, 2H, $CO_2CH_2CH_3$), 4.35 (1H, s, CH), 7.19–7.25 (4H, m, ArH), 13.3 (1H, b, NH) ppm. $^{13}$C NMR (500 MHz, DMSO-$d_6$): δ = 14.46 ($CH_3CH_2$), 18.95 (C7-$CH_3$), 21.28 (C2-$CH_3$), 34.46 (C5), 61.60 ($CH_2O$), 100.10 (C4a), 107.15 (C6), 128.00–141.43 (6 aromatic carbon atoms),158.61 (C7), 160.59 (CO), 159.40 (C8a), 162.00 (C2), 166.09 (CO, carboxylate) ppm *Anal*. Calcd for $C_{18}H_{17}ClN_2O_4$; MW = (360.79): C, 59.92; H, 4.75; N, 7.76. Found: C, 59.90; H, 4.73; N, 7.75%.

***Ethyl 5-(3-bromophenyl)-2,7-dimethyl-4-oxo-3,5-dihydro-4H-pyrano[2,3-d]pyri-midine-6-carboxylate (3d).*** White crystals; yield 78%, mp 220–222°C (EtOH). $R_f$ = 0.12. IR (potassium bromide): υ: $cm^{-1}$ = 3399 (NH), 1712 (CO), 1668 (CO), 1605 (CN) $cm^{-1}$. MS (*m*/*z*: %): 406 (15.55%), 404 (14.95%). $^1$H NMR (500 MHz, $CDCl_3$): δ = 1.14 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 2.38 (3H, s, $CH_3$), 2.50 (3H, s, $CH_3$), 4.06 (q, *J* = 7.2 Hz, 2H, $CO_2CH_2CH_3$), 4.87 (1H, s, CH), 7.1–7.47 (4H, m, ArH), 13.27 (1H, b, NH) ppm. $^{13}$ C NMR (500 MHz, DMSO-$d_6$): δ = 14.27 ($CH_3CH_2$), 18.98 (C7-$CH_3$), 21.44 (C2-$CH_3$), 39.80 (C5), 60.78 ($CH_2O$), 100.49 (C4a), 107.63 (C6), 121.72, 127.62, 130.00, 130.78, 131.51, 147.29 (6 aromatic carbon atoms),159.33 (C7), 160.39 (CO), 159.52 (C8a), 162.44 (C2), 165.87 (CO, carboxylate) ppm. *Anal*. Calcd for $C_{18}H_{17}BrN_2O_4$; MW = (405.24): C, 53.35; H, 4.23; N, 6.91. Found: C, 53.31; H, 4.20; N, 6.88%.

***Ethyl 5-(4-methoxyphenyl)-2,7-dimethyl-4-oxo-3,5-dihydro-4H-pyrano[2,3d]-pyrimidine-6-carboxylate (3e).*** White crystals; yield 84%, mp 240–242°C (EtOH). $R_f$ = 0.08. IR (potassium bromide): υ: $cm^{-1}$ = 3412 (NH), 1713 (CO), 1668 (CO), 1602 (CN) $cm^{-1}$. MS (*m*/*z*: %): 356 (100%). $^1$H NMR (500 MHz, $CDCl_3$): δ = 1.15 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 2.36 (3H, s, $CH_3$), 2.48 (3H, s, $CH_3$), 3.72 (3H, s, $OCH_3$), 4.06 (q, *J* = 7.2 Hz, 2H, $CO_2CH_2CH_3$), 4.89 (1H, s, CH), 6.72–7.20 (4H, m, ArH), 13.19 (1H, b, NH) ppm. *Anal*. Calcd for $C_{19}H_{20}N_2O_5$; MW = (356.37): C, 64.04; H, 5.66; N, 7.86. Found: C, 64.01; H, 5.61; N, 7.82%.

***Ethyl 5-(4-nitrophenyl)-2,7-dimethyl-4-oxo-3,5-dihydro-4H-pyrano[2,3-d]pyri-midine-6-carboxylate (3f).*** White crystals; yield 62%, mp 264–266°C (EtOH). $R_f$ = 0.05. IR (potassium bromide): υ: $cm^{-1}$ = 3296 (NH), 1723 (CO), 1672 (CO), 1604 (CN) $cm^{-1}$. MS (*m*/*z*: %): 371 (44.52%). $^1$H NMR (500 MHz, $CDCl_3$): δ = 1.14 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 2.38 (3H, s, $CH_3$), 2.49 (3H, s, $CH_3$), 4.05 (q, *J* = 7.2 Hz, 2H, $CO_2CH_2CH_3$), 5.03 (1H, s, CH), 7.46–7.47(d, 2H, *J* = 8.5 Hz, ArH), 8.07–8.09 (d, 2H, *J* = 8.5 Hz, ArH), 12.98 (1H, b, NH) ppm. *Anal*. Calcd for $C_{18}H_{17}N_3O_6$; MW = (371.34): C, 58.22; H, 4.61; N, 11.32. Found: C, 58.18; H, 4.56; N, 11.28%.

***Ethyl 5-(5-methylfuryl)-2,7-dimethyl-4-oxo-3,5-dihydro-4H-pyrano[2,3-d]pyri-midine-6-carboxylate (3g).*** White crystals; yield: 65%, mp 260–262°C (EtOH). $R_f$ = 0.08. IR (potassium bromide) (υ: $cm^{-1}$); 3424.96 (NH), 1720.19 (CO), 1639.2 (CO), 1565.92 (CN). MS (*m*/*z*%): 330.12 (44.52%). $^1$H NMR (500 MHz, $CDCl_3$) : δ = 1.19 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 2.19 (3H,s, $CH_3$), 2.23 (3H,s, $CH_3$), 2.31 (3H,s, $CH_3$), 4.12 (q, *J* = 7.2 Hz, 2H, $CO_2CH_2CH_3$), 4.51 (1H, s, CH), 5.82 (1H, s, CH), 5.94 (1H, s, CH), 12,60 (H, b, NH, $D_2O$-exchangeable). $^{13}$ C NMR (500 MHz, DMSO-$d_6$): δ = 12.85 ($CH_3$-furyl), 14.50 ($CH_3CH_2$), 18.95 (C7-$CH_3$), 21.49 (C2-$CH_3$), 29.84 (C5), 60.94 ($CH_2O$), 98.07.96 (C4a), 108.19 (C6), 106.01, 107.02, 148.19, 152.16 (4 furyl carbon atoms),158.85 (C7), 161.20 (CO), 159.56 (C8a), 162.41 (C2), 166.01 (CO, carboxylate) ppm. *Anal*. Calcd for $C_{17}H_{18}N_2O_5$; MW = (330.34): C, 61.81; H, 5.49; N, 8.48. Found: C, 61.10; H, 5.02; N, 8.45%.

***Ethyl 2,7-dimethyl-5-(naphthalen-2-yl)-4-oxo-3,5-dihydro-4H-pyrano[2,3-d]py-rimidine-6-carboxylate (3 h).*** White crystals; yield 65%, mp 222–224°C (EtOH). $R_f = 0.07$. IR (potassium bromide): υ: $cm^{-1} = 3333$, 3331 (NH), 1722 (CO), 1681 (CO), 1563 (CN) $cm^{-1}$. MS: (*m/z*: %) = 376.34 (24.12%). $^1H$ NMR (500 MHz, DMSO): $\delta = 1.05$ (t, $J = 7.0$ Hz, 3H, $CO_2CH_2CH_3$), 2.29 (3H, s, $CH_3$), 2.49 (3H, s, $CH_3$), 4.02 (q, $J = 7.2$ Hz, 2H, $CO_2CH_2CH_3$), 5.08 (1H, s, CH), 7.25–7.72 (7H, m, ArH), 12.45 (1H, b, NH) ppm. $^{13}C$ NMR (500 MHz, DMSO-$d_6$): $\delta = 14.49$ ($CH_3CH_2$), 18.90 (C7-$CH_3$), 21.28 (C2-$CH_2$), 37.46 (C5), 60.73 ($CH_2O$), 101.02 (C4a), 108.32 (C6), 126.20, 126.76,126.88, 127.19, 127.55, 128.03, 128.30, 132.47, 133.26, 142.15 (10 aromatic carbon atoms), 159.32 (C7), 162.50 (CO), 160.40 (C8a), 166.17 (C2), 167.70 (CO, carboxylate) ppm. *Anal*. Calcd for $C_{22}H_{20}N_2O_4$; MW = (376.41): C, 70.20; H, 5.36; N, 7.44. Found: C, 70.17; H, 5.33; N, 7.41%.

***Synthesis of ethyl 6-acetamido-5-carbamoyl-2-methyl-4-aryl-4H-pyran-3-carboxylates (4a–e).*** *General Method*: A mixture of pyran derivative **2** (5 mmol), acetic anhydride (5 mmol), anhydrous $ZnCl_2$ (15 mmol) in $CH_2Cl_2$ (20 mL) was stirred with exclusion of moisture on an ice path for the specified time (Table 4). TCS (15 mmol) was then added, and the reaction mixture was stirred again for the specified time. The reaction mixture was then poured onto ice-cold water (~100 mL), neutralized by $Na_2CO_3$ and extracted with $CHCl_3$ ($3 \times 30$ mL). The organic liquid was dried over anhydrous $Na_2SO_4$. Excess solvent was removed under reduced pressure, and the obtained residue was triturated with ethanol to give solid products **4a–e**, which were re-crystallized in ethanol for purification.

***Ethyl 6-acetamido-5-carbamoyl-2-methyl-4-phenyl-4H-pyran-3-carboxylate (4a).*** White crystals yield 83%, mp 138–140°C. $R_f = 0.13$. IR (potassium bromide): υ: $cm^{-1} = 3411$, 3273 ($NH_2$, NH), 1709 (CO), 1659 (CO). MS (*m/z*: %): 344.15 (13.30%). $^1H$ NMR (500 MHz, $CDCl_3$): $\delta = 1.25$ (t, $J = 7.2$ Hz, 3H, $CO_2CH_2CH_3$), 2.19 (3H,s, $CH_3$), 2.16 (3H,s, $CH_3$), 4.14 (q, $J = 7.2$ Hz, 2H, $CO_2CH_2CH_3$), 4.56 (1H, s, CH), 5.60 (2H, b, $NH_2$), 7.22–7.30 (5H, m, ArH), 11.76 (1H, b, NH) ppm. *Anal.* Calcd for $C_{18}H_{20}N_2O_5$; MW = (344.36): C, 62.78; H, 5.85; N, 8.13. Found: C, 62.76; H, 5.82; N, 8.10%.

***Ethyl 6-acetamido-5-carbamoyl-4-(4-fluorophenyl)-2-methyl-4H-pyran-3-carb-oxylate (4b).*** White crystals; yield: 82%, mp 160–162°C. $R_f = 0.10$. IR (potassium bromide): (υ: $cm^{-1}$); 3421.1, 3335.28, 353.32 ($NH_2$, NH), 1704.76 (CO), 1652.7 (CO), 1604, 48 (CC). MS (*m/z*: %): 362.15(13.30%). $^1H$ NMR (500 MHz, $CDCl_3$): δ = 1.26 (t, $J = 7.2$ Hz, 3H, $CO_2CH_2CH_3$), 2.25(3H,s, $CH_3$), 2.24(3H,s, $CH_3$), 4.16 (q, $J = 7.2$ Hz, 2H, $CO_2CH_2CH_3$), 4.56 (1H, s, CH), 5.44 (2H, b, $NH_2$), 6.97–7.29 (4H, m, Ar-H), 11.77 (1H, b, NH, $D_2O$-exchangeable). $^{13}C$ NMR (500 MHz, DMSO-$d_6$): $\delta = 14.41$ ($CH_3CH_2$), 18.54 (C7-$CH_3$), 24.17 (C2-$CH_3$), 39.61 (C5), 60.79 ($CH_2O$), 97.15 (*C3*-$CONH_2$), 108.33 (C5), 115.55–144.74 (6 aromatic carbon atoms), 158.22 (C6), 166.20 (C3-$CONH_2$) 160.55 (C2), 169.79 ($COCH_3$), 167.89 (CO, carboxylate) ppm. *Anal*. Calcd for $C_{18}H_{19}FN_2O_5$; MW = (362.35): C, 59.66; H, 5.29; N, 7.73. Found: C, 59.03; H, 5.02; N, 7.72%.

***Ethyl 6-acetamido-5-carbamoyl-4-(2-chlorophenyl)-2-methyl-4H-pyran-3-carboxylate (4c).*** White crystals; yield 75%, mp 144–146°C. $R_f = 0.08$. IR (potassium bromide): υ: $cm^{-1} = 3383$, 3223 ($NH_2$, NH), 1707 (CO), 1669 (CO) $cm^{-1}$. MS: (*m/z*: %) = 378 (11.90%), 380 (3.22%). $^1H$ NMR (500 MHz, $CDCl_3$): $\delta = 1.22$ (t, $J = 7.3$ Hz, 3H, $CO_2CH_2CH_3$), 2.46(3H,s, $CH_3$), 2.33(3H,s, $CH_3$), 4.13 (q, $J = 7.3$ Hz, 2H, $CO_2CH_2CH_3$), 4.56 (1H, s, CH), 5.44 (2H, b, $NH_2$), 7.25–7.29 (4H, m, ArH), 12.0 (1H, b, NH) ppm. $^{13}C$ NMR (500 MHz, DMSO-$d_6$): $\delta = 14.46$ ($CH_3CH_2$), 18.38 (C7-$CH_3$), 23.28 (C2-$CH_3$), 37.10 (C5), 60.58 ($CH_2O$), 100.11 (C3-$CONH_2$), 107.12 (C5), 128.35-141.70 (6 aromatic carbon atoms), 158.86 (C6), 166.10 (C3-$CONH_2$) 162.20(C2), 167.46 ($COCH_3$), 166.79 (CO, carboxylate) ppm. *Anal.* Calcd for $C_{18}H_{19}ClN_2O_5$; MW = (378.81): C, 57.07; H, 5.06; N, 7.40. Found: C, 57.02; H, 5.01; N, 7.35%.

***Ethyl 6-acetamido-5-carbamoyl-4-(3-bromophenyl)-2-methyl-4H-pyran-3-carboxylate (4d).*** White crystals; yield 71%, mp 144–146°C. $R_f = 0.08$. IR (potassium bromide): υ: $cm^{-1} = 3415$, 3338 ($NH_2$, NH), 1699 (CO), 1660 (CO) $cm^{-1}$. MS (*m/z*: %): 422 (6.91%) 424 (6.75%). $^1H$ NMR (500 MHz, $CDCl_3$): $\delta = 1.27$ (t, $J = 7.2$ Hz, 3H, $CO_2CH_2CH_3$), 2.39 (3H, s, $CH_3$), 2.28 (3H,s, $CH_3$), 4.14 (q, $J = 7.2$ Hz, 2H, $CO_2CH_2CH_3$), 4.54 (1H, s, CH), 5.54 (2H, b, $NH_2$), 7.16–7.43 (4H, m, ArH), 11.80 (1H, b, NH) ppm. $^{13}C$ NMR (500 MHz, DMSO-$d_6$): $\delta = 14.42$ ($CH_3CH_2$), 18.61 (C7-*$CH_3$*), 24.33 (C2-$CH_3$), 39.88 (C5), 60.82 ($CH_2O$), 91.46 (C3-$CONH_2$), 108.12 (C5), 127.40, 130.16,131.07, 131.21, 139.34, 147.50 (6 aromatic carbon atoms), 158.86 (C6), 166.01 (C3-$CONH_2$) 162.20 (C2), 169.45 ($COCH_3$), 167.74 (CO, carboxylate) ppm. *Anal*. Calcd for $C_{18}H_{19}BrN_2O_5$; MW = (423.26): C, 51.08; H, 4.52; N, 6.62. Found: C, 51.02; H, 4.50; N, 6.58%.

***Ethyl 6-acetamido-5-carbamoyl-2-methyl-4-(4-nitrophenyl)-4H-pyran-3-carboxylate (4e).*** White crystals; yield 80%, mp 150–152°C. $R_f = 0.08$. IR (potassium bromide): υ: $cm^{-1} = 3474$, 3383 ($NH_2$, NH), 1722 (CO), 1667 (CO) $cm^{-1}$. MS (*m/z*: %): 389 (1.29%). $^1H$ NMR (500 MHz, $CDCl_3$): $\delta = 1.26$ (t, $J = 7.2$ Hz, 3H, $CO_2CH_2CH_3$), 2.25 (3H,s, $CH_3$), 2.24(3H,s, $CH_3$), 4.16 (q, $J = 7.2$ Hz, 2H, $CO_2CH_2CH_3$), 4.56 (1H, s, CH), 5.44 (2H, b, $NH_2$), 7.25–7.52 (two d, 2H, $J = 7.5$ Hz, ArH), 11.77 (1H, b, NH) ppm. $^{13}C$ NMR (500 MHz, DMSO-$d_6$): $\delta = 14.$ 34 ($CH_3CH_2$), 19.04 (C7-$CH_3$), 21.44 (C2-$CH_3$), 39.60 (C5), 60.89 ($CH_2O$), 100.06 (C3-$CONH_2$), 107.09 (C5), 123.75,124.11. 129.68, 130.00,130.68, 146.82 (6 aromatic carbon atoms), 159.84 (C6), 165.10 (C3-$CONH_2$) 162.40(C2), 169.46 ($COCH_3$), 165.73 (CO, carboxylate) ppm. *Anal*. Calcd for $C_{18}H_{19}N_3O_7$; MW = (389.36): C, 55.53; H, 4.92; N, 10.79. Found: C, 55.51; H, 4.88; N, 10.76%.

***Synthesis of ethyl 4-chloro-2,7-dimethyl-5-phenyl-5H-pyrano [2,3-d]pyrimidine-6-carboxylate (5).*** A mixture of the pyrano [2,3-*d*]pyrimidin-4(5*H*)-one (**3a**) (0.005 mol), $POCl_3$ (30 mL), and $PCl_5$ (0.5 g) was heated under reflux for 10 h. After cooling, the reaction mixture was poured onto crushed ice. The obtained crystal product was filtered off, washed with water several times, dried, and crystallized from petroleum ether (50–60) to give **5**; as white crystals, mp 108–110°C, yield: (1.3 g, 81.25%). $R_f = 0.92$. IR (potassium bromide): υ: $cm^{-1} = 1714$ (CO), 1649 (CN), 1594 (CC) $cm^{-1}$. MS (*m/z*: %): 344 (4.3%), 346 (6.61%).$^1H$ NMR (500 MHz, $CDCl_3$): $\delta = 1.14$ (t, $J = 7.2$ Hz, 3H, $CO_2CH_2CH_3$), 2.40 (3H, s, $CH_3$), 2.49 (3H,s, $CH_3$), 4.o6 (q, $J = 7.2$ Hz, 2H, $CO_2CH_2CH_3$), 4.98 (1H, s, CH), 7.16–7.26 (5H, m, ArH) ppm. *Anal*. Calcd for $C_{18}H_{17}ClN_2O_3$; MW = (344.79): C, 62.70; H, 4.97; N, 8.12. Found: C, 62.68; H, 4.94; N, 8.10%.

***Synthesis of ethyl 2,7-dimethyl-5-phenyl-4-(propylamino)-5H-pyrano[2,3-d]pyrimidine-6-carboxylate (6).*** A mixture of **5** (0.005 mol), propane-1-amine (0.01 mol), triethyl amine (few drops) in absolute ethyl alcohol was heated on boiling water-bath for ~5 h. The reaction mixture was then left to cool. The obtained solid product was filtered off, washed with 5 mL cold ethanol, dried and crystallized from methanol to give **6** as colorless crystals; mp 170–172, yield: (1.25 g, 73%). $R_f = 0.85$.

IR (potassium bromide): $\upsilon_{max}$ = 3420 (NH), 1706 (CO), 1570 (CC) $cm^{-1}$. MS (*m/z* %): 367.19 (95%), 368 (17%), 369(2.00%). $^1$H NMR (500 MHz, $CDCl_3$): δ = 0.92 ($NHCH_2CH_2CH_3$), 1.20 ($(CO)OCH_2CH_3$), 2.25 ($OCH_3CC$), 2.13 ($NCCH_3N$), 3.20 ($NHCH_2$), 4.31 ($OCH_2CH_3$), 7.42 (NH-$D_2O$-exchangeable), 7.40–7.23 (5H, m, Ar-H). *Anal*. Calcd for $C_{21}H_{25}N_3O_3$; MW = (367.44): C, 68.64; H, 6.86; N, 11.44. Found: C, 68.62; H, 6.77; N, 11.42%.

***Synthesis of ethyl 2,7-dimethyl-5-phenyl-4-thioxo-4,5-dihydro-3H-pyrano[2,3-d]pyrimidine-6-carboxylate (7).*** A mixture of **5** (0.005 mol) and thiourea (0.01 mol) in absolute ethanol (30 mL) was heated under reflux for 2 h and left to cool. The obtained product was filtered off and crystallized from ethanol to give the thione **7** as yellowish crystals; mp 156–160°C, yield: (1.2 g, 71.4%). $R_f$ = 0.43. IR (potassium bromide): *υ*: $cm^{-1}$ = 3407 (NH), 1714 (CO), 1655 (CN), 1576 (CC), 1430, 1370, 1239 (CS) $cm^{-1}$. MS (*m/z*:%): 342 (100%), 344 (33.18%).$^1$H NMR (500 MHz, $CDCl_3$): δ = 1.22 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 2.38 (3H, s, $CH_3$), 2.48 (3H,s, $CH_3$), 4.11 (q, *J* = 7.2 Hz, 2H, $CO_2CH_2CH_3$), 4.24 (1H, s, CH), 6.97–7.29 (4H, m, ArH), 12.70 (1H, b, NH) ppm. $^{13}$ C NMR (500 MHz, DMSO-$d_6$): δ = 14.45 ($CH_3CH_2$), 18.78 (C7-$CH_3$), 21.27 (C2-$CH_3$), 39.87 (C5), 60.94 ($CH_2O$), 109.76 (C4a), 113.98 (C6), 127.13, 128.32, 129.31, 143.43 (6 aromatic carbon atoms),158.08 (C7), 158.83 (C8a), 160.05 (C2), 165.89 (CO, carboxylate), 183.22 (CS) ppm. *Anal*. Calcd for $C_{18}H_{18}N_2O_3S$; MW = (342.41): C, 63.14; H, 5.30; N, 8.18; S, 9.36. Found: C, 63.11; H, 5.28; N, 8.15; S, 9.32%.

***Synthesis of ethyl 2,7-dimethyl-5-phenyl-4-(propylthio)-5H-pyrano[2,3-d]pyrimidine-6-carboxylate (8).*** To a solution of **7** (0.85 g, 0.0025 mol) in ethanol (25 mL) and triethylamine (1/2 mL), the appropriate iodopropane (0.0025 mol) was added. The reaction mixture was stirred at room temperature for 10 h. Excess solvent was then concentrated under reduced pressure and left to cool. The solid product obtained was filtered and crystallized from petroleum ether (60–70) to give **8** as white crystals. White crystals, mp 78–80°C, yield: (67.16%). $R_f$ = 1.0. IR (potassium bromide): *υ*: $cm^{-1}$ = 1714 (CO), 1649 (CN) $cm^{-1}$. MS (*m/z*: %): 384 (49.78%). $^1$H NMR (500 MHz, $CDCl_3$): δ = 0.95 (t, *J* = 7.2 Hz, 3H, $CH_2CH_3$), 1.24 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 1.64 (m, *J* = 7.2 Hz, 2H, $CH_2CH_3$), 2.47 (3H, s, $CH_3$), 2.55 (3H,s,$CH_3$),3.26 (t, *J* = 7.2 Hz, 2H, $CH_2CH_2S$), 4.13 (q, *J* = 7.2 Hz, 2H, $CO_2CH_2CH_3$), 4.90 (1H, s, CH), 7.22–7.25 (4H, m, ArH) ppm. $^{13}$C NMR (500 MHz, DMSO-$d_6$): δ = 13.66 ($CH_2CH_2CH_3$), 14.39 ($CH_3CH_2$), 19.05 (C7-$CH_3$), 22.56 (C2-$CH_3$), 25.83 ($CH_2CH_2CH_3$), 31.71($SCH_2$), 32.67 (C5), 60.99 ($CH_2O$), 109.18 (C4a), 110.26 (C6), 128.20–142.75 (6 aromatic carbon atoms), 158.54 (C7), 165.69(CS), 160.84 (C8a), 165.83 (C2), 169.54 (CO, carboxylate) ppm. *Anal*. Calcd for $C_{21}H_{24}N_2O_3S$; MW = (384.49): C, 65.60; H, 6.29; N, 7.29; S, 8.34. Found: C, 65.55; H, 6.24; N, 7.25; S, 8.30%.

## CONCLUSION

The present work was directed to carry out an efficient and a rapid catalytic reaction for the synthesis of polyfunctionalized 4*H*-pyrans and fused 4*H*-pyrans. Thus, upon stirring the selected aldehydes, malononitrile, ethyl acetoacetate, and piperidine (few drops) in deionized water at room temperature 4*H*-pyrans were obtained in good yield, in short reaction time. Also, when the obtained 4*H*-pyrans reacted with acetic anhydride and SSA, 4*H*-pyrano[2,3-*d*]pyrimidines were readily afforded in a short time and excellent yield. Moreover, upon using TCS/$ZnCl_2$ as a catalyst ethyl 6-acetamido-5-carbamoyl-2-methyl-4-aryl-4*H*-pyran-3-carboxylates were readily afforded instead of the expected 4*H*-pyrano[2,3-*d*]pyrimidines. Furthermore, when ethyl 2,7-dimethyl-4-oxo-5-phenyl-4,5-dihydro-3*H*-pyrano[2,3-*d*]pyrimidine-6-carboxylate (**3a**) reacted with $POCl_3$/$PCl_5$ yielded its corresponding chloro derivative, which in turn reacted with propane-1-amine and thiourea to afford the respective propylamino- and thione- derivatives. The latter thione gave the corresponding 4-propyl thio derivative upon reaction with iodopropane.

## ANTIOXIDANT ACTIVITY

There is an increasing interest in antioxidants, particularly in those intended to prevent the presumed deleterious effects of free radicals in the human body and to prevent the deterioration of fats and other constituents of foodstuffs. Antioxidants are defined as substances that when present at low concentrations compared with those of an oxidizable substrate significantly delay or prevent oxidation of that substrate. DPPH is a stable free radical often used as a substance to evaluate the antioxidant capacity of an oxidant [25,26].

**Results of antioxidant screening by DPPH assay.** The preliminary screening for antioxidant activity of some

**Table 5**

DPPH radical scavenging activity (cell-free system) of compounds represented as $EC_{50}$ values.

| Compound | $EC_{50}$ (mM) | Compound | $EC_{50}$ (mM) | Compound | $EC_{50}$ (mM) |
|---|---|---|---|---|---|
| **2a** | >2 | **2j** | >2 | **3h** | >2 |
| **2b** | >2 | **2k** | >2 | **4a** | >2 |
| **2c** | >2 | **3a** | >2 | **4b** | >2 |
| **2d** | >2 | **3b** | >2 | **4c** | >2 |
| **2e** | >2 | **3c** | >2 | **4d** | >2 |
| **2f** | 1.15 | **3d** | >2 | **4e** | >2 |
| **2g** | >2 | **3e** | >2 | **7** | 0.22 |
| **2h** | >2 | **3f** | >2 | **8** | >2 |
| **2i** | >2 | **3g** | 1.71 | | |

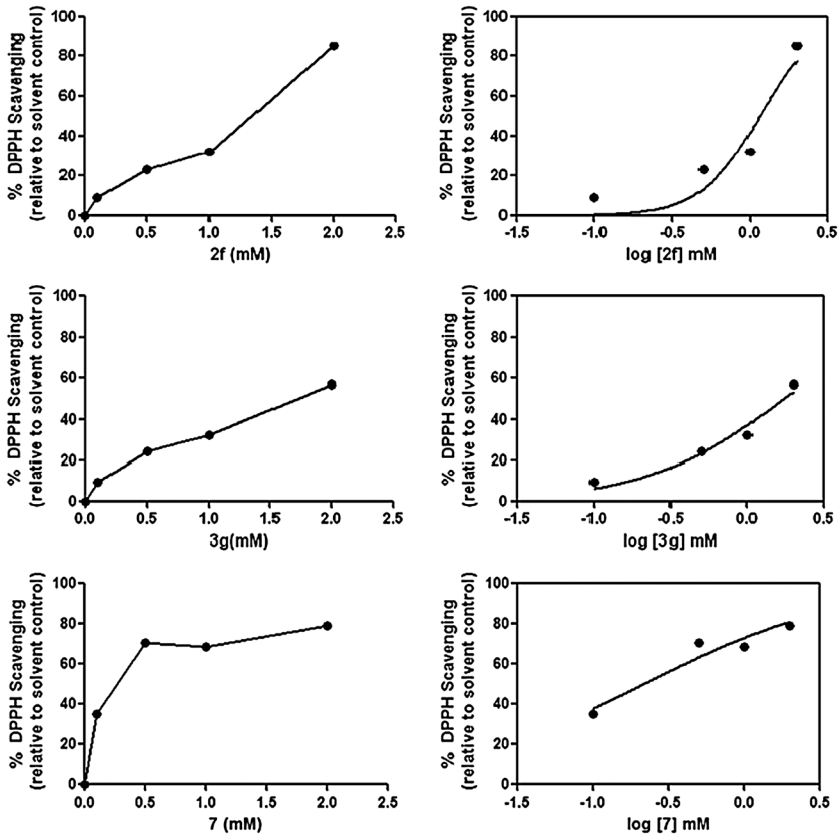



**Figure 1.** Concentration–response relation of the DPPH radical scavenging activity of compounds **2f**, **3g**, and **7** (left panel) and their corresponding nonlinear regression curves (right panel).

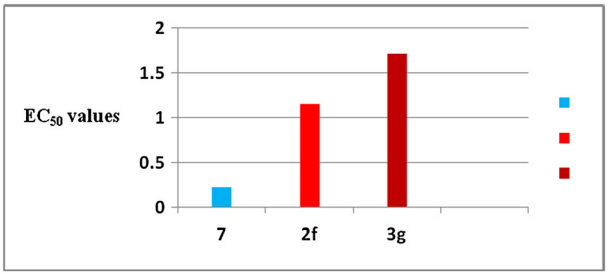



**Figure 2.** DPPH radical scavenging activity (cell-free system) of compounds **7**, **2f**, and **3g** represented as $EC_{50}$ values. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

selected pyrano- and pyrano[2,3-*d*]pyrimidine derivatives was measured by their ability to scavenge DPPH free radical. The obtained data showed that among the tested compounds, three examples in between the synthesized compounds showed concentration-dependant radical scavenging activities against DPPH radical in the order from higher to lower activities as follows: **7** > **2f** > **3g** for which the regression analysis revealed $EC_{50}$ values of 0.22, 1.15, and 1.71 mM, respectively. The remaining test compounds were either devoid of scavenging activity or did not reach 50% scavenging of DPPH radical up to the high concentration of 2 mM (i.e., $EC_{50}$ >2 mM (Table 5). The concentration–response curve fits for the most active compounds **7**, **2f**, and **3g** are shown in Figures 1 and 2.

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