FULL PAPER

Fast Efficient and General PASE Approach to Medicinally Relevant 4*H*,5*H*-Pyrano-[4,3-*b*]pyran-5-one and 4,6-Dihydro-5*H*-pyrano-[3,2-*c*]pyridine-5-one Scaffolds

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The general 'on-solvent' PASE approach was found to be medicinally relevant for 4*H*,5*H*-pyrano[4,3-*b*]pyran-5-one and 4,6-dihydro-5*H*-pyrano[3,2-*c*]pyridine-5-one scaffolds. Ammonium acetate-catalyzed multicomponent reaction of aldehydes and two different C–H acids in the presence of small amounts of EtOH results in fast (3 – 15 min) and efficient formation of scaffolds, promising for many diverse oriented medical applications.

Keywords: Multicomponent reactions, Malononitrile, 4-Hydroxy-6-methyl-2*H*-pyran-2-one, 4-Hydroxy-1-methylquinolin-2(1*H*)-one, Coumarin.

Introduction

The development of ecofriendly green approaches for the chemical synthesis and the elimination of volatile organic solvents in the synthesis of organic compounds is one of the most demanding goal in organic chemistry. Solvent-free method has more advantages, such as high efficiency, selectivity, and operational simplicity, than the classic method of synthesis on solvent method [1][2]. But 'solvent-assisted' or so-called 'on-solvent' method [3][4] when compared with solvent-less mechanochemical process has much more application due to its advantages like more flexibility, high rate, selectivity, and reduced reaction time [5].

However, not only the solvent reducing, but also reducing the number of stages makes process far less harmful [6]. Often it is connected with multicomponent processes [7], when at least three different substrates assemble a new compound.

The more bonds were constructed, the more simplified is the whole process by reducing intermediate steps, saving time, and improving many other practical aspects. In this way multicomponent processes overlap with PASE strategy [8], which claims pot and step economy, and also introduces atom economy, that means the number of atoms of all reagents which should constitute the final compound [9].

The design of functional organic and hybrid molecular systems has shown outstanding recent growth and is a high priority in the development of new technologies and novel functional materials [10]. In this connection, the concept of 'privileged medicinal structures or scaffolds' has emerged as one of the guiding principles of drug discovery design. Hence, the synthesis of new types of medicinally privileged scaffolds is an important step in drug discovery process.

Fused pyran scaffold produces an immense variety of pharmacological and biological properties; thence well-known pyran derivatives attract attention as an important class of heterocycles (*Fig. 1*).

Many of fused pyrans are nonpeptide human immunodeficiency virus (HIV) protease inhibitors [11] or compounds which exhibit antiviral, antileishmanial [12], stimulant [13], and anticonvulsant [14] properties. Among natural compounds, pyranes occur as supellapyrone, the female sex pheromone of the brownbanded cockroach [15]. UCPH 101 and UCPH-102F are selective EAAT1 inhibitors [16] (*Fig. 1*).

Pyran annulated scaffolds are used as anticancer [17], antianaphylactic [18], spasmolytics, antitumoral [19], and anti-HIV agents [20]. Moreover, warfarin is well-known anticoagulant [21], which affects the interconversion of vitamin K (*Fig. 1*).

Pyridone structural motif is a part of many natural and synthetic molecules, which exhibit diverse biological activities. Diazaquinomycin A shows antitumor and antibiotic properties [22], and it is known as nonnucleoside HIV reverse transcriptase inhibitor L-697,661 [23]. Phosphodiesterase inhibitor milrinone [24] is used in the treatment of heart failure (*Fig. 2*). Fusaricide is active as an anticancer agent [25].

Catalytic methods have been reported for the synthesis of 4*H*,5*H*-pyrano[4,3-*b*]pyran-5-one derivatives. These procedures, in which aldehydes were condensed with $CH_2(CN)_2$ and 4-hydroxy-6-methylpyran-2-one using ultrasound irradiation [26][27] or in the presence of

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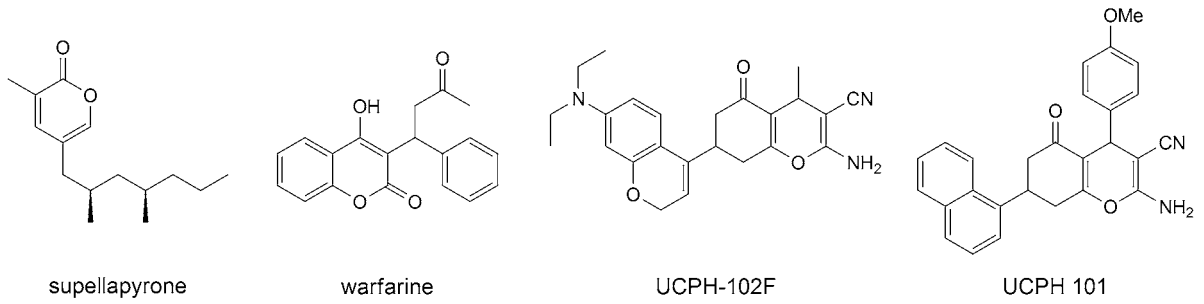


Fig. 1. Biologically active pyranes.

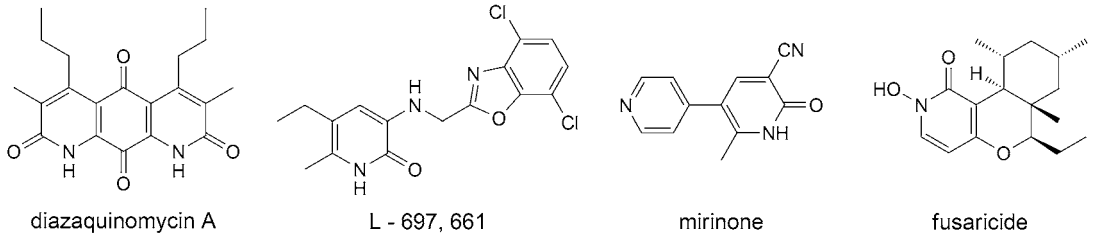


Fig. 2. Biologically active pyridones.

various catalysts, such as piperidine [28], KF/Al_2O_3 [29], MgO [30], DBU [31], DCDBTSD [32], or ionic liquids [33], suffer from long reaction times, high temperature, expensive catalysts or complicated preparation of catalysts, and insufficient yields. Moreover, some of these methods used successive two-step procedure.

Only few methods have been reported for the synthesis of pyridone annulated structures. These methods utilize nanozeolite clinoptilolite in H_2O [34], Me_3N [35], piperidine [36], or DMF [37] in EtOH, but suffer from complicated tedious preparation of catalyst, or long reaction time and insufficient yields.

Although all the above-mentioned methods have its merits, but ecofriendly general PASE-multicomponent method for synthesis of medicinally relevant 4*H*,5*H*-pyrano[4,3-*b*]pyran-5-ones and 4,6-dihydro-5*H*-pyrano[3,2-*c*]-pyridine-5-ones has yet to be developed.

Results and Discussion

In this investigation, we were prompted to design ecofriendly PASE approach for the synthesis of relevant 4*H*,5*H*-pyrano[4,3-*b*]pyran-5-ones and 4,6-dihydro-5*H*-pyrano[3,2-*c*]pyridine-5-ones. Based on the success in solvent-free noncatalytic process [38], this investigation was started with solvent-free multicomponent transformation without any catalyst by grinding PhCHO (**1a**), $CH_2(CN)_2$ (**2a**), and 4-hydroxy-6-methyl-2*H*-pyran-2-one (**3a**) in a mortar with a pestle within 15 min (*Scheme 1*). In this case, 4*H*,5*H*-pyrano[4,3-*b*]pyran **4a** was obtained in 38% yield (*Table 1*, *Entry 1*).

Using NaOH, the yield of **4a** increased to 45% (*Table 1*, *Entry 2*). Replacing NaOH by KF, the yield of **4a** increased to 57% (*Table 1*, *Entry 3*). $AcONH_4$ was found as an optimal catalyst ($AcONH_4$, 10 mol-%), which produced 4*H*,5*H*-pyrano[4,3-*b*]pyran **4a** in 64% yield (*Table 1*, *Entry 4*). Increasing the reaction time led to the increase in the yield of **4a** to 79% (*Table 1*, *Entry 5*).

Earlier we have found that small additives of H_2O or alcohols could improve multicomponent processes, which were initiated by grinding [39 – 41] (so-called 'on-water' [3] or 'on-solvent' [4] reactions). Both kinetic and thermodynamic outcomes have established that the H-bonding ability of the surface H_2O molecules plays a critical role in the 'on-water' organic reaction mechanism [42].

The next 'on-water' reaction in a mortar was carried out with addition of 2 ml of H_2O with 10 mol-% $AcONH_4$ as a catalyst (*Table 1*, *Entry 6*). However, in this case, **4a** was obtained in 65% yield, and in 81% yield with addition of EtOH (2 ml, *Table 1*, *Entry 7*).

The thermal activation, which ensured success earlier [39][43], led to 4*H*,5*H*-pyrano[4,3-*b*]pyran **4a** in 87% yield in only 3 min (*Table 1*, *Entry 8*). In this case, the mortar was replaced by a flask, and the reaction was carried out at 78 °C using a magnetic stirring bar.

Scheme 1. Multicomponent transformation of PhCHO (**1a**), $CH_2(CN)_2$ (**2a**), and 4-hydroxy-6-methyl-2*H*-pyran-2-one (**3a**) into 2-amino-7-methyl-5-oxo-4-phenyl-4*H*,5*H*-pyrano[4,3-*b*]pyran-3-carbonitrile (**4a**).

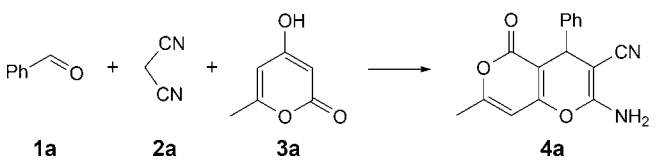
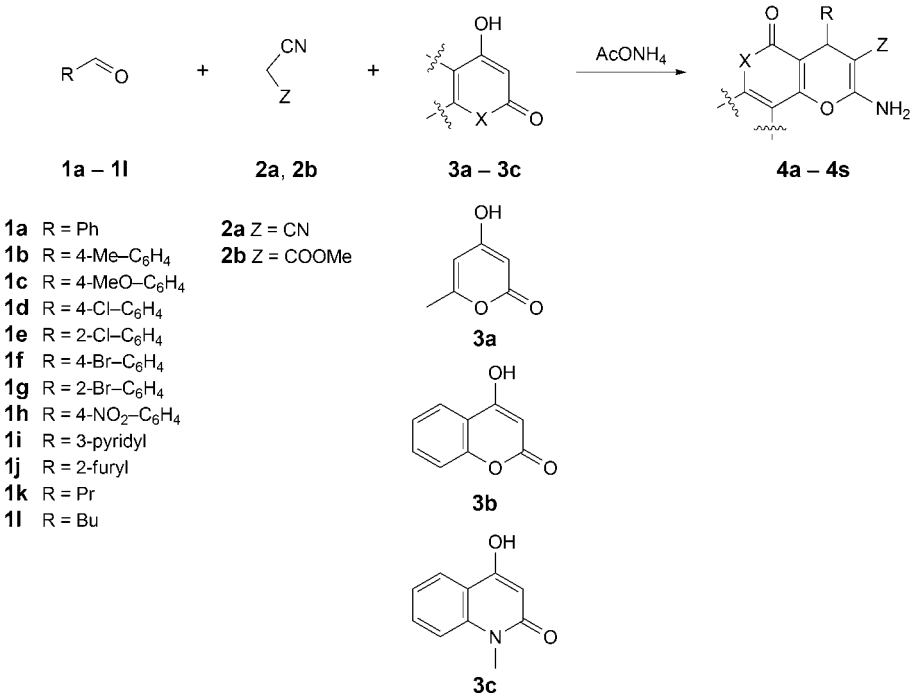


Table 1. Assembling of benzaldehyde **1a**, malononitrile **2a**, C–H acid **3a** into pyrano[4,3-*b*]pyran-5-one **4a**[a])

Entry[a])	Additive [ml]	Catalyst [mol-%]	Time [min]	Temperature [°C]	Yield [%][b])
1	Neat	Without	15	25	38
2	Neat	NaOH, 10	15	25	45
3	Neat	KF, 10	15	25	57
4	Neat	$AcONH_4$, 10	15	25	64
5	Neat	$AcONH_4$, 10	30	25	79
6	H_2O, 2	$AcONH_4$, 10	15	25	65
7	EtOH, 2	$AcONH_4$, 10	15	25	81
8[c])	EtOH, 3	$AcONH_4$, 10	3	78	87[d])
9[e])	EtOH, 3	$AcONH_4$, 10	3	78	95[d])

[a]) **1a** (3 mmol), **2a** (3 mmol), **3a** (3 mmol), and catalyst were grinded with a pestle in a mortar neat or with an additive. [b]) According to NMR data. [c]) **1a** (3 mmol), **2a** (3 mmol), **3a** (3 mmol), $AcONH_4$ (0.3 mmol), and 3 ml of EtOH were stirred at 78 °C. [d]) Yield of isolated compounds. [e]) **1a** (3.3 mmol), **2a** (3.3 mmol), **3a** (3 mmol), $AcONH_4$ (0.3 mmol), and 3 ml of EtOH were stirred at 78 °C.

Scheme 2. General PASE approach to synthesis of 4*H*,5*H*-pyrano[4,3-*b*]pyran-5-one and 4,6-dihydro-5*H*-pyrano[3,2-*c*]pyridine-5-one compounds **4a** – **4s** from aldehydes **1a** – **1l**, C–H acids **2a** and **2b**, and C–H acids **3a** – **3c**.



The next reaction was performed with excess of PhCHO (1.1 equiv.) and excess of $CH_2(CN)_2$ (1.1. equiv.) with **3a** (1 equiv.), $AcONH_4$ (0.1. equiv.), and 3 ml of EtOH (3 min reaction time at 78 °C). These conditions led to formation of **4a** in excellent 95% yield (*Table 1*, *Entry 9*).

Under these optimal conditions (10 mol-% excess of aldehyde and $CH_2(CN)_2$, $AcONH_4$ 10 mol-%, EtOH 3 ml, 78 °C), the reactions of aldehydes **1a** – **1l**, C–H acids **2a** and **2b**, and heterocyclic C–H acids **3a** – **3c** resulted in formation of substituted 4*H*,5*H*-pyrano[4,3-*b*]pyranes and 4,6-dihydro-5*H*-pyrano[3,2-*c*]pyridine-5-ones **4a** – **4s** in 88 – 97% yields (*Scheme 2*, *Table 2*).

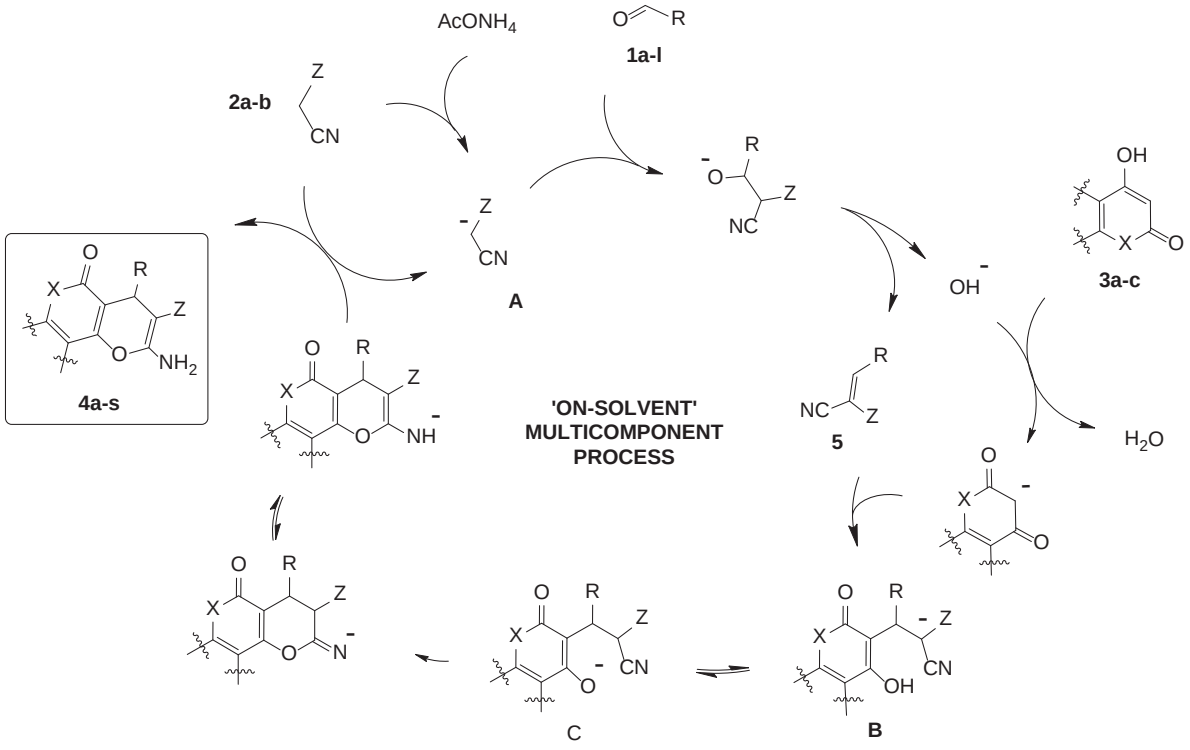
Based on above results and the data on mechanisms of the multicomponent transformation of CO compounds and C–H acids into heterocyclic systems [38][39][44], the following mechanism for the assembling of aldehydes **1a** – **1l**, C–H acids **2a** and **2b,** and heterocyclic C–H acids **3a** – **3c** into substituted 4*H*,5*H*-pyrano[4,3-*b*]pyranes or 4,6-dihydro-5*H*-pyrano[3,2-*c*]pyridine-5-ones **4a** – **4s** was proposed (*Scheme 3*). Catalytic cycle starts with deprotonation of a molecule of C–H acid **2**, induced by $AcONH_4$, which leads to the anion **A** formation (*Scheme 3*). Then the *Knoevenagel* condensation of the anion **A** with aldehyde **1** leads to the *Knoevenagel* adduct **5** with elimination of OH anion. The subsequent OH-promoted the *Michael* addition of heterocyclic C–H acids **3** to an

Table 2. General PASE approach to synthesis of 4*H*,5*H*-pyrano[4,3-*b*]pyran-5-one and 4,6-dihydro-5*H*-pyrano[3,2-*c*]pyridine-5-one compounds **4a** – **4s** from aldehydes **1a** – **1l**, C–H acids **2a** and **2b**, and C–H acids **3a** – **3c**[a]). See the structures, see *Scheme 2*

Entry[a])	Carbonyl compound	C–H acid **2**	C–H acid **3**	Time [min]	Compound **4**	Yield [%][b])
1	**1a**	**2a**	**3a**	3	**4a**	95
2	**1b**	**2a**	**3a**	3	**4b**	91
3	**1c**	**2a**	**3a**	8	**4c**	92
4	**1d**	**2a**	**3a**	3	**4d**	90
5	**1g**	**2a**	**3a**	3	**4e**	91
6	**1i**	**2a**	**3a**	5	**4f**	92
7	**1k**	**2a**	**3a**	10	**4g**	90
8	**1l**	**2a**	**3a**	10	**4h**	91
9	**1a**	**2b**	**3a**	15	**4i**	90
10	**1a**	**2a**	**3b**	3	**4j**	93
11	**1b**	**2a**	**3b**	6	**4k**	97
12	**1e**	**2a**	**3b**	3	**4l**	94
13	**1h**	**2a**	**3b**	3	**4m**	92
14	**1j**	**2a**	**3b**	6	**4n**	90
15	**1l**	**2a**	**3b**	15	**4o**	88
16	**1a**	**2a**	**3c**	3	**4p**	92
17	**1b**	**2a**	**3c**	3	**4q**	94
18	**1d**	**2a**	**3c**	3	**4r**	92
19	**1f**	**2a**	**3c**	3	**4s**	93

[a]) Aldehydes **1a** – **1l** (3.3 mmol), C–H acids **2a** and **2b** (3.3 mmol), C–H acids **3a** – **3c** (3 mmol), $AcONH_4$ (0.3 mmol), and 3 ml of EtOH were stirred at 78 °C for appropriate time. [b]) Yield of isolated products.

Scheme 3. Assembling of aldehydes **1a** – **1l**, C–H acids **2a** and **2b**, and C–H acid **3a** – **3c** into 4*H*,5*H*-pyrano[4,3-*b*]pyran-5-ones or 4,6-dihydro-5*H*-pyrano[3,2*c*]pyridine-5-ones **4a** – **4s**.



electron-deficient *Knoevenagel* adduct **5** results in the subsequent anions **B** and **C** formation. Further cyclization of anion **C** and protonation with the participation of the next molecule of C–H acid **2** leads to the corresponding 4*H*,5*H*-pyrano[4,3-*b*]pyran-5-one or 4,6-dihydro-5*H*-pyrano[3,2-*c*]pyridine-5-one **4** formation with the regeneration of anion **A** as the beginning of the next catalytic cycle.

Conclusions

In conclusion, under simple and highly efficient PASE 'on-solvent' conditions, $AcONH_4$ produces fast (3 – 15 min) and selective transformation of aldehydes and two different C–H acids; among them heterocyclic C–H acids are transformed into substituted 4*H*,5*H*-pyrano[4,3-*b*]pyran-5-ones and 4,6-dihydro-5*H*-pyrano[3,2-*c*]pyridine-5-ones, which are privileged scaffolds, promising for many diverse oriented medical applications with anti-HIV, antiviral, antileishmanial, and anticancer activities. This new general and fast approach allows to combine the synthetic virtues of conventional multicomponent reactions with ecological benefits and the convenience of 'on-solvent' processes. This method leads to excellent yields, utilizes simple equipment and it is easy to carry out. The final compounds obtained by this method needs no further purification, thereby this method reduces the waste generation.

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Experimental Part

General Remarks

All melting points were measured using a *Gallenkamp* melting point apparatus and are uncorrected. ^{1}H and ^{13}C-NMR spectra were recorded with a *Bruker AM-300* at ambient temp. in (D_6)DMSO solns. Chemical shift values are given in δ scale relative to Me_4Si. IR spectra were registered with a *Bruker ALPHA-T* FT-IR spectrometer in KBr pellets. HR-ESI-MS was measured on a *Bruker microTOF II* instrument; external or internal calibration was done with *Electrospray Calibrant Solution* (*Fluka*). All chemicals used in this study were commercially available.

General 'On-Solvent' Procedure

Aldehyde **1a** – **1l** (3.3 mmol), C–H acid **2a** or **2b** (3.3 mmol), C–H acid **3a** – **3c** (3 mmol), $AcONH_4$ (0.023 g, 0.3 mmol), and EtOH 3 ml were stirred with magnetic stirring bar 3 – 15 min. The time of the reaction was determined by TLC. The solid was filtered out after cooling, washed with 5 ml of H_2O, and dried under reduced pressure to isolate pure compounds **4a** – **4s**.

2-Amino-7-methyl-5-oxo-4-phenyl-4*H*,5*H*-pyrano[4,3-*b*]-pyran-3-carbonitrile (**4a**). Yield 0.80 g (95%). White solid. M.p. 231 – 233 °C ([12]: 231 – 233 °C). ^{1}H-NMR (300 MHz, (D_6)DMSO): 2.22 (*s*, Me); 4.28 (*s*, CH); 6.27 (*s*, CH); 7.17 (*s*, NH_2); 7.20 – 7.24 (*m*, 3 arom. H); 7.29 – 7.33 (*m*, 2 arom. H).

2-Amino-7-methyl-4-(4-methylphenyl)-5-oxo-4*H*,5*H*-pyrano[4,3-*b*]pyran-3-carbonitrile (**4b**). Yield 0.80 g (91%). White solid. M.p. 228 – 230 °C ([12]: 228 – 230 °C). ^{1}H-NMR (300 MHz, (D_6)DMSO): 2.20 (*s*, Me); 2.25 (*s*, Me); 4.24 (*s*, CH); 6.25 (*s*, CH); 7.05 – 7.12 (*m*, 4 arom. H); 7.16 (*s*, NH_2).

2-Amino-4-(4-methoxyphenyl)-7-methyl-5-oxo-4*H*,5*H*-pyrano[4,3-*b*]pyran-3-carbonitrile (**4c**). White solid. Yield 0.86 g (92%). M.p. 221 – 223 °C ([28]: 205 – 207 °C); ^{1}H-NMR (300 MHz, (D_6)DMSO): 2.21 (*s*, Me); 3.72 (*s*, MeO); 4.22 (*s*, CH); 6.24 (*s*, CH); 6.86 (*d*, *J* = 8.3, 2 arom. H); 7.09 (*d*, *J* = 8.3, 2 arom. H); 7.13 (*s*, NH_2).

2-Amino-4-(4-chlorophenyl)-7-methyl-5-oxo-4*H*,5*H*-pyrano[4,3-*b*]pyran-3-carbonitrile (**4d**). White solid. Yield 0.85 g (90%). M.p. 228 – 230 °C ([26]: 228 – 230 °C); ^{1}H-NMR (300 MHz, (D_6)DMSO): 2.22 (*s*, Me); 4.31 (*s*, CH); 6.27 (*s*, CH); 7.21 – 7.23 (*m*, 2 arom. H, NH_2); 7.35 – 7.38 (*d*, *J* = 8.4, 2 arom. H).

2-Amino-4-(3-bromophenyl)-7-methyl-5-oxo-4*H*,5*H*-pyrano[4,3-*b*]pyran-3-carbonitrile (**4e**). White solid. Yield 0.98 g (91%). M.p. 218 – 220 °C ([26]: 217 – 219 °C); ^{1}H-NMR (300 MHz, (D_6)DMSO): 2.22 (*s*, Me); 4.33 (*s*, CH); 6.27 (*s*, CH); 7.20 – 7.44 (*m*, 4 arom. H, NH_2).

2-Amino-7-methyl-5-oxo-4-(pyridin-3-yl)-4*H*,5*H*-pyrano-[4,3-*b*]pyran-3-carbonitrile (**4f**). Beige solid. Yield 0.78 g (92%). M.p. 221 – 223 °C. IR (KBr): 3409, 3129, 2886, 2192, 1704, 1668, 1646, 1621, 1379, 1258. ^{1}H-NMR (300 MHz, (D_6)DMSO): 2.23 (*s*, Me); 4.39 (*s*, CH); 6.30 (*s*, CH); 7.30 (*s*, NH_2); 7.33 – 7.37 (*m*, 1 arom. H); 7.62 (*d*, *J* = 7.6, 1 arom. H); 8.46 (*m*, 2 arom. H). ^{13}C-NMR (75 MHz, (D_6)DMSO): 19.3; 34.0; 56.9; 98.0; 99.7; 119.1; 123.7; 135.2; 138.9; 148.2; 149.0; 158.2; 158.4; 161.3; 163.2.

2-Amino-7-methyl-5-oxo-4-propyl-4*H*,5*H*-pyrano[4,3-*b*]-pyran-3-carbonitrile (**4g**). White solid. Yield 0.75 g (90%). M.p. 185 – 187 °C. IR (KBr): 3362, 3198, 2952, 2197, 1710, 1678, 1621, 1397, 1149, 1037. ^{1}H-NMR (300 MHz, (D_6)DMSO): 0.86 (*t*, *J* = 7.1, Me); 1.07 – 1.30 (*m*, CH_2); 1.42 – 1.51 (*m*, 1 H of CH_2); 1.60 – 1.72 (*m*, 1 H of CH_2); 2.23 (*s*, Me); 3.27 – 3.33 (*m*, CH); 6.17 (*s*, CH); 7.07 (*s*, NH_2). ^{13}C-NMR (75 MHz, (D_6)DMSO): 13.8; 17.4; 19.2; 30.0; 35.8; 55.3; 97.9; 100.6; 119.7; 159.0; 159.3; 161.7; 162.4. HR-ESI-MS: 247.1079 ($[M + H]^+$, $C_{13}H_{15}N_2O_3^+$; calc. 247.1077).

2-Amino-4-butyl-7-methyl-5-oxo-4*H*,5*H*-pyrano[4,3-*b*]pyran-3-carbonitrile (**4h**). White solid. Yield 0.71 g (91%). M.p. 182 – 184 °C. IR (KBr): 3366, 3200, 2195, 1708, 1622, 1397, 1266, 1147, 1041, 560. ^{1}H-NMR (300 MHz, (D_6)DMSO): 0.80 (*t*, *J* = 7.0, Me); 1.02 – 1.22 (*m*, 2 CH_2); 1.41 – 1.49 (*m*, 1 H of CH_2); 1.61 – 1.69 (*m*, 1 H of CH_2); 2.19 (*s*, Me); 3.24 – 3.33 (*m*, CH); 6.13 (*s*, CH); 7.03 (*s*, NH_2). ^{13}C-NMR (75 MHz, (D_6)DMSO): 13.6; 19.2; 22.0; 26.2; 30.0; 33.0; 55.2; 97.8; 100.5; 119.6; 159.0; 159.3; 161.7; 162.4. HR-ESI-MS: 261.1236 ($[M + H]^+$, $C_{14}H_{17}N_2O_3^+$; calc. 261.1233).

Methyl 2-Amino-7-methyl-5-oxo-4-phenyl-4*H*,5*H*-pyrano-[4,3-*b*]pyran-3-carboxylate (**4i**). White solid. Yield 0.85 g (90%). M.p. 200 – 202 °C ([28]: 197 – 199 °C). ^{1}H-NMR (300 MHz, (D_6)DMSO): 2.20 (*s*, Me); 3.55 (*s*, MeO); 4.54

(*s*, CH); 6.28 (*s*, CH); 7.10 – 7.25 (*m*, 5 arom. H); 7.70 (*s*, NH_2).

2-amino-5-oxo-4-phenyl-4*H*,5*H*-pyrano[3,2-*c*]chromene-3-carbonitrile (**4j**). White solid. Yield 0.88 g (93%). M.p. 261 – 263 °C ([27]: 260 – 261 °C). ^{1}H-NMR (300 MHz, (D_6)DMSO): 4.45 (*s*, CH); 7.21 – 7.51 (*m*, 7 arom. H, NH_2); 7.71 (*t*, *J* = 7.5, 1 arom. H); 7.91 (*d*, *J* = 7.6, 1 arom. H).

2-Amino-4-(4-methylphenyl)-5-oxo-4*H*,5*H*-pyrano[3,2-*c*]-chromene-3-carbonitrile (**4k**). White solid. Yield 0.96 g (97%). M.p. 253 – 254 °C ([32]: 253 – 254 °C). ^{1}H-NMR (300 MHz, (D_6)DMSO): 2.27 (*s*, Me); 4.41 (*s*, CH); 7.10 – 7.16 (*m*, 4 arom. H); 7.37 (*s*, NH_2); 7.44 – 7.52 (*m*, 2 arom. H); 7.71 (*t*, *J* = 9.0, 1 arom. H); 7.90 (*d*, *J* = 7.3, 1 arom. H).

2-Amino-4-(2-chlorophenyl)-5-oxo-4*H*,5*H*-pyrano[3,2-*c*]-chromene-3-carbonitrile (**4l**). White solid. Yield 0.99 g (94%). M.p. 257 – 259 °C ([32]: 257 – 259 °C). ^{1}H-NMR (300 MHz, (D_6)DMSO): 4.98 (*s*, CH); 7.24 – 7.52 (*m*, 6 arom. H, NH_2); 7.71 (*t*, *J* = 7.6, 1 arom. H); 7.92 (*d*, *J* = 7.6, 1 arom. H).

2-Amino-4-(4-nitrophenyl)-5-oxo-4*H*,5*H*-pyrano[3,2-*c*]chromene-3-carbonitrile (**4m**). White solid. Yield 1.00 g (92%). M.p. 261 – 263 °C ([32]: 260 – 262 °C). ^{1}H-NMR (300 MHz, (D_6)DMSO): 4.67 (*s*, CH); 7.45 – 7.61 (*m*, 4 arom. H, NH_2); 7.72 (*t*, *J* = 8.2, 1 arom. H); 7.91 (*d*, *J* = 7.6, 1 arom. H); 8.17 (*d*, *J* = 8.2, 2 arom. H).

2-Amino-4-(furan-2-yl)-5-oxo-4*H*,5*H*-pyrano[3,2-*c*]chromene-3-carbonitrile (**4n**). Yellowish solid. Yield 0.83 g (90%). M.p. 258 – 260 °C ([27]: 255 – 256 °C). ^{1}H-NMR (300 MHz, (D_6)DMSO): 4.62 (*s*, CH); 6.27 – 6.28 (*m*, 1 H of fur); 6.36 – 6.38 (*m*, 1 H of fur); 7.45 – 7.52 (*m*, 2 arom. H, NH_2, 1 H of fur); 7.71 (*t*, *J* = 7.7, 1 arom. H); 7.87 (*d*, *J* = 7.7, 1 arom. H).

2-Amino-4-butyl-5-oxo-4*H*,5*H*-pyrano[3,2-*c*]chromene-3-carbonitrile (**4o**). White solid. Yield 0.78 g (88%). M.p. 208 – 210 °C. IR (KBr): 3393, 3291, 3188, 2926, 2192, 1714, 1672, 1395, 1046, 755. ^{1}H-NMR (300 MHz, (D_6) DMSO): 0.80 (*t*, *J* = 7.0, Me); 1.11 – 1.24 (*m*, 2 CH_2); 1.51 – 1.59 (*m*, 1 H of CH_2); 1.68 – 1.75 (*m*, 1 H of CH_2); 3.35 – 3.42 (*m*, CH); 7.27 (*s*, NH_2); 7.40 – 7.45 (*m*, 2 arom. H); 7.67 (*t*, *J* = 7.8, 1 arom. H); 7.79 (*d*, *J* = 7.8, 1 arom. H). ^{13}C-NMR (75 MHz, (D_6)DMSO): 13.8; 22.1; 26.4; 30.8; 33.4; 55.2; 104.2; 112.9; 116.4; 119.6; 122.0; 124.4; 132.6; 152.0; 154.0; 159.4; 159.8. HR-ESI-MS: 297.1236 ([*M* + H]$^+$, $C_{17}H_{16}N_2O^+$; calc. 297.1233).

2-Amino-6-methyl-5-oxo-4-phenyl-5,6-dihydro-4*H*-pyrano-[3,2-*c*]quinoline-3-carbonitrile (**4p**). White solid. Yield 0.91 g (92%). M.p. 257 – 259 °C ([34]: 255 – 258 °C). ^{1}H-NMR (300 MHz, (D_6)DMSO): 3.53 (*s*, Me); 4.52 (*s*, CH); 7.17 – 7.30 (*m*, 5 arom. H, NH_2); 7.39 (*t*, *J* = 7.8, 1 arom. H); 7.56 (*d*, *J* = 7.8, 1 arom. H); 7.70 (*t*, *J* = 7.8,1 arom. H); 8.02 (*d*, *J* = 7.8, 1 arom. H).

2-Amino-6-methyl-4-(4-methylphenyl)-5-oxo-5,6-dihydro-4*H*-pyrano[3,2-*c*]quinoline-3-carbonitrile (**4q**). White solid. Yield 0.97 g (94%). M.p. 281 – 282 °C. IR (KBr): 3409, 3313, 2967, 2185, 1673, 1597, 1505, 1462, 1378, 1257. ^{1}H-NMR (300 MHz, (D_6)DMSO): 2.25 (*s*, Me); 3.54 (*s*, Me); 4.49 (*s*, CH); 7.05 – 7.12 (*m*, 4 arom. H); 7.24 (*s*, NH_2); 7.38 – 7.43 (*m*, 1 arom. H); 7.58 (*d*, *J* = 8.5, 1 arom. H); 7.69 – 7.74 (*m*, 1 arom. H); 8.04 (*d*, *J* = 7.9, 1 arom. H). ^{13}C-NMR (75 MHz, (D_6)DMSO): 20.5; 29.2; 36.9; 58.1; 109.1; 112.6; 114.8; 119.7; 122.0; 122.1; 127.3 (2C); 128.8 (2C); 131.4; 135.7; 138.8; 141.3; 149.9; 158.8; 159.7. HR-ESI-MS: 366.1213 ([*M* + H]$^+$, $C_{21}H_{17}N_3NaO_2^+$; calc. 366.1218).

2-Amino-4-(4-chlorophenyl)-6-methyl-5-oxo-5,6-dihydro-4*H*-pyrano[3,2-*c*]quinoline-3-carbonitrile (**4r**). White solid. Yield 1.00 g (92%). M.p. 280 – 282 °C ([34]: 280 – 282 °C). ^{1}H-NMR (300 MHz, (D_6)DMSO): 3.54 (*s*, Me); 4.55 (*s*, CH); 7.24 – 7.26 (*m*, 2 arom. H); 7.33 – 7.42 (*m*, 3 arom. NH_2); 7.57 (*d*, *J* = 8.4, 1 arom. H); 7.69 – 7.74 (*m*, 1 arom. H); 8.03 (*d*, *J* = 7.9, 1 arom. H).

2-Amino-4-(4-bromophenyl)-6-methyl-5-oxo-5,6-dihydro-4*H*-pyrano[3,2-*c*]quinoline-3-carbonitrile (**4s**). Beige solid. Yield 1.14 g (93%). M.p. 285 – 286 °C ([37]: 275 – 277 °C). ^{1}H-NMR (300 MHz, (D_6)DMSO): 3.53 (*s*, Me); 4.52 (*s*, CH); 7.19 (*d*, *J* = 7.8, 2 arom. H); 7.31 (*s*, NH_2); 7.37 – 7.42 (*m*, 1 arom. H); 7.47 (*d*, *J* = 7.8, 2 arom. H); 7.56 (*d*, *J* = 8.5, 1 arom. H); 7.68 – 7.73 (*m*, 1 arom. H); 8.02 (*d*, *J* = 7.8, 1 arom. H).

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