Chemical Papers (2019) 73:55–69
https://doi.org/10.1007/s11696-018-0566-8

ORIGINAL PAPER

A novel and efficient synthesis of 3-aryl-5-(2-hydroxybenzoyl) pyridin-2(1*H*)-ones by re-cyclization of *N*-(oxopyranochromenyl) acetamides and their antineoplastic screening

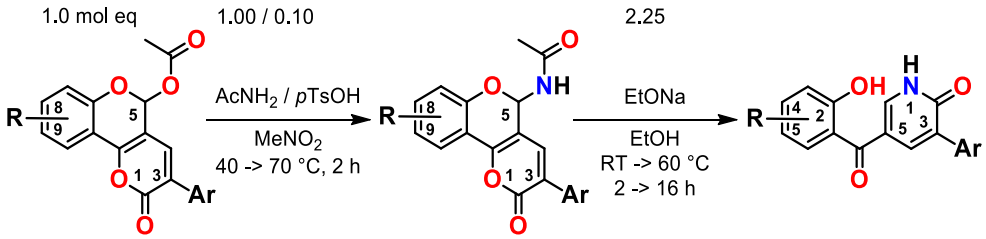
Margita Lácová[1] · Matúš Čakurda[1] · Pavol Koiš[1] · Gabriela Addová[2] · Andrej Boháč[1,3]

Received: 12 May 2018 / Accepted: 31 July 2018 / Published online: 7 August 2018

Abstract

We have developed a novel, simple and efficient methodology for preparation of yet unknown 3-aryl-5-(2-hydroxybenzoyl)pyridin-2(1*H*)-ones **3(a–g)** by EtONa driven re-cyclization of *N*-(3-aryl-2-oxo-2,5-dihydropyrano[3,2-*c*]chromen-5-yl)acetamides **2(a–g)** in good yields (80–95%). A mechanism for this reaction was proposed. The 3-aryl-2-oxo-2,5-dihydropyrano[3,2-*c*]chromen-5-yl acetates **1(a–g)** were prepared by cyclocondensation from 3-formylchromones (4-oxo-4*H*-chromene-3-carbaldehydes) and acetic acids in 64–86% yields. Acetamides **2(a–g)** were obtained by reaction of 3-aryl-2-oxo-2,5-dihydropyrano[3,2-*c*]chromen-5-yl acetates **1(a–g)** with $AcNH_2$ catalyzed by *p*TsOH in 80–93% yields. Click chemistry precursors **4(a,d)** and **5(a,d)** were prepared by propargylation of **3(a,d)** in 92–98% yields. They can serve for construction of more complex molecules possessing pyridone skeleton of **3**. Eleventh novel compounds **3(a–g)**, **4(a,d)** and **5(a,d)** were screened on their anticancer activity on a panel of human tumour cell lines by NCI USA. We found that pyridones **3**–**5** selectively inhibit the growth of some of the tumour cell lines at 10^{-5} M (up to -33% compared to a control). The most sensitive tumour cell lines originated from kidney, breast, skin, ovary, blood and lung.

Graphical Abstract



Ar	R	2(a-g)	3(a-g)
1a (71 %) Ph	H	**2a** (88%)	**3a** (91%)
1b (86 %) Ph	9-Me	**2b** (85%)	**3b** (93%)
1c (64 %) 4-MeOPh	9-NO_2	**2c** (80%)	**3c** (95%)
1d (55 %) 4-MeOPh	8,9-diMe	**2d** (81%)	**3d** (88%)
1e (76 %) 4-NO_2Ph	H	**2e** (88%)	**3e** (90%)
1f (85 %) 4-NO_2Ph	8,9-diMe	**2f** (93%)	**3f** (85%)
1g (83 %) 1*H*-tetrazol	8,9-diMe	**2g** (81%)	**3g** (80%)

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11696-018-0566-8) contains supplementary material, which is available to authorized users.

Extended author information available on the last page of the article

Keywords 3-aryl-5-(2-hydroxybenzoyl)pyridin-2(1*H*)-ones · *N*-(3-aryl-2-oxo-2,5-dihydropyrano[3,2-*c*]chromen-5-yl) acetamides · re-cyclization mechanism · NCI tumour cell lines · Click chemistry precursors

Introduction

Known 5-(2-hydroxybenzoyl)pyridin-2(1*H*)-ones

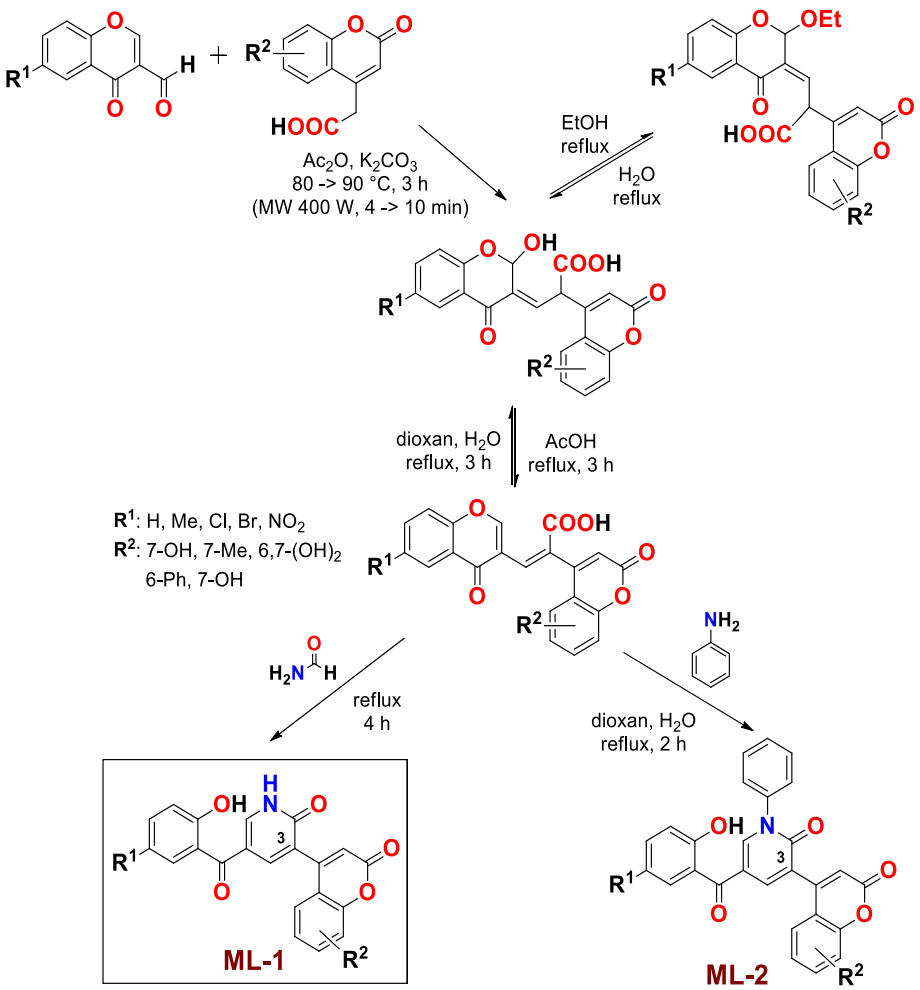
According to the SciFinder database, there are 789 registered structures possessing skeleton **ML-4** (Scheme 1). None of these structures has an aryl or heteroaryl substituent at C-(3) on the pyridone ring as present in our novel compounds **3–5**. Except a registered structure with benzimidazolyl group at C(3) [CAS: 785791-96-0] with no properties and synthesis published. Two other compounds similar to **3** [CAS: 339076-12-9 **ML-1** and 339076-09-4 **ML-2**] (Scheme 2) (Lácova et al. 1999 and 2000) do not have a full aromatic substituent at C(3) and were prepared by different methodology as described for **3–5** (Scheme 9 and 11).

So far, several synthetic pathways were developed for the preparation of compounds **ML-4** differing by starting materials and nitrogen containing reactants (Scheme 2).

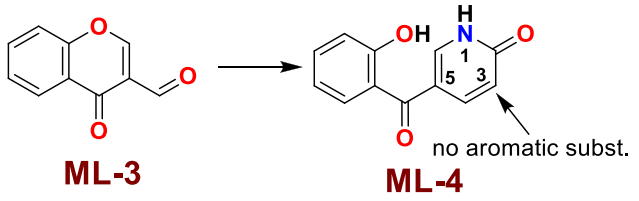
After a reaction of chromenecarbaldehydes **ML-5** with amide derivatives **ML-6** in the presence of TMSC pyridones **ML-7** were prepared in good yields. This type of reaction performs with both primary and secondary amides having an acidic methylene group in an alpha position in **ML-6** (Ryabukhin et al. 2004) (Scheme 3). Similar reactions are described also elsewhere (Bari et al. 2014), (Sengupta et al. 2012) and (Nohara et al. 1974).

Other pyridones **ML-10** were prepared from **ML-8**, esters of malonic acid **ML-9** and aliphatic or aromatic amines (Bari et al. 2016), (Rajkumar et al. 2015); NH_3(liq) (Gosh et al. 2001) and ammonium acetate (Maezono et al. 2016) (Scheme 4). This methodology was also used by others (Poudel et al. 2015), (Mehrparvar et al. 2014).

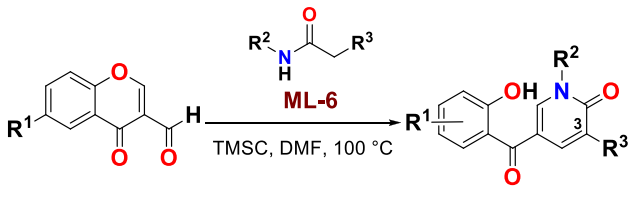
Pyridones **ML-12** were prepared in good yields from oxochromenylacrylates **ML-11** and primary amines in the presence of Et_3N (or K_2CO_3) in refluxing MeOH (Zhang



Scheme 1 Synthesis of pyridones **ML-1** and **ML-2**



Scheme 2 Synthesis of pyridones **ML-4** from chromenecarbaldehydes **ML-3**



R¹: H, F, Cl, Me, OMe
R²: H, Bn, ^{i}Pr, $(CH_2)_2OMe$, cyclohex, ^{c}Pr, Ph *m*-CF_3Ph, py-2-yl, *p*-NO_2Ph, *p*-MePh, ^{i}Bu *p*-MeOPh(CH_2), tiazol-2-yl
R³: CN, $CONHCH_2Ph$, CONHPh, COMe CONHcyclohex

Scheme 3 Synthesis of pyridones **ML-7** from chromenecarbaldehydes **ML-5**

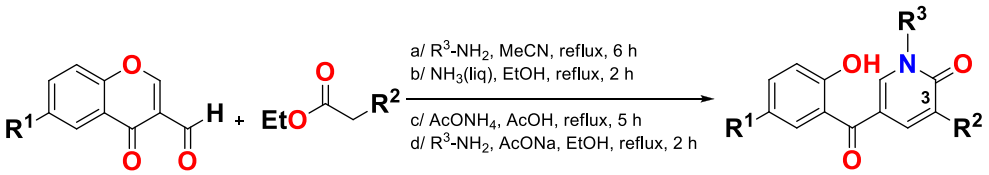
et al. 2010 and 2013) (Scheme 5). This method has been used also by others (Sarma et al. 2016) and (Lv et al. 2010).

Biological activity of 5-(2-hydroxybenzoyl)pyridin-2(1*H*)-ones

Pyridones **3–5** are not known and their biological activity was not yet investigated. Therefore, we found the most significant bioactivities of their analogues possessing **ML-4** skeleton (Scheme 2). They are active against some gram-negative bacteria strains: *Escherichia coli, Salmonella typhi, Pseudomonas aeruginosa*. They also have antifungal properties against *Candida albicans, Aspergillus niger and Aspergillus flavus* (Bari et al. 2014). Pyridones conjugated with tacrine fragment **ML-(13–15)** are potent AChE inhibitors (Chand et al. 2016) (Fig. 1).

The antiproliferative activity of pyridones was investigated on cancer cell lines (A549, HeLa, QGY7701, SGC7901, MDA-MB231, SW480). Fourteen compounds **ML-18(a,b, g, h, k)** and **ML-20(g–k, o, r–t)** have had an interesting antitumour properties (GI_{50}: from 0.11 to 0.99 μM), some of them also on multiple tumour cell lines (Lv et al. 2010) (Scheme 6).

The antineoplastic activity of other 5-(2-hydroxybenzoyl) pyridine-2(1*H*)-ones

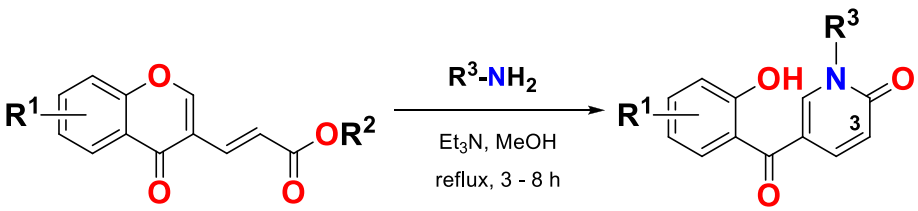


a/ R^1: H, Me, Cl; R^2: CO_2Et; R^3: Bn, *p*-$AcPhCH_2$, *p*-$FPhCH_2$
b/ R^1: H, Me, Cl; R^2: CO_2Et, CN; R^3: H
c/ R^1: OH; R^2: CN; R^3: H
d/ R^1: H, Me, Cl; R^2: CO_2Et, CO_2Me; R^3: cyclohex, *p*-Cl; *o*-NO_2Ph

a/ 60 - 78 %
b/ 66 - 85 %
c/ 48 %
d/ 61 - 77 %

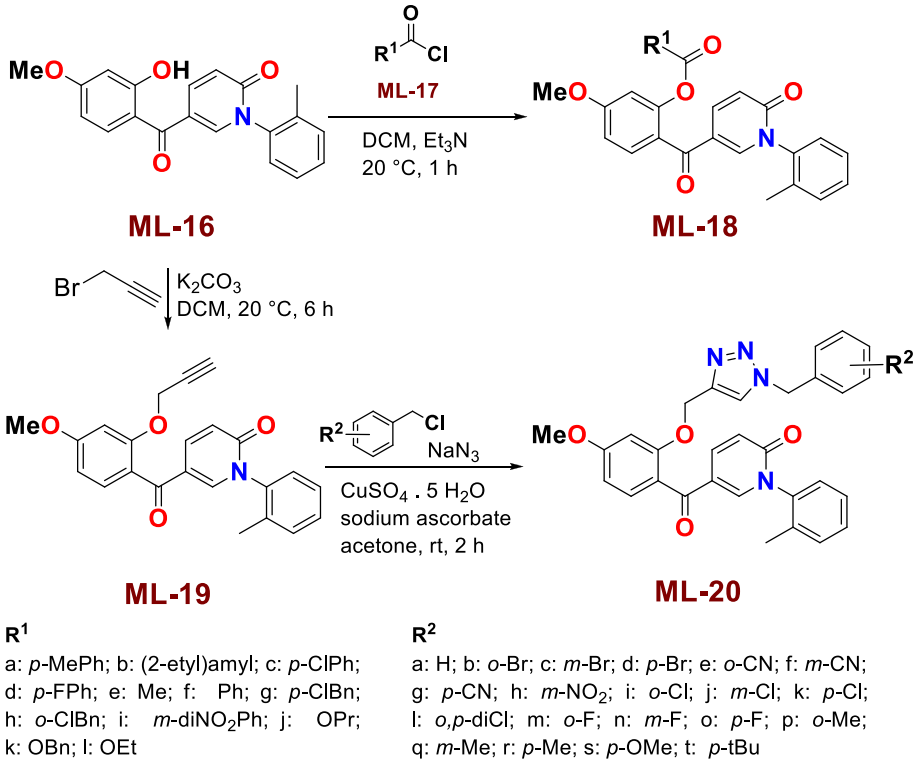
Scheme 4 Synthesis of pyridones **ML-10** from **ML-8**. The particular yields and conditions are described as follows **a**/(Rajkumar et al. 2015), **b**/(Gosh et al. 2001), **c**/(Abdel-Rahman et al. 2005), **d**/(Bari et al. 2016)

Scheme 5 Synthesis of pyridones **ML-12** from **ML-11** and primary amines



R^1: 7-OMe; R^2: Me
R^3: allyl, $(CH_2)_2CH_3$

Scheme 6 Structures and synthesis of pyridones **ML-18** and **ML-20**



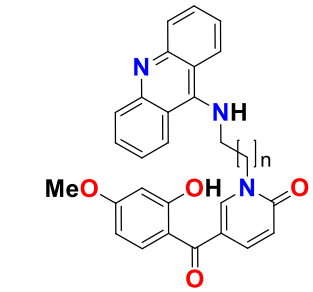


Fig. 1 Structures and activities of AChE inhibitors **ML-(13–15)**

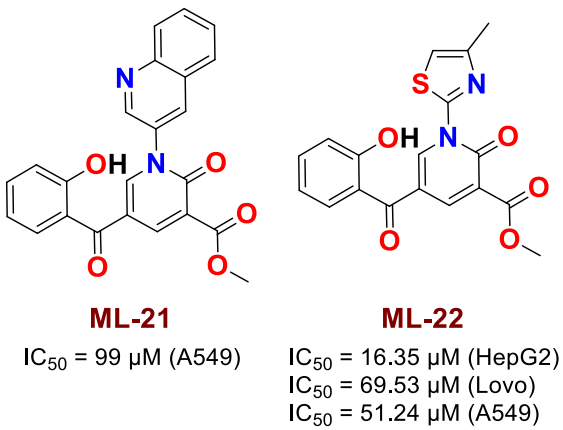


Fig. 2 Structures and antineoplastic activities of pyridones **ML-21** and **ML-22**

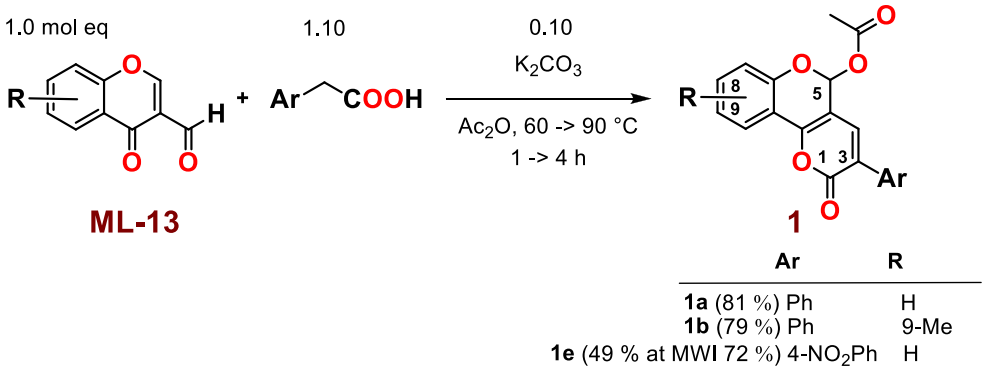
ML-21 and **ML-22** was investigated on five human cancer cell lines (HepG2, Lovo, A549, HT, MDA-MB 231) (Bari et al. 2016), (Fig. 2).

The synthesis and biological activity of presented compounds **3–5** is not yet described in the literature. We have developed a methodology for the synthesis of pyridones **3** and their analogues **4–5** starting from 3-aryl-2-oxo-2,5-dihydropyrano[3,2-*c*]chromen-5-yl acetates **1**.

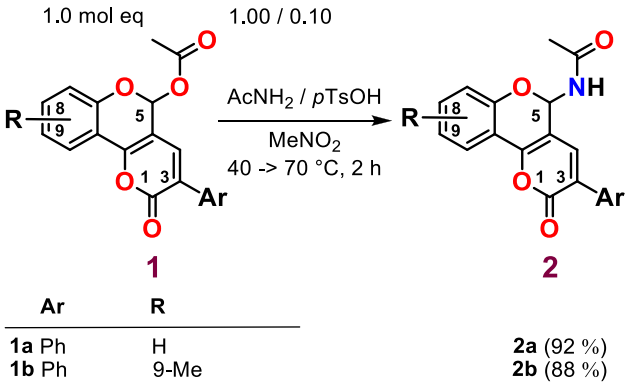
In 2010, we published a synthesis of acetates **1(a–b)** from 4-oxo-4*H*-chromen-3-carbaldehydes **ML-13** and substituted acetic acid (Lácová et al. 2010). We also described the preparation of acetate **1e** (Kováčiková et al. 2010) (Scheme 7).

The biological activity of acetates 1

We found that some pyranochromenyl acetates **1** have an interesting antineoplastic activity (NCI-60 human tumour cell lines screen 2018). The most active was a compound **1** (**R: 8,9-diMe, Ar: Ph** with NCI code NSC: 745523) (NCI data 2018).This compound allowed an average cell mean growth up to only 11% at 10^{-5} M compared to a control



Scheme 7 Synthesis of acetates **1(a–b,e)**. MWI means a reaction carried out under microwave irradiation



Scheme 8 Synthesis of acetamides **2** from acetates **1**

(100%) (One dose NCI assay). In a concentration-dependent screening, this compound has an average GI_{50} = 436 nM and the best result for a particular cell line was GI_{50} = 40 nM (Melanoma: MDS-MB-435) (NCI Search for all data by compound identifiers 2018). Although the mechanism of antitumour properties for this compound was not yet determined, based on a comparative analysis (The Compare Analysis 2018) of its GI_{50} activity profile on tumour cell lines, tubulins were proposed as a target for this acetate **1** (Kováčiková et al. 2010).

By examining the reactivity of pyranochromenyl acetates **1**, we found an efficient method for their conversion to acetamides **2** (Lácová et al. 2010) (Scheme 8).

The biological activity of acetamides 2

Only one acetamide **2b** (NSC: 747828) was screened on its antineoplastic activity at NCI USA (Lácová et al. 2010). This compound influenced several tumour cell lines. The best antineoplastic effect at 10^{-5} M (One-dose NCI assay) was obtained on a cell line of leukaemia (RPMI-8226) where **2b** reduced 45% of a cell growth compared to a control (100%).

The aim of this work was to investigate the reactivity of the 2*H*-pyran-2-one part of the acetamides **2** under basic conditions, to confirm the structure of products **3** and to screen novel compounds for their antineoplastic activities.

Results and discussion

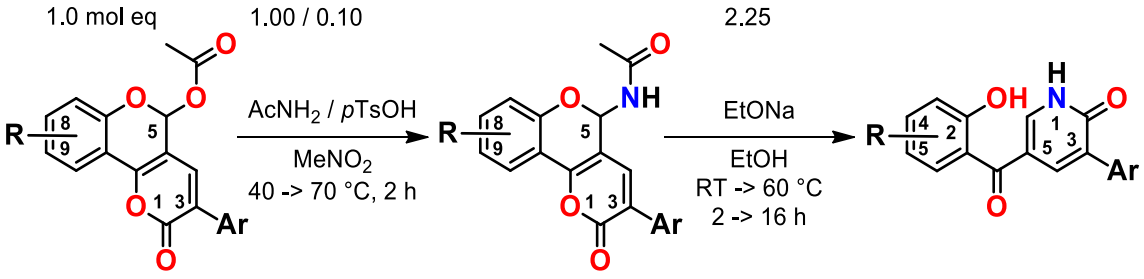
We have found that 3-aryl-5-(2-hydroxybenzoyl)pyridin-2(1*H*)-ones **3** are formed after treatment of acetamides **2** by EtONa in EtOH. The conversion of acetamides **2** to pyridones **3** is not yet described in the literature (SciFinder 2018). To prove the versatility of the above methodology, a series of seven pyranochromenyl acetates **1(a–g)** was prepared by the conditions described in Scheme 7. Obtained yields of **1(a–g)** are depicted in Scheme 9. Subsequently, acetamides **2(a–g)** were prepared from acetates **1(a–g)** according to the conditions described in Scheme 9. In the end, the acetamides **2(a–g)** were used to prepare pyridones **3(a–g)** confirming that the method converting compounds **2** to **3** by EtONa in EtOH is general and efficient (80–95%) (Scheme 9).

A re-cyclization mechanism for the conversion of acetamides **2** to pyridones **3** was proposed. (Scheme 10).

Pyridones **3(a, d)** were derivatized by propargyl bromide to prepare **4(a, d)** and **5(a, d)** (Scheme 11) They can serve as precursors for a synthesis of more complex pyridone compounds, e.g., via a Click chemistry approach.

Results of NCI biological assay

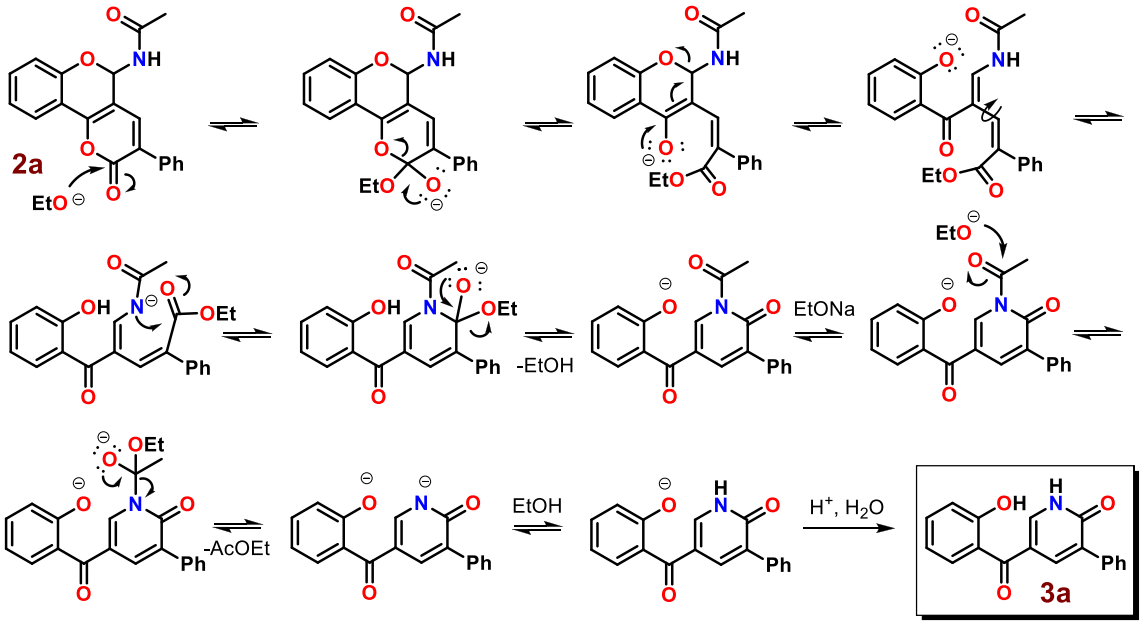
Eleven 5-(aroyl)-3-arylpyridin-2-ones **3(a–g)**, **4(a, d)** and **5(a, d)** were screened on 59 human tumour cell lines in the NCI USA. These compounds have shown a mild antitumour activity at 10^{-5} M concentration (One dose NCI assay). The most active pyridone is **3d** (NSC: 804246), which has been shown to reduce the growth of some breast, ovarian and



1(a-g) 2(a-g) 3(a-g)

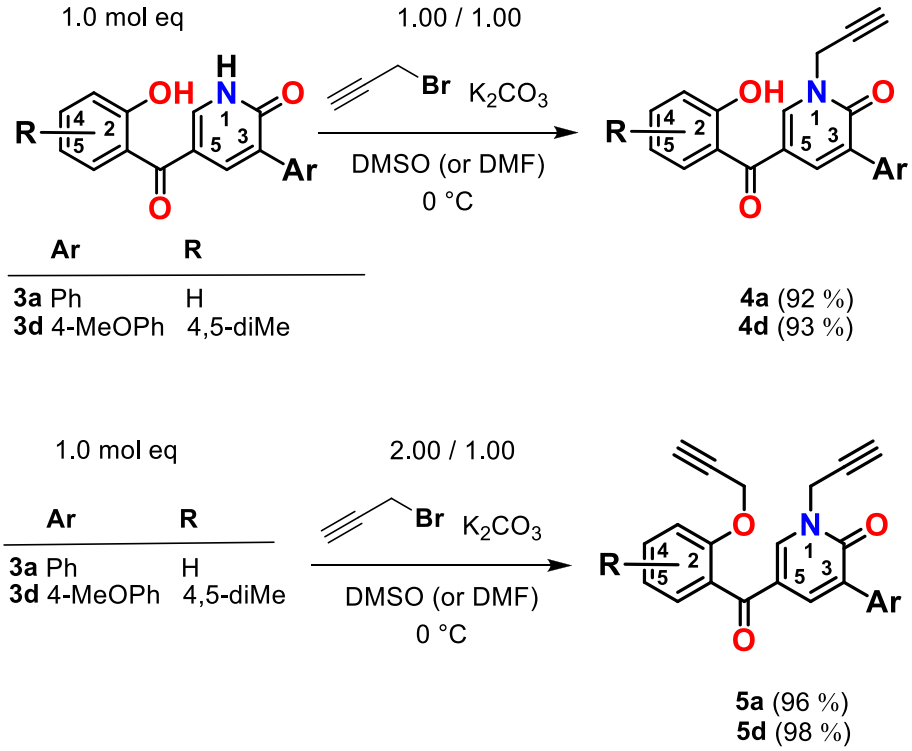
Ar	R		
1a (71 %) Ph	H	**2a** (88%)	**3a** (91%)
1b (86 %) Ph	9-Me	**2b** (85%)	**3b** (93%)
1c (64 %) 4-MeOPh	9-NO_2	**2c** (80%)	**3c** (95%)
1d (55 %) 4-MeOPh	8,9-diMe	**2d** (81%)	**3d** (88%)
1e (76 %) 4-NO_2Ph	H	**2e** (88%)	**3e** (90%)
1f (85 %) 4-NO_2Ph	8,9-diMe	**2f** (93%)	**3f** (85%)
1g (83 %) 1*H*-tetrazol	8,9-diMe	**2g** (81%)	**3g** (80%)

Scheme 9 The conversion of acetates **1** to acetamides **2** and further to pyridones **3**



Scheme 10 The proposed mechanism for the re-cyclization of the acetamide **2a** to the pyridone **3a** by EtONa in EtOH

melanoma tumour cell lines from 25 to 32% compared to a control. Other interesting pyridones are both *N*-propargylated derivatives **4d** and **5d** (NSC 804248 and 804249) having the best inhibitory activity on two types of kidney tumour cell lines (UO-31 and CAKI-1) and slowing the growth of these lines from 28 to 33% compared to the control (100%) (Table 1).



Scheme 11 Derivatization of pyridones **3(a,d)** by propargyl bromide under various conditions performing mono- **4(a,d)** or disubstituted **5(a,d)** propargyl derivatives

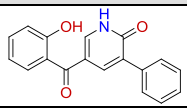
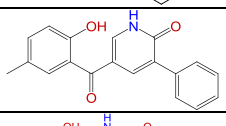
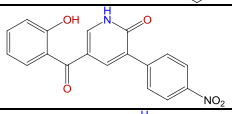
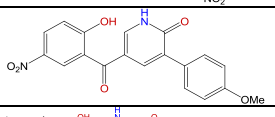
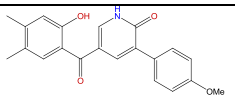
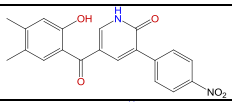
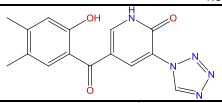
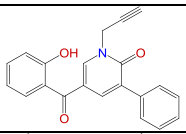
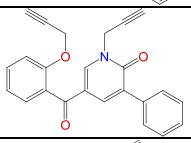
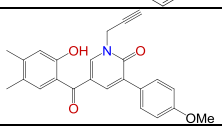
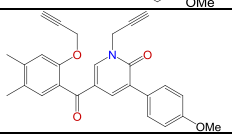
Conclusions

We have prepared and characterized 25 compounds **1–5**, of which only acetates **1(a–b,e)** and acetamides **2(a-b)** are already published by us previously (Lácová et al. 2010). Other 20 compounds **1–5** are novel. On seven derivatives, we tested the methodology for synthesis of acetates **1(a–g)** as well as the efficiency of their acetoxy group replacement to produce the acetamides **2(a–g)**. We have developed a novel, simple and convenient methodology for preparing the previously unknown 3-aryl-5-(2-hydroxybenzoyl)pyridine-2(1*H*)-ones **3(a–g)** from acetamides **2(a–g)**. The mechanism of acetamides **2** conversion to pyridones **3** was proposed. Eleven pyridones **3(a–g)**, **4 (a,d)** and **5(a,d)** were screened on their antineoplastic properties by the NCI in USA. We have found that tested pyridones **3–5** selectively inhibit a growth of some tumour cell lines up to −33% compared to the control (100%). The results of antineoplastic screens on 59 types of human tumour cell lines are present in Table 1 and the data from NCI assays are present in the Supplementary material.

Experimental

Melting points were measured using a Kofler apparatus or Barnstead Electrothermal IA9200 and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded on Varian Gemini (300 or 600 MHz and 75 or 150 MHz, resp.), chemical shifts are given in parts per million (ppm), tetramethylsilane was used as an internal standard and DMSO-*d6* as the solvent, unless otherwise specified. IR spectra were acquired on FT-IRATR REACT IR 1000 (ASI Applied Systems) with diamond probe and MTS detector. Mass spectra were performed on LC–MS (Agilent Technologies 1200 Series equipped with Mass spectrometer Agilent Technologies 6100 Quadrupole LC–MS). The course of the reactions was followed by TLC analysis (Merck Silica gel 60 F254). UV lamp (254 nm, 366 nm) and iodine vapours were used for the visualization of TLC spots. Starting chemicals were purchased from Sigma-Aldrich, Fluorochem, Alfa Aesar or Acros vendors. Used abbreviations EA, Hexsol, FLC and TLC mean ethyl acetate, a fraction of hexanes similar with polarity to petrol ether, flash liquid chromatography and thin-layer chromatography, resp. All novel compounds are characterized by their M.p., NMR diagrams, NMR and IR textual solutions, their spectra figures and elemental analysis (see Supplementary material). ^{1}H-NMR diagrams allow smart check of both chemical shifts and coupling constants for their completeness and correctness. The numbers in the diagrams mean chemical shift in δ ppm and number(s) in parenthesis represent(s) coupling constant(s) in Hz.

Table 1 The best results of eleven 5-(aroyl)-3-arylpyridin-2(1*H*)-ones **3(a-g)**, **4(a,d)** and **5(a,d)** screened on the panel of 59 human tumour cell lines at 10^{-5}M concentration (One-dose NCI assay)

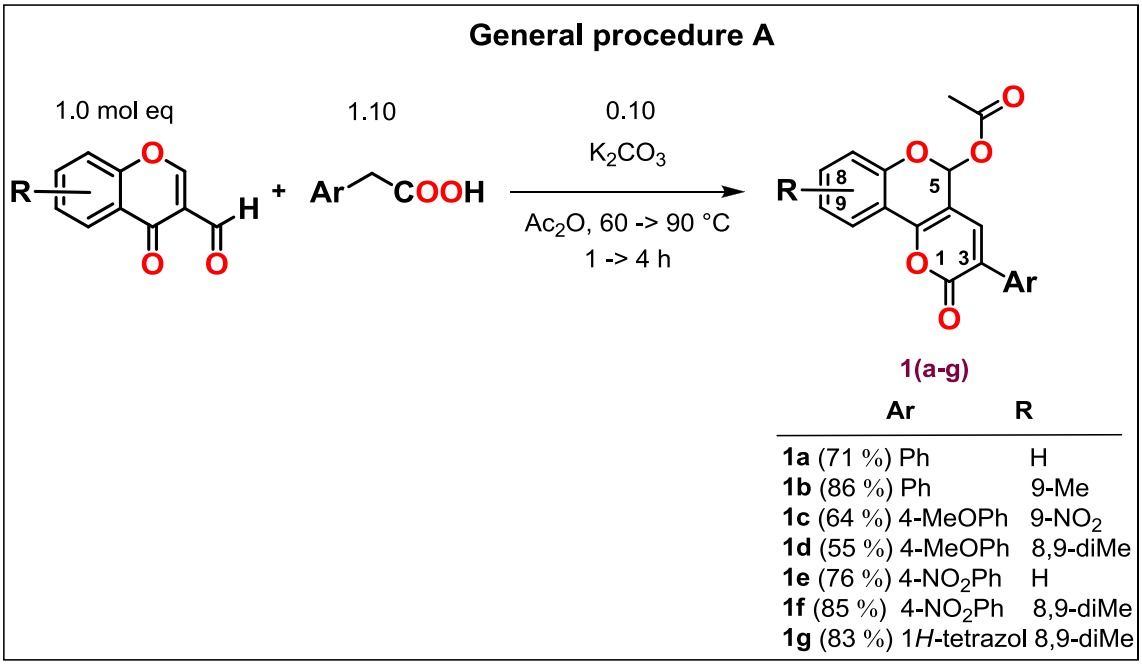
No.	The structure	NSC[a]	Mean[b]	The most growth inhibited human tumour cell lines[c]
3a		802890	90 %	**Renal:** -21 % (UO-31) **NSCL:** -20 % (HOP-92)
3b		804243	96 %	**Renal:** -24 % (UO-31) -17 % (CAKI-1)
3e		802892	90 %	**Renal:** -17 % (UO-31)
3c		802893	95 %	**NSCL:** -14 % (NCI-H226) **Renal:** -12 % (UO-31)
3d		804246	87 %	**Breast: -32 %** (T-47D) **Ovarian: -26 %** (OVCAR-4) **Melanoma: -26 %** (UACC-62) **-25 %** (SK-MEL-5) **Renal:** -21 % (UO-31) -19 % (CAKI-1)
3f		804244	103 %	**Renal:** -18 % (UO-31) -15 % (CAKI-1)
3g		802894	94 %	**Melanoma:** -19 % (UACC-257)
4a		802898	95 %	**Breast:** -24 % (T-47D) **Renal:** -24 % (UO-31) **Leukaemia:** -22 % (K-562)
5a		802899	91 %	**Breast: -25 %** (T-47D) **Renal:** -19 % (UO-31) -18 % (CAKI-1)
4d		804248	97 %	**Renal: -31 %** (UO-31) **-28 %** (CAKI-1)
5d		804249	91 %	**Renal: -33 %** (CAKI-1) **-28 %** (UO-31)

[a]**NSC** means a NCI screening code

[b]The **mean** represents an average of growth % through all 59 human tumour cell lines at used compound concentration 10^{-5} M compared to 100% for untreated tumour cell lines. The used cell lines were from leukaemia, NSCL, colon, CNS, melanoma, ovarian, renal, prostate and breast tumours

[c]% number represents a decrease of a growth in a particular human tumour cell line (abbreviated in parenthesis) compared to the control. The numbers marked in bold are growth inhibitions above 25%. One-dose NCI USA mean graphs of each screened compound can be found in the Supplementary material

Synthesis of 3-aryl-2-oxo-2,5-dihydropyrano[3,2-*c*]chromen-5-yl acetates 1(a–g)



General procedure A

A mixture of 1.74 g (10.0 mmol, 1.00 mol eq) of 4-oxo-4*H*-chromone-3-carbaldehyde together with 1.50 g (11.0 mmol, 1.10 mol eq) 2-phenylacetic acid and 138 mg (1.00 mmol, 0.10 mol eq) of K_2CO_3 (abs) was stirred in 15 mL of freshly distilled Ac_2O at 70 °C for 2 h. After cooling the reaction mixture to rt, the precipitated product **1a** was filtered off, washed with H_2O (3 × 10 mL), Et_2O (3 × 10 mL) and dried under *vacuum* to yield 2.374 g (7.1 mmol, 71%) of **1a**.

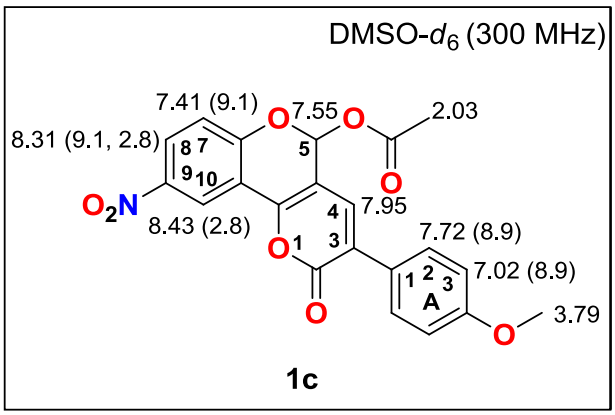
Characterization of all novel compounds from **1(a–g)** are given in an electronic supplementary material (ESM) to this paper. As an example, representative spectral data set of the substance **1c** is also given here.

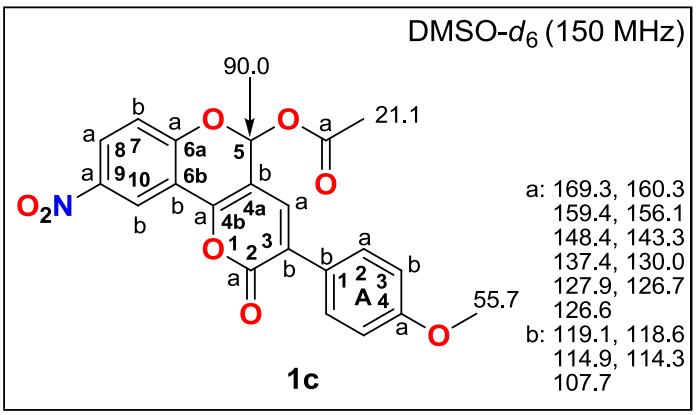
3-(4-Methoxyphenyl)-9-nitro-2-oxo-2,5-dihydropyrano[3,2-*c*]chromen-5-yl acetate (1c)

Compound **1c** was prepared according to the **General procedure A**. In this case, the reaction was performed at 70 °C within 2 h to yield 64% of product **1c**.

Novelty compound **1c** is not yet described in the literature.

M.p. 253 °C (dec).





^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.43 (d, 1H, J(8,10) = 2.8 Hz, H–C(10)), 8.31(dd, 1H, J(7,8) = 9.1 Hz, J(8,10) = 2.8 Hz, H–C(8)), 7.95 (s, 1H, H–C(4)), 7.72 (dm, 2H, among others $J(2_A,3_A)$ = 8.9 Hz, H–C_A(2)), 7.55 (s, 1H, H–C(5)), 7.41 (d, 1H, J(7,8) = 9.1 Hz, H–C(7)), 7.02 (dm, 2H, among others $J(2_A,3_A)$ = 8.9 Hz, H–C_A(3)), 3.79 (s, 3H, –OCH_3), 2.03 (s, 3H, –OCOC$\underline{H}_3$).

^{13}C-NMR (150 MHz, DMSO-d_6) δ 169.3, 160.3, 159.4, 156.1, 148.4, 143.3, 137.4, 130.0, 127.9, 126.7, 126.6, 119.1, 118.6, 114.9, 114.3, 107.7, 90.0 C(5), 55.7 (–OCH_3), 21.1 (–OCO$\underline{C}H_3$).

IR (neat, ν in cm^{-1}): 2125 (w), 1988 (w), 1760 (m, C=O), 1733 (m), 1699 (s, C=O), 1653 (m), 1604 (m), 1582 (m), 1558 (m), 1527 (s, –NO_2), 1488 (m), 1404 (m), 1371 (m), 1341 (s, –NO_2), 1294 (m), 1254 (s), 1187 (s), 1127 (m), 1075 (m), 1038 (m), 1002 (s), 949 (s), 836 (s), 793 (m), 743 (s), 635 (m), 620 (m), 595 (m), 532 (m), 488 (m), 486 (m).

Anal. calcd for $C_{21}H_{15}NO_8$ (409.35): C, 61.62; H, 3.69; N, 3.42 **Found**: C, 61.87; H, 3.78; N, 3.52.

Synthesis of 3-aryl-*N*-(2-oxo-2,5-dihydropyrano[3,2-*c*]chromen-5-yl)acetamides 2(a-g) and3-aryl-5-(2-hydroxybenzoyl)pyridin-2(1*H*)-ones 3(a-g)

For structures, reaction conditions and yields see Scheme 9.

General procedure B

A mixture of 334 mg (1.00 mmol, 1.00 mol eq) 2-oxo-3-phenyl-2,5-dihydropyrano[3,2-*c*]chromen-5-yl acetate (**1a**) together with 59.0 mg (1.00 mmol, 1.00 mol eq) $AcNH_2$ and 19.0 mg (0.10 mmol, 0.10 mol eq) *p*TsOH was stirred in 7 mL of $MeNO_2$at 70 °C for 2 h. After cooling the reaction mixture to rt, a precipitated product was filtered off, washed with $MeNO_2$ (4 mL), Et_2O (2 × 5 mL) and dried under *vacuum* yielding 293 mg (0.88 mmol, 88%) of **2a**.

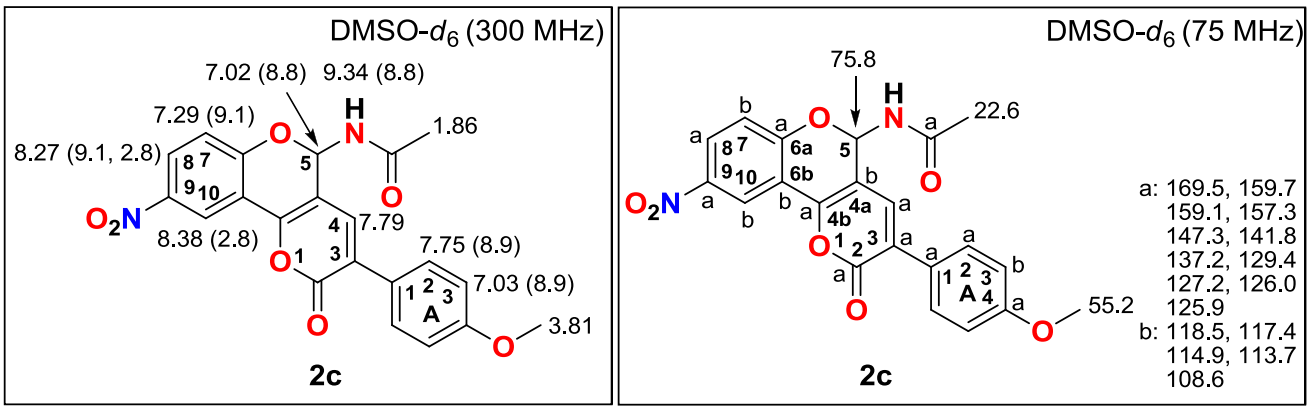
Characterization of all novel compounds from **2(a-g)** are given in an electronic supplementary material (ESM) to this paper. As an example, representative spectral data set of the substance **2c** is also given here.

N-(3-(4-methoxyphenyl)-9-nitro-2-oxo-2,5-dihydropyrano[3,2-*c*]chromen-5-yl)acetamide (2c)

Compound **2c** was prepared according to the **General procedure B**. In this case, the reaction was performed at 70 °C within 2 h to yield 80% of product **2c**.

Novelty compound **2c** is not yet described in the literature.

M.p. 256.2–258.9 °C [$MeNO_2$].



^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.34 (d, 1H, J(HN,5) = 8.8 Hz, –HN–), 8.38 (d, 1H, J(8,10) = 2.8 Hz, H–C(10)), 8.27 (dd, 1H, J(7,8) = 9.1 Hz, J(8,10) = 2.8 Hz, H–C(8)), 7.79 (s, 1H, H–C(4)), 7.75 (dm, 2H, among others $J(2_A,3_A)$ = 8.9 Hz, H–C_A(2)), 7.29 (d, 1H, J(7,8) = 9.1 Hz, H–C(7)), 7.03 (dm, 2H, among others $J(2_A,3_A)$ = 8.9 Hz, H–C_A(3)), 7.02 (d, 1H, J(HN,5) = 8.8 Hz, H–C(5)), 3.81 (s, 3H, –OCH_3), 1.86 (s, 3H, –HNCOC$\underline{H}_3$).

^{13}C-NMR (75 MHz, DMSO-d_6) δ 169.5, 159.7, 159.1, 157.3, 147.3, 141.8, 137.2, 129.4, 127.2, 126.0, 125.9, 118.5, 117.4, 114.9, 113.7, 108.6, 75.8 C(5), 55.2 (–OCH_3), 22.6 (–HNCO$\underline{C}H_3$).

IR (neat, ν in cm^{-1}): 3448 (w), 3356 (m, -NH-), 3031 (w), 2966 (w), 2924 (w), 2835 (w), 2832 (w), 2322 (w), 2109 (w), 1996 (w), 1801 (w), 1727 (s, C=O), 1692 (s, C=O), 1648 (m), 1604 (m), 1577 (m), 1550 (m), 1508 (s, –NO_2), 1479 (s), 1450 (m), 1396 (m), 1364 (m), 1332 (s, –NO_2), 1292 (s), 1249 (s), 1233 (s), 1175 (s), 1096 (s), 1070 (s), 1030 (s), 942 (s), 917 (s), 895 (s), 876 (s), 837 (s), 790 (s), 756 (m), 739 (s), 683 (m), 634 (m), 606 (m), 569 (s), 546 (s), 528 (s), 484 (s), 452 (s).

Anal. calcd for $C_{21}H_{16}N_2O_7$ (408.36): C, 61.77; H, 3.95; N, 6.86 Found: C, 61.49; H, 3.71; N, 6.76.

General procedure C

To a mixture of 200 mg (0.60 mmol, 1.00 mol eq) *N*-(2-oxo-3-phenyl-2,5-dihydropyrano[3,2-*c*]chromen-5-yl)acetamide (**2a**) in 5 mL of EtOH (abs), a solution of 81.0 mg (1.35 mmol, 2.25 mol eq) of EtONa dissolved in 1.5 mL of EtOH (abs) was added. The reaction mixture was stirred at RT for 3 h. Then, 0.5 M HCl (aq solution) was added until a product precipitation was observed. A light yellow solid material was filtered off, washed with water, Et_2O and dried under *vacuum* to afford 160 mg (0.55 mmol, 91%) of **3a**.

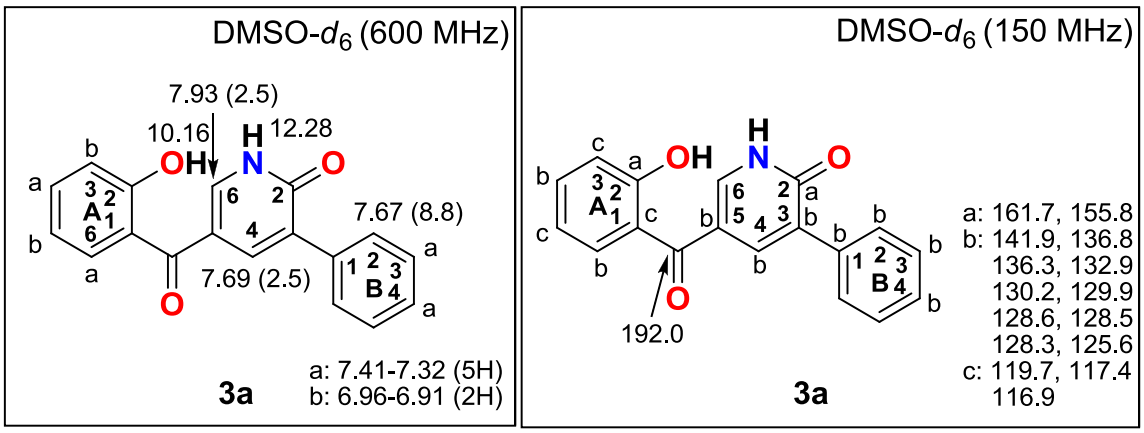
Characterization of novel compounds **3(a–g)** are given in an electronic supplementary material (ESM) to this paper. As an example, representative spectral data set of the substance **3a** is also given here.

5-(2-Hydroxybenzoyl)-3-phenylpyridin-2(1*H*)-one (3a)

Compound **3a** was prepared according to the **General procedure C**. In this case, the reaction was performed at RT within 3 h to yield 91% of product **3a**.

Novelty compound **3a** is not yet described in the literature.

M.p. 214.4–216.7 °C [EtOH].



^{1}H-NMR (600 MHz, DMSO-d_6) δ 12.28 (br s, 1H, –HN–), 10.16 (s, 1H, –HO), 7.93 (d, 1H, $J(4,6) = 2.5$ Hz, H–C(6)), 7.69 (d, 1H, $J(4,6) = 2.5$ Hz, H–C(4)), 7.67 (dm, 2H, $J(2_B,3_B) = 8.8$ Hz, H–C_B(2)), 7.41–7.32 (m, 5H, 2 x H–C_B(3), H–C_B(4), H–C_A(4), H–C_A(6)), 6.96–6.91 (m, 2H, H–C_A(3) and H–C_A(5)).

^{13}C-NMR (150 MHz, DMSO-d_6) δ 192.0 (C<u>C</u>OC), 161.7, 155.8, 141.9, 136.8, 136.3, 132.9, 130.2, 129.9, 128.6, 128.5, 128.3, 125,6, 119.7, 117.4, 116.9.

IR (neat, ν in cm^{-1}): 3086 (w, -NH-), 2995 (w), 2853 (w, –OH), 2796 (w), 2738 (w), 2322 (w), 2277 (w), 2114 (w), 2087 (w), 1999 (w), 1652 (s, C=O), 1627 (s, C=O), 1591 (s), 1480 (s), 1446 (m), 1400 (m), 1331 (m), 1300 (m), 1281 (m), 1238 (s), 1219 (s), 1159 (m), 1140 (m), 1080 (m), 1026 (m), 979 (m), 949 (m), 906 (m), 877, 826 (m), 798 (s), 743 (s), 705 (s), 649 (s), 626 (s), 592 (s), 560 (s), 497 (m), 473 (m), 450 (m), 435 (m).

Anal. calcd for $C_{18}H_{13}NO_3$ (291.3): C, 74.22; H, 4.50; N, 4.81 Found: C, 74.49; H, 4.22; N, 4.99.

Synthesis of *N*-propargyl derivative of 3-aryl-5-(2-hydroxybenzoyl)pyridin-2(1*H*)-ones 4(a,d)

For structures, reaction conditions and yields see Scheme 11.

General procedure D

A solution of 100 mg (0.343 mmol, 1.00 mol eq) 5-(2-hydroxybenzoyl)-3-phenylpyridin-2(1*H*)-one **(3a)** and 47.0 mg (0.343 mmol, 1.00 mol eq) K_2CO_3 in 6 mL of a wet DMSO (or DMF) was stirred and cooled to 0 °C. A solution of 49.0 mg (0.343 mmol, 1.00 mol eq) propargyl bromide (80% solution in toluene) in 1 mL of DMSO (or DMF) was added dropwise to the reaction mixture. Afterwards, the mixture was stirred 30 min at 0 °C and 2 h at RT. Then, the reaction was diluted with 10 mL of water and extracted with EA (3 × 5 mL), combined organic layer washed with sat aq of NaCl (3 × 10 mL), water (10 mL) and dried over Na_2SO_4. After filtration, the solution was concentrated by RVO, and obtained residue purified by FLC (silica gel, Hexsol/EA, 3/1) to yield 104 mg (0.316 mmol, 92%) of 5-(2-hydroxybenzoyl)-3-phenyl-1-(prop-2-yn-1-yl)pyridin-2(1*H*)-one (**4a**) as a white solid compound.

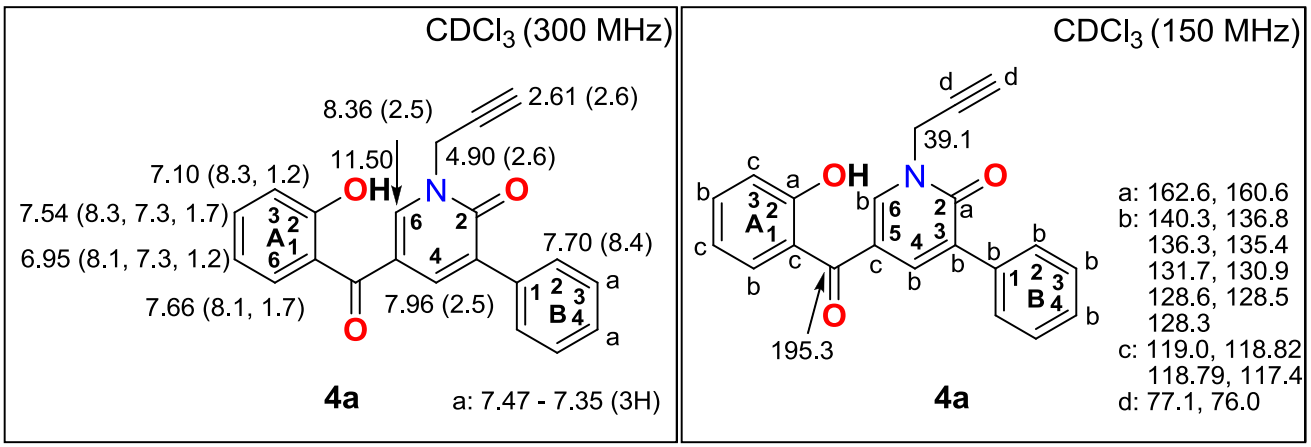
Characterization of novel compounds **4(a,d)** are given in an electronic supplementary material (ESM) to this paper. As an example, representative spectral data set of the substance **4a** is also given here.

5-(2-Hydroxybenzoyl)-3-phenyl-1-(prop-2-yn-1-yl) pyridin-2(1*H*)-one (4a)

Compound **4a** was prepared according to the **General procedure D**. In this case, the reaction was performed at 0 °C within 3 h to yield 92% of product **4a**.

Novelty compound **4a** is not yet described in the literature.

M.p. 130.7–132.9 °C [Hexsol/EA].



^{1}H-NMR (300 MHz, $CDCl_3$) δ 11.50 (s, 1H, –OH), 8.36 (d, 1H, $J(4,6) = 2.5$ Hz, H–C(6)), 7.96 (d, 1H, $J(4,6) = 2.5$ Hz, H–C(4)), 7.70 (dm, 2H, $J(2_B,3_B) = 8.4$ Hz, H–C_B(2)), 7.66 (dd, 1H, $J(5_A,6_A) = 8.1$ Hz, $J(4_A,6_A) = 1.7$ Hz, H–C_A(6)), 7.54 (ddd, 1H, $J(3_A,4_A) = 8.3$ Hz, $J(4_A,5_A) = 7.3$ Hz, $J(4_A,6_A) = 1.7$ Hz, H–C_A(4)), 7.47–7.35 (m, 3H, 2 × H–C_B(3), H–C_B(4)), 7.10 (dd, 1H, $J(3_A,4_A) = 8.3$ Hz, $J(3_A,5_A) = 1.2$ Hz, H–C_A(3)), 6.95 (ddd, 1H, $J(5_A,6_A) = 8.1$ Hz, $J(4_A,5_A) = 7.3$ Hz, $J(3_A,5_A) = 1.2$ Hz, H–C_A(5)), 4.90 (d, 2H, $J(CH,CH_2) = 2.6$ Hz, –CH_2–), 2.61 (t, 1H, $J(CH, CH_2) = 2.6$ Hz, –C≡CH).

^{13}C-NMR (150 MHz, $CDCl_3$) δ 195.3 (CCOC), 162.6, 160.6, 140.3, 136.8, 136.3, 135.4, 131.7, 130.9, 128.6, 128.5, 128.3, 119.0, 118.82, 118.79, 117.4, 77.1, 76.0, 39.1 (-NCH-).

IR (neat, ν in cm^{-1}): 3293 (w, C–H), 3060 (w), 2922 (w, –OH), 2324 (w), 2115 (w), 2098 (w), 1871 (w), 1741 (w), 1648 (s, C=O), 1603 (s, C=O), 1547 (m), 1483 (m), 1449 (m), 1416 (m), 1337 (m), 1265 (m), 1217 (s), 1158 (m), 1077 (m), 1029 (m), 991 (m), 967 (m), 913 (m), 860 (m), 822 (m), 788 (s), 757 (s), 696 (s), 671 (s), 621 (s), 562 (s), 528 (m), 467 (m), 434 (m).

Anal. calcd for $C_{21}H_{15}NO_3$ (329.35): C, 76.58; H, 4.59; N, 4.25 Found: C, 76.37; H, 4.42; N, 4.60.

Synthesis of *N,O*-bispropargyl derivative of 3-aryl-5-(2-hydroxybenzoyl)pyridin-2(1*H*)-ones 5(a,d)

For structures, reaction conditions and yields see Scheme 11.

General procedure E

To a solution of 100 mg (0.343 mmol, 1.00 mol eq) 5-(2-hydroxybenzoyl)-3-phenylpyridin-2(1*H*)-one **(3a)** and 94.0 mg (0.686 mmol, 2.00 mol eq) of K_2CO_3 in 8 mL of wet DMSO (or DMF), a solution of 98.0 mg (0.686 mmol, 2.00 mol eq) of propargyl bromide (80% solution in toluene) was added dropwise at 0 °C. Then, the reaction mixture was stirred at RT for 2 h. After completion of the reaction (monitored by TLC), 15 mL of water was added and resulting mixture was extracted with EA (3 × 5 mL). Combined organic layer was washed with sat solution of NaCl (3 × 10 mL), water (10 mL) and dried over Na_2SO_4. After filtration, the volatile parts were evaporated by RVO, and the residue purified by FLC (silica gel, Hexsol/EA, 5/1) to obtain 121 mg (0.33 mmol, 96%) of 3-phenyl-1-(prop-2-yn-1-yl)-5-(2-(prop-2-yn-1-yloxy)benzoyl)pyridin-2(1*H*)-one **(5a)** as a white solid compound.

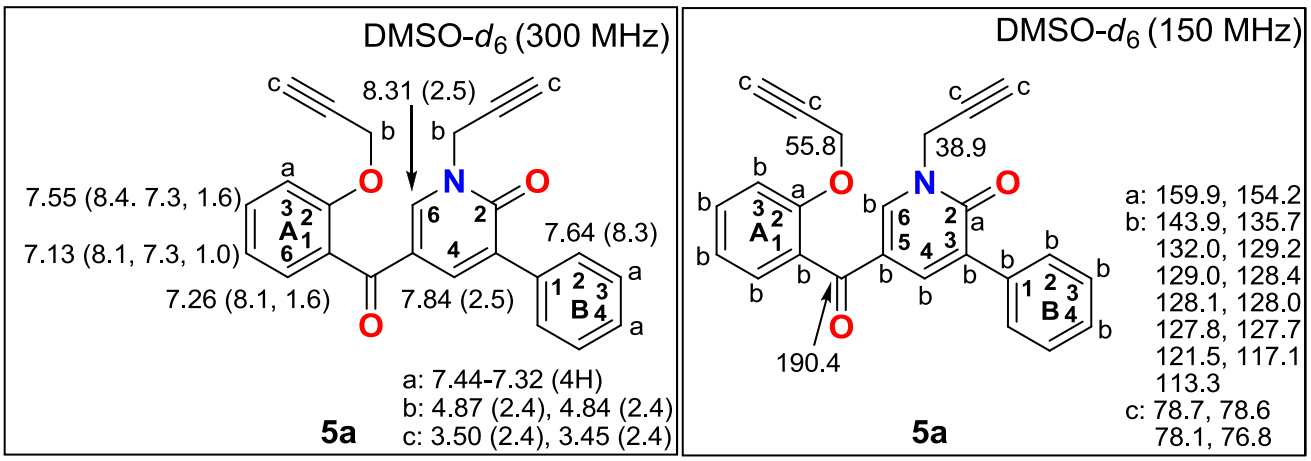
Characterization of novel compounds **5(a,d)** are given in an electronic supplementary material (ESM) to this paper. As an example, representative spectral data set of the substance **5a** is also given here.

3-Phenyl-1-(prop-2-yn-1-yl)-5-(2-(prop-2-yn-1-yl oxy)benzoyl)pyridin-2(1*H*)-one (5a)

Compound **5a** was prepared according to the **General procedure E**. In this case, the reaction was performed at RT within 2 h to yield 96% of product **5a**.

Novelty compound **5a** is not yet described in the literature.

M.p. 161.0–161.5 °C [Et_2O/EA].



^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.31 (d, 1H, $J(4,6) = 2.5$ Hz, H–C(6)), 7.84 (d, 1H, $J(4,6) = 2.5$ Hz, H–C(4)), 7.64 (dm, 2H, among others $J(2_B,3_B) = 8.8$ Hz, H–C_B(2)), 7.55 (ddd, 1H, $J(3_A,4_A) = 8.4$ Hz, $J(4_A,5_A) = 7.3$ Hz, $J(4_A,6_A) = 1.6$ Hz, H–C_A(4)),7.44–7.32 (m, 4H, 2 × H–C_B(3), H–C_B(4), H–C_A(3)) 7.26 (d, 1H, $J(5_A,6_A) = 8.1$ Hz, $J(4_A,6_A) = 1.6$ Hz, H–C_A(6)), 7.13 (ddd, 1H, $J(5_A,6_A) = 8.1$ Hz, $J(4_A,5_A) = 7.3$ Hz, $J(3_A,5_A) = 1.0$ Hz, H–C_A(5)), 4.87 (d, 2H, J(CH, CH_2) = 2.4 Hz, –CH_2–), 4.84 (d, 2H, J(CH, CH_2) = 2.4 Hz, –CH_2–), 3.50 (t, 1H, J(CH, CH_2) = 2.4 Hz, –C≡CH), 3.45 (t, 1H, J(CH, CH_2) = 2.4 Hz, –C≡CH).

^{13}C-NMR (150 MHz, DMSO-d_6) δ 190.4 (C<u>C</u>OC), 159.9, 154.2, 143.9, 135.7, 132.0, 129.2, 129.0, 128.4, 128.1, 128.0, 127.8, 127.7, 121.5, 117.1, 113.3, 78.7, 78.6, 78.1, 76.8, 55.8 (–OCH_2–), 38.9 (–NCH_2–).

IR (neat, ν in cm^{-1}): 3265 (m, C–H), 3073 (w), 2286 (w), 2016 (w), 1923 (w), 1634 (s, C=O), 1598 (s, C=O), 1547 (m), 1485 (m), 1415 (m), 1302 (s), 1262 (s), 1220 (s), 1168 (m), 1110 (m), 1005 (m), 909 (m), 863 (m), 793 (s), 751 (s), 717 (s), 691 (s), 645 (s), 620 (s), 594 (s), 552 (s), 500 (m), 425 (m).

Anal. calcd for $C_{24}H_{17}NO_3$ (367.40): C, 78.46; H, 4.66; N, 3.81 Found: C, 78.78; H, 4.93; N, 3.72.

Acknowledgements This research was supported by the Biomagi, Ltd., NCI USA, VEGA 1/0670/18, Comenius University Science Park funded by the ERDF Grant no. ITMS 26240220086 (HPLC MS).

Author contribution Matúš Čakurda importantly contributed to carrying out experiments and writing of this paper.

Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

References

Abdel-Rahman AH, Hammouda MAA, El-Desoky SI (2005) Synthesis of some new azole, azepine, pyridine, and pyrimidine derivatives using 6-Hydroxy-4*H*-4-oxo[1]-benzopyran-3-carboxaldehyde as a versatile starting material. Heteroat Chem 16:20–27. https://doi.org/10.1002/hc.20048

Bari A, Ali SS, Kadi A, Hashmi IA, Ng SW (2014) Synthesis of some new heterocyclic compounds derived from 3-formylchromones and their antimicrobial evaluation. Chem Heterocycl Compd 49:1723–1731. https://doi.org/10.1007/s10593-014-1424-4

Bari A, Parvez MK, Khan AA, Alanazi AM, Syed SA, Al-Dosari MS, Alobaid AM (2016) A facile one-pot synthesis and anticancer evaluation of novel substituted 1,2-dihydropyridine and 1,2,3,4-tetrahydropyrimidine analogues. J Heterocycl Chem 53:377–382. https://doi.org/10.1002/jhet.2400

Chand K, Alsoghier HM, Chaves S, Santos MA (2016) Tacrine-(hydroxybenzoyl-pyridone) hybrids as potential multifunctional anti-Alzheimer's agents: aChE inhibition, antioxidant activity and metal chelating capacity. J Inorg Biochem 163:266–277. https://doi.org/10.1016/j.jinorgbio.2016.05.005

Gosh ChK, Ray A, Patra A (2001) Benzopyrans. Part 42 [1]. Reactions of 4-oxo-4*H*-1-benzopyran-3-carbaldehyde with some active methylene compounds in the presence of ammonia. J Heterocycl Chem 38:1459–1463. https://doi.org/10.1002/jhet.5570380632

Kováčiková L, Gašparová R, Boháč A, Ďurana M, Lácová M (2010) Synthesis of 3-phenyl-2*H*,5*H*-pyrano[3,2-*c*]chromen-2-one derivatives and their antineoplastic activity. ARKIVOC 11:188–203. https://doi.org/10.3998/ark.5550190.0011.b16

Lácova M, Loos D, Chovancová J, Králová K (1999, 2000) Phthalides and chromones from 4-coumarin acetic acids. Study of beneficial effects of microwave irradiation on synthesis. Electronic conference proceedings of ECSOC-3 and ECSOC-4, Sept. 1–30, 1999 and 2000:181–193. http://www.mdpi.org/ecsoc/ecsoc-3/a0039/a0039.htm (accessed 20nd April 2018)

Lácová M, Gašparová R, Koiš P, Boháč A, El-Shaaer HM (2010) A facile route to phenyl, phenylsulfanyl and phenylselanyl substituted pyrano[3,2-*c*]chromenes. Tetrahedron 66:1410–1419. https://doi.org/10.1016/j.tet.2009.11.057

Lv Z, Sheng C, Wang T, Zhang Y, Liu J, Feng J, Sun H, Zhong H, Niu C, Li K (2010) Design and synthesis of novel 2′-hydroxy group substituted 2-pyridone derivatives as anticancer agents. J Med Chem 53:660–668. https://doi.org/10.1016/j.ejmech.2013.06.046

Maezono SMB, Poudel TN, Xia L, Lee YR (2016) A green synthetic approach to synthesizing diverse 2-pyridones for their exceptional UV shielding functions. RSC Adv 6:82321–82329. https://doi.org/10.1039/C6RA18661K

Mehrparvar S, Balalaie S, Rabbanizadeh M, Ghabraie E, Rominger F (2014) An efficient tandem approach for the synthesis of functionalized 2-pyridone-3-carboxylic acids using three-component reaction in aqueous media. Mol Divers 18:535–543. https://doi.org/10.1007/s11030-014-9522-x

NCI search for all data by compound identifiers (2018) https://dtp.cancer.gov/dtpstandard/dwindex/index.jsp (accessed 28th April 2018)

NCI-60 human tumour cell lines screen (2018) https://dtp.cancer.gov/discovery_development/nci-60/default.htm (accessed 28th April 2018)

Nohara A, Ishiguro T, Sanno Y (1974) A novel conversion reaction of 4-oxo-4*H*-1-benzopyran-3-carbaldehydes to 3-substituted-5-(2-hydroxybenzoyl)-2(1*H*)-pyridones. Tetrahedron Lett 13:1183–1186. https://doi.org/10.1016/S0040-4039(01)82440-0

Poudel TN, Lee YR, Kim SH (2015) Eco-friendly synthesis of diverse and valuable 2-pyridones by catalyst- and solvent-free thermal multicomponent domino reaction. Green Chem 17:4579–4586. https://doi.org/10.1039/c5gc01526j

Rajkumar K, Suman P, Raju BCh (2015) Facile construction of novel heterocyclic compounds: three-component, one-pot synthesis of 2-hydroxybenzoyl-1,2-dihydropyridine-3-carboxylates, ketones, pyridone-3-carboxylates and benzopyrido-1,3-oxazole-4-carboxylates. RSC Adv 5:73850–73858. https://doi.org/10.1039/c5ra10185a

Ryabukhin SV, Plaskon AS, Volochnyuk DM, Tolmachev AA (2004) 3-Formylchromones in Guareschi Synthesis of 5-(2-Hydroxybenzoyl)-2-pyridones. Synlett 13:2287–2290. https://doi.org/10.1055/s-2004-832852

Sarma AK, Yadav P, Chand K, Sharma SK (2016) Design and synthesis of novel 2′-hydroxy group substituted 2-pyridone derivatives as anticancer agents. Indian. J. Chem Sec B 55B:492–500

SciFinder database https://scifinder.cas.org/scifinder/ (accessed 22nd April 2018)

NCI data search (2018) https://dtp.cancer.gov/dtpstandard/dwindex/index.jsp (accessed 28th April 2018)

Sengupta T, Gayen KS, Pandit P, Maiti DK (2012) $FeCl_3{\cdot}6H_2O$-catalyzed intermolecular-cascade cyclization of acetoacetanilide: aldehyde-tuned synthesis to valuable 2-pyridone analogues. Chem Eur J 18:1905–1909. https://doi.org/10.1002/chem.201103354

The Compare Analysis https://dtp.cancer.gov/databases_tools/compare.htm (accessed 28th April 2018)

Zhang YK, Lv ZL, Niu CJ, Li K (2010) Synthesis and anti-HBV activity of novel 5-substituted pyridin-2(1H)-one derivatives. Chin Chem Lett 21:290–292. https://doi.org/10.1016/j.cclet.2009.10.010

Zhang Y, Lv ZL, Zhang M, Li K (2013) Re-cyclization of 3-(*E*)-methyl 3-(4-oxo-4*H*-chromen-3-yl)acrylate with amines and their potential mechanism. Tetrahedron 69:8839–8846. https://doi.org/10.1016/j.tet.2013.08.032

Affiliations

Margita Lácová[1] · Matúš Čakurda[1] · Pavol Koiš[1] · Gabriela Addová[2] · Andrej Boháč[1,3]

✉ Andrej Boháč
andrej.bohac@fns.uniba.sk

Matúš Čakurda
matus.cakurda@gmail.com

[1] Department of Organic Chemistry, Faculty of Natural Sciences, Comenius University in Bratislava, Mlynská dolina, Ilkovičova 6, 842 15 Bratislava, Slovakia

[2] Institute of Chemistry, Faculty of Natural Sciences, Comenius University in Bratislava, Mlynská dolina, Ilkovičova 6, 842 15 Bratislava, Slovakia

[3] Biomagi, Ltd, Mamateyova 26, 851 04 Bratislava, Slovakia