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Potassium fluoride catalysed multicomponent approach to medicinally privileged 5-[3-hydroxy-6-(hydroxymethyl)-4-oxo-4*H*-pyran-2-yl] substituted chromeno[2,3-*b*]pyridine scaffold

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Dedicated to Prof. Lorenzano Testaferri on the occasion of his 75th anniversary

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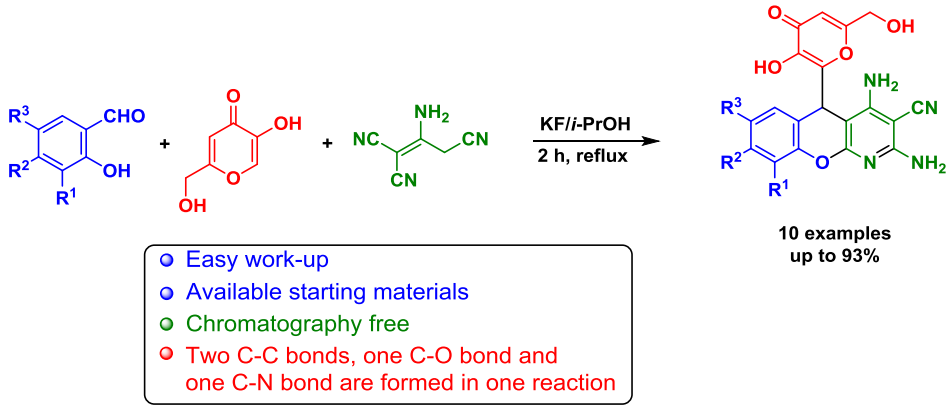
Abstract

The new efficient and facile multicomponent reaction was found: transformation of salicylaldehydes, kojic acid, and malononitrile dimer in the presence of potassium fluoride as catalyst in small amount of *i*-propanol results in formation of substituted 2,4-diamino-5-(3-hydroxy-6-(hydroxymethyl)-4-oxo-4*H*-pyran-2-yl)-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitriles in 56-93% yields. This complex "domino" transformation includes Knoevenagel condensation of salicylaldehyde with malononitrile dimer, Michael addition of kojic acid, double Pinner type reaction cyclization, and isomerization with following protonation. The novel 'one-pot' process opens an efficient and convenient way to functionalized 5*H*-chromeno[2,3-*b*]pyridine systems, which are promising compounds for different biomedical applications.



Keywords: Multicomponent reaction, catalysis, salicylaldehydes, kojic acid, malononitrile dimer, 5*H*-chromeno[2,3-*b*]pyridines

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Introduction

In last decades, the notion of "privileged structures or scaffolds" has become one of the main ideas in the new drugs search.[1] Merck researchers, in their investigation on benzodiazepines,[2] initially suggested this definition. Mainly, these privileged scaffolds have the rigid heterocyclic system, which determines the orientation type of different functional substituents for target recognition.

The creation of facile and efficient methodology for the selective assembly of biologically active scaffolds in multicomponent processes is one of the basic goals of modern organic chemistry. Multicomponent strategy has been suggested to provide high efficiency, operation simplicity and low waste formation.[3] The multicomponent methodology is based on the pot economy principle and unites it with the atom and step economy strategies.[4]

Chromenopyridines are well-known scaffolds in medicinal chemistry. Many of them show a wide spectrum of pharmacological properties such as glucocorticoid receptor (GR) agonists,[5] antiproliferative,[6] anti-tumor,[7] and anti-asthmatic.[8]

In the row of chromeno[2,3-*b*]pyridines, Amlexanox (Figure 1) is known anti-allergic drug, mainly in the case of rhinitis and asthma.[9] Pranoprofen (Figure 1) is used as a nonsteroidal anti-inflammatory drug with analgesic and antipyretic actions.[10] Chromenotacrine CT6 is applied as non-toxic antioxidant, and neuroprotective agent.[11] 2,4-Diaminochromeno[2,3-*b*]pyridines **I** (Figure 1) inhibit mitogen activated protein kinase 2 (MK-2) and suppress expression of TNFα in U937 cells as anti-rheumatoid and anti-psoriatic agents.[12]

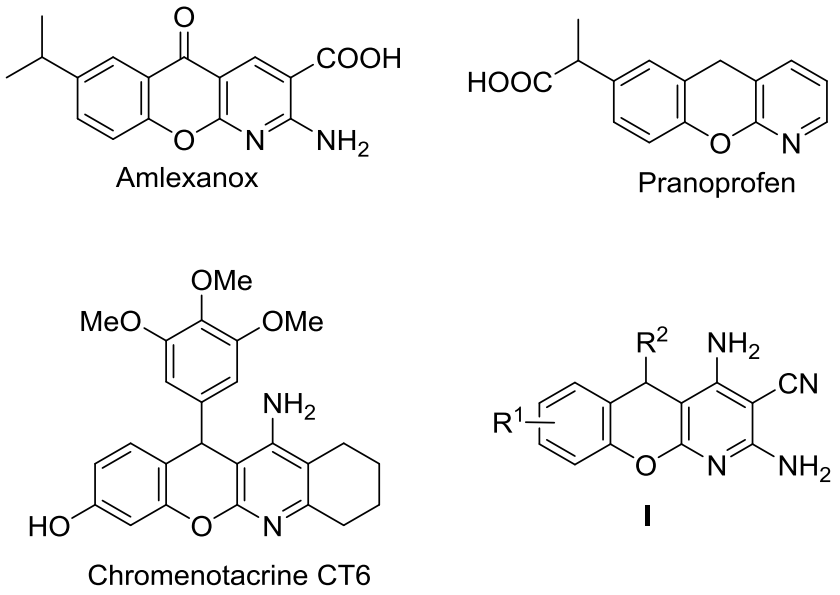


Figure 1. Bioactive molecules with chromeno[2,3-*b*]pyridine fragment.

Kojic acid (5-hydroxy-2-hydroxymethyl-4*H*-pyran-4-one) is a fungal metabolite, which is widely used in different areas. It was firstly extracted from *Aspergillus oryzae* more than one century ago.[13] Today's main applications of a kojic acid are as an additive for averting an enzymatic browning in food production and as skin-lightening agent in the cosmetic field.[14] Kojic acid is also an inhibitor of oxidases.[15-16] In last decades, it has been found that kojic acid derivatives show antibacterial,[17] anti-inflammatory,[18] anticonvulsant,[19] and anti-HIV activities.[20] Therefore, diverse therapeutic activities of chromeno[2,3-*b*]pyridines and kojic acid

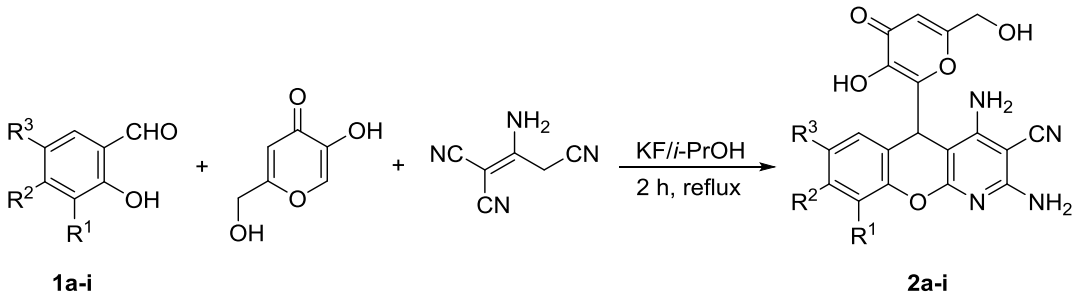
derivatives allow to assume, that combination of both scaffolds in one structure will strengthen and develop their biomedical properties.

Considering our interest in the implementation of multicomponent synthesis of new heterocyclic systems, we have accomplished different types of 'one-pot' transformations of carbonyl compounds and C-H acids.[21-26] Recently we have realized multicomponent transformation of salicylaldehydes, 2-aminoprop-1-ene-1,1,3-tricarbonitrile and 3-phenylisoxazol-5(4*H*)-one,[27] or 3-methyl-2-pyrazolin-5-one.[28]

Taking into consideration our previous results and pharmacological value of chromeno[2,3-*b*]pyridines derivatives, we would like to develop methodology for the efficient and facile multicomponent transformations salicylaldehydes **1a-j**, kojic acid and 2-aminoprop-1-ene-1,1,3-tricarbonitrile (malononitrile dimer) into functionalized chromeno[2,3-*b*]pyridines **2a-j** (Scheme 1).

Results and Discussion

Now we wish to report our results on the new 'one-pot' transformation salicylaldehydes **1a–j**, kojic acid and 2-aminoprop-1-ene-1,1,3-tricarbonitrile (malononitrile dimer) into 2,4-diamino-5-(3-hydroxy-6-(hydroxy-methyl)-4-oxo-4*H*-pyran-2-yl)-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitriles **2a**-**j** (Scheme 1, Tables 1, 2).



1a-i **2a-i**

a $R^1 = R^2 = R^3 = H$
b $R^1 = R^2 = H$, $R^3 = Me$
c $R^1 = OMe$, $R^2 = R^3 = H$
d $R^1 = R^3 = H$, $R^2 = OH$
e $R^1 = R^2 = H$, $R^3 = Cl$
f $R^1 = R^2 = H$, $R^3 = Br$
g $R^1 = R^2 = H$, $R^3 = NO_2$
h $R^1 = R^3 = Cl$, $R^3 = H$
i $R^1 = OMe$, $R^2 = H$, $R^3 = Br$

1j **2j**

Scheme 1. Multicomponent transformation of salicylaldehydes **1a-j**, kojic acid and malononitrile dimer into 5*H*-chromeno[2,3-*b*]pyridines **2a-j.**

Multicomponent synthesis without organic solvents is one of the important goals of modern green chemistry.[29] Thus, solvent-free,[30-31] as well as, on-water reactions are intensively investigated in last decades.[32, 33]

That is why, we started with the synthesis of earlier unknown 2,4-diamino-5-(3-hydroxy-6-(hydroxymethyl)-4-oxo-4*H*-pyran-2-yl)-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitrile **2a** from salicylaldehyde **1a**, kojic acid and 2-aminoprop-1-ene-1,1,3-tricarbonitrile (malononitrile dimer) under solvent-free and on-water reaction conditions (entries 1-5, Table 1). But under these conditions the yields of 5*H*-chromeno[2,3-*b*]pyridine **2a** were in the range only 10-27%.

Table 1. Multicomponent transformation of salicylaldehyde **1a**, kojic acid and malononitrile dimer into chromeno[2,3-*b*]pyridine **2a**

Entry	Solvent	Catalyst	Temperature °C	Time, h	Yield of **2a** (%)
1	Solvent-free	-	60	1	10
2	Solvent-free	NaOAc, 10%	60	1	16
3	Solvent-free	KF, 10%	60	1	13
4	H_2O	-	80	1	15
5	H_2O	NaOAc	80	1	27
6	MeCN	Et_3N	82	1	32
7	MeOH	Et_3N	65	1	37
8	EtOH	Et_3N	78	1	45 [a]
9	PrOH	Et_3N	97	1	49 [a]
10	*i*-PrOH	Et_3N	82	1	55 [a]
11	*i*-PrOH	NaOAc	82	1	63 [a]
12	*i*-PrOH	KF	82	1	75 [a]
13	*i*-PrOH	-	82	1	14
14	EtOH	KF	78	1	51 [a]
15	*i*-PrOH	KF	82	2	93 [a]
16	*i*-PrOH	KF	82	3	87 [a]

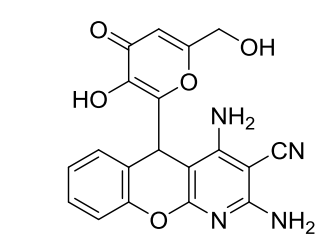
Reaction conditions: salicyaldehyde **1a** (3 mmol), kojic acid (3 mmol), malononitrile dimer (3 mmol) were heated in 5 mL of solvent or without solvent; with 10 mol% of catalyst or without catalyst.
[a] Isolated yield, in other cases NMR data.

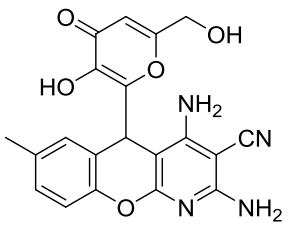
In acetonitrile, methanol, ethanol and *n*-propanol with triethylamine as catalyst the yields of 5*H*-chromeno[2,3-*b*]pyridine **2a** were increased up to 32-49% (entries 6-9, Table 1).

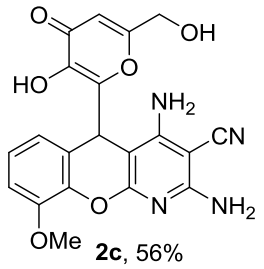
And at least, in *i*-propanol were obtained the best results. Under the optimum conditions with KF as catalyst in 2 h reaction time 5*H*-chromeno-[2,3-*b*]pyridine **2a** was isolated in 93% yield.

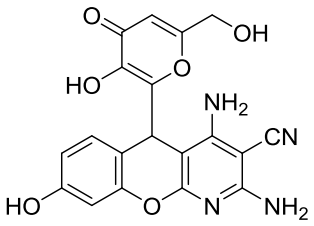
Under these optimal conditions the earlier unknown 5-[3-hydroxy-6-(hydroxymethyl)-4*H*-pyran-2-yl] substituted 5*H*-chromeno[2,3-*b*]pyridines **2a-j** were obtained in 56-93% yields (Table 2). The isolation procedure was very simple. After the reaction was finished the solid was filtered, and in main part of experiments washed with cold ethanol and dried to isolate pure 2,4-diamino-5-[3-hydroxy-6-(hydroxymethyl)-4*H*-pyran-2-yl]-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitriles **2a-j**.

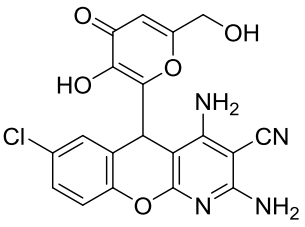
Table 2. Multicomponent assembly of substituted 5*H*-chromeno[2,3-*b*]pyridines **2a-j** [a]

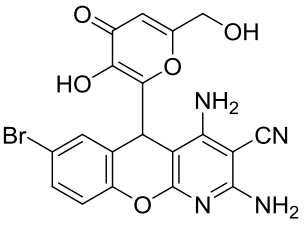

2a, 93%

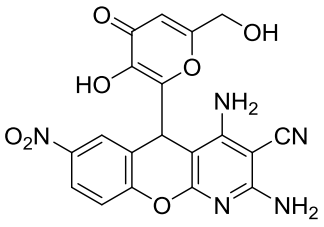

2b, 67%

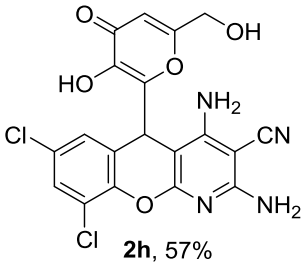

2c, 56%

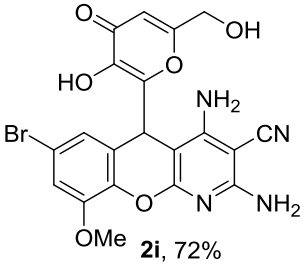

2d, 58%

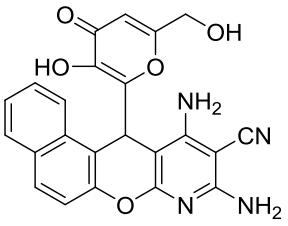

2e, 60%


2f, 68%


2g, 62%


2h, 57%


2i, 72%

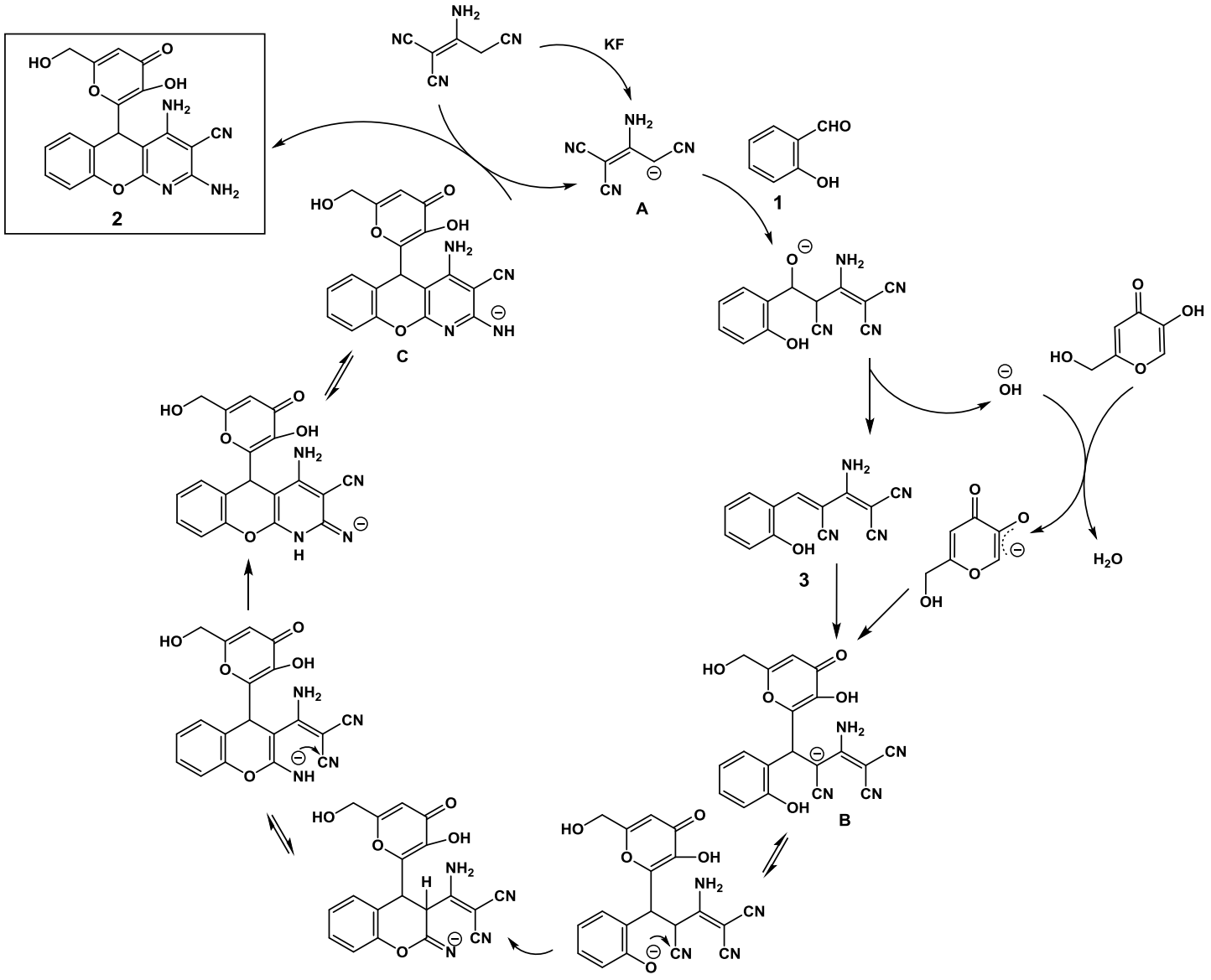

2j, 70%

Reaction conditions: salicyaldehydes **1a-j** (3 mmol), kojic acid (3 mmol), malononitrile dimer (3 mmol) were refluxed in 5 mL of *i*-propanol for 2 h with 10 mol% of KF. Isolated yields.

The structure of 5-[3-hydroxy-6-(hydroxymethyl)-4*H*-pyran-2-yl] substituted 5*H*-chromeno[2,3-*b*]pyridines **2a-j** were confirmed by NMR, IR, mass spectrometry data and elemental analyses.

The structure of the compound **2d** was additionally proven with NMR spectroscopy data using two-dimensional ^{1}H-^{13}C HSQC and ^{1}H-^{13}C HMBC techniques and complete assignment of all signals in the spectra of hydrogen and carbon-13 atoms spectra was performed.

With all above mentioned data and the results of assembly the chromenopyridine scaffold from carbonyl compounds and cyclic C-H acids,[34-36] the following mechanism for multicomponent assembling of salicylaldehydes **1**, 2-aminoprop-1-ene-1,1,3-tricarbonitrile (malononitrile dimer) and kojic acid into 5*H*-chromeno[2,3-*b*]pyridines **2** was suggested (Scheme 2).



Scheme 2. Mechanism of multicomponent transformation of salicylaldehydes **1**, malononitrile dimer and kojic acid into 5*H*-chromeno[2,3-*b*]pyridines **2.**

In the first step the formation of malononitrile dimer anion **A** takes place by the action of KF. Then reaction of anion **A** with salicylaldehyde **1** results in Knoevenagel adduct **3** formation, which reacts with anion of kojic acid to form anion **B**. The next isomerization and double Pinner type cyclization with protonation on the last step by the next molecule of malononitrile dimer produce final compound of multicomponent catalytic process, namely 2,4-diamino-5-[3-hydroxy-6-(hydroxymethyl)-4*H*-pyran-2-yl]-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitrile **2**.

Conclusions

The complex and efficient new multicomponent reaction of salicylaldehydes, 2-aminoprop-1-ene-1,1,3-tricarbonitrile (malononitrile dimer) and kojic acid leads to formation of earlier unknown 5-[3-hydroxy-6-(hydroxymethyl)-4*H*-pyran-2-yl] substituted chromeno[2,3-*b*]pyridine scaffold. This multicomponent reaction begins from Knoevenagel condensation of salicylaldehyde with malononitrile dimer. Then Michael addition of kojic acid, double Pinner type reaction cyclization, and isomerization with following protonation lead to 2,4-diamino-5-[3-hydroxy-6-(hydroxymethyl)-4*H*-pyran-2-yl]-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitriles, which are promising compounds for the treatment of human inflammatory diseases and different biomedical applications. The simple equipment, available and not expensive starting compounds, not labour intensive isolation of final compounds are the main features of this facile and efficient technique for synthesis of a novel type of 5-[3-hydroxy-6-(hydroxymethyl)-4*H*-pyran-2-yl] substituted chromeno[2,3-*b*]pyridines.

Experimental Section

General. All melting points were measured with a Gallenkamp melting-point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 with Bruker Avance II 300 spectrometer at ambient temperature. Chemical shift values are relative to Me_4Si. IR spectra were recorded with a Bruker ALPHA-T FT-IR spectrometer in KBr pellets. Mass-spectra (EI = 70 eV) were obtained directly with a Kratos MS-30 spectrometer.

General procedure for preparation of functionalized chromeno[2,3-*b*]pyridines.Potassium fluoride (0.3 mmol) was added to a stirred solution of salicylaldehyde **1** (3 mmol), 2-aminoprop-1-ene-1,1,3-tricarbonitrile (3 mmol) and kojic acid (3 mmol) in 5 mL of *iso*-propanol at ambient temperature. Then mixture was refluxed for 2 h. The resulting precipitate of chromeno[2,3-*b*]pyridine **2** was collected by filtration and dried (in some cases additional recrystallization from DMSO was needed).

2,4-Diamino-5-(3-hydroxy-6-(hydroxymethyl)-4-oxo-4*H*-pyran-2-yl)-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitrile (2a). Yellowish powder; yield 1.06 g, (93%); mp: 315-316 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.98 (dd, ^{2}J 15.5 Hz, ^{3}J 5.1 Hz, 1H, CH_2), 4.07 (dd, ^{2}J 15.5 Hz, ^{3}J 5.1 Hz, 1H, CH_2), 5.52 (t, ^{3}J 5.1 Hz,1H, OH), 5.59 (s, 1H, CH), 6.19 (br s, 2H, NH_2), 6.23 (s, 1H, CH), 6.57 (s, 2H, NH_2), 7.07-7.23 (m, 3H, 3 CH Ar), 7.31 (t, ^{3}J 7.3 Hz, 1H, CH Ar), 9.91 (br s, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 32.2 (**C**H aliphatic), 59.3 (**C**H_2), 70.8 (**C**-CN), 85.7 (**C**-C-NH_2), 109.1 (**C**H kojic acid), 116.2 (**C**N), 116.6 (**C**H Ar), 119.7 (CH-**C**-CH), 124.3 (**C**H Ar), 128.7 (**C**H Ar), 129.0 (**C**H Ar), 140.1 (**C**-OH), 150.1 (CH-**C**-O), 150.8 (O-**C**-C-OH), 156.7 (O-**C**-N), 159.5 (**C**-NH_2), 159.9 (**C**-NH_2), 167.8 (**C**-CH_2OH), 173.6 (**C**=O); IR (KBr): ν = 3631, 3346, 2205, 1654, 1629, 1567, 1455, 1258, 1231, 1192 cm^{-1}; MS (*m/z*, relative intensity %): 378 [M^+] (57), 329 (6), 277 (44), 237 (100), 221 (9), 171 (31), 145 (7), 116 (7). Found (%): C, 60.14; H, 3.61; N, 14.73. Calcd for $C_{19}H_{14}N_4O_5$ (%): C, 60.32; H, 3.73; N, 14.81.

2,4-Diamino-5-(3-hydroxy-6-(hydroxymethyl)-4-oxo-4*H*-pyran-2-yl)-7-methyl-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitrile (2b). Pale brown powder; yield 0.79 g, (67%); mp: 337-338 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.25 (s, 3H, CH_3), 3.98 (dd, ^{2}J 15.3 Hz, ^{3}J 5.9 Hz, 1H, CH_2), 4.07 (dd, ^{2}J 15.3 Hz, ^{3}J 5.9 Hz, 1H, CH_2), 5.47-5.54 (m, 2H, CH + OH), 6.15 (br s, 2H, NH_2), 6.23 (s, 1H, CH), 6.53 (s, 2H, NH_2), 6.99 (d, ^{4}J 1.5 Hz, 1H, CH Ar), 7.04 (d, ^{3}J 8.8 Hz, 1H, CH Ar), 7.12 (dd, ^{3}J 8.8 Hz, ^{4}J 1.5 Hz, 1H, CH Ar), 9.92 (br s, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.2 (**C**H_3), 32.2 (**C**H aliphatic), 59.3 (**C**H_2), 70.7 (**C**-CN), 85.6 (**C**-C-NH_2), 109.0 (**C**H kojic acid), 116.2 (**C**N), 116.3 (**C**H Ar), 119.3 (CH-**C**-CH), 128.6 (**C**H Ar), 129.6 (**C**H Ar), 133.2 (**C**-CH_3), 139.9 (**C**-OH), 148.8 (CH-**C**-O), 150.0 (O-

C-C-OH), 156.6 (O-**C**-N), 159.5 (**C**-NH_2), 159.8 (**C**-NH_2), 167.7 (**C**-CH_2OH), 173.4 (**C**=O); IR (KBr): ν = 3630, 2200, 1650, 1571, 1451, 1262, 1225, 1196 cm^{-1}; MS (*m/z*, relative intensity %): 392 [M^+] (67), 357 (3), 291 (34), 251 (100), 235 (8), 185 (20), 142 (9), 140 (8). Found (%): C, 61.07; H, 4.03; N, 14.11. Calcd for $C_{20}H_{16}N_4O_5$ (%): C, 61.22; H, 4.11; N, 14.28.

2,4-Diamino-5-(3-hydroxy-6-(hydroxymethyl)-4-oxo-4*H*-pyran-2-yl)-9-methoxy-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitrile (2c). Orange powder; yield 0.67 g, (56%); mp: 327-328 °C, dec.; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.85 (s, 3H, OCH_3), 3.99 (d, ^2J 16.1 Hz, 1H, CH_2), 4.07 (d, ^2J 16.1 Hz, 1H, CH_2), 5.48-5.59 (m, 2H, CH + OH), 6.17 (br s, 2H, NH_2), 6.23 (s, 1H, CH), 6.57 (s, 2H, NH_2), 6.74 (dd, ^3J 7.4 Hz, ^4J 1.8 Hz, 1H, CH Ar), 6.96-7.11(m, 2H, 2 CH Ar), 9.98 (br s, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 32.3 (**C**H aliphatic), 55.8 (O**C**H_3), 59.3 (**C**H_2), 70.7 (**C**-CN), 85.4 (**C**-C-NH_2), 109.0 (**C**H kojic acid), 111.6 (**C**H Ar), 116.2 (**C**N), 119.6 (**C**H Ar), 120.3 (CH-**C**-CH), 124.0 (**C**H Ar), 140.0 (**C**-OCH_3), 140.3 (**C**-OH), 147.5 (CH-**C**-O), 149.9 (O-**C**-C-OH), 156.6 (O-**C**-N), 159.3 (**C**-NH_2), 159.8 (**C**-NH_2), 167.7 (**C**-CH_2OH), 173.4 (**C**=O); IR (KBr): ν = 3630, 2203, 1654, 1589, 1450, 1335, 1229, 1196 cm^{-1}; MS (*m/z*, relative intensity %): 408 [M^+] (100), 359 (8), 307 (57), 267 (94), 224 (60), 195 (16), 152 (9), 142 (15). Found (%): C, 58.67; H, 3.83; N, 13.61. Calcd for $C_{20}H_{16}N_4O_6$ (%): C, 58.82; H, 3.95; N, 13.72.

2,4-Diamino-8-hydroxy-5-(3-hydroxy-6-(hydroxymethyl)-4-oxo-4*H*-pyran-2-yl)-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitrile (2d). Pale brown powder; yield 0.69 g, (58%); mp: 321-322 °C, dec.; ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.00 (dd, ^2J 15.7 Hz, ^3J 6.6 Hz, 1H, CH_2), 4.08 (dd, ^2J 15.7 Hz, ^3J 6.6 Hz, 1H, CH_2), 5.43 (s, 1H, CH), 5.51 (t, ^3J 6.6 Hz, 1H, OH), 6.13 (br s, 2H, NH_2) 6.22 (s, 1H, CH), 6.47-6.60 (m, 4H, 2 CH Ar + NH_2), 6.97 (d, ^3J 8.8 Hz, 1H, Ar), 9.73 (s, 1H, OH), 9.84 (br s, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 31.6 (**C**H aliphatic), 59.3 (**C**H_2), 70.7 (**C**-CN), 85.9 (**C**-C-NH_2), 102.8 (**C**H Ar), 108.9 (**C**H kojic acid), 109.9 (CH-**C**-CH), 112.1 (**C**H Ar), 116.2 (**C**N), 129.2 (**C**H Ar), 139.8 (**C**-OH), 150.4 (CH-**C**-O), 151.5 (O-**C**-C-OH), 156.6 (O-**C**-N), 157.8 (**C**-OH Ar), 159.4 (**C**-NH_2), 159.7 (**C**-NH_2), 167.7 (**C**-CH_2OH), 173.5 (**C**=O); IR (KBr): ν = 3405, 2201, 1629, 1568, 1459, 1365, 1244, 1195 cm^{-1}; MS (*m/z*, relative intensity %): 394 [M^+] (33), 319 (23), 293 (78), 253 (100), 237 (11), 186 (15), 142 (81), 113 (8). Found (%): C, 57.69; H, 3.54; N, 14.05. Calcd for $C_{19}H_{14}N_4O_6$ (%): C, 57.87; H, 3.58; N, 14.21.

2,4-Diamino-7-chloro-5-(3-hydroxy-6-(hydroxymethyl)-4-oxo-4*H*-pyran-2-yl)-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitrile (2e). Orange powder; yield 0.74 g, (60%); mp: 316-317 °C, dec.; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.99 (dd, ^2J 15.8 Hz, ^3J 5.5 Hz, 1H, CH_2), 4.08 (dd, ^2J 15.8 Hz, ^3J 5.5 Hz, 1H, CH_2), 5.51 (t, ^3J 5.5 Hz, 1H, OH), 5.61 (s, 1H, CH), 6.21 (br s, 2H, NH_2), 6.23 (s, 1H, CH), 6.60 (s, 2H, NH_2), 7.18 (d, ^3J 8.8, Hz, 1H, CH Ar), 7.20 (d, ^4J 2.2 Hz, 1H, CH Ar), 7.37 (dd, ^3J 8.8, ^4J 2.2 Hz, 1H, CH Ar), 10.02 (br s, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 32.2 (**C**H aliphatic), 59.3 (**C**H_2), 70.9 (**C**-CN), 85.1 (**C**-C-NH_2), 109.1 (**C**H kojic acid), 116.0 (**C**N), 118.5 (**C**H Ar), 121.8 (CH-**C**-CH), 127.5 (**C**-Cl), 128.0 (**C**H Ar), 128.9 (**C**H Ar), 140.1 (**C**-OH), 149.5 (CH-**C**-O), 149.7 (O-**C**-C-OH), 156.7 (O-**C**-N), 159.1 (**C**-NH_2), 159.8 (**C**-NH_2), 167.7 (**C**-CH_2OH), 173.5 (**C**=O); IR (KBr): ν = 3630, 2345, 1650, 1567, 1454, 1259, 1239, 1186, 1083 cm^{-1}; MS (*m/z*, relative intensity %): 414 [M^+] (28, ^{37}Cl), 412 [M^+] (66, ^{35}Cl), 364 (21), 313 (26, ^{37}Cl), 311(82, ^{35}Cl), 273(61, ^{37}Cl), 271(100, ^{35}Cl), 254 (17), 205 (33), 152 (23), 127 (20). Found (%): C, 55.13; H, 3.08; Cl, 8, 43; N, 13.51. Calcd for $C_{19}H_{13}ClN_4O_5$ (%): C, 55.28; H, 3.17; Cl, 8.59; N, 13.57.

2,4-Diamino-7-bromo-5-(3-hydroxy-6-(hydroxymethyl)-4-oxo-4*H*-pyran-2-yl)-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitrile (2f). Orange powder; yield 0.93 g, (68%); mp: 325-326 °C, dec.; ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.02 (dd, ^2J 15.3 Hz, ^3J 5.1 Hz, 1H, CH_2), 4.08 (dd, ^2J 15.3 Hz, ^3J 5.1 Hz, 1H, CH_2), 5.51 (t, ^3J 5.1 Hz, 1H, OH), 5.62 (s, 1H, CH), 6.21 (s, 2H, NH_2), 6.24 (s, 1H, CH), 6.60 (s, 2H, NH_2), 7.14 (d, ^3J 8.8 Hz, 1H, CH Ar), 7.34 (d, ^4J 2.2 Hz, 1H, CH Ar), 7.50 (dd, ^3J 8.7 Hz, ^4J 2.2 Hz, 1H, CH Ar), 9.95 (br s, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 32.0 (**C**H aliphatic), 59.3 (**C**H_2), 70.9 (**C**-CN), 85.2 (**C**-C-NH_2), 109.1 (**C**H kojic acid), 115.3 (CH-**C**-CH), 116.0 (**C**N), 118.9 (**C**H Ar), 122.3 (**C**-Br), 130.8 (**C**H Ar), 131.8 (**C**H Ar), 140.1 (**C**-OH), 149.5 (CH-**C**-O), 150.2 (O-**C**-C-OH), 156.7 (O-**C**-N), 159.1 (**C**-NH_2), 159.8 (**C**-NH_2), 167.7 (**C**-CH_2OH), 173.5 (**C**=O); IR (KBr): ν = 3630, 2203, 1650, 1565, 1453,

1258, 1237, 1187 cm^{-1}; MS (*m/z*, relative intensity %): 458 [M^+] (100, ^{81}Br), 456 [M^+] (97, ^{79}Br), 380 (13, ^{81}Br), 378 (8, ^{79}Br), 357 (70, ^{81}Br), 355 (73, ^{79}Br) 317 (73, ^{81}Br) 315 (69, ^{79}Br), 251 (8, ^{81}Br), 249 (9, ^{79}Br), 237 (4, ^{81}Br), 235 (3, ^{79}Br). Found (%): C, 49.78; H, 2.76; Br, 17,35; N, 12.11. Calcd for $C_{19}H_{13}BrN_4O_5$ (%): C, 49.91; H, 2.87; Br, 17,48; N, 12.25.

2,4-Diamino-5-(3-hydroxy-6-(hydroxymethyl)-4-oxo-4*H*-pyran-2-yl)-7-nitro-5H-chromeno[2,3-*b*]pyridine-3-carbonitrile (2g). Yellowish powder; yield 0.79 g, (62%); mp: 333-334 °C, dec.; ^1H NMR (300 MHz, DMSO-d_6): δ 4.01 (dd, ^2J 15.0 Hz, ^3J 6.6 Hz, 1H, CH_2), 4.09 (dd, ^2J 15.0 Hz, ^3J 6.6 Hz, 1H, CH_2), 5.51 (t, ^3J 6.6 Hz, 1H, OH), 5.79 (s, 1H, CH), 6.25 (s, 1H, CH), 6.29 (br s, 2H, NH_2), 6.68 (s, 2H, NH_2), 7.41 (d, ^3J 8.8 Hz, 1H, CH Ar), 8.07 (d, ^4J 2.2 Hz, 1H, CH Ar), 8.21 (dd, ^3J 8.8 Hz, ^4J 2.2 Hz, 1H, CH Ar), 10.05 (br s, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 32.2 (**C**H aliphatic), 59.2 (**C**H_2), 71.3 (**C**-CN), 84.8 (**C**-C-NH_2), 109.1 (**C**H kojic acid), 115.8 (**C**N), 117.9 (**C**H Ar), 121.0 (CH-**C**-CH), 124.6 (**C**H Ar), 124.8 (**C**H Ar), 140.3 (**C**-OH), 143.3 (**C**-NO_2), 149.2 (CH-**C**-O), 155.6 (O-**C**-C-OH), 156.7 (O-**C**-N), 158.5 (**C**-NH_2), 159.9 (**C**-NH_2), 167.8 (**C**-CH_2OH), 173.5 (**C**=O); IR (KBr): ν = 3390, 3173, 2202, 1649, 1567, 1520, 1448, 1334, 1257, 1195 cm^{-1}; MS (*m/z*, relative intensity %): 423 [M^+] (23), 406 (100), 357 (30), 304 (12), 282 (29), 236 (51), 192 (4), 170 (7), 63 (11), 15 (25). Found (%): C, 53.76; H, 3.14; N, 16.43. Calcd for $C_{19}H_{13}N_5O_7$ (%): C, 53.91; H, 3.10; N, 16.54.

2,4-Diamino-7,9-dichloro-5-(3-hydroxy-6-(hydroxymethyl)-4-oxo-4*H*-pyran-2-yl)-5*H*-chromeno[2,3-b]pyridine-3-carbonitrile (2h). Pale brown powder; yield 0.76 g, (57%); mp: 310-311 °C; ^1H NMR (300 MHz, DMSO-d_6): δ 4.05 (dd, ^2J 14.5 Hz, ^3J 5.9 Hz, 1H, CH_2), 4.11 (dd, ^2J 14.5 Hz, ^3J 5.9 Hz, 1H, CH_2), 5.51 (t, ^3J 5.9 Hz, 1H, OH), 5.67 (s, 1H, CH), 6.25 (s, 1H, CH), 6.27 (s, 2H, NH_2), 6.74 (s, 2H, NH_2), 7.21 (d, ^4J 2.2 Hz, 1H, CH Ar), 7.67 (d, ^4J 2.2 Hz, 1H, CH Ar), 10.00 (br s, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 32.6 (**C**H aliphatic), 59.3 (**C**H_2), 71.2 (**C**-CN), 84.9 (**C**-C-NH_2), 109.1 (**C**H kojic acid), 115.8 (**C**N), 121.6 (CH-**C**-CH), 123.2 (**C**H Ar), 127.0 (**C**-Cl), 127.4 (**C**H Ar), 128.9 (**C**-Cl), 140.3 (**C**-OH), 145.9 (CH-**C**-O), 149.0 (O-**C**-C-OH), 156.7 (O-**C**-N), 158.6 (**C**-NH_2), 159.8 (**C**-NH_2), 167.7 (**C**-CH_2OH), 173.4 (**C**=O); IR (KBr): ν = 3449, 3357, 2205, 1627, 1562, 1460, 1397, 1254, 1231, 1193 cm^{-1}; MS (*m/z*, relative intensity %): 448 [M^+] (9, ^{37}Cl, ^{35}Cl) 446 [M^+] (17, ^{35}Cl, ^{35}Cl), 370 (5, ^{37}Cl, ^{35}Cl), 368 (9, ^{35}Cl, ^{35}Cl), 347 (20, ^{37}Cl, ^{35}Cl), 345 (26, ^{35}Cl, ^{35}Cl), 309 (15, ^{37}Cl, ^{37}Cl), 307 (70, ^{37}Cl, ^{35}Cl), 305 (100, ^{35}Cl, ^{35}Cl), 271 (7), 239 (22), 214 (6), 186 (7), 132 (6), 31 (12). Found (%): C, 50.87; H, 2.75; Cl, 15.78; N, 12.41. Calcd for $C_{19}H_{12}Cl_2N_4O_5$ (%): C, 51.03; H, 2.70; Cl, 15.85; N, 12.53.

2,4-Diamino-7-bromo-5-(3-hydroxy-6-(hydroxymethyl)-4-oxo-4*H*-pyran-2-yl)-9-methoxy-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitrile (2i). Pale orange powder; yield 1.05 g, (72%); mp: 316-317 °C; ^1H NMR (300 MHz, DMSO-d_6): δ 3.87 (s, 3H, OCH_3), 3.97-4.11 (m, 2H, CH_2), 5.51 (br s, 1H, OH), 5.57 (s, 1H, CH), 6.17 (br s, 2H, NH_2), 6.23 (s, 1H, CH), 6.58 (s, 2H, NH_2),6.87 (d, ^4J 2.2 Hz, 1H, CH Ar), 7.18 (d, ^4J 2.2 Hz, 1H, CH Ar), 9.97 (br s, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 32.1 (**C**H aliphatic), 56.3 (O**C**H_3), 59.3 (**C**H_2), 70.9 (**C**-CN), 85.1 (**C**-C-NH_2), 109.1 (**C**H kojic acid), 114.7 (**C**H Ar), 115.1 (CH-**C**-CH), 116.0 (**C**N), 121.8 (**C**H Ar), 122.1 (**C**-OCH_3), 139.9 (**C**-Br), 140.2 (**C**-OH), 148.5 (CH-**C**-O), 149.4 (O-**C**-C-OH), 156.6 (O-**C**-N), 159.0 (**C**-NH_2), 159.8 (**C**-NH_2), 167.7 (**C**-CH_2OH), 173.5 (**C**=O); IR (KBr): ν = 3447, 3329, 2201, 1636, 1564, 1488, 1465, 1397, 1264, 1226 cm^{-1}; MS (*m/z*, relative intensity %): 488 [M^+] (27, ^{81}Br), 486 [M^+] (27, ^{79}Br), 410 (6, ^{81}Br), 408 (5, ^{79}Br), 387 (38, ^{81}Br), 385 (42, ^{79}Br), 347 (100, ^{81}Br), 345 (95, ^{79}Br), 304 (33, ^{81}Br), 302 (31, ^{79}Br), 285 (8), 235 (7), 195 (19), 142 (47), 29 (33). Found (%): C, 49.17; H, 3.12; Br, 16.32; N, 11.43. Calcd for $C_{20}H_{15}BrN_4O_6$ (%): C, 49.30; H, 3.10; Br, 16.40; N, 11.50.

9,11-Diamino-12-(3-hydroxy-6-(hydroxymethyl)-4-oxo-4*H*-pyran-2-yl)-12*H*-benzo[5,6]chromeno[2,3-b]pyridine-10-carbonitrile (2j). Pale brown powder; yield 0.90 g, (70%); mp: 355-356 °C, dec.; ^1H NMR (300 MHz, DMSO-d_6): δ 3.88 (d, ^2J 16.1 Hz, 1H, CH_2), 4.02 (d, ^2J 16.1 Hz, 1H, CH_2), 5.42 (br s, 1H, OH), 6.09 (s, 1H, CH), 6.17 (s, 1H, CH), 6.41 (br s, 2H, NH_2), 6.60 (s, 2H, NH_2), 7.41 (d, ^3J 8.8 Hz, 1H, CH Ar), 7.45-7.53 (m, 1H, CH Ar), 7.57 (t, ^3J 7.6 Hz, 1H, Ar), 7.92-8.06 (m, 3H, 2 CH Ar), 10.46 (br s, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 30.2 (**C**H

aliphatic), 59.7 (**C**H_2), 71.4 (**C**-CN), 86.4 (**C**-C-NH_2), 109.5 (**C**H kojic acid), 112.1 (CH-**C**-CH), 116.7 (**C**N), 118.0 (**C**H Ar), 122.6 (**C**H Ar), 125.4 (**C**H Ar), 127.9 (**C**H Ar), 129.2 (**C**H Ar), 130.3 (**C**H Ar), 130.8 (**C** quat. Ar), 131.1 (**C** quat. Ar), 139.9 (**C**-OH), 149.6 (CH-**C**-O), 149.7 (O-**C**-C-OH), 157.2 (O-**C**-N), 159.7(**C**-NH_2), 160.3 (**C**-NH_2), 168.3 (**C**-CH_2OH), 173.7 (**C**=O); IR (KBr): ν = 3435, 3182, 2201, 1650, 1627, 1571, 1450, 1265, 1240, 1195 cm^{-1}; MS (*m/z*, relative intensity %): 428 [M^+] (100), 374 (2), 327 (17), 298 (16), 287 (94), 221 (11), 215 (2), 168 (3), 127 (1), 55 (2). Found (%): C, 64.41; H, 3.69; N, 12.95. Calcd for $C_{23}H_{16}N_4O_5$ (%): C, 64.48; H, 3.76; N, 13.08.

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