Taylor & Francis
Taylor & Francis Group

Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: http://www.tandfonline.com/loi/lsyc20

3-Aminopyrazolo[4,3-c]pyridine-4,6-dione as a precursor for novel pyrazolo[4,5,1-ij][1,6]naphthyridines and pyrido[4',3':3,4]pyrazolo[1,5-a]pyrimidines

Nadia H. Metwally & Emad A. Deeb

To cite this article: Nadia H. Metwally & Emad A. Deeb (2018) 3-Aminopyrazolo[4,3-c]pyridine-4,6-dione as a precursor for novel pyrazolo[4,5,1-ij][1,6]naphthyridines and pyrido[4',3':3,4]pyrazolo[1,5-a]pyrimidines, Synthetic Communications, 48:13, 1614-1628, DOI: 10.1080/00397911.2018.1457162

To link to this article: https://doi.org/10.1080/00397911.2018.1457162

SYNTHETIC COMMUNICATIONS®
2018, VOL. 48, NO. 13, 1614–1628
https://doi.org/10.1080/00397911.2018.1457162

Taylor & Francis
Taylor & Francis Group

3-Aminopyrazolo[4,3-*c*]pyridine-4,6-dione as a precursor for novel pyrazolo[4,5,1-ij][1,6]naphthyridines and pyrido [4′,3′:3,4]pyrazolo[1,5-*a*]pyrimidines

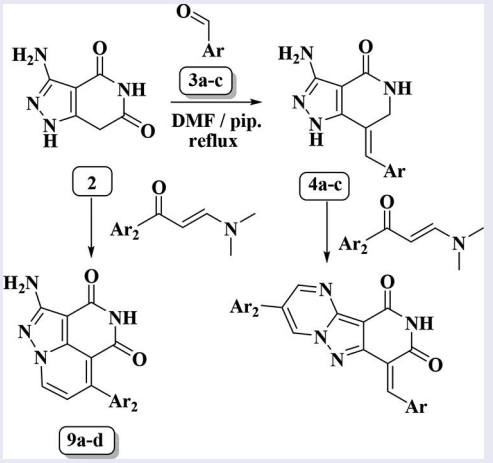
Nadia H. Metwally and Emad A. Deeb

Department of Chemistry, Faculty of Science, Cairo University, Giza, Egypt

ABSTRACT

The versatile, 3-aminopyrazolo[4,3-c]pyridine-4,6-dione (**2**) was synthesized and allowed to react with aldehydes, aryldiazonium chlorides, chalcones and enaminones to afford regioselectively the novel pyrazolo [4,3-c]pyridine derivatives **4a-c**, pyrazolo[4,5,1-ij][1,6] naphthyridines **9a-d** and pyrido[4′,3':3,4]pyrazlo[1,5-a]pyrimidines **19a-i**. The structure of all the newly synthesized compounds was assigned from elemental analysis and spectral data. Also, the mechanistic aspects for the formation of the newly synthesized compounds is discussed.

GRAPHICAL ABSTRACT



ARTICLE HISTORY
Received 30 December 2017

KEYWORDS
Pyrazolo[4,5,1-ij][1,6] naphthyridines; pyrazolo [4,3-*c*]pyridines; pyrido [4′,3′:3,4]-pyrazlo[1,5-*a*] pyrimidines

Introduction

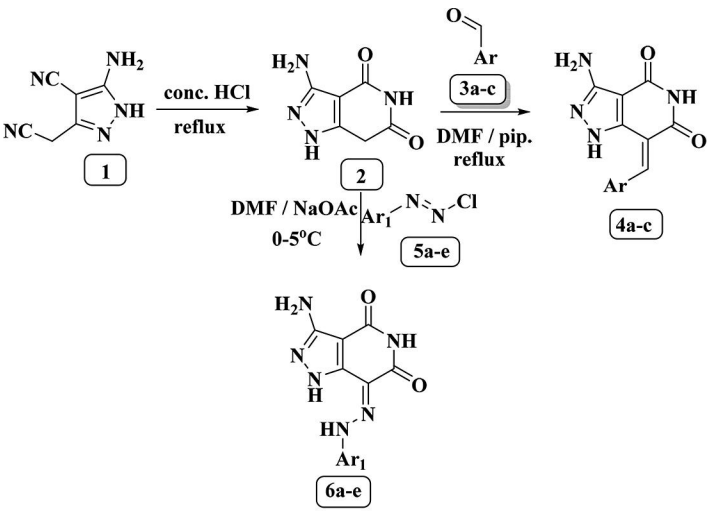
Fused heterocyclic compounds containing pyrazole moiety are considered as the most versatile bioactive compounds in pharmaceutical and medicinal chemistry. Pyrazolo[3, 4-*b*]pyridines possess extensive spectrum of biological activities such as inhibitors of xanthine oxidases,[1] trypanocidal activity,[2] treatment of Alzheimer's diseases, drug addiction and infertility.[3] Additionally, it have reported that they act as potent and selective

CONTACT Nadia H. Metwally nhmmohamed@yahoo.com Department of Chemistry, Faculty of Science, Cairo University, Giza, Egypt.
Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/lsyc.
Supplemental data for this article can be accessed on the publisher's website.

inhibitors of A1 adenosine receptors,[4] anti-inflammatory and antiplatelet agents.[5] Moreover, pyrazolo[1,5-*a*]pyridines are found as part of the skeletal backbone of many therapeutic drugs[6] and other biological activities.[7–11] Also, pyrazolo[4,3-*c*]pyridine derivative represent one of the most important building block in organic synthesis due to possess a wide range of biological activity which act as potent inhibitors of mycobacterium tuberculosis pantothenate synthetase (PS), c-Met inhibitors,[12,13] γ-secretase, an intramembrane protease[14] and used also to treatment of neuropathic pain.[15] In continuation of our interest in the synthesis of biologically, chemically valuable compounds,[16–25] and on the bases of the above findings, promoted us to design a series of novel pyrazolo[4,3-*c*]pyridine derivatives, pyrazolo[4,5,1-ij][1,6]naphthyridines and pyrido-[4′,3′:3,4]-pyrazolo[1,5-*a*]pyrimidines starting from a key intermediate 3-aminopyrazolo[4,3-*c*]-pyridinedione derivative **2.**

Results and discussion

The starting material, 3-aminopyrazolo[4,3-*c*]pyridine-4,6-dione (**2**) used in this study was synthesized by acid hydrolysis of 3-cyanomethyl-4-cyano-5-amino-1*H*-pyrazole (**1**). Condensation of compound **2** with aromatic aldehydes **3a–c** in refluxing *N*,*N*-dimethylformamide (DMF) containing a few drops of piperidene gave the respective arylidene derivatives **4a–c** (Scheme 1). The structure of **4a–c** was assigned on the basis of analytical and spectral data. The ^{1}H NMR spectrum of compound **4b** taken as an example exhibited two singlet signals at δ = 3.87 and 7.92 ppm assignable to the methoxy and vinylidene protons, respectively, in addition to three singlet signals at δ = 6. 29, 10.61



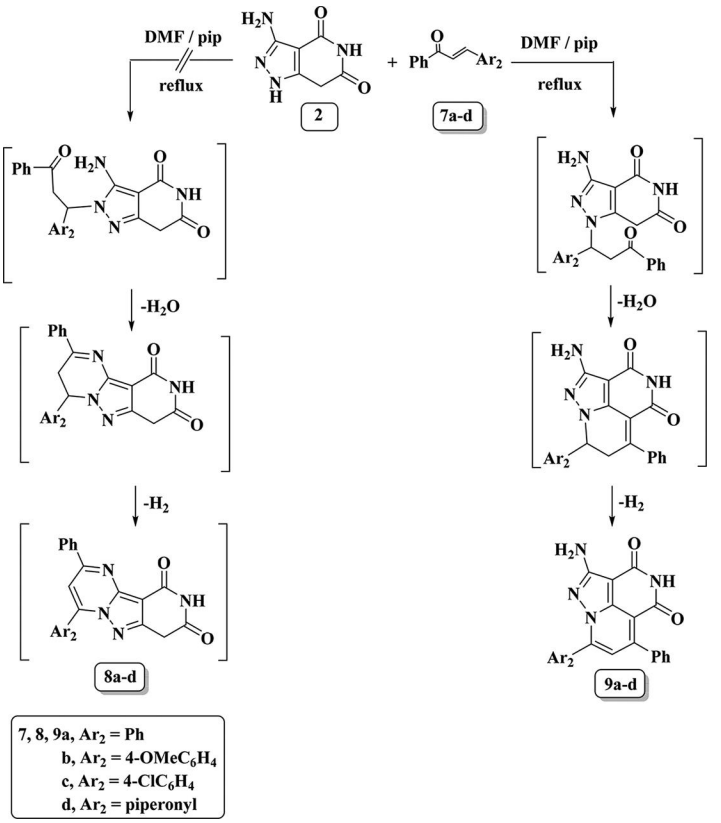
3, 4	Ar	5, 6	Ar_1
a	Ph	a	Ph
b	4-$OMeC_6H_4$	b	4-MeC_6H_4
c	4-ClC_6H_4	c	4-ClC_6H_4
		d	4-$OMeC_6H_4$
		e	3-$NO_2C_6H_4$

Scheme 1. Synthesis of 3-aminopyrazolo[4,3-*c*]pyridine derivatives **4a–c** and **6a–e**.

and 12.29 ppm due to NH_2 and two NH protons, respectively. Its ^{13}C NMR appeared the characteristic signals at 55.85 (OCH_3), 146.14 (CH), 161.75 (CO) and 167.59 (CO) ppm. Elemental analyses with spectral data are in agreement with the suggested structure **4**.

Also, compound **2** coupled with aryldiazonium chlorides **5a–e** in *N,N*-dimethylformamide containing sodium acetate under stirring at 0–5 °C to produce the arylhydrazo derivatives **6a–e** (Scheme 1). The spectral data of the isolated products was in complete agreement with structure **6**. Thus IR spectrum of compound **6b** showed the absorption bands at ν_{max} 3419, 3338, 3211, 3195 and 1691 cm^{-1} due to the NH_2, three NH and CO functions, respectively. Its ^1H NMR revealed four singlet signals exchangeable D_2O at $\delta = 6.57$, 10.63, 12.10 and 12.58 ppm attributable to NH_2 and three NH protons. Also, mass spectrum showed a corrected molecular ion peak at $m/z = 284$ (M^+, 88.3%) beside some other abundant fragments, that established the molecular formula $C_{13}H_{12}N_6O_2$. Elemental analysis with mass spectrum are in agreement with the proposed structure **6**.

It is interesting in this connection that the condensation of **2** with α,β-unsatutated carbonyl compounds **7a–d** in refluxing *N,N*-dimethylformamide in the presence of a few drops of piperedine as a catalyst does not afforded the pyrazolo[1,5-*a*]pyrimidine derivatives, as could have been expected in analogy to the formation of **8**. Actually, the products of this reaction were identified on the basis of their spectral data as 2-amino-6-phenyl-8-aryl-3*H*-pyrazolo[4,5-1-ij][1,6]naphthryidine-3,5(4*H*)-3,5-diones **9a–d** (Scheme 2). The IR

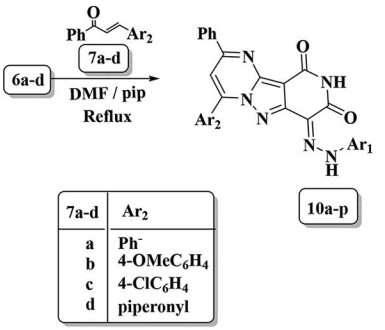


Scheme 2. 6-Phenyl-8-aryl-3*H*-pyrazolo[4,5,1-ij][1,6]naphthyridinediones **9a–d**.

spectrum of compound **9d** taken as an typical example of the prepared series showed the absorption bands at ν_{max} 3413, 3117 and 1681 cm^{-1} corresponding to NH_2, NH and CO, respectively. The ^1H NMR spectrum of **9d** supported its structure, as it revealed a singlet signal at $\delta = 6.26$ ppm assigned to methylene protons and two singlet signals exchangeable with D_2O at $\delta = 6.64$ and 10.93 ppm characteristic to NH_2 and NH protons, beside the other expected signals for aromatic protons. Its ^{13}C NMR exhibited a characteristic signals at 101.75 ($\underline{C}H_2$), 124.15 ($\underline{C}H$=C), 147.64 ($\underline{C}$-NH_2), 160.27 (CO) and 162.77 (CO). Also, mass spectrum of **9d** showed the molecular ion peak at m/z 398 (M^+, 2.8%) which was consistent with the molecular formula $C_{22}H_{14}N_4O_2$. Elemental analyses with mass spectrum are agreement with the proposed structure **9**. The above collective data with the elemental analysis are in agreement with the suggested structure **9**. The formation of **9** from the reaction of **2** with **7** is believed to proceed *via* a *Michael* addition reaction to give non-isolable adducts, which in turn undergo cyclodehydration to give the non-isolable dihydropyrazolonaphthyridine followed by spontaneous oxidation to **9**.

On the other hand, the reaction of arylhydrazo derivatives **6a-d** with α,β-unsaturated carbonyl compounds **7a–d** under the same reaction conditions afforded the isolated products **10a–p** (Scheme 3). The spectral and microanalytical data of compounds **10a–p** were consistent with their structures. For example, the IR spectrum of compound **10c** displayed absorption bands at ν_{max} 3378, 3148 and 1689 cm^{-1} corresponding to NH and CO functions. Its ^1H NMR spectrum exhibited two singlet signals exchangeable with D_2O at $\delta = 11.13$ and 12.42 ppm due to NH protons. Also, mass spectrum of **10c** showed a corrected molecular ion peaks at m/z = 492 (M^+, 30.2%) and m/z = 494 ($M^+ + 2$, 11.7%) which consistent the formula $C_{27}H_{17}ClN_6O_2$. Elemental analysis with mass spectrum are in agreement with the structure **10c**.

The behavior of the enaminones towards some *N*-nucleophiles to attain fused ring systems such as pyrazolo[1,5-*a*]pyrimidines of potential pharmaceutical interest, has been

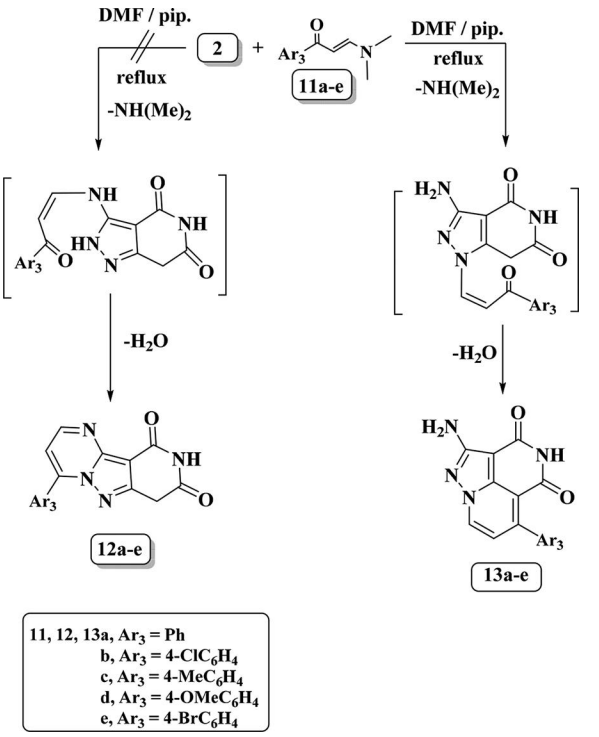


7a-d	Ar_2
a	Ph
b	4-$OMeC_6H_4$
c	4-ClC_6H_4
d	piperonyl

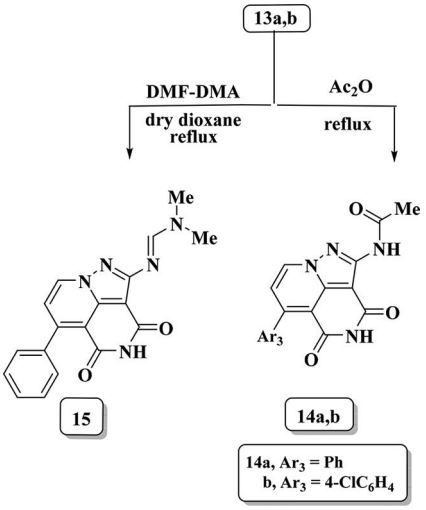
10a-h	Ar_1	Ar_2	10i-p	Ar_1	Ar_2
a	Ph	Ph	i	Ph	4-ClC_6H_4
b	4-MeC_6H_4	Ph	j	4-MeC_6H_4	4-ClC_6H_4
c	4-ClC_6H_4	Ph	k	4-ClC_6H_4	4-ClC_6H_4
d	4-$OMeC_6H_4$	Ph	l	4-$OMeC_6H_4$	4-ClC_6H_4
e	Ph	4-$OMeC_6H_4$	m	Ph	piperonyl
f	4-MeC_6H_4	4-$OMeC_6H_4$	n	4-MeC_6H_4	piperonyl
g	4-ClC_6H_4	4-$OMeC_6H_4$	o	4-ClC_6H_4	piperonyl
h	4-$OMeC_6H_4$	4-$OMeC_6H_4$	p	4-$OMeC_6H_4$	piperonyl

Scheme 3. Synthesis of 7-arylhydrazopyrido[4′,3′:3,4]pyrazolo[1,5-*a*]pyrimidine-8,10(7*H*,9*H*)-dione derivatives **10a–p**.

investigated.[26–28] Thus the key intermediate **2** reacted with enaminones **11a–e** in refluxing *N,N*-dimethylformamide containing piperidene to produce one single product in each case **13a–e** (Scheme 4). The structure of the adducts **13a–e** was determined by elemental analysis and spectral data. The IR spectrum of compound **13c** was characterized by the presence of absorption bands at ν_{max} 3,466, 3,208, and 1,701 cm^{-1} due to the NH_2, NH and CO groups, respectively. Also, its ^1H NMR spectrum revealed the presence of a singlet signal at $\delta = 2.42$ due to methyl protons with another two singlet signals exchangeable with D_2O in the region 6.66 and 10.89 ppm assigned to NH_2 and NH protons. Also, mass spectrum showed a molecular ion peak at m/z = 292 (M^+, 28.7%), which confirmed the molecular formula $C_{16}H_{12}N_4O_2$. The formation of cycloadducts **13a-e** indicates that the reaction mechanism proceeds through a *Michael* type addition of NH in pyrazole ring to the activated double in enaminoes **11** to form the non-isolable intermediate which readily undergo cyclization by loss of dimethylamine and water molecules *via* active methylene in pyridine ring to furnish the 2-amino-6-aryl-3*H*-pyrazolo[4,5,1-ij][1,6]naphthyridine-3,5(4*H*)diones rather than the expected pyrazolo[1,5-*a*]pyrimidines as a sole products from the reaction of aminopyrazoles with enaminones. Also, the structure of the isolated products **13a–e** can be confirmed chemically by acetylation reaction. Thus the treatment of compounds **13a,b** with acetic anhydride furnished the acetyl derivatives **14a,b**. The structure of the acetyl derivatives was assigned from their elemental analyses and spectral data (Scheme 5 and exp.). Moreover, treatment of compound **13a** with dimethylformamide-dimethylacetal (DMF-DMA) in dry dioxane produced the enamine derivative **15** (Scheme 5).

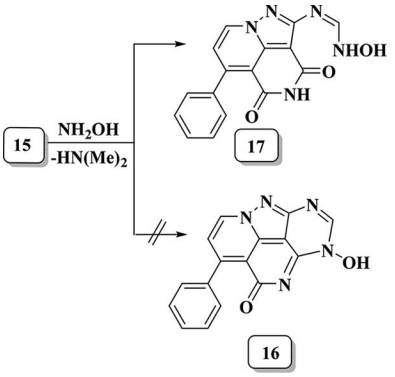


Scheme 4. Synthesis of 2-amino-6-aryl-3*H*-pyrazolo[4,5,1-ij][1,6]naphthyridine-3,5(4*H*)-diones **13a–e**.



Scheme 5. Synthesis of pyrazolo[4,5,1-ij][1,6]naphthyridine-3,5(4*H*)-dione derivatives **14a,b** and **15**.

The structure of the enamine derivative **15** was supported by its elemental analysis and spectral data. Its IR spectrum displayed the absorptions bands for NH and CO functions at ν_{max} 3,194 and 1,695 cm^{-1}. Also, its ^1H NMR spectrum revealed the two singlet signals at $\delta = 3.02$ and 3.12 ppm due to the two methyl protons and another a singlet signal at $\delta = 9.12$ ppm assigned to an iminic proton, in addition to the other expected signals for aromatic protons. The microanalytical with spectral data are in agreement with suggested structure **15**. The reaction of enamine derivative **15** with hydroxylamine hydrochloride furnished the isolated product **17** (Scheme 6). The structure of **17** was confirmed on its elemental analysis and spectral data. Its` IR spectrum exhibited the absorption bands at ν_{max} 3,411, 3,270, and 1,694 cm^{-1} assignable to OH, NH and CO groups. Its ^1H NMR spectrum confirmed the proposed structure which revealed the presence of two characteristic singlet signals exchangeable with D_2O at $\delta = 10.61$ and 11.24 ppm corresponding to NH and OH protons, respectively. In addition to the other expected signals for aromatic, NH and olefinic protons. The elemental

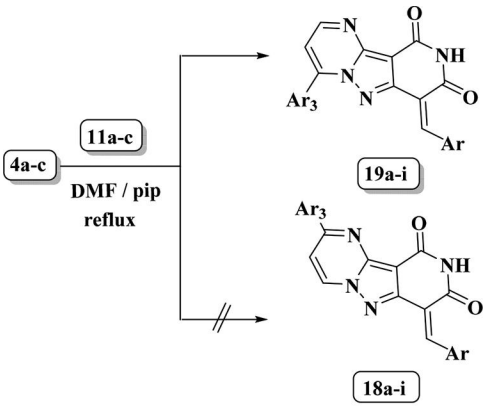


Scheme 6. Synthesis of *N′*-(3,5-dioxo-6-phenyl-4,5-dihydro-3*H*-pyrazolo[4,5,1-ij][1,6]-naphthyridin-2yl)-*N*-hydroxyformaimidamide **16**.

analyses together with spectral data are in agreement the proposed structure **17** rather than the tetracyclic compound **16**.

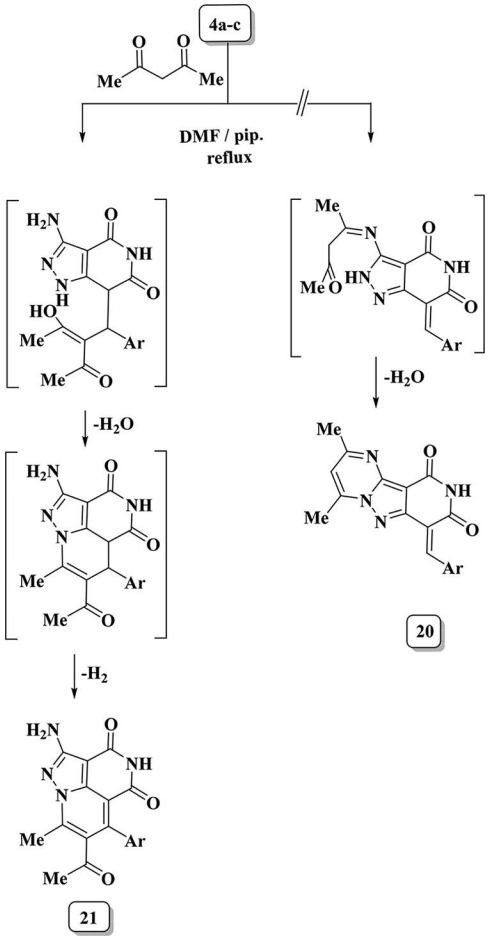
On the other hand, cyclocondensation of compounds **4a–c** with enaminones **11a–c** in refluxing *N,N*-dimethylformamide containing a few drops of piperidene afforded the isolated products **19a–i** which confirmed from their elemental analyses and spectral data (Scheme 7). The IR spectrum of compound **19c** was characterized by the presence of absorption bands at ν_{max} 3245 and 1697 cm^{-1} assignable to both NH and CO groups. Also, the ^1H NMR spectrum of **19c** confirmed the proposed structure revealed the presence of a characteristic singlet signal at $\delta = 11.0$ ppm corresponding to NH proton and a doublet of doublet signals due to the vinylic protons and another singlet signals at $\delta = 8.11$ and 8.28 ppm attributable to diene protons. Elemental analyses together with spectral data are confirmed the suggested structure **19**. The formation of compounds **19** denotes that the reaction mechanism proceeds via an initial *Michael* addition of the exocyclic amino group in the compound **4** to the α,β-unsaturated moiety in the enaminone **11** yielded the corresponding acyclic non-isolable intermediates which undergo dehydrative cyclization and aromatization gave the final product **19** rather than the isomeric structure **18** (Scheme 7).

Compounds **4a–c** reacted with acetylacetone in refluxing *N,N*-dimethylformamide in the presence of a few drops of piperidene to yield the cycloadducts **21a–c** which established by elemental analyses and spectral data (Scheme 8). The IR spectrum of compound **21b** was exhibited the presence of absorption bands at ν_{max} 3474, 3279, 1720 and 1680 cm^{-1} assignable to NH_2, NH and CO groups. The ^1H NMR spectrum of compound **21b** confirmed the suggested structures which revealed the presence of a characteristic two singlet

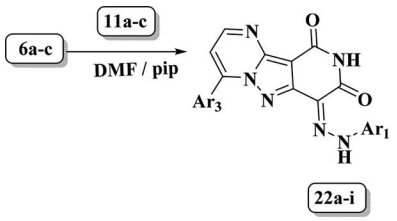


19a-i	Ar	Ar_3
a	Ph	Ph
b	4-$OMeC_6H_4$	Ph
c	4-ClC_6H_4	Ph
d	Ph	4-ClC_6H_4
e	4-$OMeC_6H_4$	4-ClC_6H_4
f	4-ClC_6H_4	4-ClC_6H_4
g	Ph	4-MeC_6H_4
h	4-$OMeC_6H_4$	4-MeC_6H_4
i	4-ClC_6H_4	4-MeC_6H_4

Scheme 7. Synthesis of pyrido[4′,3′:3,4]pyrazolo[1,5-*a*]pyrimidenes **19a–i**.



Scheme 8. Synthesis of 2-acetyl-3*H*-pyrazolo[4,5,1-ij][1,6]naphthyridine-3,5(4*H*)-diones **21a–c**.



22a-i	Ar_1	Ar_3
a	Ph	Ph
b	4-MeC_6H_4	Ph
c	4-ClC_6H_4	Ph
d	Ph	4-ClC_6H_4
e	4-MeC_6H_4	4-ClC_6H_4
f	4-ClC_6H_4	4-ClC_6H_4
g	Ph	4-MeC_6H_4
h	4-MeC_6H_4	4-MeC_6H_4
i	4-ClC_6H_4	4-MeC_6H_4

Scheme 9. Synthesis of the designed pyrido[4′,3′:3,4]pyrazolo[1,5-*a*]pyrimidines **22a–i**.

signals at δ = 1.85, 2.61 and 3.82 ppm corresponding to the two methyl and methoxy protons, respectively with another two singlet signals exchangeable with D_2O at δ = 6.80 and 10.71 assigned to NH_2 and NH, respectively. The elemental analyses together with spectral data are in agreement the suggested structure **21**. The formation of **21** from the reaction of **4** with acetylacetone is proceeds *via* a *Michael* addition reaction to give non-isolable intermediates, which in turn undergo dehydrative cyclization to give the non-isolable pyrazolo [4,5,1-ij][1,6]-naphthyridine-3,5(4*H*)-diones followed by spontaneous oxidation to afford **21**.

Additionally, the reaction of arylhydrazo derivatives **6a–c** with enaminones **11a–c** in refluxing *N,N*-dimethylformamide containing piperidene as catalyst yielded the cycloadducts **22a–i** (Scheme 9). The structure of the isolated products was determined from their elemental analyses and spectral data (Scheme 9 and exp.).

Conclusion

In conclusion, we have described an efficient synthesis of some novel pyrazolo[4,3-*c*]-pyridine-4,6-dione derives and their fused derivatives such as pyrazolo[4,5,1-ij][1,6] naphthyridine-3,5(4*H*)-dione derivatives *via* the reaction of readily accessible starting material, 3-aminopyrazolo[4,3-*c*]pyridine-4,6-dione with some chemical reagents.

Experimental

Melting points were determined on an Electrothermal Gallenkamp apparatus and are uncorrected. The IR spectra were recorded in KBr pellets using a Pye Unicam SP-1000 spectrophotometer. ^{1}H-NMR spectra (300 MHz) and ^{13}C-NMR spectra (75 MHz) were obtained on a Varian EM-300 MHz spectrometer using DMSO-d_6 as solvent with TMS as internal standard and the results are expected as δ value. Mass spectra were taken on a Shimadzu GCMS-QP 1000 Ex mass spectrometer at 70 eV. Elemental analyses were carried out by the Microanalytical Center of Cairo University, Giza, Egypt. Compounds **1** and **2** were prepared according to literature.[29,30]

Synthesis of 3-amino-1,7-dihydro-4H-pyrazolo[4,3-c]pyridine-4,6(5H)-dione (2)

A mixture of 3-cyanomethyl-4-cyano-5-aminopyrazole **1** (0.01 mol) and 5 ml of concentrated hydrochloric acid was refluxed for 15 minutes. The solid so formed was filtered off and washed with water and recrystallized from *N,N*-dimethylformamide to afford white crystals, yield 70%, m.p > 360 °C [Lit., > 360 °C],[30] ν_{max}/cm^{-1} (KBr) 3402 (NH_2), 3336 (NH), 3173 (NH), 1686 (CO); ^{1}H NMR (DMSO) δ = 3.68 (s, 2H, CH_2), 5.96 (s, 2H, NH_2), 10.38 (s, 1H, NH), 11.81 (s, 1H, NH); m/z 166 = (M^+, 40%), 143 (4.9%), 131 (7.0%), 123 (42.2%), 113 (28.3%), 101 (18.6%), 87 (22.8%), 73 (8.4%), 59 (100%); Anal. Calcd for $C_6H_6N_4O_2$: C, 43.38; H, 3.64; N, 33.72. Found: C, 43.52; H, 3.47; N, 33.49%.

General procedure of synthesis of compounds 4a–c

A solution of compound **2** (0.01 mol) in *N,N*-dimethylformamide (10 ml) containing a few drops of piperidine was added to the appropriate aldehyde **3a–c** (0.01 mol). The mixture was heated under reflux for 5 h. The solid product that precipitated by cooling was filtered off and recrystallized from *N,N*-dimethylformamide to give the respective products **4a–c**.

3-Amino-7-benzylidene-1,7-dihydro-4H-pyrazolo[4,3-c]pyridine-4, 6(5H)-dione (4a)

Yellow crystals, yield 66%, m.p. 240 °C, ν_{max}/cm^{-1} (KBr) 3402 (NH_2), 3200 (NH), 1692 (CO); ^1H NMR (DMSO) $\delta = 6.04$ (s, 2H, NH_2), 6.95–7.49 (m, 5H, Ar), 8.03 (s, 1H, CH), 10.43 (s, 1H, NH), 12.09 (s, 1H, NH); m/z 254 = (M^+, 100%), 238 (22.9%), 210 (22.9%), 166 (24.2%), 127 (29.3%), 91 (64.0%), 77 (48.1%), 66 (20.8%), 51 (16.0%); Anal. Calcd for $C_{13}H_{10}N_4O_2$: C, 61.41; H, 3.96; N, 22.04. Found: C, 61.59; H, 3.82; N, 22.31%.

General procedure of synthesis of compounds 6a–e

A solution of compound **2** (0.01 mol) and sodium acetate (0.01 mol) in *N,N*-dimethylformamide (10 ml) was cooled in an ice bath at (0–5 °C) while being stirred. To the resulting cold solution was added portionwise a cold solution of the appropriate diazonium salt **5a–e** prepared as usual by diazotizing the corresponding aromatic amine (0.01 mol) in concentrated hydrochloric acid (3 ml) with sodium nitrite (0.01 mol) in water (3 ml). After all the diazonium salt solution was added, the mixture was stirred for further one hour. while cooling in an ice-bath. The solid that precipitated was filtered off, washed with water, dried and finally crystallized from *N,N*-dimethylformamide to give products **6a–e**.

3-Amino-7-(2-(p-tolyl)hydrazono)-1,7-dihydro-4H-pyrazolo[4,3-c]pyridine-4,6 (5H)-dione (6b)

Orange crystals, yield 74%, m.p. 315 °C, ν_{max}/cm^{-1} (KBr) 3419 (NH_2), 3338, 3211, 3195 (3NH), 1691 (CO); ^1H NMR (DMSO) $\delta = 2.28$ (s, 3H, CH_3), 6.57 (s, 2H, NH_2), 7.18 (d, 2H, $J = 8.7$ Hz, CH), 7.22 (d, 2H, $J = 9$ Hz, CH), 10.63 (s, 1H, NH), 12.10 (s, 1H, NH), 12.58 (s, 1H, NH); m/z 284 = (M^+, 88.3%), 239 (9.0%), 213 (1.7%), 166 (5.6%), 135 (31.5%), 106 (92.0%), 91 (100%), 77 (69.6%), 65 (59.1%), 52 (42.6%); Anal. Calcd for $C_{13}H_{12}N_6O_2$: C, 54.93; H, 4.25; N, 29.56. Found: C, 54.81; H, 4.43; N, 29.79%.

General procedure of synthesis of compounds 9a–d

A mixture of compound **2** (0.01 mol) and α,β-unsaturated ketones **7a–d** (0.01 mol) in *N, N*-dimethylformamide (10 ml) containing a few drops of piperidine was heated under reflux for 6 hours and the reaction mixture was followed by TLC. The solid so formed was filtered off and recrystallized from *N,N*-dimethylformamide to give the respective products **9a–d**.

2-Amino-8-(benzo[d][1,3]dioxol-5-yl)-6-phenyl-3H-pyrazolo[4,5,1-ij][1,6] naphthyridine-3,5(4H)-dione (9d)

Brown crystals, yield 81%, m.p 285 °C, ν_{max}/cm^{-1} (KBr) 3413 (NH_2), 3117 (NH), 1681 (CO); ^1H NMR (DMSO) $\delta = 6.26$ (s, 2H, CH_2), 6.64 (s, 2H, NH_2), 7.18 (s, 1H, Ar), 7.27 (d, 2H, $J = 8.4$ Hz, Ar), 7.57–7.69 (m, 3H, Ar), 7.84–8.41 (m, 3H, Ar), 10.93 (s, 1H, NH). ^{13}C NMR (DMSO) $\delta = 89.32$, 101.75, 108.05, 110.10, 110.89, 117.75, 124.15, 128.97, 130.09, 130.77, 131.27, 131.61, 142.29, 145.04, 146.05, 147.64, 149.87, 160.27, 162.77; m/z 398 = (M^+, 2.8%), 386 (1.7%), 363 (0.4%), 343 (0.1%), 326 (0.1%), 317 (0.5%), 305 (1.4%), 281 (0.2%), 268 (0.8%), 247 (1.8%), 229 (0.9%), 213 (0.9%), 201

(1.6%), 189 (2.7%), 175 (2.0%), 159 (2.3%), 148 (4.4%), 131 (3.3%), 117 (17.0%), 105 (100%); Anal. Calcd for $C_{22}H_{14}N_4O_4$: C, 66.33; H, 3.54; N, 14.06. Found: C, 66.53; H, 3.65; N, 14.28%.

General procedure of synthesis of compounds 10a–p

A mixture of compounds **6a–d** (0.01 mol) and *α,β*-unsaturated ketones **7a–d** (0.01 mol) in *N,N*-dimethylformamide (10 ml) containing a few drops of piperidine was heated under reflux for 6 hours and the reaction mixture was followed by TLC. The solid so formed was filtered off and recrystallized from *N,N*-dimethylformamide to give the respective products **10a–p**.

7-(2-(4-Chlorophenyl)hydrazono)-2,4-diphenylpyrido[4′,3′:3,4]pyrazolo[1,5-a] pyrimidine-8,10(7h,9h)-dione (10c)

Brown crystals, yield 72%, m.p. 335 °C, ν_{max}/cm^{-1} (KBr) 3378 (NH), 3148 (NH), 1689 (CO); ^{1}H NMR (DMSO) $\delta = 7.18$ (d, 2H, $J = 8.4$ Hz, Ar), 7.41 (d, 2H, $J = 8.7$ Hz, Ar), 7.59–7.85 (m, 6H, Ar), 8.13 (s, 1H, CH), 8.27–8.45 (m, 4H, Ar), 11.13 (s, 1H, NH), 12.42 (s, 1H, NH); m/z 492 = (M^+, 30.2%), 494 ($M^+ + 2$, 11.7%), 452 (1.8%), 423 (1.3%), 396 (2.0%), 367 (3.6%), 346 (17.6%), 323 (24.6%), 304 (28.7%), 282 (17.0%), 231 (16.5%), 204 (21.5%), 165 (22.8%), 129 (55.3%), 111 (97.9%), 99 (48.5%), 77 (100%); Anal. Calcd for $C_{27}H_{17}ClN_6O_2$: C, 65.79; H, 3.48; Cl, 7.19; N, 17.05. Found: C, 65.62; H, 3.32; Cl, 7.41; N, 17.28%.

General procedure of synthesis of compounds 13a–e

A mixture of compound **2** (0.01 mol) and enaminones **11a–e** (0.01 mol) in *N,N*-dimethylformamide (20 ml) containing a few drops of piperidine was heated under reflux for 5 h. The solid so formed was filtered off and recrystallized from *N,N*-dimethylformamide.

2-Amino-6-(4-methoxyphenyl)-3h-pyrazolo[4,5,1-ij][1,6]naphthyridine-3,5(4H)-dione (13d)

Brown crystals, yield 70%, m.p 320 °C, ν_{max}/cm^{-1} (KBr) 3441 (NH_2), 3198 (NH), 1691 (CO); ^{1}H NMR (DMSO) $\delta = 3.85$ (s, 3H, OCH_3), 6.65 (s, 2H, NH_2), 7.09 (d, 2H, $J = 9$ Hz, Ar), 7.28 (d, 1H, $J = 7.8$ Hz, CH), 7.99 (d, 1H, $J = 7.8$ Hz, CH), 8.10 (d, 2H, $J = 8.7$ Hz, Ar), 10.86 (s, 1H, NH); ^{13}C NMR (DMSO) $\delta = 55.42$, 88.02, 113.02, 113.49, 113.90, 122.99, 128.27, 131.16, 142.68, 144.17, 158.05, 159.81, 161.17, 163.03; m/z 308 = (M^+, 100%), 289 (7.7%), 265 (4.6%), 237 (5.8%), 210 (9.2%), 194 (5.4%), 178 (2.0%), 166 (3.5%), 139 (4.8%), 117 (2.4%), 104 (3.6%), 89 (6.6%), 76 (10.0%), 63 (4.5%), 51 (2.1%); Anal. Calcd for $C_{16}H_{12}N_4O_3$: C, 62.33; H, 3.92; N, 18.17. Found: C, 62.47; H, 3.75; N, 18.43%.

General procedure of synthesis of compounds 14a–c

A mixture of compounds **13a,d** (0.01 mol) and acetic anhydride (5 ml) was refluxed for two hours. The solid so formed was filtered off and recrystallized from *N,N*-dimethylformamide.

N-(3,5-dioxo-6-phenyl-4,5-dihydro-3h-pyrazolo[4,5,1-ij][1,6]naphthyridin-2-yl) acetamide (14a)

Brown crystals, yield 60%, m.p 200 °C, ν_{max}/cm^{-1} (KBr) 3217 (NH), 3165 (NH), 1716 (CO), 1689 (CO); ^{1}H NMR (DMSO) δ = 2.20 (s, 3H, CH_3), 7.40–7.50 (m, 3H, Ar), 7.61-8.01 (m, 3H, Ar), 10.30 (s, 1H, NH), 13.60 (s, 1H, NH); m/z 320 = (M^+, 22.0%), 305 (8.1%), 278 (100%), 259 (10.2%), 235 (12.0%), 208 (32.2%), 193 (20.5%), 180 (17.6%), 178 (16.5%), 152 (15.4%), 122 (14.3%), 105 (58.7%), 102 (21.1), 77 (72.5%), 45 (20.1%), 40 (7.5%); Anal. Calcd for $C_{17}H_{12}N_4O_3$: C, 63.75; H, 3.78; N, 17.49. Found: C, 63.63; H, 3.62; N, 17.72%.

Synthesis of N,N-dimethyl-N′-(4-oxo-5-phenyl-2a,2a1,4,5-tetrahydro-3H-pyrazolo [4,5,1-ij]-[1,7]naphthyridin-2-yl)formimidamide (15)

A mixture of compound **13a** (0.01 mol) and dimethylformamide dimethylacetal (0.01 mol) in dry dioxane (20 ml) was heated under reflux for 5 hours. The solid so formed was filtered off and recrystallized from *N,N*-dimethylformamide to give brown crystals, yield 70%, m.p 350 °C, ν_{max}/cm^{-1} (KBr) 3194 (NH), 1695 (CO); ^{1}H NMR (DMSO) δ = 3.02 (s, 3H, CH_3), 3.12 (s, 3H, CH_3), 7.40 (d, 1H, J = 7.5 Hz, Ar), 7.59–7.62 (m, 3H, Ar), 8.07-8.12 (m, 3H, Ar), 9.12 (s, 1H, CH), 10.99 (s, 1H, NH); Anal. Calcd for $C_{18}H_{15}N_5O_2$: C, 64.86; H, 4.54; N, 21.01. Found: C, 64.69; H, 4.41; N, 21.23%.

Synthesis of N′-(3,5-dioxo-6-phenyl-4,5-dihydro-3H-pyrazolo[4,5,1-ij][1,6] naphthyridin-2-yl)-N-hydroxyformimidamide (17)

A mixture of compound **15** (0.01 mol), hydroxylamine hydrochloride (0.01 mol) and anhydrous sodium acetate (0.01 mol) in *N,N*-dimethylformamide (20 ml) was heated under reflux for 7 hours. The solid so formed was filtered off and recrystallized from *N,N*-dimethylformamide.

Brown crystals, yield 70%, m.p > 350 °C, ν_{max}/cm^{-1} (KBr) 3411 (OH), 3270 (NH), 1694 (CO); ^{1}H NMR (DMSO) δ = 7.53 (d, 1H, J = 7.5 Hz, Ar), 7.62-7.65 (m, 5H, Ar and CH), 8.09–8.22 (m, 4H, Ar and NH), 10.61 (s, 1H, NH), 11.24 (s, 1H, OH); Anal. Calcd for $C_{16}H_{11}N_5O_3$: C, 59.81; H, 3.45; N, 21.80. Found: C, 59.64; H, 3.26; N, 21.56%.

General procedure of synthesis of compounds 19a–i

A mixture of compounds **4a–c** (0.01 mol) and enaminones **11a–c** (0.01 mol) in *N,N*-dimethylformamide (20 ml) containing a few drops of piperidine was heated under reflux for 6 hours. The solid so formed was filtered off and recrystallized from *N,N*-dimethylformamide.

7-Benzylidene-4-phenylpyrido[4′,3′:3,4]pyrazolo[1,5-a]pyrimidine-8,10(7H,9H)-dione (19a)

Yellow crystals, yield 54%, m.p 281 °C, ν_{max}/cm^{-1} (KBr) 3189 (NH), 1693 (CO); ^{1}H NMR (DMSO) δ = 6.96-7.05 (m, 4H, Ar), 7.40–7.60 (m, 6H, Ar), 7.79 (s, 1H, CH), 8.03 (d, 1H, J = 7.5 Hz, CH), 8.18 (d, 1H, J = 8.4 Hz, CH), 11.21 (s, 1H, NH); Anal. Calcd for $C_{22}H_{14}N_4O_2$: C, 72.12; H, 3.85; N, 15.29. Found: C, 72.26; H, 3.74; N, 15.55%.

General procedure of synthesis of compounds 21a–c

A mixture of compounds **4a–c** (0.01 mol) and acetylacetone (0.01 mol) in *N,N*-dimethylformamide (20 ml) containing a few drops of piperidine was heated under reflux for 5 hours. The solid so formed was filtered off and recrystallized from *N,N*-dimethylformamide.

7-Acetyl-2-amino-8-methyl-6-phenyl-3h-pyrazolo[4,5,1-ij][1,6]naphthyridine-3,5 (4H)-dione (21a)

Yellow crystals, yield 61%, m.p. 334 °C, ν_{max}/cm^{-1} (KBr) 3417 (NH), 3284 (NH_2), 1722 (CO), 1689 (CO); ^1H NMR (DMSO) $\delta = 1.84$ (s, 3H, CH_3), 2.62 (s, 3H, CH_3), 6.86 (s, 2H, NH_2), 7.25-7.43 (m, 5H, Ar), 10.69 (s, 1H, NH); Anal. Calcd for $C_{18}H_{14}N_4O_3$: C, 64.67; H, 4.22; N, 16.76. Found: C, 64.59; H, 4.34; N, 16.51%.

General procedure of synthesis of compounds 22a–i

A mixture of arylhydrazo derivatives **6a–c** (0.01 mol) and enaminones **11a–c** (0.01 mol) in *N,N*-dimethylformamide (20 ml) containing a few drops of piperidine was heated under reflux for 6 hours. The solid so formed was filtered off and recrystallized from *N,N*-dimethylformamide

4-Phenyl-7-(2-phenylhydrazono)pyrido[4′,3':3,4]pyrazolo[1,5-a]pyrimidine-8,10 (7H,9H)-dione (22a)

Yellow crystals, yield 61%, m.p. 291 °C, ν_{max}/cm^{-1} (KBr) 3309 (NH), 1699 (CO); ^1H NMR (DMSO) $\delta = 6.87–6.97$ (m, 5H, Ar), 7.22-7.51 (m, 5H, Ar), 7.65 (d, 1H, $J = 8.1$ Hz, CH), 7.76 (d, 1H, $J = 8.4$ Hz, CH), 11.0 (s, 1H, NH), 12.20 (s, 1H, NH); Anal. Calcd for $C_{21}H_{14}N_6O_2$: C, 65.96; H, 3.69; N, 21.98. Found: C, 65.84; H, 3.50; N, 21.74%.

References

[1] Chu, I.; Lynch, B. M. Synthesis and Biological Evaluation of Xanthine Oxidase Inhibitors. Pyrazolo[3,4-*d*]Pyrimidines and Pyrazolo[3,4-*b*]Pyridines. *J. Med. Chem.* **1975**, *18*, 161–165. DOI: 10.1021/jm00236a010.

[2] Salvador, R. R. S.; Bello, M. L.; Barreto, I. R. L.; Vera, M. A. F.; Muti, E. M. F.; De-Albuquerque, S.; Dias, L. R. S. New Carbohydrazide Derivatives of 1*H*-Pyrazolo[3,4-*b*]-Pyridine and Trypanocidal Activity. *An. Acad. Bras. Cienc.* **2016**, *88*, 2341–2348.

[3] Owens, M. J.; Nemeroff, C. B. Corticotrepin-Releasing Factor Antagonists in Affective Disorder. *Exp. Opin. Invest. Drugs* **1999**, *8*, 1849–1856.

[4] Manetti, F.; Schenone, S.; Bondavalli, F.; Brullo, C.; Bruno, O.; Ranise, A.; Mosti, L.; Menozzi, G.; Fossa, P.; Trincavelli, M. L.; Synthesis and 3D QSAR of New Pyrazolo[3,4-*b*]Pyridines: Potent and Selective Inhibitors of A1 Adenosine Receptors. *J. Med. Chem.* **2005**, *48*, 7172–7185. DOI: 10.1021/jm050407k.

[5] Sharma, P. K.; Singh, K.; Kumar, S.; Kumar, P.; Dhawan, S. N.; Lal, S.; Ulbrich, H.; Dannhardt, G. Synthesis and Anti-Inflammatory Evaluation of Some Pyrazolo[3,4-*b*]Pyridines. *Med. Chem. Res.* **2010**, *19*, 107–114. DOI: 10.1007/s00044-010-9312-7.

[6] Carey, J. S.; Laffan, D.; Thompson, C.; Williams, M. T. Analysis of the Reactions used for the Preparation of Drug Candidate Molecules. *Org. Biomol. Chem.* **2006**, *4*, 2337. DOI: 10.1002/chin.200642267.

[7] Mohamed, A. E.; Hale, F. R.; Doha, M. B.; Ibrahim, Y. E. Microwave-Assisted Synthesis of Some New Pyrazolopyridines and Their Antioxidant, Antitumor and Antimicrobial Activities. *Eur. J. Med. Chem.* **2013**, *66*, 415–422. DOI: 10.1016/j.ejmech.2013.04.043.
[8] Farag, M. A. A. Synthesis and Antimicrobial Evaluation of some Novel Bis-α,β-Unsaturated Ketones, Nicotinonitrile, 1,2-Dihydropyridine-3-Carbonitrile, Fused Thieno[2,3-*b*]Pyridine and Pyrazolo[3,4-*b*]Pyridine Derivatives. *Int. J. Mol. Sci.* **2013**, *14*, 2967–2979. DOI: 10.3390/ijms14022967.
[9] Wenglowsky, S.; Rent, L.; Ahrendt, K. A.; Laird, E. R.; Aliagast, I.; Alicket, B.; Buckmelter, A. J.; Choo, E. F.; Dinkel, V.; Feng, B.; Pyrazolopyridine Inhibitors of β-Raf^{V600E}. Part 1: The Development of Selective, Orally Bioavailable, and Efficacious Inhibitor. *ACS Med. Chem. Lett.* **2011**, *2*, 342–347.
[10] Qin, J.; Zhou, W.; Huang, X.; Dhondi, P.; Palani, A.; Aslanian, R.; Zhu, Z.; Greenlee, W.; Cohen, M. W.; Jones, N.; Discovery of a Potent Pyrazolopyridine Series of γ-Secretase Modulators. *ACS Med. Chem. Lett.* **2011**, *2*, 471–476. DOI: 10.1021/ml2000438.
[11] Tucker, T. J.; Sisko, J. T.; Tynebor, R. M.; Williams, T. M.; Felock, P. J.; Flynn, J. A.; Lai, M. T.; Liang, Y.; McGaughey, G.; Liu, M.; Discovery of 3-{5-[(6-Amino-1*H*-Pyrazolo[3,4-*b*]Pyridine-3-yl)Methoxy]-2-Chlorophenoxy}-5-Chlorobenzo-nitrile (MK-4965): A Potent, Orally Bioavailable HIV-1 Non-Nucleoside Reverse Transcriptase Inhibitor with Improved Potency Against Key Mutant Viruses. *J. Med. Chem.* **2008**, *51*, 6503–6511. DOI: 10.1021/jm800856c.
[12] Ganesh, S.; Devi, P. B.; Radhika, N.; Yogeeswari, P.; Sriram, D. Development of 3-Phenyl-4,5,6,7-Tetrahydro-1*H*-Pyrazolo[4,3-*c*]Pyridine Derivatives as Novel Mycobacterium Tuberculosis Pantothenate Synthestase Inhibitors. *Eur. J. Med. Chem.* **2013**, *69*, 356–364.
[13] Zhang, L.; Zhang, B.; Zhao, J.; Zhi, Y.; Wang, L.; Lu*, T.; Chen, Y. Structure-Based Design, Synthesis, and Evaluation of 4,5,6,7- Tetrahydro-1H-Pyrazolo[4,3-c]Pyridine Derivatives as Novel cMet Inhibitors. *Eur. J. Med. Chem.* **2017**, *138*, 942–951.
[14] Ye, X. M.; Konradi, A. W.; Smith, J.; Xu, Y.-Z.; Dressen, D.; Garofalo, A. W.; Marugg, J.; Sham, H. L.; Troung, A. P. T.; Jagodzinski, J. et al. Discovery of a Novel Sulfonamide-Pyrazolopiperidine Series as Potent and Efficacious γ-Secretase Inhibitors. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2195–2199.
[15] Yogeeswari, P.; Sharma, M.; Samala, G.; Gangadhar, M.; Karthick, S.; Mallipeddi, S.; Semwal, A.; Sriram, D. Discovery of Novel Tetrahydro-Pyrazolo [4,3-c] Pyridines for the Treatment of Neuropathic Pain: Synthesis and Neuropharmacology. *Eur. J. Med. Chem.* **2013**, *66*, 211–220. DOI: 10.1016/j.ejmech.2013.05.022.
[16] Elgemeie, G. E. H.; Mansour O. A.; Metwally, N. H. Synthesis and Anti-HIV Activity of Different Noval Nonclassical Nucleosides. *Nucleosides Nucleotides* **1999**, *18*, 113–123. DOI: 10.1080/07328319908045598.
[17] Elgemeie, G. E. H.; Metwally, N. H. Synthesis of Structurally Related Purines: Benzimidazo[1,2-*a*]Pyridines, Benzimidazo-[1,2-*c*]Pyrimidines, and Pyrazolo[1,5-*a*]Pyrimidines. *Monatsh Chem.* **2000**, *131*, 779–785. DOI: 10.1007/s007060050025.
[18] Abdelrazek, F. M.; Metwally, N. H. Some Reactions with ω-Bromoacetophenone: A Novel Synthesis of Some Polysubstituted Pyridine, Pyrimidine, Pyrazolo[1,2-*a*]-Pyrimidine Derivatives. *Afinidad* **2003**, *60*, 554–557.
[19] Metwally, N. H.; Abdelrazek, F. M. Reaction of Anthranilo Nitrile with Some Active Methylene Reagents, Synthesis of Some New Quinoline & Quinazoline Derivatives. *Synth. Comm.* **2005**, *35*, 2481–2487. DOI: 10.1080/00397910500192068.
[20] Abdelrazek, F. M.; Metwally, N. H. Synthesis of Some New *N*-Substituted Pyrroles, Pyrrolo[1,2-*a*]Quinazoline, and diaza-as-in Dacene Derivatives. *Synth. Comm.* **2006**, *36*, 83–89. DOI: 10.1002/chin.200623031.
[21] Abdelrazek, F. M.; Metwally, N. H. Novel Synthesis of N-Arylpyrrole, Pyrrolo[1,2-*a*]-Quinazoline, and Pyrrolo[3,4-*d*]Pyridazine Derivatives. *Synth. Comm.* **2009**, *39*, 4088–4099.
[22] Metwally, N. H.; Abdallah, M. A.; Mosselhi, M. A.; El-Desoky, E. A. Synthesis and Antimicrobial Activity of Some New *N*-Glycosides of 2-Thioxo-4-Thiazolidinone Derivatives. *Carbohydrate Res.* **2010**, *345*, 1135–1141. DOI: 10.1016/j.carres.2010.04.011.

[23] Metwally, N. H. 3-Aryl-2-Sulfanyl Propenoic Acids as Precursors for Some Novel (Z)-5-Substituted-2-Trichloromethyl-4-Thiazlidinones. *Arkivoc* **2011**, *2011*, 254–265.
[24] Metwally, N. H. 2-Keto-3-Mercaptocinchroninic Acids as Precursors for Noval Thiazino[6,5-c] Quinoline-1,5-Dione Derivatives. *Synth. Comm.* **2013**, *43*, 398–405. DOI: 10.1080/00397911.2011.601838.
[25] Ragb, E. A.; Metwally, N. H.; Mohamed, M. S. Synthesis of Some Novel Pyrazolo[1,5-*a*]-Quinazolines and Their Fused Derivatives. *Synth. Comm.* **2017**, *47*, 148–158. DOI: 10.1080/00397911.2016.1257722.
[26] Qi, J.; Zhang, F.; Mi, Y.; Fu, Y.; Xu, W.; Zhang, D.; Wu, Y.; Du, X.; Jai, Q.; Wang, K.; Design, Synthesis and Biological Activity of Pyrazolo[1,5-a]Pyrimidine-7(4H)-Ones as Novel Kv7/KCNQ Potassium Channel Activators. *Eur. J. Med. Chem.* **2011**, *46*, 934–943.
[27] Almansa, C.; Fernando, A. F.; Cavalcanti, F. L.; Gomez, L. A.; Miralles, A.; Merlos, M.; Rafanell, J. G.; Forn, J. Synthesis and SAR of a New Series of COX-2-Selective Inhibitors: Pyrazolo[1,5-*a*] Pyrimidines. *J. Med. Chem.* **2001**, *44*, 350–361. DOI: 10.1021/jm0009383.
[28] Vrylskii, D. V.; Chuvashlev, A. S.; Arzamaslsev, A. P.; Slivkin, A. S. Synthesis of New Pyrazolo [1,5-*a*]Pyrimidines. *Pharm. Chem. J.* **2009**, *43*, 294–296. DOI: 10.1007/s11094-009-0301-4.
[29] Carboni, R. A.; Coffman, D. D.; Howard, E. G. Cyanocarbon Chemistry. XI.1 Malononitrile Dimer. *J. Amer. Chem. Soc.* **1958**, *80*, 2838–2840. DOI: 10.1021/ja01544a061.
[30] Sato, T. Reaction of Hydrazine Hydrate and Phenylhydrazine with Malononitrile. *J. Org. Chem.* **1959**, *24*, 963–966. DOI: 10.1021/jo01089a019.