Synthesis of Some Novel Pyrazolo[1,5-*a*]quinazolines and Their Fused Derivatives

Eman Ali Ragab[1], Nadia Hanafy Metwally[1], Mona Said Mohamed[1]

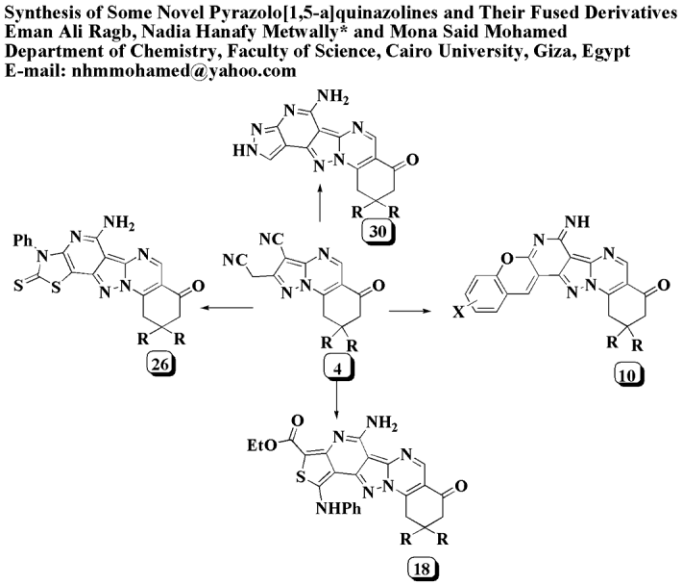
[1]Department of Chemistry, Faculty of Science, Cairo University, Giza, Egypt

Corresponding author Mona Said Mohamed E-mail: nhmmohamed@yahoo.com

Abstract

New pyrazolo[1,5-a]quinazoline-3-carbonitriles **4a,b** were obtained via cyclocondensation of 5-amino-3-cyanomethyl-1H-pyrazole-4-carbonitrile (**1**) with enaminones of 1,3-cyclohexanedione derivatives **2a,b** in refluxing glacial acetic acid. The condensation of compounds **4a,b** with various aromatic aldehydes furnished the corresponding arylidene derivatives **6a-j**. On the other hand, condensation of **4a,b** with o-hydroxybenzaldehydes yielded the polyheterocyclic compounds **10a-h**. Coupling of compounds **4a,b** with aryldiazonium chlorides led to formation of 2-arylhydrazono derivatives **12a-h**. Also, reaction of compounds **4a,b** with phenyl isothiocyanate, followed by addition of ethyl chloroacetate and chloroacetonitrile afforded the polyheterocyclic compounds **based on pyrazolo[1,5-a]quinazoline core.** The reaction of compounds **4a,b** with phenyl isothiocyanate and elemental sulfur gave the thiazole-2-thione derivatives **25a,b**. The reaction of enamines of compounds **4a,b** with each of hydrazine hydrate and guanidine hydrochloride afforded pyrazolo[4",3":5',6']pyrido[4',3':3,4]pyrazolo[1,5-a]quinazolin-8-ones **30a,b** and pyrimido[5",4":5',6']pyrido[4',3':3,4]pyrazolo[1,5-a]quinazolin-9(10H)-ones **33a,b**, respectively. The structure of all the newly synthesized compounds was elucidated by elemental analyses and spectral data. The plausible mechanisms have been postulated to account for their formation.

Graphical Abstract



KEYWORDS: 2-(Cyanomethyl)-6-oxo-pyrazolo[1,5-*a*]quinazolines; pyrazolo-[4",3":5',6']pyrido[4',3':3,4]pyrazolo[1,5-*a*]quinazolinones;pyrimido[5",4":5',6']-pyrido[4',3':3,4]pyrazolo[1,5-*a*]quinazolinones

INTRODUCTION

Pyrazolo[1,5-*a*]quinazoline derivatives have a broad spectrum of biological activity such as anticancer,[1–3] anti-inflammatory[4] and antimicrobial[5]. Also, they are effective as antisecretory agents[6] and as poly(ADP-ribose) polymerase-1(PARP-1) inhibitors[7]. Therefore, based on the previous reports and in continuation of our interest in the synthesis of new bioactive heterocyclic compounds,[8–17] we report herein the preparation of some new polyheterocyclic compounds containing pyrazolo[1,5-*a*]quinazoline moiety starting with the unreported hitherto 2-(cyanomethyl)-6-oxo-pyrazolo[1,5-*a*]quinazoline-3-carbonitriles **4a,b** as key intermediates for our objectives.

RESULTS AND DISCUSSION

Chemistry

The reaction of 5-amino-3-cyanomethyl-1*H*-pyrazole-4-carbonitrile (**1**) with enaminone of 1,3-cyclohexanedione derivatives **2a,b** in refluxing glacial acetic acid, afforded the colored products **4a,b** (Scheme 1). The structure of the isolated products was determined by their elemental analyses and spectral data (IR, ^{1}H NMR, ^{13}C NMR and MS). The IR spectrum of the isolated product **4b** showed absorption bands at ν_{max} 2227 and 1687 cm^{-1} corresponding to CN and CO groups, respectively. The ^{1}H NMR spectrum of compound **4b** revealed a singlet signal at δ = 4.47 ppm assigned to the methylene protons (C<u>H</u>$_2$CN) and a singlet signal at δ = 9.02 ppm attributable to the pyrimidine proton. Also, ^{13}C NMR spectrum of **4b** showed characteristic three signals at δ = 17.3, 154.5 and 194.3 ppm assigned for methylene (<u>C</u>H$_2$CN), pyrimidine and carbonyl (CO) carbons, respectively. Also, elemental analysis with mass spectrum of **4b** showed a correct molecular ion peak at m/z = 279 (M^+). Consistent with the formula $C_{15}H_{13}N_5O$. Thus, the reaction between aminopyrazole **1** and enaminone **2b** proceeded through an initial *Michael* addition of the exocyclic amino group in the aminopyrazole **1** to the *α,β*-unsaturated moiety in the enaminone **2b** yielded the corresponding acyclic non-isolable intermediates which undergo dehydrative cyclization and aromatization to give the final product **4b** rather than the isomeric structure **3b** (Scheme 1).

Condensation of compounds **4a,b** with various aromatic aldehydes **5a-e** in absolute ethanol in the presence of few drops of piperidine afforded the corresponding arylidene

derivatives of pyrazolo[1,5-*a*]quinazolines **6a-j** (Scheme 2). The IR spectrum of the isolated product **6b** taken as a typical example of the prepared series showed absorption bands at ν_{max} 2226 and 1688 cm^{-1} corresponding to CN and CO groups, respectively. The ^1H NMR spectrum of **6b** revealed the presence of a singlet signal at δ = 3.88 ppm assigned to the methoxy protons, in addition to a singlet signal at δ = 8.34 ppm attributable to vinylic proton and a singlet signal at δ = 9.11 ppm assigned for pyrimidine proton. Also, the elemental analyses are in agreement with the structure **6b** (Scheme 2).

On the other hand, refluxing compounds **4a,b** with *o*-hydroxybenzaldehydes **7a,b** in dry ethanol containing few drops of piperidine produced, in each case, yellowish orange solid of melting point above 300^oC (Scheme 3). The IR spectrum of compound **9a** showed absorption bands at ν_{max} 3372, 2228 and 1683 cm^{-1} corresponding to NH, CN and CO groups, respectively. The ^1H NMR spectrum of **9a** revealed the presence of a D_2O-exchangeable signal at δ = 9.13 ppm assigned to the NH proton. The elemental analyses are in agreement with the structures **9a-d** (Scheme 3). Refluxing the latter compounds in sodium ethoxide solution afforded products **10a-d**. The structure of the isolated products **10a-d** was inferred from correct analytical and spectral data. As typical example, the IR spectrum of **10a** showed disappearance of an absorption band corresponding to nitrile group near ν_{max} ~2200 cm^{-1} and instead revealed an absorption band at ν_{max} 3371 cm^{-1} due to the NH group. The^1H NMR spectrum of **10a** revealed a D_2O-exchangeable signal at δ = 9.17 ppm attributable to NH proton.

Subsequently, we extended our study in synthesizing new azodye derivatives. Thus, compounds **4a,b** were coupled with the diazotized aromatic amines **11a-d** in *N,N*-dimethylformamide (DMF) in the presence of anhydrous sodium acetate at 0-5^{o}C leading to yellow colored compounds **12a-h** (Scheme 4). The IR spectrum of the isolated compound **12a** which was taken as a typical example of the prepared series, showed absorption bands at ν_{max}3238, 2224 and 1687 cm^{-1} corresponding to the NH, CN and CO groups, respectively. The ^{1}H NMR spectrum of the isolated product **12a** revealed a singlet signal at δ = 8.99 ppm due to the pyrimidine proton, in addition, a *D_2O*-exchangeable signal appeared at δ = 12.12 ppm assigned to the NH proton, beside the other expected signals for aryl protons. ^{13}C NMR spectrum of **12a** showed characteristic signals at δ = 155.6 and 194.0 ppm assigned for pyrimidine and carbonyl carbons, respectively. The mass spectrum of **12a** showed correct molecular ion peak at m/z = 285 (M^{+}). However, our attempts to cyclize these hydrazone derivatives **12a-h to give iminopyridazino[4`,5`:3,4]pyrazolo[1,5-*a*]quinazoline** derivatives **13a-h** failed under all the different conditions reported for such cyclization[18,19] (Scheme 4).

The electronic absorption spectra of the products **12a-h** in DMF revealed, in each case, two absorption bands in the regions λ_{max} 413-390 and 314-303 nm. This absorption pattern seems to indicate that the studied compounds **12a-h** exist predominantly in solution as hydrazone form **A**. The reason is that such an absorption pattern is similar to that of typical hydrazones[20,21]. ^{1}H NMR spectra provide additional evidence that they have the hydrazone form **A** rather than the azo-forms **B**. For instance, the ^{1}H NMR spectra of compounds **12** in DMSO-d_6 exhibit, in each case, one singlet signal near 12.0 ppm

due to the =NNH-proton and this is substantiated by the literature data which indicate that the chemical shift (δ) of hydrazone NH resonance is usually observed near 13.0 ppm[22,23] (see Table 1).

The reaction of **4a,b** with phenyl isothiocyanate in *N,N*-dimethylformamide (DMF) in the presence of potassium hydroxide, followed by addition of ethyl chloroacetate **15** at room temperature, afforded in each case a single product (**17a** or **17b,** as evidenced by TLC) (Scheme 6). The IR spectrum of **17a** showed absorption bands at ν_{max} 3453, 3065, 2225, 1710 and 1691 cm^{-1} due to the NH_2, NH, CN and two CO groups, respectively. The ^1H NMR spectrum of compound **17a** revealed a triplet signal at δ = 1.12 ppm with *J* = 6.9 Hz assigned to the methyl (CH_3) protons and a quartet signal at δ = 4.13 ppm with *J* = 6.9 Hz assigned to methylene (CH_2) protons of ester group. In addition, two D_2O exchangeable signals at δ = 6.92 and 10.21 ppm attributable to NH_2 and NH protons, beside the other expected signals for pyrimidine and aromatic protons. Elemental analyses together with the spectral data are in agreement with structure **17**. Refluxing compounds **17a,b** in sodium ethoxide solution afforded compounds **18a,b** (Scheme 5). **The IR** spectrum of **18b** showed absorption bands at ν_{max} 3435, 3073, 1712 and 1693 cm^{-1} due to the NH_2, NH and two CO groups, respectively. The ^1H NMR spectrum of compound **18b** revealed signals at δ = 1.17 and 4.14 ppm with *J* = 6.9 ppm assigned to the methyl (CH_3) and methylene (CH_2) protons for ester group, respectively, in addition to, two D_2O exchangeable signals at δ = 6.89 and 10.12 ppm assigned to NH_2 and NH protons, beside the other expected signals. Also, elemental analyses are in agreement with structure **18b. T**he formation of compounds **18a,b** assumed to proceed through

formation of thiophene derivatives **17** ***via*** **non-isolable intermediate 16, followed by addition** of amino function to cyano group to generate thieno[3",4":5',6']pyrido[4',3':3,4]pyrazolo[1,5-*a*]quinazoline deri-vatives **18a,b** (Scheme 5).

In the same manner, the reaction of the non-isolable potassium salt of pyrazolo[1,5-*a*]quinazoline derivative **14** with chloroacetonitrile **19 in DMF** at room temperature, afforded a single product identified as thiophene derivatives **21a,b** *via* non-isolable intermediate *S*-alkyl derivative **20** (Scheme 6). Refluxing compounds **21a,b** in a solution of sodium ethoxide afforded products identified as thieno[3",4":5',6']pyrido[4',3':3,4]pyrazolo[1,5-*a*]quinazoline derivatives **22a,b** (Scheme 6).

The reaction of compounds **4a,b** with phenyl isothiocyanate and elemental sulfur in DMF in the presence of triethylamine as catalyst, gave isolated products **25a,b** (Scheme 7). The IR spectrum of product **25b** showed absorption bands at ν_{max} 3293, 2203 and 1682 cm^{-1} due to the NH_2, CN and CO groups, respectively. The ^1H NMR spectrum of compound **25b** revealed a multiplet signal at δ = 7.29-7.95 ppm assigned to the NH_2 and aromatic protons. Mass spectrum showed correct molecular ion peak at m/z 446 (M^+). Furthermore, elemental analyses are in agreement with the proposed structure **25b**. However, trials to cyclize the compounds **25a,b** into 5-amino-3-phenyl-2-thioxothiazolo[5",4":5',6']pyrido-[4',3':3,4]pyrazolo[1,5-*a*]quinazolin-8(9*H*)-one derivatives **26a,b** failed under reflux in a solution of sodium ethoxide (Scheme 7).

Enamines are interesting class of organic compounds; the special value of these compounds is due to their utility as valuable intermediate for the synthesis of several interesting compounds[24-29]. Based on this, we prepared the enamine derivatives of compounds **4a,b**. Thus, the reaction of compounds **4a,b** with dimethylformamide-dimethylacetal (DMF-DMA) in dry dioxane afforded the corresponding enamine derivatives **27a,b** (Scheme 8). The IR spectrum of the isolated product **27b** showed absorption bands at ν_{max} 2217, 2192 and 1692 cm^{-1} corresponding to the two CN and CO groups, respectively. The ^{1}H NMR spectrum of **27b** revealed the presence of two singlet signals at δ = 3.28 and 3.33 ppm, corresponding to the methyl protons [-$N(Me)_2$] and a singlet signal at δ = 7.89 ppm attributable to the olefinic proton. The ^{13}C NMR spectrum of the isolated product **27b** showed three characteristic signals at δ = 153.4, 156.6 and 194.2 ppm assigned to pyrimidine, olefinic [=C<u>H</u>$N(Me)_2$] and carbonyl carbons, respectively. Treatment of the enamine derivatives **27a,b** with hydrazine hydrate in **DMF** in the presence of few a drops of piperidine afforded brown solid products **30a,b** (Scheme 8). The IR spectrum of compound **30b** showed absorption bands at ν_{max} 3287, 3071 and 1692 cm^{-1} due to the NH_2, NH and CO groups, respectively. Its ^{1}H NMR spectrum revealed two D_2O exchangeable singlet signals at δ = 7.63 and 13.13 ppm attributable to the NH_2 and NH protons, beside the other expected signals assigned to aromatic and pyrimidine protons. Elemental analyses and mass spectra are in consistent with structure **30a,b** (see Exp.).

The reaction of enamines **27a,b** with guanidine hydrochloride in DMF in the presence of anhydrous sodium acetate furnished the fused pyrimidine derivatives **33a,b** (Scheme 9).

EXPERIMENTAL

Materials And Methods

Melting points were determined on an Electrothermal (9100) apparatus and are uncorrected. The IR spectra were recorded as KBr pellets on a Perkin Elmer 1430 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in deuterated dimethylsulfoxide at 300 and 75 MHz, respectively, on a Varian Gemini NMR spectrometer using tetramethylsilane as internal reference and the results are expected as δ value. Mass spectra were taken on a Shimadzu GCMS-QP 1000 Ex mass spectrometer at 70 eV. UV spectra and elemental analyses were carried out at the Microanalyses Center of Cairo University, Giza, Egypt.

Synthesis Of 2-(Cyanomethyl)-6-Oxo-6,7,8,9-Tetrahydropyrazolo[1,5-*A*]Quinazoline-3-Carbonitriles (4a,B).

A mixture of 5-amino-2-cyanomethyl-1*H*-pyrazole-4-carbonitrile **1** (0.01 mol) and 2-(dimethylaminomethylene)-1,3-cyclohexanedione derivatives **2a,b** (0.01 mol) in glacial acetic acid (10 ml) was heated under reflux for 6 h, then allowed to cool. The solid was collected by filtration and recrystallized from an ethanol-dioxane mixture to give compounds **4a,b.**

2-(Cyanomethyl)-6-Oxo-6,7,8,9-Tetrahydropyrazolo[1,5-*A*]Quinazoline-3-Carbonitrile (4a).

Brown crystals, yield 60%, m.p = 205°C, $\nu_{max\,/}$ cm^{-1} (KBr) 2225 (2CN), 1691 (CO); ^{1}H NMR (DMSO) δ = 2.24-2.28 (m, 2H, CH_2), 2.68 (t, 2H, *J* = 6.6 Hz, CH_2), 3.43 (t, 2H, *J* = 6 Hz, CH_2), 4.65 (s, 2H, CH_2), 9.09 (s, 1H, pyrimidine-H); ^{13}C NMR (DMSO) δ = 17.3, 19.7, 23.7, 36.6, 82.4, 111.8, 115.9, 116.8, 151.1, 151.4, 152.8, 156.4, 194.4; Anal. Calcd for $C_{13}H_9N_5O$: C, 62.15; H, 3.61; N, 27.87. Found: C, 62.32; H, 3.42; N, 27.62 %.

Synthesis Of Compounds 6a-J

General Procedure

A solution of the appropriate compound **4a,b** (0.01 mol) in ethanol (20 ml) containing a few drops of piperidine was added to the appropriate aldehyde **5a-e** (0.01 mol). The mixture was heated under reflux for 5 h and the reaction mixture was followed by TLC. The solid product that precipitated by cooling was filtered off and recrystallized from *N*,*N*-dimethylformamide to give the respective products **6a-j**. The physical constants and spectral data are shown below:

2-(1-Cyano-2-Phenylvinyl)-6-Oxo-6,7,8,9-Tetrahydropyrazolo[1,5-*A*]Quinazoline-3-Carbonitrile (6a).

Reddish brown crystals, yield 65%, m.p = 240°C, $\nu_{max\,/}$ cm^{-1} (KBr) 2225 (2CN), 1691 (CO); ^{1}H NMR (DMSO) δ = 2.22-2.26 (m, 2H, CH_2), 2.61 (t, 2H, *J* = 6.3 Hz, CH_2), 3.39 (t, 2H, *J* = 6 Hz, CH_2), 7.49-7.65 (m, 5H,Ar), 8.51 (s, 1H, CH), 9.09 (s, 1H, pyrimidine-

H); Anal. Calcd for $C_{20}H_{13}N_5O$: C, 70.79; H, 3.86; N, 20.64. Found: C, 70.59; H, 3.68; N, 20.92 %.

Synthesis Of Compounds 9a-D

General Procedure:

To a solution of each of **4a,b** (0.01 mol) was added the appropriate *o*-hydroxybenzaldehydes **7a,b** (0.01 mol) in absolute ethanol (20 ml) containing few drops of piperidine under reflux for 3 h. The solid product so formed was collected by filtration, washed with ethanol and recrystallized from an ethanol-dioxane mixture to give the respective products **9a-d**.

2-(2-Imino-2*H*-Chromen-3-Yl)-6-Oxo-6,7,8,9-Tetrahydropyrazolo[1,5-*A*]Quinazoline-3-Carbonitrile (9a).

Brownish yellow crystals, yield 94%, m.p >300^oC, ν_{max} /cm^{-1} (KBr) 3372 (NH), 2228 (CN), 1683 (CO); ^1H NMR (DMSO) δ = 2.23-2.26 (m, 2H, CH_2), 2.46 (t, 2H, *J* = 6.6 Hz, CH_2), 3.14 (t, 2H, *J* = 6 Hz, CH_2), 6.52-7.44 (m, 4H, Ar), 7.97 (s, 1H, CH), 8.96 (s, 1H, pyrimidine-H), 9.13 (s, 1H, NH); Anal. Calcd for $C_{20}H_{13}N_5O_2$: C, 67.60; H, 3.69; N, 19.71. Found: C, 67.43; H, 3.51; N, 19.45 %.

CONCLUSION

In conclusion, we have described an efficient synthesis of some novel pyrazolo[1,5-*a*]quinazolin-6-ones and their fused derivatives *via* the reaction of readily accessible starting material, 2-cyanomethylpyrazolo[1,5-*a*]quinazolinones with various aromatic

aldehydes furnished the corresponding arylidene derivatives. Also, formation of polyheterocyclic compounds based on pyrazolo[1,5-*a*]quinazoline core. Also, the reaction of enamines of 2-cyanomethylpyrazolo[1,5-*a*]quinazolinones with each of hydrazine hydrate and guanidine hydrochloride afforded pyrazolo[4",3":5',6']pyrido[4',3':3,4]pyrazolo[1,5-a]8-ones and pyrimido[5",4":5',6']-pyrido[4',3':3,4]pyrazolo[1,5-a]quinazolin-9(10*H*)-ones.

REFERENCES

1. Taliani**,** S.; Pugliesi, I.; Barresi, E.; Salerno, S.; Marchand, C.; Agama, K.; Simorini F.; Motta, C. L.; Marini, A. M.; Leva, F. S. D.; Marinelli, L.; Cosconati, S.; Novellino, E.; Pommier, Y.; SantoR. D.; Settimo, F. D. Phenylpyrazolo[1,5-*a*]-quinazolin-5(4*H*)-one: A suitable scaffold for the development of noncamptothecin topoisomerase I (Top1) inhibitors. *J. Med. Chem.* **2013**, 56, 7458-7462.

2. Chimichi, S.; Boccalini, M.; Selleri, S.; Costaqi, C.; Guerrini, G.; Viola, G. On the reactivity of 6-acetyl-7-(2-dimethylaminovinyl)pyrazolo[1,5-*a*]pyrimidines with 1,3- and 1,4-bisnucleophiles. *Org. Biomol. Chem.* **2008**, 6, 739-744.

3. Shekarrao, K.; Kaishap, P. P.; Saddanapu, V.; Addlagatta, A.; Gogoi, S.; Boruah, R. C. Microwave-assisted palladium mediated efficient synthesis of pyrazolo[3,4-*b*]pyridines, pyrazolo[3,4-*b*]quinolines, pyrazolo[1,5-*a*]pyrimidines and pyrazolo-[1,5-*a*]quinazolines. *R. S. C. Adv.* **2014**, 4, 24001-24006.

4. Hussein, M. A. Synthesis, anti-inflammatory, and structure antioxidant activity relationship of novel 4-quinazoline. *J. Med. Chem. Res.* **2013**, 22, 4641-4653.

5. Alexander, E. J. U. S., Patent, 4,5-Dihydro-5-oxopyrazolo[1,5-*a*]quinazoline-3-carboxylic acid derivatives. 4105766 (1978).

6. Nazeer, A.; Perveen, N.; Khan, M. A.; Munawar, M. A.; Lin, W. O. Synthesis and antibacterial activity of pyrazolo[1,5-*a*]quinazoline-3-carbonitriles. *Asian J. of Chem.* **2013**, 25, 7705-7709.

7. Niu, M.; Gu, Y. An in silico proyocol for identifying potential poly(ADP-ribose) polymerase-1 (PARP-1) inhibitors from chemical database. *New J. Chem.* **2015**, 39, 1060-1066.

8. Elgemeie, G. E. H.; Mansour O. A.; Metwally, N. H. Synthesis and anti-HIV activity of different noval nonclassical nucleosides. *Nucleosides and Nucleotides* **1999**, 18, 113-123.

9. 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.

10. 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. *A finidad* **2003**, 60, 554-557.

11. Metwally, N. H.; Abdelrazek, F. M. Reaction of anthranilo nitrile with some active methylene reagents, synthesis of some new quinoline and quinazoline derivatives. *Synth. Comm.* **2005**, 35, 2481-2487.

12. 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.

13. 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.

14. 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. *Carbohydr*. *Res.* **2010**, 345, 1135-1141.

15. Metwally, N. H. 3-Aryl-2-sulfanyl propenoic acids as precursors for some novel (Z)-5-substituted-2-trichloromethyl-4-thiazlidinones. A*rkivoc* **2011**, *x*, 254-265.

16. 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.

17. Metwally, N. H.; Abdallah, M. A.; Almabrook, S. A.Pyrazolo[1,5-*a*]pyrimidine derivatives as precursor for some novel pyrazolo[1,5-*a*]pyrimidines and tetraheterocyclic compounds. *J. Heterocycl. Chem.* **2016**, in press.

18. Hafez, T. S.; Osman, S.; Yosef, H. A. A.; Abdel-All, A.; Hassan, A.; El-Sawy, A. A.; Abdallah, M. M.; Youns, M. Synthesis, Structural elucidation, and in vitro antitumor activities of some pyrazolopyrimidines and Schiff bases derived from 5-amino-3-(arylamino)-1*H*-pyrazole-4-carboxamides. *Sci Pharm*. **2013**, 81, 339-357.

19. Krishnaiah, A.; Narsaiah, B. A facile method for the synthesis of novel fluorinated pyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidines. *J. Fluorine Chem.* **2001**, 109, 183-187.

20. Shawali, A. S.; Harb, N. M. S.; Badhdah, K. O. A study of tautomerism in diazonium coupling products of 4-hydroxycoumarin. *J. Heterocycl. Chem.***1985**, 22, 1397-1403.

21. Joneo, R.; Ryan, A. J.; Stemhell, S.; Wrifgt, S. E. The structures of some-5-pyrazolone and derived 4-arylazo-5-pyrazolones. T*etrahedron* **1963**, 19, 1497-1507.

22. G. E. Wright; *J. Heterocycl. Chem.*, **20**, 1037 (1989).

23. Shawali, S. A.;Albar, H. A.Kinetics and mechanism of dehydrochlorination of N-aryl-Cethoxycarbonylformohydrazidoyl chlorides. *Can. J. Chem.* **1986**, 64, 871-875.

24. Al-Zaydi, K. M.Microwave assisted synthesis, Part 1: Rapid solventless synthesis of 3-substituted coumarins and benzocoumarins by microwave irradiation of the corresponding enaminones. *Molecules* **2003**, 8, 541-555.

25. Al-Saleh, B.; El-Apasery, M. A.; Abdelaziz, R. S.; Elnagdi, M. H. Enaminones in heterocyclic synthesis: Synthesis and chemical reactivity of 3-anilino-1-substituted-2-propene-1- one. *J. Heterocycl. Chem.* **2005**, 42, 563-566.

26. Rossignol, E.;Youssef, A.; Moreau, P.; Prudhomme, M.; Anizon, F. Synthesis of aminopyrimidylindoles structurally related to meridianins. *Tetrahedron* **2007**, 63, 10169-10179.

27. Echalier, A.; Bettayeb, K.; Frandin, Y.; Lozach, O.; Clement, M.; Valette, A.; Liger, F.; Marquet, B.; Morris, J. C.; Endicott, J. A.; Joseph B.; Meijer, L. Meriolins (3-(pyrimidin-4-yl)-7-azaindoles): synthesis, kinase inhibitory activity, cellular effects, and structure of a CDK2/cyclin A/meriolin complex. *J. Med. Chem.* **2008**, 51, 737-751.

28. Vishwakama, J. N.; Dutta, M. C.; Chanda, K.; Das, B.; Laskar, M. A.; Nongkhlaw, R. L. Synthesis and antimicrobial activates of novel 5-isonicotinoyl-1,2,3,4-tetrahydropyrimidines and bis-(5-isonicotinoyl-1,2,3,4-tetrahydro- pyrimidine .*Arkivoc* **2009**, xii, 131-141.

29. Al-Mousaw, S. M.; El-Apasery, M. A.; Elnagdi, M. H. Enaminones in hetero-cyclic synthesis: a novel route to tetrahydropyrimidines, dihydropyridines, triacylbenzenes and naphthofurans under microwave irradiation. *Arkivoc*, **2010**, 15, 58-67.

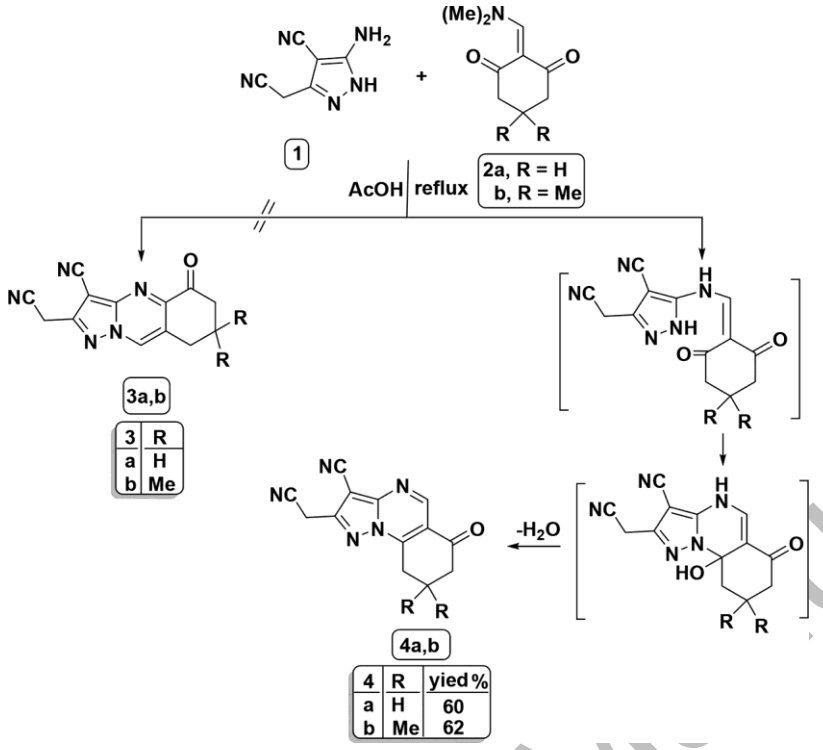
30. Carboni, R. A.; Coffman, D. D.; Howard, E. G. Cyanocarbon chemistry. XI.1 malononitrile dimer. *J. Am. Chem. Soc.* **1958**, 80, 2838-2840.

31. Claramunt, R.M..; Lopez, C.; Medina, C. P.; Pinilla, E.; Torres, M. R.; Elguero, J. Synthesis and structural study of tetrahydroindazolones. *Tetrahedron* **2006**, 62, 11704-11713.

Table 1. Electronic absorption spectral data of compounds 12a-h in *N*,*N*-dimethylformamide (DMF)

Compound No.	λ_{max}(nm) DMF	Compound No.	λ_{max}(nm) DMF
12a	390, 313	**12e**	394, 312
12b	392, 310	**12f**	400, 307
12c	413, 303	**12g**	400, 314
12d	398, 313	**12h**	395, 308

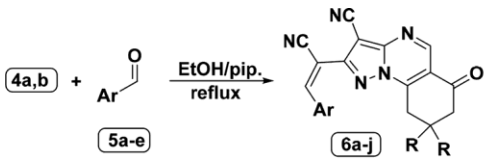
Scheme 1. Synthetic route to 2-cyanomethyl-6-oxo-pyrazolo[1.5-*a*]quinazolines **4a,b**



3	R
a	H
b	Me

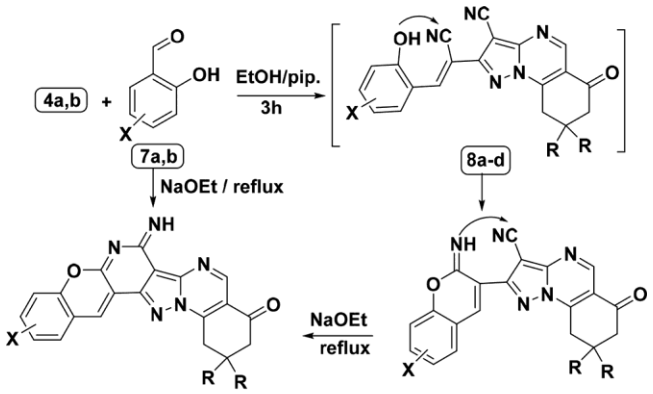
4	R	yied %
a	H	60
b	Me	62

Scheme 2. Synthetic route to 2-(1-cyano-2-arylvinyl)-6-oxo-pyrazolo[1,5-*a*]-quinazolines **6a-j**



6	R	Ar	yield %	6	R	Ar	yield %
a	H	Ph	65	f	Me	Ph	89
b	H	4-$OMeC_6H_4$	74	g	Me	4-$OMeC_6H_4$	91
c	H	4-ClC_6H_4	63	h	Me	4-ClC_6H_4	89
d	H	3,4(OCH_2O)C_6H_3	62	i	Me	3,4(OCH_2O)C_6H_3	92
e	H	2-furyl	79	j	Me	2-furyl	75

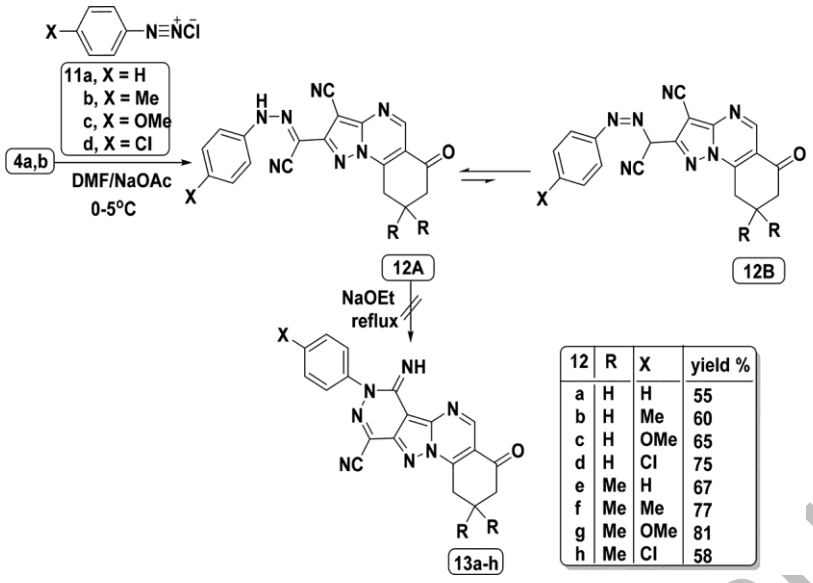
Scheme 3. Synthetic pathway to 2-(2-imino-2*H*-chromen-3-yl)-6-oxo-pyrazolo-[1,5-*a*]quinazolines **9a-d** and fused pyrazolo[1,5-*a*]quinazolines **10a-d**



10	R	X	yield %
a	H	H	89
b	H	4-OH	86
c	Me	H	65
d	Me	4-OH	61

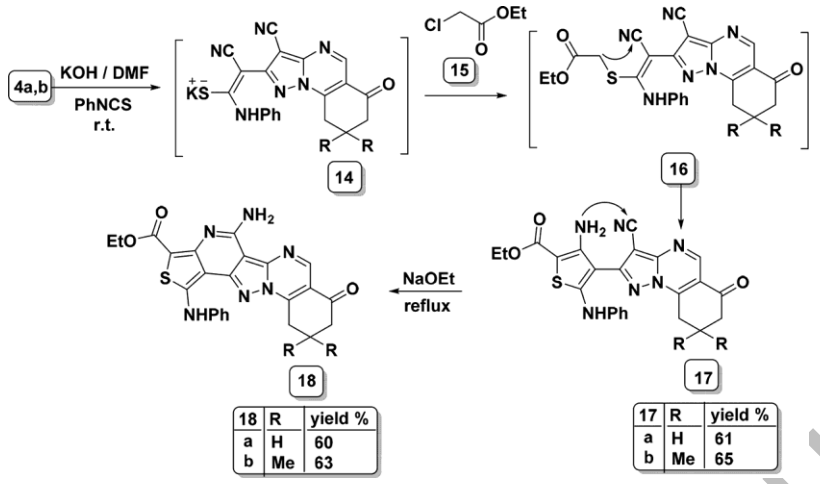
9	R	X	yield %
a	H	H	94
b	H	4-OH	90
c	Me	H	70
d	Me	4-OH	67

Scheme 4. Synthetic route to 2-arylhydrazono-6-oxo-pyrazolo[1,5-*a*]quinazolines **12a-h**



12	R	X	yield %
a	H	H	55
b	H	Me	60
c	H	OMe	65
d	H	Cl	75
e	Me	H	67
f	Me	Me	77
g	Me	OMe	81
h	Me	Cl	58

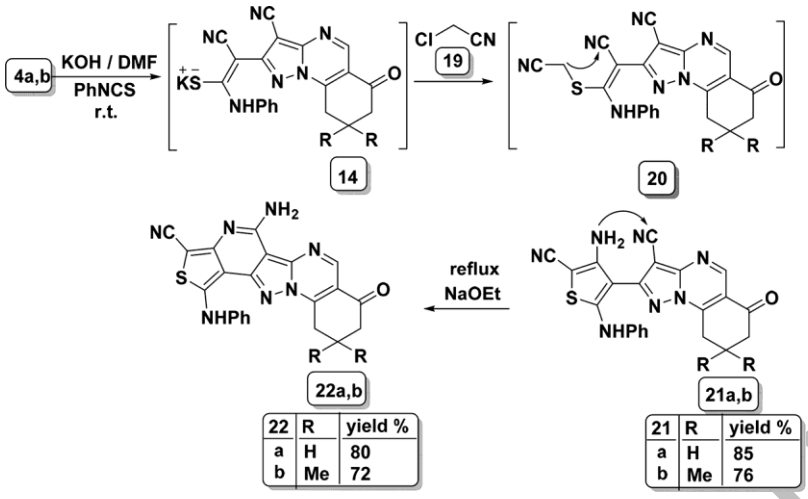
Scheme 5. Synthetic pathway to pyrazolo[1,5-*a*]quinazolines **17** and polyfused heterocyclic compounds **18**



18	R	yield %
a	H	60
b	Me	63

17	R	yield %
a	H	61
b	Me	65

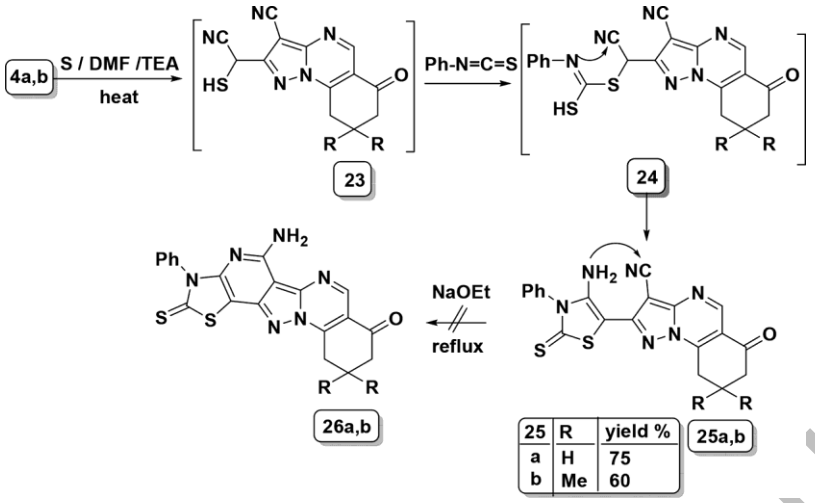
Scheme 6. Synthetic pathway to pyrazolo[1,5-*a*]quinazolines 2**1** and polyfused heterocyclic compounds **22**



22	R	yield %
a	H	80
b	Me	72

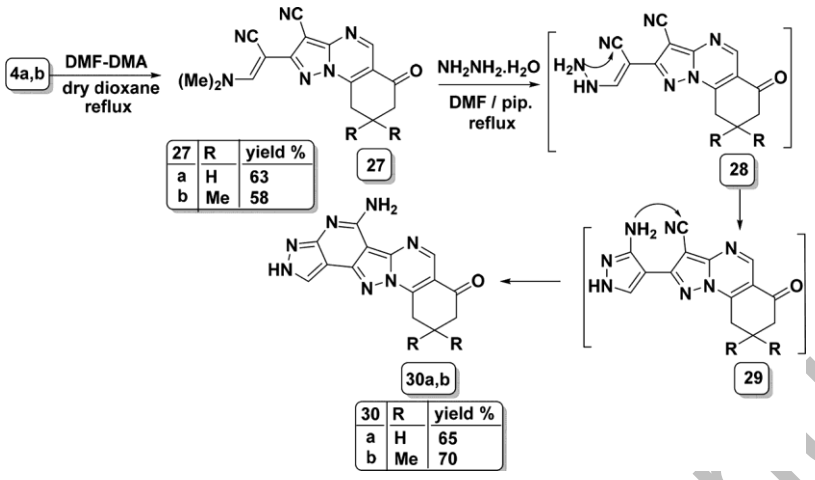
21	R	yield %
a	H	85
b	Me	76

Scheme 7. Synthetic pathway to 2-(4-amino-3-phenyl-2-thioxo-thiazol-5-yl)-6-oxo-pyrazolo[1,5-*a*]quinazoline-3-carbonitriles **25**



25	R	yield %
a	H	75
b	Me	60

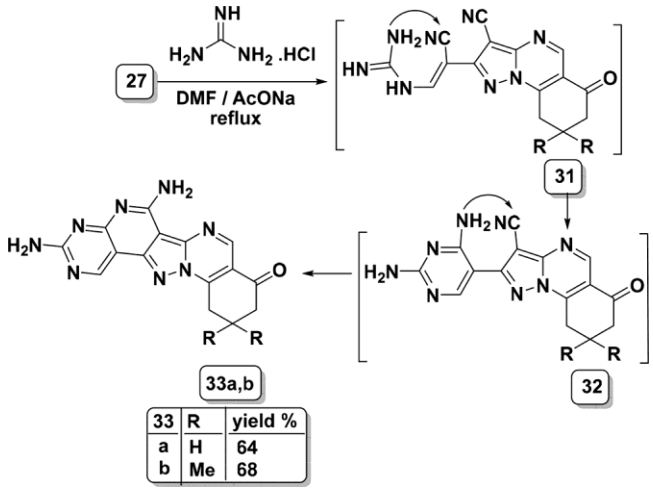
Scheme 8. Synthetic pathway to 2-[1-cyano-2-(dimethylamino)vinyl[-6-oxopyrazolo-[1,5-*a*]quinazolines **27a,b** and 5-amino pyrazolo[4",3":5',6']pyrido-[4',3':3,4]pyrazolo[1,5-*a*]quinazolin-8-ones **30a,b**



27	R	yield %
a	H	63
b	Me	58

30	R	yield %
a	H	65
b	Me	70

Scheme 9. Synthetic pathway to 3,6-diamino-11,12-dihydropyrimido[5",4":5',6']-pyrido4',3':3,4]pyrazolo[1,5-*a*]quinazolin-9(10*H*)-ones **33a,b**



33	R	yield %
a	H	64
b	Me	68