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Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

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

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To cite this article: Maher A. EL-Hashash & Safaa S. Shaban (2019): Synthesis and biological assessment of novel cyanopyridine derivatives, Synthetic Communications, DOI: 10.1080/00397911.2019.1616096

To link to this article: https://doi.org/10.1080/00397911.2019.1616096

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https://doi.org/10.1080/00397911.2019.1616096

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Synthesis and biological assessment of novel cyanopyridine derivatives

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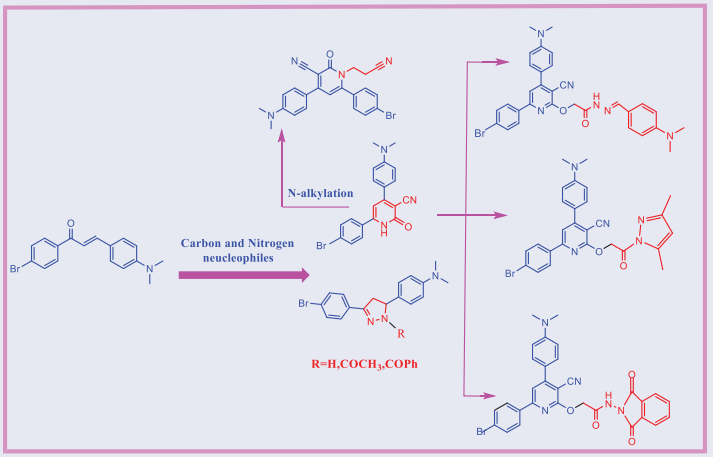
ABSTRACT

New pyridine derivatives bearing *p*-dimethyl amino phenyl and *p*-bromophenyl moieties at position-4 and 6 have been prepared. The behavior of pyridone derivative **2** toward ethyl chloroacetate followed by hydrazine hydrate gave pyridinyl acetohydrazide derivative **7**, and its behavior toward carbon electrophiles has been investigated by its reaction with aromatic aldehydes, ethyl acetoacetate, acetyl acetone, cyclohexanone, phthalic anhydride, maleic anhydride, and isatin affording the pyridine derivatives **8a–e** to **16**, respectively. Treatment of compound **2** with acrylonitrile in Et_3N, yielded the N- alkylated derivative **17**. Some pyrazole derivatives have been synthesized by interaction of the chalcone **1** with hydrazine hydrate afforded pyrazole derivative **18**. Treatment of compound **18** with benzoyl chloride and or acetic anhydride resulted in the formation of the acylated compounds **19** and **20**. Elemental and spectroscopic pieces of evidence characterized all the newly synthesized compounds. Some of the synthesized compounds were tested for their antibacterial activities against Gram-positive and Gram-negative bacteria.

GRAPHICAL ABSTRACT



ARTICLE HISTORY
Received 22 February 2019

KEYWORDS
Antibacterial activities; chalcone; pyrazole; pyridine

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Introduction

Pyridine nucleus is an essential component in natural products like Nudifluorine and Ricinine. Also, different Pyridine derivatives and fused pyridines have remarkable pharmaceutical importance because of their pronounced activities as antimicrobial,[1–3] antiviral agents,[4–8] anticancer,[9] anti-inflammatory agents,[10] antihelminthic,[11] psychotropic, nootropic or antiepileptic activity,[12–14] antimycotic,[15] vasodilating agents,[16] and as intermediate in the bacterial metabolism.[17] A survey of literature in the recent past reveals that some pyrazole derivatives have antimicrobial·[18] anti-cyclooxygenase,[19] anticonvulsing,[20] antitubercular,[21] antitumor,[22] anti-inflammatory,[23] analgesic,[24] antidiabetic,[25] and antifungal effects.[26] In the view of the aforementioned facts and our continuing efforts[27–29] directed toward the synthesis of new heterocyclic compounds with anticipated biological activities, we report in this study the synthesis of new pyridone and pyrazole derivatives for the sake of their biological activity.

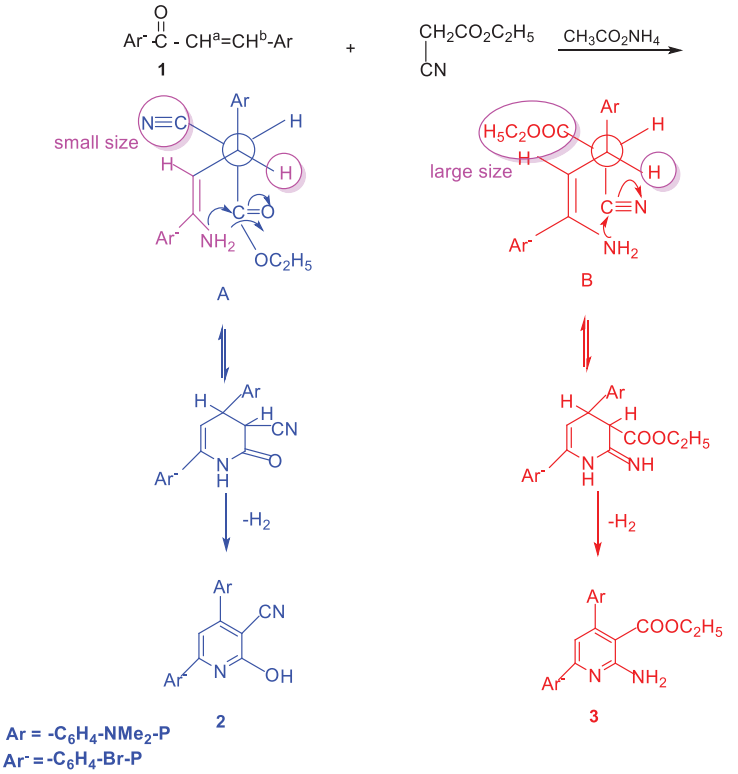
Result and discussion

The enone (1-(4-bromophenyl)-3-(4-(dimethyl amino) phenyl) prop-2-en-1-one (**1**)[30–34] was a starting material for the synthesis of 6-(4-bromophenyl)-4-(4-(dimethylamino) phenyl)-2-oxo-1, 2-dihydropyridine-3-carbonitrile (**2**)[35] through the reaction of enone **1** with ethyl cyanoacetate in the presence of ammonium acetate. The carbanion generated from ethyl cyanoacetate using ammonium acetate undergoes Michael addition to the β-position (CH_b-carbon) of the chalcone to yield the enol which undergoes nucleophilic displacement of –OH group by ammonia (generated from ammonium acetate) to yield the conformational intermediates A/B. In the Neumann projection A, the carboethoxy group lies in between hydrogen and nitrile groups. Both these groups being smaller in molecular size and structure brings the amino and carboethoxy functional groups in close vicinity leading to nucleophilic substitution to finally yield (**2**). On the contrary, in the projection B, the nitrile lies in between hydrogen and bulky carboethoxy groups, which makes the nucleophilic addition of amine with the nitrile group difficult due to steric hindrance thus not leading to the formation of (**5**) as depicted in Scheme 1.

The structure of compound **2** was elucidated from its spectral data, where its IR spectrum revealed bands at 3279, 2216, and 1657 cm^{-1} corresponding to NH, CN, and CO groups, respectively. While. The ^{1}H-NMR spectrum exhibited a singlet at δ 4.32 and 12.52 ppm, attributed to NH and OH proton, respectively. The aforementioned spectral data revealed the existence of lactam–lactim Tautomerism. When compound **2** was reacted with ethyl chloroacetate in anhydrous K_2CO_3/dry acetone,[36] it gave **4**. The structure of compound **4** was confirmed by IR spectrum which showed a strong absorption band at 1734 cm^{-1} (CO ester). The ^{1}H NMR spectrum showed signals at 4.13, 1.21, and 5.11 ppm as a quartet, triplet, and singlet, respectively, attributable to (OCH_2CH_3) and (OCH_2CO) protons.

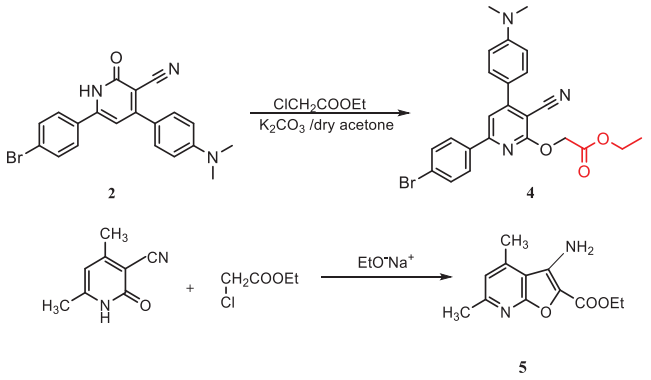
It was reported that[37] 4,6-dimethyl-2-oxo-1,2-dihydro pyridine-3-carbonitrile has been reacted with ethyl chloroacetate in the presence of sodium ethoxide and yielded the furopyridine derivative **5**.

In the present work when the pyridone derivative **2** was subjected to react with ethyl chloroacetate in the presence of sodium ethoxide it yielded the corresponding ester **4**



Scheme 1. Formation of compound 2.

and no ring closure takes place to yield the furo derivative **6.** Here, the lone pair of N,N′-dimethyl amino group of **4** is delocalized in the aromatic ring thus making the pyridyl group electron rich and the nitrile group less electrophilic. Thus, the carbanion generated in the presence of sodium ethoxide does not cyclize with the nitrile group of **4** to yield the furyl derivative **6**.

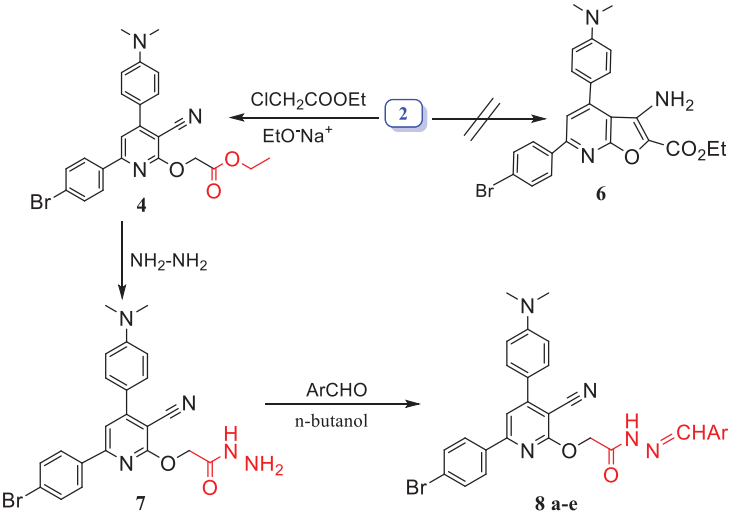


Moreover, compound **4** was treated with hydrazine hydrate in ethanol, which gave the pyridinyl acetohydrazide derivative **7**. The structure of compound **7** was elucidated from its elemental analyses and spectral data. The IR spectrum displayed the following

absorption bands 3325, 3309, and 1617 cm^{-1} corresponding to NH_2, NH, and CO groups, respectively. While ^{1}H-NMR exhibited three singlet signals at 9, 9.2, and 9.5 ppm attributed to NH_2 and NH protons, respectively.

The behavior of pyridinyl acetohydrazide derivative **7** towards carbon electrophiles has been investigated by its reaction with differently substituted benzaldehydes, ethyl acetoacetate, acetyl acetone, cyclohexanone, phthalic anhydride, maleic anhydride and isatin with a view to obtain some interesting new pyridine derivatives.

Interaction of acetohydrazide derivative **7** with aromatic aldehydes,[38] namely benzaldehyde, P-dimethylaminobenzaldehyde, *P*-nitrobenzaldehyde, *P*-methoxy benzaldehyde, and *P*-chloro-benzaldehyde, afforded the condensation products **8a–e**, respectively. The structures of compounds **8a–e** were confirmed by their spectral data. The ^{1}H NMR spectrum of compound **8b** (as an example) showed the presence of two singlet signals at 2.98 and 5.4 ppm, corresponding to 2 ($-N(CH_3)_2$) and $-OCH_2$ protons, respectively. In addition to the appearance of two singlet signals at 8.4 and 11.22 ppm attributed to N = C–H and NH protons, respectively. Also, its IR spectrum showed bands at 3421, 2216, 1656 cm^{-1} for NH, CN, and CO groups, respectively.



Reaction of ethyl acetoacetate with compound **7** in boiling butanol,[38] afforded mixture of the corresponding ethyl 3-(2-(2-(6-(4-bromophenyl)-3-cyano-4-(4-(dimethylamino) phenyl) pyridin-2- yloxy)acetyl) hydrazono)butanoate (**9**) and 6-(4-bromophenyl)-4-(4-(dimethylamino) phenyl)-2-(2-(3-methyl-5-oxo-4,5-dihydropyrazol-1-yl)-2-oxoethoxy) nicotinonitrile (**10**).[39,40] The IR spectrum of compound **9** displayed absorption bands at 3356, 1731 cm^{-1} attributed to NH, CO ester, respectively. While the ^{1}H-NMR spectrum exhibited the OCH2CH_3 protons as quartet and triplet at δ 4.15, 1.12, in addition to singlet signal at 10.79 ppm attributed to NH with D_2O exchangeable. Similarly, the ^{1}H-NMR spectrum of **10** was in agreement with the predicted structure as

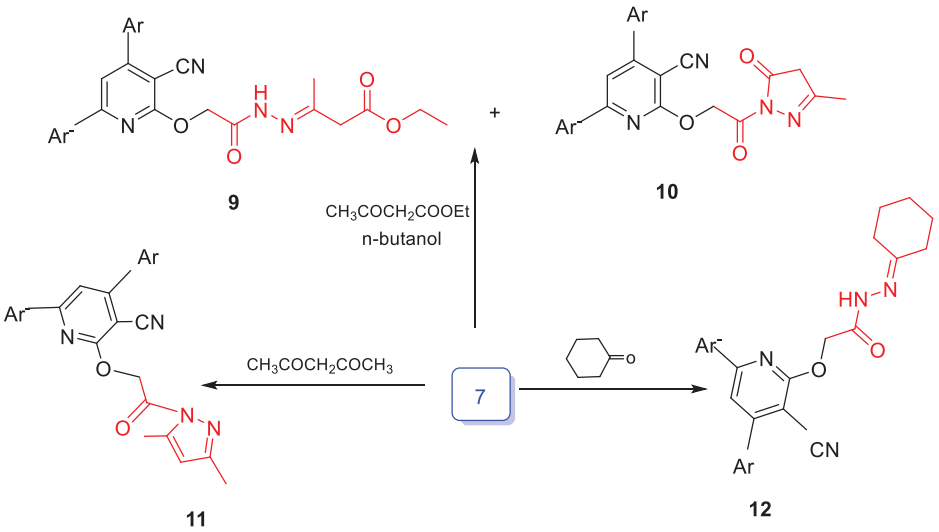
it showed singlet signals at 2.93 and 4.84 corresponding to CH_2 of pyrazolone ring and OCH_2CO protons. The IR spectrum showed the disappearance of NH_2 and NH bands.

Condensation of compound **7** with acetyl acetone,[38,41,42] gave the pyrazole derivative **11.** The IR spectrum of compound **11** displayed bands at 2218 and 1648 cm^{-1} corresponding to CN and CO groups, respectively. The ^{1}H-NMR spectrum of compound **11** showed the presence of three singlet signals at δ 2.35, 2.65, and 6.11 ppm, corresponding to pyrazole $-CH_3$ and CH, respectively. Also, signals of NH, NH_2 protons were not seen in the ^{1}H-NMR spectrum, proving that they were involved in the cyclization.

Moreover, when compound **7** reacted with cyclohexanone, it gave **12.**[36] The IR spectrum of compound **12** show no absorption bands for NH_2 but absorption bands appear at 3324 cm^{-1} for NH. ^{1}H-NMR showed signals at 1.58, 2.28, and 10.5 ppm attributed to cyclohexylidene protons ($3CH_2 + 2CH_2$–C=N–) and NH group, respectively. Scheme 2.

The reaction of phthalic anhydride with compound **7** afforded the pyridine derivatives **13**, **14** and the phthalazinone derivative **13a**-was not obtained. The IR spectrum of compound **13** displayed bands at 1740 and 1652 cm^{-1} corresponding to 2CO of imide and amide groups, respectively. While the ^{1}H-NMR spectrum showed singlet signals at δ 10.88 attributed to NH proton (D_2O exchangeable).

Similarly, Elemental analyses, IR, ^{1}H-NMR, and mass spectra supported the structure of compound **14**. IR spectrum of **14** revealed band at 1692 cm^{-1} and sub maxima between 2500–3300 cm^{-1} account for CO acid, OH, and NH groups, respectively. The ^{1}H-NMR showed signals at 9.98–10.17 and at 13.8 ppm, attributed to 2NH and acidic OH with D_2O exchangeable. Also, the structure of compound **14** was confirmed by mass-spectrum which showed the molecular ion peak corresponding to its molecular weight.



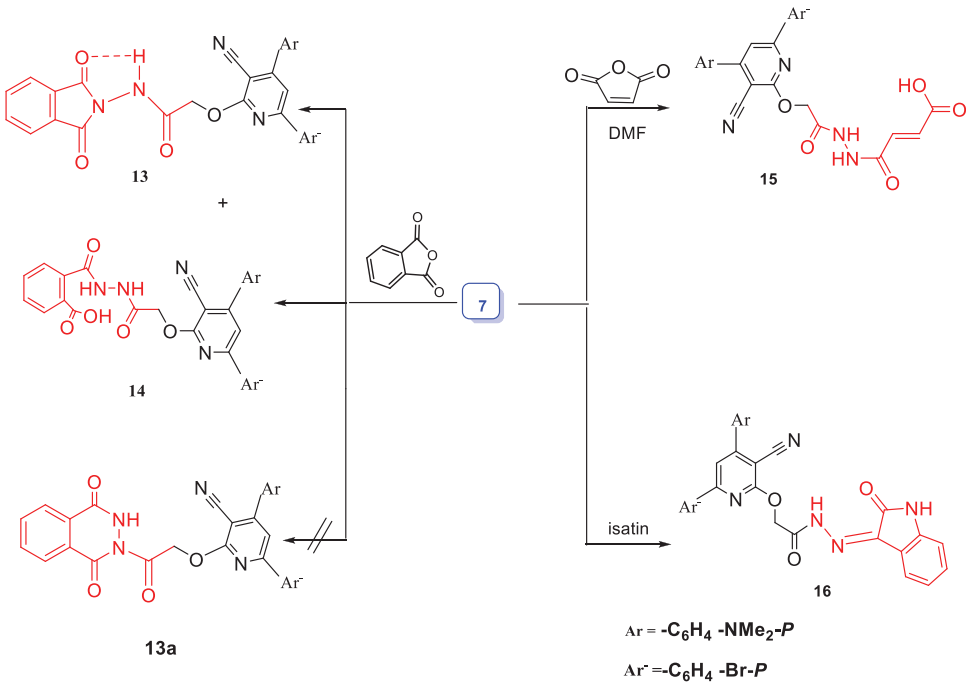
Scheme 2. Formation of compounds 9-12.

The overall ease of ring closure may be derived from two factors: a monotonous decrease in the ease of having the ends of the ring meet and a strain factor, which becomes more favorable to closure as the ring size increases from three- to six-membered. The ease of formation of six-membered ring is less than for a five-membered one because the slight improvement in the strain factor is outweighed by a deterioration in the distance factor.[43]

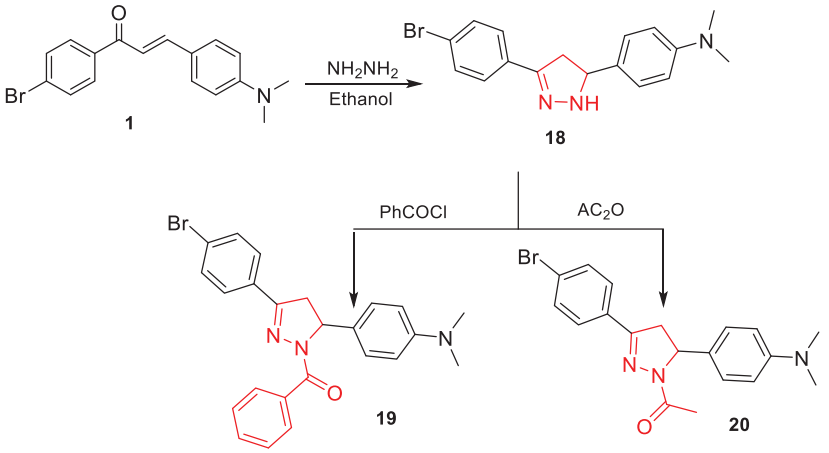
This compound (**13**) was isolated as a sole product because its formation is kinetically favored than the phthalazinone derivative (**13a**). Also, it is thermodynamically stable through intramolecular H-bonding.

On the other hand, when compound **7** reacted with maleic anhydride in DMF, gave **15** as the sole product. Scheme 3. Compound **15** gets support from its spectral data, where its IR spectrum displayed bands at 3409, 2927, and 1722 cm^{-1} attributed to chelated OH group or NH, (C–H) aliphatic, and CO acid. At the same time, the ^{1}H-NMR revealed peaks at 6.41, from 10.20–12.5, and at 15.98 ppm, attributed to olefinic protons, 2NH, OH, respectively.

Isatin derivatives are reported to show a wide variety of important biological activities like antibacterial,[44] antifungal,[45] antiviral,[46] and anti-inflammatory.[47] In view of these facts, novel isatin derivative **16** has been synthesized through the interaction of compound **7** with isatin in ethanol and drops of acetic acid[44,48] The structure of compound **16** was approved by its elemental and spectral data, where the IR spectrum exhibited bands at 3381, 1647 cm^{-1} corresponding to NH and C=N groups, respectively.



Scheme 3. Formation of compounds 13-16.



Scheme 4. Formation of componds 18-20.

The ^{1}H-NMR showed signals at 11.22, 12.52 ppm corresponding to 2NH protons exchangeable with D_2O.

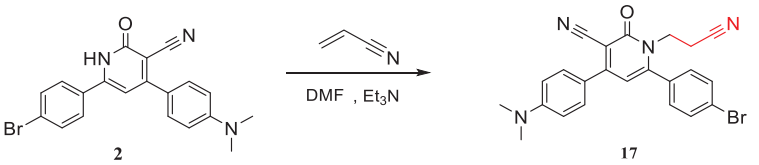
Usually, Compounds with activated double bond react with 2- pyridone derivatives and afford the N- alkylated derivatives. Thus the dihydropyridine **2** reacted with acrylonitrile in the presence of triethylamine,[38] giving the N-propionitrile derivative **17** as a Michael type product, the lone pair of N,N-dimethyl amino group of **2** is delocalized in the pyridyl ring making the pyridyl nitrogen more nucleophilic, thus facilitating the Michael addition of **2** with acrylonitrile to yield **17**. The IR spectrum of compound **17** revealed the existence of bands at 2248, 2213, and 1642 cm^{-1} corresponding to 2CN and CO groups, respectively. Also, the NH group is devoid of any absorption. Similarly, the^{1}H-NMR spectrum was devoid of any signal for NH group (cf. the Experimental section).

Chalcones possess high reactivity because of the presence of the carbonyl group conjugated with the double bond. Nucleophiles can react with chalcones at both the carbonyl group and the double bond. The author investigated the reaction of chalcone **1** with hydrazine hydrate (as binucleophile),[29] and suggested the formation of some novel pyrazole derivatives **18–20.** Scheme 4, evaluate their antibacterial activity. The reaction takes place through aza-Michael 1,4-addition followed by heterocyclization of the polarized system leading to the desired pyrazole derivative **18**. The polar factor of 4-(N,N)-dimethyl amino moiety has no significant role in the course of the reaction. It decreases the reactivity but not opposed the mode of addition. The structure of **18** was confirmed by IR spectrum which revealed bands at 3339 and 1607 cm^{-1} corresponding to NH and C=N groups, and ^{1}H-NMR showed signal at 10.22 ppm corresponding to NH proton, exchangeable with D_2O.

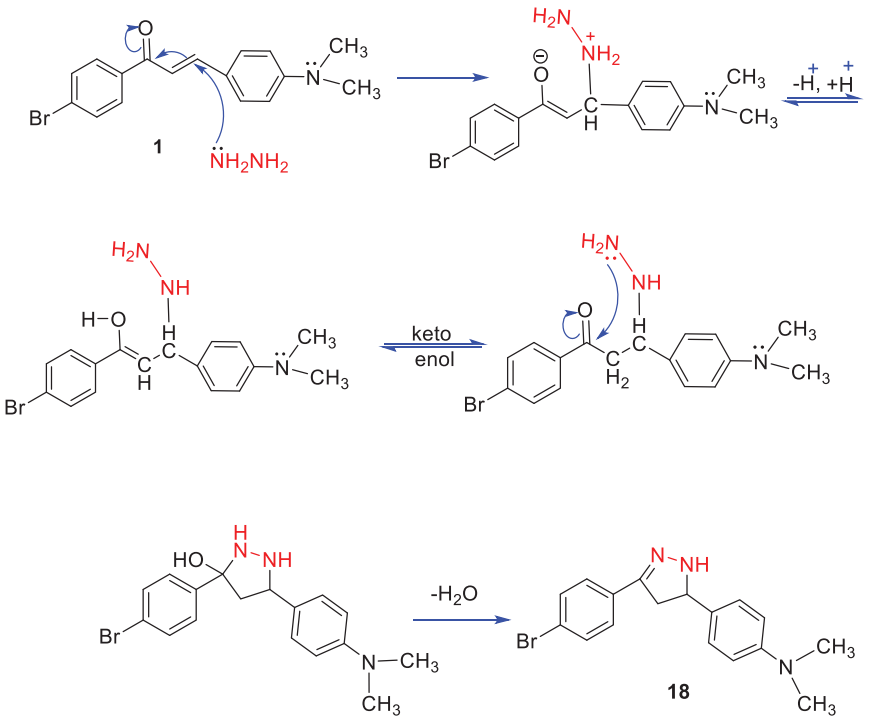
Furthermore, the reaction of Pyrazole derivative **18** with benzoyl chloride and/or acetic anhydride[49] resulted in the formation of the acylated compounds **19** and **20**.

The IR and the ^{1}H-NMR spectra of 1-benzoyl-pyrazole derivative **19** and 1-acetyl-pyrazole derivative **20** revealed the existence of bands at 1636, 1645 cm^{-1} corresponding

to 2CO groups, and devoid of any absorption for NH group. The ^{1}H-NMR spectrum of **20** revealed singlet signal at 2.52 ppm corresponding to $COCH_3$ protons.



The following mechanism was suggested for the formation of compound 18



Antibacterial activity

Antibacterial activity of some of the synthesized compounds has been evaluated.[50] The results are depicted in Table 1.

Conclusion

Our results as given in Table 1 showed that compounds **4**, **7** exhibited the highest activity against Gram-negative bacteria *Escherichia coli*. Compounds **2**, **8a**, **8b**, **8e**, **9**, **13**, **17** showed moderate activity. Meanwhile compounds **8d**, **11**, **18**, **19**, **20** demonstrated weak activity. Compounds **8c**, **12** were inactive against *Escherichia coli*.

Table 1. Response of various microorganisms to some selected synthesized compounds in *in vitro* culture.

		Escherichia Coli Gm(−) bacteria		*Staphylococcus aureus* Gm(+) bacteria	
No.	Compound	Diameter of inhibition zone (mm)	% Activity index	Diameter of inhibition zone (mm)	% Activity index
1	**2**	14	56.0	10	40.0
2	**4**	16	64.0	16	64.0
3	**7**	1.5	60.0	NA	0.00
4	**8a**	10	40.0	10	40.0
5	**8b**	10	40.0	14	56.0
6	**8c**	NA	0.00	10	40.0
7	**8d**	8	32.0	9	36.0
8	**8e**	13	52.0	11	44.0
9	**9**	11	44.0	13	52.0
10	**11**	8	32.0	12	48.0
11	**12**	NA	0.00	10	40.0
12	**13**	10	40.0	11	44.0
13	**17**	11	44.0	NA	0.00
14	**18**	8	32.0	20	80.0
15	**19**	5	20.0	15	60.0
16	**20**	7	28.0	21	84.0
Cefoxitin		25	100	25	100

NA: No activity.

Compounds **4**, **18**, **19**, **20** showed strong activity against Gram-positive bacteria (*Staphylococcus aureus*). Also, compound 20 has the maximum activity, while compounds **2**, **8a**, **8b**, **8c**, **8e**, **9**, **11**, **12**, **13** have moderate activity. compound **8d** showed weak activity. The remaining compounds **7**, **17** were inactive against *Staphylococcus aureus*.

Experimental

All melting points were uncorrected and recorded on a Gallen Kamp electric melting point apparatus (Shimadzu, Japan). The infrared spectra were recorded using potassium bromide disks on a PyeUnicamSP-3-300 infrared spectrophotometer (Thermo Scientific, Waltham, MA, USA), ^{1}H NMR spectra were run at 300 MHz, on a Varian Mercury VX-300 NMR spectrophotometer (Billerica, Massachusetts, USA) and Brukeravance III 400 MHz (Billerica, Massachusetts, USA) using TMS as an internal standard in deuterated dimethyl sulphoxide. Chemical shifts – are quoted in ppm. The mass spectra were recorded on Shimadzu GCMS-QP-1000EX mass spectrophotometer at 70 ev. All the spectral measurements were carried out at the NMR laboratory of Cairo University, Egypt, at the NMR laboratory of Faculty of Pharmacy, Ain Shams University, Egypt, the Microanalytical data were measured in Central Lab of Cairo University, Egypt, and the Ministry of Defence Chemical Laboratories, Egypt, and at the Micro Analytical Center of Ain Shams University, Egypt, All the chemical reactions were monitored by TLC on silica gel coated aluminum sheets (Silica Gel 60 F254, Merck).

Starting materials

The chemicals used in this study were commercially available.

Synthesis of 1-(4-bromophenyl)-3-(4-(dimethyl amino) phenyl) prop-2-en-1-one (1)

The mixture of (1.99 g, 0.01 mol) of 4-bromo acetophenone and (1.49 g, 0.01 mol) 4-dimethylamino benzaldehyde was dissolved in 30 mL ethanol and 10 mL of 5% KOH was added portion wise then stirred in an ice bath for 1 h. The separated solid was filtered, washed with water, dried, crystallized from ethanol, yellow crystals, yield 98%, mp 120–122 °C. IR (KBr, ν/cm^{-1}):1649, 1584 (C=O, C=C). ^{1}H NMR (DMSO-d$_6$), δ, ppm: 2.98 (s, 6H, –N(CH$_3$)$_2$), 6.77 (d, 2H, ortho-N(CH$_3$)$_2$), 7.56 (d, 1H, CH$_a$=), 7.8 (*d*, 2 H, ortho bromophenyl moiety), 7.5–8.02 (m, 4H, Ar–H), 8.12 (d, 1H, =CH$_b$). MS *m*/*z* (%): 330 [M] $^+$(16). Found, %: C 61.97, H 4.70, Br 24.08, N 3.98 for C$_{17}$H$_{16}$BrNO (330).Calculated,%: C 61.83, H 4.88, Br 24.20, N 4.24.

Synthesis of 6-(4-bromophenyl)-4-(4-(dimethylamino) phenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (2)

The mixture of compound **1** (3.3 g, 0.01 mol), ethyl cyanoacetate (0.01 mol), and ammonium acetate (0.08 mol) in ethanol (40 mL) was refluxed 3 h, an orange precipitate formed while hot was filtered off, dried, and recrystallized from glacial acetic acid, orange crystals, yield 68%, mp 310–312 °C. IR (KBr, ν/cm^{-1}): 3279, 2216, 1657 (NH, CN, C=O); ^{1}H NMR (DMSO-d$_6$), δ, ppm: 2.99 (s, 6H, –N(CH$_3$)$_2$), 4.32 (s, 1H, NH D$_2$O exchangeable), 6.68 (d, 2H, ortho-N(CH$_3$)$_2$), 7.8 (m, 5H, Ar–H + pyridine–H5), 8.12 (d, 2H, ortho bromophenyl moiety), 12.52 (s, 1H, OH, D$_2$O exchangeable). MS *m*/*z* (%): 394 [M] $^{\cdot+}$(2), 377 (4.2), 351 (100), 156 (13.09), 158 (11.07), 75 (50). Found, %: C 61.12, H 3.89, Br 20.21, N 10.79 for C$_{20}$H$_{16}$BrN$_3$O (394). Calculated, %: C 60.93, H 4.09, Br 20.27, N 10.66.

Synthesis of ethyl 2-(6-(4-bromophenyl)-3-cyano-4-(4-(dimethylamino) phenyl) pyridin-2-yloxy) acetate (4): Method A

The mixture of compound **2** (3.94 g, 0.01 mol), ethyl chloroacetate (4.4 g, 0.04 mol), and anhydrous potassium carbonate (5.5 g, 0.04 mol) in dry acetone (30 mL) was refluxed for 10 h. The excess solvent was evaporated, and the solid obtained was diluted with H$_2$O to remove excess K$_2$CO$_3$ then filtered off, dried, and recrystallized from ethanol, yellow crystals, yield 96%, mp 179–180 °C.

Synthesis of 2-((6-(4-bromophenyl)-3-cyano-4-(4-(dimethylamino) phenyl) pyridin-2-yl) oxy) acetohydrazide (7)

A solution of compound **4** (4.80 g, 0.01 mol) in EtOH (50 mL) and hydrazine hydrate (0.02 mol, 99%) was refluxed for 6 h. After cooling, the separated solid was collected and recrystallized from butanol, yellow powder, and yield 88%, mp 208–210° C. IR (KBr, ν/cm^{-1}): 3400–3309, 2216, 1617 (NH$_2$, NH, CN, C=O); ^{1}H NMR (DMSO-d$_6$), δ, ppm: 3.3 (s, 6H, (–N(CH$_3$)$_2$), 5.3 (s, 2H, –OCH$_2$–CO), 6.67 (d, 2H, ortho (–N(CH$_3$)$_2$), 7.65 (m, 5H, Ar–H + pyridine–H5), 8.23 (d, 2H, ortho bromophenyl moiety), 9–9.2 (2H, NH$_2$, D$_2$O exchangeable), 9.5 (1H, NH, D$_2$O exchangeable). MS *m*/*z* (%): 466 [M] $^{\cdot+}$(21.4), 468 [M + 2] $^{\cdot+}$(25.3), 378 (12.2), 316 (8.1), 279 (100), 91(10),77(7); Found,%: C

56.73, H 4.19, Br 17.02, N 15.00 for $C_{22}H_{20}BrN_5O_2$ (466). Calculated, %: C 56.66, H 4.32, Br 17.13, N 15.02.

Synthesis of hydrazone derivatives 8a–e

General method

A solution of the hydrazide compound **7** (4.66 g 0.01 mol) in butanol (40 mL) and (0.01 mol) of aromatic aldehydes namely, benzaldehyde, *P*-dimethylaminobenzaldehyde, *P*-nitrobenzaldehyde, *P*-methoxy benzaldehyde, and *P*-chlorobenzaldehyde, respectively was refluxed for 10 h. Then the excess solvent was evaporated under reduced pressure and the residue was recrystallized from the appropriate solvent to give compounds **8a–e.**

Acknowledgment

The authors would like to extend their sincere appreciation to, Ain Shams University, and Egypt Microanalysis Armed Force for their cooperation in this research.

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