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Synthesis and Characterization of Some Interesting Heterocyclic Compounds Derived from 1-(4-bromophenyl)-3-(4-(dimethyl amino) phenyl) prop-2-en-1-one

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Abstract

3- Cyano pyridone derivatives were synthesized by treating 1-(4-bromophenyl)-3-(4-(dimethyl amino) phenyl) prop-2-en-1-one with compounds containing active methylene group in the presence of ammonium acetate. The behavior of 3-cyanopyridone derivative toward ethyl chloroacetate followed by nitrogenous nucleophile as hydrazine hydrate was reported; also, the reactivity of the hydrazide toward carbon electrophiles (different aldehydes, ethyl acetoacetate, acetyl acetone, cylohexanone, phthalic anhydride, and maleic anhydride) was investigated with the aim of obtaining some interesting heterocyclic compounds. Also some pyrazole derivatives have been synthesized via the interaction of the chalcone with hydrazine hydrate. In addition the antimicrobial activity of some selected derivatives was reported.

***Keywords:** Chalcone; Cyanopyridone; Hydrazide; Hydrazone; Pyrazole*

Introduction

In our program for investigation of the reactivity of α, β-unsaturated carbonyl compounds [1-5], the author sought to investigate the behavior of the olefinic double bond activated by electron attracting and repelling groups towards base catalyzed addition of ethyl cyanoacetate as preparative method for substituted 2(1H)-pyridones [6], the polar factor of these groups in the benzal moiety does not increase the additive capacity of the double linking under such conditions. The main aim of our original work in this paper is to synthesize new pyridone derivatives for the sake of their biological evaluation [7].

Materials and Methods

Apparatus and chemicals

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All melting points were uncorrected and recorded on a Gallen Kamp electric melting point apparatus. The infrared spectra were recorded using potassium bromide disks on a PyeUnicamSP-3 -300 infrared spectophotometer, 1H NMR spectra were run at 300MHz,on a Varian Mercury VX-300 NMR spectrophotometer and BrukeravanceIII 400MHz,using TMSas an internal standard in deuterated dimethylsulphoxide. 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 Universty, Egypt, the Micro analytical data were measured in Central Lab of Cairo university, Egypt, and the Ministry of Defense 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). All common reagents and solvents were used as obtained from commercial suppliers without further purification.

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

Mixture of (1.99 g, 0.01 mol) of 4-bromo acetophenone , (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 1h . The separated solid was filtered, washed with water, dried, and crystallized from ethanol as yellow crystals. Yield: 98%, Melting point: 120-122°C. IR (KBr): showed absorption bands at frequency 1649 cm^{-1} for carbonyl group, and 1584 cm^{-1} (C=C). 1H NMR (DMSO-d6),the chemical shift δ (ppm): 2.98 (s, 6H, -N(CH_3)$_2$); 6.77 (d, 2H,ortho-N(CH_3)$_2$); 7.56 (d, 1H, CHa=C); 7.8 (d, 2H, ortho bromophenyl moiety); 7.5 -8.02 (m,4H,Ar-H); 8.12 (d,1H,=CHb). Ms, (m/z): 330 $[M]^+$ Anal. For: $C_{17}H_{16}BrNO$ (330). Calc: C, 61.83; H, 4.88; Br, 24.20; N, 4.24; Found: C, 61.97; H, 4.70; Br 24.08; N, 3.98.

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

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 3hrs., an orange precipitate was formed while hot was filtered off, dried and recrystallized from glacial acetic acid as orange crystals. Yield: 68%, Melting point: 310 -312°C; IR (KBr): 3279 cm^{-1} (NH), 2216 cm^{-1} (CN) and 1657 cm^{-1} (C=O). 1H NMR (DMSO-d6), the chemical shift δ (ppm): 2.99 (s ,6H , -N(CH_3)$_2$); 6.68 (d ,2H, ortho-N(CH_3)$_2$); 7.8 (m,5H, Ar-H^+ pyridine H_5); 8.12 (d, 2H, ortho bromophenyl moiety); 12.52 (s,1H,NH, D_2O exchangeable). Ms, (m/z): 394 $[M]^+$ Anal. For: $C_{20}H_{16}BrN_{3O}$ (394). Calc: C, 60.93; H, 4.09; Br, 20.27; N, 10.66. Found: C, 61.12; H, 3.89; Br, 20.21; N, 10.79.

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

Method A: 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 hrs. The excess solvent was evaporated, and the solid obtained was diluted with H_2O to remove excess K_2CO_3 then filtered off, dried, and recrystallized from ethanol as yellow crystals. Yield: 96%, Melting point: 179-180°C.

Method B: Mixture of compound 2 (3.94 g, 0.01mol) and ethyl chloro acetate (0.04 mol) in absolute ethanol (20 ml) containing sodium ethoxide (0.68 gm., 0.01mol) was refluxed for 6 hrs. The reaction mixture was left to cool to room temperature, and then poured onto ice cold water (50 ml) and neutralized with dilute hydrochloric acid; the separated material was filtered off and recrystallized from ethanol as yellow crystals. Yield: 89%, Melting point: 178-180°C. It was also, identified via melting point and mixed melting point determination. IR (KBr): show no absorption band for (NH), 2222 cm^{-1}

(CN) and 1734 cm^{-1} (C=O) of ester group. 1H NMR (DMSO-d6),the chemical shift δ: (ppm) 1.2 (t,3H,CH_3 ester) ; 3.2 (s ,6H, -N(CH3)$_2$); 4.13 (q, 2H, CH_2 ester); 5.11 (s, 2H,-OCH_2- CO); 6.86 (d,2H,ortho (-N(CH_3)$_2$); 7.72 (m, 5H ,Ar-H^+ pyridine H_5); 8.12 (d,2H ,ortho bromophenyl moiety). Ms, (m/z): 480 $[M]^+$; 482$[M+2]^+$. Anal. For: $C_{24}H_{22}BrN_3O_3$ (480). Calc: C, 60.01; H, 4.62; Br, 16.63; N, 8.75. Found: C, 60.29; H, 4.48; Br, 16.58; N, 8.8.

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 hrs. After cooling, the separated solid was collected and recrystallized from butanol, as yellow powder. Yield: 88% .Melting point 208-210°C. IR (KBr): 3400-3309 cm^{-1}. (NH_2, NH), 2216 cm^{-1} (CN) and 1617 cm^{-1} (C=O). 1H NMR (DMSO-d6),the chemical shift 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 H_5); 8.23 (d, 2H,ortho bromophenyl moiety); 9-9.2 (2H, NH_2 , D_2O exchangeable); 9.5 (1H, NH, D_2O exchangeable) .Ms,(m/z):466$[M]^{\cdot+}$. Anal. For: $C_{22}H_{20}BrN_5O_2$ 466). Calc: C,56.66; H,4.32; Br,17.13; N,15.02. Found: C,56.73; H,4.19; Br,17.02; N,15.00.

Synthesis of hydrazone derivatives 8 a-e

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

N'-benzylidene-2-(6-(4-bromophenyl)-3-cyano-4-(4-(dimethylamino) phenyl) pyridin-2-yloxy) acetohydrazide (8a)

Crystallized from methanol as yellow crystals. Yield: 66%, Melting point 168-170°C. IR (KBr): no absorption bands for (NH_2) but appear absorption bands at 3419 cm^{-1} for (NH) , at 2215 cm^{-1} (CN) and 1665 cm^{-1} (C=O). 1H NMR (DMSO-d6), the chemical shift δ (ppm): 3.08 (s, 6H , -N(CH_3)$_2$); 4.68 (s,2H,-OCH2- CO); 6.88 -8.22 (m,14H,Ar-H^+ pyridine-H_5); 8.46 (s,1H,N=C-H); 11.28 (1H , NH , D_2O exchangeable). Ms, (m/z): 554 $[M]^+$. Anal. For: $C_{29}H_{24}BrN_5O_2$ (554). Calc: C, 62.82;H,4.36;Br,14.41;N,12.63.Found: C,63.00;H,4.42;Br,14.32;N,12.76.

Synthesis of N'-(4-(dimethylamino) benzylidene)-2-(6-(4-bromophenyl)-3-cyano-4-(4- (dimethylamino) phenyl) pyridin-2-yloxy) acetohydrazide (8b)

Crystallized from ethanol as yellow crystals. Yield: 68%, Mp 181-182°C. IR (KBr): no absorption bands for (NH_2) but appear absorption bands at 3421 cm^{-1} for (NH), at 2216 cm^{-1} (CN), and 1656 cm^{-1} (C=O). 1H NMR (DMSO-d6), the chemical shift δ (ppm):2.98 (s, 12H, 2 (-N(CH_3)$_2$); 5.4 (s,2H,-OCH_2- CO); 6.8 (d,4H,ortho, 2(-N(CH_3)$_2$); 7.64 -7.81 (m,7H,6Ar-H^+ pyridine -H_5); 7.92 (d,2H,ortho bromophenyl moiety); 8.4 (s,1H,N=C-H); 11.22 (1H, NH, D_2O exchangeable). Ms, (m/z): 597 $[M]^+$. Anal. For: $C_{31}H_{29}BrN_6O_2$ (597). Calc, 62.31; H, 4.89; Br, 13.37; N, 14.07. Found: C, 62.61; H, 4.81; Br, 13.31; N, 14.0 0.

Synthesis of N'-(4-nitrobenzylidene)-2-(6-(4-bromophenyl)-3-cyano-4-(4-(dimethylamino) phenyl) pyridin-2-yloxy) acetohydrazide (8c)

Crystallized from ethanol as yellow crystals. Yield: 79%, Melting point: 281-283°C. IR (KBr): no absorption bands for (NH_2) but appear absorption bands at 3416 cm^{-1} for (NH); at 2211 cm^{-1} (CN), and 1647 cm^{-1} (CO). 1H NMR (DMSO-d6), the chemical shift δ (ppm): 3.04 (s ,6H, -N(CH_3)$_2$); 4.88 (s,2H,-OCH_2-CO); 6.96-8.32 (m,13H,Ar-H^+ pyridine-H_5); 8.7 (s,1H,N=C-H) ;11.04 (1H, NH, D_2O exchangeable). Ms, (m/z): 599 $[M]^+$. Anal. For: $C_{29}H_{23}BrN_6O_4$ (599). Calc: C, 58.11; H, 3.87; Br, 13.33; N, 14.02. Found: C, 58. 29; H, 3.98; Br, 13.25; N, 14.00.

Synthesis N'-(4-methoxybenzylidene)-2-(6-(4-bromophenyl)-3-cyano-4-(4-(dimethylamino) phenyl) pyridin-2-yloxy) acetohydrazide (8 d)

Crystallized from ethanol as brown crystals in yield: 67%. Melting point 189-191°. IR (KBr). No absorption bands for (NH_2) but appear absorption bands at 3394 cm^{-1} for (NH); at 2216 cm^{-1} (CN), and at 1656 cm^{-1} (CO). 1H NMR (DMSO-d6), the chemical shift δ (ppm): 3.12 (s,6H,-N(CH_3)$_2$);3.87 (s,3H,OCH_3) 4.78 (s,2H,-OCH_2-CO); 6.98 -8.32 (m,13H,Ar-H^+ pyridine-H_5); 8.48 (s,1H,N=C-H); 11.01 (1H, NH, D_2O exchangeable). Ms, (m/z): 584 $[M]^+$. Anal. For: $C_{30}H_{26}BrN_5O_3$ (584). Calc: C, 61.65; H, 4.48; Br, 13.67; N, 11.98. Found: C, 61.82; H, 4.35; Br, 13.55; N, 11.84.

N'-(4-chlorobenzylidene)-2-(6-(4-bromophenyl)-3-cyano-4-(4-(dimethylamino) phenyl) pyridin-2-yloxy) acetohydrazide (8 e)

Crystallized from ethanol as orange -yellow crystals. Yield: 78%. Melting point 169-171°C .IR (KBr): no absorption bands for (NH_2) but appear absorption bands at 3378 cm^{-1} for (NH) , at 2217 cm^{-1} (CN),and 1672 cm^{-1} (C=O) . 1H NMR (DMSO-d6), the chemical shift δ (ppm): 3.02 (s,6H,(-N(CH_3)$_2$);5.24 (s,2H,-OCH_2- CO); 6.86 -8.20 (m,13H,Ar-H^+ pyridine -H_5); 8.68 (s,1H,N=C-H);11.09 (1H, NH, D_2O exchangeable). Ms, (m/z): 588 $[M]^+$. Anal. For: $C_{29}H_{23}BrClN_5O_2$ (588). Calc: C, 59.15; H, 3.94; Br, 13.57; Cl, 6.02; N, 11.89; Found: C, 59.38; H, 3.73; Br, 13.26; Cl, 6.00; N, 11.67.

Reaction of (6-(4-bromophenyl)-3-cyano-4-(4-(dimethylamino) phenyl) pyridin-2-yloxy) acetohydrazide (7) with ethyl acetoacetate

Synthesis of 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): A mixture of 7 (4.66 g, 0.01 mol) and ethyl acetoacetate (0.02 mol) in butanol (50 ml) was refluxed for 8 hrs., and the solid that separated after concentration and cooling, was filtered off, dried, and fractionally crystallized from light petroleum (60-80) to give pale yellow crystal of ethyl 3-(2-(2-(6-(4-bromophenyl)-3-cyano-4-(4-(dimethylamino) phenyl) pyridin-2-yloxy)acetyl)hydrazono)butanoate (9).

Yield: 58 %, Mp 278-280 0C. IR (KBr): 3356 cm^{-1} (NH), 2219 cm^{-1} (CN), and 1731 cm^{-1} (C=O) ester. 1H NMR (DMSO-d6),the chemical shift δ (ppm): 1.12 (t,3H,OCH_2-CH_3 ester); 1.74 (s,3H,CH_3); 2.46 (s,2H,CH_2COO), 3.22 (s ,6H , -N(CH_3)$_2$); 4.15 (q,2H,OCH_2CH_3 ester); 5.02 (s,2H,-OCH_2-CO); 6.98-8.32 (m,9H, Ar-H^+ pyridine- H_5);10.79 (s,1H,NH,D_2O exchangeable). Ms, (m/z): 578 $[M]^+$. Anal. For: $C_{28}H_{28}BrN_5O_4$ (578). Calc: C, 58.14; H, 4.88; Br, 13.81; N, 12.11. Found: C, 58.33; H, 4.76; Br, 13.72; N, 12.00.

The insoluble part crystallized from benzene to give brown crystals of 6-(4-bromophenyl)-4-(4-(dimethylamino) phenyl)-2-(2-(3-methyl-5-oxo-4, 5-dihydropyrazol-1-yl)-2-oxoethoxy) nicotinonitrile (10) .Yield: 32%. Melting point >300°C. IR (KBr): 2221 cm^{-1} (CN) and 1640 cm^{-1} (C=O). 1 H-NMR ($CDCl_3$) δ: 1.58 (s, 3H, CH_3); 2.32 (s, 2H, pyrazolone); 3.02(s, 6H,-N

$(CH_3)_2$) 4.84 (s, 2H, OCH_2CO), 7.12–8.40 (m, 9H, 8Ar-H + pyridine - H_5). Ms, (m/z): 532 $[M]^+$. Anal. For: $C_{26}H_{22}BrN_5O_3$ (532). Calc: C, 58.66; H,4.17; Br,15.00; N,13.15.Found: C,58.72; H,4.29; Br,14.92; N, 13.08.

Synthesis of 6-(4-bromophenyl)-2-(2-(3, 5-dimethyl-1H-pyrazol-1-yl)-2-oxoethoxy)-4-(4-di-methylamino) phenyl) nicotinonitrile (11)

A mixture of 7 (4.66 g, 0.01 mol) and acetyl acetone (0.02 mol) in butanol (50 ml) was refluxed for 8 hrs. And the solid that separated after concentration and cooling, was filtered off, dried, and crystallized from ethanol as orange crystals. Yield: 79%. Melting point 192-193$^{\circ C}$. IR (KBr): 2218 cm^{-1} (CN) and 1648 cm^{-1} (C=O). 1H NMR ($CDCl_3$), δ (ppm): 2.35 (s ,3H , CH_3); 2.65 (s ,3H, CH_3), 2.98 (s,6H,-N $(CH_3)_2$); 5.05 (s,2H,-O CH_2CO); 6.11(s ,1H,pyrazole); 7.28-8.02 (m,9H, 8Ar-H^+ pyridine-H_5) .Ms, (m/z): 530 $[M]^+$. Anal.For: $C_{27}H_{24}BrN_5O_2$ (530). Calc: C, 61.14; H, 4.56; Br, 15.06; N, 13.20. Found: C, 60.98; H, 4.29; Br, 15.00; N, 13.22.

Synthesis of 2-(3-cyano-4-(4-(dimethylamino) phenyl)-6-p-bromophenylpyridin-2-yloxy)-N'-cyclohexylideneacetohydrazide (12)

A mixture of 7 (4.66 g, 0.01mol) and cylohexanone (0.01mol) in DMF (50 ml) was refluxed for 3 hrs. Then the reaction mixture was diluted with water and the solid obtained was recrystallized from methanol as yellow crystals. Yield: 88%. Melting point 229-230°C. IR (KBr): no absorption bands for (NH_2) but appear absorption bands at 3324 cm^{-1} for (NH) , 2923 cm^{-1} (CH) aliphatic, 2217cm^{-1} (CN) and 1644 cm^{-1} (C=O). 1H NMR (DMSO-d6),the chemical shift δ (ppm): 1.58(m 6H, 3 × CH_2-cyclohexylidene); 2.28 (t,4H, 2 × CH_2-C=N- cyclohexylidene); 3.22 (s, 6H , -N$(CH_3)_2$); 5.02 (s,2H,-OCH_2-CO); 6.9-8.32 (m,9H, Ar-H^+ pyridine-H_5);10.5 (s,1H,NH,D_2O exchangeable). Ms, (m/z): 546, $[M]^+$. Anal. For: $C_{28}H_{28}BrN_5O_2$ (546). Calc: C, 61.54; H, 5.16; Br, 14.62; N, 12.82. Found: C, 61.68; H, 5.30; Br; 14.54; N, 12.68.

Reaction of (6-(4-bromophenyl)-3-cyano-4-(4-(dimethylamino) phenyl) pyridin-2-yloxy) acetohydrazide (7) with phthalic anhydride

Synthesis of 2-(6-(4-bromophenyl)-3-cyano-4-(4-(dimethylamino)phenyl)pyridin-2-yloxy)-N-(1,3-dioxoisoindolin-2-yl)acetamide (13) and 2-(2-(2-(6-(4-bromophenyl)-3-cyano-4-(4-(dimethylamino)phenyl)pyridin-2-yl)oxy)acetyl)hydrazine-1-carbonyl)benzoic acid (14): A mixture of 7 (4.66 g, 0.01mol) and phthalic anhydride (0.01mol) in DMF (50 ml) was refluxed for 10 hrs. Then the reaction mixture was diluted with water, and the solid obtained was filtered off, dried, and fractionally crystallized from light petroleum (60-80) to give 2-(6-(4-bromophenyl)-3-cyano-4-(4-(dimethylamino)phenyl)pyridin-2-yloxy)-N-(1,3-dioxoisoindolin-2-yl)acetamide (13) as yellow crystals. Yield: 69 %. Melting point 236-238$^{\circ C}$. IR (KBr): 3363 cm^{-1} (NH); 2217 cm^{-1} (CN); 1740 cm^{-1} (C=O) imide, and 1652 cm^{-1} (C=O) amide. 1H NMR (DMSO-d6), the chemical shift δ (ppm): 3.06 (s,6H,-N$(CH_3)_2$); 4.89 (s,2H,-OCH_2-CO); 6.96 -8.21 (m,13H,Ar-H^+ pyridine-H_5);10.88 (1H, NH, D_2O exchangeable). Ms, (m/z): 596 $[M]^+$ Anal. For: $C_{30}H_{22}BrN_5O_4$ (596). Calc: C, 60.41; H, 3.72; Br, 13.40; N, 11.74. Found: C, 60.22; H, 3.84; Br; 13.28; N, 11.52.

The light-petrol-insoluble part, crystallized from benzene to give brown crystals of 2-(2- (2-(6-(4-bromophenyl)-3-cyano-4-(4-(dimethylamino) phenyl) pyridin-2-yl) oxy) acetyl) hydrazine-1-carbonyl) benzoic acid (14). Yield: 22 %. Melting point 279-280$^{\circ C}$. IR (KBr): show sub maxima between 2500-3300 cm^{-1} ν OH and ν NH , 2216 cm^{-1} (CN), 1692 cm^{-1} (C=O) of acid and 1633 cm^{-1} (C=O). 1H NMR (DMSO-d6), the chemical shift δ (ppm): 2.98 (s,6H,-N$(CH_3)_2$); 5.02(s,2H,-OCH_2- CO);

6.98-8.30 (m,13H,Ar-H^+ pyridine-H_5); 9.98 -10.17 (bs,2H,2NH,D_2O exchangeable). 13.8 (bs, 1H, OH, COOH, acidic, D_2O exchangeable).Ms, (m/z): 614 $[M]^+$. Anal. For: $C_{30}H_{24}BrN_5O_5$ (614). Calc: C, 58.64; H, 3.94; Br, 13.00; N, 11.40. Found: C, 58.38; H, 3.98; Br, 12.92; N, 11.28.

Synthesis of 4-(2-(2-(6-(4-bromophenyl)-3-cyano-4-(4-(dimethylamino) phenyl) pyridin-2-yl) oxy) acetyl) hydrazinyl)-4-oxobut-2-enoic acid (15)

A mixture of 7 (4.66 g, 0.01mol) and maleic anhydride (0.01mol) in DMF (50 ml) was refluxed for 6 hrs. Then the reaction mixture was diluted with water and the solid obtained was recrystallized from methanol as brown crystals. Yield: 92%. Melting point 290-292$^{\circ C}$, IR (KBr): 3409 cm^{-1} broad band attributed for chelated OH group, or (NH) , 2927cm^{-1} C-H aliphatic ,2218 cm^{-1} (CN) , 1722 cm^{-1} (C=O) of acid and 1637 cm^{-1} (C=O). 1H NMR (DMSO-d6), the chemical shift δ (ppm): 3.3 (s,6H,-N(CH_3)$_2$); 4.88 (s,2H,-OCH_2-CO); 6.4 -8.2 (m, 11H, 9 Ar-H^+ 2H olefinic protons); 10.2-12.5 (bs,2H, 2NH, D_2O exchangeable); 15.98 (bs, 1H, OH, COOH acid, D_2O exchangeable). Ms, (m/z): 564 $[M]^+$. Anal. For: $C_{26}H_{22}BrN_5O_5$ (564). Calc: C, 55.33; H, 3.93; Br, 14.16; N, 12.41. Found: C, 55.65; H, 3.98; Br, 13.98; N, 12.32.

Synthesis of 2-(6-(4-bromophenyl)-3-cyano-4-(4-(dimethylamino) phenyl) pyridin-2-yl) oxy)-N'-(2-oxoindolin-3-ylidene) acetohydrazide (16)

A mixture of 7 (4.66 g, 0.01mol) was condensed with isatin (0.01 mol) in ethyl alcohol (25 mL) in the presence of few drops of acetic acid reflux for 6h. The solvent was evaporated and the reaction mixture was poured into crushed ice. The separated solid was filtered off, dried and recrystallized from methanol to give 16 as Brown crystals. Yield: 42%. Melting point 235-237°C. IR (KBr): no absorption bands for (NH_2) but appear absorption bands at 3381 cm^{-1} for (NH); at 2211 cm^{-1} (CN), 1694 cm^{-1} (CO). and 1647 cm^{-1} (C=N) , 1H NMR (DMSO-d6),the chemical shift δ (ppm): 3.11 (s ,6H , (-N(CH_3)$_2$); 5.19 (s,2H,-OCH_2-CO); 6.68-8.34 (m,13H; 12Ar-H^+ pyridine H_5); 11.22 (s,1H), 12.52 (s,1H), D_2O exchangeable. Ms, (m/z): 595 $[M]^+$; 597 $[M+2]^+$. Anal. For: $C_{30}H_{23}BrN_6O_3$ (595). Calc C, 60.51; H, 3.89; Br, 13.42; N, 14.11.Found: C, 60.72; H, 3.92; Br, 13.28; N, 14.00.

Synthesis of 6-(4-bromophenyl)-1-(2-cyanoethyl)-4-(4-(dimethylamino) phenyl)-2-oxo-1, 2-dihydropyridine-3-carbonitrile- (17)

To a mixture of acrylonitrile (1.06 g, 0.02mol) and Et3N (0.01mol) in DMF (30 ml), (3.94 g, 0.01mol) of 2 was added. The reaction mixture was refluxed for 6 h and the obtained precipitate, after cooling, was filtered off, dried, and recrystallized from ethanol as yellow powder. Yield: 61%. Melting point 240-241°C. IR (KBr): show no absorption band for (NH), 3105 cm^{-1} (C-H) aromatic, 2855 cm^{-1} (C-H) aliphatic, 2248 cm^{-1}, 2213 cm^{-1} (2CN) and 1642 cm^{-1} (C=O). 1H NMR spectrum ($CDCl_3$), δ, ppm, (J, Hz): 2.95 (2H,t, J=6.7,CH_2-CH_2CN); 3.18 (s, 6H, -N(CH_3)$_2$); 4.21 (2H,t,J=6.7,CH_2-CH_2-CN); 6.74 (d ,2H,ortho (-N(CH_3)$_2$); 7.78 (m,5H, Ar-H^+ pyridine H_5); 8.18 (d,2H ,ortho bromophenyl moiety). Ms (m/z): 447 $[M]^+$. Anal.For: $C_{23}H_{19}BrN_4O$ (447). Calc: C, 61.75; H, 4.28; Br, 17.86; N, 12.52. Found: C, 61.98; H, 4.16; Br, 17.68; N, 12.39.

Synthesis of 4-(3-(4-bromophenyl)-4 5-dihydro-1H-pyrazol-5-yl)-N, N-dimethylbenzenamine (18)

A solution of compound 1 (3.3 g, 0.01 mol) in ethanol (40 ml) and hydrazine hydrate (0.02 mol, 99%) was refluxed for 3 hrs. After cooling, the separated solid was collected and recrystallized from ethanol as white crystals. Yield: 88 %. Melting point 140-142°C. IR (KBr): 3339 cm^{-1} (NH), and 1607 cm^{-1} (C=N). 1H NMR (DMSO-d6),the chemical shift δ (ppm): 3.28 (s, 6H ,

-N(CH_3)$_2$); 3.71-3.96 (dd,2H,CH_2 pyrazole); 3.98 (2dd ,1H ,CH pyrazole); 6.92-7.78 (m,8H, Ar-H); 10.22 (s,1H,NH,D_2O exchangeable) . Ms, (m/z): 344 $[M]^+$. Anal. For: C17H18BrN3 (344).Calc. C, 59.31; H, 5.27; Br, 23.21; N, 12.21.Found: C, 59.11; H, 5.35; Br, 23.14; N, 12.08.

Synthesis of 4-(3-(4-bromophenyl)-4, 5-dihydro-1-benzoyl-pyrazol-5-yl)-N, N-dimethylbenzenamine (19)

To a solution of compound 18 (3.44g, 0.01 mol) in 20 ml pyridine, (0.01 mol) of benzoyl chloride was added. The mixture was refluxed 6 hrs. The reaction mixture was allowed to cool and poured in crushed ice, then acidified with HCl, the separated solid was filtered, washed with water, dried, and crystallized from ethanol as buff powder .Yield:80%. Melting point 158-160$^{\circ C}$. IR (KBr): showed no absorption band for (NH), and show absorption bands for carbonyl group at 1636 cm^{-1} and 1616 cm^{-1} (C=N).1H NMR (DMSO-d6),the chemical shift δ (ppm): 3.08 (s ,6H , -N(CH_3)$_2$); 3.68 – 3.89 (dd,2H,CH_2 pyrazole); 5.02 (2dd,1H ,CH pyrazole); 6.78 (d ,2H,ortho (-N(CH_3)$_2$); 7.12- 8.02 (m,9H, Ar-H); 7.68 (d,2H, ortho bromophenyl moiety). Ms, (m/z): 448 $[M]^+$ Anal. For: $C_{24}H_{22}BrN_3O$ (448).Calc. C, 64.29; H, 4.95; Br, 17.82; N, 9.37. Found: C, 64.66; H, 4.73; Br, 17.78; N, 9.28.

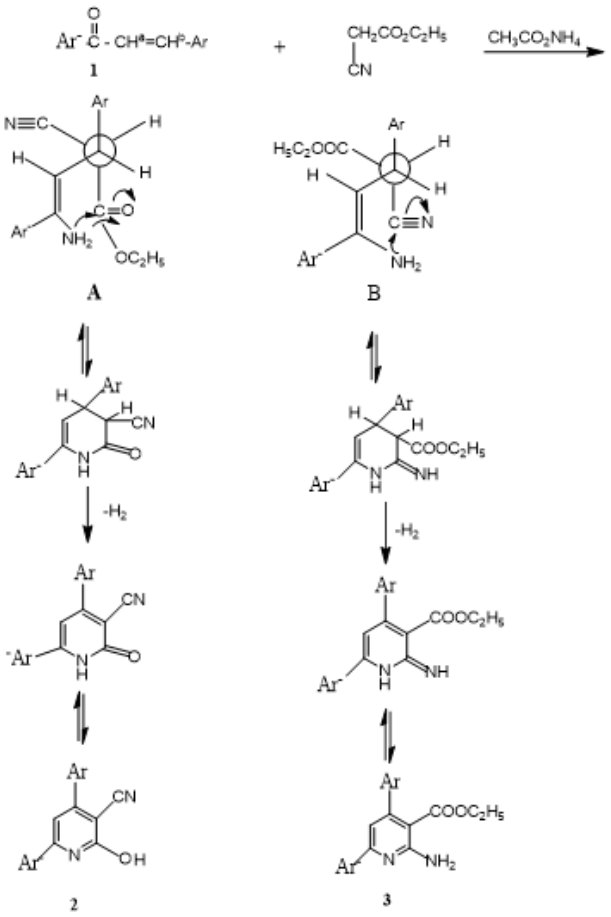
Synthesis of 4-(3-(4-bromophenyl)-4, 5-dihydro-1-acetyl-pyrazol-5-yl)-N, N-dimethylbenzenamine (20)

A solution compound 18 (3.44 g, 0.01 mol) in acetic anhydride (20ml) was refluxed 4 hrs. The reaction mixture was allowed to cool and poured in crushed ice; the separated solid was filtered, washed with water, dried, and crystallized from ethanol as white crystals. Yield: 78%. Melting point 165-167$^{\circ C}$. IR (KBr): showed no absorption band for (NH) and show absorption bands for carbonyl group at 1645 cm^{-1}. 1H NMR spectrum ($CDCl_3$), δ, ppm: 2.52(s,3H, $COCH_3$); 2.96 (s, 6H, -N(CH_3)$_2$); 3.19 (dd,2H,CH_2 pyrazole); 4.98 (2dd,1H, CH pyrazole) 7.22-7.98 (m,8H,Ar-H); M.s, (m/z): 386 $[M]^+$. Anal. For: $C_{19}H_{20}BrN_3O$ (386). Calc: C, 59.08; H, 5.22; Br, 20.69; N, 10.88. Found: C, 59.27; H, 4.98; Br, 20.27; N, 10.56.

Result and Discussion

The enone (1-(4-bromophenyl)-3-(4-(dimethyl amino) phenyl) prop-2-en-1-one (1)was a starting material for the synthesis of 4-(4-(dimethylamino) phenyl)-2-oxo-6-p-bromophenyl-1, 2-dihydropyridine-3-carbonitrile (2) via the reaction of the enone 1 with ethyl cyanoacetate in the presence of ammonium acetate, **Scheme 1** .The predominance of pyridine-2 can be explained as follows: in conformation (A) the ester group on one asymmetric carbon lies between a group of small size (viz. H) and a group of large size (-CH = C Ar NH_2) on the other asymmetric carbon which makes this conformation the more stable and at the same time the preferred (lowest energy) conformation, it needs a lower activation energy and can undergo nucleophilic attack on the ester group by nitrogen nucleophile more readily than conformation (B).

The structure of 2 was proved by IR spectra which show absorption bands at 3279 cm^{-1} (NH) , 2216 cm^{-1} (CN) and 1657 cm^{-1} (C=O).



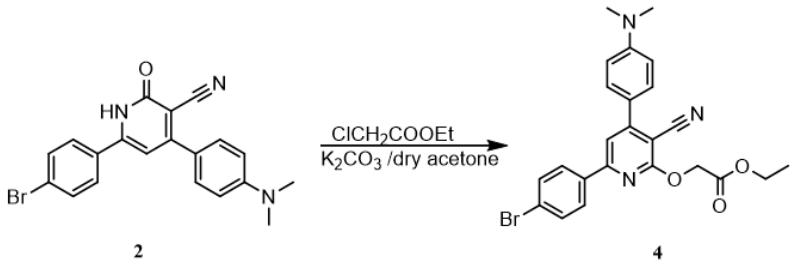
Ar= -C6H4-NM2-P

Ar-= -C6H4 –Br-P

Scheme 1. 2216 cm^{-1} (CN) and 1657 cm^{-1} (C=O).

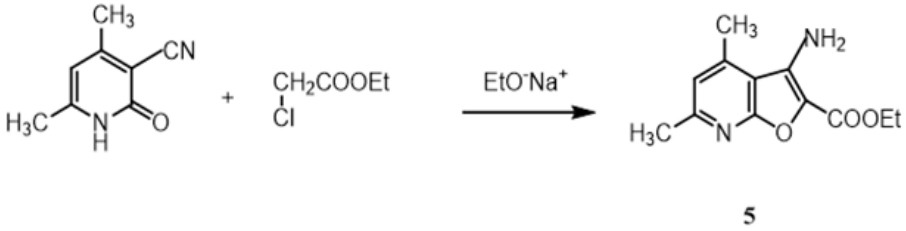
When compound 2 was reacted with ethyl chloroacetate in anhydrous K_2CO_3/dry acetone [8], ethyl 2-(6-(4-bromophenyl)-3-cyano-4-(4-(dimethylamino) phenyl) pyridin-2- yloxy) acetate (4) was obtained the structure was confirmed by IR spectrum which show absorption band at 1734 cm^{-1} carbonyl of ester. The signals of CH_2 and CH_3 protons was seen in the 1H NMR spectrum as quartet and triplet.

It was reported that [9] 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 .



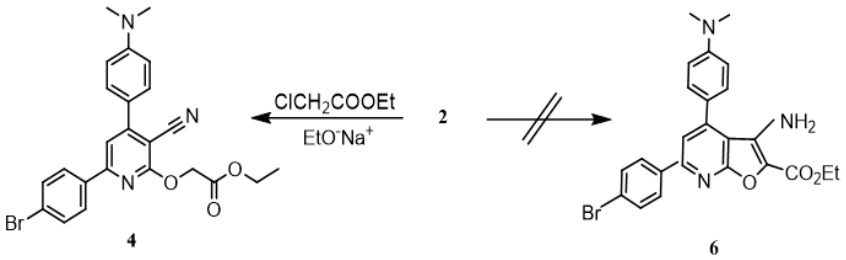
Compound 2 and 4

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 and no ring closure takes place to yield the furo derivative 6. Here the author offer an explanation for the ring closure not occur the 4-(N, N-di- methyl amino) phenyl (strong electron repelling group) and decreases the electrophilicity of carbon of the nitrile group.



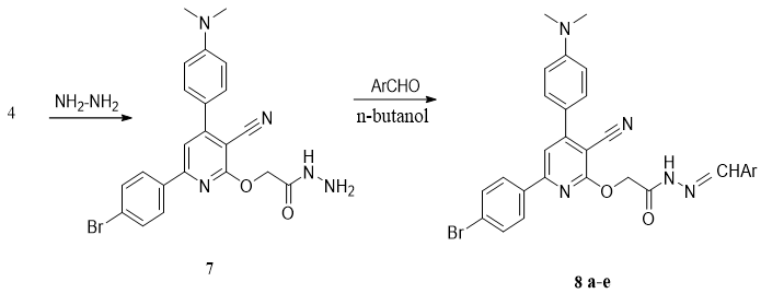
Compound 5

Moreover compound 4 was treated with hydrazine hydrate in ethanol. The hydrazide derivative 2-(6-(4-bromophenyl)-3-cyano-4-(4-(dimethylamino) phenyl) yridine-2-yl) oxy) acetohydrazide (7) was obtained. The IR spectrum of compound 7 displayed absorption bands at 3325 cm^{-1}, 3309 cm^{-1} (NH_2, NH) and 1617 (C=O), 1H NMR exhibits NH protons with D_2O exchangeable .



Compound 4 and 6

The hydrazide 7 was reacted with aromatic aldehydes [10], namely benzaldehyde, P-dimethylaminobenzaldehyde, P-nitrobenzaldehyde, P-methoxy benzaldehyde, and P-chlorobenzaldehyde, affording the condensation products 8 a-e, respectively.



a , Ar = - C_6H_5
b , = -C_6H_4 -NMe_2-p
c , = -C_6H_4 -NO_2 -p
d , = -C_6H_4-OCH_3-p
e, = C_6H_4-Cl -p

Compound 8a-e

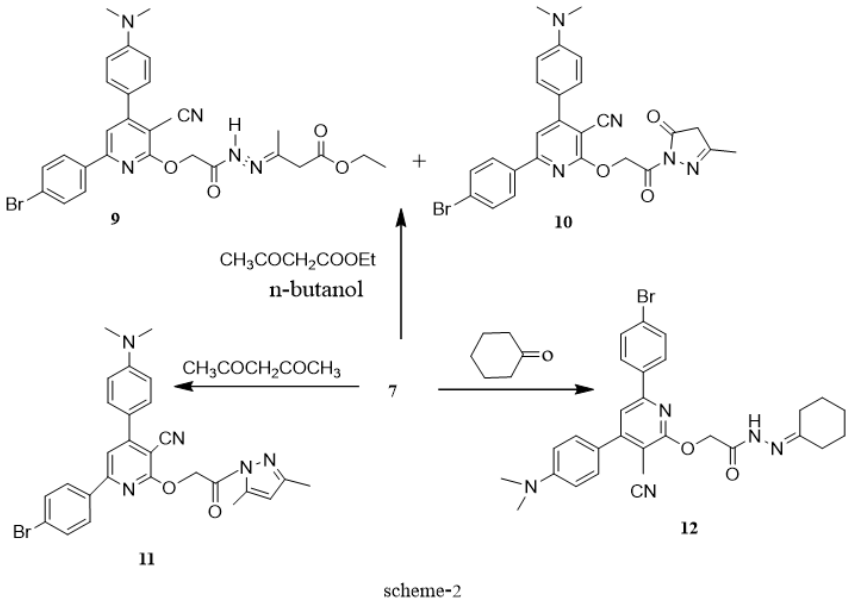
Reaction of ethyl acetoacetate with 7 in boiling butanol [10], afforded ethyl 3-(2-(2-(6-(4-bromophenyl)-3-cyano-4-(4-(dimethylamino)phenyl)pyridin-2-yloxy)acetyl)hydrazono) butanoate (9) and 6-(4-bromophenyl)-4-(4-(dimethylamino)phenyl)-2-(2-(3-methyl-5-oxo-4,5-dihydropyrazol-1-yl)-2-oxoethoxy)nicotinonitrile (10). The IR spectrum of compound 9 displayed absorption bands at 1731 cm^{-1} due to(C=O) of ester. While IR spectrum of compound 10 showed absorption band at 1640 cm^{-1} (C=O).

Condensation of compound 7 with acetyl acetone [10], gave 6-(4-bromophenyl)-2-(2-(3, 5-dimethyl-1H-pyrazol-1-yl)-2-oxoethoxy)-4-(4-di-methylamino) phenyl) nicotinonitrile (11). The structure of compound 11 was proved by IR, 1H NMR, and mass spectral data, which were in agreement with the assigned structure. Moreover, the signals of NH, NH_2 protons were not seen in the 1H NMR spectrum, proving that they were involved in the cyclization.

Moreover, compound 7 reacted with cylohexanone and gave 2-(3-cyano-4-(4-(dimethylamino) phenyl)-6-p-bromophenylpyridin-2-yloxy)-N'-cyclohexylideneacetohydrazide (12). The IR spectrum of 12 shows no absorption bands for (NH_2) but appear absorption bands at 3324 cm^{-1} for (NH), at 2923 cm^{-1} for C-H aliphatic. **Scheme 3.**

Reaction of phthalic anhydride with compound 7 afforded 2-(6-(4-bromophenyl)-3-cyano-4-(4-(dimethylamino) phenyl) pyridin-2-yloxy)-N-(1, 3-dioxoisoindolin-2-yl) acetamide (13) and N'-(2-(3-cyano-4-(4-(dimethyl amino) phenyl)-6-p-bromophenylpyridin-2-yloxy) acetyl)-2'-carboxybenzoylhydrazide (14) .The IR spectrum of compound 13 showed absorption bands at 1740 cm^{-1} , 1652 cm^{-1} attributable for (C=O) of imide and (C=O) of amide.

While IR spectrum of compound 14 show absorption band at 1692 cm^{-1} due to (C=O) of acid and sub maxima between 2500-3300 ν OH and ν NH. On the other hand, when compound 7 reacted with maleic anhydride and gave 4-(2-(2-(6-(4-bromophenyl)-3-cyano-4-(4-(dimethylaminophenyl)pyridin-2-yl)oxyacetyl hydrazinyl)-4-oxobut-2-enoic acid (15). **Scheme 2.**



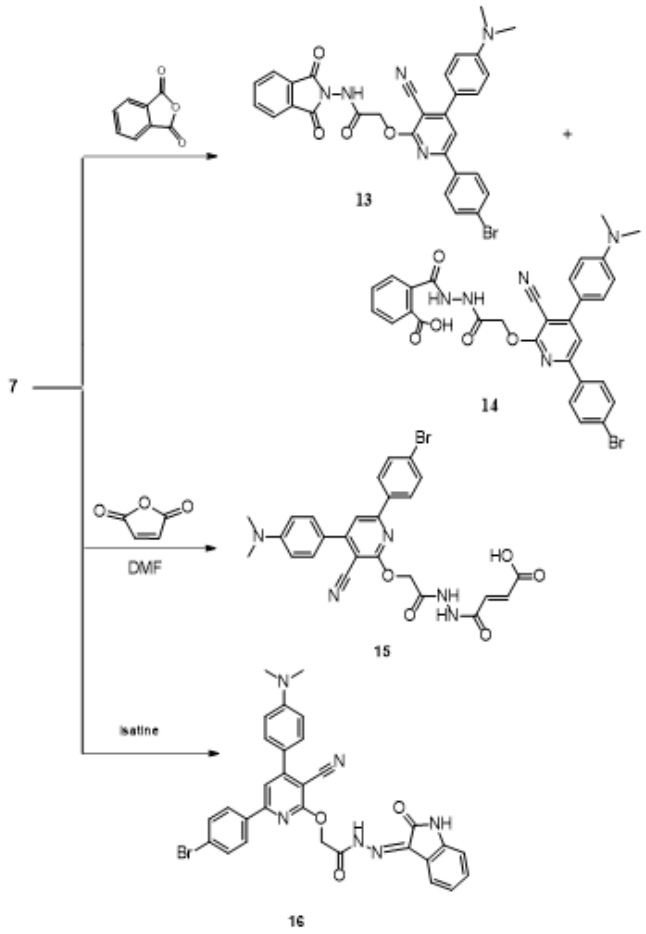
Scheme 2

The IR spectrum of 15 show broad band attributed for chelated OH group at 3409 cm^{-1} or (NH) , 2927cm^{-1} C-H aliphatic; 1722 cm^{-1} (C=O) of acid. When compound 7 reacted with isatin in ethanol and drops of acetic acid gave 2-(6-(4-bromophenyl)-3-cyano-4-(4-(dimethylamino) phenyl) pyridin-2-yl) oxy)-N'-(2-oxoindolin-3-ylidene) acetohydrazide (16).
The structure of 16 was confirmed by IR spectrum which show absorption band at 1647 cm^{-1} due to (C=N), 3381 cm^{-1}(NH), and 1H NMR showed signals for (2NH) protons with D_2O exchangeable.

Compounds with activated double bond reacted with 2-pyridone derivatives and gave N-alkylated derivatives .Thus treating 2 with acrylonitrile in Et3N [10], gave the N-propionitrile derivative 17 as a Michael type product. The structer of 17 was proved by IR spectrum which show two absorption bands at 2248, 2213 for (2CN); 1642 (C=O), and no absorption band for (NH).

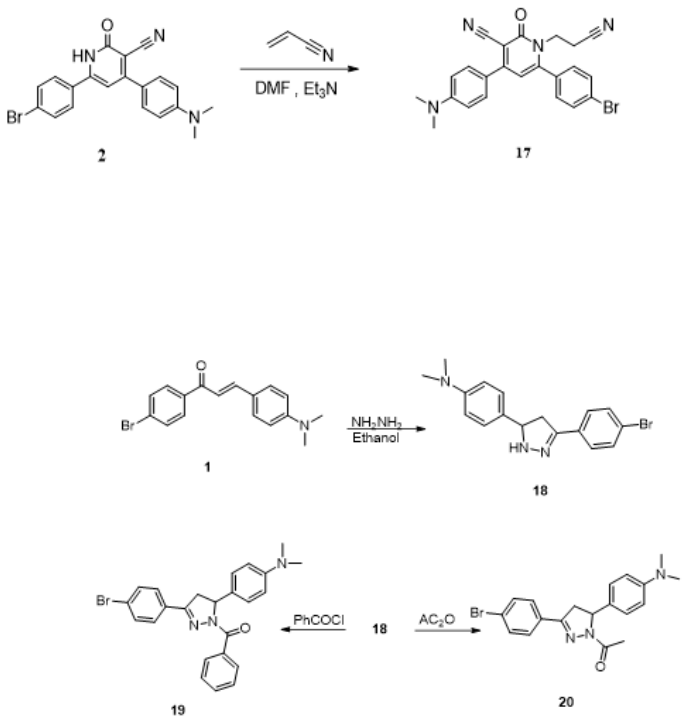
Author investigates the action of hydrazine hydrate on - 1-(4-bromophenyl)-3-(4-(dimethyl amino) phenyl) prop-2-en-1-one (1) and suggested the formation of pyrazole derivative 18.

The structure of 18 was confirmed by IR spectra which show absorption band at 3339 cm^{-1} attributable for (NH) , C=N at 1607 cm^{-1} and 1H NMR showed (NH) proton with D_2O exchangeable.



Scheme 3

On The other hand, when compound 18 was refluxed with benzoyl chloride in pyridine and with acetic anhydride affording 19 and 20, respectively in a good yield. **Scheme 4.**



Scheme 4

Antibacterial activity

Screening of the antimicrobial activity was performed at Microbiology Lab in Faculty of Science, Ain shams University, Cairo, Egypt. The tested microorganisms were chosen on bases of their pathogenicity where Staphylococcus aureus can cause mild or severe diseases[11], like Most Abscesses and pyogenic Infections Such as (Endocarditis, osteomyelitis and Meningitis) it can also cause Food poisoning, Scalded Skin syndrome and Toxic shock syndrome it's Also the cause of most Nosocomial Infections. While *Escherichia Coli* can cause many Gastro Intestinal Tract (GIT) infections by the 4 types: entero toxogenic (ETEC), entero phogenic (EPEC), Entero invasive (EIEC) and Shiga toxin (STEC). Also, the Entero-Hemorrhagic. *E.coli* can cause Hemolytic Uremic Syndrome which causes Kidney Failure *E. coli* also, causes Urinary Tract Infection (UTI) especially in females and the major cause of Cystitis.

The anti-bacterial activity of the selected derivatives 2, 4, 7, 8a-e, 9, 11, 12, 13, 17, 18, 19 and 20 were tested against a panel of gram positive bacteria (*Staphylococcus aureus*), and Gram-negative bacteria (*Escherichia coli).* Each compound was dissolved in DMSO and solutions of the concentration 1 mg /ml were prepared separately .Paper discs of Whatman filter paper were cut with standard size (5cm) and sterilized in an autoclave. The paper discs were soaked in the desired concentration of the complex solution and placed aseptically in the petri dishes containing nutrient agar media (agar 20g + beef extract 3g+peptone 5g) seeded with *Staphylococcus aureus* , *E. coli* ,The petri dishes were incubated at 36 c and the inhibition zones were recorded after 24 h of incubation. Each treatment was replicated three times. The antibacterial activity of a common standard antibiotic (Cefoxitin) was also recorded using the same procedure as above at the same concentration and solvents [12]. The % activity index for each tested compound was calculated by the formula as under:

% Activity Index= (Zone of inhibition by test compound (diametre))/(Zone of inhibition by standard (diametre))X 100

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

No.	Compound	Escherichia Coli Gm (-ve) bacteria		Staphylococcus aureus Gm(+) bacteria	
		Diameter of inhibition zone (mm)	% Activity index	Diameter of inhibition zone (mm)	% Activity index
1	2	14	56	10	40
2	4	16	64	16	64
3	7	1.5	60	NA	0
4	8a	10	40	10	40
5	8b	10	40	14	56
6	8c	NA	0	10	40
7	8d	8	32	9	36
8	8e	13	52	11	44
9	9	11	44	13	52
10	11	8	32	12	48
11	12	NA	0	10	40
12	13	10	40	11	44
13	17	11	44	NA	0
14	18	8	32	20	80
15	19	5	20	15	60
16	20	7	28	21	84
Cefoxitin		25	100	25	100

• NA → No Activity.

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 activities. Meanwhile compounds 8d, 11, 18, 19, 20 demonstrated weak activities. Compounds 8c, 12 were inactive against *Escherichia Coli*.

Compounds 4,18,19,20 showed strong activity against Gram positive bacteria (*Staphylococcus aureus*). Also, (compound 20 have the maximum activity), Compounds 2, 8a, 8b, 8c, 8e, 9, 11, 12, 13 have moderate activity .While compound 8d showed weak activity. The remaining compounds 7, 17 was inactive against *Staphylococcus aureus* (**FIG. 1.**).

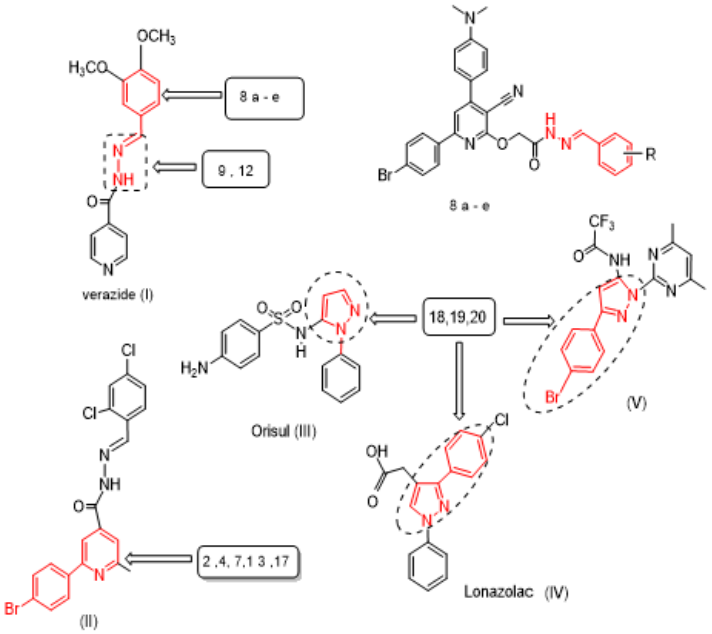


FIG . 1. **Structure of antibacterial and antitubercular (I-V) and compounds 8a-e, 9, 12 and 2-20.**

TABLE 2. **Energy values of LUMO and HOMO in eV.**

No	**E_{LUMO}**	**E_{HOMO}**	**$\Delta E = E_{LUMO}-E_{HOMO}$**	**% Activity *E.coli***	**% Activity *S. aureus***
2	-2.185 eV	-8.918 eV	6.733	56.0	40.0
4	-3.290 eV	-8.890 eV	5.600	64.0	64.0
7	-3.283 eV	-7.049 eV	3.766	60.0	0.00
8a	3.310 eV-	-8.889 eV	5.579	40.0	40.0
8b	-3.288 eV	-8.263 eV	4.975	40.0	56.0
8c	-5.724 eV	-8.889 eV	3.165	0.00	40.0
8d	-3.293 eV	-8.889 eV	5.596	32.0	36.0
8e	-3.292eV	-8.888 eV	5.596	52.0	44.0
9	-3.302 eV	-7.059 eV	3.757	44.0	52.0
11	-3.290 eV	-7.377 eV	4.087	32.0	48.0
12	-3.582 eV	-8.786 eV	5.204	0.00	40.0
13	-5.407 eV	-8.574 eV	3.167	40.0	44.0
17	-1.875 eV	-7.503 eV	5.628	44.0	0.00
18	-1.082 eV	-7.501 eV	6.419	32.0	80.0
19	-2.430 eV	-8.268 eV	5.838	20.0	60.0
20	-1.452 eV	-8.349 eV	6.897	28.0	84.0

It is well known that high EHOMO are likely to indicate a strong tendency of the molecule to donate electrons. The low values of the energy gap (ΔE=ELUMO-EHOMO) will render good antimicrobial efficiencies, because the energy needed to remove an electron from the last occupied orbital will be low [13,14]. The ΔE of a molecule is a measure of the hardness or softness of a molecule. Hard molecules are characterized by larger values of ΔE and vice versa. The linear correlation between EHOMO energy level and the microbial inhibition efficiency of the inhibitors proved that the higher the HOMO energy (less negative values) of the inhibitor or antibacterial, the greater the trend of offering electrons. The order of decreasing EHOMO, increasing ELUMO values and the energy gap (ΔE) are directly proportional with increasing the inhibition of bacteria and fungi efficiency and the reagents as considered as antimicrobial agents [14]. From the calculated values of EHOMO (**TABLE 2** and **FIG. 2**).

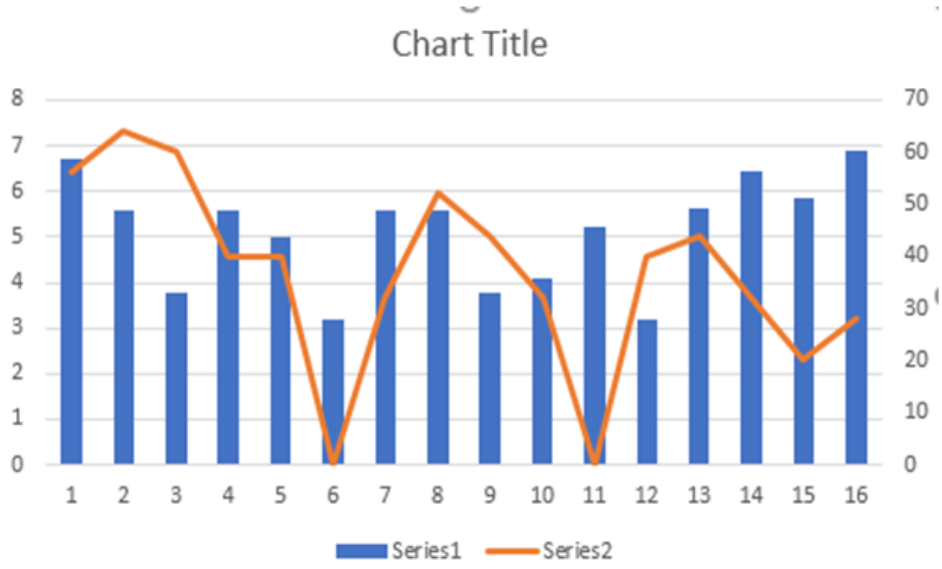


FIG. 2. **Outline the EHOMO values with antibacterial properties.**

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