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CHLOROACETONITRILE IN HETERO CYCLIC SYNTHESIS; NOVEL ROUTE FOR THE SYNTHESIS OF THIAZOLIDINE, CHORMENE, PYRROLE, AND PYRAZOLE DERIVATIVES AS ANTIMICROBIAL AGENTS

GAMEEL EL-HAG-ALI
Chemistry Department, Faculty of Science, Al-Azhar University, 11284 Nasr City, Cairo, Egypt,
elhag1970@yahoo.com

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CHLOROACETONITRILE IN HETERO CYCLIC SYNTHESIS; NOVEL ROUTE FOR THE SYNTHESIS OF THIAZOLIDINE, CHORMENE, PYRROLE, AND PYRAZOLE DERIVATIVES AS ANTIMICROBIAL AGENTS

GAMEEL A. M. EL-HAG-ALI

Chemistry Department, Faculty of Science, Al-Azhar University, 11284 Nasr City, Cairo, Egypt
Address correspondence to G. A. M. Elhagali, Email; Elhag1970 @ yahoo.Com.

Abstract

Thiazolidinone **(5b)**, chormeno [2,3-b] pyrrole **(11)** and 2-(2-ethoxyphenylamino) acetonitrile **(16)**, were obtained from the reaction of chloroacetonitrile **(1)** with thioglycollic acid **(2)** , salicyaldehyde in presence of malononitrile, and *o*-phentidine ,respectively. Fusion of compound **(5b)** with hydrazine hydrate furnished **(6),** while fusion chloroacetonitrile **(1)**, 2-chlorobenzaldehyde and thioglycollic acid **(2)** gave **(8)**. Treatment of **(1)**, and **(16)** with a mixture of aromatic aldehyde and hydrazine hydrate gave the corresponding Pyrazole derivatives **(18,24**,and **25)**. The reaction of compound **(11)** with each of acetic anhydride, carbon disulphide, and formic acid gave the corresponding chormeno [2,3-b] pyrrole derivatives**(13-15)**,respectively. Refluxing **(16)** with salicyaldehyde in presence of ammonium acetate afforded- *N*-(2-ethoxyphenyl)-2-imino-2H-chromen -3-amine **(19)** .The novel pyrrole derivative **(20)** was obtained through reaction of **(16)** with a mixture of 2-chlorobenzaldehyde and malononitrile.

Key words: Thiazolidine, chormene, and pyrazole derivatives

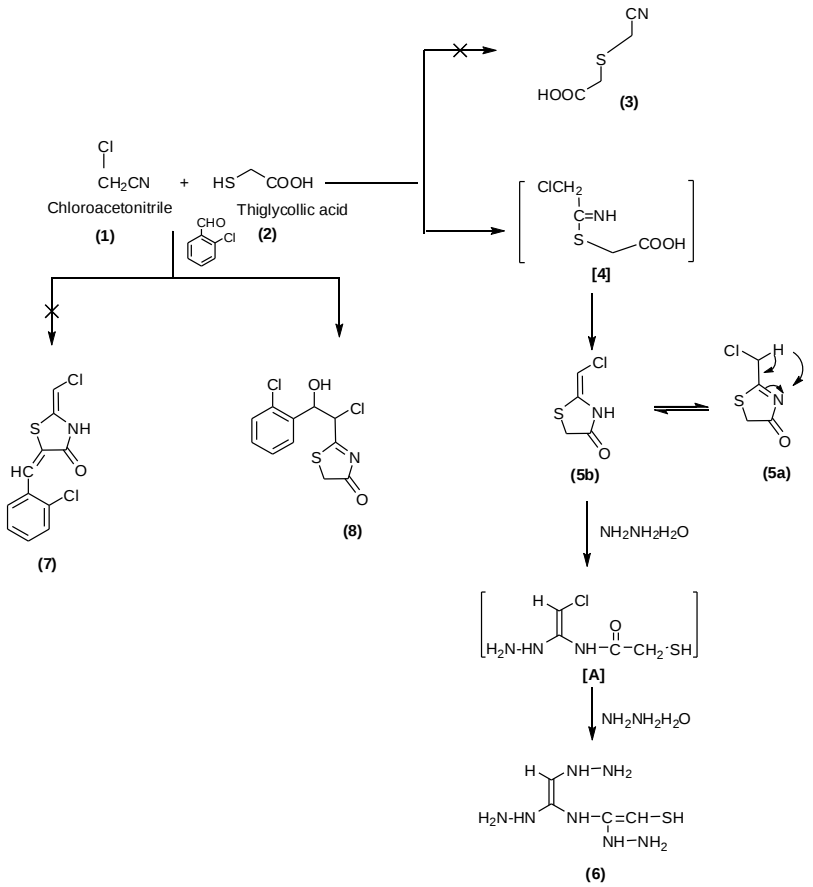
Introduction

Chloroacetonitrle was used as a starting material for synthesis of biologically active compounds such as suitably substituted pyrroles and thiazoles which are the basic skeleton of many biologically important substances.[1-8] Pyrazole derivatives are well established in the literature as important biologically active heterocyclic compounds. These derivatives are the subject of many research studies due to their widespread potential biological activities such as anti-inflammatory,[9] antipyretic,[10] antimicrobial,[11] antiviral ,[12] antitumour ,[13] anticonvulsant, [14] antihistaminic.[15] Thus, in the course of our studies devoted to the synthesis of some novel heterocyclic compounds from readily available starting materials, [16-20] we report here the synthesis of some novel thiazole, chormene, pyrrole, and pyrazole derivatives.

Results and Discussion

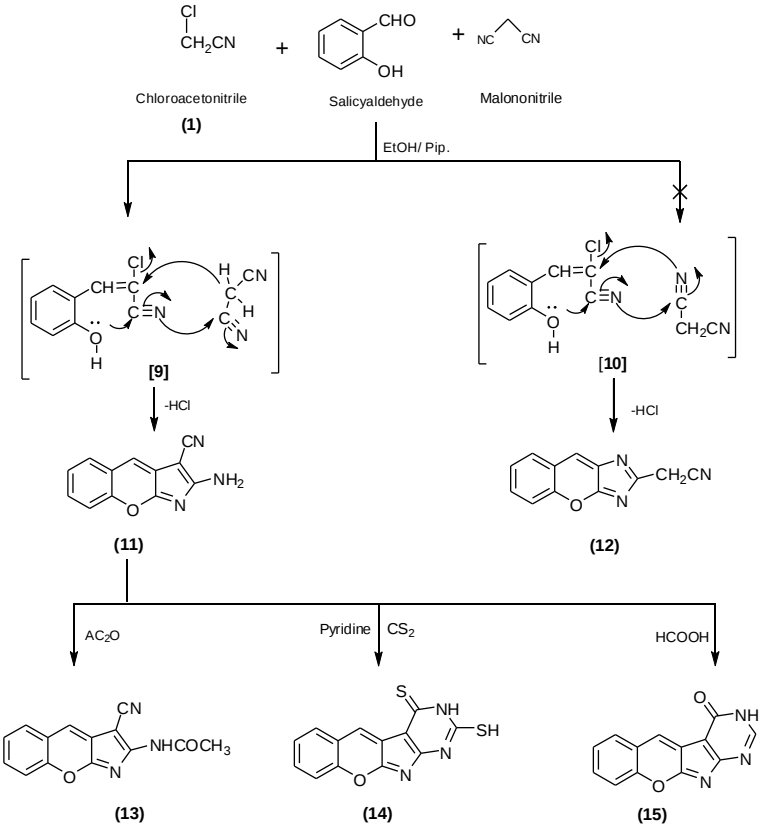
When chloroacetonitrile **(1)** was refluxed with thioglycollic acid **(2)** in DMF for 3h, 2-(chloromethylene) thiazolidin-4-one **(5b)** was readily obtained in 88% isolated yield. Elemental analysis and spectral data were in a complete accordance with

thiazolidinone structure **(5b)** and ruled out the open chain and thiazolidinone structures **(3)** and **(5a)**, respectively. IR spectrum of **(5b)** sho-wed strong absorption bands for (NH) at 3166 and (C=O thiazolidinone) at 1710cm^{-1}, and absence of absorption band for cyano absorption band. ^{1}H NMR spectrum of compound **(5b)** showed a singlet at δ 3.41, characteristic for CH_2, together with singlet at 7.48 ppm for methine and (NH) protons. Fusion of compound **(5b)** with hydrazine hydrate resulted in the formation of thiazolidinone derivative **(6)** in 67% yield based on spectral and analytical data; Scheme 1. IR spectrum of compound (**6)** was free of (C=O) thiazoildinone absorption band and showed broad bands for (SH), (NH2), and (NH) groups. One pot reaction of Chloroacetonitrile **(1)**, 2-chlorobenzaldehyde, and thioglycolic acid **(2)** in equal molar ratios afforded **(8)**.^{1}H NMR spectrum of **(8)** was in a complete agreement with the assigned structure **(8)** and rejects the other expected structure **(7)**; (Scheme 1).



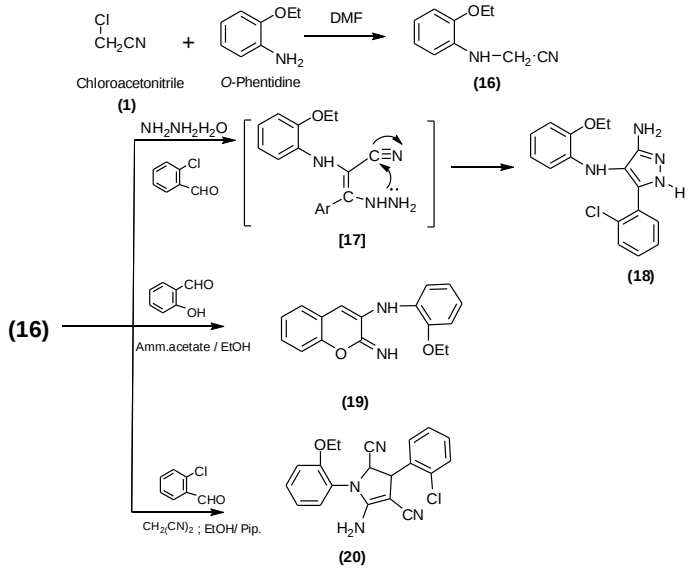
Scheme 1

As apart of this research work , 2-aminochromeno [2,3-b] pyrrole-3-carbonitrile **(11)** was obtained as a single product examined by TLC, via one pot reaction of chloroacetonitrile **(1)**, salicyaldehyde and malononitrile. The formation of **(11)** proceeds via double cyclization through formation of the non isolated 3-chloro-2H-chromen-2-imine intermediate as in Scheme 2. The identity of **(11)** was confirmed by IR, ^{1}H NMR, Ms spectral data.Its IR spectrum revealed presence of absorption bands for (NH_2), and (C≡N) at 3342, 3190, and 2202 cm^{-1}, respectively. ^{1}H NMR spectrum of compound **(11)** showed a singlet at δ 8.95, characteristic for chormen-H. Also, its mass spect-rum assigned a molecular ion peak at m /z (209). Chromeno [2,3-b] pyrrole derivatives **(11)** having enaminonitrile centre in its structure and, thus it's a key starting material for the preparation of chormeno [2',3'-4,5] pyrrolo [2,3-d] pyrimidine derivatives**.** Thus, treatment of compound **(11)** with each of acetic anhydride, carbon disulphide in pyridine and formic acid gave the corresponding chromeno derivatives **(13-15)**, respectively ; (Scheme 2) .



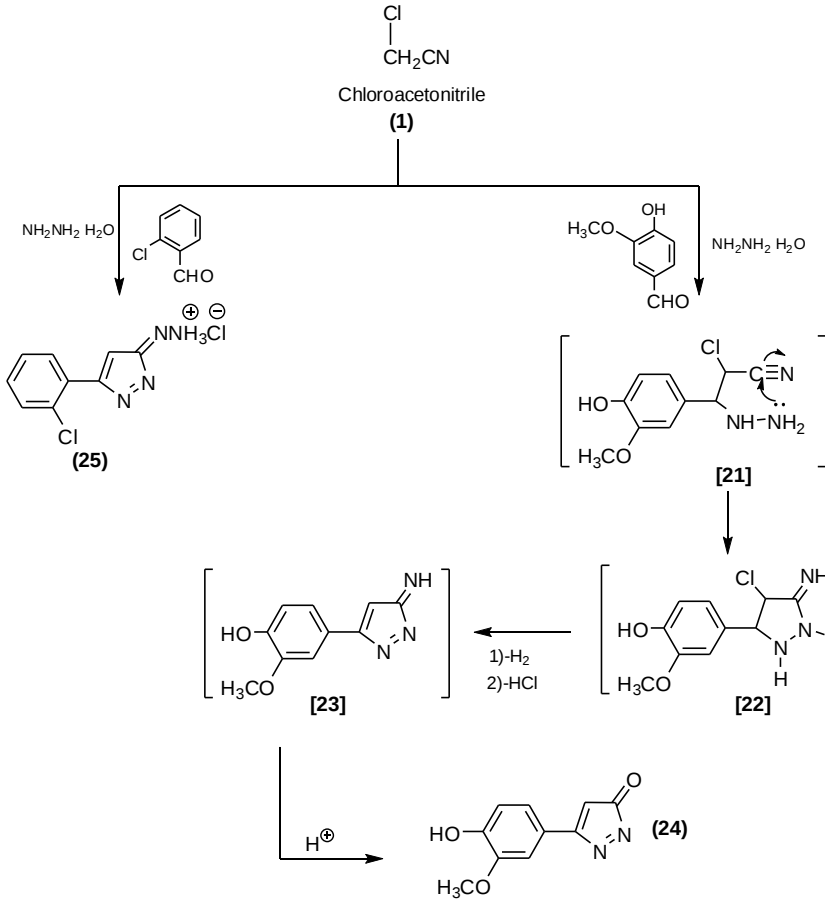
Scheme 2

Next, chloroacetonitrile **(1)** was reacted with *o*-phentidine in refluxing DMF to give the corresponding 2-(2-ethoxyphenylamino) acetonitrile **(16**), compound **(16)** was confirmed by spectral and analytical data. IR spectrum of compound **(16)** showed bands due to (C≡N) and (NH) at 3386, and 2200 cm^{-1}, respectively .Its mass spectrum assigned a molecular ion peak at m\ z 176. Compound **(16)** was reacted with a mixture of 2-chlorobenzaldehyde and hydrazine hydrate in refluxing ethanol and gave a single product which was assigned as 5-(2-chlorophenyl)-N^4-(2-ethoxyphenyl)-1H-pyrazole-3,4-diamine **(18**) on the basis of its elemental analysis and spectral data. Treatment of compound **(16)** with salicyaldehyde at reflux temperature in the presence of ammonium acetate, afforded the novel chormeno [2,3-b] pyrrole derivative **(19)**. The structure of compound (**19**) was confirmed by its correct elemental analysis and spectral data. IR spectrum of compound **(19)** showed no band due to (C≡N) function group. Compound **(16)**, when refluxed with a mixture of 2-chlorobenzaldehyde and malononitrile, it afforded 5-amino-3-(2-chlorophenyl)-1-(2-ethoxyphenyl)-2,3-dihydro-1H-pyrrole-2,4-dic-arbonitrile**(20)** on the basis of spectral and analytical data. IR spectrum of **(20)** showed absorption bands at 3388 ,3321 (NH_2), and 2188 (C≡N) cm^{-1}. Its ^1H NMR spectrum showed doublet-doublet signals at δ 4.23, and 4.25 characteristic for 2H and 3H pyrrole; (Scheme 3).



Scheme 3

5-(4-Hydroxy-3-methoxyphenyl)-3H-pyrazole-3-one **(24)** and 5-(2-chlorophenyl) -3-hydrazono-3H-pyrazole hydrochloride **(25)** were produced in good yields via fusion of chloroacetonitrile **(1)** with either vanillin or 2-chlorobenzaldehyde, and hydrazine hydrate respectively. The formation of pyrazole derivatives **(24,25)** proceeds via Micheal addition of hydrazine hydrate to β-carbon of the non isolated arylidine intermediate followed by cyclization, elimination and hydrolysis ; (Scheme 4). The analytical and spectral data were in a complete accordance with the assigned structure **(24,25)** . The IR spectrum of compound **(24)** revealed presence of absorption band for (C=O) group at 1648 cm^{-1}, whereas IR spectrum of (**25)** showed lack of (C=O) absorption band. The mass spectrum of the separated pyrazole derivative **(25)** revealed a molecular ion peak at m/ z 242.



Scheme 4

Experimental

Melting points are uncorrected. IR spectra were recorded on a Shimadzu 440 infrared spectrophotometer (υ; cm^{-1}) using the KBr technique (Shimadzu, Japan). ^1H NMR spectra were recorded on a Varian Gemini spectrometer (δ; ppm) 300 MHz using TMS as internal standard. Mass spectra were recorded on a Jeol-JMS-600 mass spectrometer. Micro analytical data were obtained from the Micro analytical Research Centre, Faculty of Science, Cairo University.

2-(chloromethylene) thiazolidin-4-one (5b)

A mixture of chloroacetonitrile **(1)** (0.01mol), and thioglycollic acid **(2)** (0.01mol) in DMF (20 mL) was heated under reflux for 3h. The solid product formed was collected by filtration and recrystallized from benzene.

5b: colorless crystals, yield 81 %, m.p. 258-60 ºC. IR (KBr, cm^{-1}): 3166 (NH), and 1710 (C=O thiazolidinone). ^1H NMR (DMSO-d_6) δ 3.41 (s, 2H, CH_2-thiazolidinone), 7.48 (s, 2H, methine-H and NH). .Anal. Calcd for C_4H_4ClNOS (149): C; 32.11, H; 2.67; N; 9.36. Found: C; 32.26, H; 2.55, N; 9.65.

2-(1,2-dihydrazinylvinylamino)-2-hydrazinylethenethiol (6)

A mixture of **(5b)** (0.01mol) and hydrazine hydrate (0.0mol) was fused for 30 minutes. The solid product formed was collected by filtration and recrystallized from benzene.

6: colorless crystals, yield 79 %, m.p. 280-82 ºC. IR (KBr, cm^{-1}): 3450-3136 (br,SH, NH_2 and NH). MS m/z (%): (191) (100%) .Anal. Calcd for $C_4H_{13}N_7$ S (191): C; 25.12, H; 6.80; N; 51.30. Found: C; 25.32, H; 6.63, N; 51.41.

2-(1-chloro-2-(2-chlorophenyl)-2-hydroxyethyl) thiazol-4(5H)-one (8)

A mixture of **(1)** (0.01mol), and 2-chorobezaldehyde (0.01mol) was fused for 1h, then thioglycollic acid **(2)** (0.01mol) was added and the fusion was continued for 2h. The solid product formed was collected by filtration and recrystallized from ethanol.

8: colorless crystals, yield 79 %, m.p. 130-32 ºC. IR (KBr, cm^{-1}): 3400-3100 (broad OH),and 1706 (C=O thiazolidinone). ^1H NMR (DMSO-d_6) δ 3.42 (s, 2H, CH_2), 3.44 (d, 1H, CH), 3.55 (d, 1H, CH), 5.69 (s, 1H, OH; exchangeable with D_2O), 7.31-7.62 (m, 4H, Ar-H). Anal. Calcd for $C_{11}H_9Cl_2NO_2S$ (289): C; 45.67, H; 3.11; N; 4.84. Found: C; 45.22, H; 3.32, N; 4.65.

2-aminochromeno[2,3-b]pyrrole-3-carbonitrile(11)

A mixture of **(1**) (0.01mol) and salicyaldehyde (0.0mol) was fused for 2h, then malononitrile (0.01 mol) and catalytic amount piperidine (0.05 mL) in absolute ethanol (20 mL) were added . The reflux was continued for 3h, and the solid product formed was collected by filtration and recrystallized from ethanol.

11: colorless crystals, yield 79 %, m.p. < 300 ºC. IR (KBr, cm^{-1}): 3342, 3190 (NH_2),and 2202(C≡N). ^1H NMR (DMSO-d_6) δ 7.52-7.81 (m, 6H, Ar-H + NH_2; exchangeable with D_2O), 8.95 (s, 1H, chormen-H) . MS m/z (%): 209 (32.4%). Anal. Calcd for $C_{12}H_7N_3O$ (209): C; 68.89, H; 3.34; N; 20.09. Found: C; 68.51, H; 3.22, N; 20.22.

***N*-(3-cyanochromeno[2,3-b]pyrrol-2-yl)acetamide(13)**

A mixture of **(11**) (0.01mol) and acetic anhydride (20 mL) was heated under reflux for 3h.The solid product formed was collected by filtration and recrystallized from ethanol.

13: brown powder, yield 61 %, m.p. 260-62ºC . IR (KBr, cm^{-1}): 3206(NH), 2200 (C≡N),and 1720(C=O). ^1H NMR (DMSO-d_6) δ 1.88 (s, 3H, CH_3), 7.00-7. 48 (m,5H,Ar-H,and chormene-H), 11.91(s,1H,NH; exchangeable with D_2 O) .Anal. Calcd for $C_{14}H_9N_3O_2$ (251): C; 66.93, H; 3.58; N; 16.73. Found: C; 66 .68, H; 3.39, N; 16.92.

3,4-dihydro-4-thioxo-chormeno[2'3'-4,5]pyrrolo[2,3-d]pyrimidine-2-thiol(14)

A mixture of **(11**) (0.01mol) and carbon disulphide (0.0mol) in pyridine (20 mL) was heated under reflux for 3h. The solid product formed was collected by filtration and recrystallized from ethanol.

14: brown powder, yield 68 %, m.p. 200-02 ºC .IR (KBr, cm^{-1}): 3172(NH). ^1H NMR (DMSO-d_6) δ 7.06-7.99 (m,5H,Ar-H and chromene-H), 11.91 (s,1H,NH ; exchangeable with D_2O),13.00(s,1H,SH ; exchangeable with D_2O). Anal. Calcd for $C_{13}H_7N_3OS_2$ (285): C; 54.73, H; 2.46; N; 14.73. Found: C; 54.93, H; 2.63, N; 14.56.

3,4-dihydro-4-oxo- chormeno [2'3'-4,5]pyrrolo[2,3-d]pyrimidine (15)

A mixture of **(11**) (0.01mol) and formic acid (20 mL) was heated under reflux for 3h.The solid product formed was collected by filtration and recrystallized from ethanol.

15: colorless crystals , yield 68 %, m.p. 170-72 ºC. IR (KBr, cm^{-1}): 3192(NH), and 1734 (C=O). ^{1}H NMR (DMSO-d_6) δ 6.77(s,1H,pyrimidine-H), 3.79 (s, 1H, NH; exchangeable with D_2O), 7.06-7.82 (m,5H,Ar-H and chromene-H). Anal. Calcd for $C_{13}H_7N_3O_2$ (237): C; 65.82, H; 2.95; N; 17.72. Found: C; 65.55, H; 3.21, N; 17.82.

2-(2-ethoxyphenylamino)acetonitrile(16)

A mixture of **(1)** (0.01mol) and *o*-phentidine (0.01 mol) in DMF (20 mL) was heated under reflux for 3h. The solid product formed was collected by filtrati- on and recrystallized from ethanol.

16: grey crystals, yield 68 %, m.p. 100-02 ºC .IR (KBr, cm^{-1}): 3386 (NH), and 2200 (C≡N). ^{1}H NMR (DMSO-d_6) δ 1.33 (t,3H,CH_3; J= 6 Hz), 4.01 (q,2H,CH_2; J= 6 Hz), 4.24 (s,2H,CH_2),5.50 (humb,1H,NH; exchangeable with D_2O), 6.65-6.87 (m,4H,Ar-H). MS m/z 176 (45.52%). Anal. Calcd for $C_{10}H_{12}N_2O$ (176): C ; 68 .18, H; 6.81; N; 15.90. Found: C; 68.35, H; 6.62, N; 15.75.

5-(2-chlorophenyl)-*N*^{4}-(2-ethoxyphenyl)-1H-pyrazole-3,4-diamine (18)

A mixture of **(16)** (0.01mol) and 2-chorobenzaldehyde (0.01 mol) was heated for 1h,then hydrazine hydrate (0.01 mol) and absolute ethanol (20 mL) were added . The reflux was continued for 2h, and the solid product formed was collected by filtration and recrystallized from ethanol.

18: colorless crystals, yield 52 %, m.p. 66-68 ºC. IR (KBr, cm^{-1}): 3454 ,3390, 3212(NH_2,NH). MS m/z (%):328 (0.18%).Anal. Calcd for $C_{17}H_{17}$-N_4ClO (328) : C; 62.10, H; 5.17; N; 17.04. Found: C; 62.35, H; 5.01, N; 16.87.

***N*-(2-ethoxyphenyl)-2-imino-2H-chromen-3-amine (19)**

To a solution of **(16)** (0.01mol) in absolute ethanol (20 mL), salicyaldehyde (0.01 mol) and ammonium acetate (0.01 mol) were added .The reaction mixture was heated under reflux for 3h. The solid product formed was collected by filtration and recrystallized ethanol.

19: brown crystals, yield 47 %, m.p 86-88 ºC. IR (KBr, cm^{-1}) 3390 (NH). ^{1}H NMR (DMSO-d_6) δ 1.33(t,3H,CH_3; J= 6 Hz), 4.01(q,2H,CH_2; J= 6 Hz), 4.23 (s,1H,NH ; exchangeable with D_2O),5.50 (s,1H,NH; exchangeable with D_2O), 6.68-6.87 (m,9H, Ar-H and chormene-H). Anal. Calcd for $C_{17}H_{16}N_2O_2$ (280): C; 72.85, H; 5.71; N; 10.00. Found: C; 72.91, H; 5.55, N; 10.23.

5-amino-3-(2-chlorophenyl)-1-(2-ethoxyphenyl)-2,3-dihydro-1H-pyrrole-2,4-dicarbonitrile(20)

A mixture of **(16)** (0.01mol), 2-chlorobenzaldehyde (0.01mol), and malononitrile (0.01 mol) was refluxed for 3h in absolute ethanol (20mL) catalyzed with piperidine (0.05 mL). The solid product formed was collected by filtration and recrystallized from ethanol.

20: grey powder, yield 59 %, m.p. 65-67 ºC. IR (KBr, cm^{-1}): 3388 ,3321 (NH_2), and 2188(C≡N). ^{1}H NMR (DMSO-d_6) δ 1.35(t,3H,CH_3; J= 6 Hz), 4.01 (q,2H ,CH_2; J= 6 Hz), 4.23(d,1H,CH), 4.25(d,1H,CH)), 5.53(s,2H,NH_2; exchange-eable with D_2O),6.65-6.87 (m,8H,Ar-H) . Anal. Calcd for $C_{20}H_{17}ClN_4O$ (364): C; 65.93, H; 4.67; N; 15.38. Found: C; 65.59, H; 4.22, N; 15.69.

5-(4-hydroxy-3-methoxyphenyl)-3H-pyrazol-3-one (24)

A mixture of **(1)** (0.01mol) and vanillin (0.01 mol) was fused for 1h , then hydrazine hydrate (0.01 mol) was added and the fusion was continued for 2h.The solid product formed was collected by filtration and recrystallized ethanol.

24: yellow crystals, yield 62 %, m.p. 198-200 ºC. IR (KBr, cm^{-1}): 3400-3200(broad OH),3042(CH-Aromatic), and 1648(C=O).^{1}H NMR (DMSO-d_6) δ 3.82(s, 3H,OCH_3), 6.88 (d,1H,Ar-H), 7.26 (d,1H,Ar-H), 7.50 (s,1H,Ar-H),8.64 (s,1H, pyrazole-H),9.90 (s,1H, OH; exchangeable with D_2O) .Anal. Calcd for $C_{10}H_8N_2O_3$ (204): C; 58.82, H; 3.92; N; 13.72. Found: C; 58.51, H; 3.71, N; 13.52

5-(2-chlorophenyl)-3-hydrazono-3H-pyrazole hydrochloride (25)

A mixture of **(1)** (0.01mol) and 2-chlorobenzaldehyde (0.01 mol) was fused for 1h, then hydrazine hydrate (0.01 mol) was added and the fusion was continued for 2h. The solid product formed was collected by filtration and recrystallized from benzene.

25: yellow crystals, yield 53 %, m.p . 140-42 ºC IR (KBr, cm^{-1}): 3400-3200 (broad NH).^{1}HNMR (DMSO-d_6) δ 7.54-7.58(m,4H,Ar-H),8.16 (s,3H ,$\oplus NH_3$;exchangeable with D_2O), 8.96 (s,1H, pyrazole-H) . MS m/z (%) :242(7.3%) .Anal. Calcd for C_9H_8 Cl_2N_4 (242): C; 44.62, H; 3.30; N; 23.14. Found: C; 44.75, H; 3.72, N; 22.85.

Antimicrobial activity

Most of the synthesized compounds were evaluated in vitro for their antibacterial activity against Bacillus subtillus, Staphylococcus aureus, E.coli, and pseudomonas aeruginosa. Also, the antifungal activity against Aspergillus niger was evaluated using the agar-diffusion technique [21].A1mgmL^{-1} solution in (DMF) was used. The bacteria and fungi were grown on nutrient agar and Czapek's–Dox agar media, respectively. DMF as a negative control did not show inhibition zones. The agar media were incubated with different microorganism cultures tested. After 25 h of incubation at 30 ºC for bacteria and 48 h for fungi, the diameter of inhibition zone (mm) was measured. A mikacin (25 mgmL-^{1}) was used as reference drug for antibacterial and antifungal activities.

Table 1; Antimicrobial activity some synthesized compounds (diameter zones in mm).

Compound no.	**Gram-positive bacteria**	**Gram-positive bacteria**	Aspergillus niger
	Bacillus Subtillus Staphylococcus aureus	E.coli Pseudomonas aeruginosa	
5			
8			
11			
14			
15			
18			
25			
20			
St.			

Less active 1–1.2 cm; moderately active: 1.2–1.8cm; highly active 1.8–2.5cm; very highly active 2.5–3.5 cm_1.
St; A mikacin

The results for antibacterial and antifungal activities depicted in Table 1, revealed that pyrrole derivative **(20)** and 2-aminochromeno [2,3-b] pyrrole-3-carbonitrile **(11)** exhibited high activity against Bacillus subtillus, Staphylococcus aureus, E.coli and Aspergilus niger. Also, all the synthesized compounds exhibited high antifungal activity than the reference drug. On the other hand, all the prepared compounds

exhibited moderate antibacterial and antifungal activities against the reference drug. From the above results, its found that pyrrole derivative **(20)** and chormeno derivative **(11)** are biologically active rather than the other synthesized compounds.

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