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Utility of 2-cyano-*N*-(1-(4-morpholinophenyl)ethylidene)aceto hydrazide for the synthesis of some new acrylohydrazide, 2-oxo-1,2-dihydropyridine, bispyridine and chromene derivatives as potent antimicrobial agents

M. H. Helal[1,2]

[1]*Department of Chemistry, Faculty of Science, Al-Azhar University, PO box 11284, Nasr City, Cairo, Egypt*
[2]*Department of Chemistry, Faculty of Arts and Science, Northern BorderUniversity, Rafha, KSA*

Abstract

*Hydrazine derivative **2** underwent a series of hetrocyclization reactions through its reaction with different chemical reagents to produce acrylohydrazide, pyridine, bispyridine and chromene derivatives. The structure of the newly synthesized compounds was confirmed on the basis of analytical and spectral data. Antimicrobial activity for the newly synthesized products were tested against Gram positive bacteria and Gram negative bacteria and Fungi, compared with Amphotericin B, Ampicillin and Gentamycin as reference drugs.*

Keywords: Pyridine, Bispyridine, Chromene, *Knoevenagel* condensation and Antimicrobial activity.

INTRODUCTION

In recent years, heterocycle is important developing orientation in many fields, especially in drug discovery [1-5]. Pyridine derivatives represent one of the most biologically active classes of heterocyclic compounds [6, 7], and their derivatives are synthesized with a broad spectrum and diversity of biological activity, including fungicidal activity [8-10], herbicidal activity [11,12],PI3K alpha inhibitor [13], human immunodeficiency virus-reverse transcriptase inhibition activity [14], antituberculosis activity [15], androgenic-anabolic activities [16], and so on. Furthermore, Schiff's base structures are considered as an important nucleus in drug discovery [17, 18]. It is reported that hydrazone derivatives exhibited diverse bioactivities, such as urease inhibitory activities[19], insecticidal activity [20], leishmanicidalactivity [21], anti-cancer activity [22] and antifungal activity [23].Additionally, *N*-functionalized morpholines have found to possess diverse pharmacological activities. They are reported to exert a number of important physiological activities such as antidiabetic [24], antihyperlipo-proteinemics [25] and anti-inflammatory [26]. These were also used in treatment of inflammatory diseases, pain, migraine and asthma [27]. In view of these facts mentioned above, and also as a part of our work [28-31] on the synthesis of bioactive lead compounds for drug discovery, the presence work is aim to synthesize of novel pyridine, bispyridine and chromene derivatives, starting from 2-cyano-*N*-(1-(4-morpholinophenyl) ethylidene) acetohydrazide in order to evaluate their antimicrobial activity.

MATERIALS AND METHODS

All melting points are uncorrected. IR spectra (KBr) were measured on Shimadzu 440 spectrometer, ^{1}HNMR spectra were obtained in DMSO-d_6 on a Varian Gemini 300 MHz spectrometer using TMS as internal standard; chemical shifts are reported as (ppm). Mass spectra were obtained on GCMS\QP 1000Ex mass spectrometer at 70 ev. Elemental analyses were carried out at the Department of Chemistry, Faculty of Science, Cairo University, Egypt. Microbiology screening was carried out in the Regional Center for Microbiology and Biotechnology (RCMB), Antimicrobial unit test organisms, Al-Azhar University, Cairo, Egypt.

Chemistry

*Preparation of compounds (**4 &6a, b**): General procedure:*

Equimolecular mixture of **2** (0.01 mol), and either furfural **3** (0.01 mol),*4-(dimethylamino)benzaldehyde***5a,** (0.01 mol) or 3,4-dimethoxybenza-ldehyde **5b** (0.01mol) and piperidine in EtOH (50 mL) was heated under reflux for 1h.The resulting precipitate was filtered off, dried, and recrystallized from the proper solvent.

*2-cyano-3-(furan-2-yl)-N'-(1-(4-morpholinophenyl)ethylidene)acrylohyd- razide(**4**)*

Brown sheets (AcOH); Yield (50%); m.p. 350ºC; IR (KBr, $\overline{\nu}$, cm^{-1}): 3137 (NH), 2944, 2858 (aliph. CH), 2184 (C≡N) and 1653 (C=O; amide).^{1}HNMR (300 MHz, DMSO-d_6): δ =1.54 (s, 3H, CH_3), 3.20, 3.74 (2t, 8H, morpholinyl-H), 6.83-8.03 (m, 8H, Ar-H + methylidene-H), 8.89 (s, 1H, NH, exchangeable with D_2O) ppm. MS m/z (%): 364 (M^+, 70), 310 (9.2), 298 (18), 265 (27), 236 (22.3), 96(37.8), 81(100) 53 (38.3).Anal.Calcd. For $C_{20}H_{20}N_4O_3$: C, 65.92; H, 5.53; N, 15.38. Found C, 65.50; H, 5.00; N, 14.98.

*2-cyano-3-(4-(dimethylamino)phenyl)-N'-(1-(4-morpholinophenyl)ethyli- dene) acrylohydrazide(**6a**)*

White sheets (EtOH); Yield (40%); m.p. 262-263 ºC; IR (KBr, $\overline{\nu}$, cm^{-1}): 3304 (NH), 2891 (aliph. CH), 2197(C≡N), and 1670 (C=O; amide).^{1}HNMR (300 MHz, DMSO-d_6): δ =2.26 (s, 3H, CH_3), 3.06, 3.16 (2s, 6H, $2CH_3$),3.18, 3.75 (2t, 8H, morpholinyl-H), 6.76-8.23 (m, 9H,Ar-H + methylidene-H), 11.32 (s, 1H, NH, exchangeable with D_2O) ppm.MS m/z (%): 417 (M^+, 50), 223 (11), 157 (16), 142 (19), 77 (100), 53 (21).Elemental analysis for$C_{24}H_{27}N_5O_2$.Calcd.C, 69.04; H, 6.52; N, 16.77. Found: C, 68.60; H, 6.10; N, 16.32.

*2-Cyano-3-(3,4-dimethoxyphenyl)-N'-(1-(4-morpholinophenyl)ethylidene) acrylohydrazide(**6b**).*

White sheets (AcOH); Yield (60%); m.p. 142-143 ºC; IR (KBr, $\overline{\nu}$, cm^{-1}): 3326 (NH), 2958, 2834(aliph. CH), 2203 (C≡N), 1684 and (C=O; amide).^{1}HNMR (300 MHz, DMSO-d_6): δ =2.28 (s, 3H, CH_3), 3.20, 3.74(2t, 8H, morpholinyl-H), 3.85, 3.87 (2s, 6H, OCH_3), 6.87-7.83 (m, 7H,Ar-H), 8.19 (s, 1H, methylidene-H), 10.24 (s, 1H, NH, exchangeable with D_2O) ppm. MS m/z (%): 434 (M^+, 41), 248 (33.2), 229 (58.5), 203 (17), 142 (22.3), 77(100) 53 (65.3).Elemental analysis for$C_{24}H_{26}N_4O_4$.Calcd.C, 66.34; H, 6.03; N, 12.89.Found: C, 65.98; H, 5.60; N, 12.44.

*6-amino-4-(3,4-dimethoxyphenyl)-1-((1-(4-morpholinophenyl)ethylidene) amino)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (**8**)*

Method (A): To a solution of compound **6b** (0.01 mol) in 1,4-dioxane (40 mL) containing piperidine (0.5mL)and malononitrile (0.01 mol) was added. The mixture was cooled and the separated crystalline product was filtered, washes with ethanol, dried and recrystallized from 1,4-dioxane.

Method (B): A mixture of **2** (0.01 mol), α-cinnamonitrile**7** (0.01 mol) and piperidine (0.5 mL) in ethanol (30 mL) was heated under reflux for 6h. The reaction mixture was poured onto ice/water and the formed solid product was collected by filtration. Colorless crystals; Yield (55%); m.p. 327-328 ºC; IR (KBr, $\overline{\nu}$, cm^{-1}): 3286, 3207 (NH_2), 2958, 2932 (aliph. CH), 2214 (C≡N), and 1678 (C=O; pyridone).^{1}HNMR (300 MHz, DMSO-d_6): δ =2.15 (s, 3H, CH_3), 3.27, 3.71 (2t, 8H, morphonyl-H), 3.83, 3.85(2s, 6H, $2OCH_3$), 7.00-7.98 (m, 7H, Ar-H), 8.11 (s, 2H, NH_2 ,exchangeable with D_2O) ppm. MS m/z (%): 499 (M^{+1}, 87), 345 (7), 301 (37.2), 280(11.5), 246 (28), 96 (100), 64 (82), 53 (25).Elemental analysis for$C_{27}H_{26}N_6O_4$.Calcd.C, 65.05; H, 5.26; N, 16.86. Found: C, 64.70; H, 4.79; N, 16.32.

*2-Cyano-3-(4-(2-cyano-3-(2-(1-(4-morpholinophenyl)ethylidene)hydraz- inyl)-3-oxoprop-1-en-1-yl)phenyl)-N'-(1-(4-morpholinophenyl)ethylidene) acrylohydrazide(**9**).*

To a solution of **2** (0.02 mol) in ethanol (30 mL), terephthalaldehyde (0.01 mol) and piperidine (0.5 mL) were added and the mixture was heated under reflux for 1 h; the solid product which was produced on heating was collected and recrystallized from 1,4-dioxane as orange solid. Yield (45%); m.p. 273-274 ºC; IR (KBr, $\overline{\nu}$, cm^{-1}): 3374 (br, NH), 2960, 2855 (aliph. CH), 2200 (C≡N) and 1665 (C=O; amide). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.21 (s, 6H, $2CH_3$), 3.17, 3.72 (2t, 16H, morpholinyl-H), 6.99-7.95 (m, 12H,Ar-H), 8.19 (s, 2H, methylidene-H), 10.23 (s, 2H, NH, exchangeable with D_2O) ppm. MS m/z (%): 671 (M^+, 22), 662 (8), 501 (12.5), 439 (7.3), 385 (12), 242 (8), 149 (13), 85 (45), 71 (73), 57 (100). Elemental analysis for $C_{38}H_{38}N_8O_4$.Calcd.C, 68.04; H, 5.71; N, 16.71. Found: C, 67.65; H, 5.27; N, 16.26.

*Preparation of compounds (**10 & 11**): General procedure*

A mixture of **9** (0.01 mol), active methylene (malononitrile and / or ethyl cyanoacetate (0.01 mol)) and piperidine (0.5mL) in dioxan (50 mL) was heated under reflux for 3 h; the solid product which was produced on heating was collected and recrystallized from DMF as yellow solid.

*4,4'-(1,4-phenylene)bis(6-amino-1-((1-(4-morpholinophenyl)ethylidene) amino)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile) (**10**).*

Yield (40%); m.p. 310-311 ºC; IR (KBr, $\bar{\nu}$, cm^{-1}): 3391, 3315 (NH_2), 2961, 2855 (aliph. CH), 2215 (C≡N), and 1698 (C=O; pyridone). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.15 (s, 6H, $2CH_3$), 3.01, 3.76 (2t, 16H, morpholinyl-H), 7.00-8.21 (m, 16H, Ar-H + $2NH_2$) ppm.MS m/z (%): 799 (M^+, 29.7), 610 (8), 543 (42.5), 462 (15), 313 (5), 212 (9), 114 (19), 92 (100), 57 (87). Elemental analysis for $C_{44}H_{38}N_{12}O_4$. Calcd.C, 66.15; H, 4.79; N, 21.04. Found: C, 65.70; H, 4.40; N, 20.67.

*Diethyl 4,4'-(1,4-phenylene)bis(2-amino-5-cyano-1-((1-(4-morpholinoph-enyl)ethylidene)amino)-6-oxo-1,6-dihydropyridine-3-carboxylate) (**11**).*

Yield (50%); m.p. 350-351 ºC; IR (KBr, $\bar{\nu}$, cm^{-1}): 3422, 3330 (NH_2), 2964 (aliph. CH), 2209 (C≡N) and 1687 (C=O; pyridone). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.54 (t, 6H, CH_3) 2.21 (s, 6H, $2CH_3$),3.18, 3.73 (2t, 16H, morpholinyl-H), 4.33 (q, 4H, $2CH_2$) 6.94-7.83 (m, 16H,Ar-H + $2NH_2$) ppm.MS m/z (%): 893 (M^+, 12), 625 (50.8), 563 (15), 303 (22), 243 (17), 168 (88), 96 (84), 77 (100), 66 (40). Elemental analysis for $C_{48}H_{48}N_{10}O_8$. Calcd. C, 64.56; H, 5.42; N, 15.69. Found: C, 64.10; H, 5.03; N, 15.20.

*Preparation of compounds (**13&15**): General procedure:*

A mixture of compound **2** (0.01mol), and eithersalicylaldehyde**12** (0.01 mol), 2-hydroxy-1-naphthaldehyde **14** (0.01 mol), and piperidine (0.01mol) in EtOH (50 mL) was heated under reflux for 2 h. The resulting precipitate was filtered off, dried, and recrystallized from the proper solvent.

*2-Imino-N'-(1-(4-morpholinophenyl)ethylidene)-2H-chromene-3-carboh- ydrazide(**13**)*

Yellow powder (dioxane); Yield (70%); m.p. 266-267 ºC; IR (KBr, $\bar{\nu}$, cm^{-1}): 3306 (NH), 3054 (arom. CH), 2967, 2845 (aliph. CH), and 1658 (C=O; amide).^{1}HNMR (300 MHz, DMSO-d_6):δ = 2.26 (s, 3H, CH_3),3.21, 3.76 (2t, 8H, morpholinyl-H), 6.96-7.85 (m, 9H,Ar-H+ chromene-H), 9.25,13.42 (2s, 2H, 2NH, exchangeable with D_2O)ppm.MS m/z (%): 390 (M^+, 100), 315 (4.5), 252 (78.5), 221 (45), 180 (51), 119 (39.3), 92(18), 76(42), 53 (78).Elemental analysis for$C_{22}H_{22}N_4O_3$.Calcd.C, 67.68; H, 5.68; N, 14.35; Found: C, 67.26; H, 5.21; N, 13.97.

*3-Imino-N'-(1-(4-morpholinophenyl)ethylidene)-3H-benzo[f]chromene-2-carbohydrazide (**15**)*

Yellow powder (dioxane); Yield (66%); m.p. 250-251 ºC; IR (KBr, $\bar{\nu}$, cm^{-1}): 3274 (NH), 2954, 2842 (aliph. CH), 1665(C=O; amide).^{1}HNMR (300 MHz, DMSO-d_6):δ = 2.26 (s, 3H, CH_3),3.17, 3.75 (2t, 8H, morpholinyl-H), 6.94-8.45 (m, 11H,Ar-H+ chromene-H), 9.21, 13.43 (2s, 2H, 2NH, exchangeable with D_2O) ppm.MS m/z (%):440 (M^+, 12), 371 (9.5), 283 (12.2), 263 (15), 251 (6), 231 (15), 92(100), 53 (10).Elementalanalysis for $C_{26}H_{24}N_4O_3$. Calcd. C, 70.89; H, 5.49; N, 12.72. Found: C, 70.50; H, 5.00; N, 12.34.

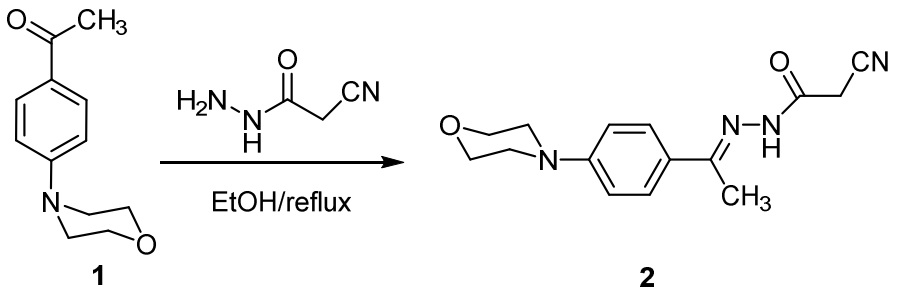
Antimicrobial screening

The disks of Whitman filter paper were prepared with standard size (6.0 mm diameter) and kept into 1.0 Oz screw capped wide mouthed containers for sterilization. These bottles are kept into hot air oven at a temperature of 150 ºC. Then, the standard sterilized filter paper disks impregnated with a solution of the test compound in DMF (100 µL, 5 mg/mL) were placed on nutrient agar plate seeded with the appropriate test organism in triplicates. Standard concentrations of 10^6 CFU/mL (Colony Forming Units/mL) and 10^4 CFU/mL were used for antibacterial and antifungal assay, respectively. Pyrex glass Petri dishes (9 cm in diameter) were used and two disks of filter paper were inoculated in each plate. The utilized test organisms were *S.aureus*, *S.epidermidis* and *B.subitilis* as examples of Gram-positive bacteria and *P.aeruginosa*, *P. vulgaris* and *K. pneumonia* as examples of Gram-negative bacteria. They were also evaluated for their in vitro antifungal potential against *A.fumigatus*, *A.clavatus* and *G.candidium* fungal strain. Ampicillin and gentamycin were used as standard antibacterial agents; while amphotericin B was used as standard antifungal agent. DMF alone was used as control at the same above-mentioned concentration and due this there was no visible change in bacterial growth. The plates were incubated at 37 ºC for 24 h for bacteria and for 48 h at 25 ºC for fungi. The mean zone of inhibition measured in mm ± standard deviation beyond well diameter (6 mm) produced on a range of environmental and clinically pathogenic microorganisms.

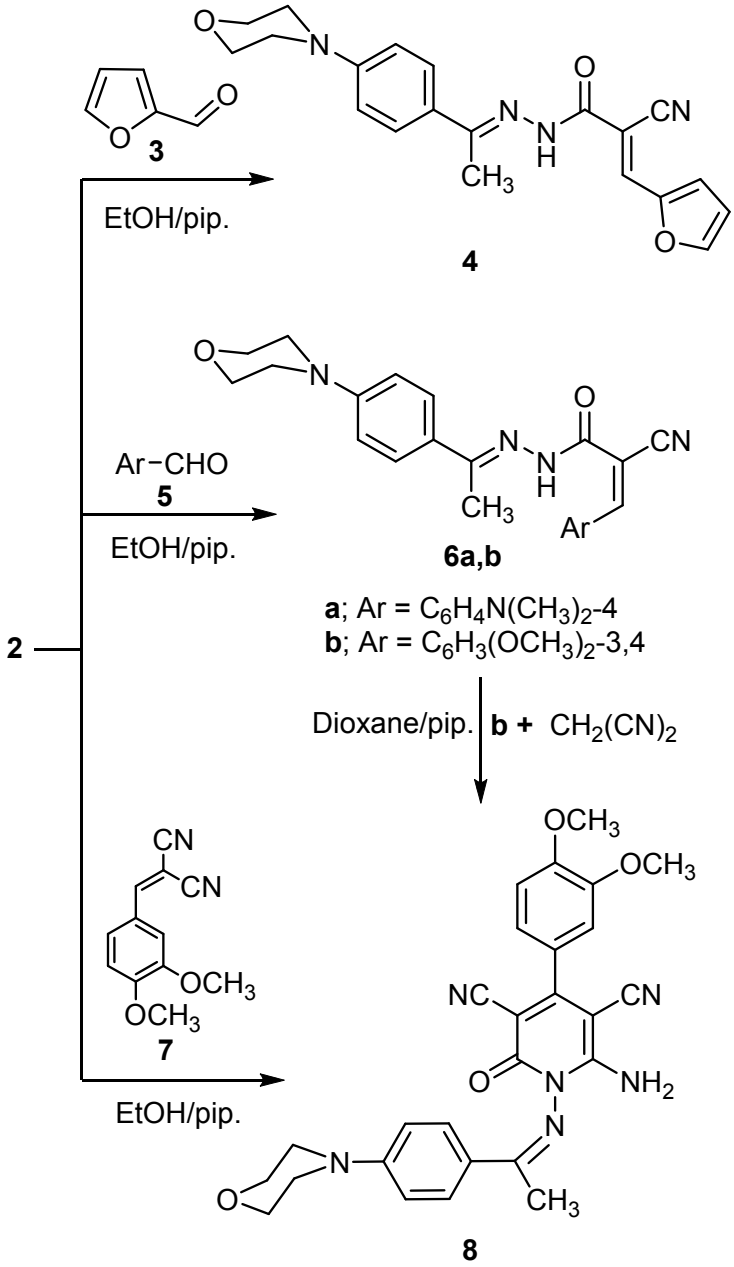
RESULTS AND DISCUSSION

Chemistry

The key intermediate 2-cyano-*N*-(1-(4-morpholinophenyl)ethylidene) acetohydrazide **2** was obtained by the reaction of cyanoacetic acid hydrazide with ethanone **1**[32] by refluxing in ethanol [33] (Scheme 1).



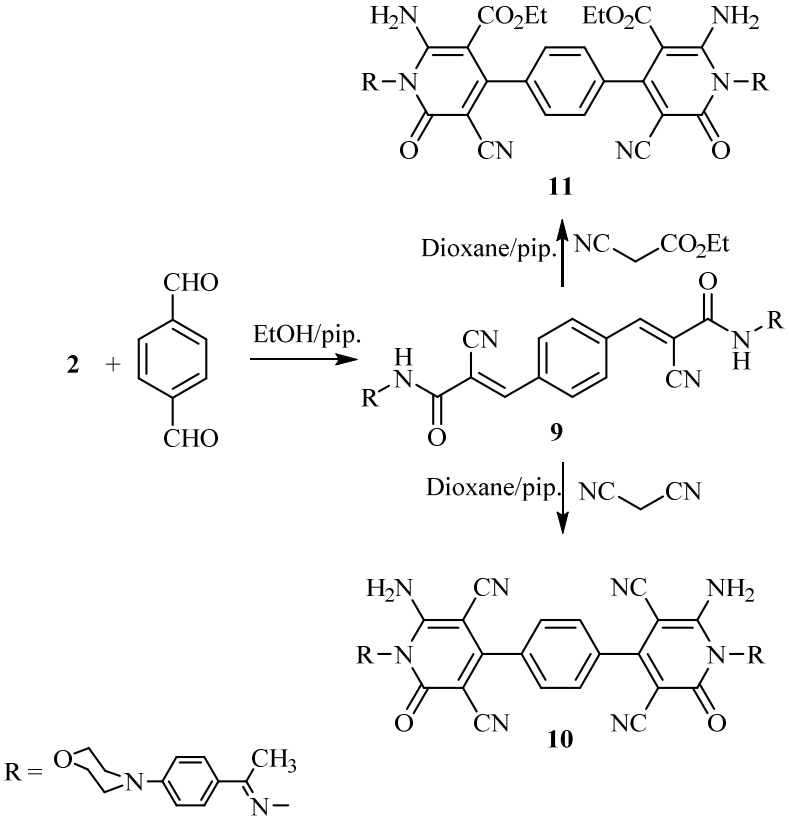
Scheme 1. Synthetic pathway for compound 2



Scheme 2. Synthetic pathways for compounds 4, 6a, b and 8

The reactivity of methylene moiety in hydrazone derivative **2** towards some electrophilic reagents was investigated. The novel acrylohydrazide **4** was synthesized by condensation of compound **2** with furan-2-carboxaldehyde **3** in ethanol in the presence of piperidine under reflux. The structure of acrylohydrazide **4** was established on the basis of its elemental analysis and spectral data. The IR spectrum of acrylohydrazide **4** was characterized by the presence of NH, C≡N and C=O groups. The ^{1}H-NMR spectrum of compound **4** (DMSO-d_6) showed a singlet signal at δ 1.54

ppm assigned to the methyl protons, a two singlets at δ 3.20, 3.74 ppm assigned to morpholinyl protons in addition to the presence of methine, NH and aromatic protons. Also, the mass spectrum showed a molecular ion peak at m/z =364 (70%) corresponding to the molecular formula $C_{20}H_{20}N_4O_3$ with base peak at m/z =81. Similarly, condensation of compound **2** with aromatic aldehydes under reflux in ethanol/ piperidine furnished the acrylohydrazides **6a,b.** The structures of the acrylohydrazides **6a,b** were established on the basis of their elemental analysis and spectral data. The mass spectrum of compound **6a** showed a molecular ion peak at m/z =417(50%) and the base peak was found in the spectrum at m/z=77 (phenyl moiety). A molecular ion peak was observed in the mass spectrum of compound **6b** at m/z =434 (41%) corresponding to the molecular formula $C_{24}H_{26}N_4O_4$.Treatment of compound **6b** with malononitrile in 1,4-dioxane in the presence of piperidine as a catalyst afforded pyridine derivative **8** (Scheme 2).The structure of the isolated product was confirmed on the basis of elemental analyses and spectral data. For example, The ^{1}H NMR spectrum (DMSO-d_6) of the compound **8** revealed a singlet at δ 2.15 ppm assigned to the CH_3 protons, a singlet at δ 3.83, 3.85 ppm assigned to the two OCH_3 protons, a singlet at δ 8.11 ppm assigned to the NH_2 protons in addition to the presence of morpholinyl and aromatic protons. Additionally, the structure of compound **8** was established chemically through the reaction of compound **2** with substituted cinnamonitrile **7** in refluxing ethanol containing a catalytic amount of piperidine (Scheme **2**).

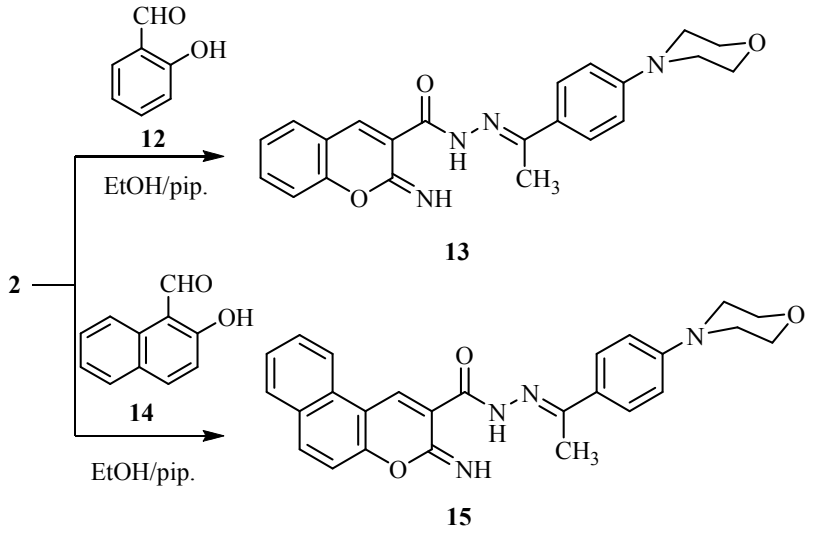


Scheme 3. Synthetic pathways for compounds 9-11

Knoevenagel condensation of compound **2** with terephthalaldehyde in ethanolic/piperidine solution under reflux conditions afforded bis(acrylohydrazide) **9** (Scheme **3**). A molecular ion peak at m/z = 671 (22%) was observed in the mass spectrum of compound **9** together with a base peak at m/z=57.The reactivity of 1-(4-morpholinophenyl) ethylidene)hydrazinyl)-3-oxoprop-1-en-1-yl)phenyl)-N'-(1-(4-morpholin- ophenyl)ethylidene)acrylohydrazide**9** towards some nucleophilic reagents was investigated. Thus, the reaction of compound **9** with malononitrile and/or ethyl cyanoacetate in boiling 1,4-dioxane in the presence of a catalytic amount of piperidine afforded bispyridine derivatives **10** and **11**, respectively (Scheme 3). The IR spectrum of compound **10** showed the presence of absorption peaks at 3391,3315 cm^{-1} due to stretching vibration of NH_2 group and at 1698 cm^{-1} for the C=O absorption peak (pyridone), in addition to the presence of C≡N group at 2215 cm^{-1}. The mass spectrum of compound **11** showed a molecular ion peak at m/z = 893 (12%) corresponding to the molecular formula $C_{48}H_{48}N_{10}O_8$ with base peak at m/z = 77.

Cyclocondensation of compound **2** with *o*-hydroxyaldehydes (salicylaldehyde**12**and /or 2-hydroxy-1-naphthaldehyde **14**) in refluxing ethanol in the presence of piperidine furnished 2-imino-*N'*-(1-(4-morpholinophenyl)ethylidene)-2*H*-chromene-3-carbohydrazide **13** and 3-imino-*N'*-(1-(4-morpholinophenyl) ethylidene)-3*H*-benzo[*f*]chromene-2-carbohydrazide **15**,respectively(scheme 4).The ^{1}HNMR spectrum of compound

13 in DMSO-d_6 revealed the absence of methylene moiety and exhibited the presence of methyl, morpholinyl, chromene H, NH and aromatic protons. The mass spectrum of compound **15** showed a molecular ion peak at m/z=440(12%) corresponding to the molecular formula $C_{26}H_{24}N_4O_3$ with base peak at m/z 92.



Scheme 4. Synthetic pathways for compounds 13, 15

Antimicrobial evaluation

The antimicrobial screening and minimal inhibitory concentrations of the tested compounds were carried out at the Regional Center for Mycology and Biotechnology, Al-Azhar University, Cairo, Egypt. The newly synthesized target compounds were evaluated for their *in vitro* antibacterial activity againstfour strains of bacteria, two Gram positive bacteria; *Staphylococcus aureus* (RCMB 010010) and *Bacillus subtilus* (RCMB 010067) and two gram negative bacteria;*Salmonella sp*. (RCMB 010043) and *Escherichia coli* (RCMB 010052). Also, the antifungal activity was evaluated against *Aspergillusfumigatus* (RCMB 02568) and *Candida albicans* (RCMB 05036).

Agar-diffusion method [34] was used for the determination of the preliminary antibacterial and antifungal activity. Ampicillin, Gentamycin and Amphotericin B were used as reference drugs. The results were recorded in table 1 for each tested compound as the average diameter of inhibition zones (IZ) of bacterial or fungal growth around the disks in mm.

Table 1: Antibacterial inhibition zone in mm (µg/ml) of some new synthesized compounds

Compounds no.	Gram-positive bacteria		Gram-negative bacteria		Fungi	
	S. aureus	*B. subitilis*	*Salmonella sp.*	*E. coli*	*A. fumigatus*	*C. albicans*
4	10	11	9	9	14	15
6a	18	17	12	12	14	16
6b	14	15	11	12	13	14
8	20	28	14	17	21	23
9	19	26	14	16	18	21
10	23	31	17	19	21	23
11	21	32	16	18	22	23
13	NA	14	13	10	NA	NA
15	NA	10	NA	NA	NA	NA
Ampicillin	23	32	*NT	NT	NT	NT
Gentamycin	NT	NT	17	19	NT	NT
Amphotericin B	NT	NT	NT	NT	23	25

**NA: no activity, *NT: not tested*

Antibacterial activity

Regarding the antibacterial activities of bisacrylohydrazide **9** was more potent than acrylohydrazides **6a** and **6b** which showed moderate activates against both Gram-positive and Gram-negative bacteria (fig.1 &2). While, acrylohydrazide **4** showed moderate activities toward all the tested bacterial strains. Concerning the antibacterial activity of pyridine derivatives, pyridine **8** and bispyridine**11** have comparable activity to Ampicillin and Gentamycin against the tested bacterial strains. Bis-pyridine **10** was equipotent to Ampicillin and Gentamycin against *Staphylococcus aureus, Bacillus subtilus, Salmonella sp*., and *Escherichia coli*. Regarding the activity of chromene derivatives, the results revealed that, chromene derivative **13** showed weak activity when compared with gentamycin against *Salmonella sp*., *Escherichiacoli*., and showed no activities against Gram positive bacteria.

Unfortunately, chromene derivative **15** showed completely inactive toward Gram-positive and Gram-negative bacteria.

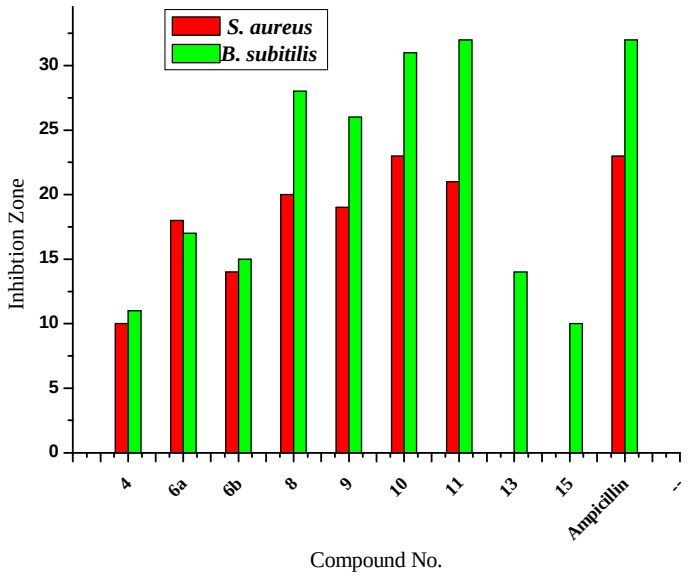


Fig. 1: Antibacterial activity of the synthesized compounds against Gram-positive bacteria

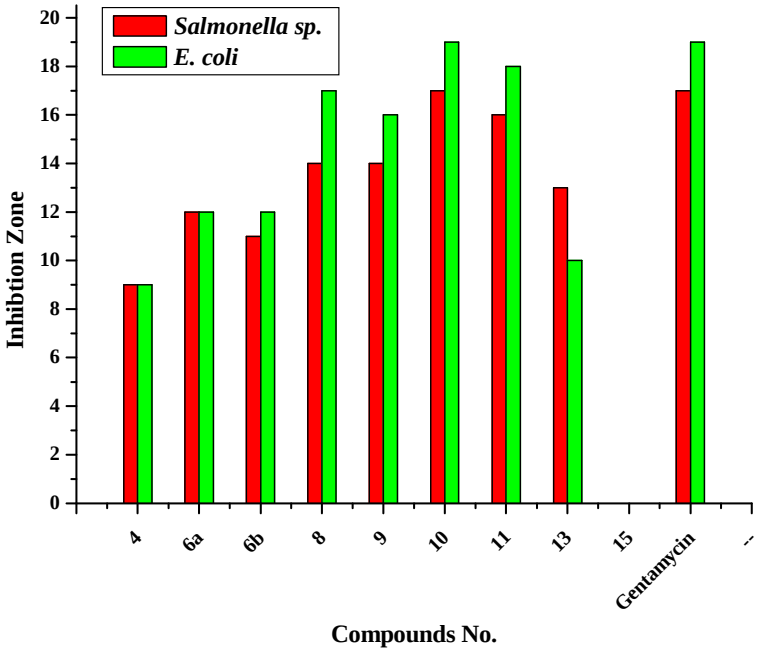


Fig. 2: Antibacterial activity of the synthesized compounds against Gram-negative bacteria

Antifungal activity

Regarding the activity of synthesized compounds against antifungal strains, Pyridine **8** and bispyridines **10** and **11**have comparable activity to Amphotericine B versus of *Aspergillusfumigatus* (RCMB 02568) and *Candida albicans* (RCMB 05036). Bis-acrylohydrazide**9** was more potent than acrylohydrazides **4**, **6a** and **6b** which showed moderate activates when compared to Amphotericine B in inhibiting the growth of antifungal strains. While, all chromene derivatives **13** and **15** showed completely inactive when compared with Amphotericine B (fig.3).

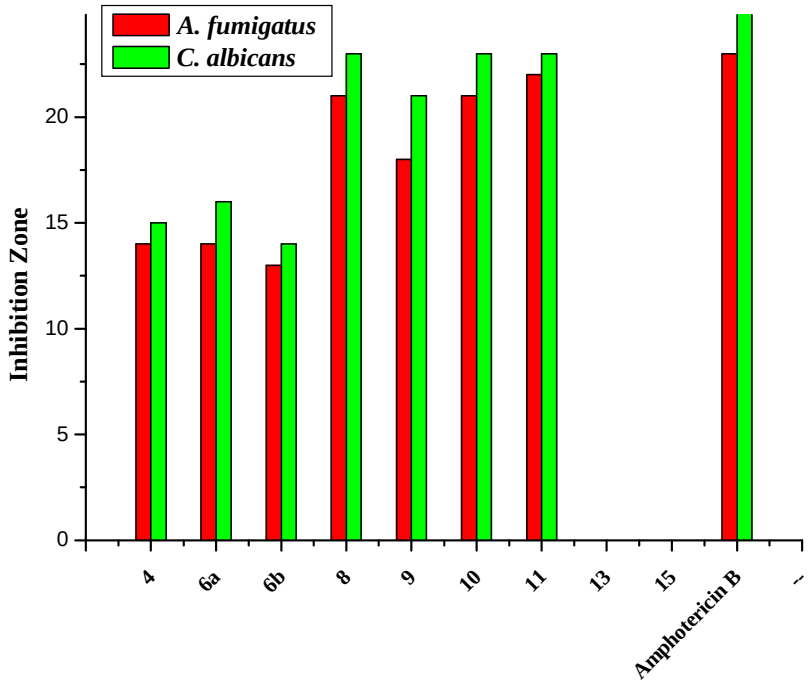


Fig. 3: Antifungal activity of the synthesized compounds

CONCLUSION

The objective of the present study was to synthesize and evaluate the antimicrobial activity of some novel pyridine, bispyridine and chromene anchored to 4-morpholine with the hope of discovering new structure serving as antimicrobial agent. The data showed clearly that most of compounds displayed good to moderate antimicrobial activity compared with Ampicillin, Gentamycin and Amphotericin B.

REFERENCES

[1] Liu, X. H.; Tan, C. X.; Weng, J. Q. *Phosphorus Sulfur Silicon Relat. Elem.* **2011**, 186, 552−557.
[2] Liu, X. H.; Pan, L.; Ma, Y.; Weng, J. Q.; Tan, C. X.; Li, Y. H.; Shi, Y. X.; Li, B. J.; Li, Z. M.; Zhang, Y. G. *Chem. Biol. Drug Des*. **2011**, 78, 689−694.
[3] Liu, X. H.; Weng, J. Q.; Wang, B. L.; Li, Y. H.; Tan, C. X.; Li, Z. M. *Res. Chem. Intermed*. **2014**, 40, 2605−2612.
[4] Zhai, Z. W.; Yang, M. Y.; Sun, Z. H.; Liu, X. H.; Weng, J. Q.; Tan, C. X. *J. Chem. Res*. **2015**, 39, 340−342.
[5] Yan, S. L.; Yang, M. Y.; Sun, Z. H.; Min, L. J.; Tan, C. X.; Weng, J. Q.; Wu, H. K.; Liu, X. H. *Lett. Drug Des.Discov*.**2014**, 11, 940−943.
[6] Zhang, L. J.; Yang, M. Y.; Hu, B. Z.; Sun, Z. H.; Liu, X. H.; Weng, J. Q.; Tan, C. X. *Turk. J. Chem*. **2015**, 39, 867−873.
[7] Zhang, L. J.; Yang, M. Y.; Sun, Z. H.; Tan, C. X.; Weng, J. Q.; Wu, H. K.; Liu, X. H. *Lett. Drug Des.Discov*.**2014**, 11, 1107−1111.
[8] Sun, Z. H.; Zai, Z. W.; Yang, M. Y.; Liu, X. H.; Tan, C. X.; Weng, J. Q. *Chin. J. Struct. Chem.* **2014**, 33, 1779−1783.
[9] Liu, X. H.; Sun, Z. H.; Yang, M. Y.; Tan, C. X.; Weng, J. Q.; Zhang, Y. G.; Ma, Y. *Chem. Biol. Drug Des*. **2014**, 84, 342−347.
[10] Yang, M. Y.; Zhai, Z. W.; Sun, Z. H.; Yu, S. J.; Liu, X. H.; Weng, J. Q.; Tan, C. X.; Zhao, W. G. *J. Chem. Res*. **2015**, 39, 521−523.
[11] Liu, X. H.; Xu, X. Y.; Tan, C. X.; Weng, J. Q.; Xin, J. H.; Chen, *J. Pest Manag. Sci*. **2015**, 71, 292−301.
[12] Liu, X. H.; Zhai, Z. W.; Xu, X. Y.; Yang, M. Y.; Sun, Z. H.; Weng, J. Q.; Tan, C. X.; Chen, J. *Bioorg. Med. Chem. Lett.* **2015**, 25, 5524–5528.
[13] Gerspacher, M.; Fairhurst, R. A.; Mah, R.; Roehn-Carnemolla, E.; Furet, P.; Fritsch, C.; Guthy, D. A. *Bioorg. Med. Chem. Lett.* **2015**, 25, 3582−3584.

[14] Yasuno, T.; Ohe, T.; Takahashi, K.; Nakamura, S.; Mashino, T. *Bioorg. Med. Chem. Lett*. **2015**, 25, 3226−3229.
[15] Moraski, G. C.; Oliver, A. G.; Markley, L. D.; Cho, S.; Franzblau, S. G.; Miller, M. *J. Bioorg. Med. Chem. Lett.* **2014**, 24, 3493−3498.
[16] Kaplancikli, Z. A.; Altintop, M. D.; Ozdemir, A.; Turan-Zitouni, G.; Goger, G.; Demirci, F. *Lett. Drug Des.Discov.***2014**, 11, 355−362.
[17] Altintop, M. D.; Ozdemir, A.; Ilgin, S.; Atli, O. *Lett. Drug Des.Discov*.**2014**, 11, 833−839.
[18] Li, W. Q.; Zhang, Z. J.; Nan, X.; Liu, Y. Q.; Hu, G. F.; Yu, H. T.; Zhao, X. B.; Wu, D.; Yan, L. T. *Pest Manag*. Sci. **2014**, 70, 667−673.
[19] Khan, K. M.; Rahim, F.; Khan, A.; Ali, S.; Taha, M.; Saad, S. M.; Khan, M.; Najeebullah; Shaikh, A.; Perveen, S. *J. Chem. Soc. Pak*. **2015**, 37, 479−483.
[20] Wu, J.; Song, B. A.; Hu, D. Y.; Yue, M.; Yang, S. *Pest Manag. Sci*. **2012**, 68, 801−810.
[21] Khan, M.; Khan, K. M.; Rahim, F.; Samreen; Perveen, S.; Karim, A.; Imtiazuddin; Choudhary, M. I. *J. Chem. Soc. Pak*. **2015**, 37, 520−526.
[22] Fu, Y.; Zhou, S. F.; Liu, Y. X.; Yang, Y. L.; Sun, X. Z.; Li, C. Z. *Biomed. Res.* J. **2014**, 527042.
[23] Casanova, B. B.; Muniz, M. N.; de Oliveira, T.; de Oliveira, L. F.; Machado, M. M.; Fuentefria, A. M.; Gosmann, G.; Gnoatto, S. C. B. *Molecules*, **2015**, 20, 9229−9241.
[24] Balamurugan, K.; Perumal, S.; Reddy, A.S.K.; Yogeeswari, P.; Sriram, D. *Tetrahedron Lett*. **2009**, 50, 6191–6195.
[25] Manfred, R.; Michael, M.; Robert, S.; Wolfgang, G.; Eckhard, R. *Ger. Offen. Chem. Abstr*. **1989**, 111, 134172.
[26] Helal, M. H. M.; Salem, M. A.; El-Gaby, M. S. A.; Aljahdali, M. *Eur. J. Med. Chem*. **2013**, 65, 517–526.
[27] Avramova, P.; Danchev, N.; Buyukliev, R.; Bogoslovova, T. *Arch. Pharm*. (**1998**)331–342.
[28] Helal, M. H.; Salem, M. A.; Gouda, M. A.; Ahmed, N. S.; El-Sherif, A. A. *SpectrochimicaActa Part A: Molecular and Biomolecular Spectroscopy*, **2015**, 147, 73–83.
[29] Gouda, M. A.; Helal, M. H. *European Journal of Chemistry* **2015**, 6, 84-88.
[30] Helal, M. H.; El-Awdan, S.A.; Salem, M.A.; Abd-elaziz, T.A.; Moahamed, Y.A.; El-Sherif, A.A.; Mohamed, G.A.M. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, **2015**, 135, 764–773.
[31] Helal, M. H. M.; Ahmed, N. S.; Elwessaly, M.; Ammar, Y. A. *Arch. Pharm. Chem. Life Sci*. **2014**, 347, 123–133.
[32] Bader, H.; Hansen, A. R.; McCarty, F. J. *J. Org. Chem.* **1966**, *31*, 2319-2321.
[33] Abdel Motaal, E. A.; EL-Gaby, M. S. A.; Salem, M. A.*Oriental J. of Chem.* **2015,** 31, 1-10.
[34] Cooper, R. E.; An analytical Microbiology, Ed. Kavangeh, F.W. Academic press:New York and London, **1972**, *I,II*.