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Synthesis and Biological Evaluation of Fused Pyrrolo– Pyrano– Pyrmidine and Pyrrolo– Pyrano– Pyridine Derivatives

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Abstract

New Fused Pyrrolo – Pyrano – Pyrimidine, and Pyrrolo – Pyrano – Pyridine Derivatives were synthesized and characterized by FT-IR and ^{1}HNMR, to obtains these cycles, 2-amino-4-(4-(dimethylamino)phenyl)-7-methyl-4,5,6,7-tetrahydropyrano[2,3-b] pyrrole - 3-carbonitrile [1]. which was synthesized by cyclization of compound 4-(dimethylamino)benzaldehyde with malononitrile and N-methyl-2-pyrrolidinone in ethanol in the presence of tetraethylammonium bromide as a catalyst. Reaction [1] with triethylorthoformate in acetic anhydride gave ethyl(E)-N-(3-cyano-4-(4-(dimethylamino) phenyl)-7-methyl-4,5,6,7-tetra hydropyrano[2,3-b]pyrrol-2-yl)formimidate [2].

Compounds [3], [4] and [5] were synthesized by cyclization of compound [2] with hydrazine hydrate, ethylenediamine, and phenylhydrazine respectively in methanol. Other cycles [7,8] were synthesized by hydrolysis of [1] with alcoholic solution of KOH" in dry DMF containing concentrated HCl to 5-amino-1-phenyl-1H-pyrazole-4-carboxamide [6], then cyclization with 4(dimethylamino) benzaldehyde and 3,5-dinitrobenzaldehde, and gave compounds [7] [8] respectively, cyclization of (1) with benzoyl chloride in presence of pyridine gave (9).

Pyrrolo – Pyrano – Pyridine cycles [10-13] were synthesized by cyclization [1] with some of the aliphatic ketones namely; acetone, 2-butanone and 4-methyl-2-pentanone and cyclohexanone, respectively in presence of $FeCl_3$ as catalysis and NaOH. These compounds were evaluated biological against (gram +ve) bacteria (Staphylococcus aureus and Staphylococcus epidermidis), and (gram –ve) bacteria (Escherichia coli and Klebsiella pneumonia); and antifungal activity against (Candida albicans) and the data obtained show that all compounds show activity against all bacteria and candida.

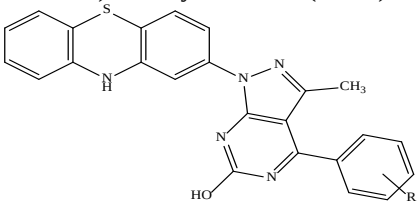
Key words: **pyrmidine, cyclic fused, biological activity**

INTRODUCTION

Pyrimidine derivatives and heterocyclic annealed pyrimidines continue to attract great interest due to the wide variety of interesting biological activities observed for these compounds, such as antiviral[1], anticancer[2], antitumor[3], anti-inflammatory[4], antimicrobial[5], antifungal[6], antihistaminic[7], anti-HIV[8], antitubercular[9], anti-neoplastic[10], antihypertensive[11], antibacterial[12], antidiabetic[13], antioxidant[14], antileshimanial[15], diuretic[16], analgesic[17] activities, and cardio-protective effects[18], and many of pyrimidines derivatives are reported to possess potential central nervous system (CNS) depressant properties[19] and also act as calcium channel blockers[20].

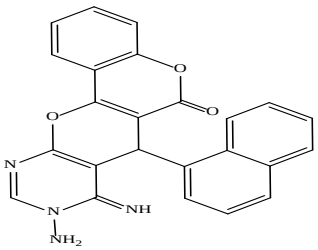
Pyrrolopyrimidines is a class of fused pyrimidine scaffolds which was found to exhibit good pharmacological properties. So, one can improve the activity of heterocyclic compounds by fusing the pyrimidine analogs with different heterocyclic moieties[21].

Pyridopyrimidine derivatives were recognized for their anticonvulsant and antidepressant activities but showed no neurotoxicity[22]. Some novel 2-heterocycle-substituted phenothiazines having a pyrazolo[3,4-d]pyrimidine (I) nucleus were achieved by using the biginelli multi-component cyclocondensation reaction. The products were evaluated for their antitubercular activity against Mycobacterium tuberculosis H37 Rv[23]. Hamid H.M. and coworkers[24] synthesized 9-amino-8-imino-7-(naphthalene-1-yl)-8,9-dihydrochromeno[3',4':5,6]pyrano[2,3-d] pyrimidine-6-one (II) and methyl-7-(naphthalene-1-yl) chromeno[3,4:5,6]pyrano[2,3-d]pyrimidin-6,8-dione (111) and tested for their in vitro anti-HIV-1 (strain IIIB) and HIV-2 (strain ROD) activity in human (MT-4) cells.



R = H , 2-Cl , 2-OH , 4-OH

(I)



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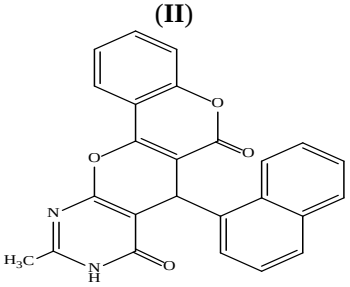


(III)

The aim of this work synthesis new fused cyclic compounds, fused pyrrolo – pyrano – pyrimidine and pyrrolo – pyrano – pyridine derivatives and study the biological activity.

2. EXPERIMENTAL

2.1. Chemical materials

All reactants and solvents used in this study were reagents grade and they are available from Sigma-Aldrich and Fluka companies. Melting points are determined in open capillary tubes in a Germany, Stuarts, SMP30 Melting points apparatus and are uncorrected. Infrared spectra (FT-IR) were recorded using a SHIMADZU FT-IR8400S spectrophotometer at the Department of Chemistry/College of Science/ University of Mustansiriyah. ^{1}HNMR spectra were recorded on a Bruker, Ultra Shield 400Mhz, spectrometer (Switzerland) using DMSO-d_6 and CD-Cl_3 as a solvent with a tetramethylsilane (TMS) as an internal standard, at the Iran polymer & petrochemical institute. All progress of the reactions and checking the purity were performed with thin layer chromatography (TLC) technique and revealed by a mixture of n-hexane and ethyl acetate (3: 2) as eluent in the

2.2 Synthesis of compounds

2.2.1. Synthesis of 2-amino-4-(4-(dimethylamino)phenyl)-7-methyl-4,5,6,7-tetrahydropyrano[2,3-b]pyrrole-3-carbonitrile [1]

In a typical procedure, equimolar amounts of 4-(dimethylamino) benzaldehyde (1.49g, 0.01mol), malononitrile (0.66g, 0.01mol) and N-methyl-2-pyrrolidinone (0.99g, 0.01mol) were mixed with tetraethylammonium bromide (10mol %) in (15ml, 90%) of ethanol and refluxed with stirring for 95min. After the completion of the reaction, the mixture was cooled to room temperature and poured into the ice to get the crude products. The crude products were purified by recrystallization from 1,4-dioxane to give [1]. The physical properties of compound [1] are listed in table (1).

2.2.2. Synthesis of ethyl(E)-N-(3-cyano-4-(4-(dimethylamino) phenyl) -7-methyl-4,5,6,7-tetrahydropyrano[2,3-b]pyrrol-2-yl) formimidate [2]

A mixture of compound [1] (2.96g, 0.01mol) and triethylorthoformate (1.48g, 0.01mol) and acetic anhydride (16ml) was refluxed for 5hs. The solvent was removed under reduced pressure and the resulting solid product is recrystallized from benzene to give [2]. The physical properties of compound [2] are listed in table (1).

2.2.3. Synthesis of 5-(4-(dimethylamino)phenyl)-4-imino-8-methyl-5,6,7,8-tetrahydropyrrolo[3',2':5,6]pyrano[2,3-d]pyrimidin-3(4H)-amine [3] ;4-(3-(2-aminoethyl)-4-imino-8-methyl-3,4,5,6,7,8-hexahydro pyrrolo [3',2':5,6]pyrano[2,3-d]pyrimidin-5-yl)-N,N-dimethylaniline [4]; and 5-(4-(dimethylamino)phenyl)-4-imino-8-methyl-N-phenyl-5,6,7,8-tetra hydropyrrolo[3',2':5,6]pyrano[2,3-d]pyrimidin-3(4H)-amine [5]

To a solution of [2] (3.52g, 0.01mol) in methanol (25ml), a solution of hydrazine hydrate (0.50g, 0.01mol), or ethylenediamine (0.60g, 0.01mol), or phenylhydrazine (1.08g, 0.01mol) was added and the mixture stirred for 1hr. Then it is allowed to stand overnight. The precipitate formed is filtered, dried and crystallized from 1,4-dioxane to give compounds [3], [4] and [5] respectively. The physical properties of compounds [3], [4] and [5] are listed in the table (1).

2.2.4. Synthesis of 2-amino-4-(4-(dimethylamino)phenyl)-7-methyl-4, 5,6,7-tetrahydropyrano[2,3-b]pyrrole-3-carboxamide[6]

To (100ml) of an alcoholic solution of KOH (5%) (2.96g, 0.01mol) of [1] was added and the reaction mixture was refluxed for 30min. After cooling the reaction mixture was diluted with water and the formed solid was filtered off, washed with water and recrystallized from DMF to give [6]. The physical properties of compound [6] are listed in table (1).

2.2.5. Synthesis of 2,5-bis(4-(dimethylamino)phenyl)-8-methyl-5,6,7,8-tetrahydropyrrolo[3',2':5,6]pyrano[2,3-d]pyrimidin-4(3H)-one [7]; and 5-(4-(dimethylamino)phenyl)-2-(3,5-dinitrophenyl)-8-methyl-5,6,7,8-tetrahydro pyrrolo[3',2':5,6]pyrano[2,3-d]pyrimidin-4(3H)-one [8]

A mixture of [6] (3.14g, 0.01mol) and 4-(dimethylamino) benzaldehyde (1.49g, 0.01mol) or 3,5-dinitrobenzaldehyde (1.96g, 0.01mol) in dry DMF (25ml) containing concentrated HCl (0.2ml) was refluxed for 24hrs. The reaction mixture was cooled filtered and the precipitate was crystallized from ethanol to give compounds [7], and [8] respectively. The physical properties of compounds [7], and [8] are listed in the table (1).

2.2.6. Synthesis of 5-(4-(dimethylamino)phenyl)-8-methyl-2-phenyl -5,6,7,8-tetrahydropyrrolo[3',2':5,6]pyrano[2,3-d]pyrimidin-4(3H)-one [9]

A mixture of compound [1] (2.96g, 0.01mol) and benzoyl chloride (1.40g, 0.01mol) in pyridine (20ml) was refluxed for 18hrs. The solid product formed upon pouring onto ice-water is collected by filtration and recrystallized from benzene to give [9]. The physical properties of compound [9] are listed in the table (1).

2.2.7. Synthesis of 4-(4-(dimethylamino)phenyl)-1,7-dimethyl-1,2,3,4-tetrahydropyrrolo[3',2':5,6]pyrano[2,3-b]pyridin-5-amine [15]; 4-(4-(dimethylamino)phenyl)-1,6,7-trimethyl-1,2,3,4-tetrahydropyrrolo[3',2':5,6]pyrano[2 ,3-b]pyridin-5-amine [16]; 4-(4-(dimethylamino)phenyl)-6-isopropyl-1,7-dimethyl-1,2,3,4-tetrahydropyrrolo[3',2':5,6]pyrano[2,3-b] pyridin-5-amine [17]; and 4-(4-dimethylamino)phenyl)-1-methyl-1,2,3,4,6,7,8,9-octahydro- pyrrolo [3',2':5,6]pyrano[2,3-b]quinolin-5-amine [18]

To a mixture of compound [1] (2.96g, 0.01mol) and ketone (10ml) : (acetone, or 2-butanone, or 4-methyl-2-pentanone, or cyclohexanone) placed in a round bottom flask connected to a reflux condenser, was added Lewis acid (1.62g, 0.01mol). The mixture was heated at 120°C for 24hrs. under stirring. After cooling to r.t, the remaining solids were treated with NaOH solution (2mol.L-1, 8ml) and this mixture was heated at reflux for 24hrs. On cooling to r.t, the reaction mixture was extracted

with $CHCl_3$ (3x8ml), the organic layers were combined and dried over
Na_2SO_4. The solvent was evaporated under reduced pressure and recrystallized from ethanol/water to give compounds [10], [11], [12], and [13] respectively. The physical properties of compounds [10], [11], [12], and [13] are listed in the table (1).

2.3. Biological activity

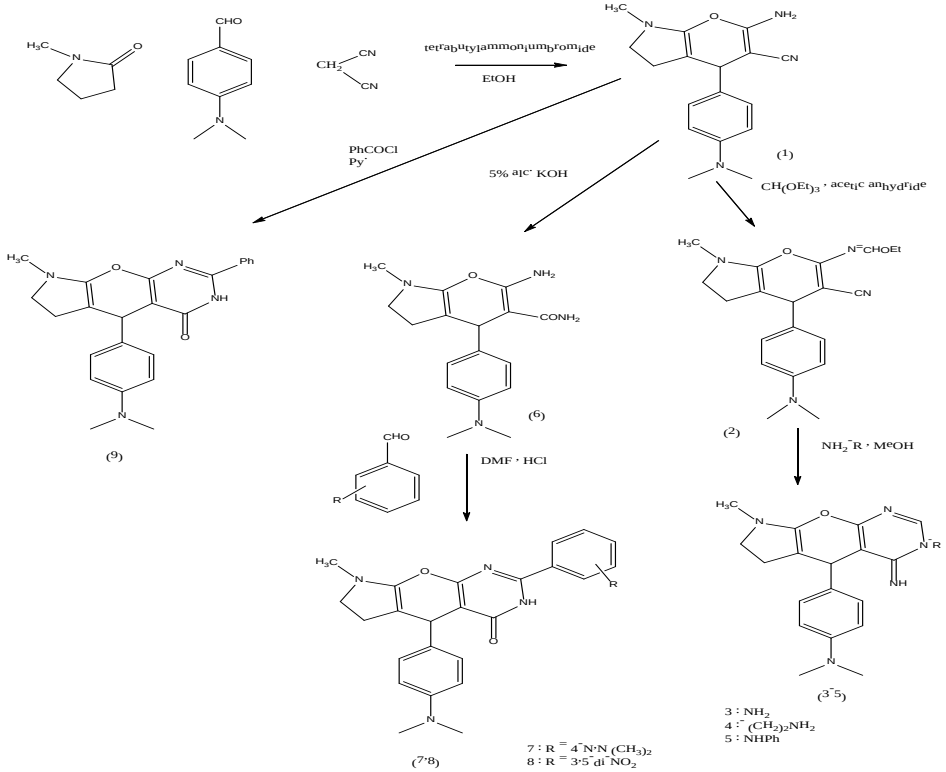
Applying the agar plate diffusion technique[25] some of the synthesized compounds were screened in vitro for antibacterial activity against (gram +ve) bacteria (Staphylococcus aureus and Staphylococcus epidermidis), and (gram –ve) bacteria (Escherichia coli and Klebsiella pneumniae); and antifungal activity against (Candida albicans). Prepared agar and petri-dishes were sterilized by autoclaving for (15 min) at 121°C. The ager plates were surface inoculated uniformly from the broth culture of the tested microorganisms. In the solidified medium suitably spaced apart holes were made all (6 mm) in diameter, were filled with (100 µl) of the prepared compounds.

The synthesized compounds [**1**], [**3**], [**5**], [**6**], [**10**], [**11**], [**12**] and [**13**] were dissolved in DMSO in concentration (10^{-3} mol.L^{-1}).

These plates were incubated at (37°C) for (24hrs.). The inhibition zones caused by the various compounds on the bacteria were examined as in the table (7).

Table (1) : The physical properties of compounds

Comp. symbol	M.F	M.W *gm/mole*	Rec. solvent	R_f	Yield(%*t*)	Color	m.p/°C
[1]	$C_{17}H_{20}N_4O$	296.37	1,4-dioxane	0.72	92	orange	178-180
[2]	$C_{20}H_{24}N_4O_2$	352.43	benzene	0.64	77	brown	162-164
[3]	$C_{18}H_{22}N_6O$	338.41	1,4-dioxane	0.91	80	yellow	261-263
[4]	$C_{20}H_{26}N_6O$	366.46	1,4-dioxane	0.89	76	reddish brown	232-234
[5]	$C_{24}H_{26}N_6O$	414.51	1,4-dioxane	0.51	84	light brown	140-142
[6]	$C_{17}H_{22}N_4O_2$	314.38	DMF	0.20	81	light brown	211-213
[7]	$C_{26}H_{29}N_5O_2$	443.54	ethanol	0.63	59	brown	121-123
[8]	$C_{24}H_{22}N_6O_6$	490.47	ethanol	0.68	67	dark brown	187-189
[9]	$C_{24}H_{24}N_4O_2$	400.48	benzene	0.57	77	dark brown	88-90
[10]	$C_{20}H_{24}N_4O$	336.43	ethanol /water	0.23	78	light brown	72-74
[11]	$C_{21}H_{26}N_4O$	350.46	ethanol /water	0.30	75	dark brown	58-60
[12]	$C_{23}H_{30}N_4O$	378.51	ethanol /water	0.43	74	yellowish brown	94-96
[13]	$C_{23}H_{28}N_4O$	376.50	ethanol /water	0.82	62	brown	104-106



Scheme (1): Synthesis of compounds (1-9)

Table (2) : The bands of compounds [3-5]

Comp.	Stretching bands (cm^{-1})					
	NH_2	NH	C-H arom.	C-H aliph.	C=N	C=C
3	3319, 3416	3192	3122	2810-3072	1602	1550
4	3355, 3406	3240	3173	2918-3091	1601	1554
5	-	3269, 3227	3186	2999-3064	1643	1595

Table (3) : The bands of compounds [7 – 9]

Comp.	Stretching bands (cm^{-1})						
	NH	C-H arom.	C-H aliph.	C=O	C=N	C=C	NO_2
7	3311	3194	2852-2955	1680	1610	1566	-
8	3347	3263	2850-2929	1683	1608	1562	1516(asymm.), 1329 (symm.)
9	3318	3097	2843–2875	1681	1600	1581	-

3. Results And Discussion

All derivatives in this work were prepared by cyclization reaction between NH_2 and C≡N with different reagent through nucleophilic substitution and disappearance of stretching bands of (NH_2 and C≡N) groups gave a good indication for successful all cyclization reactions.

3.1. Synthesize and characterization of fused pyrrolo–pyrano-pyrimidine derivatives

3.1.1. Synthesize and characterization of compounds [1-9]

To synthesise these compounds, compound (1) was selected as starting compound and it synthesized from reaction malononitrile, N,N-dimethylbenzaldehyde and 1-methyl pyrrolidine-2-one in presence of tetraethylammonium bromide as phase transfer catalysis, compound [1] was reacted with triethyl orthoformate in acetic anhydride to gave imidoformate derivative [2], the compound [2] was reacted for one hour at room temperature with hydrazine hydrate, ethylenediamine and phenylhydrazine to give fused pyrimidine derivatives [3-5].

These compounds were characterized by FT-IR and ^{1}HNMR, the FTIR of compound [1], shows stretching bands symmetrical and unsymmetrical at 3335 , 3433 cm^{-1} for (NH_2), 3213 cm^{-1} for (C-H) aromatic, 2860 - 3076 cm^{-1} for (C-H) aliphatic, 2208 cm-1 for (C≡N), 1610 cm^{-1} for N-H bending, 1562 cm^{-1} for (C=C), band at 1234 cm^{-1} for asymmetrical (C-O-C) and band at 1072 cm^{-1} for symmetrical (C-O-C). The FTIR of compound [2], shows disappearance stretching bands of (NH_2) at 3335 , 3433 cm^{-1} and appearance stretching bands at 3165 cm^{-1} for (C-H) aromatic, 2866 - 3066 cm^{-1} for (C-H) aliphatic, 2206 cm^{-1} for (C≡N), 1612 cm^{-1} for (C=N), 1564 cm-1 for (C=C) , band at 1233 cm^{-1} for asymmetrical (C-O-C) and band at 1072 cm^{-1} for symmetrical (C-O-C).The FTIR of compounds [3 –5], shows disappearance stretching band of (C≡N), this indication to successful of cyclization reaction, and the other characteristic bands shows in the table (2).

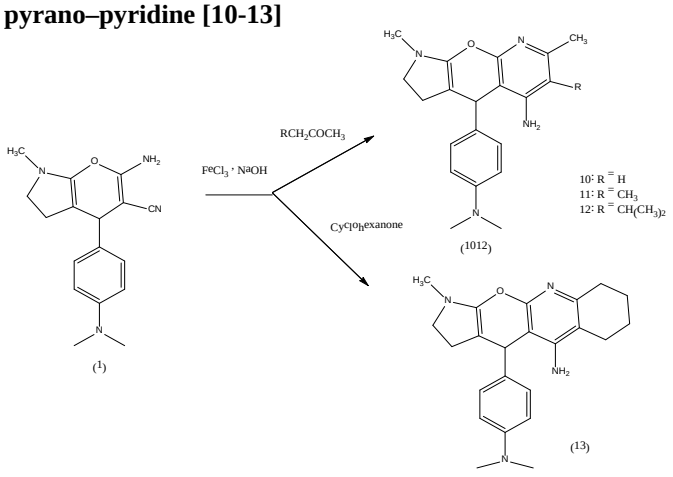
The ^{1}HNMR spectrum of compound [1], shows signals at δ = 2.28 ppm (s, 3H, NCH_3), δ = 2.36-2.44 ppm (t, 2H, CH_2), δ = 2.54-2.64 ppm (t, 2H, NCH_2), δ = 2.82 ppm (s, 6H, $N(CH_3)_2$), δ = 4.45 ppm (s, 1H, CH), δ = 6.34 ppm (s, 2H, NH_2), δ = 6.58-7.24 ppm (m, 4H, ArH). The ^{1}HNMR spectrum of compound [**3**], shows signals at δ = 2.29 ppm (*s*, 3H, N–CH_3), δ = 2.59–2.66 ppm (*t*, 2H, CH_2), δ = 2.75–2.81 ppm (*t*, 2H, N–CH_2), δ = 2.90 ppm (*s*, 6H, $N(CH_3)_2$), δ = 4.12 ppm (*s*, 1H, CH), δ = 5.05 ppm (*s*, 2H, NH_2), δ = 6.68–7.13 ppm (*m*, 4H, ArH), δ = 7.96 ppm (*s*, 1H, C=NH) and δ = 8.49 ppm (*s*, 1H, N=CH).

Compound [6] was synthesized by hydrolysis of [1] in alcoholic solution of KOH (5%), then it reacts with substituted aromatic aldehyde, such as N,N-dimethylaldehyde, and 3,5-dinitroaldehyde to give [7] and [8] respectively, while the reaction [1] with benzoyl chloride in presence of pyridine gave [9]. Compounds [6-9] were characterized by FT-IR and ^{1}HNMR, the FTIR of compound [6], shows disappearance of stretching bands (C≡N) at 2208 cm^{-1}, appearance stretching bands at 3325, 3427 cm^{-1} for symmetrical and unsymmetrical (NH_2), 3205 cm^{-1} for (C=C-H) aromatic, 2854-2935 cm^{-1} for (C-H) aliphatic, 1699 cm^{-1} for (C=O amid), 1608 cm^{-1} for (C=N), 1560 cm^{-1} for (C=C).

The FTIR of compounds [7 –9], shows disappearance stretching band of (NH_2), and the other characteristic bands show in the table (3).

The ^{1}HNMR spectrum of compound [9], shows signals at δ = 2.28 ppm (s, 3H, NCH_3), δ = 2.39-2.49 ppm (t, 2H, CH_2CH_2), δ = 2.66-2.75 ppm (t, 2H, NCH_2), δ = 2.98 ppm (s, 6H, $N(CH_3)_2$), δ = 4.38 ppm (s, 1H, CH), δ = 6.69-7.25 ppm (m, 4H, ArH) (N, N-dimethyl benz. ring), δ = 7.33-7.98 ppm (m, 5H, ArH) (benz. ring) and δ = 11.28 ppm (s, 1H, NH).

3.2. Synthesize and characterization of fused pyrrolo–pyrano–pyridine [10-13]



Scheme (2): Synthesis of compounds (10-13)

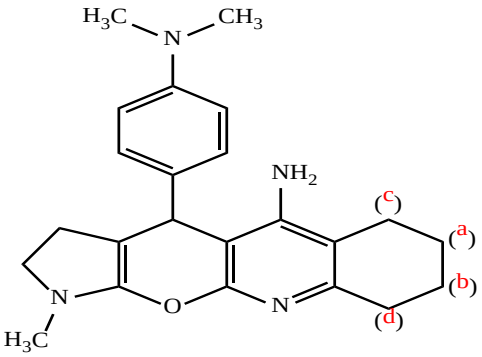
Compound [10-13] were synthesis by treatment (1) with some aliphatic ketone such as acetone, 2-butanone , 4-methyl-2-pentanone and cycohexanone respectively in presence $FeCl_3$[26].

Compounds [10-13] were characterized by FT-IR and ^{1}HNMR, the FTIR of compound [10-13], shows disappearance stretching band of (NH_2) at 3335 , 3433 cm^{-1}, (C≡N) at 2208 cm^{-1}, and the other characteristic bands shows in the table (4).

Table (4) : The bands of compounds [10-13]

Comp.	Stretching bands (cm^{-1})				
	NH_2	C-H arom.	C-H aliph.	C=N	C=C
10	3336, 3400	3111	2841-2955	1594	1579
11	3363, 3462	3203	2850-2960	1654	1595
12	3319, 3416	3192	2850-3072	1593	1558
13	3331, 3423	3213	2852-3080	1641	1610

The ^{1}HNMR spectrum of compound [13], shows signals at δ = 1.42-1.55 ppm (m, 2H, CH_2a), δ = 1.59-1.74 ppm (m, 2H, CH_2b), δ = 2.27 ppm (s, 3H, NCH_3), δ = 2.39 ppm (t, 2H, CH_2c), , δ = 2.52 ppm (t, 2H, $CH2CH_2N$), δ = 2.63 ppm (t, 2H, NCH_2), δ = 2.75 ppm (t, 2H, CH_2d), δ = 2.87 ppm (s, 6H, $N(CH_3)_2$), δ = 3.98 ppm (s, 2H, NH_2), δ = 4.35 ppm (s, 1H, CH), δ = 6.62-7.24 ppm (m, 4H, ArH).



Compound [13]

3.4. Biological activity

The results of the preliminary screening test are listed in (**table 5**) and the data obtained showed all compounds have biological activity against bacteria and candida and compounds [**3**], [**5**], [**11**] and [**12**] have highest activity than other compounds against all bacteria and candida, and other compounds gave slight activity against some bacteria and candida. It's found that compounds [**5**] and [**6**] have the highest activity against *Staphylococcus aureus*, compounds [**12**] are found to have the highest activity against *Staphylococcus epidermidis*, compounds [**13**] are found to have the highest activity against *Escherichia coli*, while the other compounds show either slight or no activity at all. this high activity due to the presence of poly heterocyclic which contains heteroatoms such as nitrogen, oxygen, and sulfur.

Table (5) : Antibacterial activities of some of synthesized compounds

Comp. symbol	Grame positive		Grame negative		Fungi
	S. aureus	***S. epidermidis***	***E. coli***	***Klebsiella pneumniae***	***Candida albicans***
[**1**]	12	11	10	10	-
[**3**]	17	14	17	16	18
[**5**]	19	19	16	10	20
[**6**]	20	16	18	14	12
[**10**]	12	10	16	6	7
[**11**]	18	23	16	13	6
[**12**]	18	9	20	12	17
[**13**]	14	6	8	12	12

*Zone diameter of growth inhibition (*mm*) after 24 hours, at the conc. $1x10^{-3}$ $mol.L^{-1}$ in DMSO.

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