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SYNTHESIS, STRUCTURAL CHARACTERIZATION AND ANTIBACTERIAL EVALUATION OF SOME NEW PYRROLIDINE DERIVATIVES

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ABSTRACT

2-naphthyl chalcones where prepared by using Claisen-Schmidt condensation. In addition, Schiff bases were produced by condensation of benzyl amine with substituted benzaldehyde, adding the latter to the chalcones by 1,3-anionic cyclo addition to the double bond of chalcones afforded the corresponding heterocycles pyrrolidines (1-24). Spectral data and some physical properties were used to support the structure of the new products. The proposed reaction mechanism was investigated using (H.F) and steric energy (S.E) calculation the antibacterial activity for pyrrolidines had been tested through it's effects on two kinds of bacteria.

KEYWORDS: 1,3-anionic cycloaddition, 2-naphthyl chalcones, Schiff's Bases, pyrrolidines, antibacterial activity.

INTRODUCTION

Pyrrolidine also known as tetrahydro pyrrole is an organic compound C_4H_9N which is cyclic secondary amine and is classified within saturated heterocyclic compounds[1] it's colourless liquid blends with water and most organic solvents. Similar to ammonia but with a distinctive aroma. It could be prepared by reaction between succinic anhydride with 2,4-di chloro-4-tri flouro methyl aniline in the presence of acetyl chloride[2] coupling of pyrrolidine with diazonium salt results 1-{4-[(*E*)-pyrrolidin-1-yl diazenyl]phenyl}ethanone.[3]

These compounds undergo to typical reaction of secondary or tertiary amine[4] for this reason it could be used as a precursors for building some important compounds like alkaloids and

pharmacological active compounds.[5-8] Pyrrolidine derivatives used as potential new hybrid antifungal molecules[9] some showed anti-microbial[10] and anti-proliferative[11] analgesic potency[12], anti-bacterial[13], dipeptidyl-4-peptidase inhibitors[14] and antitumar.[15]

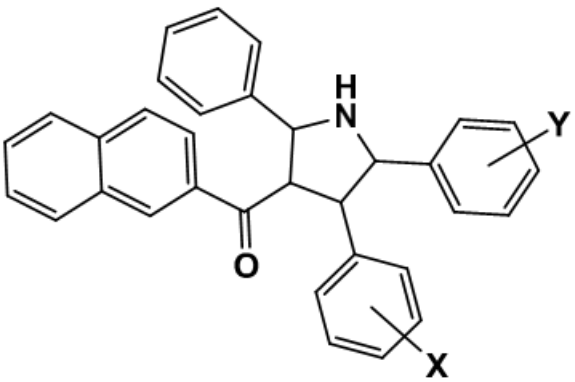
EXPERIMENTAL

Melting points were determined by Stuart SMP11 - melting point apparatus, Ultra violent spectra were determined by UV PG+ 92, Fourier-Transform Infrared Spectra were recorded by FT-IR Nicolet 100 thrmo scientific using KBr-disk, Nuclear Magnetic Resonance ^{1}H-NMR, ^{13}C-NMR spectra were registeredat 400 MHz Varian spectrometer (Selçuk University / Turkey) using TMS as an internal standard and $CDCl_3$ as solvent. Theoretical study of heat of formation (H.F) and steric energy (S.E) was achieved by using AM1 (Austin - Model 1) to explain the effect of different groups (electron donating or drawing) on the reaction.

Experimental method

General method for the synthesis of pyrrolidine[16]

in a round bottomed flask (0.001 mole) of chalcone[17] (0.001 mole) of Schiff bases[18] was dissolved in 10 ml of DMSO the mixture was magnetically stirred for 10 min at r.t. then addition of (3 ml) of 50% NaOH drop wise with continuously stirring for 3-4 hrs. at r.t., following by addition of cold water to the mixture, washing the separated precipitate with water till the filtrate become clear and neutral precipitate was dried and recrystallized from ethanol.



2,3-Diaryl-4-(β-naphthoyl)-5-phenyl pyrrolidine

Table 1: Physical properties of pyrrolidines (1-23).

Comp. No.	X	Y	m.p (°C)	Yield %	Colour
1	H	H	118 - 120	75	yellow
2	H	4-OCH_3	64 - 66	73	white
3	H	4-$N(CH_3)_2$	80 – 83	65	dark yellow
4	H	4-Cl	58 - 60	84	light yellow
5	H	4-NO_2	75 - 77	87	yellow
6	4-OCH_3	H	65 - 67	76	white
7	4-OCH_3	4-OCH_3	67 - 65	70	light brown
8	4-OCH_3	4-$N(CH_3)_2$	79 – 81	89	orange
9	4-OCH_3	4-Cl	56 - 57	74	creamy
10	4-OCH_3	4-NO_2	82 - 85	54	dark yellow
11	4-$N(CH_3)_2$	H	64 - 67	63	yellow
12	4-$N(CH_3)_2$	4-OCH_3	57 - 59	79	white
13	4-$N(CH_3)_2$	4-$N(CH_3)_2$	56 - 58	80	brown
14	4-$N(CH_3)_2$	4-Cl	64 - 67	77	yellow
15	4-$N(CH_3)_2$	4-NO_2	83 - 85	89	white
16	4-Br	4-OCH_3	105 - 108	73	light yellow
17	4-Br	4-$N(CH_3)_2$	78 - 80	65	yellow
18	4-Br	4-Cl	65 - 68	74	white
19	4-Br	4-NO_2	80 - 83	80	yellow
20	4-NO_2	H	130 - 133	79	white
21	4-NO_2	4-OCH_3	90 - 88	81	white
22	4-NO_2	4-$N(CH_3)_2$	100 - 98	87	light brown
23	4-NO_2	4-Cl	90 - 93	67	yellow

Biological activity

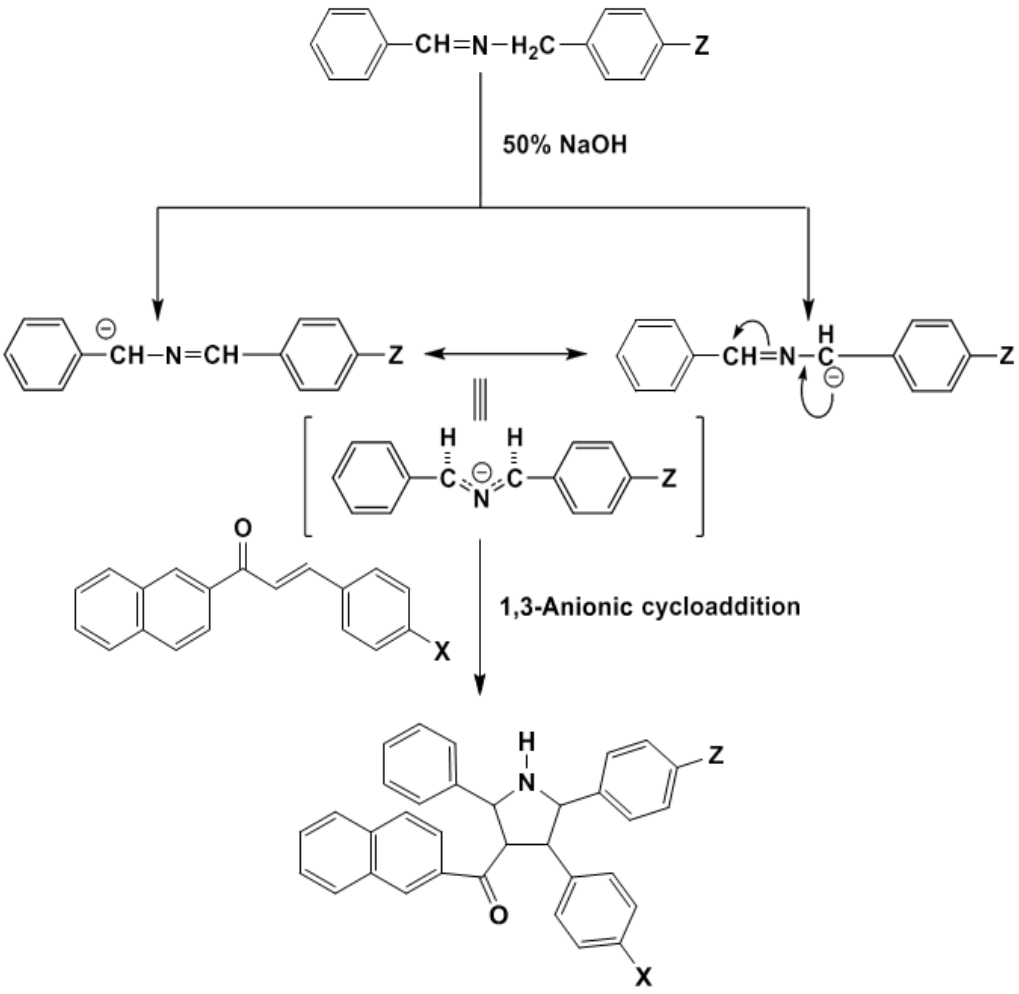
Source of microorganism: ***Staphylococcus aureus*** (Gram +ve) and ***Escherichia Coli***) Gram **–** ve was used as micro organism for present investigation. The synthesized pyrazoline derivatives were screend for their invitro antibacterial activity against ***Escherichia Coli (E. coli) Staphylococcus aureus (Staph)*** bacterial strains at a concentration (12.5 mg/ml, 100 mg/ml) by well diffusion method.[19] A standard drugs (tetracycline and ciprofloxacine) was used for comparison. Approximately (20 ml) of freshly prepared liquid agar medium was poured into each Petri dish and then the Petri dishes were dried in an incubator at (37^0C) for duration of (1h) an L-shaped spreader was used to spread the standardized culture of micro organism on each petri dish. Cups of approximately (6 mm) diameter were made in petri dishes using sterile cork borer and were A labeled. a solvent control was also tested to see the effect of control on the growth of the microbes. Dimethyl sulfoxide (DMSO) was used to prepare the solutions of synthesized compounds and ciprofloxacine and tetracycline (12.5 mg/ml, 100 mg/ml). The prepared solution were added to each cup in petri dishes and were kept aside in an aseptic area for (1h) to allow diffusion of the drug / sample, followed by

incubation at (37°C) for (24 h). The diameter of the zone of inhibition (in mm) was measured and the results are shown in (Table 5).

RESULT AND DISCUSSION

2,3-Diaryl-4-(β-naphthoyl)-5-phenyl pyrrolidine (1-23)

Were prepared by using equal moles of chalcones and Schiff bases using DMSO as solvent and 50% NaOH as base. Suggested mechanism for pyrrolidines formation is by 1,3-anionic cyclic addition[16] as following:



Scheme 1: Mechanism of pyrrolidine formation.

The IR spectrum[16] of (4) showed many distinctive absorption bands at (1664) cm^{-1} belongs to (C=O), another absorption band at (3240) cm^{-1} from (N-H) group, while (C…C) aromatic double bond showed a band at (1489) cm^{-1} and a band at (1925) cm^{-1} belongs to aliphatic (C-H) finally a band at (698) cm^{-1} for (C-Cl) bond as shown in (Table 2). The UV spectrum of (4) was measured by $CHCl_3$ solvent which exhibit a wave length at maximum absorption (λ

max) at (258) nm for electronic transition (π□π*) for (C=C) and (λ max) at (298) nm belongs to the electronic transition (n□π*) for (C=O) bond which showed blue shift because of the removal of conjugation see (Table 2). The ^{1}H-NMR spectrum[16] of (4) showed a singlet signal at (4.4) ppm belongs to (H1) proton, a singlet signal at (2.4) ppm for (H3) proton, and another singlet signal at (3.8) ppm for (H4), Singlet signal at (7.3) ppm for (H5) and multiple signals at (7.4-7.8) ppm for aromatic rings protons, see (Table 3).

Table 2: Some of the spectral properties (IR,UV) for compounds (1-23).

Comp.No.	X	Z	IR υ cm-1 (KBr)					UV λ max (nm)
			-NH	C=O	C=C	C-H aliphatic	others	
1	**H**	**H**	3240	1671	1453	2925	—	256 296
2	**H**	**4-OCH3**	3250	1660	1590	2900	C-O-C 1145 1244	212 228
3	**H**	**4-N(CH3)2**	3255	1676	1594	2980	—	254 286
4	**H**	**4-Cl**	3240	1664	1489	2925	C-Cl 698	258 298
5	**H**	**4-NO2**	3245	1667	1596	2920	N…O 1341 1516 C-O-C 1270 1145	254 295
6	**4-OCH3**	**H**	3240	1668	1512	2921	C-O-C 1178 1248	256 286
7	**4-OCH3**	**4-OCH3**	3240	1668	1511	2931	C-O-C 1247 1122	254 318
8	**4-OCH3**	**4-N(CH3)2**	3260	1690	1554	2926	C-O-C 1251 1150	223 254
9	**4-OCH3**	**4-Cl**	3250	1660	1512	2910	C-O-C 1145 1248 C-Cl 699	235 254
10	**4-OCH3**	**4-NO2**	3244	1660	1598	2930	C-O-C 1249 1176 N…O 1343 1511	244 262

11	**4-N(CH3)2**	**H**	3240	1667	1522	2867	—	217 254
12	**4-N(CH3)2**	**4-OCH3**	3250	1671	1440	2928	C-O-C 1246 1145	249 315
13	**4-N(CH3)2**	**4-N(CH3)2**	3230	1660	1594	2950	—	256 300
14	**4-Cl**	**4-N(CH3)2**	3255	1668	1522	2900	C-Cl 754	258 298
15	**4-N(CH3)2**	**4-NO2**	3210	1677	1594	2924	N…O 1362 1521	243 256
16	**4-Br**	**4-OCH3**	3240	1652	1437	2927	C-O-C 1121 1247 C-Br 560	242 318
17	**4-Br**	**4-N(CH3)2**	3245	1687	1596	2923	C-Br 523	206 256
18	**4-Br**	**4-Cl**	3250	1690	1488	2900	C-Cl 751 C-Br 570	258 288
19	**4-Br**	**4-NO2**	3250	1670	1595	2910	C-Br 570 2910 N…O 1341 1521	237 256
20	**4-NO2**	**H**	3260	1686	1595	2900	N…O 1341 1513	258 276
21	**4-NO2**	**4-OCH3**	3200	1690	1596	2928	C-O-C 1248 1176 N…O 1345 1511	257 369
22	**4-NO2**	**4-N(CH3)2**	3250	1690	1594	2923	N…O 1343 1520	256 340
23	**4-NO2**	**4-Cl**	3200	1660	1596	2910	C-Cl 697 N…O 1341 1513	229 258

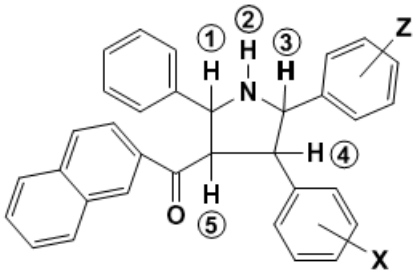


Table 3: ^{1}H-NMR spectra for compounds (4,9,13,15).

Comp.No.	X	Z	H1	H2	H3	H4	H5	X	Z	Ar-H
4	**H**	**4-Cl**	4.4 1H s	2.4 1H s	4.6 1H s	3.8 1H s	3.7 1H s	—	—	7.8-7.4 22H m
9	**4-OCH3**	**4-Cl**	4.5 1H s	2.5 1H s	4.6 1H s	3.7 1H s	3.6 1H s	3.0 1H s	—	7.9-6.9 20H m
13	**4-N(CH3)2**	**4-N(CH3)2**	3.9 1H s	2.4 1H s	4.9 1H s	3.6 1H s	3.3 1H s	2.9 6H s	3.0 6H s	8.1-6.7 20H m
15	**4-N(CH3)2**	**4-NO2**	4.1 1H s	2.4 1H s	4.9 1H s	3.3 1H s	2.9 1H s	3.1 6H s	—	8.1-6.9 20H m

Table 4: H.F (Kcal/mole) & S.E (Kcal/mole) for compounds (1,2,4).

Comp. No.	X	Z	H.F Kcal/Mole	S.E Kcal/Mole
1	H	H	100.11873	7.0830
2	H	4-OCH3	156.6052	9.7898
4	H	4-Cl	91.38203	7.6747

Biological Activity

From the (Table 1) we obtain that compounds (6) had sensitive activity against ***(E. coli***) in (100 mg/ml) concentration, compound (13) had sensitive activity against (***Staph. Aureus)*** at the same concentration but in (12.5 mg/ml) don't had activity against (***Staph. Aureus)*** in comparison with control drugs (ciprofloxacin, tetracycline). The compound (10) had moderately sensitive activity in (12.5 mg/ml) against (***E. coli***), the compound (1) had moderately sensitive activity against (***E. coli***) in (100 mg/ml) concentration, compounds (8,10) showed moderately sensitive activity against ***(E. coli***) and (***Staph. Aureus)*** at (100 mg/ml) and the compounds (1,3,5,6,8) had no activity (resistant) against (***E. coli***), (***Staph. Aureus)*** in (12.5 mg/ml) concentration, and the compounds (13) was resistant against (***E. coli***) and compounds (1,6) were resistant against (***Staph. Aureus)*** in (100 mg/ml) concentration

with control drug (ciprofloxacin, tetracycline) in the same concentration. See (Table 5).

Table 5: Shows the biological activity of some compounds and the control drugs against some bacteria Inhibitions (zones measured in mm).

12.5			100	
COMP. NO.	***Staph***	***E. Coli***	***Staph***	***E. Coli***
1	**4**	**11**	**8**	**16**
3	**5**	**5**	**7**	**8**
5	**4**	**8**	**10**	**10**
6	**5**	**5**	**7**	**17**
8	**5**	**5**	**12**	**16**
10	**10**	**12**	**12**	**15**
13	**10**	**7**	**20**	**9**
CIPROFLOXACIN	**22**	**20**	**21**	**24**
TETRACYCLINE	**19**	**20**	**20**	**22**

R = resistant (R < 11 mm)

MS = moderately sensitive (MS = 12-16 mm) S = sensitive (S > 16 mm)

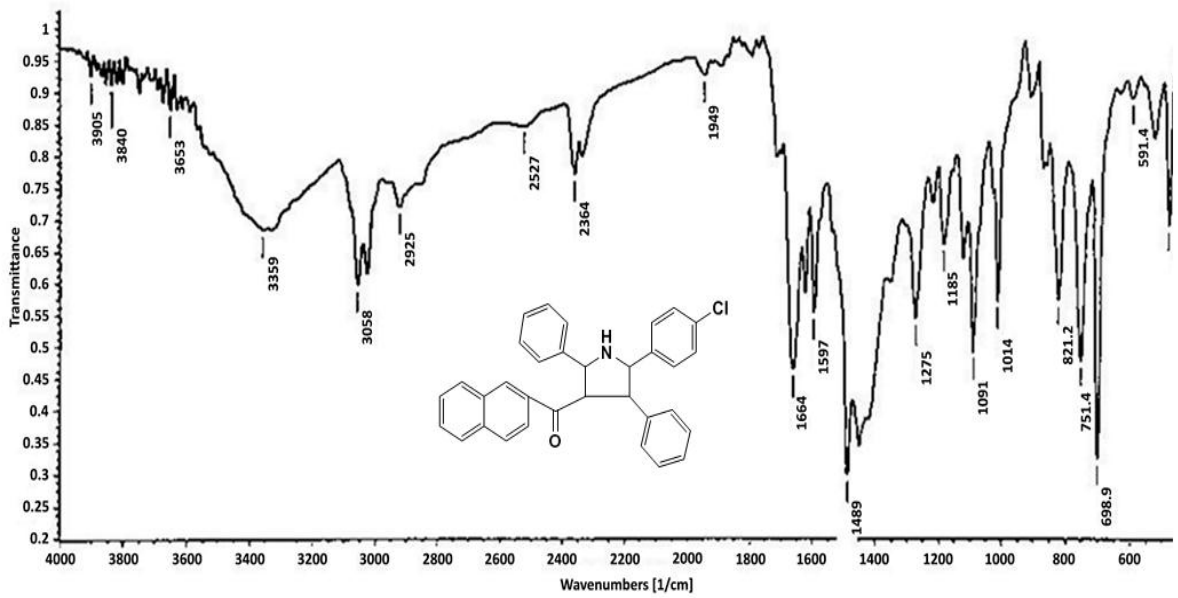


Figure 1: IR spectrum for (4).

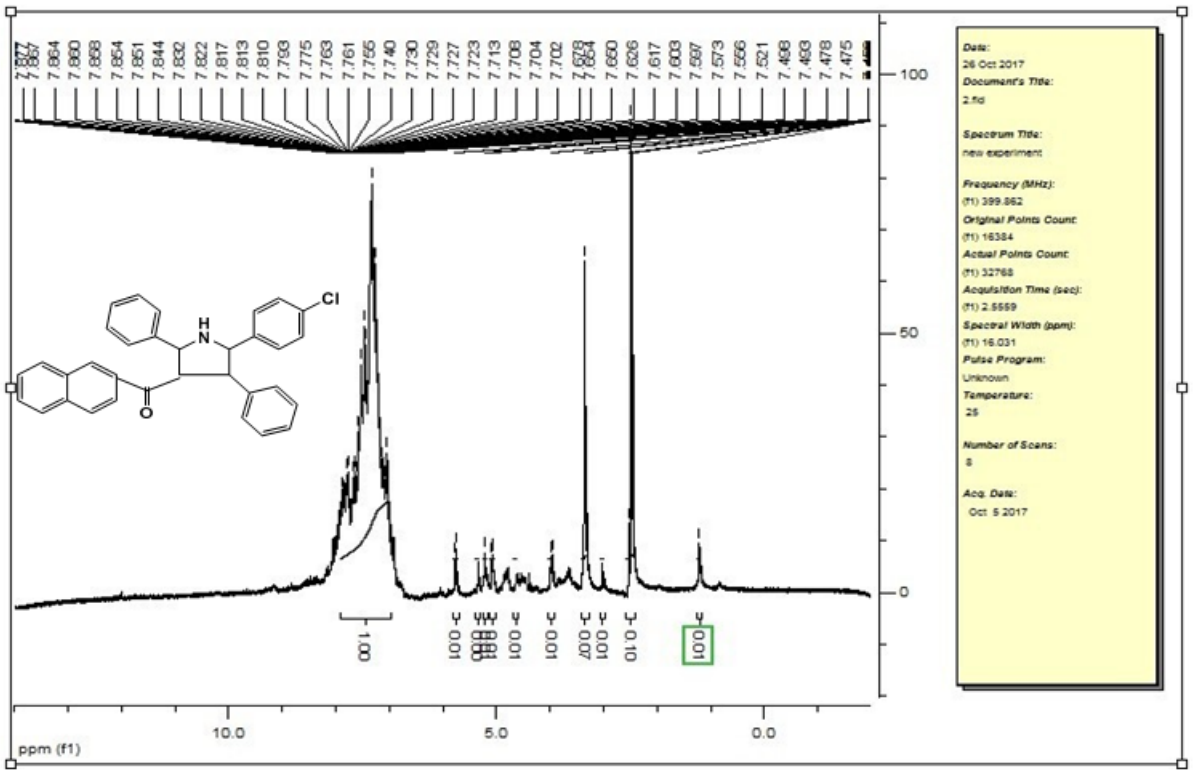


Figure 2: ^{1}H-NMR spectrum for (4).

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