

Synthesis of Spiropyrrolidines via 1, 3 Anionic Cycloaddition

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ABSTRACT

In this work, series of substituted α , β -unsaturated carbonyl compounds (A1-8) had been prepared using Claisen-Schmidt condensation. Also, series of substituted Schiff bases (N-arylidene-4-picolyamine) (B1-6) were prepared by the condensation of 4-picolyamine with various aromatic aldehydes.

The reaction of the above mentioned materials (A+B) afforded the desired products [Spiropyrrolidines (S1-15)]. The reaction occurred through the formation of azallyl anion which acted as a nucleophile that has the ability to attack the exocyclic double bond of chalcones through the 1,3-anionic cycloaddition mechanism to form the product.

The structure for all synthesized compounds (chalcones, Schiff bases, pyrrolidines) had been confirmed by the spectral data obtained by (UV, IR, $^1\text{H-NMR}$) as well as the determination of physical properties.

Keywords: spiropyrrolidine, 1,3-anionic cycloaddition.

3 1

(A 1- 8) - -
- 4 -N) (B1-6) (-)
-4 ()
(A , B)
(S1-15))
(C=C)
) (1 3)

(UV, IR, ¹H-NMR) (

3 1 :

INTRODUCTION

Spiro compounds having cyclic structure fused at a central carbon are of recent interest due to their interesting structural implications on biological system (Jayashankaran *et al.*, 2005). The asymmetric characteristics of the molecule due to the chiral spiro carbon is one of the important criteria of the biological activities (Ghandi *et al.*, 2009).

Spiro compounds represent an important class of naturally occurring substances characterized by highly pronounced biological properties (Raj and Raghunathan, 2005).

The most developed route for the synthesis of these compounds depends on the cycloaddition to an exocyclic bond. (Poornachandran and Raghunathan, 2010) (Fisera *et al.*, 1994).

The 1,3-Anionic cycloaddition provides a way for the synthesis of many spiroheterocycles through the cycloaddition reaction of nonstabilised azomethine ylides with the Chalcones (Waldmann, 1995). Also highly substituted pyrrolidines have attracted much interest as they contribute the central structural element of many alkaloids and pharmacological active compounds (Luibineau *et al.*, 1995) (Deshong and Leginus, 1983) (Manikandan *et al.*, 2001) (Subramaniyan and Raghunathan, 2001) on the synthesis of novel spiropyrrolidinyl derivatives we have examined the 1,3-Anionic cycloaddition reaction of *E*-2-arylidene-1-tetralones with the azomethine ylide generated by treatment the Schiff bases with sodium hydroxide.

EXPERIMENTAL

Melting points were determined by Electrothermal 9300 Engineering LTD Apparatus (the melting points are uncorrected), the boiling points were determined by inverted capillary in a thiele tube using paraffin colorless oil (Shriner *et al.*, 1964). A shimadzu UV-Visible spectrophotometer UV-1650/PC connected to a computer with pentium 4 processor Quartz cells (1×1×3cm) were used to for UV measurements. Fourier –Transform Infrared (FT-IR) spectrophotometer, Tensor Co. Bruker, 2003 Germany, was used to run IR spectra. The nuclear magnetic resonance (¹H-NMR) spectra were performed using (300MHz) Bruker, tetramethyl silane (TMS) as an internal standard, and CDCl₃ as a solvent in Al Al-Bayt University, Jordan.

Preparation of chalcones (arylidenecycloalkanone and derivatives (A1-8)

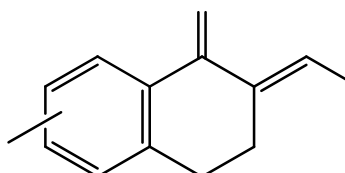
A solution of 2.2g of sodium hydroxide in 20 ml of water and 12.25 ml of ethanol were placed in a 50 ml round –bottomed flask provided with a mechanical stirrer. The flask is immersed in a bath of crushed ice. A (0.0215) mol of freshly distilled cycloalkanone was added. Stirring is then started and 0.043 mole of pure aldehyde was added. The temperature of the mixture is kept at about 25 °C (the limits are 15-30 °C) with vigorous stirring until

turns to a very thick consistency. The stirrer was stopped and the reaction mixture was left in an ice crushed bath or refrigerator overnight. The product was filtered using Buchner funnel or a sintered glass funnel, washed with cold water until the washings were neutral to litmus, and then with 20 ml of ice –cold ethanol. After drying in air, the crude chalcone was recrystallized from ethanol. The product was always handled with care as it caused a skin irritation (Vogel, 1989). The physical properties of synthesized compounds and spectral data illustrated in Tables 1 and 2. The melting points, infrared and ultraviolet data, were in a good agreement with the reported values. (Parikh, 1974).

Preparation of Schiff bases [N-Arylidene 4-picolylamine] (B1-B6)

In a 100 ml beaker, 0.01 mole of (4-picolyl amine) was heated with 0.01 mole of substituted benzaldehyde and 10 ml of n-butanol for 10 minutes at (100°C). The reaction mixture was then cooled and filtered. The precipitate was dried and recrystallized from ethanol (the liquid products were purified by distillation). The physical properties and spectral data of Schiff bases (B1-6) illustrated in Table 3 and 4 respectively. The Infrared and ultraviolet data were in a good agreement with the reported values. (Bin *et al.*, 2009).

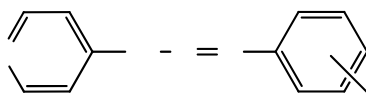
Table 1: Names and some physical properties of substituted chalcones A (1-8).



Compd. No.	Y	Ar	Reaction time /h	Color	m.p., °C	Yield %
A1	H	2-furfuryl	3	Yellow	71-73	75
A2	6-Meo	phenyl	3	Yellow	95-97	65
A3	6-Meo	4-anisyl	4	Yellow	141-143	61
A4	6-OCH ₃	p-nitro phenyl	3	Yellow	98-101	58
A5	6-OCH ₃	p-chloro phenyl	4	White	91-93	60
A6	H	phenyl	4.5	Yellow	105-107	80
A7	H	4-anisyl	3	Yellow	109-111	60
A8	H	p-chloro phenyl	3	White	72-75	83

Table 2: Spectral data of Chalcones (A1-8).

Compd. No.	IR (KBr), v cm ⁻¹				N ----- O	U.V. (CHCl ₃) λ _{max} (nm)
	C=O	C=C	C ---C	C-O-C		
A1	1664	1620	1591	1233		352
A2	1604	1660	1586	-----		324
A3	1663	1593	1508	-----		338
A4	1681	1639	1506	-----	1333 Sym 1549A sym	390
A5	1656	1606	1590	1226		304
A6	1660	1624	1589	-----		310
A7	1666	1600	1508	1222		342
A8	1662	1604	1514	-----		386

Table 3: Physical properties of the Schiff bases (B1-6).

Compd. No.	X	Color & phase	m.p. or b.P / °C	Yield %
B1	H	Yellow precipitate	70-72	76
B2	4-OCH ₃	Orange liquid	205-208	62
B3	4-NO ₂	Brown liquid	130-132	73
B4	4-Cl	Pale yellow precipitate	62-64	69
B5	3,4-di4-OCH ₃	Orange liquid	143-146	60
B6	4-CH ₃	White precipitate	40-43	75

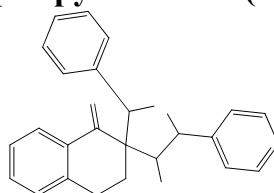
H₂
C N

Table 4 : Spectral data of the Schiff bases (B1-6).

Compd. No.	IR(KBr), $\nu(\text{cm}^{-1})$					U.V $\lambda_{\text{max}}/\text{nm}$
	C=N	C-O-C	Asym N-----O	Sym N-----O	C-Cl	
B1	1594	----	-----	-----	-----	280
B2	1606	1251	-----	-----	-----	288
B3	1600	-----	1519	1342	-----	285
B4	1633	-----	-----	-----	752	292
B5	1602	1251	-----	-----	-----	284
B6	1606	-----	-----	-----	-----	282

Condensation of chalcones with Schiff bases

A mixture of Schiff bases (0.01 mole) and chalcone (0.01 mole) was magnetically stirred in the presence of (3 ml) of (0.01mole) alcoholic sodium hydroxide solution (Popandova *et al.*, 1989). The mixture was allowed to stand overnight, water (100 ml) was then added to the reaction mixture. The separated precipitate was washed with water until the filtrate became clear and neutral. The solid product was then dried and recrystallized from methanol-ethyl acetate (8:2). The physical properties and the spectral data were listed in Table (5 and 6) respectively.

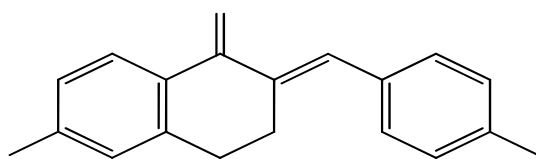
Table 5: Physical properties of Spiropyrrolidines (S1-15)

Compd. No.	Ar	X	Color	m.p/°C	Yield %
S1	2-furfuryl	H	Pale orange	167-171	51
S2	2-furfuryl	H	Pale yellow	15-139	45
S3	2-furfuryl	4-OCH ₃	Pale red	110-115	56
S4	Phenyl	H	Brown	198-204	50
S5	Phenyl	4-Cl	Yellowish brown	149-153	56
S6	Phenyl	4-OCH ₃	Brown	132-136	58
S7	4-anisyl	H	Pale brown	121-125	38
S8	Phenyl	4-NO ₂	Dark brown	220-225	41
S9	4-Chloro phenyl	4-OCH ₃	Dark orange	155-158	43
S10	4-Chloro phenyl	H	Pale brown	141-144	45
S11	4-anisyl	4-Cl	Dark brown	110-113	36
S12	4-anisyl	4-NO ₂	Pale red	135-139	45
S13	4-Cl	4-NO ₂	Dark brown	160-164	57
S14	Phenyl	3,4-diOCH ₃	Pale yellow	176-180	47
S15	Phenyl	4-CH ₃	Pale brown	184-187	50

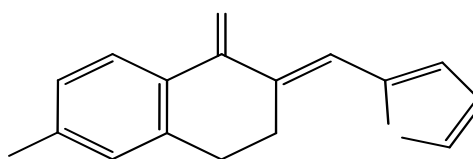
RESULTS AND DISCUSSION

α - β Unsaturated carbonyl compounds are very attractive starting materials. They are considered as precursors to build other important compounds (March, 1992) such as compounds (Katritzky, 1997) through their reaction with other different compounds.

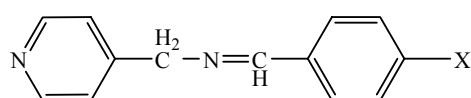
In this paper, some chalcones ATs and FTs are synthesized by condensation reaction of α - β unsaturated ketones such as:



Substituted-2(arylidene)-1-tetralone(AT)

Substituted-2(α -furfurylidene)-1-tetralone(FT)

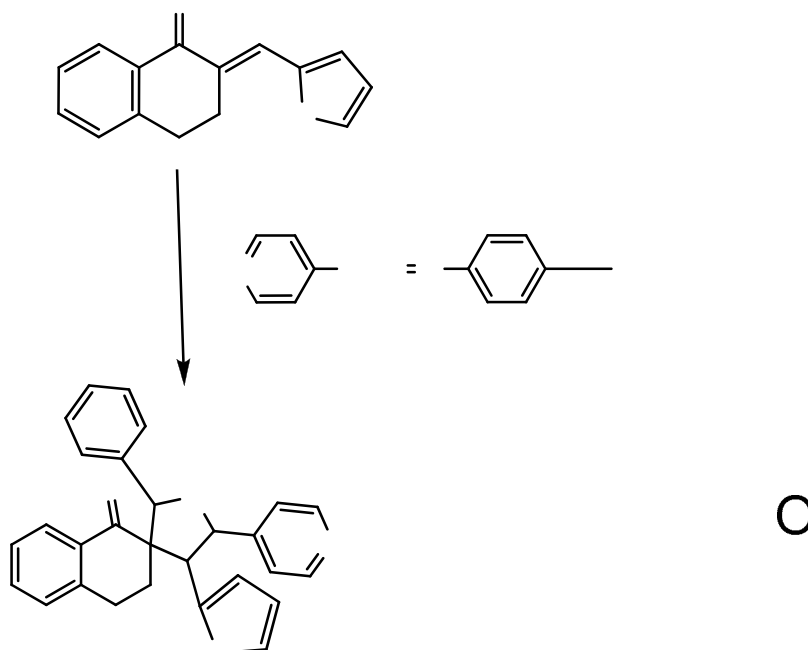
The chalcones (ATs and FTs) (A1-8) were then condensed with different Schiff bases (B1-6) of the formula



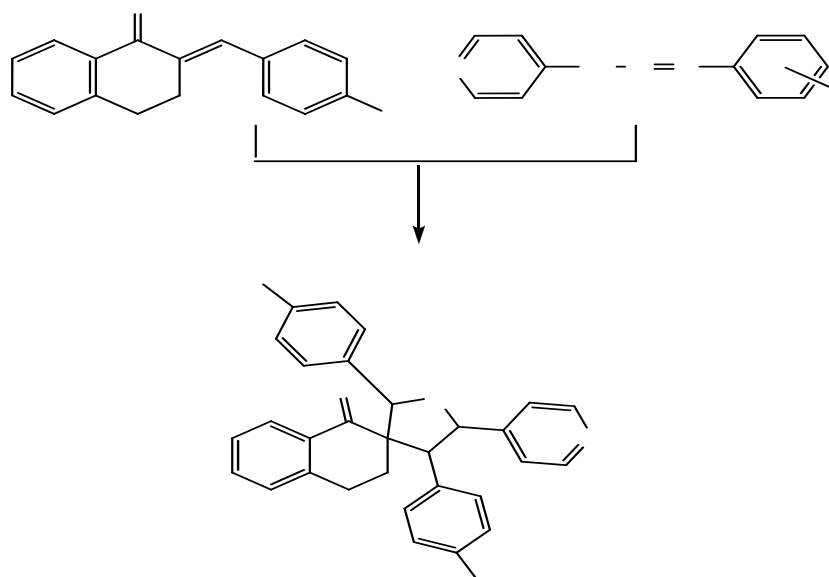
N-Arylidene-4-picolyamine

To afford the corresponding substituted spiropyrrolidines (S1-15). The prepared unsaturated ketones and Schiff bases were confirmed by spectroscopic means. The physical properties and the spectral data were in quite good agreement with the published values (Parich, 1974), Table (6 and 7).

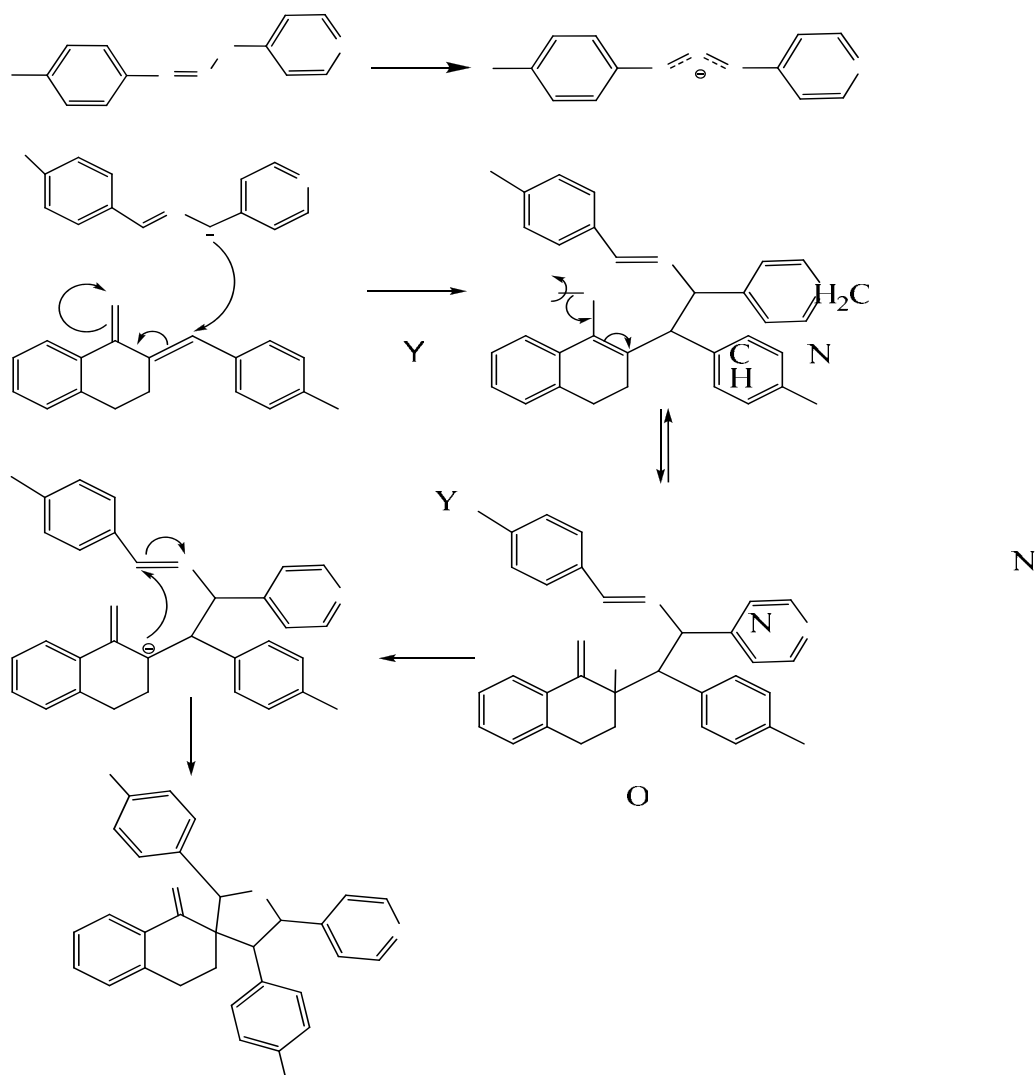
The Schemes (1 a and b) show the synthetic rout of compounds A,B and S



Scheme 1a : Reaction of 2-furfurylidene-1-tetralone (chalcones FTs) with Schiff bases



Scheme 1b: The reaction of 2-arylidene-1-tetralone with Schiff bases (A6-8)



Scheme (2): Suggested Mechanism for the formation of spiropyrrolidine compounds

The structures of the synthesized compounds (or spiropyrrolidens) have been confirmed by the spectral methods.

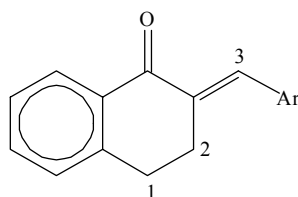
The ¹H-NMR spectrum of compound A6 is taken as a representative sample for the discussion which showed a triplet signal appeared at δ 2.0 ppm for two protons attached to (C₁), another triplet signal appeared at δ 2.2 ppm for two protons attached to (C₂), a singlet significant band for the proton attached to (C₃) showed at δ 6.3 ppm, while the aromatic protons showed a multiple bands at the range δ (6.4-7.2) ppm (Table 6).

The (FT-IR) spectra of compounds (A1-8) bands showed an absorption in the range of (1721-1656) cm⁻¹ which is related to the stretching vibration of the carbonyl group, while the absorption bands in the range of (1660-1593) cm⁻¹ related to the stretching vibration of (C=C)(double bond) (Table2).

Y

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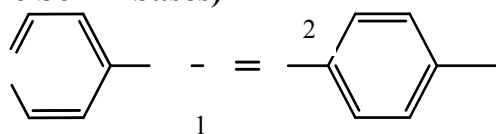
NH

Table 6: $^1\text{H-NMR}$ spectra data of 2-Arylidene-1-tetralones

Compd. No.	$^1\text{H-NMR}(\text{CDCl}_3) \delta\text{ppm}$				
	$\text{C}_1\text{-H}$	$\text{C}_2\text{-H}$	$\text{C}_3\text{-H}$	(OCH ₃)	Ar-H
A1	2.0(t) (2H)	2.4 (t) (2H)	6.3 (S) (1H)	-----	5.5-7.1(m) (7H)
A6	2.0 (t) (2H)	2.2 (t) (2H)	6.3 (S) (1H)	-----	6.4-7.2 (m) (9H)
A7	2.0 (t) (2H)	2.1 (t) (2H)	6.0 (S) (1H)	2.9 (S)(1H)	6.3-7.1 (m) (8H)
A8	2.0 (t) (2H)	2.2 (t) (2H)	6.3 (S) (1H)	-----	6.3-7.2(m) (8H)

The $^1\text{H-NMR}$ spectra of compound B1 is taken as a representative model for the discussion, which showed a singlet signal at δ 4.6 ppm related to methylene protons (CH_2) (C_1), another singlet signal at δ 7.2 ppm related to (CH) benzyl proton ($=\text{CH}$), (Table 7).

The (FT-IR) showed absorption bands in the range of (1606-1594) cm^{-1} related to the stretching vibration of the ($\text{C}=\text{N}$) bond, (Table4).

Table 7: $^1\text{H-NMR}$ of (some Schiff bases)

Compd. NO.	$^1\text{H-NMR}(\text{CDCl}_3) \delta\text{ppm}$			
	methylene group ($\text{C}_1\text{-H}$)	($\text{C}_2\text{-H}$)	others	Ar-H
B1	4.6 (S) (2H)	7.2 (S) (1H)	-----	7.3-8.4 (m) (9H)
B2	3.7 (S) (2H)	7.4 (S) (1H)	O-CH ₃ 4.8 (S) (3H)	7.5-8.8 (m) (8H)
B3	4.7 (S) (2H)	7.5 (S) (1H)	-----	7.7-8.4 (m) (8H)
B6	4.6 (S) (2H)	7.2 (S) (1H)	CH ₃ 2.3 (S) (3H)	7.7-8.4 (m) (8H)

The Schiff base [N-Arylidene-4-picolyamine] (B1-6) were reacted with chalcones (FTs) 2- (2-furfurylidene-1-tetralone) (A1) under basic conditions to afford the corresponding substituted spiro-pyrrolidenes (S1-3), also Schiff base [N-Benzylidene-4-picolyamine] (B1) and its substituted analogue [N- Arylidene-4-picolyamine] (B2-6) were reacted with 2-benzylidene-1-tetralone (A6) and substituted 2-benzylidene-1-tetralone (A7, A8) under basic conditions to afford the corresponding substituted spiro- pyrrolidenes (S4-15).

The $^1\text{H-NMR}$ spectrum of compound S1 and S4 are taken as representative models for the discussion.

The Spectrum of compound (S1) showed significant bands at the following chemical shifts:

A broad singlet signal at δ 2.5 ppm related to N-H proton, a singlet signal at δ 4.7 ppm to C_2 protons, a doublet signal at δ 3.8 ppm due to C_4 protons, another doublet signal at δ 4.4 ppm due to C_5 protons.

The aromatic protons (16H) resonate at the range of δ (6.2-8.1) ppm.

Spectrum of compound (S4) showed significant bands at the following chemical shifts:

A singlet signal at δ 2.3 ppm related to N-H proton. a singlet signal at δ 4.6 ppm related to C_2 protons, a doublet signal at δ 3.6 ppm due C_4 protons, and a doublet signal at δ 4.4 ppm due to C_5 protons.

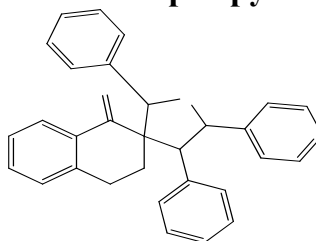
The aromatic protons (18H) resonate within the range of δ (7.0-8.0) ppm.

The $^1\text{H-NMR}$ spectra for the other synthesized pyrrolidines are listed in Table (8).

The (FT-IR) spectral (Table 9) exhibit the main absorption bands for compounds (S1-15).

A bands at the range of (1654-1715) cm^{-1} , related to the stretching vibration of the carbonyl group. a band at 3393-3446 cm^{-1} corresponds to the stretching vibration of N-H. In the case of the compounds (S1, S2, S3, S6, S7, S11, S12, S14), the absorption bands appeared at the range of (1218-1292) cm^{-1} related to the bonds of C-O-C, but in case of compounds (S3, S8, S12, S13) the nitro groups, showed absorption bands in the range of (1313-1560) cm^{-1} due to the symmetric and asymmetric stretching $\text{N}=\text{O}$ respectively (Table 9). Also in the case of compounds (S5, S9, S10, S13), the band at (741-772) cm^{-1} is related to the C-Cl stretching vibration.

The UV spectra (Field *et al.*, 2007) (Mistry, 2009) (Table 9) show a maximum absorption of compounds S(1-15) in the range of (266-352)nm, which indicates blue shift with respect to λ_{max} of the Chalcones (ATs and FTs).

Table 8: $^1\text{H-NMR}$ spectral data of some spiropyrrolidine compounds

Compd. No.	$^1\text{H-NMR}(\text{CDCl}_3)$ δ ppm							
	<u>C₆-H</u>	<u>C₇-H</u>	<u>C₄-H</u>	<u>OCH₃</u>	<u>C₅-H</u>	<u>C₂-H</u>	<u>Ar-H</u>	<u>N-H</u>
S1	2.3(t) (2H)	2.4(t) (2H)	3.8(d) 1H	----	4.4(d) 1H	4.7(S) 1H	6.2-8.1(m) 16H	8.5(S) 1H
S4	2.2(t) (2H)	2.3 (t) (2H)	3.6(d) 1H	----	4.4(d) 1H	4.6(S) 1H	7.0-8.0(m) 18H	8.4(S) 1H
S5	2.3(t) (2H)	2.4(t) (2H)	3.7(d) 1H	----	4.3(d) 1H	4.6(S) 1H	7.0-7.9(m) 17H	8.4(S) 1H
S7	2.3(t) (2H)	2.4(t)(2H)	3.6(d) 1H	3.5(S) 3H	4.2(d) 1H	4.7(S) 1H	6.9-7.8(m) 17H	8.4(S) 1H
S8	2.1(t) (2H)	2.3(t) (2H)	3.7(d) 1H	----	4.7(d) 1H	4.8(S) 1H	7.0-7.8(m) 17H	8.6(S) 1H
S10	2.3(t) (2H)	2.4t (2H)	3.6(d) 1H	----	4.4(d) 1H	4.7(S) 1H	7.0-7.6(m) 17H	8.3(S) 1H
S11	2.1(t) (2H)	2.3(t) (2H)	3.7(d) 1H	3.9(S) 3H	4.6(d) 1H	4.8(S) 1H	6.7-8.0(m) 16H	8.6(S) 1H
S12	2.3(t) (2H)	2.4(t) (2H)	3.4(d) 1H	3.7(S) 3H	3.9(d) 1H	4.7(S) 1H	6.7-8.1(m) 16H	8.4(S) 1H
S13	2.1(t) (2H)	2.4(t) (2H)	3.7(d) 1H	----	4.3(d) 1H	4.6(S) 1H	7.0-8.0(m) 16H	8.4(S) 1H
S14	2.1(t) (2H)	2.2(t) (2H)	3.7(d) 1H	3.89S) 3H	4.5(d) 1H	4.6(S) 1H	7.0-8.1(m) 16H	8.2(S) 1H
S15	2.2(t) (2H)	2.3(t) (2H)	3.6(d) 1H	CH ₃ 2.6(S) 3H	4.5(d) 1H	4.7(S) 1H	7.0-8.1(m) 17H	8.2 (S) 1H

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Table 9: U.V and IR Spectral data of pyrrolidines (S1-15).

Compd. No.	IR (KBr) , $\nu(\text{cm}^{-1})$				U.V λ_{max} (nm)
	C=O	C=C	N-H	Others	
S1	1681	1530	3415	C-O-C 1232	270,328
S2	1654	1592	3446	C-O-C 1250	340
S3	1652	1594	3393	C-O-C 1233 N=O sym 1313 asym 1560	352
S4	1715	1597	3432	-----	282
S5	1656	1598	3412	C-Cl 741	270
S6	1661	1598	3414	C-O-C 1218	292
S7	1657	1598	3413	C-O-C 1231	270
S8	1666	1579	3418	N=O sym 1345 asym 1518	282
S9	1650	1576	3438	C-Cl 772	266
S10	1681	1601	3452	C-Cl 747	268
S11	1666	1590	3430	C-O-C 1230	274
S12	1665	1592	3439	C-O-C 1219 N=O sym 1324 asym 1543	270,318
S13	1665	1597	3480	N=O sym 1334 asym 1494 C-Cl 752	286
S14	1686	1628	3415	C-O-C 1258	292,350
S15	1697	1598	3427	-----	268,402

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