Synthesis and study of Drug likeness property of "(E)-3-Substituted phenyl-1-Piperidino-2-Propen-1-one Cinnamamide

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Abstract : Cinnamamides constitute an important class of compounds with a variety of biological properties, such as central nervous system depressant, anticonvulsant, muscle relaxant, antiallergic, antineoplastic, antitumor, anesthetic, analgesic and anti-infective activities and anti-infective activities, etc. In the agrochemical field, insecticidal, their avian repellent, herbicidal activities, and several excellent cinnamamide are fungicides. Inspire of wide range of their applications and very less attention is paid towards the synthesis of cinnamamides derivatives containing heterocyclic moiety. In present work synthesized "(E)-3-Substituted phenyl-1-Piperidino-2-Propen-1-one cinnamamide" compounds before the antimicrobial screening tests, compounds under the study of drug likeness properties by using data visualization and analysis tool for chemical and biological data. The data obtained in drug likeness study is useful for selection of synthesized compounds for antimicrobial screening test.

Keywords:- Synthesis, Piperidino-Cinnamamides, Druglikeness properties.

I. INTRODUCTION

In today's technical era researchers are because to minimize expenseful work related with time, many and energy by using advance technique in various field. Similarly in drug design, Drug likeness concept helps to optimize pharmacodynamics and pharmaceutical properties, such as solubility, chemical stability, bioavailability, and distribution profile. Drug likeness is a qualitative concept used in drug design for how druglike a substance is with respect to factors like bioavailability. It is a model of various molecular properties and structural features which identify the molecule can be a potential of drug or not. Drug likeness is a broad term used to define absorption distribution metabolism excretion and toxic (ADMET) properties of a drug molecule. It is estimated from the molecular structure before the substance is even synthesized and tested. Drug-likeness rules are set of guidelines for the structural properties of compounds, used for fast calculation of drug like properties of a molecule. Now a day's Several Cinnamamides and their derivatives were received much more attention due to variety of activities such as in medicinal field, insecticidal, herbicidal, CNS depressant, antitumor, bird repellent, anesthetic, analgesic etc. Cinnamamides may be used as an intermediate or precursor in many organic syntheses and pharmaceutical formulations. After going through the detail literature survey it was observed that there is no evidence for the use of simple Wittig reaction in the synthesis of Cinnamamides. H_2O is demonstrated to be an excellent medium for the Wittig reaction employing ylides and aldehydes. Although the solubility in water appears to be an unimportant characteristic in achieving good chemical yields. The rate of Wittig reactions in water is unexpectedly accelerated. Due to wide range of such applications Cinnamamides and their derivatives acquires a great value in various fields. In present work synthesized "(E)-3-Substituted phenyl-1-Piperidino-2-Propen-1-one cinnamamide" compounds before the antimicrobial screening tests, compounds under the study of drug likeness properties by using data visualization and analysis tool for chemical and biological data. The data obtained in drug likeness study is useful for selection of synthesized compounds for antimicrobial screening test.

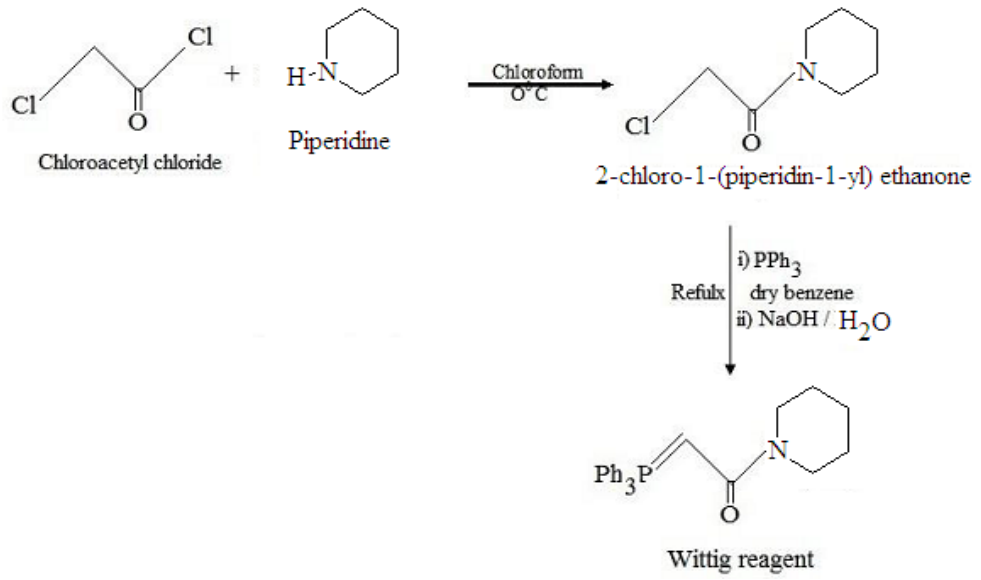
II. METHOD AND MATERIALS

All reagents and solvents were procured from high quality chemicals. Progress of the reactions was monitored by Thin Layer Chromatography. The synthesized compounds were purified by using column chromatography and identity of compounds was confirmed by Melting Points, Elemental analysis, I.R., ^{1}H NMR, ^{13}C NMR and Mass spectral data.

The IR spectra were recorded on Perkin Elmer spectrometer and 1HNMR spectra were recorded on Varian; USA makes Mercury plus 400 MHz, NMR Spectrometer by using $CDCl_3$ with TMS as internal standard. H NMR Spectrometer by using $CDCl_3$ with TMS as internal standard.

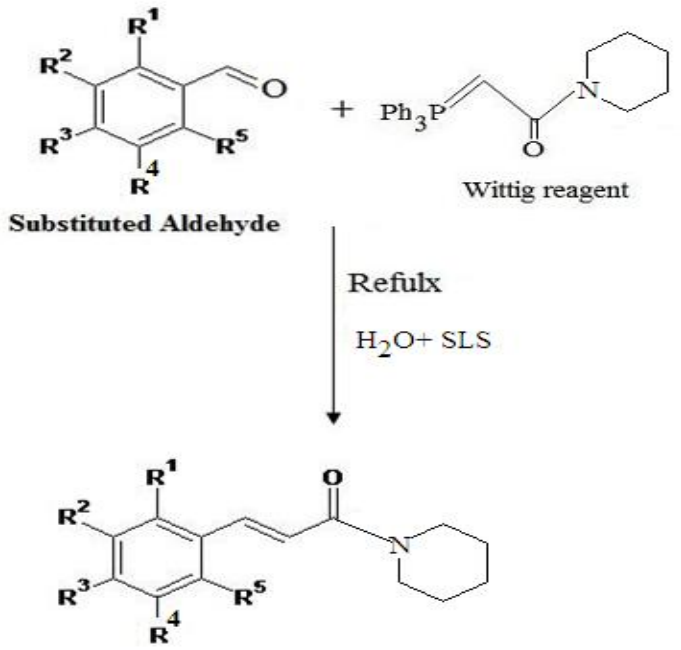
Part-I:-Preparation of Wittig Reagent:

Chloroacetyl chloride (0.1M) was added to the (0.1M) solution of piperidine in Chloroform at 0°C with constant stirring for 30 minutes. The reaction mixture was stirred at room temperature for 20 minutes and then washed with 10% Na_2CO_3 solution, the organic layer was separated and dried over Na_2SO_4, then evaporated to about 1/3rd volume and chloracetamide was collected as yellowish liquid. This liquid was added to the stirred solution of triphenyl phosphine in dry benzene and refluxed for 03 hours. White crystalline solid was obtained; it was dissolved in dry benzene (90ml) and water (10ml) solution. To this solution 1-2 drops of phenolphthalein indicator were added followed by the addition of 10% NaOH, till the pink color persist. Organic layer was separated, washed with water and evaporated to about 1/3rd volume. Finally, the liquid was scratched with hexane to obtain Wittig reagent.



Synthesis of Piperidino Cinnamamides (Scheme 2):

In a 100 ml round bottom flask, 10 ml H_2O and a pinch of Sodium Lauryl Sulphate (SLS) were taken and flask was equipped with stir bar. To this solution aromatic aldehyde was added and the reaction mixture was stirred for 10 minutes at the room temperature. Then 01 g of Wittig reagent was added with constant stirring and the reaction mixture was refluxed for 3-4 hours. The progress of reaction was monitored by thin layer chromatography. After completion of reaction, crude product was filtered off and purified by column chromatography by using silica (mesh 160) to obtained piperidino Cinnamamides (IIa-IIj).



III. **RESULTS AND DISCUSSION**

Piperidino cinnamamides (IIa-IIj) were prepared by simple, convenient and green reaction pathway and the representative compounds were characterized by suitable techniques and the results were discussed as fallows.

Table-1:-Substituted aromatic aldehydes used in the synthesis of Cinnamamides

Sr. No.	Entries	R1	R2	R3	R4	R5
1	**IIIa**	H	H	H	H	H
2	**IIIb**	H	H	OMe	H	H
3	**IIIc**	H	OMe	OMe	H	H
4	**IIId**	H	OMe	OMe	OMe	H
5	**IIIe**	H	-O-CH_2-O-		H	H
6	**IIIf**	NO_2	H	H	H	H
7	**IIIg**	H	H	Cl	H	H
8	**IIIh**	H	H	NO_2	H	H
9	**IIIi**	H	H	$N(Me)_2$	H	H
10	**IIIj**	H	H	OH	H	H

Table-2:- Characteristics data for synthesized Cinnamamides

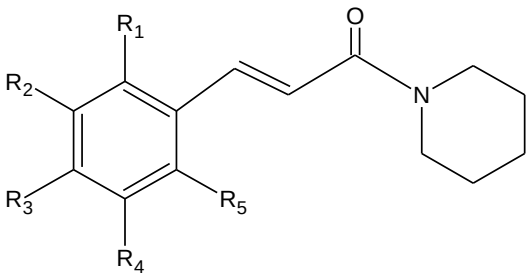
Sr. No.	Entries	Molecular Formula	Molecular weight	Yield %	M.P. ^{0}C
1	**IIIa**	$C_{14}H_{17}ON$	215	62	162
2	**IIIb**	$C_{15}H_{19}O_2N$	245	64	174
3	**IIIc**	$C_{16}H_{21}O_3N$	275	70	186
4	**IIId**	$C_{17}H_{23}O_4N$	305	64	202
5	**IIIe**	$C_{15}H_{17}O_3N$	259	68	192
6	**IIIf**	$C_{14}H_{16}O_3N_2$	260	72	160
7	**IIIg**	$C_{14}H_{16}ONCl$	249	52	180
8	**IIIh**	$C_{14}H_{16}O_3N_2$	260	66	212
9	**IIIi**	$C_{16}H_{22}ON_2$	258	60	188
10	**IIIj**	$C_{14}H_{17}O_2N$	231	62	184

Table-3:-Elemental analysis of synthesized compounds-

Sr. No.	Entries	Molecular Formula	Mol. Wt.	% C	% H	% O	% N	% Cl
1	**IIIa**	$C_{14}H_{17}ON$	215	78.10 (78.14)	7.96 (7.91)	7.43 (7.44)	6.51 (6.51)	--
2	**IIIb**	$C_{15}H_{19}O_2N$	245	73.44 (73.47)	7.81 (7.76)	13.04 (13.06)	5.71 (5.71)	--
3	**IIIc**	$C_{16}H_{21}O_3N$	275	69.79 (69.82)	7.69 (7.64)	17.43 (17.45)	5.09 (5.09)	--
4	**IIId**	$C_{17}H_{23}O_4N$	305	66.86 (66.89)	7.59 (7.54)	20.96 (20.98)	4.59 (4.59)	--
5	**IIIe**	$C_{15}H_{17}O_3N$	259	69.48 (69.50)	6.61 (6.56)	18.51 (18.53)	5.40 (5.41)	--
6	**IIIf**	$C_{14}H_{16}O_3N_2$	260	64.60 (64.62)	6.20 (6.15)	18.44 (18.46)	10.76 (10.77)	--
7	**IIIg**	$C_{14}H_{16}ONCl$	249	67.33 (67.33)	6.46 (6.41)	6.41 (6.41)	5.61 (5.61)	14.20 (14.23)
8	**IIIh**	$C_{14}H_{16}O_3N_2$	260	64.60 (64.62)	6.20 (6.15)	18.44 (18.46)	10.76 (10.77)	--
9	**IIIi**	$C_{16}H_{22}ON_2$	258	74.38 (74.42)	8.58 (8.53)	6.19 (6.20)	10.84 (10.85)	--
10	**IIIj**	$C_{14}H_{17}O_2N$	231	72.70 (72.73)	7.41 (7.36)	13.83 (13.85)	6.06 (6.06)	--

In bracket calculated percentages of element.

Drug likeness properties of (E)-3- substituted phenyl-2-piperidino-2-propen-1-one cinnamamides (IIIa-IIIj)-



General structure of piperidino cinnamamides (IIIa-IIIj)

Table :-4- Drug likeness properties of piperidino cinnamamides (IIIa-IIIj):

Entry	Molecular Formula	Mol. Wt.	Drug Likeliness Value	Drug Score	Health Hazards/ Risk Property
IIIa	$C_{14}H_{17}ON$	215	-0.93	0.57	No risk
IIIb	$C_{15}H_{19}O_2N$	245	0.53	0.35	Irritant, Reproductive effect
IIIc	$C_{16}H_{21}O_3N$	275	2.26	0.85	No risk
IIId	$C_{17}H_{23}O_4N$	305	3.43	0.86	No risk
IIIe	$C_{15}H_{17}O_3N$	259	0.47	0.41	Reproductive effect
IIIf	$C_{14}H_{16}O_3N_2$	260	-6.57	0.45	No risk
IIIg	$C_{14}H_{16}ONCl$	249	1.17	0.72	No risk
IIIh	$C_{14}H_{16}O_3N_2$	260	-9.85	0.45	No risk
IIIi	$C_{16}H_{22}ON_2$	258	-4.1	0.16	Mutagenic, Tumorigenic
IIIj	$C_{14}H_{17}O_2N$	231	0.57	0.75	No risk

The Spectroscopic data- The Spectroscopic data as IR, 1H NMR and Mass spectra of representative compounds of piperidino cinnamamides (IIIa-IIIj) series were recorded are as follows-

IIIa=(E)-3- phenyl-1-piperidino-2-propen-1-one Cinnamamides-

IR spectra: (KBr) λmax (cm^{-1})1607cm^{-1}(-C=C-, olefinic), 1595;

1H NMR-(400 MHz, CDCl3, δ ppm) 1.2(m), (2H), CH_2; 1.4(m), (4H) CH_2; 3.4(t), (4H), $2CH_2$-N; 6.8(d), (1H), (CH=CHCO), J=15.94 HZ; 7.2(d), (1H), (CH=CH-Ar) J=15.94 HZ; 7.2-7.5(m), (5H), (Ar-H).

Mass: m/z (%): 215.13 (100) (M)+, 216.0 (15.50).

IIIb- =(E)-3-(p-methoxyphenyl)-1-piperidino-2-propen-1-one Cinnamamides-

IR spectra : (KBr) λmax (cm^{-1}) 1685, 1600;

1H NMR-(400 MHz, CDCl3, δ ppm))- 1.2(m),(2H), CH_2; 1.4(m), (4H) CH_2; 3.4(t), (4H), $2CH_2$-N; 6.8(d), (1H), (CH=CHCO), J=15.94 HZ; 7.0(d), (1H), (CH=CH-Ar) J=15.94 HZ; 7.2-7.5(m), (4H), (Ar-H); 3.2(s), (3H), (-O-CH_3).

Mass: m/z (%): 245.15 (100) (M)+, 246.14 (16.59).

IV. CONCLUSIONS

The percentage yield of this compounds of series ranged from 52% to 72%, the highest percentage yield is 72% of compound (E)-3-(o-nitrophenyl)-1-piperidino -2-propen-1-one. The molecular weight range of this series (III) is 215 to 305, the highest the molecular weight compound is (E)-1-piperidino-3-(3, 4, 5-trimethoxy phenyl)-2-propen-1-one (305).

The melting point range of this series is 160^0C to 212^0C, the highest melting point is 212^0C of compound (E)-3-(p-nitrophenyl)-1-piperidino-2-propen-1-one. On the basis of analytical data, chemical properties and spectral analysis the structure of the compounds piperidino cinnamamides are assigned.

The compounds IIIa, IIIc, IIId, IIIf, IIIg, IIIh and IIIj showed good drug likeness and also have good drug score. The good drug likeness of these compounds is due to presence of methoxy, nitro and chloride functional group of molecule. These compounds does not shows any toxicity risk and health hazards. The compounds IIIb, IIIe, and IIIi showed poor drug likeness and minimum drug score. These compounds showed toxicity risk and health hazards like tumorigenic, mutagenic, irritant and reproductive effects.

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