Kabachnik–Fields synthesis of novel 2-oxoindolin methyl phosphonate derivatives using CAN.

Presented by

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One pot three componant Kabachnik–Fields synthesis of novel 2-oxoindolin methyl phosphonates derivatives as anticancer agents.

Abstract

The work reports ultrasound promoted facile synthesis of novel ten α-aminophosphonate derivatives coupled with indole-2,3-dione moiety, namely diethyl(substituted phenyl/heteryl)(2-(2-oxoindolin 3ylidene)hydrazinyl)methylphosphonates derivatives **4(a-j)**. The derivatives **4(a-j)** were synthesized through one-pot three component Kabachnik-Fields reaction, by stirring at room temperature in presence of Cerric Ammonium Nitrate (CAN) as a catalyst, to give the final compounds in better yields and in shorter reaction time. Isatin, chemically known as *H*-indole-2,3-dione, and its derivatives possess a broad range of biological and pharmacological properties. Isatin is widely used as starting material for the synthesis of a broad range of heterocyclic compounds and as substrates for drug synthesis. The α-amino phosphonate derivatives constitute an important class of organophosphorus compounds on account of their versatile biological activity. The general low mammalian toxicity of these compounds made them attractive for use in agriculture and medicine. Considering the importance of the two pharmacophores, promoted us to club both the pharmacophores in a single molecule using green synthetic protocol. The structures of the ultrasound synthesized compounds were confirmed by spectral analysis like IR, ^{1}H NMR, ^{13}C NMR, ^{31}P NMR and MS.

Keywords: Kabachnik-Fields reaction; Cerric Ammonium Nitrate; Isatin; α-amino phosphonate.

CONTENTS

INTRODUCTION

The basic method for the preparation of α-aminophosphonates, valuable synthetic equivalents and biologically active substrates, involves the condensation of a primary or secondary amine, a carbonyl compound (aldehyde or ketone) and dialkyl phosphit[1]. List of various catalysts used for synthesis of various types α-aminophosphonates and the time (minutes) required for synthesis of α-aminophosphonates are shown in **Table 1**.

Among the synthetic routes towards α-aminophosphonates two main pathways exist[2] .

1) Three-component reactions (**Kabachnik-Fields reaction**): In this an aldehyde, an amine and di- or trialkyl phosphite are reacted in a one-pot set-up.

2) Pudovik reaction:

In this dialkyl phosphites are added to compound containing an imino-bond.

α-aminophosphonates are among the most studied bioactive organo phosphorus derivatives and have been used as enzyme inhibitors [3], inhibitors of serine hydrolase [4], peptide mimics [5], antiviral [6], antibacterial [7], antifungal [8], anticancer [9], anti-HIV [10], antibiotics [11], herbicidal [12] etc.

Indole possesses various medicinal properties like antibacterial, antifungal, anti-malarial, anticonvulsant and anti-inflammatory etc. [13].

INTRODUCTION

Isatin, chemically known as 1-*H*-indole-2,3-dione, and its derivatives possess a broad range of biological and pharmacological properties and are widely used as starting materials for the synthesis of a broad range of heterocyclic compounds and as substrates for drug synthesis. It is also used for the inhibition of pro-apoptotic jurkat T cells. In terms of its mode of action, isatin itself is proposed to inhibit cancer cell proliferation via interaction with extracellular signal-related protein kinases (ERKs), thereby promoting apoptosis. These compounds inhibit cancer cell proliferation and tumor growth via interaction with a variety of intracellular targets such as DNA, telomerase, tubulin, P glycoprotein, protein kinases and phosphatases [14]. Isatin-based hydrazones have been identified as inhibitors of the protein tyrosine phosphatase Shp2, which plays an important role in cell signaling, cell proliferation, differentiation and migration [15].The marketed anticancer drug Sunitinib [16] and Oratinib contains 2-oxoindolin-3-ylidene moiety where as Ilmofosin and Edelfosin contains phosphonate moiety and a recently marketed anticancer drug, Toceranib phosphate [17] contains 2-oxoindol-3-ylidene as well as phosphonates moiety. Considering the biological importance of 2-oxoindolin-3-ylidene and α-aminophosphonates prompted us to synthesize coupled derivatives containing isatin based hydrazone and α-aminophosphonates with the hope to get novel hybrid derivatives with a better anticancer activity and minimized toxicity. The designing protocol for the target molecules is as shown in **Fig.1**.

INTRODUCTION

Most remarkable pathway to the synthesis of α-aminophosphonates is the Kabachnik-Fields reaction, the one pot three-component reaction of aromatic/heterocyclic aldehyde, amine and triethylphosphite, also known as Kabachnik–Fields reaction [18]. The novel trends in carrying out this reaction are connected with the application of (i) microwave irradiation itself or in combination with catalyst [19], (ii) ionic liquids as solvents [20], (iii) use of appropriate dehydrating agents [21] and, probably most important, (iv) the use of catalysts, was achieved by using various catalyst like $ZrOCl_2.8H_2O$ [22], $YbCl_3$ [23], lanthanide triflates [24], $Mg(ClO_4)_2$ [25], $LiClO_4$ [26] etc.

Kabachnik–Fields reaction was promoted by using Cerric (IV) ammonium nitrate (CAN) as a catalyst because of its advantages like high solubility in organic solvent, ease of handling, and low toxicity [27]. List of various catalysts used for synthesis of various types α-aminophosphonates and the time (minutes) required for synthesis of α-aminophosphonates are shown in **Table 5.**

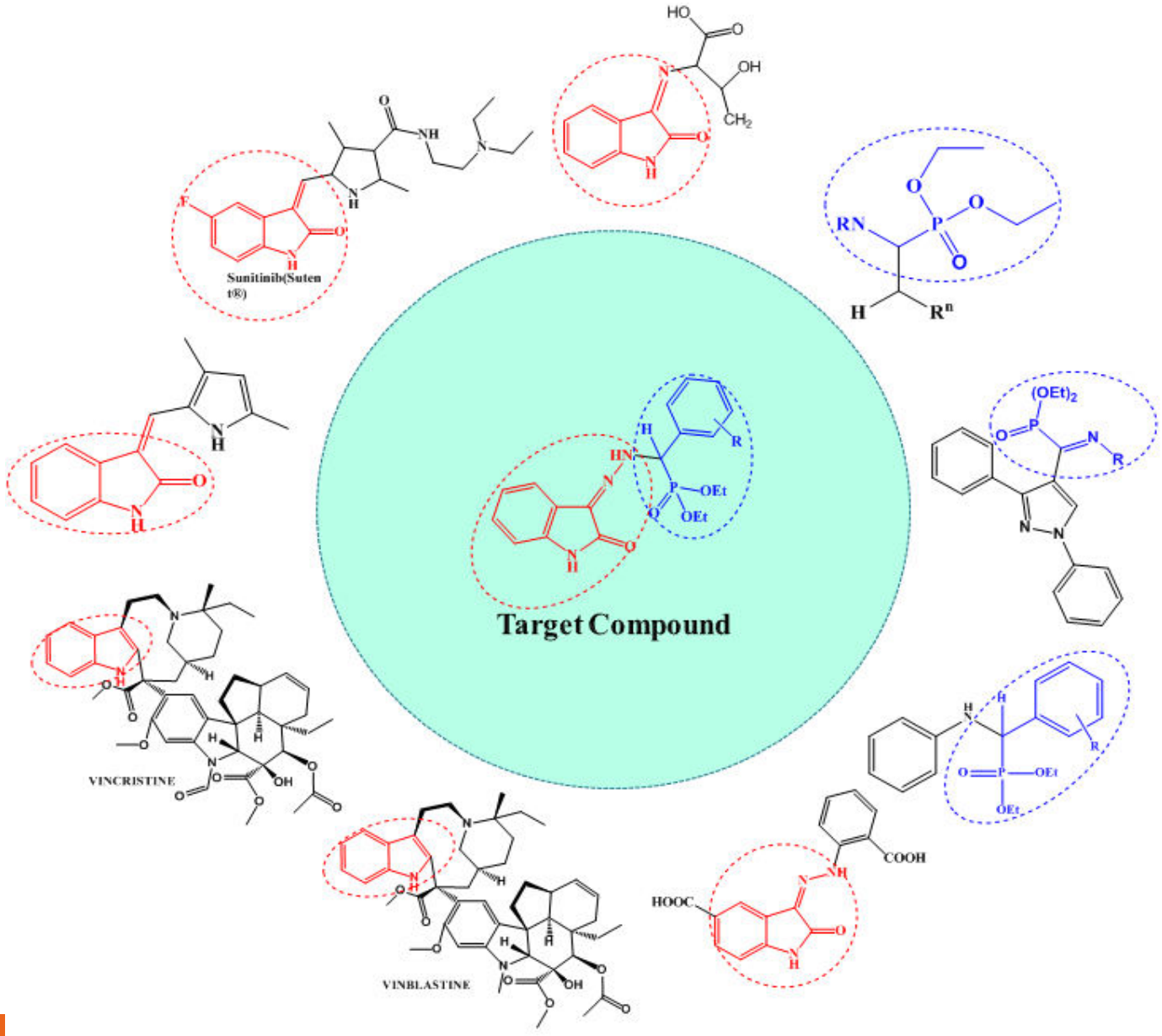
NEED OF THE STUDY

Green Chemistry Tools such as Ultrasound Synthesizer, multi component reactions, use of CAN catalyst, Molecular sieves, have become a promising alternative tools for various chemical processes due to their economty status like less time and electricity consumption, faster reaction and Cerric (IV) ammonium nitrate (CAN) as a catalyst because of its advantages like high solubility in organic solvent, ease of handling, and low toxicity respectively.

OBJECTIVE OF THE STUDY

- To design and synthesis of novel isatin coupled (α-aminophosphonate**)** derivatives with appropriate pharmacophore/suitable substituents like Imine linkage (azomethine linkage) i.e. **Diethyl(substituted phenyl/heteryl)(2-(2-oxoindolin-3-ylidene)hydrazinyl)methyl phosphonates derivatives 4(a-j).**
- To synthesize intermediates and final derivatives by Green Chemistry Tools such as Ultrasound Synthesizer, multi component reactions, use of CAN catalyst, Molecular sieves.
- Characterisation and structural confirmation of the synthesized intermediates & final α-aminophosphonate derivatives by analytical tests and spectral analysis such as TLC, IR, ^{1}HNMR, ^{13}CNMR, ^{31}PNMR and MASS.

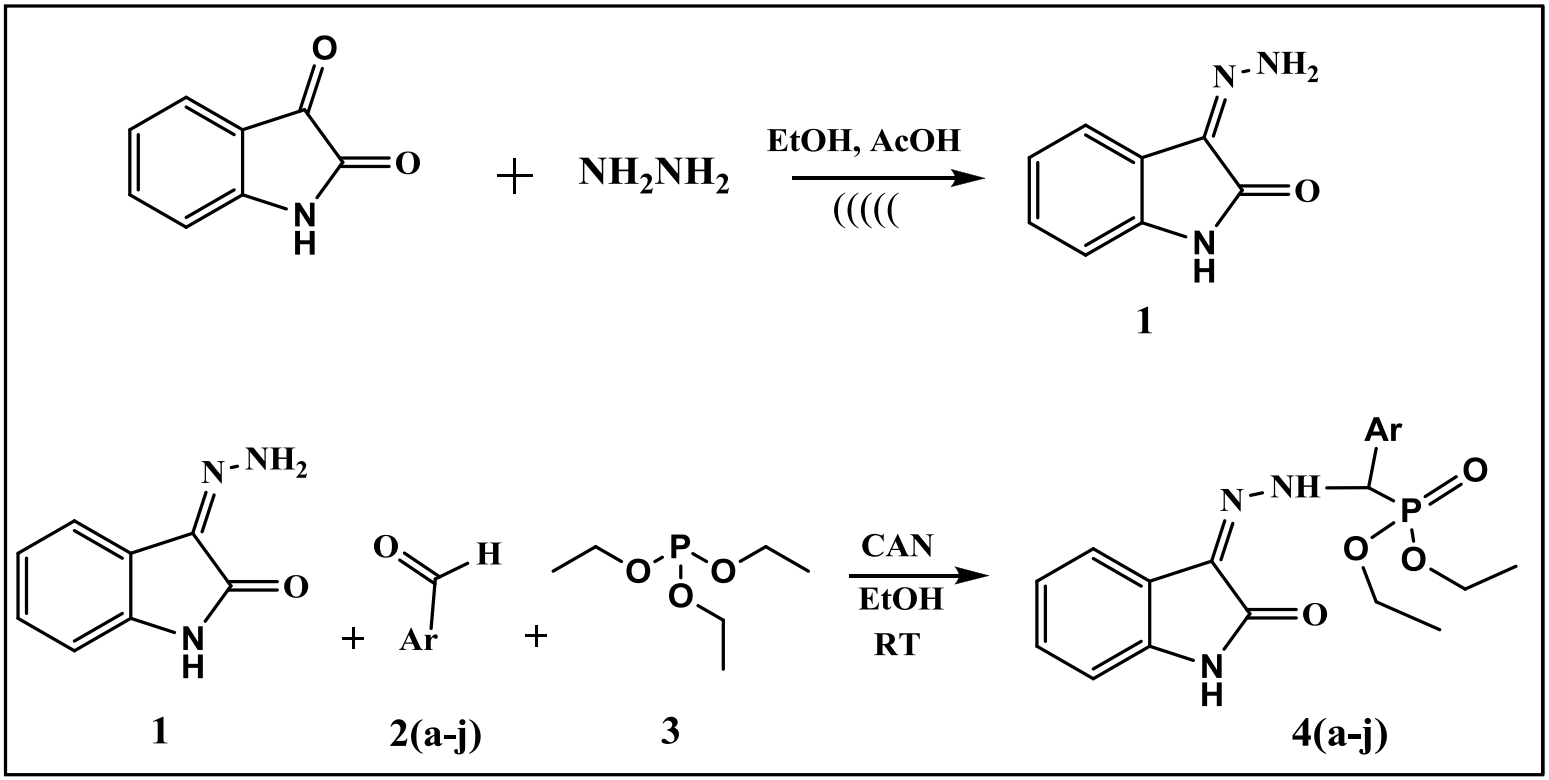
Fig. 1: The Designing protocol



MATERIALS AND METHODS

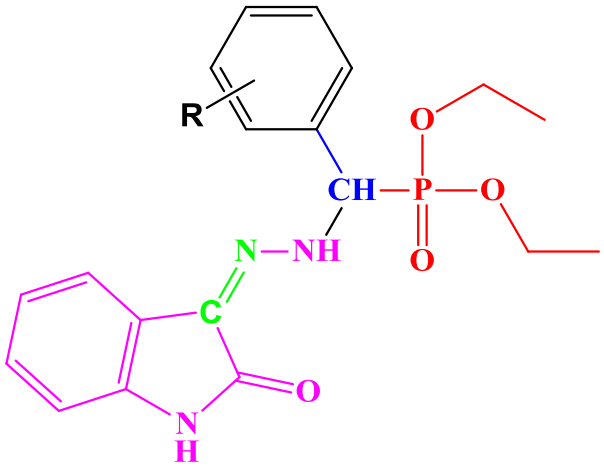
- All the chemicals used for synthesis are of Research lab, Merck, Sigma, Qualigens make and Himedia.
- The reactions were carried out by conventional method and using Ultrasound synthesizer with solid probe (**Ultrasonic Processor VCX-500-220**) at 40^0C.
- Melting points were determined in the open capillaries using melting point apparatus and are uncorrected.
- FTIR spectra were recorded by JASCO FTIR (PS-4000) using KBr powder technique, ^{1}H NMR and ^{13}C NMR spectra of synthesized compounds were recorded on Bruker Avance II 400 NMR Spectrometer at 400 MHz Frequency in $CDCl_3$ and using TMS as internal standard (chemical shift δ in ppm), Mass spectra of some compounds were scanned on Water's Micromass Q-Tof system. ^{31}P NMR of compounds were recorded at δ250 to - δ250 in $CDCl_3$ and using Phosphoric acid (H_3PO_4) as an external standard (chemical shift δ in ppm)

Scheme of synthesis



Scheme 1

Structural Activity Relationship (SAR) diethyl(substituted phenyl/heteryl)(2-(2-oxoindolin-3-ylidene)hydrazinyl)methyl phosphonates derivatives. 4(a-j)



- **Isatin i**s essential for biological and pharmacological activity activity.
- **C=N linkage** Schiff base in isatin is essential for biological and pharmacological activity.
- **Phosphonate group** is essential for biological and pharmacological but it should not be free.

EXPERIMENTAL WORK

Procedures:

Step I: Synthesis of 3-hydrazonoindolin-2-one (1) (Schiff base)[28]

A) Conventional method [28]

A mixture of indole-2,3-dione (isatin) (1 mmol) and hydrazine hydrate (1 mmol) in 15 ml of methanol was refluxed for 3-4 hr in presence of molecular sieves. Microporous 3Å molecular sieves are alumino silicate minerals with chemical composition of $^{2}/_{3}K_2O \cdot {}^{1}/_{3}Na_2O \cdot Al_2O_3 \cdot 2SiO_2 \cdot {}^{9}/_{2}H_2O$.[29] Since the 1990's, these molecular sieves have attracted considerable attention due to their potential use in catalysis, as they absorb water formed in the reaction and drive the reaction to completion. The separated crystals were filtered, washed with a little amount of methanol, dried and recrystallized with chloroform solvent(s), M.P. 284°C, Yield 82%.

B) Ultrasonication Method

Equimolar quantities of indole-2,3-dione (isatin) (1 mmol) and hydrazine hydrate (1mmol) in the presence of catalytic amount of glacial acetic acid in absolute ethanol (5 ml) was sonicated by keeping the reaction mixture in acoustic box containing Ultrasonic solid probe at 25-40°Cand at 25 amplitude for 15 -20 min. The completion of reaction was monitored by TLC. The reaction mixture was concentrated and cooled. The obtained solid was filtered and dried. The product was recrystallized from ethanol. 3-Hydrazonoindolin-2-one, $C_8H_7O_1N_3$, MW: 161.13. Yield: 95%; melting point: 279-284°C. The melting point was uncorrected.

Table 1: Difference in parameters for Conventional method and Ultrasound Method

Parameters	Conventional method	Ultrasound Method
Catalyst	glacial acetic acid, molecular sieves	glacial acetic acid
Solvent	absolute methanol	absolute ethanol
Temperature	40-50^{0}C	25-40^{0}C
Time	3-4 h	15-20 min.
yield	82%	95%

Characterization

I) Conventional Method (3-4 h)

Table 2: Physical constants data for 3-hydrazonoindolin-2-one **(1)**

Molecular formula	Molecular weight (gm)	% Yield(%)	M. P.(^{0}C)	R_f value
$C_8 H_7 O_1 N_3$	161.13	82	279-284	0.70

II) Ultrasound Method (15-20 min.)

Table 3: Physical constants data for 3-hydrazonoindolin-2-one **(1)**

Molecular formula	Molecular weight (gm)	% Yield(%)	M. P.(^{0}C)	R_f value
$C_8 H_7 O_1 N_3$	161.13	95	280-285	0.70

Solvent system chosen for R_f value determination was benzene : methanol (8:2).

Step II: diethyl(substituted phenyl/heteryl)(2-(2-oxoindolin-3-ylidene)hydrazinyl)methylphosphonates derivatives 4(a-j) [One pot Kabachnik–Fields reaction]

Equimolar quantity of 3-hydrazonoindolin-2-one **(1)** (1mmol), substituted aromatic aldehyde/heteryl aldehydes **2(a-j)** (1mmol) and tri-ethyl phosphite **(3)** (1mmol) was stirred at room temperature in absolute ethanol, in presence of Cerric Ammonium Nitrate (CAN) as a catalyst. The progress of reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled and poured in water, filtered and the solid obtained was dried and recrystallized with ethanol. The time required for completion of reaction varies from 70 min. to 90 min.

Table 4: Physical constant data diethyl(substituted phenyl/heteryl)(2-(2-oxoindolin-3-ylidene)hydrazinyl)methylphosphonates derivatives 4(a-j)

Code	-Ar	Molecular formula	Molecular weight (gm)	Time required (min)	%Yield	Melting point (^{0}C)
4a	Phenyl	$C_{19}H_{22}N_3O_4P$	387.37	75	90	195-196
4b	p-chloro Phenyl	$C_{19}H_{21}ClN_3O_4P$	421.81	70	92	150-152
4c	p-hydroxy Phenyl	$C_{19}H_{21}FN_3O_4P$	405.36	75	95	176-180
4d	p-methoxy Phenyl	$C_{20}H_{24}N_3O_5P$	417.40	85	89	179-180
4e	3,4-dimethoxy Phenyl	$C_{21}H_{26}N_3O_6P$	447.42	90	90	189-190
4f	p-fluoro Phenyl	$C_{19}H_{22}N_3O_5P$	403.37	80	88	140-142
4g	4-hyroxy-3-methoxy Phenyl	$C_{20}H_{24}N_3O_6P$	433.39	75	94	112-114
4h	4-hyroxy-3-ethoxy Phenyl	$C_{21}H_{26}N_3O_6P$	447.44	80	92	160-162
4i	Thiophen-2-yl	$C_{17}H_{20}N_3O_4PS$	393.40	80	87	178-180
4j	Furan-2-yl	$C_{17}H_{20}N_3O_5P$	377.33	80	84	176-178

Solvent system chosen for R_f value determination was benzene : methanol (8:2).

Table 5: Catalyst used for the synthesis of α-aminophosphonate (4a-j) as compared with other reported time and catalyst used.

Entry	Catalyst used	Time(minutes)	References
1	Bismuth salt (10 mol%)	120-360	30
2	Yb $(OTf)_3$ (10mol%)	270-2160	31
3	2 mol % $HfCl_4$	300-2880	32
4	CBr_4 (5 mol%)82	180	33
5	Oxalyl chloride (1.5 mmol)	360	34
6	$AlCl_3$ (10 mol%)80	570	35
7	**CAN(Reflux)**	**30**	**36**
8	**CAN(RT)**	**180-210**	**37**
9	**CAN**	**75-90**	**Present work**

I R SPECTROSCOPY
Spectrum no.1:

Diethyl ((4-methoxyphenyl)(2-(2-oxoindolin-3-ylidene)hydrazinyl)methyl)phosphonate

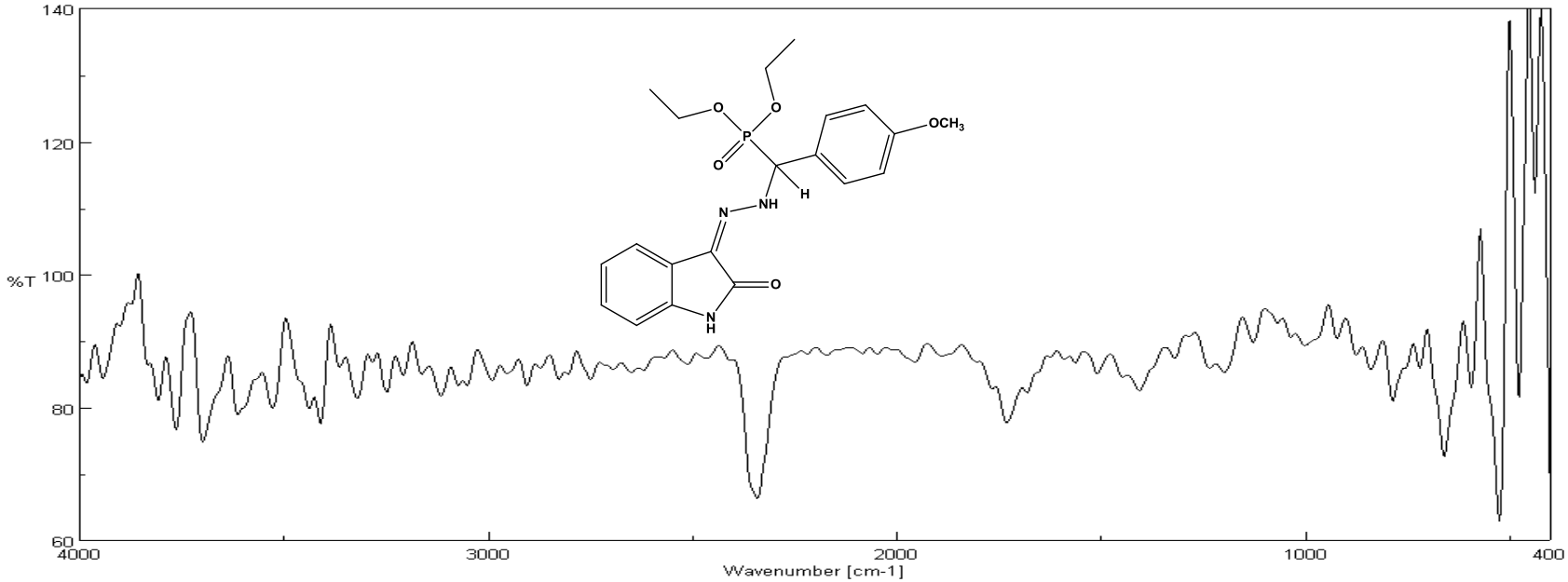


Table 6: IR interpretation of diethyl ((4-methoxy phenyl)(2-(2-oxoindolin-3-ylidene)hydrazinyl)methyl)phosphonate

Sr. No.	Functional group	Wavelength (cm^{-1})
1.	N-H stretching	3350.41
2.	C-H stretching of aromatics	2970.76
3.	CH stretching of alkyl	2800
4.	C=N Streching	2200-2300
5.	C=O stretching of Amide	1610.26
6.	C-H bending of $–CH_2-$	1456.58
7.	C-N Streching	1230-1030

I R SPECTROSCOPY
Spectrum no.2:

Diethyl ((3,4-dimethoxyphenyl)(2-(2-oxoindolin-3ylidene)hydrazinyl)methyl)phosphonate

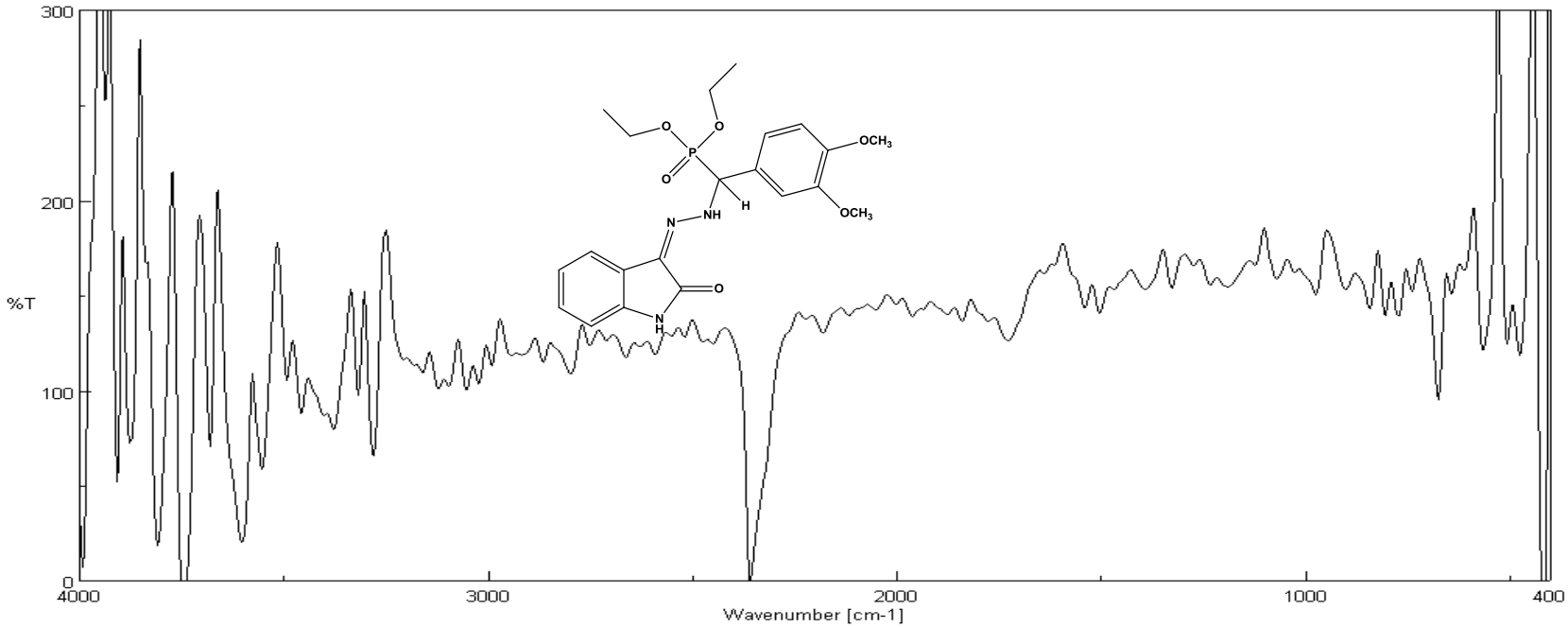


Table 7: IR interpretation of diethyl ((3,4-dimethoxy phenyl)(2-(2-oxoindolin-3-ylidene)hydrazinyl)methyl)phosphonate

Sr. No.	Functional group	Wavelength (cm^{-1})
1.	N-H stretching	3352
3.	C-H stretching of aromatics	3000.76
4.	CH stretching of alkyl	2800.53
5.	C=N Streching	2350
6.	C=O stretching of Amide	1650.23
7.	C-N Streching	1232-1040
8.	C-H bending of $-CH_2-$	1456.58

I R SPECTROSCOPY

Spectrum no.3:

Diethyl ((furfuryl)(2-(2-oxoindolin-3-ylidene)hydrazinyl)methyl)phosphonate.

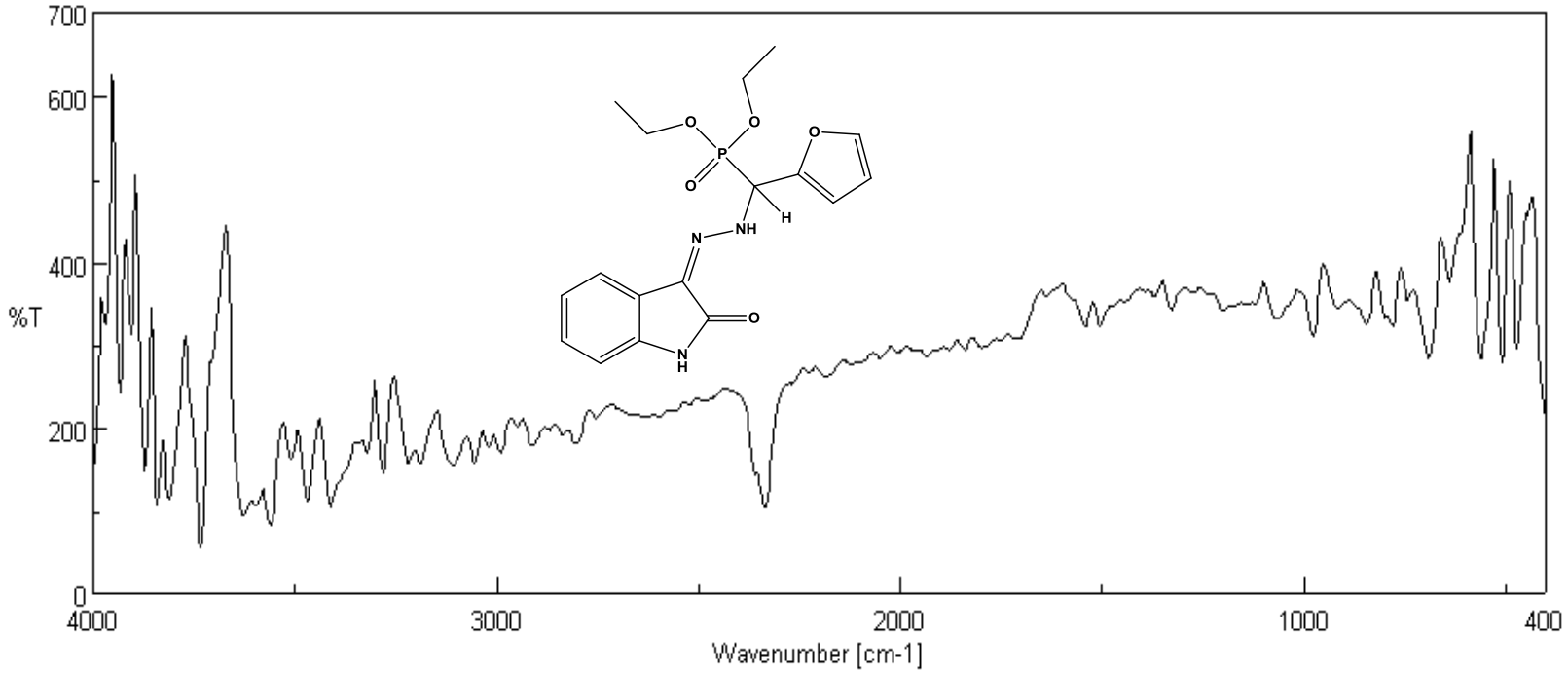


Table 8 IR interpretation of diethyl ((furfuryl)(2-(2-oxoindolin-3-ylidene)hydrazinyl)methyl)phosphonate

Sr. No.	Functional group	Wavelength (cm^{-1})
1.	N-H stretching	3350.11
2.	C-H stretching of aromatics	2970
3.	CH stretching of alkyl	2890.02
4.	C=N Streching	2330
5.	C=O stretching of Amide	1710.66
6.	C-H bending of $-CH_2-$	1416.88
7.	C-N Streching	1230-1130
8.	-O- Streching	1050.52

I R SPECTROSCOPY

Spectrum no.4:

Diethyl ((phenyl)(2-(2-oxoindolin-3ylidene)hydrazinyl)methyl)phosphonate

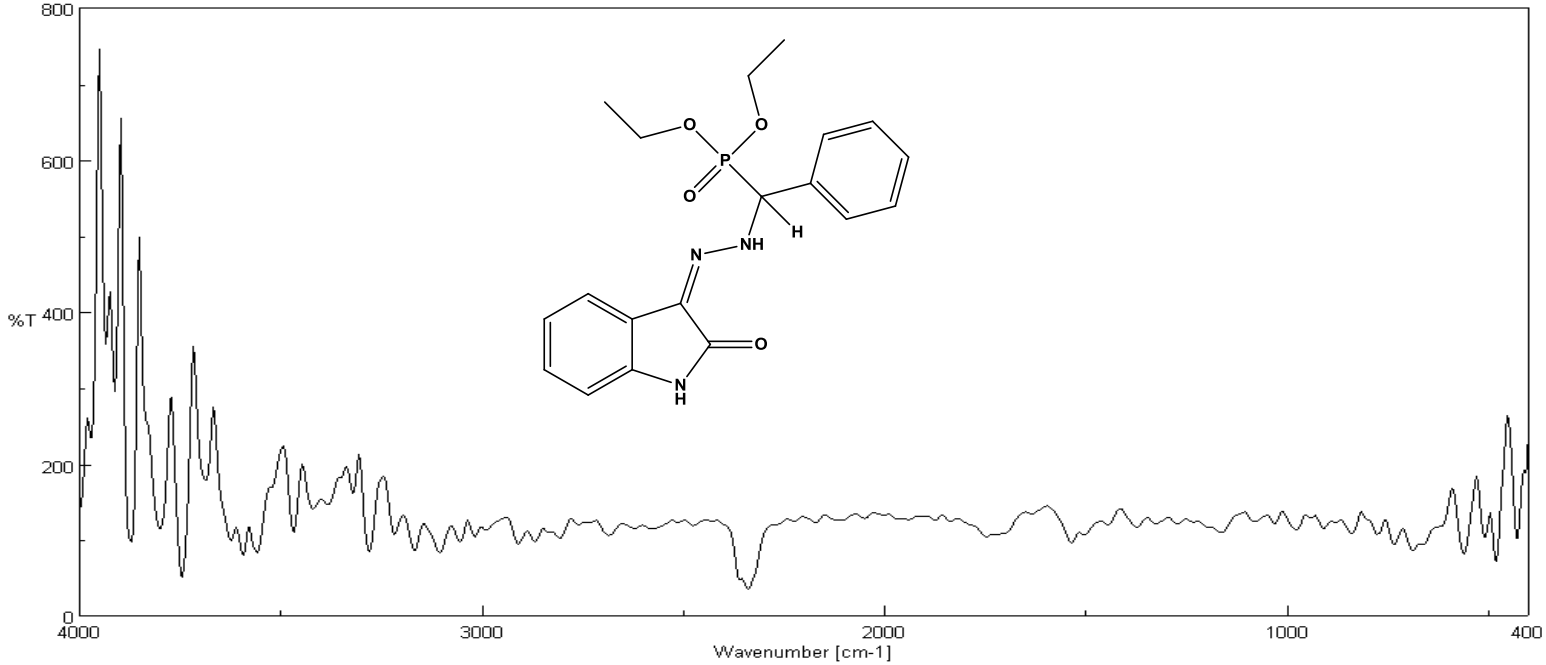


Table 9: IR interpretation of diethyl ((phenyl)(2-(2-oxoindolin-3-ylidene)hydrazinyl)methyl)phosphonate

Sr. No.	Functional group	Wavelength (cm^{-1})
1.	N-H stretching	3340.21
2.	C-H stretching of aromatics	2960.76
3.	CH stretching of alkyl	2870
4.	C=N Streching	2200-2350
5.	C=O stretching of Amide	1610.66
6.	C-H bending of $-CH_2-$	1466.55
7.	C-N Streching	1250-1020

MASS SPECTROSCOPY
Spectrum no.5:

Diethyl ((4-chlorophenyl)(2-(2-oxoindolin-3-ylidene)hydrazinyl)methyl)phosphonate (4b)

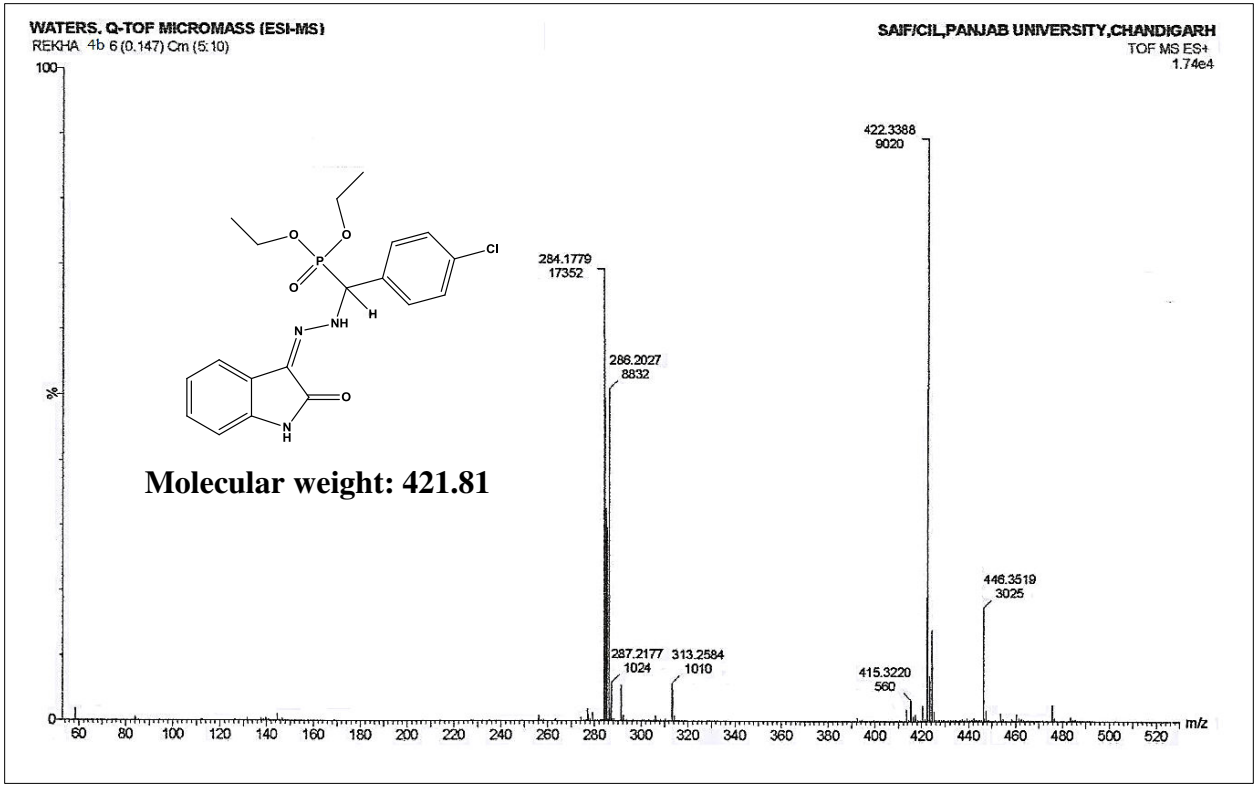


Table 10: Mass interpretation of diethyl ((4-chloro phenyl)(2-(2-oxoindolin-3-ylidene)hydrazinyl)methyl)phosphonate

Sr. No.	Fragmentation	m/e
1.	M+1	422.33(base peak)
2.	M+2	423
3.	M-$C_4H_{11}O_3P$	284.17

MASS SPECTROSCOPY

Spectrum no.6:

Diethyl ((4-methoxyphenyl)(2-(2-oxoindolin-3-ylidene)hydrazinyl)methyl)phosphonate (4d)

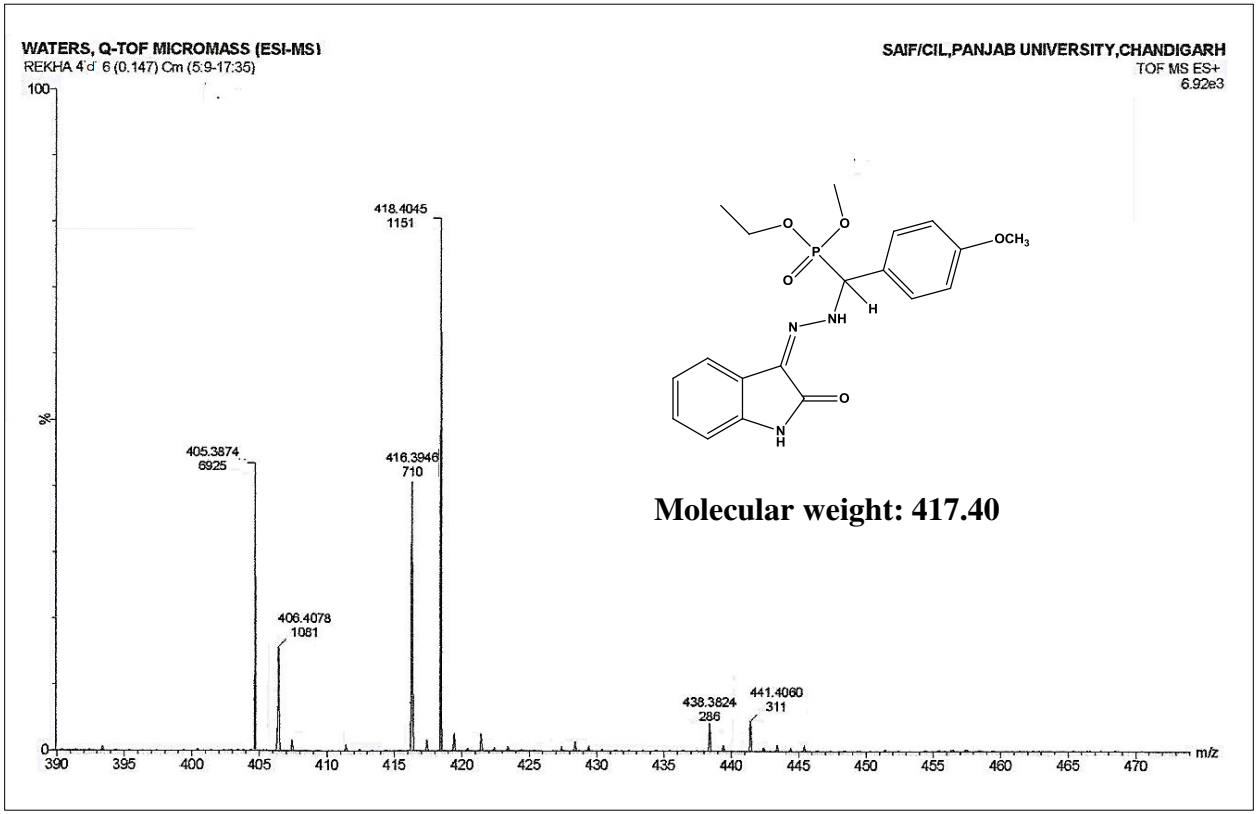


Table 11: Mass interpretation of diethyl ((4-methoxy phenyl)(2-(2-oxoindolin-3-ylidene)hydrazinyl)methyl)phosphonate

Sr. No.	Fragmentation	m/e
1.	M+1	418.40(base peak)
2.	M-CH_3	405.38

MASS SPECTROSCOPY
Spectrum no.7:

Diethyl ((4-hydroxy-3-methoxyphenyl)(2-(2-oxoindolin-3-ylidene)hydrazinyl)methyl)phosphonate (4g)

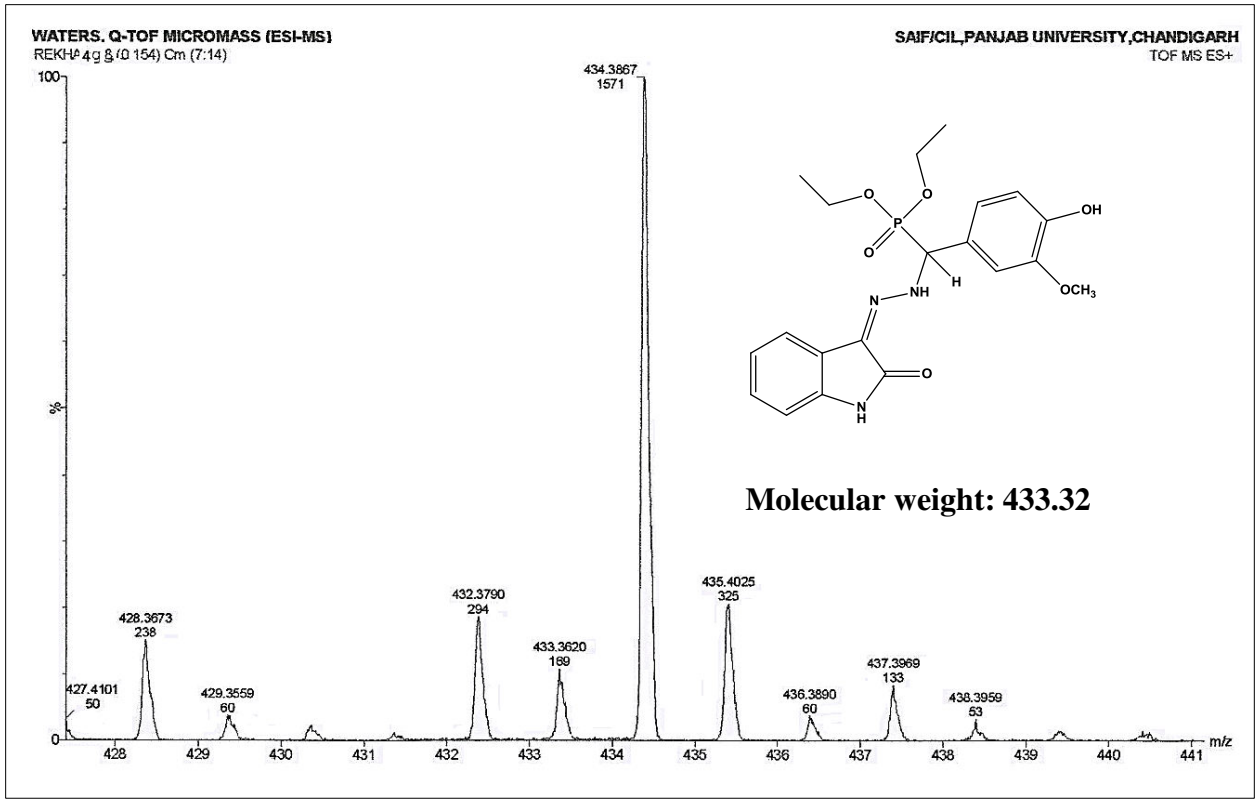


Table 12: Mass interpretation of diethyl ((4-hydroxy-3-methoxy phenyl)(2-(2-oxoindolin-3-ylidene)hydrazinyl)methyl)phosphonate

Sr. No.	Fragmentation	m/e
1.	M+1	334.31(base peak)

^{1}H NMR SPECTROSCOPY
Spectrum no.8

Diethyl ((4-chlorophenyl)(2-(2-oxoindolin-3-ylidene)hydrazinyl)methyl)phosphonate(4b)

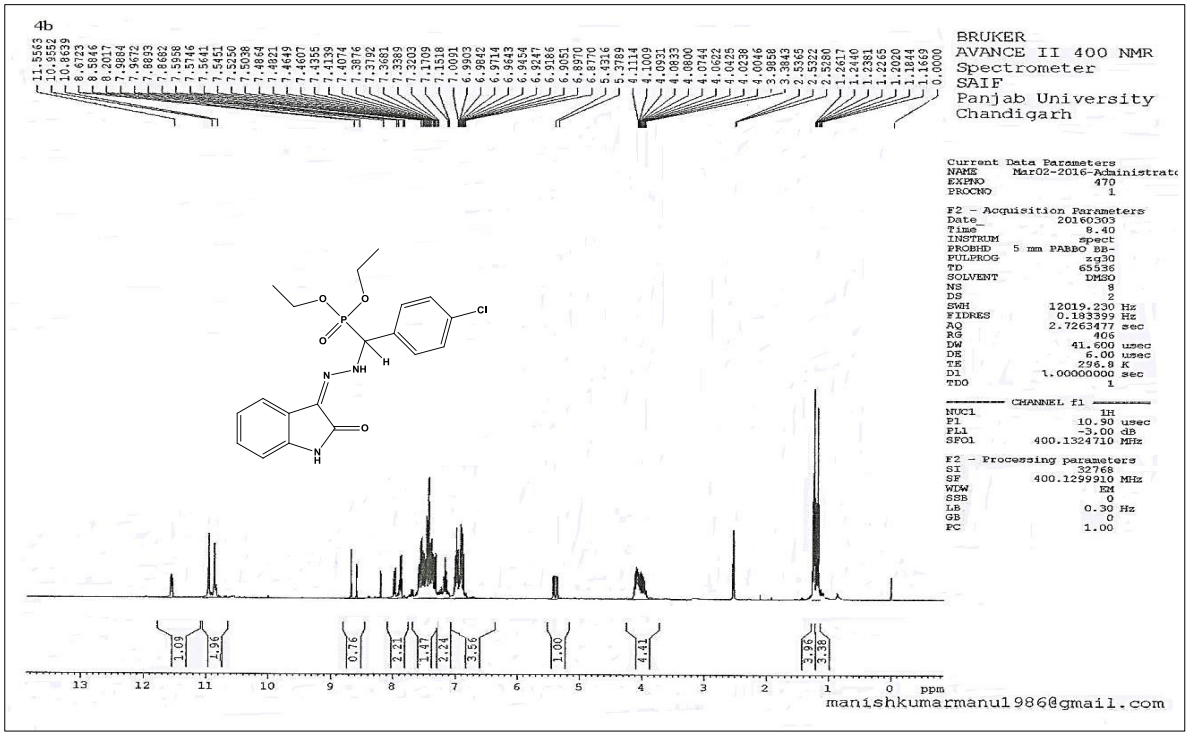


Table 13 : ^{1}H NMR interpretation of diethyl ((4-chloro phenyl)(2-(2-oxoindolin-3-ylidene)hydrazinyl)methyl)phosphonate

Sr. No.	δ Values (ppm)	Multiplicity	No. of proton	Group
1	1.1-1.2	T	6H	$-CH_3$
2	4.41	Q	4H	$-CH_2$
3	3.4-4	D	1H	-CH
4	7-7.19	M	8H	Aromatic protons
5	8.6	S	1H	Aliphatic-NH
6	11.55	S	1H	Indole-NH

^{1}H NMR SPECTROSCOPY
Spectrum no.9:

Diethyl ((4-methoxyphenyl)(2-(2-oxoindolin-3-ylidene)hydrazinyl)methyl)phosphonate (4d)

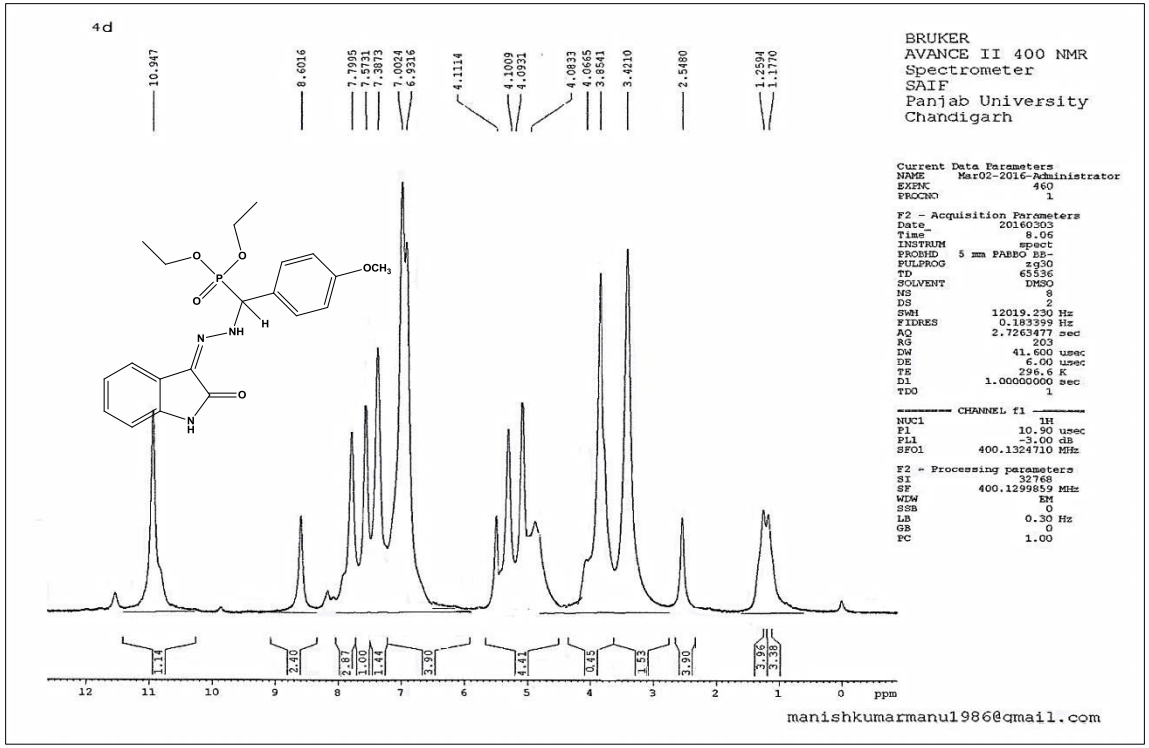


Table 14: ^{1}H NMR interpretation of diethyl ((4-methoxy phenyl)(2-(2-oxoindolin-3-ylidene)hydrazinyl)methyl)phosphonate

Sr. No.	δ Values (ppm)	Multiplicity	No. of proton	Group
1	1.1-1.2	T	6H	$-CH_3$
2	2.5	S	3H	$-OCH_3$
3	3.42-3.85	D	1H	-CH
4	4.08-4.11	Q	4H	CH_2
5	6.9-8.40	M	8H	Aromatic protons
6	8.6	S	1H	Aliphatic-NH
7	10.94	S	1H	Indole-NH

^{1}H NMR SPECTROSCOPY
Spectrum no.10:
Diethyl ((4-hydroxy-3-methoxyphenyl)(2-(2-oxoindolin-3-ylidene)hydrazinyl)methyl)phosphonate.(4g)

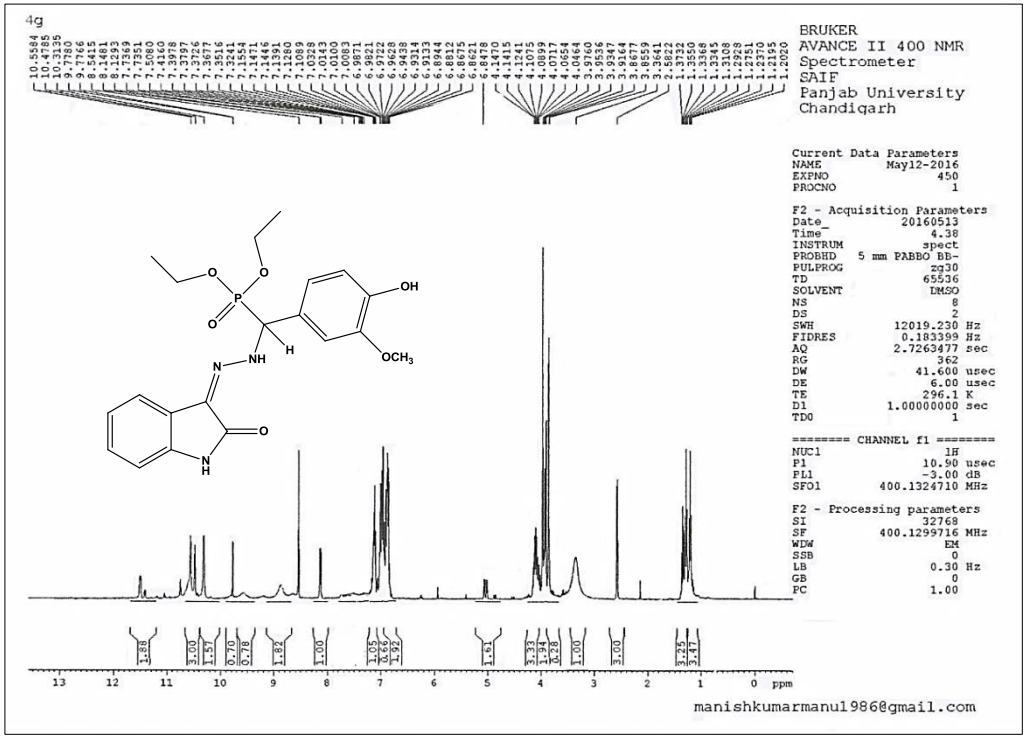


Table 15: ^{1}H NMR interpretation of diethyl ((4-hydroxy-3-methoxy phenyl)(2-(2-oxoindolin-3-ylidene)hydrazinyl)methyl)phosphonate

Sr. No.	δ Values (ppm)	Multiplicity	No. of proton	Group
1	1.2-1.3	T	6H	$-CH_3$
2	2.54	S	3H	$-OCH_3$
3	3.36-3.86	D	1H	-CH
4	3.86-4.24	Q	4H	$-CH_2$
5	5.14	S	1H	-OH
6	6.84-7.73	M	7H	Aromatic protons
7	8.14	S	1H	Aliphatic-NH
8	10.31	S	1H	Indole-NH

^{13}C NMR SPECTROSCOPY
Spectrum no.11:
Diethyl ((4-methoxyphenyl)(2-(2-oxoindolin-3ylidene)hydrazinyl)methyl)phosphonate (4d)

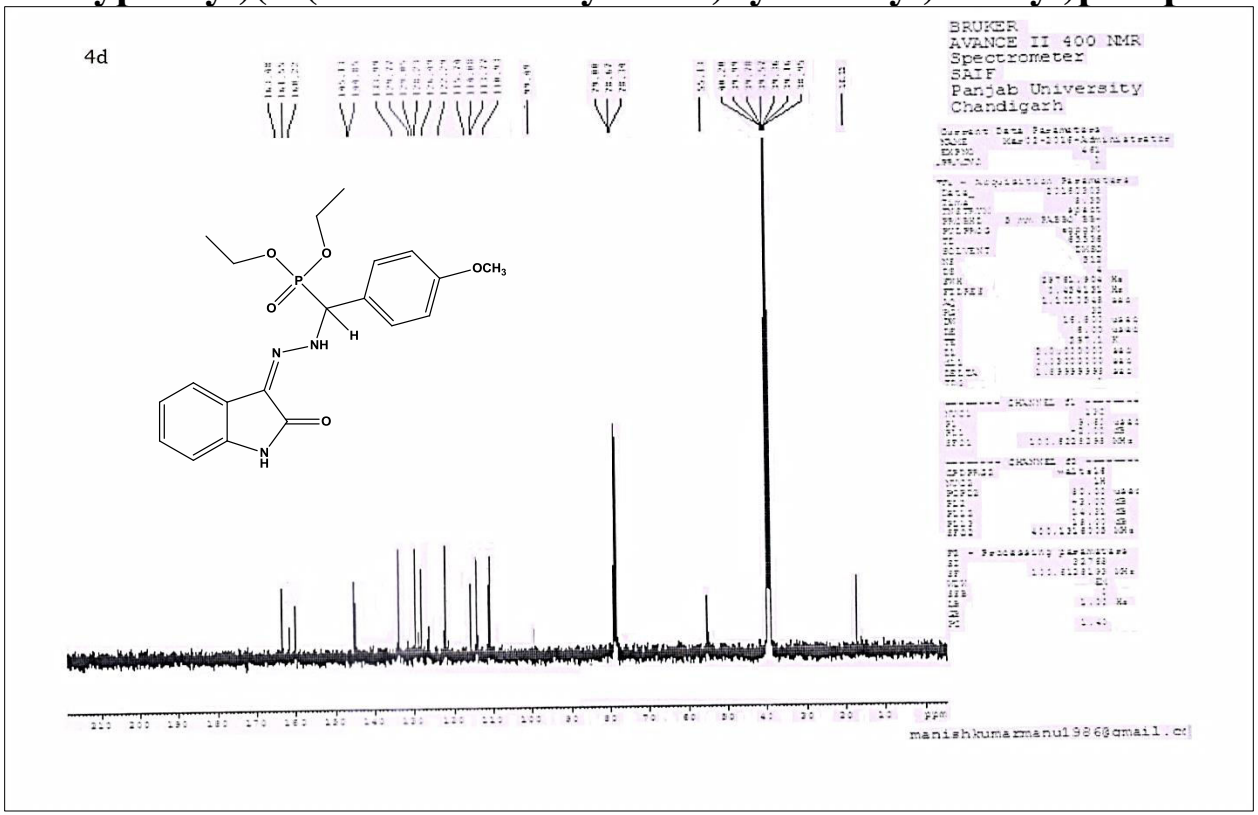


Table 16: ^{13}C NMR interpretation of diethyl ((4-methoxy phenyl)(2-(2-oxoindolin-3-ylidene)hydrazinyl)methyl)phosphonate

Sr. No.	δ Values (ppm)	Carbon group
1	16	$-CH_3$
2	40	$-OCH_3$
3	57	$-CH_2$
5	100	-CH
6	134	Aromatic
7	145	$-C-OCH_3$
9	164	C=O

^{13}C NMR SPECTROSCOPY
Spectrum no.12:
Diethyl ((4-chlorophenyl)(2-(2-oxoindolin-3-ylidene)hydrazinyl)methyl)phosphonate (4b)

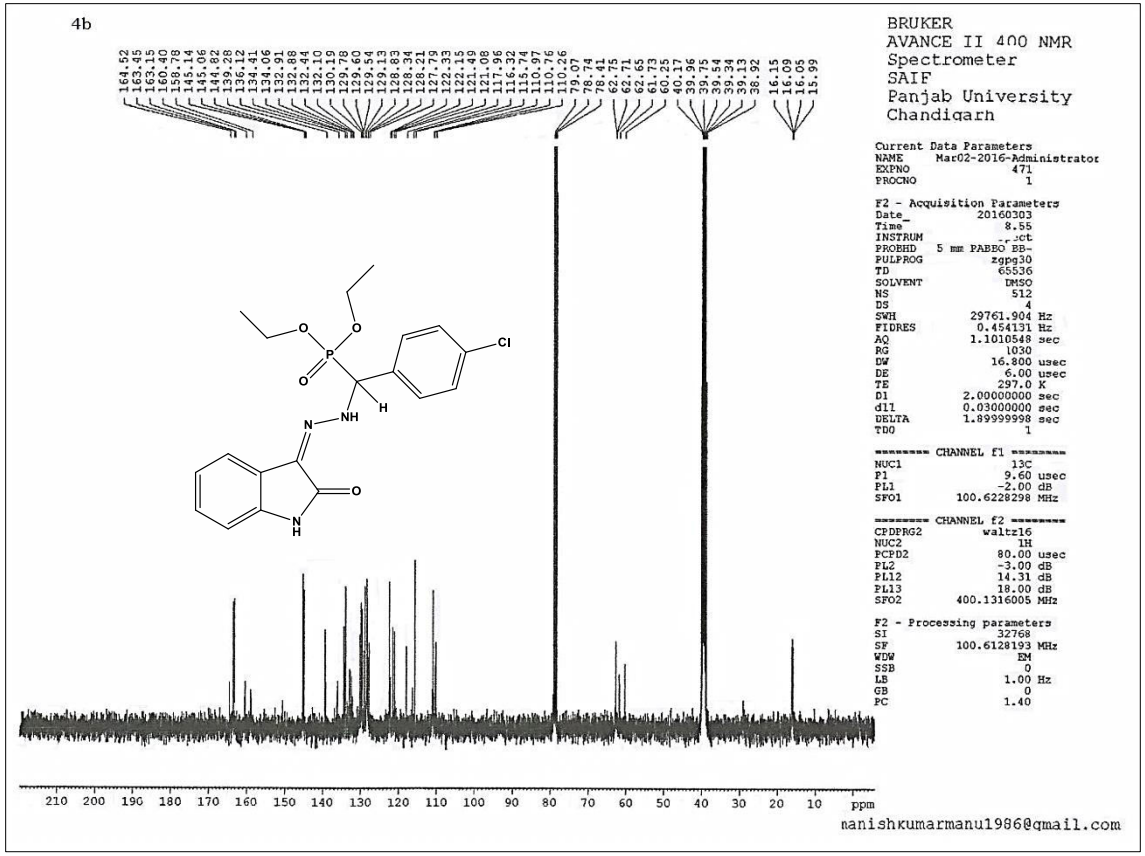


Table 17: ^{13}C NMR interpretation of diethyl ((4-chloro phenyl)(2-(2-oxoindolin-3-ylidene)hydrazinyl)methyl)phosphonate

Sr. No.	δ Values (ppm)	Carbon group
1	16	$-CH_3$
2	62	$-CH_2$
3	80	-CH
4	110-134	Aromatic
5	164	C=O

^{13}C NMR SPECTROSCOPY

Spectrum no.13:

Diethyl ((4-hydroxy-3-methoxyphenyl)(2-(2-oxoindolin-3-ylidene)hydrazinyl)methyl)phosphonate (4g)

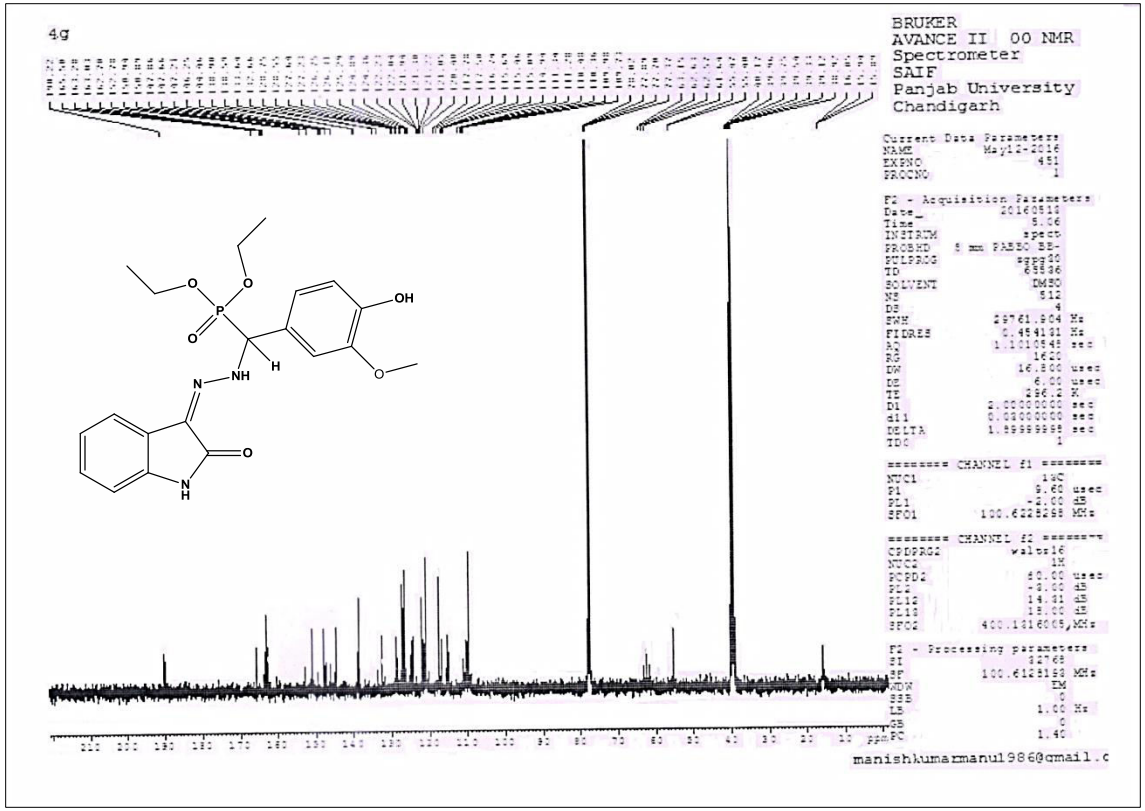


Table 18: ^{13}C NMR interpretation of diethyl ((4-hydroxy-3-methoxyphenyl)(2-(2-oxoindolin-3-ylidene)hydrazinyl)methyl)phosphonate

Sr. No.	δ Values (ppm)	Carbon group
1	16	$-CH_3$
2	40	$-OCH_3$
3	62	$-CH_2$
4	78	-CH
5	109-165	Aromatic CH
6	190	C=O

^{31}P NMR SPECTROSCOPY

Spectrum no.14:

diethyl ((4-chlorophenyl)(2-(2-oxoindolin-3-ylidene)hydrazinyl)methyl)phosphonate.(4b)

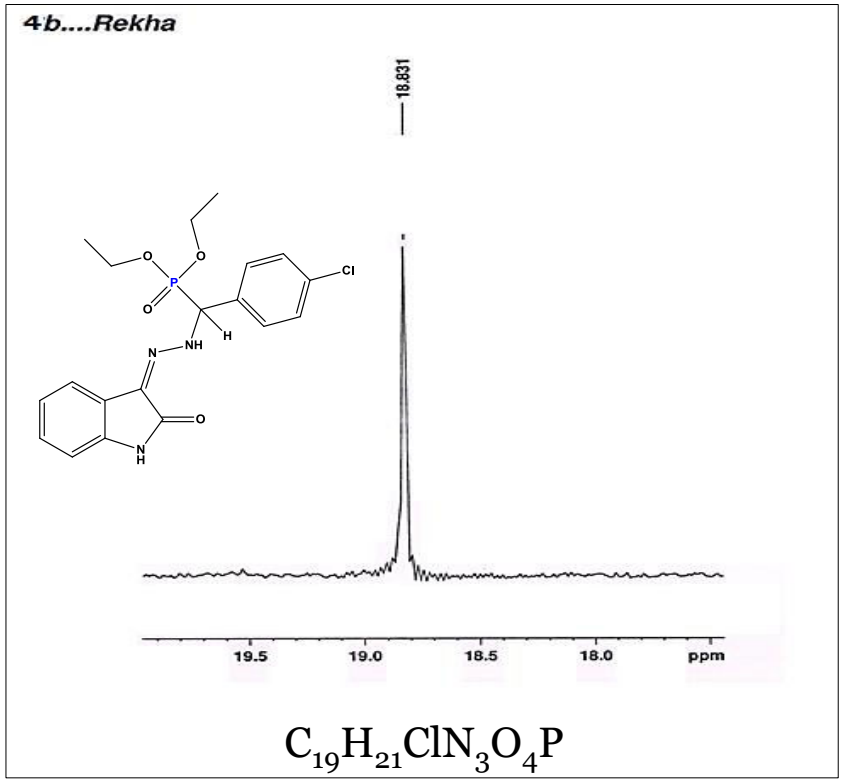


Table 19: ^{31}P NMR interpretation of diethyl ((4-choro phenyl)(2-(2-oxoindolin-3-ylidene)hydrazinyl)methyl)phosphonate.

Sr. No.	Obtained Values (ppm)	Theoretical value (ppm)
1	18.831	15-25

RESULT AND DISCUSSION

Diethyl (substituted phenyl/heteryl)(2-(2-oxoindolin-3ylidene)hydrazinyl)methyl phosphonates derivatives 4(a-j) were synthesized by Green protocol as outlined in **Scheme 1**. 3-hydrazonoindolin-2-one **(1)** was synthesized by reacting indole-2,3-dione (isatin) (1mmol) with hydrazine hydrate (1mmol) in the presence of glacial acetic acid as a catalyst by conventional method in methanol using molecular sieves and **by ultrasonication method** by replacing methanol with ethanol. Ultrasound method is better than the conventional method because, methanol being toxic solvent is replaced by benign solvent ethanol. The amount of solvent required is also less than that required for conventional method. Ultrasound assisted method gives better yield in 15-20 minutes against 3-4 hrs required for conventional method. α-Aminophosphonate derivatives **4(a-j)** were synthesized by reacting 3-hydrazonoindolin-2-one **(1)**, substituted/heteryl aldehydes **2(a-j)** and triethylphosphite **(3)** via **one pot synthetic step in presence of CAN as a catalyst**. CAN activates the imine formation due to which addition of phosphite is facilitated to give a phosphonium intermediate. This phosphonium intermediate undergoes reaction with water to give the title compounds. CAN catalyst being water soluble can be easily removed after completion of reaction. The synthesized compounds were characterized and confirmed by FTIR, ^{1}H NMR, ^{13}C NMR, ^{31}P NMR, MS and elemental analyses. The purity of the synthesized compounds was checked by TLC and melting points were determined in open capillary tubes and are uncorrected. Physical constant data for diethyl (substituted phenyl/hetery)(2-(2-oxoindolin-3-ylidene)hydrazinyl) methyl phosphonates **4(a-j)** is shown in Table 4.

CONCLUSION

- **Ultrasound synthesizer** have become a promising alternative green tool for various chemical reactions due to their economical status like less time and electricity consumption by faster reaction.
- **Intermediates (1)** were synthesized by Green protocol such as by using **ultrasound synthesizer,** gives better yield in 15-20 minutes while conventional method reqiures 3-4 hrs. **Final compounds 4(a-j)** were synthesized by **one pot synthetic step in presence of CAN as a catalyst.**
- Novel diethyl (substituted phenyl/heteryl)(2-(2-oxoindolin-3ylidene)hydrazinyl)methylphosphonate derivatives **4(a-j)** were synthesized at room temperature in facile one pot reaction using CAN as a catalyst, gives faster reaction at room temperature, CAN catalyst being water soluble can be easily removed after completion of reaction
- The compounds were characterized by TLC, IR, NMR, and Mass spectrometry.

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THANK YOU