Ultrasound assisted synthesis of Diethyl (2-(1-(morpholinomethyl)-2-oxoindolin-3-ylidene)hydrazinyl) (substituted phenyl/heteryl) methylphosphonate Derivatives.

Presented By

Shailee V. Tiwari[1], Julio A. Seijas[2], M. Pilar Vazquez-Tato[2], Anna Pratima G. Nikalje[3]*

[1] Department of Pharmaceutical Chemistry, Durgamata Institute of Pharmacy, Dharmapuri, Parbhani, Maharashtra, India;

[2] Departamento de QuímicaOrgánica, Facultad de Ciencias, Universidad of Santiago DeCompostela, Alfonso X el Sabio, Lugo 27002, Spain.

[3] Y.B. Chavan College of Pharmacy, Dr. Rafiq Zakaria Campus, Rauza Baug, Aurangabad, Maharashtra 431001, India;

Abstract

The work reports Ultrasound assisted diethyl (2-(1-(morpholinomethyl)-2-oxoindolin-3-ylidene)hydrazinyl) (substituted phenyl/heteryl) methylphosphonate **9(a-j)** derivatives. The derivatives are synthesized using green protocol. In the first step 3-hydrazonoindolin-2-one is synthesized using ultrasound. In the second step diethyl (substituted phenyl/heteryl)(2-(2-oxoindolin-3-ylidene)hydrazinyl) methylphosphonate **6(a-j)** derivatives using cerric ammonium nitrate as catalyst. In the third step diethyl (2-(1-(morpholinomethyl)-2-oxoindolin-3-ylidene)hydrazinyl) (substituted phenyl/heteryl) methylphosphonate **9(a-j)** derivatives are synthesized using ultrasound. 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. morpholine moiety has been found to be of an eminent pharmacophore in medicinal chemistry. A number of molecules possessing morpholine moiety are clinically approved drugs. The importance of this ring is well understood by medicinal chemists, since they play a major role in molecular properties such as an electronic distribution, three dimensionality, scaffold flexibility/rigidity, lipophilicity or polarity and metabolic stability. Considering the importance of the three pharmacophores, promoted us to club these pharmacophores together 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: Ultrasound assisted; Cerric Ammonium Nitrate; Isatin; α-amino phosphonate.

The designing protocol for the target compound

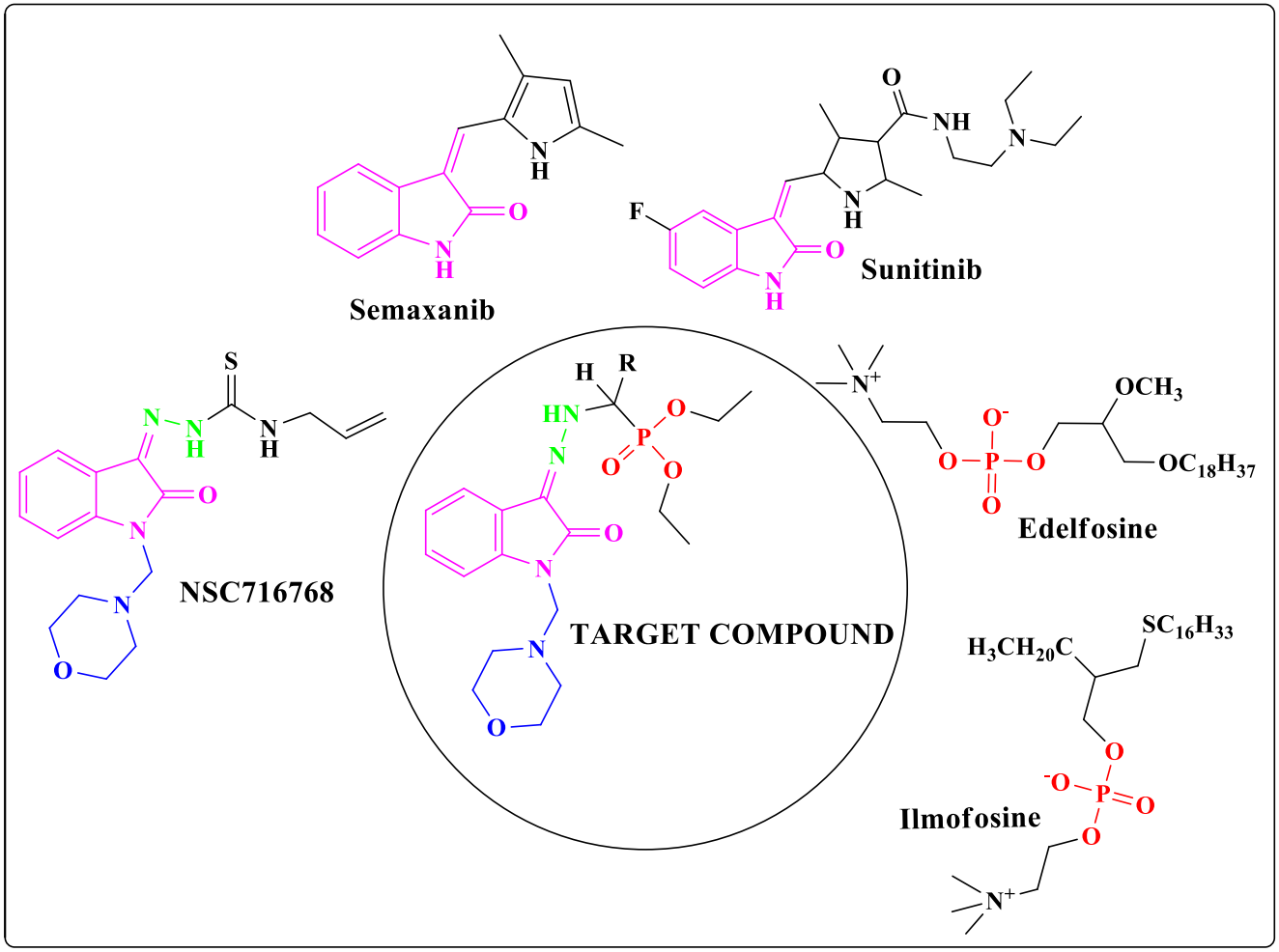
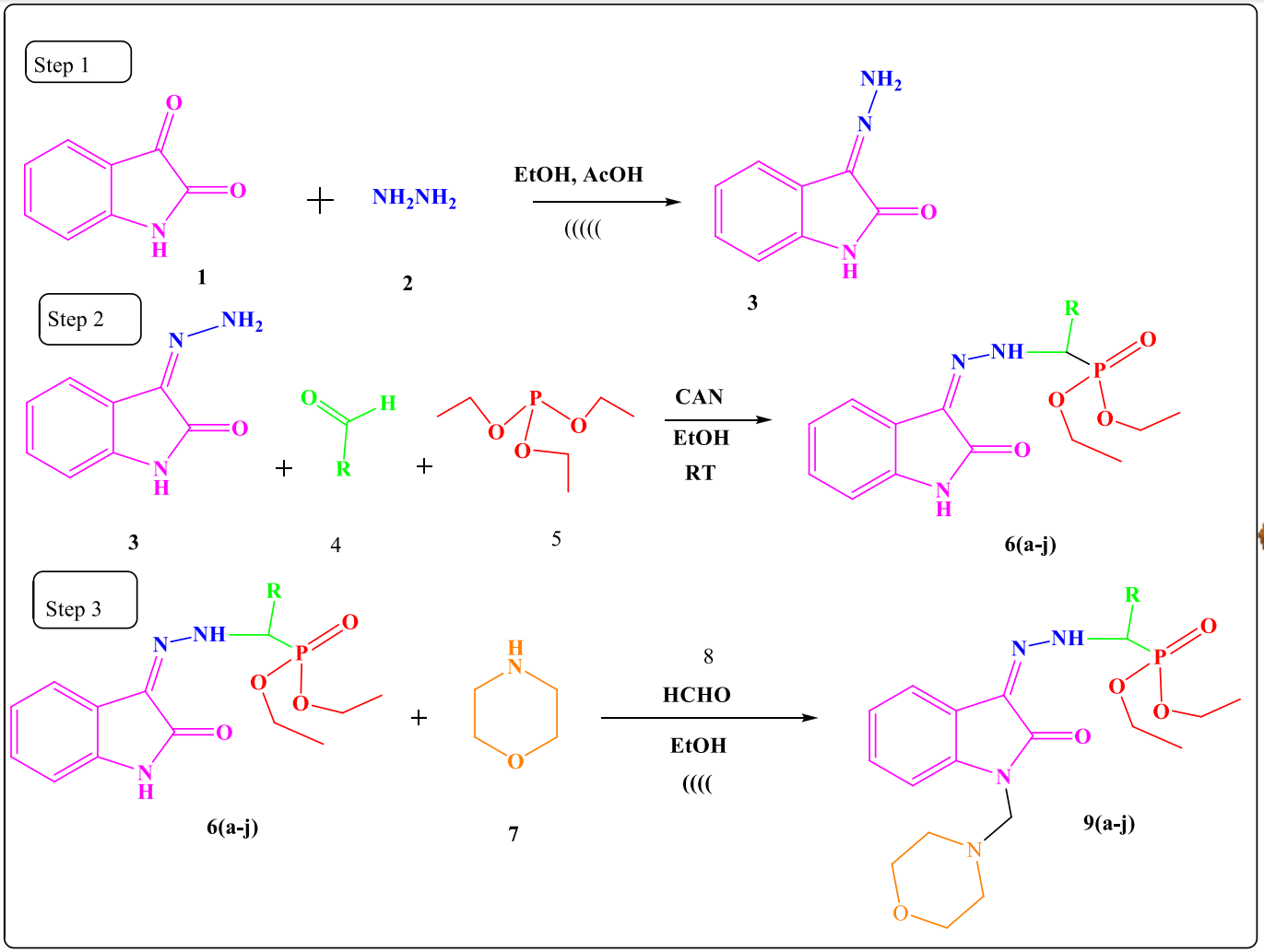
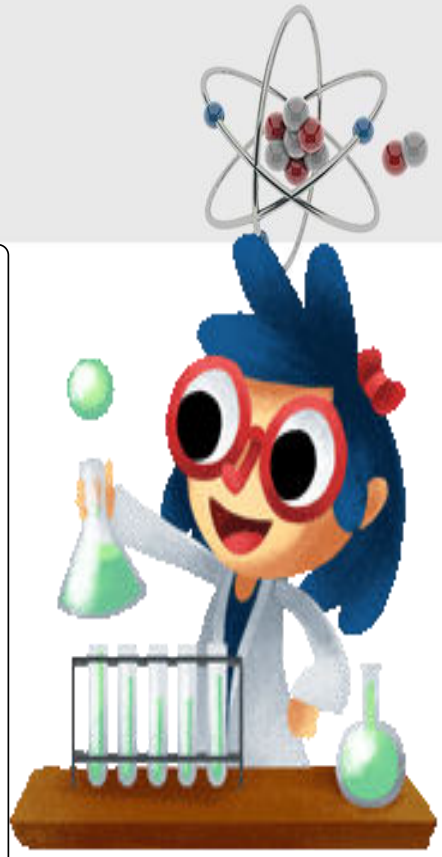


Figure 4.C.1 The designing protocol for the synthesis of the target compound

EXPERIMENTAL
SYNTHESIS





Scheme 1 Scheme of synthesis of the target compounds.

SYNTHESIS

Step I: Synthesis of 3-hydrazonoindolin-2-one

A) Conventional method

A mixture of indole-2,3-dione (isatin) (1 mmol) (**1**) and hydrazine hydrate (1 mmol) (**2**) 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 $^{2}/_{3}K_2O\cdot{}^{1}/_{3}Na_2O\cdot Al_2O_3\cdot 2SiO_2\cdot{}^{9}/_{2}H_2O$. 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 [22]. The separated crystals were filtered, washed with a little amount of methanol, dried and recrystallized with ethanol solvent, M.P. 280-284 ˚C, Yield 82 %.

B) Ultrasonication Method

Equimolar quantities of indole-2,3-dione (isatin) (1 mmol) **(1)** and hydrazine hydrate (1mmol) **(2)** 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 °C and at 25 amplitude for 15 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 was formed as the product with molecular formula $C_8H_7O_1N_3$, MW: 161.13. Yield: 95 %; melting point: 282-284 °C. The melting point was uncorrected.

Step II: Cerric Ammonium Nitrate catalyzed synthesis of Diethyl (substituted phenyl/heteryl)(2-(2-oxoindolin-3-ylidene)hydrazinyl) methylphosphonate 6(a-j) derivatives.

Equimolar quantity of 3-hydrazonoindolin-2-one (1mmol) (**3**), substituted aromatic aldehyde/heteryl aldehyde (1mmol) (**4**) and tri-ethylphosphite (**5**) (1mmol) was stirred at room temperature in absolute ethanol, in presence of Cerric Ammonium Nitrate (CAN) as a catalyst. The progress of the 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.

Step III: Synthesis of Diethyl (2-(1-(morpholinomethyl)-2-oxoindolin-3-ylidene)hydrazinyl) (substituted phenyl/heteryl) methylphosphonate 9(a-j).

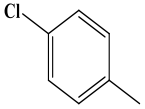
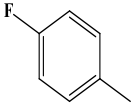
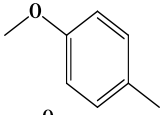
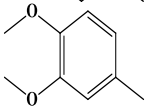
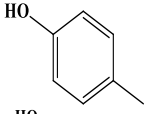
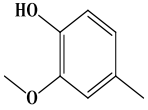
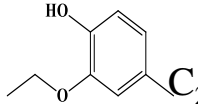
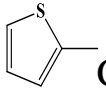
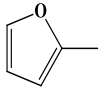
•Conventional method for of 9(a-j) derivatives

Diethyl (substituted phenyl/heteryl) (2-(2-oxoindolin-3-ylidene) hydrazinyl) methylphosphonates (0.002 mol) **6(a-j)** was dissolved in absolute ethanol (3-5 mL). Then morpholine (0.002 mol) (**7**) and formaldehyde (37 %, 0.5 mL) (**8**) were added drop-wise with vigorous stirring. After combining all the reagents, the reaction mixture was stirred at room temperature for 7-12 hrs. The solid product was filtered and washed with petroleum ether. The solid that separated was recrystallized from ethanol-dioxane (1:2) to give the title compounds.

•Ultrasound method for synthesis of 9(a-j) derivatives

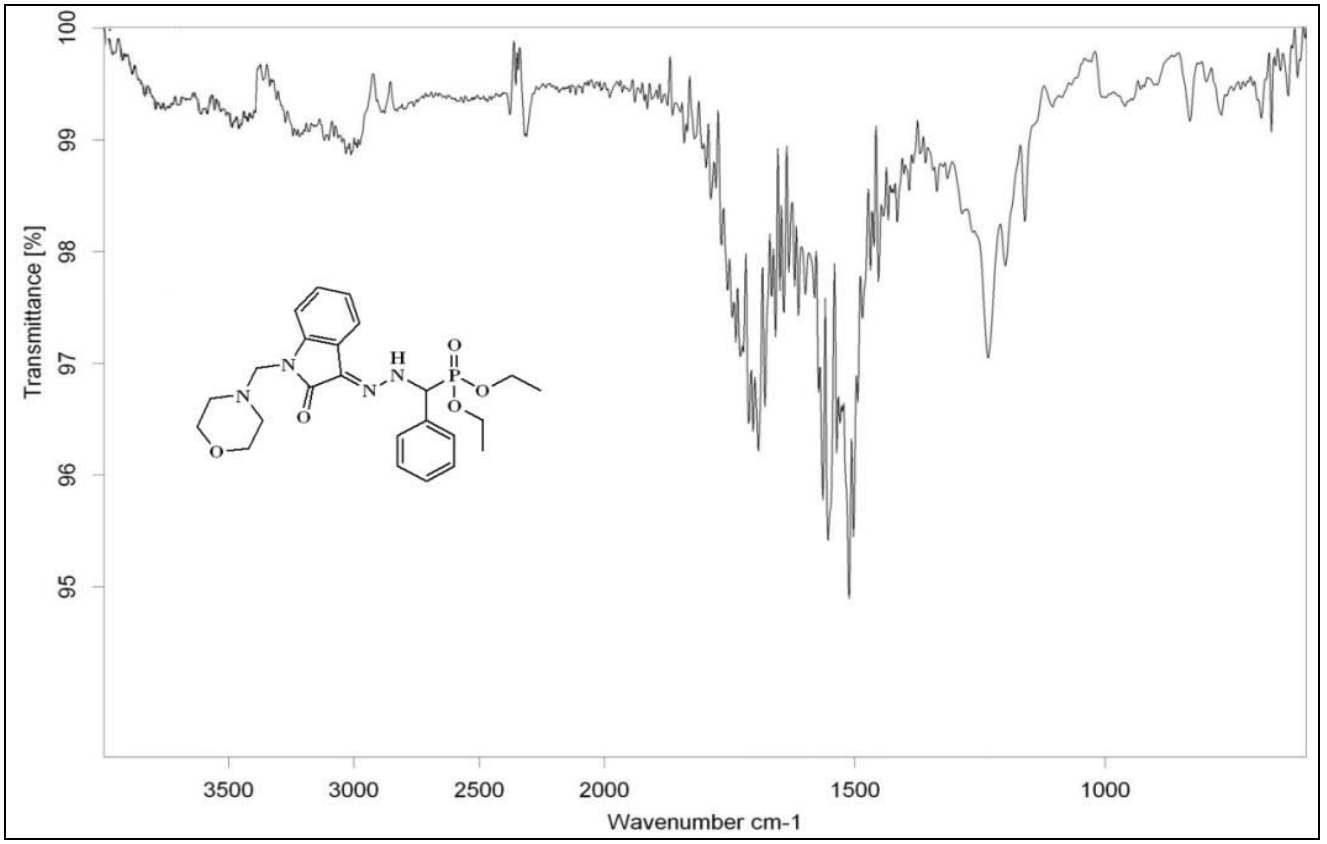
Diethyl (substituted phenyl/heteryl) (2-(2-oxoindolin-3-ylidene)hydrazinyl) methylphosphonates (0.002 mol) **6(a-j)** was dissolved in absolute ethanol (3-5 mL). Then Morpholine (0.002 mol) (**7**) and Formaldehyde (37 %, 0.5 mL) (**8**) were added drop-wise with vigorous stirring. Sonication was achieved at frequencies of 20 kHz (amplitude of 50 %). The reaction was carried out at room temperature. After completion of the reaction (monitored by TLC), the mixture was poured into ice cold water. The resultant solid was filtered, dried and purified by recrystallisation.

Table 4.C.2 Physical characterization data of the synthesized derivatives **9(a-j)**.

Compound	R	Molecular formula	M.W	M. P (°C)	Time required (hrs)		% Yield	
					Conventional method	Ultrasound method	Conventional method	Ultrasound method
9a		$C_{24}H_{31}N_4O_5P$	486.5	144-148	12	4:10	68	88
9b		$C_{24}H_{30}ClN_4O_5P$	520.9	132-134	8	2:20	70	90
9c		$C_{24}H_{30}FN_4O_5P$	504.4	156-158	8	2:45	62	92
9d		$C_{25}H_{33}N_4O_6P$	516.5	166-168	9	3:15	56	86
9e		$C_{26}H_{35}N_4O_7P$	546.5	172-174	12	4:30	72	82
9f		$C_{24}H_{31}N_4O_6P$	502.5	132-134	10	3:00	78	82
9g		$C_{25}H_{33}N_4O_7P$	532.5	126-128	10	2:40	58	88
9h		$C_{25}H_{35}N_4O_7P$	546.2	156-158	8	2:10	62	90
9i		$C_{22}H_{29}N_4O_5PS$	492.1	168-170	7	2:00	54	84
9j		$C_{22}H_{29}N_4O_6P$	476.4	162-164	7	3:30	68	82

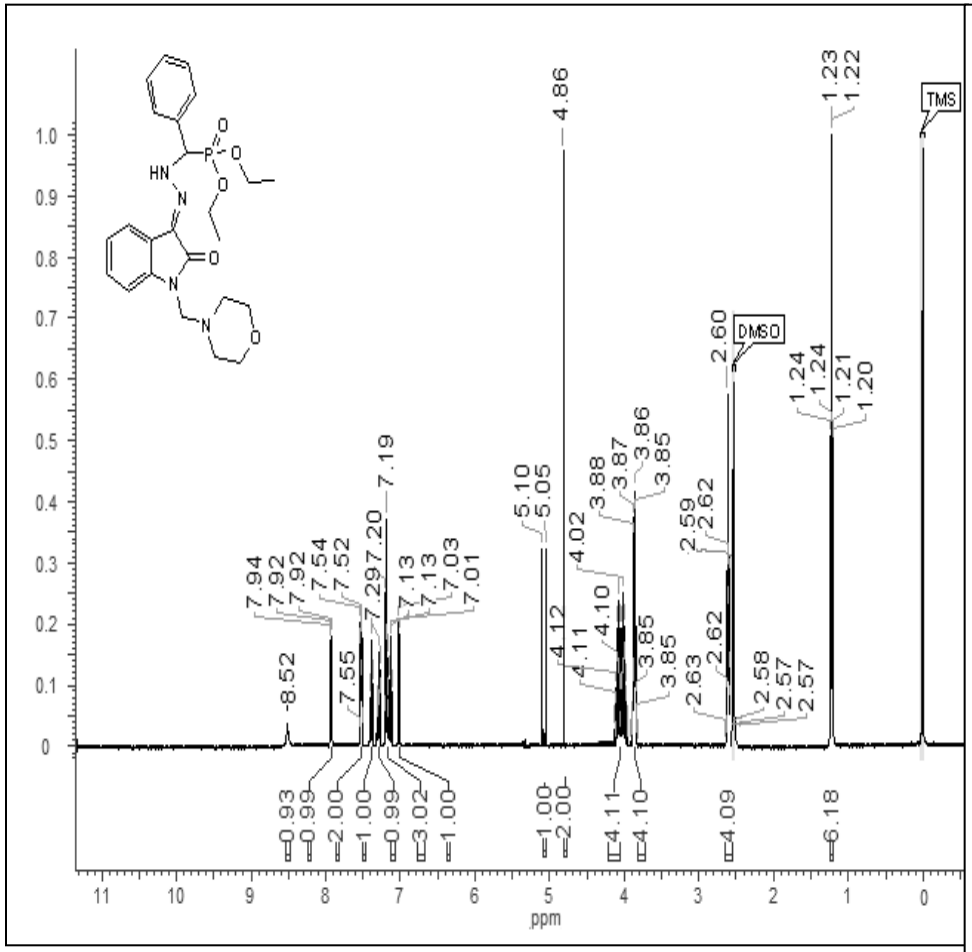
Spectra of the Synthesized Compounds

IR spectra of compound 9a



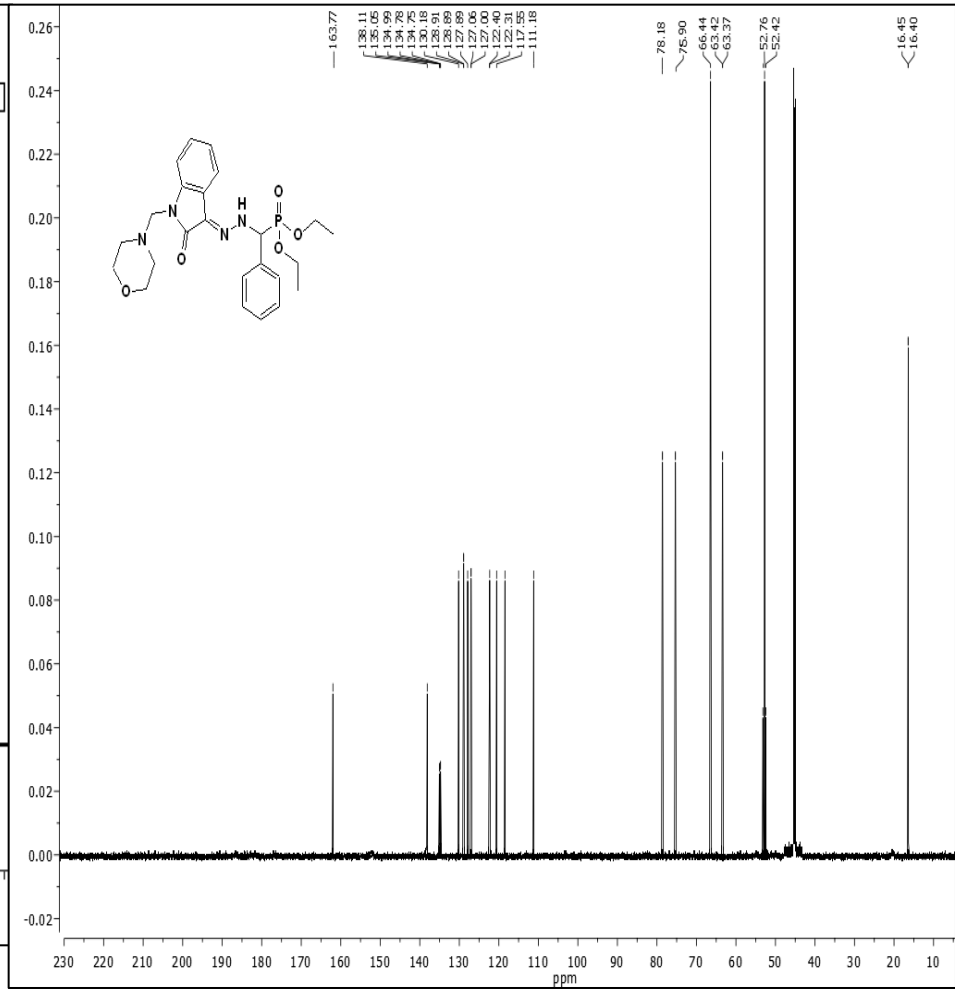
2960 (CH stretching of aromatic), 2300 (N-H stretching), 1620 (C=O stretching of amide), 1466 (CH Bending of CH_2)

^{1}H NMR spectrum of compound 9a



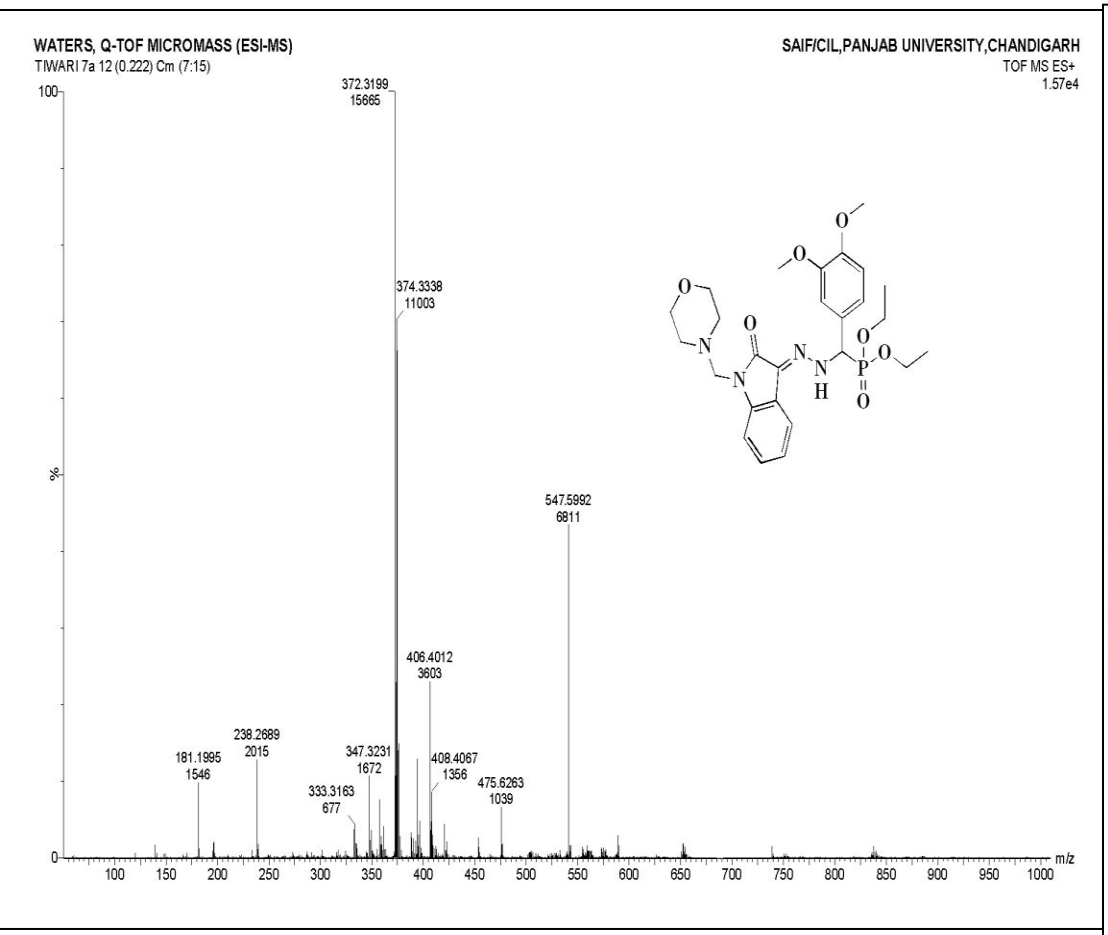
1.20 (t, 6H, 2×OCH$_2$CH$_3$), 2.57-3.88 (m, 8H, morpholine ring), 4.70 (q, 4H, 2×OCH$_2$CH$_3$), 4.86 (s, 2H, CH$_2$), 5.05 (d, 1H, -CH), 7.10-7.94 (m, 9H, -CH), 8.52 (s, 1H, -NH)

^{13}C NMR spectrum of compound 9a

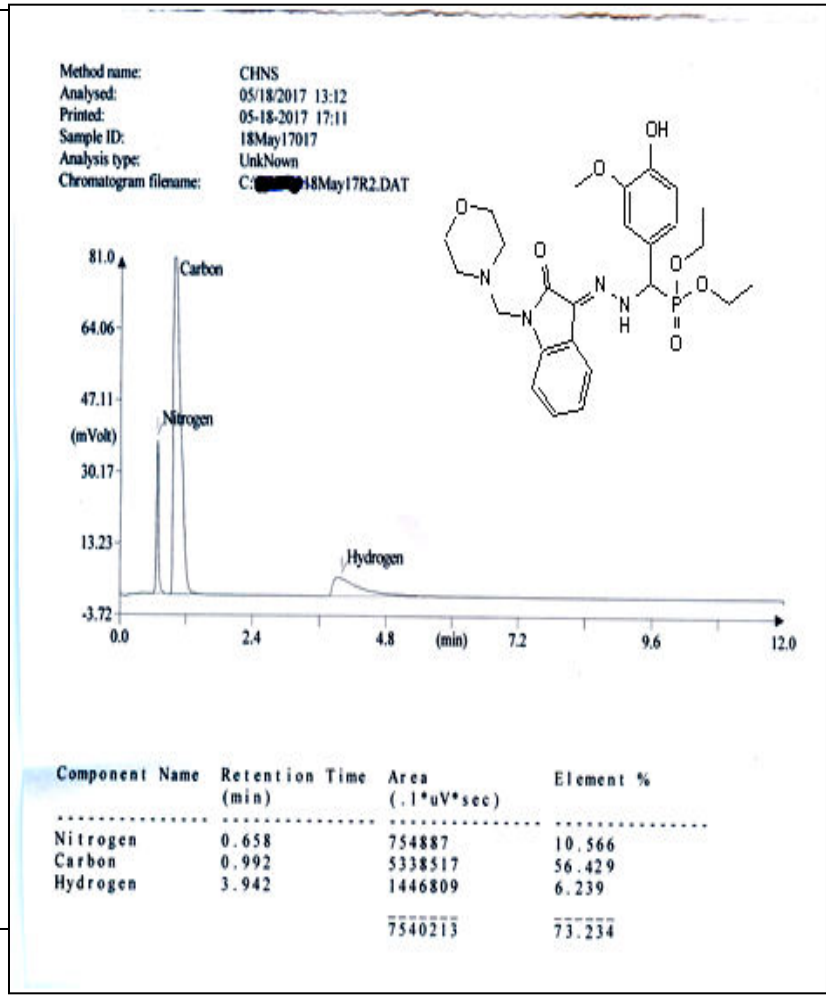


16.4, 52.4, 63.3, 66.4, 75.9, 78.1, 111.1, 117.5, 122.3, 122.4, 127.0, 127.8, 128.9, 130.1, 134.9, 136.0, 138.1, 163.7

Mass spectra of compound 9e
Molecular Weight: 546.55, Molecular ion peak: 547.59.



Elemental analysis of 9g



Component Name	Retention Time (min)	Area (.1*uV*sec)	Element %
Nitrogen	0.658	754887	10.566
Carbon	0.992	5338517	56.429
Hydrogen	3.942	1446809	6.239
		7540213	73.234

CONCLUSION

In conclusion, we have synthesized a suite of novel diethyl (2-(1-(morpholinomethyl)-2-oxoindolin-3-ylidene) hydrazinyl) (substituted phenyl/heteryl) methylphosphonate derivatives **9(a-j)** using a Green 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. The mild reaction conditions, excellent yields in shorter reaction time and evasion of cumbersome work-up procedures make this process economically lucrative for industrial application.

REFERENCES

•Millemaggi, A., Taylor, RJK. *Eur. J. Org. Chem.,* **2010**, 24, 4527.

•Singh, G.S., Desta, Z.Y. *Chem. Rev.,* **2012**, 112, 6104.

•Bhaskar, G., Arun, Y., Balachandran, C., Saikumar, C., Perumal, P.T. *Eur. J. Med. Chem.,* **2012**, 51, 79.

•Kia, Y., Osman, H., Kumar, R.S., Murugaiyah, V., Basiri, A., Perumal, S., Wahab, H.A., Bing, C.S. *Biorg. Med. Chem.,* **2013**, 21, 1696.

•Leoni, A., Locatelli, A., Morigi, R., Rambaldi, M. *Expert Opin. Ther. Pat.,* **2016**, 26, 149.

•Zefirov, N.S., Matveeva, E.D. *ARKIVOC*, **2008**, 1.

•Kukhar, V.P., Hudson, H.R., Eds. Aminophosphonic and Aminophosphinic Acids: Chemistry and Biological Activity; Wiley: Chichester, UK, **2000**.

•Fields, S.C. *Tetrahedron*, **1999**, 55, 12237.

•Kafarski, P., Lejczak, B. *Curr. Med. Chem. Anticancer Agents,* **2001**, 1, 301.

•Bird, J., De Mello, R.C., Harper, G.P., Hunter, D.J., Karran, E.H., Markwell, R.E., Miles-Williams, A.J., Rahman, S.S., Ward, R.W. *J. Med. Chem.*, **1994**, 37, 158.

•Liu, W.S., Rogers, C.J., Fisher, A.J., Toney, M.D. *Biochemistry*, **2002**, 41, 12320.

•Mucha, A., Kafarski, P., Berlicki, L. *J. Med. Chem.,* **2011**, 54, 5955.

•Andrs, M., Korabecny, J., Jun, D., Hodny, Z., Bartek, J., Kuca, K. *J. Med. Chem.,* **2015**, 58, 41.

•Taylor, R.D., MacCoss, M., Lawson, A.D.G. *J. Med. Chem.*, **2014**, 57, 5845.

•Tiwari, S.V.; Seijas, J., Vazquez-Tato, M.P.; Sarkate, A. P.; Lokwani, D.K.; Nikalje, A.G. *Molecules*, **2016,** 21, 1-13.

THANK YOU