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Ultrasound Assisted Synthesis of Diethyl (2-(1-(morpholinomethyl)-2-Oxoindolin-3-ylidene)hydrazinyl) (Substituted Phenyl/heteryl) MethylphosphonateDerivatives †

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Abstract: This work reports ultrasound assisted synthesis diethyl (2-(1-(morpholinomethyl)-2-oxo indolin-3-ylidene)hydrazinyl) (substituted phenyl/heteryl) methylphosphonate **9(a–j)** derivatives. The derivatives are synthesized using a 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 are synthesized using cerric ammonium nitrate as catalyst. In the third step, diethyl (2-(1-(morpholino methyl)-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 a 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 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, this promoted us to club these pharmacophores together in a single molecule using a green synthetic protocol.The structures of the ultrasound synthesized compounds were confirmed by spectral analysis like IR, 1H NMR, 13C NMR, 31P NMR and MS.

Keywords: ultrasound assisted; cerric ammonium nitrate; isatin; α-amino phosphonate

1. Introduction

Isatin (indolin-2,3-dione) a "privileged scaffold" has been found to be an important class of heterocyclic compound capable of interesting pharmacological [1,2] and biological activities such as antimicrobial [3], cholinesterases [4], anticancer properties [5], etc.

α-Aminophosphonic acids, considered as phosphorus analogues of α -amino acids, have attracted much attention in drug research due to their low mammalian toxicity. They are eminent targets in the development of antibiotics, antiviral species, anti-hypertensive and anti-tumor agents based on their effect as inhibitors of GABA-receptors, enzyme inhibitors and anti-metabolites [6–12].

On the other hand, morpholine moiety has been found to be an eminent pharmacophore in medicinal chemistry [13]. A number of molecules possessing morpholine moiety are clinically approved drugs [13]. 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 [14].

In view of these facts, we synthesized novel diethyl (2-(1-(morpholinomethyl)-2-oxoindolin-3-ylidene)hydrazinyl) (substituted phenyl/heteryl) methylphosphonate**9(a–j)** derivatives under ultrasound irradiation using a green protocol. Ultrasound assisted techniques were reported to be more effective in terms of environment, reaction time, high yields, ease of work-up and isolation of products [15].

The amalgamation of two dissimilar bioactive pharmacophores made into a single molecule is a successful and frequently used approach in modern medicinal chemistry for the exploration of novel and highly active compounds which may have synergistic effects on biological properties [16]. Hence, in the pursuit of developing a novel agent, the coupling of the three important pharmacophores i.e., indole-2-one, morpholine and α-aminophosphonate in a single molecule is designed by aiming at the identification of new molecules with enhanced biological activity. The synthesis of aforementionedconjugates could be possible by a pharmacophore hybrid approach of modern medicinal chemistry. The designed protocol for the synthesis of the target compounds is as shown in Figure 1.

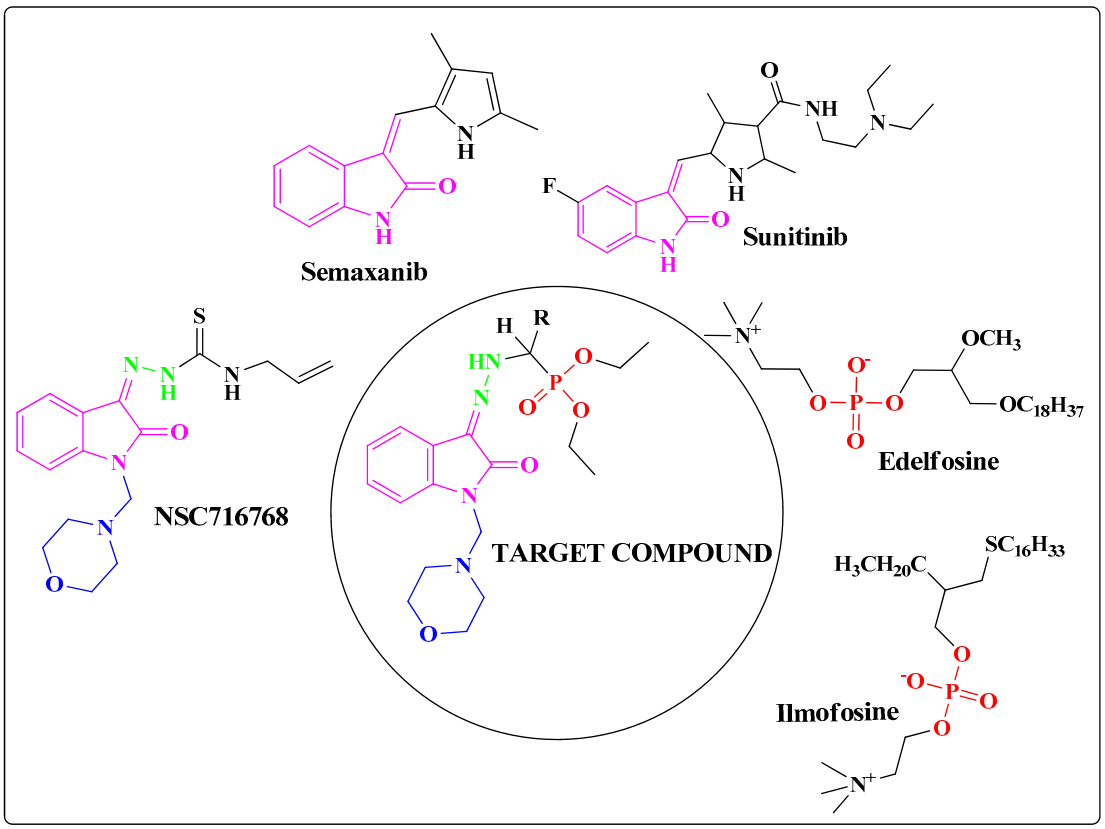


Figure 1. The designed protocol for the synthesis of the target compound.

2. Experimental

All the chemicals, unless otherwise specified, were purchased from commercial sources and were used without further purification. The major chemicals were purchased from Sigma Aldrich

and Avralabs. The progress of the reactions was monitored by thin layer chromatography (TLC) analysis on Merck pre-coated silica gel 60 F254 aluminum sheets, visualized by UV light. The Ultrasound Sonicator (Sonics Vibra-cell, Model no. VCX 500) equipped with solid synthetic probe, 13 mm in tip diameter, operating at 20 kHz with a maximum power output of 500 W, was used for synthesis of final title compounds. Infrared (IR) spectra were recorded on JASCO FTIR (PS 4000) using KBr pallet. Melting points were determined in open capillary tubes and are uncorrected. The ^{1}H-NMR and ^{13}C-NMR spectra of synthesized compounds were recorded on Bruker Advance II 400 NMR Spectrometer (Billerica, MA, USA) at 400 MHz frequency in deuterated DMSO. Tetra methylsilane (TMS) was used as an internal standard. The chemical shifts are reported as NMR spectra δppmunits. The following abbreviations are used; singlet (s), doublet (d), multiplet (m). Mass spectra were taken with WATERS, Q-TOF MICROMASS (E SI-MS). Elemental analyses were done with a FLASHEA 112 Shimadzu' analyzer (Mumbai, Maharashtra, India) and all analyses were consistent (within 0.4%) with theoretical values.

Synthesis

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

(A) Conventional method [17]

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 to 4 h in the presence ofmolecular sieves. Microporous 3Å molecular sieves are alumino silicate minerals with the 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 1990s, 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[18]. The separated crystals were filtered, washed with a small amount of methanol, dried and recrystallized with ethanol solvent; M.P: 280–284 °C; yield: 82%.

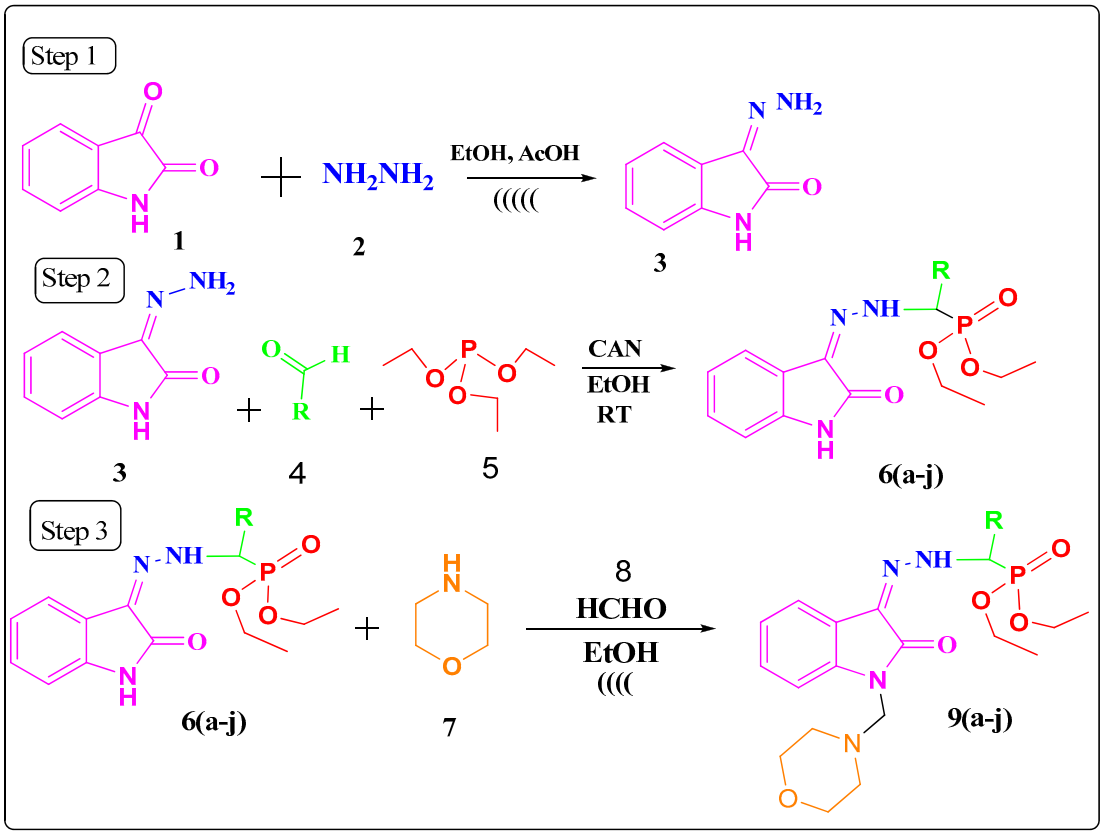
(B) Ultrasonication Method

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 an 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.

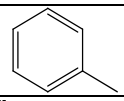
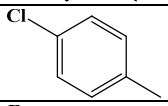
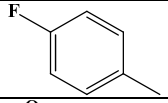
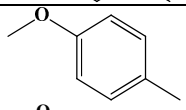
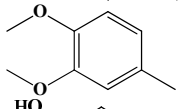
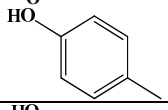
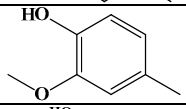
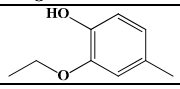
An equimolar quantity of 3-hydrazonoindolin-2-one (1mmol) (**3**), substituted aromatic aldehyde/heteryl aldehyde (1mmol) (**4**) and tri-ethylphosphite (**5**) (1mmol) was stirred at room temperature in absolute ethanol, in the presence of Cerric Ammonium Nitrate (CAN) as a catalyst. The progress of 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. The time required for completion of reaction varied from 70 to 90 min as shown in Table 1.

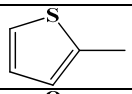
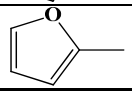
The novel derivatives **6(a–j)** were synthesized as shown in Scheme 1 using a green protocol. The derivatives were synthesized at room temperature using green catalyst i.e., Cerric Ammonium Nitrate (CAN).



Scheme 1. Scheme of synthesis of the target compounds.

Table 1. The physical characterization data of the synthesized derivatives **6(a–j)**.

Entry	R	Molecular Formula	Molecular Weight	Time Required (min)	%Yield	Melting Point (°C)
6a		$C_{19}H_{22}N_3O_4P$	387.37	75	90	195–196
6b		$C_{19}H_{21}ClN_3O_4P$	421.81	70	92	150–152
6c		$C_{19}H_{21}FN_3O_4P$	405.36	75	95	176–180
6d		$C_{20}H_{24}N_3O_5P$	417.40	85	89	178–179
6e		$C_{21}H_{26}N_3O_6P$	447.42	90	90	189–190
6f		$C_{19}H_{22}N_3O_5P$	403.37	80	88	140–142
6g		$C_{20}H_{24}N_3O_6P$	433.39	75	94	112–114
6h		$C_{21}H_{26}N_3O_6P$	447.44	80	92	160–162

6i		$C_{17}H_{20}N_3O_4PS$	393.40	80	87	179–182
6j		$C_{17}H_{20}N_3O_5P$	377.33	80	84	176–178

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

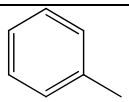
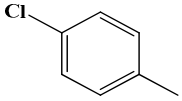
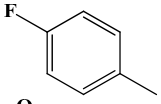
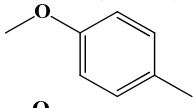
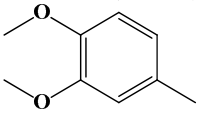
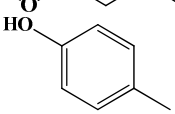
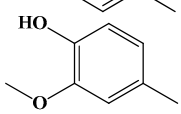
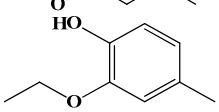
A Conventional method for of 9(a–j) derivatives

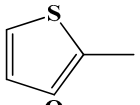
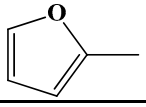
Diethyl (substituted phenyl/heteryl) (2-(2-oxoindolin-3-ylidene) hydrazinyl) methylphosphonates (0.002 mol) **6(a–j)** was dissolved in absolute ethanol (3–5 mL). Then, morpholine (0.002 mol) (**7**) and formaldehyde (37%, 0.5 mL) (**8**) were added drop-wise with vigorous stirring. After combining all the reagents, the reaction mixture was stirred at room temperature for 7–12 h. 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.

B 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. Physical characterization data of the synthesized derivativesdiethyl (2-(1-(morpholinomethyl)-2-oxoindolin-3-ylidene) hydrazinyl)(substituted phenyl/heteryl) methylphosphonate **9(a–j)** is as shown in **Table 2.**

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

Compound	R	Molecular Formula	Molecular Weight	Melting Point (°C)
9a		$C_{24}H_{31}N_4O_5P$	486.50	144–148
9b		$C_{24}H_{30}ClN_4O_5P$	520.95	132–134
9c		$C_{24}H_{30}FN_4O_5P$	504.49	156–158
9d		$C_{25}H_{33}N_4O_6P$	516.53	166–168
9e		$C_{26}H_{35}N_4O_7P$	546.55	172–174
9f		$C_{24}H_{31}N_4O_6P$	502.50	132–134
9g		$C_{25}H_{33}N_4O_7P$	532.51	126–128
9h		$C_{25}H_{35}N_4O_7P$	546.22	156–158

9i		$C_{22}H_{29}N_4O_5PS$	492.16	168–170
9j		$C_{22}H_{29}N_4O_6P$	476.46	162–164

The time required for completion of reaction for synthesis of diethyl (2-(1-(morpholinomethyl)-2-oxoindolin-3-ylidene) hydrazinyl) (substituted phenyl/heteryl) methylphosphonate **9(a–j)** using conventional and ultrasound method is as shown in Table 3. The novel derivatives **9(a–j)** were synthesized as shown in Scheme 1.

Table 3. Synthesis of **9(a–j)** derivatives using conventional and ultrasound methods.

Compound	Time Required (h)		% Yield	
	Conventional Method	Ultrasound Method	Conventional Method	Ultrasound Method
9a	12	4:10	68	88
9b	8	2:20	70	90
9c	8	2:45	62	92
9d	9	3:15	56	86
9e	12	4:30	72	82
9f	10	3:00	78	82
9g	10	2:40	58	88
9h	8	2:10	62	90
9i	7	2:00	54	84
9j	7	3:30	68	82

Spectral characterization of the synthesized derivatives 9(a–j).

(E)-diethyl (2-(1-(morpholinomethyl)-2-oxoindolin-3-ylidene)hydrazinyl)(phenyl)methylphosphonate [9a]

IR: (KBr υ_{max} in cm^{-1}): 2960 (CH stretching of aromatic), 2300 (N-H stretching), 1620 (C=O stretching of amide), 1466 (CH Bending of CH_2); ^{1}H NMR (400 MHz, DMSO, δ_H ppm): 1.20 (t, 6H, 2×OCH$_2$<u>CH$_3$</u>),2.57–3.88 (m, 8H, morpholine ring), 4.70 (q, 4H, 2×O<u>CH$_2$</u>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 (100 MHz, DMSO, δ_C ppm): 16.40, 52.42, 63.37, 66.44, 75.90, 78.18, 111.18, 117.55, 122.31, 122.40, 127.00, 127.89, 128.91, 130.18, 134.99, 136.05, 138.11, 163.77; ^{31}PNMR (200 MHz,DMSO) δ: 19.90; MS: *m*/*z*487.50 $[M+1]^+$; Anal. Calcd. for $C_{24}H_{31}N_4O_5P$: C, 59.25; H, 6.42; N, 11.52. Found: C, 59.29; H, 6.40; N, 11.55.

(E)-diethyl (4-chlorophenyl)(2-(1-(morpholinomethyl)-2-oxoindolin-3-ylidene)hydrazinyl)methylphosphonate [9b]

IR: (KBr υ_{max} in cm^{-1}): 2970 (CH stretching of aromatic), 2800 (CH stretching of alkyl), 2350 (N-H stretching), 1710 (C=O stretching of amide), 1454 (CH Bending of CH_2); ^{1}H NMR (400 MHz, DMSO, δ_H ppm): 1.20 (t, 6H, 2×OCH$_2$<u>CH$_3$</u>),2.57–3.88 (m, 8H, morpholine ring), 4.70 (q, 4H, 2×O<u>CH$_2$</u>CH$_3$), 4.88 (s, 2H, CH_2), 5.10 (d, 1H, -CH), 7.01–7.94 (m, 8H, -CH), 8.61 (s, 1H, -NH); ^{13}C NMR (100 MHz, DMSO, δ_C ppm): 16.42, 52.76, 63.37, 66.45, 75.90, 78.44, 111.18, 117.51, 122.31, 127.61, 129.13, 130.18, 132.29, 134.00, 134.07, 134.75, 138.16, 163.76; ^{31}PNMR (200 MHz,DMSO) δ: 18.84; MS: *m*/*z*522.95 $[M+2]^+$; Anal. Calcd. for $C_{24}H_{30}ClN_4O_5P$: C, 55.33; H, 5.80; N, 10.75. Found: C, 55.35; H, 5.78; N, 10.79.

(E)-diethyl (4-fluorophenyl)(2-(1-(morpholinomethyl)-2-oxoindolin-3-ylidene)hydrazinyl)methylphosphonate [9c]

IR: (KBr υ_{max} in cm^{-1}): 2910 (CH stretching of aromatic), 2800 (CH stretching of alkyl), 2200 (N-H stretching), 1620 (C=O stretching of amide), 1464 (CH Bending of CH_2); ^1H NMR (400 MHz, DMSO, δ_H ppm): 1.31 (t, 6H, 2×$OCH_2\underline{CH_3}$), 2.68–3.99 (m, 8H, morpholine ring), 4.23 (q, 4H, 2×$O\underline{CH_2}CH_3$), 4.96 (s, 2H, CH_2), 5.21 (d, 1H, -CH), 7.12–8.05 (m, 8H, -CH), 8.82 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO, δ_C ppm): 16.40, 52.76, 63.37, 66.45, 75.44, 78.45, 111.18, 116.03, 117.51, 122.31, 124.31, 128.51, 127.66, 129.44, 131.26, 131.38, 133.09, 138.12, 161.51, 163.56; ^{31}PNMR (200 MHz,DMSO) δ: 18.54; MS: *m*/*z*505.45 $[M+1]^+$; Anal. Calcd. for $C_{24}H_{30}FN_4O_5P$: C, 57.14; H, 5.99; N, 11.11. Found: C, 57.18; H, 5.97; N, 11.14.

(E)-diethyl (4-methoxyphenyl)(2-(1-(morpholinomethyl)-2-oxoindolin-3-ylidene)hydrazinyl)methylphosphonate [9d]

IR: (KBr υ_{max} in cm^{-1}): 2910 (CH stretching of aromatic), 2800 (CH stretching of alkyl), 2300 (N-H stretching), 1619 (C=O stretching of amide), 1025 (-O- stretching); ^1H NMR (400 MHz, DMSO, δ_H ppm): 1.25 (t, 6H, 2×$OCH_2\underline{CH_3}$), 2.68–2.74 (m, 4H, morpholine ring), 3.78 (s, 3H, $O\underline{CH_3}$), 3.91–3.93 (m, 4H, morpholine ring), 4.05 (q, 4H, 2×$O\underline{CH_2}CH_3$), 4.96 (s, 2H, CH_2), 5.15 (d, 1H, -CH), 6.81–7.99 (m, 8H, -CH), 8.62 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO, δ_C ppm): 16.40, 52.76, 55.32, 63.37, 66.44, 75.90, 78.44, 111.18, 114.08, 117.55, 122.31, 127.25, 130.18, 131.09, 131.16, 134.75, 138.11, 158.66, 163.76; ^{31}PNMR (200 MHz,DMSO) δ: 19.84; MS: *m*/*z*517.56 $[M+1]^+$; Anal. Calcd. for $C_{25}H_{33}N_4O_6P$: C, 58.13; H, 6.44; N, 10.85. Found: C, 58.15; H, 6.40; N, 10.89.

(E)-diethyl (3,4-dimethoxyphenyl)(2-(1-(morpholinomethyl)-2-oxoindolin-3-ylidene)hydrazinyl)methylphosphonate [9e]

IR: (KBr υ_{max} in cm^{-1}): 2890 (CH stretching of aromatic), 2800 (CH stretching of alkyl), 2350 (N-H stretching), 1650 (C=O stretching of amide), 1002(-O- stretching); ^1H NMR (400 MHz, DMSO, δ_H ppm): 1.21 (t, 6H, 2×$OCH_2\underline{CH_3}$), 2.57–2.63–3.87 (m, 4H, morpholine ring), 3.86 (s, 6H, $O\underline{CH_3}$), 3.87–4.00 (m, 4H, morpholine ring), 4.05 (q, 4H, 2×$O\underline{CH_2}CH_3$), 4.87 (s, 2H, CH_2), 5.06 (d, 1H, -CH), 6.87–7.95 (m, 7H, -CH), 8.62 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO, δ_C ppm): 16.40, 52.76, 55.87, 55.89, 63.42, 66.44, 75.55, 78.80, 111.18, 112.86, 117.55, 121.04, 122.31, 130.18, 131.79, 131.65, 134.78, 138.11, 150.08, 150.11, 163.67; ^{31}PNMR (200 MHz,DMSO) δ: 18.94; MS: *m*/*z*547.59 $[M+1]^+$; Anal. Calcd. for $C_{26}H_{35}N_4O_7P$: C, 57.14; H, 6.45; N, 10.25. Found: C, 57.18; H, 6.42; N, 10.29.

(E)-diethyl (4-hydroxyphenyl)(2-(1-(morpholinomethyl)-2-oxoindolin-3-ylidene)hydrazinyl)methylphosphonate [9f]

IR: (KBr υ_{max} in cm^{-1}): 3600 (aromatic OH), 2980 (CH stretching of aromatic), 2800 (CH stretching of alkyl), 2280 (N-H stretching), 1710 (C=O stretching of amide); ^1H NMR (400 MHz, DMSO, δ_H ppm): 1.21 (t, 6H, 2×$OCH_2\underline{CH_3}$), 2.57–3.89 (m, 8H, morpholine ring), 4.11 (q, 4H, 2×OCH_2CH_3), 4.96 (s, 2H, CH_2), 5.11 (d, 1H, -CH), 6.72–7.95 (m, 8H, -CH), 8.45 (s, 1H, OH), 8.53 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO, δ_C ppm): 16.40, 52.76, 63.37, 66.44, 75.55, 78.80, 111.18, 115.94, 117.55, 122.40, 130.29, 130.35, 131.08, 131.68, 134.75, 138.11, 157.23, 163.67; ^{31}PNMR (200 MHz,DMSO) δ:19.64; MS: *m*/*z*503.50 $[M+1]^+$; Anal. Calcd. for $C_{24}H_{31}N_4O_6P$: C, 57.36; H, 6.22; N, 11.15. Found: C, 57.38; H, 6.20; N, 11.18.

(E)-diethyl (4-hydroxy-3-methoxyphenyl)(2-(1-(morpholinomethyl)-2-oxoindolin-3-ylidene)hydrazinyl)methylphosphonate [9g]

IR: (KBr υ_{max} in cm^{-1}): 3610 (aromatic OH), 2996 (CH stretching of aromatic), 2830 (CH stretching of alkyl), 2310 (N-H stretching), 1680 (C=O stretching of amide), 1030 (-O-stretching); ^1H NMR (400 MHz, DMSO, δ_H ppm): 1.20 (t, 6H, 2×$OCH_2\underline{CH_3}$), 2.52–3.78 (m, 8H, morpholine ring), 3.79 (s, 3H, $O\underline{CH_3}$), 4.08 (q, 4H, 2×$O\underline{CH_2}CH_3$), 4.87 (s, 2H, CH_2), 5.00 (d, 1H, CH), 6.73–7.89 (m, 7H, CH), 8.15 (s, 1H, OH), 9.08 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO, δ_C ppm): 16.40, 52.70, 55.38, 63.37, 66.44,

75.50, 78.82, 111.18, 112.91, 115.90, 117.55, 120.40, 129.70, 131.09, 131.18, 134.75, 138.11, 146.11, 146.71, 157.23, 163.67; ^{31}PNMR (200 MHz,DMSO) δ: 19.94; MS: *m*/*z*533.51 [M+1]$^+$; Anal. Calcd. for $C_{25}H_{33}N_4O_7P$: C, 56.39; H, 6.25; N, 10.52. Found: C, 56.42; H, 6.23; N, 10.56.

(E)-diethyl (3-ethoxy-4-hydroxyphenyl)(2-(1-(morpholinomethyl)-2-oxoindolin-3-ylidene)hydrazinyl)methyl phosphonate [9h]

IR: (KBr υ_{max} in cm^{-1}): 3550 (aromatic OH), 2999 (CH stretching of aromatic), 2813 (CH stretching of alkyl), 2350 (N-H stretching), 1710 (C=O stretching of amide), 1020 (-O- stretching); ^{1}H NMR (400 MHz, DMSO, δ_H ppm): 1.15 (t, 6H, 2×OCH$_2$<u>CH$_3$</u>), 1.43 (t, 3H, OCH$_2$<u>CH$_3$</u>), 2.52–3.82 (m, 8H, morpholine ring), 4.11(m, 6H, 3×O<u>CH$_2$</u>CH$_3$), 4.76 (s, 2H, CH$_2$), 5.06 (d, 1H, CH), 6.72–6.95 (m, 3H, CH), 6.99 (s, 1H, OH), 7.10–7.89 (m, 4H, CH), 8.81 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO, δ_C ppm): 14.88, 16.40, 52.70, 63.37, 66.44, 75.50, 78.82, 112.55, 115.31, 115.90, 117.55, 119.33, 124.40, 129.70, 131.29, 133.18, 137.75, 138.11, 146.11, 148.11, 163.67; ^{31}PNMR (200 MHz,DMSO) δ: 18.65; MS: *m*/*z*547.21 [M+1]$^+$; Anal. Calcd. for $C_{25}H_{35}N_4O_7P$: C, 57.14; H, 6.45; N, 10.25. Found: C, 57.17; H, 6.43; N, 10.29.

(E)-diethyl (2-(1-(morpholinomethyl)-2-oxoindolin-3-ylidene)hydrazinyl)(thiophen-2-yl)methylphosphonate [9i]

IR: (KBr υ_{max} in cm^{-1}): 2912 (CH stretching of aromatic), 2800 (CH stretching of alkyl), 2340 (N-H stretching), 1710 (C=O stretching of amide);^{1}H NMR (400 MHz, DMSO, δ_H ppm): 1.17 (t, 6H, 2×OCH$_2$<u>CH$_3$</u>), 2.52–3.84 (m, 8H, morpholine ring), 4.07 (q, 4H, 2×O<u>CH$_2$</u>CH$_3$), 4.96 (s, 2H, CH$_2$), 5.02 (d, 1H, CH), 6.82–7.89 (m, 7H, CH), 8.81 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO, δ_C ppm): 16.40, 52.70, 63.37, 66.44, 75.50, 78.82, 115.33, 117.55, 119.33, 124.40, 125.55, 126.78, 127.98, 129.44, 131.29, 133.18, 138.33, 139.41, 163.67; ^{31}PNMR (200 MHz,DMSO) δ: 18.45; MS: *m*/*z*493.11 [M+1]$^+$; Anal. Calcd. for $C_{22}H_{29}N_4O_5PS$: C, 53.65; H, 5.93; N, 11.38. Found: C, 53.68; H, 5.90; N, 11.40.

(E)-diethyl furan-2-yl(2-(1-(morpholinomethyl)-2-oxoindolin-3-ylidene)hydrazinyl)methylphosphonate [9j]

IR: (KBr υ_{max} in cm^{-1}): 2945 (CH aromatic), 2850 (CH stretching of alkyl), 2440 (C=N stretching), 1710 (C=O stretching), 1070 (-O- stretching); ^{1}H NMR (400 MHz, DMSO, δ_H ppm): 1.25 (t, 6H, 2×OCH$_2$<u>CH$_3$</u>), 2.53–3.84 (m, 8H, morpholine ring), 4.12 (q, 4H, 2×O<u>CH$_2$</u>CH$_3$), 4.32 (s, 2H, CH$_2$), 4.55 (d, 1H, CH), 6.11–7.89 (m, 7H, CH), 8.44 (s, 1H, -NH); ^{13}C NMR (100 MHz, DMSO, δ_C ppm): 16.40, 52.70, 61.22, 66.44, 75.50, 78.82, 106.44, 110.34, 115.33, 117.55, 124.40, 129.84, 131.29, 133.18, 138.33, 142.31, 163.67; ^{31}PNMR (200 MHz,DMSO) δ: 18.56;MS: *m*/*z*477.41 [M+1]$^+$; Anal. Calcd. for $C_{22}H_{29}N_4O_6P$: C, 55.46; H, 6.13; N, 11.76. Found: C, 55.49; H, 6.10; N, 11.79.

3. Results and Discussion

Chemistry

Diethyl(substituted phenyl/heteryl)(2-(2-oxoindolin-3ylidene)hydrazinyl) methylphosphonates derivatives **6(a–j)** and diethyl (2–1-(morpholinomethyl)-2-oxoindolin-3-ylidene)hydrazinyl)(substituted phenyl/heteryl) methylphosphonate derivatives **9(a–j)** were synthesized as presented in Scheme 1. 3-hydrazonoindolin-2-one (**3**) was synthesized using green tool i.e., Ultrasound synthesizer. Indoline-2,3-dione (1mmol) (**1**) and hydrazine hydrate (1mmol) (**2**) were allowed to react in the presence of ethanol as a solvent and glacial acetic acid as a catalyst under ultrasonic irradiation. In order to justify the use of ultrasound, these reactions were also carried out in the absence of ultrasound under reflux condition. The ultrasound method is better than the conventional method because the amount of solvent required is also less than that required for the conventional method, and the ultrasound assisted method gives better yield in 15 min against the 3–4 h required for the conventional method. According to the Kabachnik–Fields method, diethyl (substituted phenyl/heteryl) (2-(2-oxoindolin-3ylidene)hydrazinyl) methylphosphonates derivatives **6(a–j)** were synthesized by reaction of3-hydrazonoindolin-2-one

(1mmol) (**3**), substituted aromatic aldehyde/heteryl aldehyde (1mmol) **4(a–j)** and triethylphosphate (1mmol) (**5**) in the presence of green catalyst CAN. CAN activates the imine formation due to which the addition of phosphite is facilitated to give a phosphonium intermediate. This phosphonium intermediate undergoes a reaction with water to give the title compounds.The CAN catalyst, being water soluble, can be easily removed after completion of the reaction. (E)-diethyl(2-(1-(morpholinomethyl)-2-oxoindolin-3-ylidene)hydrazinyl)(substituted phenyl/heteryl)methylphosphonate derivatives **9(a–j)** were synthesized according to the Mannich reaction. Diethyl (substituted phenyl/heteryl) (2-(2-oxoindolin-3-ylidene)hydra zinyl) methylphosphonates (0.002 mol) **6(a–j)** were 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 adding all reagents, the reaction mixture was stirred on a magnetic stirrer at room temperature for 12 h. The same step was also carried out using the ultrasound green method which gave better yield in the short reaction time, as specified in Table 3. The purity of the synthesized compounds was checked by TLC and melting points were determined in open capillary tubes and are uncorrected. The synthesized compounds were characterized and confirmed by FTIR, ^{1}H NMR, ^{13}C NMR, ^{31}P NMR, MS and elemental analyses.

4. Conclusions

In conclusion, we have synthesized a suite of novel diethyl (2-(1-(morpholinomethyl)-2-oxoind olin-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 analyses like IR, ^{1}H NMR, ^{13}C NMR, ^{31}P NMR and MS. The mild reaction conditions, excellent yields in shorter reaction times and evasion of cumbersome work procedures make this process economically lucrative for industrial application.

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