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Original article

Synthesis of new α aminophosphonate system bearing Indazole moiety and their biological activity

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ABSTRACT

We are reporting herein for the first time the synthesis of α-aminophosphonates containing Indazole moiety in two steps. In the first step, imines of substituted N-benzylidene-1-methyl-1*H*-indazole-3-carbohydrazide are synthesized and in the next step it has converted to α-aminophosphonates using chlorotrimethylsilane (TMSCl) and triethyl phosphite. Some of the synthesized derivatives are evaluated for antibacterial activity against different bacterial strains.

1. Introduction

Among the heterocyclic compounds, which are available for the preparation of potentially valuable new building-blocks in medicinal chemistry, the Indazole nucleus is probably one of the least studied. In contrast to the abundance of publications on its bioisosteres *e.g.*, indole [1,2] or benzimidazole [3–5], there are limited number of publications based on Indazole chemistry, may be due to the fact that the Indazole moiety is rather scarce in natural products [6–8]. Even though, a large number of synthetically prepared compounds have displayed biological and pharmacological properties [9]. Bendazac, a non-steroidal anti-inflammatory agent, used as an anti-cataract drug [10] and Granisetron, a serotonin 5-HT3 receptor antagonist used to treat and prevent nausea and vomiting induced by cancer chemotherapy [11,12] this are the two examples of bioactive molecules of current interest. Other compound of interest isYC-I (a guanylyl cyclase activator) [13–15] used for the treatment of cardiovascular diseases or erectile dysfunction and lonidamine [16–18] drug used for treatment of cancer.

Apart from this Indazoles constitute an important class of heterocycles that displays an interesting biological properties [19], such as anti-depressant [20], anti-inflammatory [21,22], analgesic, antipyretic [23], dopamine antagonistic [24], anti-tumor [25], antiemetic [26], and anti-HIV activities [27].

As natural amino acid analogues, α-aminophosphonate compounds has attracted the current interest in organic and medicinal chemistry due to biological and pharmacological properties of this organophosphorus compounds [28]. As structure analogues of amino acid ('bioisosterism') has received considerable attention owing to their pronounced biological activities. These entities has also been shown to serve as inhibitors of GABA-receptors, inhibitors of various proteolytic enzymes, inhibitors of dialkylglycine decarboxylase, peptide mimetic, antibiotics, and pharmacological agent, including anti-tumor, antihypertensive and antibacterial agents [29]. Apart from this, their potential as herbicides [30], insecticides [31], fungicides [32], antiviral agents [33], as well as their role for antibody generation [34] is well known.

2. Result and discussion

Owing to their synthetic and biological values, the chemistry of α-aminophosphonates has stimulated increasing interest and the development of new organophosphorus compounds are still remains of great interests. Moreover literature survey has revealed that compounds containing α-aminophosphonates with Indazole moiety has not been reported so far.

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Therefore, we have synthesized α-aminophosphonates containing Indazole moiety in two steps. In the first step, imines of substituted N-benzylidene-1-methyl-1*H*-indazole-3-carbohydrazide are synthesized. Synthesis of these compounds proceeds through the formation of methyl-1-methyl-1*H*-indazole-3-carboxylate, by acidic esterification, and then it is converted into 1-methyl-1*H*-indazole-3-hydrazideby using hydrazine hydrate in ethanol at reflux temperature. The 1-methyl-1*H*-indazole-3-hydrazide was condensed with different substituted benzaldehyde using catalytic amount of conc. sulphuric acid in ethanol and in the next step it has finally converted to α-aminophosphonates using chlorotrimethylsilane (TMSCl) and triethyl phosphite (Figs. 1 and 2).

3. Antimicrobial activity

Some of the synthesized derivatives are then assayed for their *in-vitro* antibacterial activity against a panel of pathogenic as well as standard bacterial strains such as *K*lebsiella *pneumoniae*, *Staphylococcus aureus*, *Salmonella typhimurium*, *Bacillus Subtilis*, *P. auroginosa* and *Escherichia coli*. Based on previous literature and scope of the bacterial species are selected. Gentamycin and Kinamycin are procured from commercial sources. The purities and potencies of the agents recovered from commercial preparations were documented by showing that the MICs of antibacterial arewithin acceptable limits against the known strains.

4. Determination of MIC in terms of zone of inhibition

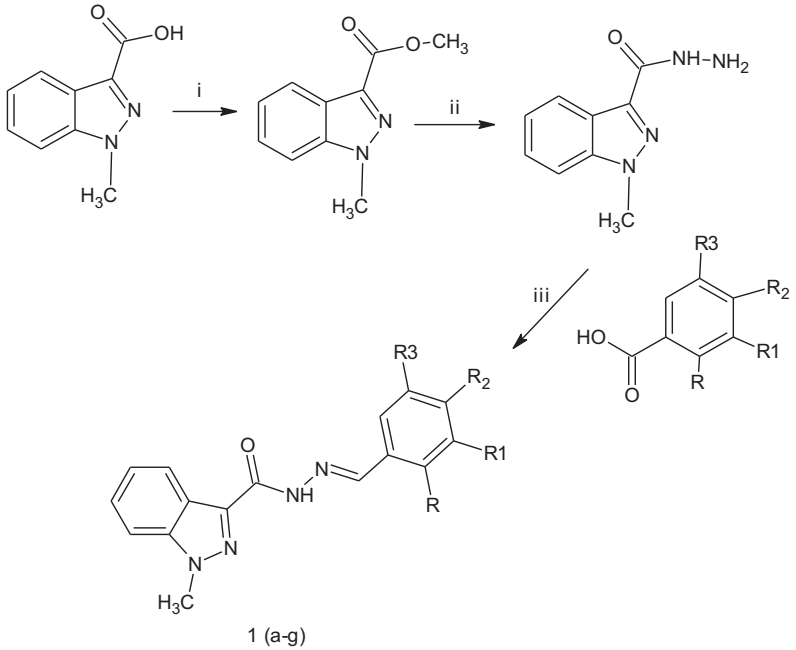
The antibacterial activity has tested by agar disc diffusion method. The killing or growth inhibition properties of the agents are scored as clear zone of inhibition surrounding the disc and are measured in mm scale.

5. Materials & method

- The bacterial strains are inoculated into fresh sterile MHB (Muller Hinton Broth) media tube (4.5 ml) and were incubated for 18–24 h at 37 °C in a B. O. D. incubator
- Standard antibiotic Gentamycin and Kinamycin clear solutions are prepared with final (1 mg/ml).
- The above antibiotic solutions are poured on sterile disc at a final concentration of 40 mcg/disc for Gentamycin and Kinamycin drugs.
- All discs were dried completely by incubating into hot air oven in sterile Petri dishes.
- On MHA (Muller Hinton Agar) plates, the bacterial suspension was poured and spread evenly with the help of glass spreader.
- After drying the plates completely, the antibiotic loaded discs were kept on the plates.
- All plates were incubated at 37 °C in a B.O.D. (Biological Oxygen Demand) incubator for 24 h.
- Results were recorded and antibiotic activity had quantified by measuring the zone of inhibition surrounded to the disc in 'mm' scale and presented in Table 1.

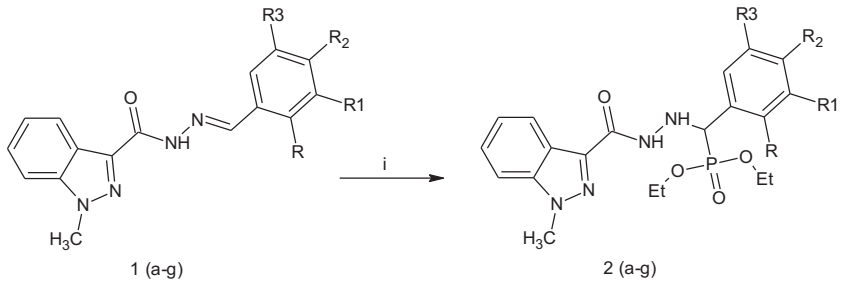
6. Conclusion

A new series of α-aminophosphonate derivatives containing highly bioactive Indazole moiety is synthesized in two steps. In the first step, imines of Indazole moiety synthesized and in next step it has converted to α-aminophosphonates using TMSCl and triethyl phosphite. Some of the synthesized derivatives are then evaluated for antibacterial activity against different bacterial strains respect to agar disc method. The fluoro groups **2b** and **2c** has improved the antibacterial property as compared to the other derivatives of series **2**. The derivatives **2b** and **2c** has good killing properties for



Reagents and conditions: i) Methanol/H_2SO_4/Reflux ii) Hydrazine hydrate/Ethanol iii) Ethanol/Acetic acid/Reflux

Fig. 1. Synthetic Scheme 1.



Reagents and conditions: i) $(EtO)_3P$, TMSCL/CH_3CN/Reflux

Fig. 2. Synthetic Scheme 2.

K. pneumoniae in the group. The bactericidal properties of **2b** and 2c against the species of *P. aeroginosa* have improved over other derivatives of the same group. But the overall killing or inhibiting the growth of bacteria is inferior as compared to the standard Gentamycin and Kinamycin drugs.

7. Experimental

Melting points are taken on a precision melting point apparatus (DBK) instrument and are uncorrected. IR spectra are obtained in potassium bromide (KBr)disks on a Bruker IR spectrometere, and ^{1}H NMR spectra were obtained on deuteriochlroform (CDCL3) on a Varian 400 MHz spectrometer. Mass spectra were recorded on a MicroMass spectrometer by Waters. The yields unless otherwise mentioned are for pure product. All the raw materials, reagents and solvents used were of commercial grade only.

7.1. Synthesis of methyl 1-methyl-1H-indazole-3-carboxylate

To the stirred suspension of N-methyl indazolic acid (10 g, 0.056 mol) in 100 ml methanol added 10 ml sulphuric acid dropwise. The reaction mixture heated to reflux for 4 h. After completion of reaction, reaction mass concentrated and neutralized with saturated sodium bicarbonate solution and extracted with 100 ml ethyl acetate, ethyl acetate layer wash with 50 ml water, dried over anhydrous sodium sulphate and concentrate on *Rotavapor* solid obtained was filtered, washed with chilled ethyl acetate (10 ml), Yield. 85%

7.2. Synthesis of 1-methyl-1H-indazole-3-hydrazide

To the suspension of 1-methyl-1*H*-indazole-3-carboxylate (10 g, 0.52 mol) in ethanol 20 ml were added hydrazine hydrate (5.2 g, 0.10 mol) and 1 ml of glycial acetic acid. The reaction mass was heated at reflux temp for 4–6 h. After completion of reaction, reaction mixture was cooled to room temperature separated solid was filtered and washed with chilled 5 ml ethanol and dried at 50-60 °C. Yield. 89%

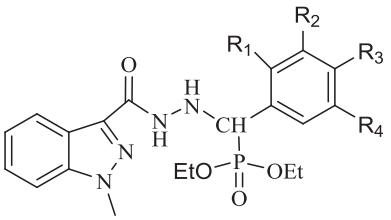
*7.3. Synthesis of 1-methyl N-(4-(trifluoromethyl) benzylidene) 1H-indazole-3-carbohydrazide (**1b**)*

To the stirred solution of 1-methyl-1*H*-indazole-3-carbohydrazide (2.0 g, 0.010 mol) in 20 ml of absolute ethanol added 4-(trifluoro methyl) benzaldehyde (1.8 g, 0.010 mol) and 1 ml of conc. sulphuric acid. The reaction mixture was heated to reflux for 6 h. After the completion of the reaction, 60 ml of water was added to the reaction mixture and stirred for 1 h. The solid obtained was filtered and washed with water, dried at 45–50 °C.

*7.4. Synthesis of diethyl (2-(1-methyl-1-H-indazole-3 carbonyl) hydrazinyl (phenyl) methyl phophonate (**2b**)*

To the mixture of 1-methyl-N-(4-(trifluoromethyl) benzylidene)-1*H*-indazole-3-carbohydrazide (1 g, 0.0028 mol) and triethylphosphite (1.40 g, 0.0084 mol) in 20 ml acetonitrile, added chlorotrimethylsilane (TMSCl)(0.90 g, 0.0084 mol) The reaction mixture was heated to reflux for 12 h. The progress of the reaction

Table 1
Antibacterial data of substituted diethyl (2-(1-methyl-1-H-indazole-3 carbonyl) hydrazinyl (phenyl) methyl phophonate (**2a**–**d**).



Antibacterial activity in terms of zone of inhibition (mm) when tested at 40 mcg/disc)

Entry	*R*	R_1	R_2	R_3	*K. pneumonia*	*S. typhy*	*P. auroginosa*	*B, Subtilis*	*E. coli*	*S. auerues*
2a	H	H	H	H	3	2	1	5	0	2
2b	H	H	CF_3	H	7	5	6	4	3	5
2c	H	F	H	H	8	4	7	4	5	3
2d	Br	H	H	H	2	3	4	7	1	1
Gentamicin(40 mcg/disc)					13	11	17	15	11	7
Kanamycin(40 mcg/disc)					18	14	21	15	13	9

was monitored by TLC. After completion of the reaction, reaction mixture was concentrated under reduced pressure to obtain an oily residue. The oily residue was dissolved in methanol and again concentrated, and then triturated with hexane. It was recrystallised by N-N-dimethylformide and water till compound has obtained in semi solid state.

Similarly the other derivatives of this series are prepared. Their structures have been confirmed by IR, ^{1}HNMR and Mass spectra.

7.5. N-(4-benzylidene-1-methyl-1H-indazole-3-carbo hydrazide (**1a**)

IR (KBr) cm^{-1}:- 3213(−NH), 2944 and 2816 (Ar-CH stretching & bending), 1656(CONH). ^{1}H NMR $CDCl_3$:- δ 4.14 (s,3H, N-C$\underline{H}_3$ protons), δ 7.21–8.41 (9H, Ar-H), δ 8.46 (s, 1H, N=C$\underline{H}$ imine proton), δ 10.15 (s, 1H, CON$\underline{H}$ proton, exchangeable with D_2O)., ^{13}C NMR(CDCl3):- δ 41.8, 108.4, 119.6, 120.1, 122.8, 125.5, 127.5, 127.9, 128.5, 129.2, 130.3, 133.1, 138.5, 140.1, 145.4, 155.9, Mass (m/z):- 279 (M+1) M.P. 190-92 °C., Yield 88%

7.6. 1-Methyl-N-(4-(trifluoromethyl)benzylidene)-1H-indazole-3-carbo hydrazide (**1b**)

IR (KBr) cm^{-1}:- 3203(−NH), 2940 and 2806 (Ar-CH stretching & bending), 1652(CONH) ^{1}HNMR $CDCl_3$:- δ 4.1 (s, 3H, N-C$\underline{H}_3$ protons), δ 7.25–8.46 (8H, Ar-H), δ 8.42 (s, 1H, N=C$\underline{H}$ imine proton), δ 10.21(s, 1H, CON$\underline{H}$ proton, exchangeable with D_2O)., ^{13}C NMR(CDCl3):- δ 42.1, 108.9, 120.1, 120.6, 123.2, 123.9, 125.8, 127.9, 128.2, 128.8, 129.8, 130.7, 133.5, 138.9, 140.6, 145.8, 156.4., Mass (m/z):- 347 (M+1) M.P. 197-199 °C Yield 90%.

7.7. N-(3-Fluorobenzylidene)-1-methyl-1H-indazole-3-carbohydrazide (**1c**)

IR (KBr) cm^{-1}:- 3222(−NH), 2945 and 2816 (Ar-CH stretching & bending), 1659(CONH) ^{1}H NMR $CDCl_3$:- δ 3.98 (s, 3H, N–C$\underline{H}_3$ protons), δ 7.11–8.32 (8H, Ar-H), δ 8.46 (s, 1H, N=C$\underline{H}$ imine proton), δ 9.98 (s, 1H, CONH proton, exchangeable with D_2O). ^{13}C NMR(CDCl3):- δ 42.6, 109.4, 113.5.118.6, 124.2, 124.8, 126.2, 128.6, 128.9, 129.8, 130.9, 133.9, 139.8146.2, 157.4, 162.3, Mass (m/z):- 297 (M+1) M.P. 200-02 °C, Yield 86%.

7.8. N-(2-Bromobenzylidene)-1-methyl-1H-indazole-3-carbohydrazide (**1d**)

IR (KBr) cm^{-1}:-3200(−NH), 2934 and 2800 (Ar-CH stretching & bending), 1645(CONH).^{1}H NMR $CDCl_3$:- δ 3.94 (s, 3H, N-C$\underline{H}_3$ protons), δ 7.15–8.37 (8H, Ar-H), δ 8.32 (s, 1H, N=C$\underline{H}$ imine proton), δ 9.90 (s, 1H, CONH proton, exchangeable with D_2O). ^{13}C NMR(CDCl3):- δ 42.6, 109.4, 119.4, 120.5, 121.4, 124.8, 125.5, 126.9, 129.6, 130.2, 131.9, 133.9, 139.8, 140.5, 141.2, 145.5, 156.2, Mass (m/z):- 357 (M+1), M.P. 230-32 °C, Yield 84%

7.9. 1-Methyl-N-(2-nitrobenzylidene)-1H-indazole-3-carbohydrazide (**1e**)

IR (KBr) cm^{-1}:-3200(−NH), 2934 and 2800 (Ar-CH stretching & bending), 1645(CONH). ^{1}H NMR $CDCl_3$:- δ 3.90 (s, 3H, N-C$\underline{H}_3$ protons), δ 7.05–8.11 (8H, Ar-H), δ 8.26 (s, 1H, N=C$\underline{H}$ imine proton), δ 9.84 (s, 1H, CONH proton, exchangeable with D_2O). ^{13}C NMR(CDCl3):-δ 42.2, 108.7, 119.9, 120.7, 123.2, 124.8, 126.8, 128.3, 129.5, 130.5, 131.3, 138.9, 140.1, 141.2, 142.5, 155.9, Mass (m/z) 324(M+1), M.P. 237-39 °C, Yield 79%.

7.10. N-(2-Chlorobenzylidene)-1-methyl-1H-indazole-3-carbohydrazide (**1f**)

IR (KBr) cm^{-1}:- 3211(−NH), 2940 and 2814 (Ar-CH stretching & bending), 1654(CONH) ^{1}H NMR $CDCl_3$:- δ 3.93 (s, 3H, N-C$\underline{H}_3$ protons), δ 7.15–8.19 (8H, Ar-H), δ 8.28 (s, 1H, N=C$\underline{H}$imine proton), δ 9.89(s, 1H, CONH proton, exchangeable with D_2O). ^{13}C NMR(CDCl3):- δ 41.8, 108.4, 119.1, 120.2, 122.6, 124.1, 125.8, 127.9, 129.9, 130.8, 132.6, 138.2, 140.7, 141.9, 143.5, 155.2, Mass (m/z):- 313(M+1) M.P. 237-39 °C., Yield 84%

7.11. Diethyl(2-(1-methyl-1H-indazole-3-carbonyl) hydrazinyl)(phenyl)methyl phosphonate (**2a**)

IR (KBr) cm^{-1}:- 3423 (NH), 2977 and 2911 (Ar-CH streching & bending), 1636(C=N), 1227(−P=O), 968 (−P–O–C). ^{1}H NMR $CDCl_3$:- δ 1.16–1.20 (t, 3H, O–CH_2–CH_3), δ 1.23-0.1.34 (t, 3H, O–CH_2–CH_3), δ 3.82 (s, 3H, N-C$\underline{H}_3$ proton), δ 3.84–3.89 (t, 1H, NH–NH–CH, proton, exchangeable with D_2O), δ 4.14–4.22 (q, 4H, O–CH_2–CH_3methylene protons), δ 4.78–4.83 (d, 1H, −NH–C$\underline{H}$–P=O), δ 6.63–8.32 (9H, aromatic protons), δ 8.54–8.60(d, 1H, CON$\underline{H}$ proton, exchangeablewithD_2O), ^{13}C NMR(CDCl3):-δ 16.7, 16.7, 42.1, 61.9., 61.9, 67.5, 108.5, 119.6, 120.4, 123.4, 125.5, 126.4, 127.5, 127.5.127.9, 128.5, 135.5, 138.6, 141.2, 160.3. Mass (m/z):- 416 (M+1) Yield 83%

7.12. Diethyl(2-(1-methyl-1H-indazole-3-carbonyl)hydrazinyl)(4-(trifluoro) phenyl)methylphosphonate (**2b**)

IR (KBr) cm^{-1}:- 3417 (NH), 2985 and 2907 (CH streching & bending), 1624(C=N), 1231 (−P=O), 978 (-P-O-C). ^{1}H NMR $CDCl_3$:- δ 1.21–1.27 (t, 3H, O–CH_2–CH_3), δ 1.3–0.1.42 (t, 3H, O–CH_2–CH_3), δ 3.94 (s, 3H, N-C$\underline{H}_3$ proton), δ 3.96–3.99 (t, 1H, NH–NH–CH, proton, exchangeable with D_2O), δ 4.14–4.29 (q, 4H, O–CH_2–CH_3 methylene protons), δ 0.85–4.93 (d, 1H, −NH–C$\underline{H}$–P=O), δ 6.6–7.9 (8H, aromatic protons), δ 8.59 (s, 1H, CON$\underline{H}$ proton, exchangeable with D_2O, ^{13}C NMR(CDCl3):- δ 16.6, 16.6, 42.7, 62.4, 62.4, 68.1, 108.9, 119.9, 120.6, 123.8, 124.5, 124.5, 125.2, 126.2, 127.8, 127.8, 128.9, 138.5, 138.8, 141.8, 160.9. Mass (m/z):- 485 (M+1) Yield 86%

7.13. Diethyl(3-fluorophenyl)(2-(1-methyl-1H-indazole-3-carbonyl) hydrazinyl) methyl phosphonate (**3c**)

IR (KBr) cm^{-1}:- 3444 (NH), 2989 and 2934 (CH streching & bending), 1649 (C=N), 1236 (−P=O), 981 (-P-O-C). ^{1}H NMR $CDCl_3$:- δ 1.19–1.27 (t, 3H, O–CH_2–CH_3), δ 1.31–1.39 (t, 3H, O–CH_2–CH_3), δ 3.92(s, 3H, N-C$\underline{H}_3$protons), δ 3.95–3.99(t, 1H, NH–NH–CH, proton exchangeable with D_2O), δ 4.18–4.29 (q, 4H, O–CH_2–CH_3methyleneprotons), δ 4.84–4.90(d, 1H, −NH–C$\underline{H}$–P=O), δ 6.68–8.39(8H, aromatic protons), δ 8.87 (s, 1H, CON$\underline{H}$, proton, exchangeable with D_2O). ^{13}C NMR(CDCl3):δ 16.4, 16.4, 42.5, 62.7, 62.7, 67.5, 109.4, 114.1, 114.1, 120.1, 120.4, 123.5, 123.8, 125.8, 125.9, 129.8, 137.4, 138.9, 141.9, 161.1., Mass (m/z):- 435 (M+1) Yield 77%.

7.14. Diethyl(2-bromophenyl)(2-(1-methyl-1H-indazole-3-carbonyl)hydrazinyl methyl phosphonate (**2d**)

IR (KBr) cm^{-1}:- 3421 (NH), 2989 and 2932 (CH streching & bending), 1643(C=N), 1231 (−P=O), 977 (−P–O–C). ^{1}H NMR $CDCl_3$:- δ 1.11–1.20 (t, 3H, O–CH_2–CH_3), δ 1.23-0.1.30 (t, 3H, O–CH_2–CH_3), δ 3.81 (s, 3H, N-C$\underline{H}_3$ proton), δ 3.91–3.97 (t, 1H, NH–NH–CH, proton, exchangeable with D_2O), δ 4.11–4.21 (q, 4H, O–CH_2–CH_3 methylene protons), δ 4.80 (d, 1H, −NH–C$\underline{H}$–P=O),

δ 6.61–8.23 (8H, aromatic protons), δ 8.51 (s, 1H, CONH proton, exchangeable with D_2O). ^{13}C NMR(CDCl3):-δ 16.3, 16.3, 42.6, 62.8, 62.8, 64.9, 109.7, 120.1, 120.6, 121.5, 123.4, 126.5, 127.1, 128.8, 129.4, 132.2, 139.8, 142.3, 144.9, 161.2., Mass (m/z):- 496 (M+1)., Yield 79%.

7.15. Diethyl(2-(1-methyl-1H-indazole-3-carbonyl)hydrazinyl)(2-nitrophenyl) methylphosphonate (**2e**)

IR (KBr)cm^{-1}:- 3412 (NH), 2965 and 2913 (CH streching & bending), 1634 (NO_2), 1651(C=N), 1239 (−P=O), 988 (−P−O−C). ^1H NMR $CDCl_3$:- δ 1.14–1.22 (t, 3H, O−CH_2−CH_3), δ 1.26–0.1.34 (t, 3H, O−CH_2−CH_3), δδ 3.86 (s, 3H, N-CH_3 proton), δ 3.94–3.99 (t, 1H, NH−NH−CH, proton, exchangeable with D_2O), δ 4.15–4.24 (q, 4H, O−CH_2−CH_3 methylene protons), δ 4.83–4.88–4.93(d, 1H,−NH−CH−P=O), δ 6.67–8.27(8H, aromatic protons), δ 8.47 (s, 1H, CONH, proton, exchangeable withD_2O)., ^{13}C NMR(CDCl3):-δ 16.1, 16.1, 42.3, 62.2, 62.2, 63.5, 109.2, 120.3, 120.8, 123.5, 124.4, 126.1, 127.3, 128.1, 133.4, 136.7, 139.2, 142.1, 146.9, 160.8., Mass (m/z):- 462 (M+1), Yield 75%.

7.16. Diethyl(2-chlorophenyl)(2-(1-methyl-1H-indazole-3-carbonyl)hydrazinyl) methylphosphonate (**2f**)

IR (KBr) cm^{-1}:- 3454 (NH), 2956 and 2910 (CH streching & bending), 1654(C=N), 1226 (−P=O), 971 (-P-O-C). ^1H NMR $CDCl_3$:-δ 1.17–1.26 (t, 3H, O−CH_2−CH_3), δ 1.29-0.1.38 (t, 3H, O−CH_2−CH_3), δ 3.89 (s, 3H, N-CH_3 proton), δ 3.92–3.95 (t, 1H, NH−NH−CH, proton, exchangeable withD_2O), δ 4.17–4.28 (q, 4H, O−CH_2−CH_3 methylene protons), δ 4.87–4.95 (d, 1H, −NH−CH−P=O), δ 6.60–8.21 (8H, aromatic protons), δ 8.41 (s, 1H, CONH proton exchangeable with D_2O). ^{13}C NMR(CDCl3):-δ 15.9, 15.9, 41.7, 61.6, 61.6, 63.1, 108.7, 119.8, 120.1, 123.2, 126.2, 126.5, 127.8, 128.2, 128.6, 131.7, 139.5, 141.7, 142.4, 161.1., Mass (m/z)451 (M+1), Yield 80%.

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