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Short communication

Synthesis and biological evaluation of novel N-aryl maleimide derivatives clubbed with α-hydroxyphosphonates

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ABSTRACT

A series of novel molecules **5a–g** containing N-aryl maleimide and α-hydroxyphosphonate moieties were synthesized. A distinct approach for high-yielding synthesis of α-hydroxyphosphonates has been discovered using various catalyst and solvents. The structures of the synthesized compounds were elucidated by IR, NMR, MS and CHN analysis. All the synthesized compounds were tested for qualitative (Zone of inhibition) and quantitative (MIC) antimicrobial activities against two pathogenic bacteria such as *Bacillus subtilis* (NCIM 2250) and *Escherichia coli* (ATCC 25922) and four pathogenic fungi such as *Candida albicans* (MTCC 277), *Candida tropicalis* (MTCC184), *Aspergillus niger* (MCIM 545) and *Aspergillus clavatus* (MTCC 132). The investigation of antimicrobial screening data revealed that most of the tested compounds are moderate to good microbial inhibitors.

1. Introduction

Infectious diseases caused by microbes are more rampant world wide than during the last century. Scientists are working hard to find ways that will control theses germs but trying to conquer them is not an easy task. At the present time, different classes of antibacterial drugs [1–4] such as sulfa drugs, nitrofuranes, penicillins, cephalosporins, tetracyclines, macrolides and oxazolidinones, and antifungal drugs [5–10] such as fluconazole, ketoconazole and miconazole are available. Nevertheless, many of them encounter diverse limitations. For example, the strong antifungal drug Amphotericin B suffers from its clinical applications due to its serious nephrotoxicity [11]. Methicillin-resistant staphylococcus aureus and multidrug resistant gram-positive bacteria cause serious problems. Disease causing microbes are very good at adapting to new environments making it hard to find a way to get rid of them. Microbes can quickly develop new features that make them resistant to the drugs that were once able to kill them [12]. This situation highlights the need to develop new and more effective antimicrobial drugs [13].

Maleimides are emerging as important pharmacophores in recent times and play a vital role as medicinal agents with a range of biological activities such as antibacterial [14], analgesic [15], antistress agents [16], antiprotozoal [17], antiangiogenic [18], cytotoxic, DNA binding and apoptotic inducing activity [19]. Several derivatives of maleimides are reported as selective inhibitors of monoglyceride lipase [20], GSK-3α [21], Cdc25B [22], Bfl-1 [23] and DNMT-1 [24] etc. Synthesis and biological activity of N-aryl maleimide analogous have been extensively investigated. N-aryl maleimides provide the scaffold for many natural products such as polycitrin [25], camphorataimides [26], rebeccamycine and staurosporine [27]. These compounds exhibit angiogenesis inhibition [27], protein kinase inhibition [28] and antiproliferative [29] activities.

S. Zacchino and group have reported the antimicrobial activities of N-substituted maleimide derivatives against *Candida* spp. and it was concluded that the intact maleimide ring is essential for excellent activities [30]. The maleimide skeleton in naturally occurring himanimide and their unnatural analogues were found to exhibit good antimicrobial activities [31]. The maleimide molecules contain general structure –CO–N(R)–CO–, so they are

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hydrophobic and neutral, and can therefore penetrate biological membranes [32]. Sortino and co-workers have demonstrated that, substituents on 3 and 4 positions in maleimides show variable effect on activity [33]. These findings encourage us to choose maleimide skeleton for the biological study.

Synthesis of the organophosphorous compounds has recently attracted much attention [34–39] due to their wide-spread biological activities. These compounds act as prodrugs and analogues of natural phosphates [40]. They are reported to possess various biological activities such as anti bacterial and anti fungal [41–46], anti HIV [47,48], anticancer [49–53], anti-inflammatory [54], antiviral [55–57], antihypertensive [58], antituberculor [59] and bone seeking agents [60]. Thus, they are shown to be good pharmacophores for the design of bioactive molecules.

In view of the high degree of bioactivity shown by both N-aryl maleimides and phosphonate analogs (Fig. 1, I–V), we have focused on the design of novel structural entities that incorporate both of these structural and functional moieties into a single molecular scaffold (5a–g) to evaluate the potential additive effects of these two systems on biological activity, especially with regard to antimicrobial activity. Fig. 1 describes the biological activities of the various maleimide derivatives and phosphonate scaffold. Till date, adequate efforts have not been made to combine N-aryl maleimide and phosphonates as a single molecular scaffold.

Recently, various methodologies have been developed for the synthesis of α-hydroxyphosphonates from aldehydes [39,61–63]. We developed new, protocols to synthesize these desired compounds. In the present work, we achieved excellent yields of desired compounds with just the 5 mol% of the catalyst, with short reaction time and easy work-up procedures.

We herein report the synthesis of novel N-aryl maleimide derivatives clubbed with phosphonates (Scheme 1) from novel carbaldehydes using efficient, high yielding catalysts, in aqueous medium with the aim of investigating their antimicrobial activity.

2. Result and discussion

2.1. Chemistry

The synthetic route to compounds **5a**–**g** is outlined in Scheme 1. Derivatives of substituted N-arylmaleimide **1a**–**g** were synthesized by using our reported procedure [64]. The compounds **2a**–**g** was prepared by refluxing **1a**–**g** with bromine in CCl_4 [65]. **2a**–**g** were reacted further with N, N-dimethylamine in DMF at 10 °C to afford 3-(dimethylamino)-1-aryl-1H-pyrrole-2,5 dione **3a**–**g** in quantitative yield. The Vilsmeier Haack formylation of **3a**–**g** at 0–5 °C yielded 4-(dimethylamino)-2,5-dihydro-2,5-dioxo-1-aryl-1-H-pyrrole-3-carbaldehyde **4a**–**g** in excellent yield.

There are several conventional methods reported in literature such as Abramov reaction [62,63], Field reaction [66], Pudovik reaction [67] for the synthesis of phosphonate compounds from aldehydes/ketones and di/trialkyl phosphite using various bases such as sodium alkoxide [62,67], triethylamine [66], ethyl magnesium bromide [68], potassium or cesium fluoride [69], LDA [70], MgO [71] etc or acid catalyst such as BF_3Et_2O and $AlCl_3$ or HCl [72], alumina [73], TFA or TfOH [74], Ti(OPri) [75] etc. In most cases these reactions suffer from the long reaction time or exotic reaction conditions. In order to find the more efficient reaction condition for the synthesis of **5a** from **4a**, we perform the analogues reactions using various catalysts and solvents as depicted in Table 1. The synthesis of **5a** from **4a** was attempted by using a number of catalysts such as $FeCl_3$, $CdCl_2$, NH_4VO_3, TMSCl, Amberlite IR etc. and various solvents. The reaction of **4a** with equimolar amount of triethylphosphite using TMSCl as a catalyst and acetonitrile as a solvent at reflux temperature for 50 min afforded **5a** in 85% yield (Entry-1) while analogues reaction using toluene as a solvent took 2.0 h to give **5a** in 72% yield (Entry-2). Use of $FeCl_3$, $CdCl_2$, Amberlite IR 400 (Entry-3,4,5) does not give satisfactory results in terms of both reaction time and yield.

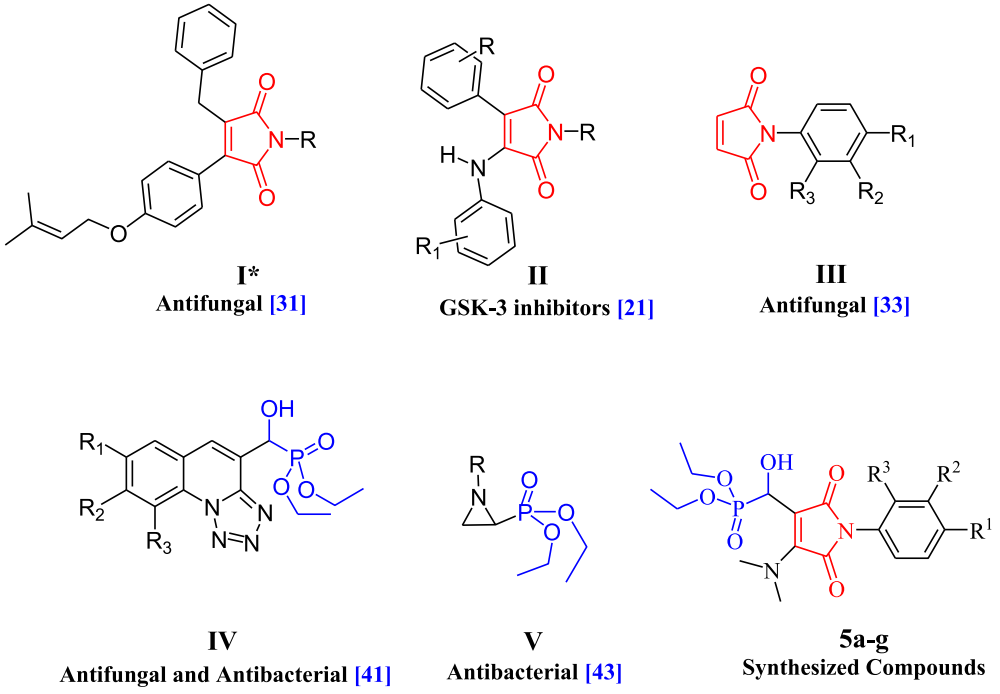
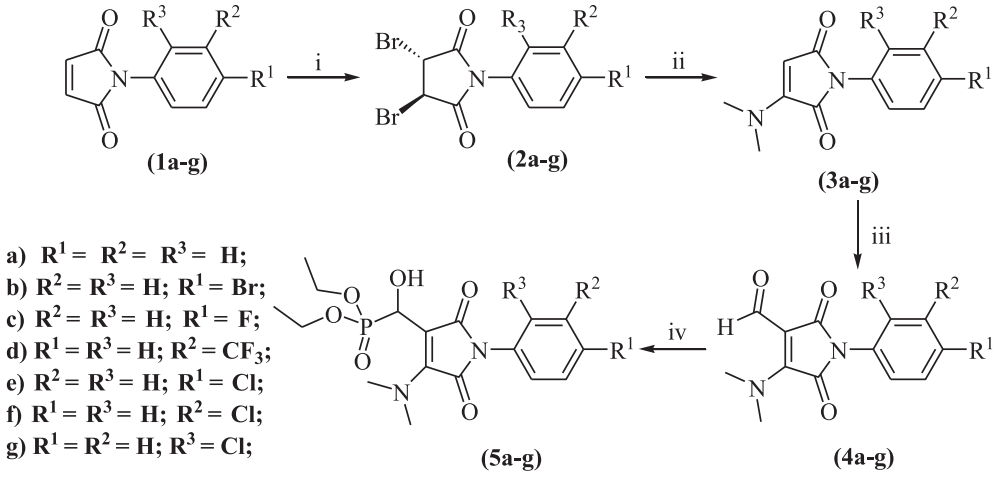


Fig. 1. Biological activities of the natural*/unnatural Maleimide derivatives and phosphonate scaffold.



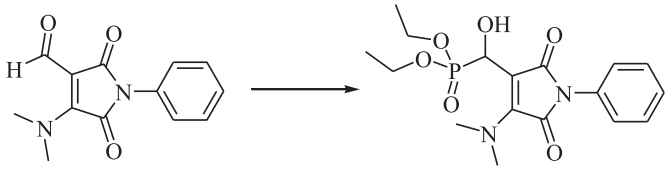
Scheme 1. Reagent and conditions: (i) Br_2, CCl_4, Reflux, 1 h; (ii) N, N dimethylamine, DMF, 10 °C, 30 min; (iii) DMF:$POCl_3$, 0–5 °C, 30 min; (iv) $P(OEt)_3$, NH_4VO_3, Water, Reflux, 20.0 min.

NH_4VO_3 have been reported as an effective catalyst for the synthesis of α-hydroxyphosphonates [61]. Use of NH_4VO_3 as a catalyst and acetonitrile as a solvent at reflux condition afforded 89% yield of the desire compound in 40 min while analogues reaction using water as a solvent in contrast to previous reports [61] give almost quantitative yield (98%) of the **5a** in only 20 min. With optimized reaction conditions, further derivatives **5b**–**g** was synthesized and characterized by spectral and analytical methods.

2.2. Spectroscopic analysis

IR spectrum of the compounds **3a**–**g** showed stretching frequencies in the range of 1751–1757 cm^{-1} and 1691–1710 cm^{-1} attributed to carbonyl groups (Table 2). The ^1H NMR peaks at 4.94–4.99 ppm are due to olefinic proton (CH=). The appearance of the aldehydic group in compound **4a**–**g** was confirmed by IR spectrum (Table 3); ^1H NMR spectrum showed the aldehydic proton singlet in the range of 9.78–9.81 ppm and ^{13}C NMR spectrum showed aldehydic carbonyl carbon in the range of 182.1–182.4 ppm.

Table 1
Effect of various catalyst and solvent condition on the synthesis of α-hydroxyphosphonate from **4a**.



Entry	Catalyst[a]	Solvent	Temperature °C	Time	Yield[b] %
1	TMSCl	Acetonitrile	Reflux	50 min	85
2	TMSCl	Toluene	Reflux	2.0 h	72
3	$FeCl_3$	Acetonitrile	Reflux	18 h	18
4	$CdCl_2$	Toluene	Reflux	4.0 h	26
5	Amberlite IR 400	Acetonitrile	Reflux	3.5 h	30
6	NH_4VO_3	Acetonitrile	Reflux	40 min	89
7	NH_4VO_3	Water	Reflux	20 min	98

[a] **4a** (1 mmol) was treated with Triethylphosphite (1 mmol) in the presence of the catalyst 5 mol % (except entry 1and 2, where equivalent amount of TMSCl were used).
[b] Yield refers to isolated yield.

IR spectrum of the compounds **5a**–**g** showed characteristics absorption peaks due to O–H, P–C, P=O and P–O (Table 4). ^1H NMR spectra of the compounds **5a, 5c** showed multiplet centered at 5.31 due to (CH–P) proton due to coupling with O–H proton while compounds **5b, 5d** to **5g** showed doublet due to (CH–P) proton with ^1H resonance in the range of δ 5.26–5.45 ppm in which O–H proton coupling was not observed. ^{13}C NMR spectrum showed doublet in the range of 64.4–65.1 ppm with $^1J_{P\text{-}C}$ in the range of 163.2–168.2 Hz.

The ^{13}C spectrum of the compounds **3c, 4c** and **5c** containing flurosubstituted benzene showed doublet for ipso (C_1–F, $^1J_{F\text{-}C}$ in the range of 246.15–243.82 Hz), ortho (C_2–F, $^2J_{F\text{-}C}$ in the range of 22.87–22.83 Hz) and meta (C_3–F, $^1J_{F\text{-}C}$ in the range of 9.15–9.14 Hz) carbons to the fluorine due to C to F one bond, two bond and three bond couplings respectively.

The CF_3 carbon in the compounds **3d, 4d** and **5d** appeared as a quartet in the range of 123.4–123.7 ppm ($^1J_{F\text{-}C}$ in the range of 271.20–270.15 Hz). The α-carbon to the CF_3 also appeared as quartet ($^2J_{F\text{-}C}$ in the range of 35.47–33.22 Hz) and δ value in the range of 131.2–131.1 ppm.

2.3. Antimicrobial activity

The himanimide C (Fig. 1, I) exhibited antifungal activity against *Alternaria porri*, *Aspergillus ochraceus* and *Pythium irregulare* from concentration 25 μg/mL on. It also showed moderate or weak antibacterial activity [31]. The N-aryl substituted maleimides reported as fungicidal against many antifungal strains with no clear influence of the different substituents on the benzene ring [33]. The phosphonates coupled with tetrazolo [1,5-a] quinoline derivatives

Table 2
M.P., yield and IR of the compounds (**3a**–**g**).

Entry	R^1	R^2	R^3	M.P. (°C)	Yield[a] (%)	(KBr, ν_{max}/cm^{-1}) C=O
3a	H	H	H	142–144	98	1753, 1691
3b	Br	H	H	144–146	96	1757, 1691
3c	F	H	H	148–150	96	1757, 1704
3d	H	CF_3	H	70–72	94	1751, 1701
3e	Cl	H	H	136–138	96	1751, 1693
3f	H	Cl	H	112–114	98	1755, 1710
3g	H	H	Cl	86–88	96	1753, 1706

[a] Yield refers to isolated yield.

Table 3
M.P., yield and IR of the compounds (**4a**–**g**).

Entry	R^1	R^2	R^3	M.P. (°C)	Yield[a] (%)	(KBr, ν_{max}/cm^{-1})	
						C=O	CHO
4a	H	H	H	166–168	84	1757, 1708	2866, 1656
4b	Br	H	H	186–188	83	1762, 1706	2868, 1664
4c	F	H	H	164–166	81	1758, 1704	2874, 1662
4d	H	CF_3	H	110–112	78	1760, 1706	2871, 1676
4e	Cl	H	H	172–174	83	1764, 1704	2870, 1660
4f	H	Cl	H	162–164	84	1758, 1704	2850, 1664
4g	H	H	Cl	90–92	81	1762, 1708	2860, 1662

[a] Yield refers to isolated yield.

Table 4
M.P., yield and IR of the compounds (**5a**–**g**), using NH_4VO_3, water.

Entry	R^1	R^2	R^3	M.P.(°C)	Yield[a] (%)	(KBr, ν_{max}/cm^{-1})				
						O–H	C=O	P–C	P=O	P–O
5a	H	H	H	170–172	98	3267	1751, 1689	1400	1207	1054
5b	Br	H	H	136–138	96	3226	1753, 1693	1392	1211	1053
5c	F	H	H	158–160	94	3245	1747, 1691	1396	1226	1054
5d	H	CF_3	H	118–120	95	3190	1755, 1704	1386	1197	1053
5e	Cl	H	H	160–162	96	3249	1749, 1691	1394	1211	1054
5f	H	Cl	H	138–140	97	3259	1753, 1691	1396	1207	1053
5g	H	H	Cl	106–108	95	3244	1755, 1699	1396	1209	1060

[a] Yield refers to isolated yield.

[41] and aziridine derivatives [43] showed significant antimicrobial activity.

Results of antimicrobial screening revealed that of the compounds tested **4a**–**g** and **5a**–**g**, the phosphonates **5a**–**g** showed moderate to good activity while **4a**–**g** showed very low or no significant activity compared to reference antibiotics. As shown in Table 5, most of the compounds were active against Gram positive and Gram negative bacteria as well as all of the fungal species. Careful analysis of the primary screening (zone of inhibition) and MICs in Tables 5 and 6 provides some lead molecules with p-F, m-CF_3 and m-Cl substituents on the phenyl ring showed good antibacterial and antifungal activity against most of the tested pathogens; they inhibited the Gram negative and Gram positive pathogens equally and antifungal species with MIC value in between 10 and 25 μg/mL.

Against *B. subtilis*, both **5c** and **5f** required 10 μg/mL. Compound **5c** and **5d** showed better activity and required 10 μg/mL while compound **5g** required 15 μg/mL against *Escherichia coli*. For antifungal strains compounds **5c**, **5f** required 15 and 10 μg/mL respectively against *C. albicans*. Excellent MIC's were observed against *Candida tropicalis* for each of the compounds **5b**, **5c** required 15 μg/mL, and for **5d, 5f** required 10 μg/mL. Against *Aspergillus niger* moderate activity were observed with MIC of 15 μg/mL for each of the **5c**, **5d** and **5g**. In case of *Aspergillus clavatus* compounds, **5c** and **5d** exhibited good activity which required 10 μg/mL and compound **5g** required 15 μg/mL.

From the data, it is clear that antimicrobial activity of the compounds **5a**–**g** is influenced by changing the substituents on the aromatic ring. Among compounds **5b**, **5c** and **5e** with Br, F, Cl respectively on 4-position of the aromatic ring, **5c** was consistently excellent with respect to the standard antibiotics used; **5b** showed better activity than **5e**. Substituent at 3-position of the aromatic ring in **5d** and **5f** showed good activity. **5a** with no substituent on aromatic ring showed the least activity among synthesized compounds.

3. Conclusion

A series of novel N-aryl maleimide derivatives clubbed with α–hydroxy phosphonates **5a**–**g** were successfully synthesized using readily available catalyst, water as the green solvent, with high yield, short duration and avoidance of tedious work-up procedure. The pharmacological studies were undertaken to evaluate the effect of substituents for their antimicrobial activities against two pathogenic bacteria and four pathogenic fungi. Most of the synthesized compounds exhibited moderate to good activity towards Gram-positive and Gram-negative bacteria as well as all of the fungal species. The enhancement in antibacterial and antifungal activity can be attributed to the presence of pharmacologically active F, Cl, Br, CF_3 substituents, irrespective of their position in the molecule. The present study promises to be very useful to get lead antimicrobial agents.

4. Experimental section

Melting points are uncorrected. The ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Varian NMR Mercury 300 spectrometer. Chemical shifts were reported in ppm relative to tetramethylsilane (TMS), and multiplicities are given as s (singlet), brs (broad singlet), d (doublet), t (triplet), q (quartet), or m (multiplet). Infrared spectra were recorded as KBr pellets on a Shimadzu FTIR-408 spectrophotometer. Mass spectra were recorded on a Shimadzu LC-MS: EI QP 2010A mass spectrometer with an ionization potential of 70 eV. Elemental analyses (C, H and N) were performed on Thermo Finnigan Eager 300 EA 1112 series analyzer.

Table 5
Antimicrobial screening of synthesized compounds **5a**–**g** (zone diameter of growth inhibition in mm).

Entry	*Bacillus subtilis* NCIM 2250	*Escherichia coli* ATCC 25922	*Candida albicans* MTCC 277	*Candida tropicalis* MTCC 184	*Aspergillus niger* MCIM 545	*Aspergillus clavatus* MTCC 1323
5a	13.4	13.2	–	16.1	–	16.3
5b	15.1	13.1	13.8	**16.8**	15.5	16.4
5c	**15.6**	**15.8**	**16.5**	**16.7**	**16.4**	**17.3**
5d	**15.4**	**15.7**	15.2	**17.2**	**16.6**	**17.4**
5e	–	13.4	–	15.9	15.8	–
5f	**15.8**	13.5	**16.6**	**17.1**	13.6	16.2
5g	13.6	**15.4**	15.1	16.2	**16.6**	**16.8**
Strept.	16.2	16.4	n.t.	n.t.	n.t.	n.t.
Gris.	n.t.	n.t.	16.8	17.3	16.9	17.6

Bold values indicates better results.
n.t. not tested.
Strept. : Streptomycine (100 μg/disc).
Gris. : Griseofulvin (100 μg/disc).
Test Compound: (100 μg/disc).
(–): Inactive.

Table 6
Antimicrobial screening of synthesized compounds **5a–g** and minimum inhibitory concentration (MIC) in μg/mL.

Entry	*Bacillus subtilis* NCIM 2250	*Escherichia coli* ATCC 25922	*Candida albicans* MTCC 277	*Candida tropicalis* MTCC 184	*Aspergillus niger* MCIM 545	*Aspergillus clavatus* MTCC 1323
5a	25	20	–	20	–	20
5b	20	25	25	**15**	20	20
5c	**10**	**10**	**15**	**15**	**15**	**10**
5d	**15**	**10**	20	**10**	**15**	**10**
5e	–	25	–	25	20	–
5f	**10**	20	**10**	**10**	25	20
5g	20	**15**	20	20	**15**	**15**
Strept.	05	05	n.t.	n.t.	n.t.	n.t.
Gris.	n.t.	n.t.	05	05	05	05

Bold values indicates better results.
n.t. not tested.
Strept. : Streptomycine (μg/mL).
Gris. : Griseofulvin (μg/mL).
Test compound: (μg/mL).
(–): Inactive.

Reactions were monitored by thin layer chromatography (TLC), carried out on 0.2 mm silica gel 60 F_{254} (Merck) plates using UV light (254 and 366 nm) for detection and compounds were purified by column chromatography by using silica gel of 5–20 μm (Merck, 60–120 mesh). Column dimension is 39 × 2 cm^2 and elution volume used is about 200–400 mL for each product where necessary. Common reagent grade chemicals are commercially available and were used without further purification.

4.1. General procedure for the synthesis of compound (**1a–g**)

To a solution of the substituted anilines (0.01 mol) in acetic acid (10 mL), the maleic anhydride was added. The reaction mixture was stirred for 10 min. To this suspension, sulfuric acid (0.025 mol) was added while stirring. The temperature of the reaction mixture was then maintained at 60 °C for 30–45 min. The cooled reaction mixture was poured onto crushed ice. The solid separated was collected, washed with aqueous sodium bicarbonate and then with water, and recrystallized from aqueous ethanol [64].

4.2. General procedure for the synthesis of compound (**2a–g**)

To a solution of *N*-arylpyrrolidine-2,5-dione **1a–g** (0.01 mol) in CCl_4 (8 mL) was added dropwise a solution of bromine (0.011 mmol) in CCl_4 (4 mL) at 25 °C and reflux for 1–1.5 h (TLC, hexane:ethyl acetate, 2:1). White solid separated was then filtered, washed with cold CCl_4 (4–8 mL), dried and recrystallized using ethanol [65].

4.3. General procedure for the synthesis of compound (**3a–g**)

To a solution of trans-3,4-dibromo-1-arylpyrrolidine-2,5-dione **2** (0.01 mol) in DMF (10 mL) N,N-dimethylamine (0.03 mol) was added dropwise at 10 °C and stirred for 30.0 min. The reaction mixture was poured over crushed ice. The golden yellow solid separated out was filtered and recrystallized from aqueous ethanol.

4.3.1. 3-(Dimethylamino)-1-phenyl-1H-pyrrole-2,5-dione (**3a**)

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.22 (brs, 6H, 2 × CH_3, NMe_2), 4.95 (s, 1H, C═CH), 7.33–7.43 (m, 5H, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$): 41.0 (CH_3, NMe), 41.9 (CH_3, NMe), 87.4 (HC═), 126.2 (2C's, Ar–C), 127.1 (Ar–C), 128.2 (2C's, Ar–C), 131.8 (Ar–C), 150.3 (N–C═), 165.5 (C═O), 169.4 (C═O); MS: (*m*/*z*) 217 (M+1); Elemental analysis: $C_{12}H_{12}N_2O_2$, Calcd.: C: 66.65%; H: 5.59%; N: 12.96%. Found: C: 66.32%; H: 5.41%; N: 12.75%.

4.3.2. 1-(4-Bromophenyl)-3-(dimethylamino)-1H-pyrrole-2,5-dione (**3b**)

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.21 (brs, 6H, 2 × CH_3, NMe_2), 4.94 (s, 1H, C═CH), 7.25 (d, 2H, *J* = 8.7 Hz, Ar–H), 7.55 (d, 2H, *J* = 8.7 Hz, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$): 41.0 (CH_3, NMe), 41.8 (CH_3, NMe), 87.4 (HC═), 120.5 (Ar–C), 127.5 (2C's, Ar–C), 130.9 (Ar–C), 131.7 (2C's, Ar–C), 150.2 (N–C═), 165.1 (C]O), 168.8 (C═O); MS: *m*/*z* 295 (M+1), 297 (M+3); Elemental analysis: $C_{12}H_{11}BrN_2O_2$, Calcd.: C: 48.84%; H: 3.76%; N: 9.49%. Found: C: 48.62%; H: 3.61%; N: 9.22%.

4.3.3. 3-(Dimethylamino)-1-(4-fluorophenyl)-1H-pyrrole-2,5-dione (**3c**)

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.20 (brs, 6H, 2 × CH_3, NMe_2), 4.96 (s, 1H, C═CH), 7.08–7.14 (m, 2H, Ar–H), 7.28–7.33 (m, 2H, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$): 41.2 (CH_3, NMe), 41.8 (CH_3, NMe), 87.5 (HC═), 115.7 (d, 2C's, $^2J_{F\text{-}C}$ = 22.87 Hz, Ar–C), 127.9 (Ar–C), 128.1 (d, 2C's, $^3J_{F\text{-}C}$ = 9.15 Hz, Ar–C), 150.4 (N–C═), 169.3 (d, $^1J_{F\text{-}C}$ = 244.95 Hz, Ar–C), 165.5 (C═O), 169.4 (C═O); MS: *m*/*z* 235 (M+1); Elemental analysis: $C_{12}H_{11}FN_2O_2$, Calcd.: C: 61.53%; H: 4.73%; N: 11.96%. Found: C: 61.28%; H: 4.58%; N: 11.77%.

4.3.4. 3-(Dimethylamino)-1-(3-(trifluoromethyl)phenyl)-1H-pyrrole-2,5-dione (**3d**)

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.26 (brs, 6H, 2 × CH_3, NMe_2), 4.98 (s, 1H, C═CH), 7.56 (s, 3H, Ar–H), 7.68 (s, 1H, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$): 39.8 (CH_3, NMe), 40.7 (CH_3, NMe), 87.6 (HC═), 122.8 (Ar–C), 123.5 (Ar–C), 123.7 (q, $^1J_{F\text{-}C}$ = 270.15 Hz, Ar–C), 129.2 (2C's, Ar–C), 131.1 (q, $^2J_{F\text{-}C}$ = 33.22 Hz, Ar–C), 132.5 (Ar–C), 150.3 (N–C═), 165.2 (C═O), 168.8 (C═O); MS: *m*/*z* 285 (M+1); Elemental analysis: $C_{13}H_{11}F_3N_2O_2$, Calcd.: C: 54.93%; H: 3.90%; N: 9.86%. Found: C: 54.71%; H: 3.77%; N: 9.62%.

4.3.5. 1-(4-Chlorophenyl)-3-(dimethylamino)-1H-pyrrole-2,5-dione (**3e**)

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.24 (brs, 6H, 2 × CH_3, NMe_2), 4.96 (s, 1H, C═CH), 7.28–7.46 (m, 4H, Ar–H); MS: *m*/*z* 251 (M+1), 253 (M+3); Elemental analysis: $C_{12}H_{11}ClN_2O_2$, Calcd.: C: 57.49%; H: 4.42%; N: 11.17%. Found: C: 57.37%; H: 4.58%; N: 11.39%.

4.3.6. 1-(3-Chlorophenyl)-3-(dimethylamino)-1H-pyrrole-2,5-dione (**3f**)

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.21 (brs, 6H, 2 × CH_3, NMe_2), 4.97 (s, 1H, C═CH), 7.25–7.39 (m, 4H, Ar–H); MS: *m*/*z* 251 (M+1), 253 (M+3); Elemental analysis: $C_{12}H_{11}ClN_2O_2$, Calcd.: C: 57.49%; H: 4.42%; N: 11.17%. Found: C: 57.37%; H: 4.13%; N: 11.23%.

*4.3.7. 1-(2-Chlorophenyl)-3-(dimethylamino)-1H-pyrrole-2,5-dione (**3g**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.26 (brs, 6H, 2 × CH_3, NMe_2), 4.99 (s, 1H, C═CH), 7.24–7.28 (m, 1H, Ar–H), 7.32–7.38 (m, 2H, Ar–H), 7.49–7.52 (m, 1H, Ar–H); MS: *m/z* 251 (M+1), 253 (M+3); Elemental analysis: $C_{12}H_{11}ClN_2O_2$, Calcd.: C, 57.49%; H, 4.42%; N, 11.17%. Found: C, 57.32%; H, 4.21%; N, 11.04%.

*4.4. General procedure for the synthesis of compound (**4a**–**g**)*

To a Vilsmeier Haack adduct prepared from DMF (0.012 mol) and $POCl_3$ (0.05 mol) at 0 °C was added solution of **4a**–**g** (0.01 mol) in 2 mL DMF, reaction mixture was then stirred at 0–5 °C for 30 min. The reaction mixture was poured into cold water. The yellow product separated on neutralization with aqueous $NaHCO_3$ was filtered, washed with cold water, dried and purified by column chromatography (Hexane:Ethyl Acetate, 6:4).

*4.4.1. 4-Dimethylamino)-2,5-dihydro-2,5-dioxo-1-phenyl-1H-pyrrole-3-carbaldehyde (**4a**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.62 (s, 6H, 2 × CH_3, NMe_2), 7.32–7.45 (m, 5H, Ar–H), 9.78 (s, 1H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$): 42.5 (CH_3, NMe), 48.3 (CH_3, NMe), 98.0 (HC=), 126.3 (2C's, Ar–C), 127.9 (Ar–C), 128.8 (2C's, Ar–C), 130.9 (Ar–C), 149.4 (N–C=), 163.3 (C═O), 169.4 (C═O), 182.1 (CHO); MS: *m/z* 245 (M+1); Elemental analysis: $C_{13}H_{12}N_2O_3$, Calcd.: C: 63.93%; H: 4.95%; N: 11.47%. Found: C: 63.71%; H: 4.67%; N: 11.37%.

*4.4.2. 1-(4-Bromophenyl)-4-(dimethylamino)-2,5-dihydro-2,5-dioxo-1H-pyrrole-3-carbaldehyde (**4b**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.62 (s, 6H, 2 × CH_3, NMe_2), 7.26 (d, 2H, *J* = 9.60 Hz, Ar–H), 7.59 (d, 2H, *J* = 9.60 Hz, Ar–H), 9.79 (s, 1H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$): 42.7 (CH_3, NMe), 48.5 (CH_3, NMe), 98.2 (HC=), 121.7 (Ar–C), 127.8 (2C's, Ar–C), 130.0 (Ar–C), 132.1 (2C's, Ar–C), 149.4 (N–C=), 163.1 (C═O), 169.1 (C═O), 182.2 (CHO); MS: *m/z* 323 (M+1), 325 (M+3); Elemental analysis: $C_{13}H_{11}BrN_2O_3$, Calcd.: C: 48.32%; H: 3.43%; N: 8.67%. Found: C: 48.22%; H: 3.28%; N: 8.51%.

*4.4.3. 4-(Dimethylamino)-1-(4-fluorophenyl)-2,5-dihydro-2,5-dioxo-1H-pyrrole-3-carbaldehyde (**4c**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.68 (s, 6H, 2 × CH_3, NMe_2), 7.13–7.18 (m, 2H, Ar–H), 7.30–7.35 (m, 2H, Ar–H), 9.80 (s, 1H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$): 42.7 (CH_3, NMe), 48.6 (CH_3, NMe), 98.2 (HC=), 116.0 (d, 2C's, $^2J_{F\text{-}C}$ = 22.87 Hz, Ar–C), 126.9 (Ar–C), 128.3 (d, 2C's, $^3J_{F\text{-}C}$ = 9.14 Hz, Ar–C), 149.5 (N–C=), 161.9 (d, $^1J_{F\text{-}C}$ = 243.82 Hz, Ar–C), 163.5 (C═O), 169.4 (C═O), 182.4 (CHO); MS: *m/z* 263 (M+1); Elemental analysis: $C_{13}H_{11}FN_2O_3$, Calcd.: C: 59.54%; H: 4.23%; N: 10.68%. Found: C: 59.44%; H: 4.42%; N: 10.46%.

*4.4.4. 4-(Dimethylamino)-1-(3-(trifluoromethyl)phenyl)-2,5-dihydro-2,5-dioxo-1H-pyrrole-3-carbaldehyde (**4d**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.67 (s, 6H, 2 × CH_3, NMe_2), 7.58–7.68 (m, 4H, Ar–H), 9.81 (s, 1H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$): 42.7 (CH_3, NMe), 48.5 (CH_3, NMe), 98.1 (HC=), 123.1 (Ar–C), 123.4 (q, $^1J_{F\text{-}C}$ = 271.20 Hz, CF_3), 124.5 (Ar–C), 129.5 (2C's, Ar–C), 131.1 (q, $^2J_{F\text{-}C}$ = 35.47 Hz, Ar–C), 131.6 (Ar–C), 149.2 (N–C=), 163.0 (C═O), 168.9 (C═O), 182.1 (CHO); MS: *m/z* 313 (M+1); Elemental analysis: $C_{14}H_{11}F_3N_2O_3$, Calcd.: C: 53.85%; H: 3.55%; N: 8.97%. Found: C: 53.61%; H: 3.32%; N: 8.68%.

*4.4.5. 1-(4-Chlorophenyl)-4-(dimethylamino)-2,5-dihydro-2,5-dioxo-1H-pyrrole-3-carbaldehyde (**4e**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.73 (s, 6H, 2 × CH_3, NMe_2), 7.31 (dd, 2H, *J* = 8.7 Hz, Ar–H), 7.43 (dd, 2H, *J* = 8.7 Hz, Ar–H), 9.80 (s, 1H, CHO); MS: *m/z* 279 (M+1), 281 (M+3); Elemental analysis: $C_{13}H_{11}ClN_2O_3$, Calcd.: C: 56.03%; H: 3.98%; N: 10.05%. Found: C: 56.27%; H: 4.23%; N: 10.32%.

*4.4.6. 1-(3-Chlorophenyl)-4-(dimethylamino)-2,5-dihydro-2,5-dioxo-1H-pyrrole-3-carbaldehyde (**4f**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.69 (s, 6H, 2 × CH_3, NMe_2), 7.26–7.29 (m, 1H, Ar–H), 7.34–7.41 (m, 3H, Ar–H), 9.81 (s, 1H, CHO); MS: *m/z* 279 (M+1), 281 (M+3); Elemental analysis: $C_{13}H_{11}ClN_2O_3$, Calcd.: C: 56.03%; H: 3.98%; N: 10.05%. Found: C: 56.33%; H: 4.22%; N: 10.32%.

*4.4.7. 1-(2-Chlorophenyl)-4-(dimethylamino)-2,5-dihydro-2,5-dioxo-1H-pyrrole-3-carbaldehyde (**4g**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.67 (s, 6H, 2 × CH_3, NMe_2), 7.20–7.35 (m, 1H, Ar–H), 7.22–7.44 (m, 2H, Ar–H), 7.50–7.61 (m, 1H, Ar–H), 9.80 (s, 1H, CHO); MS: *m/z* 279 (M+1), 281 (M+3); Elemental analysis: $C_{13}H_{11}ClN_2O_3$, Calcd.: C: 56.03%; H: 3.98%; N: 10.05%. Found: C: 56.29%; H: 4.19%; N: 10.19%.

*4.5. General procedure for the synthesis of compound (**5a**–**g**)*

To a suspension of **4a**–**g** (0.01 mol) in water (5 mL), catalyst NH_4VO_3 (5 mol %) was added. The suspension was heated (50–60 °C) under stirring and then triethylphosphite (0.01 mol) was added slowly, and refluxed for 20 min. The suspension turns into clear solution, followed by separation of yellow solid. It was filtered, dried and purified by using column chromatography (Ethyl acetate : Hexane, 6:4).

*4.5.1. Diethyl (4-(dimethylamino)-2,5-dihydro-2,5-dioxo-1-phenyl-1H-pyrrol-3-yl)(hydroxy)methylphosphonate (**5a**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.30–1.37 (m, 6H, 2 × CH_3), 3.43 (s, 6H, NMe_2), 4.15–4.26 (m, 4H, 2 × OCH_2), 5.01 (d, 1H, $^3J_{HC\text{-}OH}$ = 9.6 Hz, OH), 5.26 (dd, 1H, $^2J_{P\text{-}CH}$ = 10.2 Hz and $^3J_{HC\text{-}OH}$ = 9.6 Hz, P–CH–O), 7.25–7.34 (m, 3H, Ar–H), 7.40–7.45 (m, 2H, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$): 16.4 (2C's, CH_3), 43.1 (2C's, NMe_2), 63.0 (d, $^2J_{P\text{-}O\text{-}C}$ = 8.02 Hz, P–O–CH_2), 63.4 (d, $^2J_{P\text{-}O\text{-}C}$ = 8.02 Hz, P–O–CH_2), 65.0 (d, $^1J_{P\text{-}C}$ = 167.10 Hz, P–CH–O), 93.9 (HC =), 126.1 (2C's, Ar–C), 127.5 (Ar–C), 128.8 (2C's, Ar–C), 131.2 (Ar–C), 145.3 (=C–N), 165.0 (C═O), 171.4 (C═O); MS: *m/z* 383 (M+1), 381 (M−1); Elemental analysis: $C_{17}H_{23}N_2O_6P$, Calcd.: C: 53.40%; H: 6.06%; N: 7.33%. Found: C: 53.24%; H: 5.86%; N: 7.03%.

*4.5.2. Diethyl (1-(4-bromophenyl)-4-(dimethylamino)-2,5-dihydro-2,5-dioxo-1H-pyrrol-3-yl)(hydroxy)methylphosphonate (**5b**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.31–1.43 (m, 6H, 2 × CH_3), 3.44 (s, 6H, NMe_2), 4.17–4.27 (m, 4H, 2 × OCH_2), 4.95 (brs, 1H, OH), 5.26 (d, 1H, $^2J_{P\text{-}CH}$ = 13.2 Hz, P–CH–O), 7.24 (d, 2H, *J* = 8.7 Hz, Ar–H), 7.55 (d, 2H, *J* = 8.7 Hz, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$): 16.4 (2C's, CH_3), 43.2 (2C's, NMe_2), 63.1 (d, $^2J_{P\text{-}O\text{-}C}$ = 8.02 Hz, P–O–CH_2), 63.5 (d, $^2J_{P\text{-}O\text{-}C}$ = 8.02 Hz, P–O–CH_2), 65.1 (d, $^1J_{P\text{-}C}$ = 167.10 Hz, P–CH–O), 94.2 (HC=), 121.2 (Ar–C), 127.5 (2C's, Ar–C), 128.0 (Ar–C), 132.0 (2C's, Ar–C), 145.5 (=C–N), 164.7 (C═O), 170.9 (C═O); MS: *m/z* 461 (M+1), 463 (M+3); Elemental analysis: $C_{17}H_{22}BrN_2O_6P$, Calcd.: C: 44.27%; H: 4.81%; N: 6.07%. Found: C: 44.40%; H: 4.56%; N: 6.33%

*4.5.3. Diethyl (4-(dimethylamino)-1-(4-fluorophenyl)-2,5-dihydro-2,5-dioxo-1H-pyrrol-3-yl)(hydroxy)methylphosphonate (**5c**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28–1.37 (m, 6H, 2 × CH_3), 3.41 (s, 6H, NMe_2), 4.16–4.25 (m, 4H, 2 × OCH_2), 4.95 (d, 1H, $^3J_{HC\text{-}OH}$ = 9.6 Hz, OH), 5.26 (dd, 1H, $^2J_{P\text{-}CH}$ = 9.0 Hz and $^3J_{HC\text{-}OH}$ = 9.6 Hz P–CH–O), 7.09–7.14 (m, 2H, Ar–H), 7.25–7.29 (m, 2H, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$): 16.3 (2C's, CH_3), 43.0 (2C's, NMe_2), 62.9

(d, $^{2}J_{P\text{-}O\text{-}C}$ = 6.90 Hz, P–O–CH_2), 63.3 (d, $^{2}J_{P\text{-}O\text{-}C}$ = 8.02 Hz, P–O–CH_2), 64.4 (d, $^{1}J_{P\text{-}C}$ = 163.2 Hz, P–CH–O), 94.0 (HC=), 115.6 (d, 2C's, $^{2}J_{F\text{-}C}$ = 22.87 Hz, Ar–C), 127.1 (Ar–C), 127.8 (d, 2C's, $^{3}J_{F\text{-}C}$ = 9.15 Hz, Ar–C), 145.5 (=C–N), 161.3 (d, $^{1}J_{F\text{-}C}$ = 246.15 Hz, Ar–C), 165.0 (C=O), 171.0 (C=O); MS: *m/z* 401 (M+1), 399 (M−1); Elemental analysis: $C_{17}H_{22}FN_2O_6P$, Calcd.: C: 51.00%; H: 5.54%; N: 7.00%. Found: C: 51.28%; H: 5.31%; N: 7.22%.

*4.5.4. Diethyl (4-(dimethylamino)-1-(3-(trifluoromethyl)phenyl)-2,5-dihydro-2,5-dioxo-1H-pyrrol-3-yl)(hydroxy) methylphosphonate (**5d**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.32–1.44 (m, 6H, 2 × CH_3), 3.46 (s, 6H, NMe_2), 4.12–4.27 (m, 4H, 2 × OCH_2), 4.98 (brs, 1H, OH), 5.31 (d, 1H, $^{2}J_{P\text{-}CH}$ = 14.4 Hz, P–CH–O), 7.31–7.66 (m, 4H, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$): 16.3 (2C's, CH_3), 43.1 (2C's, NMe_2), 62.9 (d, $^{2}J_{P\text{-}O\text{-}C}$ = 6.90 Hz, P–O–CH_2), 63.4 (d, $^{2}J_{P\text{-}O\text{-}C}$ = 6.90 Hz, P–O–CH_2), 64.4 (d, $^{1}J_{P\text{-}C}$ = 168.3 Hz, P–CH–O), 94.3 (HC =), 122.7 (Ar–C), 123.5 (q, $^{1}J_{F\text{-}C}$ = 270.15 Hz, CF_3), 123.9 (Ar–C), 129.0 (Ar–C), 129.3 (Ar–C), 131.2 (q, $^{2}J_{F\text{-}C}$ = 33.22 Hz, Ar–C), 131.9 (Ar–C), 145.5 (=C–N), 164.7 (C=O), 170.5 (C=O); MS: *m/z* 451 (M+1), 449 (M−1); Elemental analysis: $C_{18}H_{22}F_3N_2O_6P$, Calcd.: C: 48.01%; H: 4.92%; N: 6.22%. Found: C: 48.29%; H: 4.71%; N: 6.47%.

*4.5.5. Diethyl (1-(4-chlorophenyl)-4-(dimethylamino)-2,5-dihydro-2,5-dioxo-1H-pyrrol-3-yl)(hydroxy)methylphosphonate (**5e**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.31–1.43 (m, 6H, 2 × CH_3), 3.48 (s, 6H, NMe_2), 4.21–4.24 (m, 4H, 2 × OCH_2), 5.03 (brs, 1H, OH), 5.27 (d, 1H, $^{2}J_{P\text{-}CH}$ = 13.2 Hz, P–CH–O), 7.28 (d, 2H, *J* = 7.8 Hz, Ar–H), 7.40 (d, 2H, *J* = 7.8 Hz, Ar–H); MS: *m/z* 417 (M+1), 419 (M+3); Elemental analysis: $C_{17}H_{22}ClN_2O_6P$, Calcd.: C: 48.99%; H: 5.32%; N: 6.72%. Found: C: 48.71%; H: 5.04%; N: 6.58%.

*4.5.6. Diethyl (1-(3-chlorophenyl)-4-(dimethylamino)-2,5-dihydro-2,5-dioxo-1H-pyrrol-3-yl)(hydroxy)methylphosphonate (**5f**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25–1.40 (m, 6H, 2 × CH_3), 3.44 (s, 6H, NMe_2), 4.15–4.31 (m, 4H, 2 × OCH_2), 5.02 (brs, 1H, OH), 5.27 (d, 1H, $^{2}J_{P\text{-}CH}$ = 14.4 Hz, P–CH–O), 7.25–7.37 (m, 4H, Ar–H); MS: *m/z* MS: *m/z* 415 (M−1), 417 (M+1), 419 (M+3); Elemental analysis: $C_{17}H_{22}ClN_2O_6P$, Calcd.: C: 48.99%; H: 5.32%; N: 6.72%. Found: C: 48.76%; H: 5.11%; N: 6.47%.

*4.5.7. Diethyl (1-(2-chlorophenyl)-4-(dimethylamino)-2,5-dihydro-2,5-dioxo-1H-pyrrol-3-yl)(hydroxy)methylphosphonate (**5g**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24–1.41 (m, 6H, 2 × CH_3), 3.58 (s, 6H, NMe_2), 4.02–4.21 (m, 4H, 2 × OCH_2), 4.93 (brs, 1H, OH), 5.43 (d, 1H, $^{2}J_{P\text{-}CH}$ = 13.2 Hz, P–CH–O), 7.28–7.46 (m, 4H, Ar–H); MS: *m/z* 417 (M+1), 419 (M+3); Elemental analysis: $C_{17}H_{22}ClN_2O_6P$, Calcd.: C: 48.99%; H: 5.32%; N: 6.72%. Found: C: 48.81%; H: 5.17%; N: 6.61%.

4.6. Antimicrobial assay

The antimicrobial activity of the synthesized compounds was evaluated by the agar cup plate method. The antibacterial and antifungal assays were performed in Muller–Hinton broth and Czapek Dox broth respectively. Evaluation was performed using the bacteria reseeded in broth for 24 h at 37 °C, and the fungi were reseeded in broth for 48 h at 25 °C. The antibacterial activity of tested samples was studied against one Gram positive bacteria *Bacillus subtilis* NCIM 2250, one Gram negative bacteria *Escherichia coli* ATCC 25922 while *Candida albicans* MTCC 277, *C. tropicalis* MTCC 184, *A. niger* MCIM 545 and *A. clavatus* MTCC 1323 were used as standard fungal strain. The compounds were diluted in DMF with required concentration for bioassay. DMF was also loaded as control. Streptomycin and griseofluvin were used as standards to evaluate the potency of the tested compounds under the same conditions. The zone of inhibition was determined from the diameter of the zone of inhibition using caliper. Each inhibition zone was measured three times to get average value. The minimum inhibitory concentration (MIC) values were determined on MH agar plates by pouring the molted agar in Petri dishes according to National Committee for Clinical Laboratory Standards (NCCLS, M7-A5 January 2000), containing the following concentrations (mg/mL): 0 (control), 3, 5, 10, 15, 20, 30, 40. The MIC was defined as the lowest concentration tested samples showing no visible bacterial growth after 24 h incubation period at 37 °C.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.ejmech.2014.06.053. These data include MOL files and InChiKeys of the most important compounds described in this article.

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