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Ceric(IV) Ammonium Nitrate Mediated Cross Dehydrogenative Coupling of ortho-benzoylbenzofurans with Phosphites and their Anti-microbial evaluation

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Abstract

A low-cost cross-dehydrogenative coupling process of ortho-benzoylbenzofuran mediated by Ceric(IV) ammonium nitrate has been created. A simple one-pot method is used to create several ortho-benzoyl-3-phosphonylbenzofurans without the need for costly metals and other oxidants. Ceric(IV) ammonium nitrate converts organophosphorus compounds into phosphoryl radicals, which is followed by an electron transfer, electrophilic addition, and intermediate rearrangement, all of which result the required ortho-benzoyl-3-phosphonylbenzofuran. In moderate to good yields, a number of phosphorylated products with various functional groups were produced. Using the swab streak method, these compounds were tested for antibacterial and in vitro antifungal screening against four microorganisms. A few of the compounds exhibited remarkable activity.

Keywords:*ortho*-benzoyl-3-phosphonylbenzofuran, ortho-benzoylbenzofuran, dialkyl phosphites, Ceric(IV) ammonium nitrate, cross dehydrogenative coupling.

Introduction

Numerous bacterial illnesses in humans have occurred within the past 10 years, including skin, lung, digestive and urinary tract infections[1–10]. Furthermore, there has been a spike in interest in creating new and more potent antibiotics as a result of bacterial strains becoming more resistant to current ones. Natural substances like benzofurans, chromones, coumarins, pyran, flavones, and their synthetic hybrids have gained a lot of attention lately for their advantageous uses against bacterial strains[11–31]. Additionally, the most significant heterocyclic compounds in medicinal chemistry are benzofurans and their derivatives, which have a wide range of pharmacological activities[32], including antibacterial, anti-Alzheimer's, antileishmanial, anti-inflammatory, anti-tubercular, and antihypertensive properties. However, the antibacterial and anti-Alzheimer's properties of phosphonylbenzofurans (phosphorus-substituted heterocycles) have not been as well studied.

In synthetic chemistry, phosphorus-substituted heterocycles (such as N-, O-, S-, and even Se-heterocycles) have significant uses as reagents[33–37], ligands[38–40], flame retardants[41–42], physiologically active compounds, and building blocks[43–48] . Based on these, much work has inevitably been done to create highly effective synthetic processes for phosphorus-substituted heterocycle production[49–51], which in turn helps discover new medicinal agents[52–53]. Phosphorus-substituted heterocycles synthesis has therefore advanced significantly during the last few decades. Hence, last few decades have witnessed much progress in the synthesis of phosphorous-substituted heterocycles with the development of metal catalysis[54], photocatalysis[55–62], organocatalysis[63], and electrochemical catalysis[64–69]. Moreover, chemists have mostly unravelled the addition of C-P bonds with P-centered radicals[70–72], which are easily created through single-electron transfer (SET) and include phosphine oxides, phosphonates, and phosphites, among others. As a result, there has been a resurgence of interest in the use of P-centered radicals in the formation of significant organophosphorus compounds within the last ten

years[73–77]. High reactivity while undergoing radical addition to unsaturated compounds is the primary feature of non-planar P-centered radicals **[Figure 1].** In general, one of the main methods for producing P-centered compounds is the homolytic cleavage of P-H bonds.

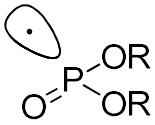


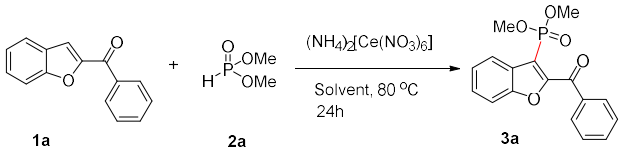
Figure 1

Particularly, there have been notable developments in the P-centered radical-based cross-dehydrogenative coupling (CDC) reactions of heterocyclic compounds, which are mediated by transition metals[78–87]. There are still a lot of chances and problems in this profession, though. Since radical intermediates are typically quite reactive, stereo control in CDC is still challenging. Mechanistic awareness is still weak and lacking in many circumstances when inactivated C-H activation is used to supply radical intermediates, and harsh reaction conditions are required. Our attention has been focused on the discovery of cross-dehydrogenative coupling techniques for C-P bond production via P-centered radicals[88]. Therefore, the development of supplementary and alternative synthetic strategies for the production of C-P bonds remains very desirable, particularly in the context of environmentally benign and sustainable reaction circumstances.

Results and Discussion

First, in the presence of a $(NH_4)_2[Ce(NO_3)_6]$ (CAN) and THF as the solvent, ortho-benzoylbenzofuran (**1a, Table 1**) was selected to investigate its dehydrogenative cross coupling with dimethyl phosphite (**2a**). The reaction was run with CAN (3 equiv) for 24 hours at 80 °C. As expected, there was a good yield of the required ortho-benzoyl-3-phosphonylbenzofuran (**3a**) (**Table 1, Entry 1**). The yield did not increase when the temperature was increased to 100 °C (**Table 1, Entry 2**).

Table 1: Reaction conditions optimization.



Entry[a]	Additives	solvent	Yield (%)[b]
1	CAN	THF	70
2	CAN	THF	69
3	CAN	THF	60
4	I_2	THF	Trace
5	PIDA	THF	24
6	---	DMF	n. d

7c	CAN	THF	45
8d	CAN	**THF**	**68**
9	CAN	DMF	n. d
10	CAN	DMSO	n. d.
11	CAN	DCE	n. d
12	CAN	CH_3CN	n. d
13	CAN	Toluene	10
14	CAN	EtOH	50
15	CAN	MeOH	20
16	CAN	PEG800	Trace

[a]Reaction conditions: **1a** (1 equiv), $(NH_4)_2[Ce(NO_3)_6]$(CAN) (0.5 mmol), dimethyl phosphite **2a** (3.0 equiv), and solvent (2 mL) for 24 h at 80 °C. [b]Isolated yield. [C] CAN(4.0 eqivalents), [d] CAN(1.0 eqivalents),

Additionally, the yield dropped to 60% when the temperature was lowered to 60 °C (**Table 1, Entry 3**). Ortho-benzoyl-3-phosphonylbenzofuran (**3a**) was produced in trace and 24% yields, respectively, when additional additives such iodine and phenyliodine (III) diacetate (PIDA) were present (**Table 1, Entries 4 and 5**). However, when the reaction was carried out without an additive, **3a** was not produced (**Table 1, Entry 6**). Thus, this highlights how crucial the additive is to propelling the reaction. The impact of the additive loadings on the yield of the product was then examined. When the quantity of CAN is increased to 4.0 equivalents, the yield of the product dropped to 45% (**Table 1, item 7**). There was no difference in the yield of **3a** when 1.0 equiv of CAN was utilized (**Table 1, entry 8**). However, there was no evidence of the usage of additional solvents, including DMF, DMSO, DCE, and CH_3CN, **3a** (**Table 1, Entries 9-12**). In contrast, **3a** was produced in 10%, 50%, 20%, and trace amounts when Toluene, EtOH, MeOH, and PEG800 were used (**Table 1, Entries 13-16**).

With the above optimized conditions **1a** (0.5 mmol), **2a** (1.0 equiv), $(NH_4)_2[Ce(NO_3)_6]$ (1.0 equiv), , and THF (2 mL) for 24 h at 80 °C (**Table 1, Entry 8**) to hand, in order to check the scope and compatibility of the strategy, dehydrogenative cross coupling was performed between different *ortho*-benzoylbenzofurans (**1a**–**1f)** and dialkyl phosphites (**2a**–**2e)**. To our delight, the dehydrogenative cross coupling showed good substrate scope and furnished the *ortho*-benzoyl-3-phosphonylbenzofuran products (**3a**–**3j)** in fair to good yields (**Table 2**). The process was amenable to the presence of various functional groups ranging from simple to electron-donating substituents on the aromatic ring of *ortho*-benzoylbenzofuran (**1a**–**1f)**. In addition, the reaction was compatible with simple meyhyl, ethyl, propyl and phenyl moieties in the phosphites. Notably, cross dehydrogenative coupling proceeded smoothly with *ortho*-benzoylbenzofuran (**1**) to afford the *ortho*-benzoyl-3-phosphonylbenzofuran **3a** in 35 to 68% yields (**Table 2**).

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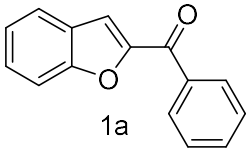
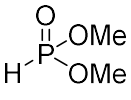
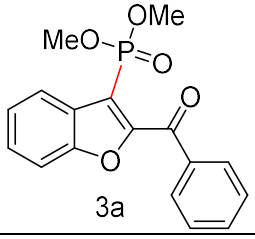
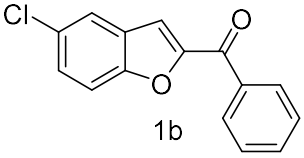
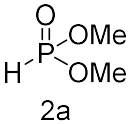
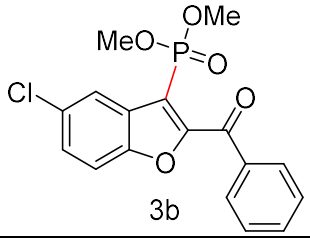
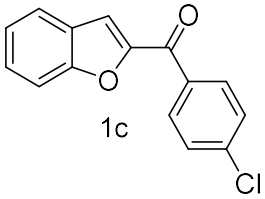
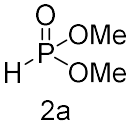
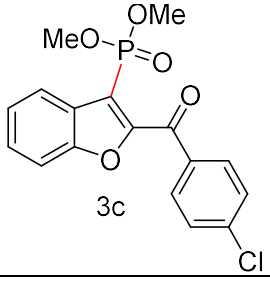
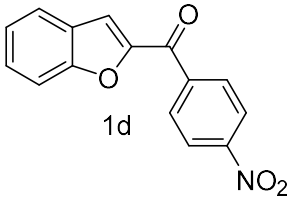
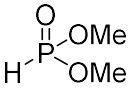
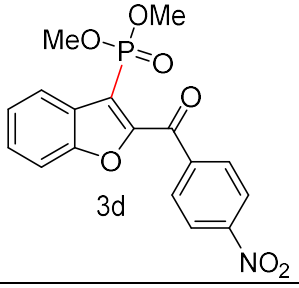
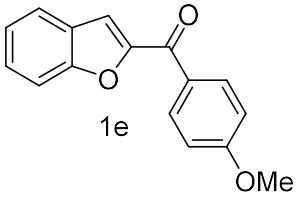
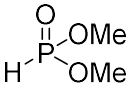
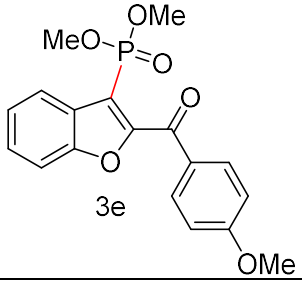
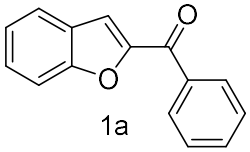
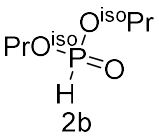
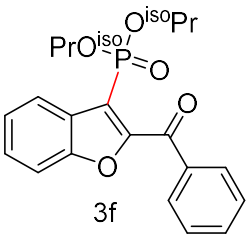
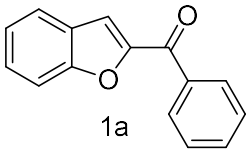
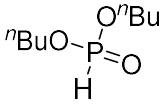
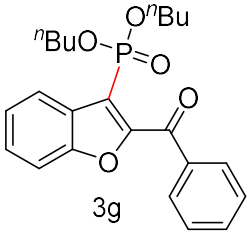
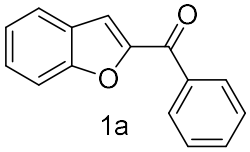
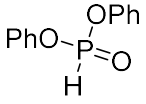
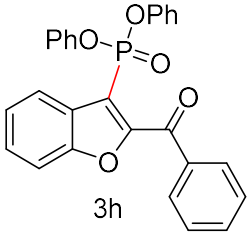
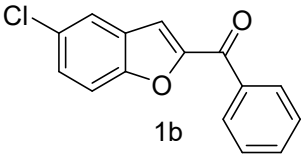
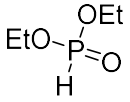
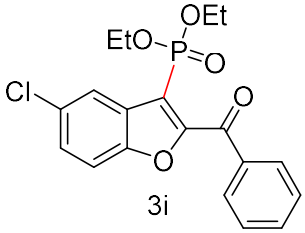
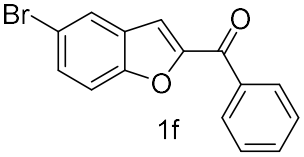
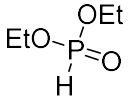
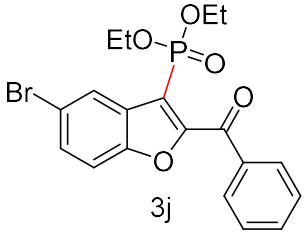
Table 2: Synthesis of *ortho*-benzoyl-3-phosphonylbenzofuran derivatives.

Entry[a]	*ortho*-benzoylbenzofuran(**1**)	Dialkyl/aryl phosphites (**2**)	Product (**3**)	Yields[b]
1	 1a	 2a	 3a	68
2	 1b	 2a	 3b	61
3	 1c	 2a	 3c	59
4	 1d	 2a	 3d	51
5	 1e	 2a	 3e	59
6	 1a	 2b	 3f	45

7	 1a	 2c	 3g	63
8	 1a	 2d	 3h	35
9	 1b	 2e	 3i	61
10	 1f	 2e	 3j	64

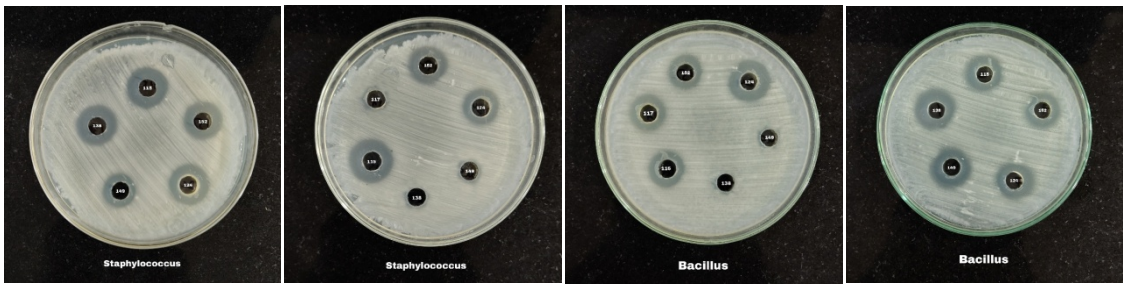
[a] Conditions of reaction: *ortho*-benzoylbenzofuran (0.5 mmol), Dialkyl/aryl phosphites (0.5 mmol), Ceric(IV) Ammonium Nitrate (0.5 mmol), THF (2mL). [b] Isolated products.

Antimicrobial activity results: Synthesised posphorylated benzofuran compounds were evaluated for their antibacterial properties. All of them shown good activity against the gram-positive bacteria **Bacillus cereus** and **Staphylococcus aureus**, according to the results of the antibacterial evaluation. Comparing compounds **3c** and **3f** to the reference drug **Streptomycin**, which has a zone of inhibition (ZoI) of 14 mm against **Staphylococcus aureus** bacteria, the former showed greater action (ZoI ≥ 16 mm) (**Table-3, entry 3**). The range of ZoI for the remaining compounds, **3a**, **3b**, **3d**, **3i**, **3g**, and **3h**, was 10 mm to 16 mm. Similarly, against **Bacillus cereus** bacteria, the compounds **3i**, **3f**, **3g** and **3d** exhibited effective activity in the range of 14mm to 18m ZoI compared to the reference drug Streptomycin which showed only 12mm ZoI, rest of the compounds **3a**, **3b**, **3c** and **3h** were exhibited the activity equal to the reference drug Streptomycin with 12mm ZoI. No chemical was shown to be effective against the gram-negative bacteria **E. coli** and **Klebsiella pneumonia**. **Aspergillus** and **Candida** were used in the antifungal experiment, and no activity was detected.

Table 3: Antibacterial activity of *ortho*-benzoyl-3-phosphonylbenzofuran derivatives.

S. No	Product code	Gram Positive Bacterial pathogens	
		Staphylococcus aureus	*Bacillus cereus*
1	3a	12mm	12mm
2	3b	14mm	12mm
3	3c	16mm	12mm
4	3d	12mm	14mm
5	3f	16mm	16mm
6	3g	10mm	16mm
7	3h	14mm	12mm
8	3i	13mm	18mm
9	Standard Streptomycine 10 µg/mL	14mm	12mm

The antimicrobial activity was recorded as zone of inhibition in millimeters were measured from one end to other end of clear inhibition zone (zone prevent the bacterial growth). Wider the zone of clearance (mm), stronger is the antimicrobial activity.



To determine the minimum inhibitory concentrations (MIC) of the antibacterially active samples, 25 µL, 50 µL, 75 µL, and 100 µL of samples diluted with water or solvent were added to each plate well until the level reached 100 µL. The corresponding dilutions were prepared using samples containing 10 mg/ml. The compounds showed MIC starting from 50µL to 100µL concentration, according to the MIC data. Taking into account the minimum inhibitory concentration (MIC) against **Staphylococcus aureus** bacteria, compound **3b** (**Table 4, entry 1**) showed the lowest concentration at 50µL, while the remaining compounds showed concentrations of 75µL, respectively. Compound **3h** demonstrated action against **Bacillus cereus** at a MIC of 50µL, while compounds **3b**, **3i**, and **3g** showed activity at a MIC of 75µL, while the remaining compounds at concentration of 100 µL . No chemical was discovered to exhibit MIC action at concentrations of 25 µL or less. It is also interesting to note that, for all compounds, the ZoI increased as concentration increased, except for **Bacillus cereus** compound **3f** at 50 and 75µL dilution, where the ZoI remained constant. Increase in concentration resulted in increase in inhibition zone for the same compound at 100µL This suggests that all compounds must have a

minimum concentration of 5.0 mg/mL of sample to prevent bacterial growth, and that compounds' antibacterial action will be enhanced by concentration increases. Inhibitory activity will not manifest below this dose.

Table 4: Minimum inhibitory concentration of *ortho*-benzoyl-3-phosphonylbenzofuran derivatives

S. No	Product code	Minimum inhibitory concentration- MIC (mm)				MIC of sample (µL)
		Staphylococcus aureus				
		25 µL	50 µL	75 µL	100 µL	
1	3a	-	-	10mm	12mm	75 µL
2	3b	-	08mm	10mm	18mm	50 µL
3	3c	-	-	12mm	16mm	75 µL
4	3d	-	-	08mm	12mm	75 µL
5	3f	-	-	08mm	10mm	75 µL
6	3g	-	-	-	10mm	100 µL
7	3h	-	-	12mm	14mm	75 µL
8	3i	-	-	10mm	12mm	75 µL
	Bacillus cereus					
1	3a	-	-	-	12mm	100 µL
2	3b	-	-	07mm	12mm	75 µL
3	3c	-	-	-	12mm	100 µL
4	3d	-	-	-	10mm	100 µL
5	3f	-	10mm	10mm	11mm	50 µL
6	3g	-	-	10mm	14mm	75 µL
7	3h	-	-	-	10mm	100 µL
8	3i	-	-	10mm	12mm	75 µL

Conclusions:

To sum up, we have created a productive one-pot method for creating ortho-benzoyl-3-phosphonylbenzofurans. Importantly, this tactic worked when CAN was used exclusively as an additive. Notably, this approach demonstrated exceptional regioselectivity with dialkyl phosphites, in contrast to previous studies. The ortho-benzoyl-3-phosphonylbenzofurans that were produced showed strong antibacterial properties. Additionally, it was discovered that compounds **3c** and **3f** showed promise as antibacterial agents.

Experimental Section:-

General:

A Bruker Tensor 37 (FTIR) spectrophotometer was used to record the infrared spectra. A Bruker Avance 400 (400 MHz) spectrometer was used to record ^{1}H NMR spectra at 295 K in $CDCl_3$. Chemical shifts (δ, ppm) and coupling constants [Hz] are presented in a standard manner using either internal standard tetramethylsilane as a reference.

Experimental Section

*Materials and methods*When necessary, the solvents were dried using conventional techniques. A 400 MHz spectrometer was used to record ^{1}H and ^{13}C spectra (^{1}H, 400 MHz; ^{13}C, 100 MHz)

in $CDCl_3$ with shifts referenced to SiMe4 (δ = 0 ppm). An FT-IR spectrophotometer was used to record the infrared spectra. ESI–MS (Micromass VG Autospec) and HRMS (ESI-TOF analyser) equipment were used to record mass spectra. The anhydrous Na_2SO_4 was used to dry the organic extracts. An Elementar Vario Microcure Analyser was used to do the CHN elemental analysis, and the findings showed good agreement with the calculated values. On silica gel (100–200 mesh), column chromatography was carried out with a combination of ethyl acetate (EtOAc) and hexane.

General methods for the synthesis of diakyl-2-aroylbenzofuran-3-ylphosphonates (3a)

Ceric (IV) ammonium nitrate (0.2741 g, 0.5 mmol), ortho-aroyl benzofuran (0.111 g, 0.5 mmol), dialkyl phosphite (0.165 g, 1.5 mmol), and THF (2 mL) were added to a 25 mL round-bottomed flask in air to start the reaction. After 24 hours of stirring at 80 °C, the mixture was let to cool at ambient temperature. The mixture was extracted using EtOAc. After being cleaned with 75 mL of brine, the combined ethyl acetate extract was dried over anhydrous Na_2SO_4 and filtered. Compound **3a** was obtained by vacuum-removing the solvent and purifying the resultant crude product using silica gel chromatography with a hexane/ethyl acetate (80:20) mixture. **Table 2** provides information on the yields for each compound.

Dimethyl (2-benzoylphenylbenzofuran-3-yl) phosphonate (3a) The compound was isolated as a yellow oil. **IR (KBr, cm^{-1}):**"Peaks at 2981, 1661, 1539, and 1441 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.14 (d, *J* = 7.15 Hz, 1H), 8.06 (d, *J* = 7.01 Hz, 2H), 7.66 (t, *J* = 7.6 Hz, 1H), 7.63 (dd, *J* = 8.6, 6.6 Hz, 1H), 7.57 (d, *J* = 7.01 Hz, 2H), 7.55 (dd, *J* = 7.8, 6.2 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 1H), 3.88 (s, 3H), 3.88 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 184.6, 156.5, 156.3, 156.4 (d, *J* = 23.3 Hz), 154.6 (d, *J* = 14.2 Hz), 136.1, 139.1, 130.1, 128.5, 127.8, 127.6, 127.5, 124.8, 123.7, 112.2, 53.39, 53.38. **^{31}P NMR** (162 MHz, $CDCl_3$): δ 13.1 (s). **ESI-MS:** m/z = 331 $[M+H]^+$. **Elemental analysis:** Calculated for $C_{17}H_{15}O_5P$: C = 61.83%, H = 4.59%. Found: C = 61.95%, H = 4.55%".

Dimethyl (2-benzoyl-5-chlorobenzofuran-3-yl) phosphonate (3b) Yellow oil. **IR (KBr, cm^{-1}):**"Absorption at 2983, 1656, 1542, and 1445 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.05 (s, 1H), 7.95 (dd, *J* = 8.5, 1.4 Hz, 2H), 7.57 (q, *J* = 14.1, 7.5 Hz, 1H), 7.48–7.46 (m, 4H), 7.42 (dd, *J* = 8.31, 2.2 Hz, 1H), 3.83 (s, 3H), 3.78 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 184.6, 157.2 (d, *J* = 22.9 Hz), 152.7 (d, *J* = 14.6 Hz), 135.9, 134.1, 133.3, 130.7, 130.2, 129.5, 128.8, 128.7, 128.01, 123.4, 113.1, 53.4. **^{31}P NMR** (162 MHz, $CDCl_3$): δ 13.2 (s). **ESI-MS:** m/z = 365 $[M+H]^+$. **Elemental analysis:** Calculated for $C_{17}H_{14}ClO_5P$: C = 55.99%, H = 3.88%. Found: C = 55.88%, H = 3.94%".

Dimethyl (2-(4-chlorobenzoyl)benzofuran-3-yl) phosphonate (3c) Yellow oil. **IR (KBr, cm^{-1}):**"Bands at 2982, 1657, 1541, 1443 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.09–8.02 (m, 3H), 7.87–7.84 (m, 3H), 7.64–7.57 (m, 1H), 7.55 (d, *J* = 7.0 Hz, 2H), 3.83 (s, 3H), 3.78 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 184.36, 158.01, 152.6, 135.3, 131.7 (d, *J* = 21.6 Hz), 128.8, 128.11 (d, *J* = 14.01 Hz), 123.8, 112.11, 53.4. **^{31}P NMR** (162 MHz, $CDCl_3$): δ 13.11 (s). **ESI-MS:** m/z = 365 $[M+H]^+$. **Elemental analysis:** Calculated for $C_{17}H_{14}ClO_5P$: C = 55.97%, H = 3.88%. Found: C = 55.88%, H = 3.94%".

Diisopropyl (2-benzoylbenzofuran-3-yl) phosphonate (3f) Yellow oil. **IR (KBr, cm^{-1}):**"Peaks at 2977, 1668, 1546, and 1448 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.21 (d, *J* = 7.01 Hz, 1H), 8.05 (d, *J* = 7.01 Hz, 2H), 7.66 (t, *J* = 7.61 Hz, 1H), 7.61 (d, *J* = 7.0 Hz, 1H), 7.56 (d, *J* = 7.0 Hz, 2H), 7.55 (d, *J* = 7.01 Hz, 1H), 7.46 (t, *J* = 7.01 Hz, 1H), 7.48–7.84 (m, 2H), 1.38 (d, *J* = 5.3 Hz, 6H), 1.30 (d, *J* = 5.9 Hz, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 185.2, 155.6 (d, *J* = 15.11 Hz), 154.4 (d, *J* = 9.0 Hz), 136.3, 133.8, 130.1, 128.5, 127.8, 127.6, 127.4, 124.5, 123.9, 114.5, 112.4, 111.9, 71.6, 71.5, 24.0, 23.8. **^{31}P NMR** (162 MHz, $CDCl_3$): δ 7.5 (s). **ESI-MS:** m/z = 387 $[M+H]^+$. **Elemental analysis:** Calculated for $C_{21}H_{23}O_5P$: C = 65.29%, H = 6.01%. Found: C = 65.31%, H = 5.96%".

Dibutyl (2-benzoylbenzofuran-3-yl) phosphonate (3g) Yellow oil. **IR (KBr, cm^{-1}):**"Bands at 2959, 1667, 1541, 1453 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.16 (d, *J* = 7.01 Hz, 1H), 8.02 (d, *J* = 7.01 Hz, 2H), 7.67 (t, *J* = 7.51 Hz, 1H), 7.61 (dd, *J* = 8.01, 6.11 Hz, 1H), 7.56 (d, *J* = 7.01 Hz, 2H), 7.51 (dd, *J* = 8.01, 6.11 Hz, 1H), 7.43 (t, *J* = 7.01 Hz, 1H), 4.13–4.07 (m, 4H), 1.68–1.62 (m, 4H), 1.38–1.33 (m, 4H), 0.93 (t, *J* = 7.01 Hz, 3H), 0.88 (t, *J* = 7.01 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 182.8, 162.7, 154.8, 154.5, 139.3, 132.3, 130.4, 128.5, 125.0, 124.01, 117.8, 116.8, 113.10, 112.5, 63.01, 62.10, 29.6, 29.12, 16.5, 16.3, 14.01. **^{31}P NMR** (162 MHz, $CDCl_3$): δ 7.3 (s). **ESI-MS:** m/z = 415 $[M+H]^+$. **Elemental analysis:** Calculated for $C_{23}H_{27}O_5P$: C = 66.67%, H = 6.58%. Found: C = 66.79%, H = 6.52%".

Diethyl (2-benzoyl-5-chlorobenzofuran-3-yl) phosphonate (3i): A yellow-colored oil was obtained. **IR Spectrum** (KBr, cm^{-1}): "Peaks observed at 2983, 1656, 1541, and 1444 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.14 (dd, *J* = 7.0, 1.0 Hz, 1H), 7.99 (dd, *J* = 8.6, 1.3 Hz, 2H), 7.67 (td, *J* = 7.3 Hz, 1H), 7.54 (singlet, 1H), 7.52 (dd, *J* = 8.3, 2.2 Hz, 2H), 7.46 (dd, *J* = 8.9, 2.2 Hz, 1H), 4.29–4.17 (m, 4H), 1.33 (t, *J* = 6.5 Hz, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 184.5, 157.1 (d, *J* = 22.8 Hz), 152.6 (d, *J* = 14.5 Hz), 135.8, 134.0, 133.2, 130.6, 130.1, 129.4, 128.7, 128.6, 128.0, 123.3, 113.0, 63.0, 62.9, 16.3, 16.2. **^{31}P NMR** (162 MHz, $CDCl_3$): δ 9.1 (singlet). **ESI-MS**: m/z = 393 corresponding to $(M+H)^+$. **Elemental Analysis** calculated for $C_{19}H_{18}ClO_5P$: C = 58.10%, H = 4.62%; Found: C = 58.22%, H = 4.56%".

Diethyl (2-benzoyl-5-bromobenzofuran-3-yl) phosphonate (3j) The product was obtained as a yellow-colored oil.**IR (KBr, cm^{-1}):**"Characteristic absorption bands appeared at 2925, 1667, 1590, and 1446 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.31 (d, *J* = 7.0 Hz, 1H), 8.11 (d, *J* = 7.0 Hz, 2H), 7.65 (t, *J* = 7.5 Hz, 1H), 7.60 (dd, *J* = 8.0, 6.0 Hz, 1H), 7.55 (d, *J* = 7.0 Hz, 2H), 7.54 (dd, J = 8.0, 6.1 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 1H), 4.28–4.21 (m, 4H), 1.35–1.32 (m, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 184.4, 156.9 (d, *J* = 22.1 Hz), 153.0 (d, *J* = 13.0 Hz), 135.8, 133.4, 130.7, 130.1, 129.4, 128.7, 128.6, 128.4, 126.4, 125.9, 118.1, 113.5, 63.0, 16.3, 16.2. **^{31}P NMR** (162 MHz, $CDCl_3$): δ 12.07 (singlet). **ESI-MS:** m/z = 437 corresponding to the molecular ion peak $[M+H]^+$. **Elemental analysis:** Calculated for $C_{19}H_{18}BrO_5P$: C = 52.19%, H = 4.15%. Found: C = 52.31%, H = 4.09%".

Antibacterial activity against Gram positive and Gram-negative bacteria.

"A single bacterial colony of pure culture was transferred into a 150 mL conical flask with 50 mL of nutrient broth media to create active bacterial cultures, which were then incubated for 8–12 hours at 37 °C". To create aliquots of varying concentrations for the MIC test, powdered

sample compounds were dissolved in 1 millilitre of an appropriate solvent, such as water, methanol, DMSO, etc. Depending on the necessary concentrations, liquid samples were diluted with water or a solvent before being employed directly. **E. Coli** and **Klebsiella** were chosen as gram-negative bacteria, while **Staphylococcus** and **Bacillus** were chosen as gram-positive microorganisms. The swab streak method was used to perform the antibacterial assay. Nutrient agar medium was made for this purpose and sterilised for 15 minutes at 121 °C and 15 pounds of pressure. After being placed into the petri plates, the sterile media was left to harden. The culture was evenly spinton to the nutrient agar surface using a sterile cotton swab. After obtaining active bacterial cultures, 100 µl of the culture was applied to the agar surface. "Following the solidification of the plates, sterile well borer was used to create wells, and 100µl of each sample was placed into each well. In a bacterial incubator, plates were incubated for 18 to 24 hours at 37 °C". Following the incubation period, the bacterial plates were examined, and the findings were recorded(**Table-3**): The clear inhibition zone, also known as the zone of inhibition (the region that prevents bacteria from developing), is measured from one end to the other. The higher the antibacterial activity, the wider the zone of inhibition (mm).

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