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Synthesis and anti-microbial activity evaluation of phosphorylated urea/ thio-urea derivatives

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ABSTRACT

Synthesis of phosphorylated urea/ thio-urea derivatives was accomplished by the reaction of isocayanates/isothiocayanates with diethyl phosphoramidate at 10 to 40 ^{0}C. All the compounds were characterized by IR, NMR (^{1}H, ^{13}C, ^{31}P), Mass spectral analysis. These compounds were screened for Anti-microbial activity and exhibited promising results.

Key words: Isocyanates, isothiocyanates, diethyl phosphoramidate, Anti-microbial activity

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INTRODUCTION

Microbial resistance is a significant evolutionary process based on selection for organisms that have enhanced ability to continue doses of antibiotics that would have previously been treacherous. Survival of bacteria often results from an inheritable resistance [1, 2]. Moreover, antibiotic resistance may carry out a biological cost and consequently, spread of antibiotic resistant bacteria may be hindered by reduced fitness associated with the resistance. However, additional mutations may compensate for this fitness cost and aids the survival of bacteria [3-6].

Urea and thiourea derivatives show a broad spectrum of biological activities such as anti-HIV, antiviral, HDL-elevating, antibacterial and analgesic properties [7-10]. In addition, urea and thioureas have emerged as structurally novel anticonvulsant agents. In the past 15 years, 13 new antiepileptic drugs (AEDs) have been introduced, some of which are advantageous in terms of pharmacokinetics, tolerability and potential for drug interactions [11-13]. These AEDs are regarded as second generation compared with older AEDs, such as phenobarbital, phenytoin, carbamazepine, ethosuximide, and valproic acid. However, the second-generation AEDs marketed so far have not been a break through because, altogether, their use leads to freedom from seizures in no more than 15–20 % of patients with epilepsy that are refractory to older AEDs. Therefore, despite the current availability of more than 15 drugs, about 30 % of people with epilepsy have uncontrolled disease, novel and more effective third-generation AEDs are needed [14]. Several previous reports reveal that the role of urea/thio urea in biological function is very important [15]. Phosphorylation of the drugs also increases the biological activity [16].

Hence, the search for new and potent antimicrobial agents is gaining interest. Urea derivatives are showing a broad spectrum of role in pharmacological activities such as anti-cancer, anti-HIV, anti-inflammatory, anti-diabetic and anti-microbial activities. The previous reports from our laboratory demonstrated that the phosphorylation of the drugs increase the biological activity [17-19]. In view of all the above important applications, we focused on the synthesis of phosphorylated urea and thiourea derivatives which showed good antimicrobial activity.

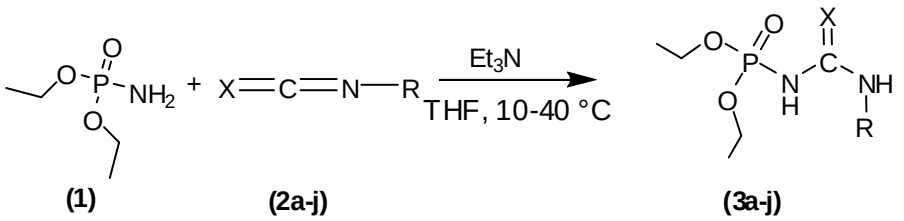
MATERIALS AND METHODS

Chemistry

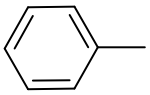
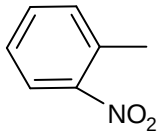
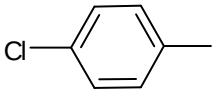
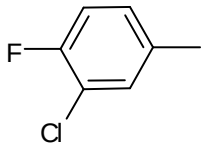
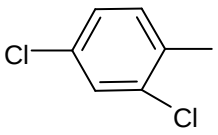
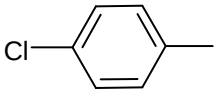
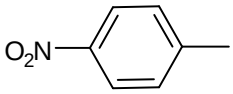
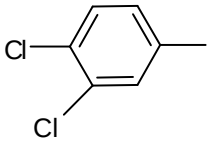
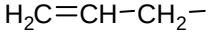
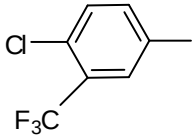
Chemicals were purchased from Sigma – Aldrich, Merck and Lancaster, and were used as such without further purification. All solvents used for spectroscopic and other physical studies were reagent grade and were further purified by literature methods [20]. Melting points were determined using a calibrated thermometer by Guna Digital Melting Point apparatus. IR Spectra were recorded as KBr discs on a Nicolet 380 FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded as solutions in DMSO-d_6 on a Bruker AMX 400 MHz spectrometer operating at 400 MHz for ^{1}H, 100 MHz for ^{13}C and 161.9 MHz for ^{31}P. The ^{1}H and ^{13}C chemical shifts were referenced to tetramethylsilane and ^{31}P chemical shifts to 85 % H_3PO_4. LC mass spectra were recorded on a Jeol SX 102 DA / 600 Mass spectrometer. Elemental analyses were performed on a Thermo Finnigan Instrument at University of Hyderabad, Hyderabad, India.

Synthesis of diethyl phenylcarbamothioylphosphoramidate (3a)

To a stirred solution of diethyl phosphoramidate (**1**) (0.001 mole) in dry THF (20 mL), isothiocyanatobenzene (**2a**) (0.001 mole) in dry THF (20 mL) was added drop wise in presence of triethyl amine with stirring at 10 ^{0}C over a period of 15 minutes. The reaction mixture was stirred further at 40 ^{0}C for 3 hours. The reaction progress was monitored by TLC. The solvent was removed in a rota-evaporator to obtain crude product. The product was purified by column chromatography on silica gel using petroleum ether–ethyl acetate (3:2) as eluent to afford the pure compound. The final product, diethyl phenylcarbamothioylphosphoramidate (**3a**) was obtained with 76 % yield. Same experimental procedure was adopted for the preparation of remaining compounds (**3b-j**).



(1) **(2a-j)** **(3a-j)**

Compound	R	X	Compound	R	X
3a		S	**3f**		O
3b		S	**3g**		O
3c		S	**3h**		O
3d		S	**3 i**		O
3e		S	**3 j**		O

Scheme 1. Synthesis of title compounds 3a-j.

Spectral data of compound 3a-j.

Diethyl phenylcarbamothioylphosphoramidate (3a):

Yield: 76%. M.P. 106-108 ^{0}C. IR (KBr) ν: 3413 (NH), 3004 (Ar-=CH), 1222 (P=O), 1092 (C=S) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.05 (s, 1H, Ar-NH), 7.60- 6.94 (m, 5H , Ar-H), 4.40 (s, 1H, (P=O)-NH), 3.81 (m, 4H, -O$\underline{CH_2}$-CH_3), 1.20 (t, 6H, J =6.8 Hz, -OCH_2-$\underline{CH_3}$); ^{13}C-NMR (DMSO-d_6): δ 180.2, 137.7, 129.8, 126.6, 125.4, 62.5, 16.2; ^{31}P-NMR (DMSO-d_6): δ 18.9; LCMS (m/z): 289 [M+H]$^+$; Anal. Calcd. for $C_{11}H_{17}N_2O_3PS$: C, 45.83; H, 5.94; N, 9.72 %. Found: C, 45.76; H, 5.89; N, 9.65 %.

Diethyl 4-chlorophenylcarbamothioylphosphoramidate (3b):

Yield: 72 %. M.P. 129-130 ^{0}C. IR (KBr) ν: 3414 (NH), 3004 (Ar-=CH), 1224 (P=O), 1094 (C=S) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.18 (s, 1H, Ar-NH), 7.49-7.31 (m, 4H, Ar-H), 4.50 (s, 1H, (P=O)-NH), 3.83 (m, 4H –O$\underline{CH_2}$-CH_3), 1.21 (t, 6H, J =6.9 Hz, -OCH_2-$\underline{CH_3}$); ^{13}C-NMR (DMSO-d_6): δ 180.5, 137.8, 134.6, 129.8, 126.2, 63.6, 16.5; ^{31}P-NMR (DMSO-d_6): δ 19.3; LCMS (m/z): 323 [M+H]$^+$, 325 [M$^+$+2]; Anal. Calcd. for $C_{11}H_{16}ClN_2O_3PS$: C, 40.94; H, 5.00; N, 8.68 %. Found: C, 40.87; H, 4.92; N, 8.62 %.

Diethyl 2, 4-dichlorophenylcarbamothioylphosphoramidate (3c):

Yield: 68%. M.P. 133-134 ^{0}C. IR (KBr) ν: 3416 (NH), 3004.5 (Ar-=CH), 1225 (P=O), 1096 (C=S) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.29 (s, 1H, Ar-NH), 8.14-7.32 (m, 3H, Ar-H), 4.55 (s, 1H, (P=O)-NH), 3.90 (m, 4H -O$\underline{CH_2}$-CH_3), 1.23 (t, 6H, J =7.1 Hz, -OCH_2-$\underline{CH_3}$); ^{13}C-NMR (DMSO-d_6) δ: 182.55, 135.34, 134.11, 133.38, 132.10, 131.36, 124.22, 61.89, 63.90, 16.72; ^{31}P-NMR (DMSO-d_6): δ 20.1; LCMS (m/z): 357 [M+H]$^+$, 359 [M$^+$+2]; Anal. Calcd. For $C_{11}H_{15}Cl_2N_2O_3PS$: C, 36.99; H, 4.23; N, 7.84. Found: C, 36.92; H, 4.18; N, 7.79 %.

Diethyl 4-nitrophenylcarbamothioylphosphoramidate (3d):

Yield: 74%. M.P. 140-141 ^{0}C. IR (KBr) ν: 3414 (NH), 3004 (Ar-=CH), 1566 (C-NO_2), 1366 (C-NO_2), 1228 (P=O), 1102 (C=S) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.38 (s, 1H, Ar-NH), 8.24- 7.94 (m, 4H, Ar-H), 4.51 (s, 1H, (P=O)-NH), 3.89 (m, 4H, -O$\underline{CH_2}$-CH_3), 1.21 (t, 6H, J =7.0 Hz, -OCH_2-$\underline{CH_3}$); ^{13}C-NMR (DMSO-d_6): δ 181.2, 146.3, 143.1, 126.3, 124.1, 61.8, 16.7; ^{31}P-NMR (DMSO-d_6): δ 20.8; LCMS (m/z): 334 [M+H]$^+$; Anal.Calcd. for $C_{11}H_{16}N_3O_5PS$: C, 39.64; H, 4.84; N, 12.61. Found: C, 39.56; H, 4.79; N, 12.56 %.

Diethyl allylcarbamothioylphosphoramidate (3e):

Yield: 70%. Semi solid. IR (KBr) ν: 3413 (NH), 1222 (P=O), 1097 (C=S) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.93 (S, 1H, allylic-NH), 5.92- 4.65 (m, 5H, allylic ^{1}H), 3.89 (m, 4H -O$\underline{CH_2}$-CH_3), 3.65 (S, 1H, (P=O)-NH), 1.22 (t, 6H, J =6.5 Hz, -OCH_2-$\underline{CH_3}$); ^{13}C-NMR (DMSO-*d6)*: δ 180.9, 136.3, 119.1, 61.8, 45.3, 16.6; ^{31}P-NMR (DMSO-d_6): δ 19.5; LCMS (m/z): 253 [M+H]$^+$; Anal.Calcd. for $C_8H_{17}N_2O_3PS$: C, 38.09; H, 6.79; N, 11.10. Found: C, 38.05; H, 6.73; N, 11.02 %.

Diethyl 2-nitrophenylcarbamoylphosphoramidate (3f):

Yield: 73%. M.P. 126-127 ^{0}C. IR (KBr) ν: 3415 (NH), 3004 (Ar-=CH), 1560 (C-NO_2), 1719 (C=O), 1360 (C-NO_2), 1224 (P=O); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.82 (S, 1H, Ar-NH), 8.24-7.94 (m,4H, Ar-H), 4.50 (S, 1H, (P=O)-NH), 3.89 (m, 4H -O$\underline{CH_2}$-CH_3), 1.23 (t, 6H, J =7.2 Hz, -OCH_2-$\underline{CH_3}$); ^{13}C-NMR(DMSO-*d6)*: δ 158.2, 146.3, 143.2, 134.3, 122.1, 122.6, 116.2, 60.8, 16.8; ^{31}P-NMR (DMSO-d_6): δ 20.4; LCMS (m/z): 318 [M+H]$^+$; Anal.Calcd. for $C_{11}H_{16}N_3O_6P$: C, 41.65; H, 5.08; N, 13.25. Found: C, 41.59; H, 5.03; N, 13.21 %.

Diethyl 3-chloro-4-fluorophenylcarbamoylphosphoramidate (3g):

Yield: 70 %. M.P. 136-137 ^{0}C. IR (KBr) ν: 3417 (NH), 3004 (Ar-=CH), 1718 (C=O), 1227 (P=O) cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.84 (s, 1H, Ar-NH), 7.70-7.35 (m, 3H, Ar-H), 4.51 (s, 1H, (P=O)-NH), 3.89 (m, 4H –O$\underline{CH_2}$-CH_3), 1.29 (m, 6H, -OCH_2-$\underline{CH_3}$, J =7.1 Hz); ^{13}C-NMR (DMSO-d_6): δ 159.3, 150.3, 137.7, 126.4, 124.5, 119.5, 114.3, 61.7, 16.9; ^{31}P-NMR (DMSO-d_6): δ 21.2; LCMS (m/z): 325 [M+H]$^+$, 327 [M$^+$+2]; Anal. Calcd. for $C_{11}H_{15}ClFN_2O_4P$: C, 40.69; H, 4.66; N, 8.63 %. Found: C, 40.63; H, 4.62; N, 8.55 %.

Diethyl 4-chlorophenylcarbamoylphosphoramidate (3h):

Yield: 69 %. M.P. 120-121 ^{0}C. IR (KBr) ν: 3413 (NH), 3004 (Ar-=CH), 1717 (C=O), 1223 (P=O) cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.75 (s, 1H, Ar-NH), 7.31-7.49 (m, 4H), 4.51 (s, 1H, (P=O)-NH), 3.80 (m, 4H, –O$\underline{CH_2}$-CH_3), 1.24 (m, 6H, J =6.9 Hz, -OCH_2-$\underline{CH_3}$); ^{13}C-NMR (DMSO-*d6) δ*ppm: 153.5, 136.7, 132.6, 128.2, 119.9, 62.6, 16.2; ^{31}P-NMR (DMSO-d_6): δ 19.3; LCMS (m/z): 307.0 [M+H]$^+$, 309 [M$^+$+2]; Anal. Calcd. for $C_{11}H_{16}ClN_2OP$: C, 43.08; H, 5.26; N, 9.13%. Found: C, 43.01; H, 5.19; N, 9.05 %.

Diethyl 3, 4-dichlorophenylcarbamoylphosphoramidate (3i):

Yield: 71 %. M.P. 145-146 ^{0}C. IR (KBr) ν: 3414 (NH), 3004 (Ar-=CH), 1718 (C=O), 1224 (P=O) cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.82 (s,1H, Ar-NH), 7.98-7.39 (m,3H,Ar-H), 4.55 (s, 1H, (P=O)-NH), 3.85 (m, 4H –

$O\underline{CH_2}$-CH_3), 1.26 (m, 6H, J=7.0 Hz, -OCH_2-$\underline{CH_3}$); ^{13}CNMR(DMSOd_6): δ 162.4, 138.4, 132.5, 131.1, 130.6, 128.5, 120.8, 60.4, 16.5; ^{31}P-NMR (DMSO-d_6): δ 21.1; LCMS (m/z): 341 $[M+H]^+$, 343 $[M^+ +2]$; Anal. Calcd. for $C_{11}H_{15}Cl_2N_2O_4P$: C 38.73, H 4.43, N 8.21. Found: C, 38.69; H, 4.37; N, 8.15 %.

Diethyl 4-chloro-3-(trifluoromethyl)phenylcarbamoylphosphoramidate (3j):
Yield: 73%. semi solid. IR (KBr): ν 3418 (NH), 3004 (Ar-=CH), 1717 (C=O), 1227 (P=O) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.20 (s, 1H, Ar-NH), 8.18-7.70 (m, 3H, Ar-H), 4.52 (s, 1H, (P=O)-NH), 3.82 (m, 4H -$O\underline{CH_2}$-CH_3,), 1.29 (t, 6H, J=7.1 Hz, -OCH_2-$\underline{CH_3}$); ^{13}C-NMR(DMSO-d_6): δ 161.8, 132.4, 128.1, 127.8, 127.6,126.5, 116.8, 60.4, 16.5; ^{31}P-NMR (DMSO-d_6): δ 21.3; LCMS (m/z): 375 $[M+H]^+$, 377 $[M^+ +2]$; Anal. Calcd. for $C_{12}H_{15}ClF_3N_2O_4P$: C, 38.47; H, 4.04; N, 7.48. Found: C, 38.42; H, 3.98; N, 7.43 %.

Pharmacology

Antibacterial Activity

Antibacterial activity was assayed by the disk diffusion method with minor modifications. The bacterial strains used are *Staphylococcus aureus* (AUMC B54), *Bacillus cereus* (AUMC B52) as representatives for the Gram positive strains, while the Gram negative strains were *Pseudomonas aeruginosa* (AUMC B73) and *Escherichia coli* (AUMC B53) [21]. Stains were sub -cultured in BHI medium and incubated for 18 h at 37 ^oC, and then the bacterial cells were suspended, according to the McFarland protocol in saline solution to produce a suspension of about 10^{-5} CFU mL^{-1}: 10 mL of this suspension was mixed with 10 mL of sterile antibiotic agar at 40 ^oC and poured onto an agar plate in a laminar flow cabinet. Four paper disks (6.0 mm diameter) were fixed onto nutrient agar plate. One milligram of each test compound was dissolved in 100 mL of DMSO to prepare stock solution and from stock solution different concentrations 50 and 100 µg/mL of each test compound were prepared. These compounds of different concentrations were poured over disk plate. Ciprofloxacin was used as standard drug. The susceptibility of the bacteria to the test compounds was determined by the formation of an inhibitory zone after 18 h of incubation at 36 ^oC. **Table 1** reports the inhibition zones (mm) of each compound and the controls.

Table1. Antibacterial activity of compounds 3a-j and Ciprofloxacin (inhibition zone in mm)

Compound	*Bacillus cereus* (+ve)		*Staphylococcus aureus* (+ve)		*Escherichia coli* (-ve)		*Pseudomonas aeruginosa*(-ve)	
	50 µg/mL	100 µg/mL	50 µg/mL	100 µg/mL	50 µg/mL	100 µg/mL	50 µg/mL	100 µg/mL
3a	9±0.6	15±0.3	11±0.4	18±0.6	11±0.5	21±0.5	10±0.6	20±0.9
3b	8±0.5	14±0.3	12±0.7	21±0.9	5±0.4	8±0.7	6±0.3	11±0.8
3c	11±0.7	18±0.6	9±0.5	15±0.3	6±0.7	11±0.6	8±0.6	13±0.9
3d	12±0.6	21±0.6	14±0.4	26±0.9	11±0.3	19±0.4	7±0.9	11±0.7
3e	7±0.4	10±0.8	7±0.3	13±0.5	NA	NA	NA	NA
3f	10±0.3	20±0.3	14±0.5	27±0.8	5±0.5	9±0.7	8±0.6	14±0.8
3g	13±0.2	21±0.9	13±0.7	25±0.7	4±0.6	7±0.2	6±0.4	11±0.6
3h	7±0.4	12±0.5	8±0.6	14±0.9	8±0.8	15±0.3	9±0.7	17±0.2
3i	9±0.5	16±0.8	10±0.7	19±0.7	12±0.3	20±0.3	11±0.3	20±0.3
3j	14±0.7	22±0.5	14±0.9	26±0.8	11±0.4	21±0.4	10±0.5	19±0.2
Ciprofloxacin	13±0.8	20±0.6	15±0.4	28±0.7	14±0.5	25±0.3	12±0.8	21±0.4

Note: The concentration of the drug was taken as 50 µg/mL, 100 µg/mL in DMSO.

Antifungal Activity

The title compounds were screened separately *in vitro* for their antifungal activity against various fungi viz. *Aspergillus fumigatus*, *Geotrichum candidum*, *Candida albicans*, *Syncephalastrum racemosum*, and these species were isolated from the infected organs of some patients on *Sabouraud dextrose agar* plates. The cultures of fungi were purified by single spore isolation technique. The antifungal activity was done by agar well diffusion method.

A homogeneous mixture of glucose-peptone-agar (40:10:15) was sterilized by autoclaving at 121 °C and 15 lb/cm^2 for 20 min. The sterilized solution (25 mL) was poured in each sterilized Petri dish in laminar flow and left for 20 min to form the solidified sabouraud dextrose agar plate. These plates were inverted and kept at 30 °C in incubator to remove the moisture and to check for any contamination. *Antifungal assay*: Fungal strain was grown in 5 mL *Sabouraud dextrose broth* (glucose:peptone, 40:10) for 3-4 days to achieve 105 CFU/mL cells. The fungal culture (0.1mL) was spread out uniformly on the sabouraud dextrose agar plates by sterilized triangular folded glass rod. Plates were left for 5-10 min so that culture is properly adsorbed on the surface of *Sabouraud dextrose agar* plates. Small wells of size (4 mm×2 mm) were cut into the plates with the help of well cutter and bottom of the wells were sealed with 0.8% soft agar to prevent the flow of test sample at the bottom of the well. 100 µL of the tested samples (10 µg/mL) was loaded into the wells of the plates. All compounds were prepared in dimethylsulfoxide (DMSO), DMSO was loaded as control. The plates were kept for incubation at 30 °C for 3-4 days and then the plates were examined for the formation of inhibition zone. All the compounds were compared their inhibition zone with the

standard Amphotericin B. Each inhibition zone was measured three times by caliper to get an average value. The test was performed three times for each fungus.

Table 2.Antifungal activity of compounds 3a-j and Amphotericin B (inhibition zone in mm)

Compound	*Aspergillus Fumigates*	*Geotrichum Candidum*	*Candida albicans*
3a	13±0.4	15±0.9	19±0.28
3b	11±1.32	15±1.06	10±1.02
3c	16±0.48	16±0.057	13±0.23
3d	12±0.5	14±0.7	11±0.23
3e	7±0.07	18±0.7	15±0.55
3f	11±0.5	11±0.04	10±0.52
3g	17±1.02	15±0.88	13±1.4
3h	15±0.64	12±1.95	09±1.34
3i	09±1.13	20±1.33	13±0.02
3j	16±0.3	16±0.3	12±1.06
Amphotericin B	15±0.96	16±1.9	14.1±1.7

RESULTS AND DISCUSSION

General procedure for the preparation of compounds 3a-j

The synthetic route involves reaction of diethyl phosphoramidate (**1**) with phenyl isocyanates or isothiocyanates (**2a-j**) in dry THF in presence of triethylamine at 10-40 ^{o}C to yield diethyl substituted phenyl/allyl carbamoyl/carbamothioyl phosphoramidates (**3a-j**). The solvent was removed in a rota-evaporator to get the crude products. They were further purified by column chromatography. The title compounds were obtained with moderate to high yields (68–76 %). The chemical structures of all the title compounds **3a-j** were characterized by IR, ^{1}H, ^{13}C, ^{31}P NMR, mass spectral data and elemental analyses and their data are presented in experimental section. IR absorptions were observed in the regions 3418-3412, 1719-1717, 1222-1228 and 1102-1092 cm^{-1} are assigned to N-H, C=O, P=O and C=S respectively for **(3a-j).** The ^{1}H NMR spectra exhibited broad signals at 8.82-11.38 ppm, due to the aromatic N–H protons. The proton signals of P-O$\underline{CH_2}$-CH_3 appeared as a multiplet and P-OCH_2-$\underline{CH_3}$ gave a triplet at δ 3.80-3.90 and δ 1.20-1.29 respectively. ^{13}C NMR chemical shifts were observed in the regions, δ 174.1-182.8, 153.5-158.7 for C=S and C=O respectively. The P-O-$\underline{CH_2}$-CH_3 and P-OCH_2-$\underline{CH_3}$ in the title compounds resonated as doublet at δ 62.3-61.4, 16.0-16.9 respectively. ^{31}P NMR signals appeared in the region 18.9–21.3 ppm for all the compounds (**3a–j**). The title compounds showed potent antimicrobial activities.

Pharmacology

Antimicrobial Activity

All the title compounds exhibited good antimicrobial activities when compared with the standard. The compounds **3j, 3d** and **3g** showed better results than that of Ciprofloxacin. This is mainly due to nitro, triflouro methyl and fluoro substituents on the phenyl ring.

Antifungal Activity

The title compounds were showed good antifungal activity when compared with that of the standard. **3g**, **3j**, **3h** and **3c** exhibited good results when compared to **Amphotericin B** due to the presence of fluoro and chlorine atoms in the phenyl ring.

CONCLUSION

This work reports that phenyl carbamoyl/carbamothioyl phosphoramidates (**3a-j**) synthesized can be treated as better antimicrobial drugs. All the title compounds exhibited good antimicrobial activity.

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