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Synthesis and Antimicrobial Activity of Some New α-Aminophosphonates

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ABSTRACT

Syntheses of new α-aminophosphonates 4a–l **were achieved through a one-pot, three-component reaction process (the Kabachnik-Fields reaction). It involves the reaction with substituted salicylaldehydes, amines and dialkyl/diaryl phosphites in dry toluene at reflux temperature. The structures of the novel products were established by elemental analyses, IR, ^{1}H, ^{13}C and ^{31}P NMR and mass spectroscopy. All the title compounds were screened for their antibacterial and antifungal activity. Most of the compounds exhibited moderate antimicrobial activity.**

KEYWORDS

α-Aminophosphonates, alkyl/aryl phosphites, aldehydes, amines, antimicrobial activity.

1. Introduction

The Kabachnik–Fields reaction is one of the most effective methods for the synthesis of biologically important α-aminophosphonates and has received a great deal of attention in recent years.[1,2] The reason is that α-aminophosphonates are phosphorus analogues of α-aminocarboxylic acids, and therefore exhibit biological importance both in themselves and when used as building blocks of peptides. The addition of compounds containing P-H bonds to C-C or C-X double bonds provides a method for the synthesis of organophosphorus derivatives. Among phosphorus compounds, (*R*)-amino phosphonic acids and their derivatives have received considerable attention in recent years because they exhibit intriguing biological activities.[3,4] Being considered as (*R*)-amino acid analogues,[5] they have found widespread use as biologically attractive peptide mimics which have been employed, for example, as inhibitors of protease[6] and as catalytic antibodies.[7] In addition, they have been used as antibacterial[8] and anti-HIV agents.[9]

These entities have been shown to serve as inhibitors of GABA-receptors, inhibitors of various proteolytic enzymes, dialkylglycine decarboxylase, peptide mimetics, antibiotics, and pharmacological agents, including antitumour and antihypertensive agents.[8] Various synthetic methods for α-aminophosphonic acids and α-aminophosphonates have been reported. However, the classical approach of synthesis is the Kabachnik–Fields reaction, which is a one-pot, three-component operation with a carbonyl compound, amine and dialkyl phosphite. An efficient solvent-free and catalyst-free method for the synthesis of α-aminophosphonates was developed by a microwave-assisted three-component Kabachnik–Fields reaction involving an aldehyde, amine and dimethyl phosphite.[9b] Among the reported literature methods, the Kabachnik–Fields reaction is one of the most convenient approaches to α-aminophosphonates. We report herein the syntheses of a series of new α-aminophosphonates, listed in Table 1. All the new α-aminophosphonates were screened for their antimicrobial activity.

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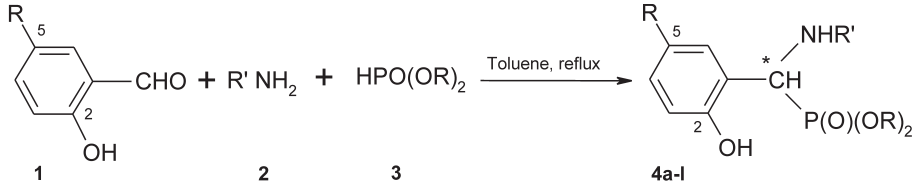
2. Results and Discussion

Syntheses of new α-aminophosphonates were accomplished by the reaction of equimolar quantities of different amines, substituted salicylaldehydes and diphenyl/diethyl/dimethyl phosphite in dry toluene at reflux temperature for 8–10 h in 67–80% yield. Xue-Jun Mu *et al*[9b] recently reported the synthesis of α-aminophosphonates up to 98% yield in solvent-free, catalyst-free and in heterogeneous medium under microwave irradiation (2 min) conditions. Thin layer chromatography (TLC) was employed to determine the purity of the products. All the title compounds **4a–l** were readily soluble in polar solvents and melted in the range of 145–184 °C. It is worth mentioning that many of the synthesized α-aminophosphonates are novel compounds and inaccessible to preparation by other methods. All the structures of the novel synthesized α-aminophosphonates **4a–l** were established by elemental analysis, infrared (IR), ^{1}H, ^{13}C and ^{31}P nuclear magnetic resonance (NMR) and mass spectroscopy.

All the compounds **4a–l** showed absorption bands in the regions 3375–3421, 1235–1295 and 739–769 cm^{-1} for NH, P=O and P-C$_{(aliphatic)}$, respectively[10] (see Table 2).

The ^{1}H NMR spectral data of **4a–**l are furnished in Table 3. The



Scheme 1

Table 1 Syntheses of new α-aminophosphonates **4a–l**.

Compound	R	R'	$(OR)_2$	Compound	R	R'	$(OR)_2$
4a	NO_2	2,4-$Cl_2C_6H_3$	C_6H_5	4g	Br	2,4-$Cl_2C_6H_3$	C_2H_5
4b	NO_2	3-$NO_2C_6H_4$	C_6H_5	4h	Br	3-$NO_2C_6H_4$	C_2H_5
4c	Br	2,4-$Cl_2C_6H_3$	C_6H_5	4i	NO_2	2,4-$Cl_2C_6H_3$	CH_3
4d	Br	3-$NO_2C_6H_4$	C_6H_5	4j	NO_2	$C_{10}H_7(\alpha)$	CH_3
4e	NO_2	2,4-$Cl_2C_6H_3$	C_2H_5	4k	Br	2,4-$Cl_2C_6H_3$	CH_3
4f	NO_2	3-$NO_2C_6H_4$	C_2H_5	4l	Br	3-$NO_2C_6H_4$	CH_3

aromatic protons of α-aminophosphonates showed a complex multiplet at δ 6.52–8.26 ppm. The P-*C-H proton resonated as a multiplet at δ 4.00–4.55 ppm due to its coupling with phosphorus and the neighbouring N-H proton. The N-H proton signal appeared as a singlet at δ 5.12–5.68 ppm. The OH proton gave a signal at δ 9.00–10.11 ppm, which was confirmed by D_2O exchange experiments. The proton signal of P-O$CH_2$$CH_3$ showed a multiplet and P-$OCH_2$$CH_3$ showed a triplet at δ 3.78–4.05 and 1.11–1.56 ppm, respectively. The proton signal of P-OCH_3 resonated as a doublet at δ 3.52–3.74 ppm ($^2J_{PH}$ = 10.4–10.7 Hz).[11]

There is corresponding duplication of signals of the ethoxy group in the ^{13}C NMR spectra (Table 4). In fact, the CH_3 groups resonated as two doublets at δ 16.4–18.0 ppm ($^3J_{PC}$ = 6.5–6.7 Hz) and the OCH_2 group as two doublets at δ 63.2–64.2 ppm ($^2J_{PC}$ = 8.7 to 8.9 Hz), the P-OCH_3 groups also gave two doublets at δ 56.0–57.6 ppm ($^2J_{PC}$ = 7.0 Hz). These values are in agreement with the literature data.[11,12,13a,b,14,15a,b,16] The chiral methine carbon (*C*H-P) resonated at δ 46.6–49.5 ppm (d, $^1J_{PC}$ = 148.2–151.0 Hz).[11]

^{31}P NMR chemical shifts[14,15a,b] of these compounds **4a–l** appeared in the region of δ 21.69–24.63 ppm (Table 2). Compounds **4a**, **4h** and **4j** showed two signals each in the region δ 23.72–25.36 ppm. The magnetic non-equivalence in organophosphorus esters may be due to restricted rotation at the phosphorus centre.[16] It is also evident that the two methoxy and the two ethoxy groups which are linked to the phosphorus atom are not magnetically equivalent in these three compounds as they gave two different signals (for each group) in the ^{13}C NMR spectra. The existence of the two isomers is termed intrinsic non-equivalence or unequal conformer populations or a combination of both factors.[16]

The fast atom bombardment (FAB) mass spectrum of **4c** exhibited $[M^{+\bullet}+2Na^+]$ and $[M+2]^{+\bullet}$ in the expected ratio for the presence of bromine and chlorine atoms (see Table 5). Significant ions were observed at m/z 625, 563, 501, 346 and 344 corresponding to $[M^+ + 2Na^+]$, $[M\text{-}C_{25}H_{19}NBrO_3PCl_2]^+$, $[M^+\text{-}C_{19}H_{14}O_4BrCl_2P]^+$, $[M\text{-}OC_{13}H_9BrNCl_2]^+$ and $[M\text{-}C_{13}H_7BrNCl_2]^+$, respectively.[17]

All the title compounds **4a–l** were screened for their antibacterial and antifungal activity. Most of the compounds showed moderate activity against bacteria and low activity against fungi.

3. Experimental

3.1. General Procedure

Progress of the reaction and purity of the compounds were monitored by TLC using hexane and ethyl acetate (3:1 by volume) as eluting system and iodine as visualizing agent. Melting points were determined in open capillary tubes on a Mel-temp apparatus and were uncorrected. Microanalysis was performed at the Indian Institute of Science, Bangalore, India. IR spectra were recorded in the Environmental Engineering Laboratory, Sri Venkateswara University, Tirupati. IR spectra ($\bar{\nu}$ in cm^{-1}) were recorded as pressed KBr discs on a Nicolet 380 FT-IR spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker AMX 400 MHz spectrometer operating at 400 MHz for ^1H, 100 MHz for ^{13}C and 161.9 MHz for ^{31}P using DMSO-d_6. ^{31}P chemical shifts were measured relative to 85% H_3PO_4. Mass spectra were recorded on a Jeol SX 102 DA/600 mass spectrometer using argon/xenon (6 kV, 10 mA) as the FAB gas and also using ion electrospray ionization (ESI) at 70 eV on a Micromass Quattro II instrument.

3. 2. Synthesis of α-Aminophosphonate 4e (Typical Procedure Used)

A mixture of 5-nitrosalicylaldehyde (0.005 mol), 2,4-dichloroaniline (0.005 mol), and diethylphosphite (0.005 mol) in dry toluene was stirred for 30 min. Then the temperature was raised to reflux and continued for 8 h. Completion of the reaction was monitored by TLC analysis. After completion of the reaction, the solvent was removed using a rota-evaporator. The residue was purified by column chromatography using 60–120 mesh silica gel as adsorbent and hexane and ethyl acetate (3:1 by volume) as an eluent to afford pure α-aminophosphonate **4e** as a solid.

3.3 Antimicrobial Activity

The compounds were assayed for antibacterial activity against six registered bacterial isolates, which were obtained from the NCIM (National Collection of Industrial Microorganisms, National Chemical Laboratories, Pune 411003, India). The bacteria include Gram positive bacterial isolates *Staphylococcus aureus* (NCIM No. 5021, ATCC No. 25923), *Escherichia coli* (NCIM No. 2931, ATCC No. 25922) and *Pseudomonas aeruginosa* (NCIM No. 5029, ATCC No. 27853*), Aspergillus niger* and *Candida albicans.* These samples are clinical isolates from the Department of Biotechnology, Sri Venkateswara Institute of Medical Sciences, Tirupati, India. The bacteria were grown on Hi-media nutrient agar and sub cultured as needed.

Compounds **4a–l** were screened for their antibacterial activity against *Staphylococcus aureus,* multi-drug resistant *Staphylococcus aureus, Escherichia coli* and *Pseudomonas aeruginosa* (10^6 cell mL^{-1}) by the disc-diffusion method[18–20] in nutrient agar medium at various concentrations (250, 500 μg $disc^{-1}$) in dimethylformamide (DMF). The solutions were added to each filter disc and DMF was used as the control. The plates were incubated at 35 °C and examined for zone of inhibition around each disc after 24 h. The results were compared with the activity of the standard antibiotic Penicillin (250 μg $disc^{-1}$). Their antifungal activity[21] was evaluated against *Candida albicans* and *Asperigillus niger* at concentrations of 250 and 500 μg $disc^{-1}$. Griseofulvin was used as the reference compound. Fungal cultures were grown on potato dextrose broth at 25 °C and finally spore suspension was adjusted to 10^5 spores mL^{-1}. Most of the compounds showed moderate activity against bacteria and low activity against fungi (Table 6).

Table 2 Physical, analytical IR and ^{31}P NMR spectral data for the compounds **4a–l**.

Compound	Molecular formula	M.p./°C	Yield/%	Elemental analysis found (calculated)/%			IR $\bar{\nu}$/cm^{-1}			$\delta(^{31}P)$/ppm
				C	H	N	NH	P=O	P-$C_{(aliphatic)}$	
4a	$C_{25}H_{19}N_2O_6Cl_2P$	181–183	70	48.10 (48.03)	3.14 (3.06)	4.39 (4.48)	3390	1251	739	23.72 24.05
4b	$C_{25}H_{20}N_3O_8P$	175–178	75	58.01 (57.90)	3.86 (3.93)	8.05 (8.12)	3385	1295	762	22.04
4c	$C_{25}H_{19}NO_4BrCl_2P$	178–180	69	51.75 (51.84)	3.35 (3.30)	2.46 (2.42)	3381	1286	769	23.13
4d	$C_{25}H_{20}N_2O_6BrP$	160–162	80	54.18 (54.07)	3.58 (3.62)	5.08 (5.04)	3410	1254	753	24.25
4e	$C_{17}H_{19}N_2O_6Cl_2P$	165–167	68	45.53 (45.45)	4.32 (4.26)	6.32 (6.24)	3400	1235	741	24.63
4f	$C_{17}H_{20}N_3O_8P$	145–147	80	48.10 (48.01)	4.67 (4.74)	9.79 (9.88)	3421	1289	756	21.69
4g	$C_{17}H_{19}NO_4BrCl_2P$	163–165	67	42.33 (42.26)	3.87 (3.96)	2.97 (2.89)	3405	1291	739	23.23
4h	$C_{17}H_{20}N_2O_6BrP$	173–175	72	44.38 (44.46)	3.44 (4.38)	6.22 (6.10)	3391	1235	762	24.52, 24.05
4i	$C_{15}H_{15}N_2O_6Cl_2P$	176–178	70	42.69 (42.78)	3.65 (3.58)	6.73 (6.65)	3399	1241	756	21.69
4j	$C_{19}H_{19}N_2O_6P$	182–184	69	56.65 (56.72)	4.80 (4.76)	6.87 (6.96)	3401	1269	762	24.68, 25.36
4k	$C_{15}H_{16}NO_4BrCl_2P$	145–147	73	40.56 (40.48)	2.46 (3.39)	3.07 (3.15)	3399	1263	749	23.93
4l	$C_{15}H_{16}N_2O_6BrP$	162–164	78	41.67 (41.78)	3.82 (3.74)	6.57 (6.49)	3375	1276	750	23.95

Table 3 ^{1}H NMR chemical shifts [a,b] of compounds **4a–l**.

Compound	Ar-H	P-CH	N-H	P-OCH_2CH$_3$/OCH$_3$	P-OCH$_2$CH_3	OH
4a	8.22–6.89 (m, 16 H)	4.25–4.15 (m, 1H)	5.43	–	–	10.10
4b	8.11–6.52 (m, 17 H)	4.27–4.14 (m, 1H)	5.45	–	–	9.99
4c	8.21–6.66 (m, 16H)	4.26–4.18 (m, 1H)	5.42	–	–	10.02
4d	8.10–6.63 (m, 17H)	4.27–4.20 (m, 1H)	5.44	–	–	10.02
4e	8.25–6.82 (m, 6H)	4.13–4.00 (m, 1H)	5.68	3.98–3.71 (m, 4H)	1.23 (t, $^{3}J_{P\text{-}H}$ = 7.1 Hz, CH$_3$) 1.04 (t, $^{3}J_{P\text{-}H}$ = 7.1 Hz, CH$_3$)	9.88
4f	8.11–6.64 (m, 7H)	4.55–4.22 (m, 1H)	5.52	4.00–3.69 (m, 4H)	1.19 (t, $^{3}J_{P\text{-}H}$ = 7.0 Hz, CH$_3$) 1.05 (t, $^{3}J_{P\text{-}H}$ = 7.0Hz, CH$_3$)	10.10
4g	8.12–6.68 (m, 6H)	4.29–4.17 (m, 1H)	5.51	4.05–3.70 (m, 4H)	1.20 (t, $^{3}J_{P\text{-}H}$ = 7.2 Hz, CH$_3$) 1.03 (t, $^{3}J_{P\text{-}H}$ = 7.2 Hz, CH$_3$)	10.11
4h	8.26–6.84 (m,7 H)	4.12–4.03 (m, 1H)	5.53	4.02–3.74 (m, 4H)	1.32 (t, $^{3}J_{P\text{-}H}$ = 7.1 Hz, CH$_3$) 1.15 (t, $^{3}J_{P\text{-}H}$ = 7.1 Hz, CH$_3$)	9.99
4i	8.10–6.59 (m, 6 H)	4.23–4.10 (m, 1H)	5.23	3.74 (d, $^{2}J_{P\text{-}H}$ = 10.7 Hz, OCH$_3$) 3.52 (d, $^{2}J_{P\text{-}H}$ = 10.7 Hz, OCH$_3$)	–	9.00
4j	7.32–6.87 (m, 10H)	4.42–4.20 (m, 1H)	5.22	3.71 (d, $^{2}J_{P\text{-}H}$ = 10.4 Hz, OCH$_3$) 3.53 (d, $^{2}J_{P\text{-}H}$ = 10.4 Hz, OCH$_3$)	–	9.23
4k	7.92–7.24 (m, 6H)	4.38–4.21 (m, 1H)	5.12	3.71 (d, $^{2}J_{P\text{-}H}$ = 10.4 Hz, OCH$_3$) 3.56 (d, $^{2}J_{P\text{-}H}$ = 10.4 Hz, OCH$_3$)	–	9.10
4l	7.93–6.62 (m, 7H)	4.25–4.15 (m, 1H)	5.19	3.70 (d, $^{2}J_{P\text{-}H}$ = 10.6 Hz, OCH$_3$) 3.53 (d, $^{2}J_{P\text{-}H}$ = 10.6 Hz, OCH$_3$)	–	9.01

– No such type of proton present.
[a] Chemical shift δ/ppm.
[b] Recorded in DMSO-d_6.

Table 4 ^{13}C NMR chemical shifts [a] of compounds **4a**, **4b**, **4e**, **4h** and **4l**.

Compound	Chemical shift/ppm
4a	122.1(C-1), 159.0 (C-2), 116.7 (C-3), 124.3 (C-4), 141.0 (C-5), 123.2 (C-6), 143.0 (C-1'), 125.1 (C-2'), 130.2 (C-3'), 127.5 (C-4'), 127.4 (C-5'), 116.6 (C-6'), 148.4 (C-1"), 120.1 (C-2"&C-6"), 128.4 (C-3"&C-5"), 126.6 (C-4"), 49.5 (d, $^{1}J_{PC}$ = 148.2 Hz, P-CH).
4b	123.7 (C-1), 157.2 (C-2), 118.2 (C-3), 121.2 (C-4), 148.3 (C-5), 123.7 (C-6), 146.4 (C-1'), 111.3 (C-2'), 148.5 (C-3'), 116.5 (C-4'), 131.7 (C-5'), 122.1 (C-6'), – (C-1"), 121.0 (C-2"&C-6"), 128.3 (C-3"&C-5"), 127.1 (C-4"), 49.2 (d, $^{1}J_{PC}$ = 149 Hz, P-CH).
4e	125.2 (C-1), 161.0 (C-2), 116.9 (C-3), 133.6 (C-4), 113.1 (C-5), 135.6 (C-6), 141.1 (C-1'), 122.3 (C-2'), 129.6 (C-3'), 124.3 (C-4'), 127.9 (C-5'), 120.2 (C-6'), 64.2 ($^{2}J_{PC}$ = 8.9 Hz, OCH$_2$), 63.8 ($^{2}J_{PC}$ = 8.9 Hz, OCH$_2$), 17.0 ($^{3}J_{PC}$ = 6.7 Hz,OCH$_2$CH$_3$), 16.4 ($^{3}J_{PC}$ = 6.7 Hz,OCH$_2$CH$_3$), 48.7 (d, $^{1}J_{PC}$ = 150 Hz, P-CH).
4h	123.1 (C-1), 161.4 (C-2), 115.5 (C-3), 120.2 (C-4), 140.7 (C-5), 123.1 (C-6), 136.2 (C-1'), 133.7 (C-2'), 124.1 (C-3'), 112.5 (C-4'), 125.1 (C-5'), 112.0 (C-6'), 63.6 ($^{2}J_{PC}$ = 8.7 Hz, OCH$_2$), 63.2 ($^{2}J_{PC}$ = 8.7 Hz, OCH$_2$), 18.0 ($^{3}J_{PC}$ = 6.5 Hz, OCH$_2$CH$_3$), 17.5 ($^{3}J_{PC}$ = 6.5 Hz, OCH$_2$CH$_3$), 46.6 (d, $^{1}J_{PC}$ = 151.0 Hz, P-CH).
4l	124.2 (C-1), 160.3 (C-2), 131.1 (C-3), 131.1 (C-4), 115.6 (C-5), 122.1 (C-6), 144.0 (C-1'), 112.6 (C-2'), 148.6 (C-3'), 113.5 (C-4'), 130.3 (C-5'), 121.0 (C-6'), 57.6 ($^{2}J_{PC}$ = 7.0 Hz, OCH$_3$), 56.7 ($^{2}J_{PC}$ = 7.0 Hz, OCH$_3$), 47.5 (d, $^{1}J_{PC}$ = 148 Hz, P-CH).

[a] Recorded in DMSO-d_6.

Table 5 FAB [a]/ESI [b] mass spectral data of compounds **4c**, **4e**, **4f** and **4l**.

Compound	(m/z)/%
4c [a]	625 [(8.3), M$^{+\bullet}$+2Na^{+}], 581 [(14.0), M$^{+\bullet}$ +2], 579 [(15.5), M$^{+\bullet}$] 563 (5.5), 503 (58.3), 501 (44.4), 425 (19.4), 408 (6.1), 408 (5.5), 391 (16.7), 346 (100), 344 (83.3), 289(13.9), 261 (8.3), 154 (50.0).
4e [a]	449 [(80), M$^{+\bullet}$], 431 (8.6), 420 (11.4), 311 (100), 294 (25.7), 265 (41.3), 154 (11.4), 136 (11.4), 120 (2.8), 102 (5.7), 93 (2.8).
4f [b]	425 [(9.1), M$^{+\bullet}$], 365 (1.8), 334 (2.4), 289 (6.7), 288 (47.1), 227 (6.1), 196 (2.4), 139 (5.4), 74 (100).
4l [a]	433 [(25.0), M$^{+\bullet}$ +2] 431 [(31.2), M$^{+\bullet}$], 399 (62.5), 309 (46.9), 294 (15.5), 259 (40.6), 109 (100), 62 (78.1).

4. Conclusions

In conclusion, we have described a convenient and efficient synthetic protocol for the preparation of some novel α-aminophosphonate derivatives *via* a one-pot, three-component system. This method not only provides an excellent complement for the synthesis of α-aminophosphonates, but also avoids the use of hazardous acids or expensive/toxic Lewis acids and harsh reaction conditions. Most of the compounds exhibited moderate activity against bacteria and less activity against fungi.

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Table 6 Antimicrobial activity of new α-aminophosphonates **4a–l**; zone of inhibition in mm.

Compound	Bacteria								Fungi			
	Staphylococcus aureus		Multi drug resistant *Staphylococcus aureus*		*Escherichia coli*		*Pseudomonas aeruginosa*		*Candida albicans*		*Aspergillus niger*	
μg disc^{-1}:	250	500	250	500	250	500	250	500	250	500	250	500
4a	12	15	10	12	9.8	11	9.2	13	2	4.8	4	6.3
4b	9	12	9.8	12	10	13.1	9	11	2.8	3.9	4.4	5.9
4c	10	13	8.9	14	11	16	10.1	14.1	3.8	4.1	3.9	5.7
4d	9	14	8.8	15	10.5	13.2	9.9	12.2	4.2	5.2	3.4	6.1
4e	10	13	9.9	13	9.5	12.5	10.5	14.3	2.9	5.5	2.8	5.2
4f	16	20	9.8	11	10	12.3	10.5	13.5	3.2	4.5	2.9	5.2
4g	13	18	10	13	9.6	14.1	10.6	13.6	3.3	4.8	3	5.9
4h	10	13	12	15.1	10.1	13	8.9	13.2	2.2	8.2	3.1	5.6
4i	9	14	9.6	13.2	8.9	12.1	9.1	11.6	3.1	4.3	3.8	5.9
4j	10	12	10	12.3	11.1	14	9	12.9	3	4.9	2.1	4.8
4k	12	15	10	13.1	9.3	13.1	11.1	14.4	3.8	5.3	3.9	5.1
4l	9	11	9	14	11.2	14	10.1	14.3	2	5.2	2	4.3
Penicillin	22		21		21		21					
Griseofulvin									20		20	

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