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Synthesis, spectral characterization and antimicrobial activity of 2-(substituted)-2,2-[1,3- dihydro-(3,4-1,2,5-oxadiazolediyl) diaza][5′, 5′-dimethyl-1′, 3′-propanediyl) dioxy] phosphoranes

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Abstract: The cyclic oxadiazolediyl dioxachlorophosphine precursor on subsequent reaction with various alcohols underwent halide displacement to give 2-substituted diaza phospholes. These phospholes on oxidative addition with di hydroxy alcohols form corresponding phosphoranes The antimicrobial activities of these compounds were evaluated and they exhibited significant antimicrobial activity.

Keywords:Spirophosphoranes; dioxaphosphoranes; antimicrobial activity; P(III) to P(V); *N*-chlorodiisopropylamine.

1. Introduction

Considering the recent progress during the last few decades a lot of unexpected structures appeared.[1] Among them, we select molecules with penta co-ordination number at phosphorus for their synthesis. P(V)-six membered heterocycles play central role in the regulations of cell physiology.[2] Several pentacoordinate phosphorus compounds are also good flame retardants.[3] There has been considerable effort aimed at synthesis of five-coordinated phosphorus derivatives containing six-and higher-membered rings.[4-7] A general and facile synthetic approaches are required to obtain analogues for biological and industrial evaluation. In our continuation of our work on the development of new bioactive and flame retardant organophosphorous compounds,[8-10]In this paper we focus mainly on the synthesis of series of substituted dihydro-oxadizolediyldiazapropanediyl-dioxy phosphoranes (**4a-h**)

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containing diaminofurazan, dimethyl propane diol and alkoxy/aryloxy substituents at the spiro phosphors atom (Scheme 1).

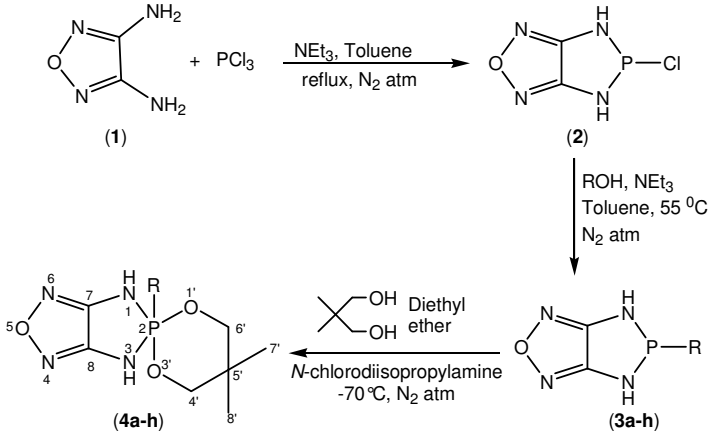
2. Results and Discussion

The synthetic route involves the preparation of title compounds in two steps. These new spirocyclic/bicyclic phosphoranes (**4a-h**) contain a dioxaphosphorinane ring as one cyclic component and a diaza phospholane as the other cyclic component.

The cyclic chlorophosphine precuros (**2**) was prepared by the cyclization of 3,4-diamino-1,2,5-oxadizole with PCl_3 in dry toluene and Et_3N as a base. The chlorophosphine (**2**) underwent halide displacement on reaction with various alcohols in toluene using Et_3N as an acid acceptor and gave 2-substituted diazaphospholes (**3a-h**) with high yield (Scheme 1).

The inclusion of a dioxaphosphorinane ring directly at phosphorus in **3a-h** was accomplished by the oxidative addition[7,11-12] of 2,2-dimethyl-1,3-propanediol in presence of *N*-chlorodiisopropylamine the reaction is highly exothermic. The progress of reaction was monitored by TLC and the structures of the products **4a-h** were confirmed by analytical and spectroscopic techniques.

Characteristic infrared spectral absorption bands[8] for P-O-(C_{ali}) and (P)-O-C_{ali} stretching frequencies of P-O-C_{ali} function are observed in the region 805-902 and 1038-1057 cm^{-1} respectively. Absorption bands for NH and CH_2 stretching frequencies [13-15] are present in the region 3333-3394 and 1430-1485 cm^{-1} respectively.



R		R	
4a.	$-OCH(CH_3)_2$	**4e**.	$-OCH_2CH_2Cl$
4b.	$-OCH_3$	**4f**.	$-OC_6H_5$
4c.	$-OCH_2CH_3$	**4g**.	$-OC_6H_4(p\text{-}CH_3)$
4d.	$-OCH_2C_6H_5$	**4h**.	$-OCH_2C\equiv CH$

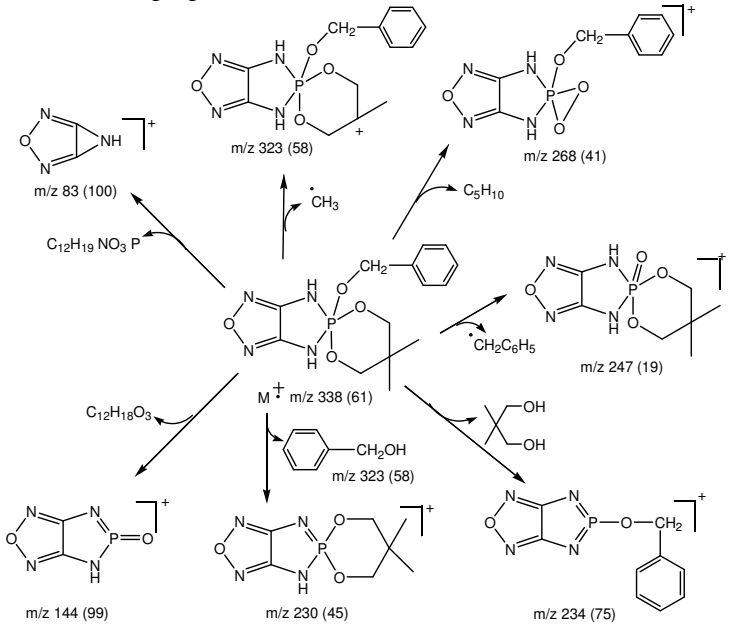
Scheme 1. Spirocyclic/bicyclic phosphoranes (**4a-h)**

Proton NMR spectra exhibited signals for endocyclic NH proton in the region δ 7.23-7.31. The multiplet at δ 3.28-3.47 to 3.84-3.93 is assigned to methylene protons (C4′ and C6′) of 1,3-dioxaphosphorine ring, indicating their non-equivalence and coupling with phosphorus. The singlets at δ 1.11-1.72 and δ 1.22-1.86 are assigned to the protons of equatorial and axial methyl groups respectively.[5,11,15] These NMR data concern rather the diastereotopic methyl groups.

In their ^{13}C NMR spectra the nitrogen bonded C-7 and C-8 of the diazaphosphole ring resonated in the downfield at δ 149.8-151.5. The oxygen bonded C-4′ and C-6′ of dioxaphosphorane ring absorbed in the upfield at δ 77.4-79 respectively. The signals for the tertiary C-5′ appeared at δ 31.4-33.9. The methyl C-7′ and C-8′ of dioxaphosphorane chemical shifts occurred at δ 20.2-22.5 and 21.1-24.6, respectively. The other carbons of the substituent group gave chemical shifts in the expected regions.[5,8,15]

^{31}P NMR chemical shift's[16] of these compounds (**4a-h**) appeared in the range of δ 12.3 to 21.4.

The mass spectral data of the representative compounds (**4a**, **4c** and **4d**) of this group is rationalized in scheme 2 with **4d** as an example. All the compounds exhibited M+ and ions with appropriate *m*/*z* values. Their mass spectral behavior is in good agreement in the formation of phosphoranes, further confirm their proposed structures.



Scheme 2. Mass fragmentation of compound **4d**

3. Conclusion

We synthesized a series of novel phosphoranes in high yields. The advantages are low cost of the starting chemicals, simple experimental procedure and also these compounds exhibited moderate antimicrobial activity.

4. Experimental

Preparation of 2-(substituted)-2,2-[1,3- dihydro-(3,4-1,2,5-oxadiazolediyl) diaza] [5′, 5′ dimethyl-1′, 3′-propanediyl) dioxy] phosphoranes (4a-h): A solution of PCl_3 (1.3 g, 0.01 mole) in 15 mL of dry toluene was added over a period of 30 minutes to an ice cooled and stirred solution of 3,4–diaminofurazan, (1.0 g, 0.01 mole) and triethylamine (2.0 g, 0.02 mole) in 10 mL of dry toluene. After the addition, the temperature of the reaction mixture was slowly raised to rt and was maintained there for 1 h. Stirring was continued for another 3 h at reflux in N_2 atmosphere to afford 2-chlorodiaza-phosphole (**2**). Then the reaction mixture was cooled to rt and then filter of the triethylaminehydrochloride in N_2 atmosphere, then filtrate was transferred into a new reaction flask. To an ice cooled solution of **2** was added dropwise a solution of 2-propanol (0.6 g, 0.01 mol) and Et_3N (1.0 g, 0.01 mol) in 10 mL of dry toluene. After the addition, the reaction mixture was stirred at rt for 1 h and then at 55 ^oC for another 4 h. Reaction progress was monitored using thin layer chromatography. After completion of the reaction, the reaction mixture was slowly cooled to rt, then solid triethylaminehydrochloride was filtered off and the solvent was removed under reduced pressure. The residue was recrystallized from ethanol to obtain **3a**.

To a solution of **3a** (1.8 g, 0.01 mol) and 2,2-dimethyl-1,3-propanediol (1.0 g, 0.01 mol) in diethylether (100 mL) at -70 ^oC was added a solution of *N*-chlorodiisoproplylamine (1.3 g, 0.01 mol) in diethylether (50 mL) with stirring and was continued at the same temperature for 2 h. The mixture was then allowed to warm up and stirred at rt for 2 h under N_2 atmosphere and the solvent was

removed under reduced pressure. The residue was washed with a mixture of diethyl ether-hexane and dried to get pure compound 4a**.** Other members of **4** were prepared employing the same procedure.

2-(Isopropoxy)-2,2-[1,3- dihydro-(3,4-1,2,5-oxadiazolediyl) diaza][5′, 5′-dimethyl-1′, 3′-propanediyl) dioxy] phosphoranes 4a: Yield 85%; m.p. 174 ^{o}C; Anal. Calcd for $C_{10}H_{19}O_4N_4P$: C, 41.37; H, 6.60; N, 19.30. Found: C, 41.28, H, 6.52; N, 19.22; IR (KBr, cm^{-1}): 3335 (N-H), 1485 (CH_2), 810,1050 cm^{-1} (P-O-C_{ali}); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (2H, s, 2 x N-H), 3.68-3.56 (1H, m, $Me_2C\underline{H}O$-), 3.52-3.35 (4H, m, 2 x -CH_2-), 1.86 (3H, s, CH_3-axial), 1.61 (6H, d, *J*=6.8 Hz, CH_3), 1.72 (3H, s, CH_3-equatorial); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.7 (C-7 & C-8), 78.0 (C-6' & C-4'), 69.7 (OCH), 33.6 (C-5'), 26.0 (2 x CH_3), 23.5 C-8'(a), 22.5 C-7'(e); ^{31}P NMR (161 MHz, $CDCl_3$): δ 21.4; GCMS *m/z* (%): 290 (M^+) (259), 275 (56), 274 (15), 248 (31), 230 (37), 212 (16), 186 (43), 180 (32), 170 (25), 162 (18), 144 (62), 127 (100), 104 (25), 100 (23), 99 (34), 83 (92).

2-(Methoxy)-2,2-[1,3- dihydro-(3,4-1,2,5-oxadiazolediyl) diaza][5′, 5′-dimethyl-1′, 3′-propanediyl) dioxy] phosphoranes 4b: Yield 86 %; m.p. 181-182 ^{o}C; Anal. Calcd for $C_8H_{15}O_4N_4P$: C, 36.64; H, 5.72; N, 21.36. Found: C, 36.47, H, 5.52; N, 21.28; IR (KBr, cm^{-1}): 3347 (N-H), 1456 (CH_2), 811,1054 cm^{-1} (P-O-C_{ali}); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (2H, s, 2 x N-H), 3.50-3.39 (4H, m, 2-$C\underline{H}_2$-), 3.46 (3H, s, $OC\underline{H}_3$), 1.23 (3H, s, CH_3-axial), 1.11 (3H, s, CH_3-equatorial); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.2 (C-7 & C-8), 78.5 (C-6 & C-4'), 55.8 (OCH_3), 33.1 (C-5'), 21.1 C-8'(a), 20.6 C-7'(e); ^{31}P NMR (161 MHz, $CDCl_3$): δ 16.2.

2-(Ethoxy)-2,2-[1,3- dihydro-(3,4-1,2,5-oxadiazolediyl) diaza][5′, 5′-dimethyl-1′, 3′-propanediyl) dioxy] phosphoranes 4c: Solid: mp 176-178 ^{o}C; Yield 68%; Anal. Calcd for $C_9H_{17}O_4N_4P$: C, 39.13; H, 6.20; N, 20.28. Found: C, 38.86, H, 6.02; N, 18.76;IR (KBr, cm^{-1}): 3394 (N-H), 1430 (CH_2), 902, 1044 cm^{-1} (P-O-C_{ali}); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (2H, s, 2 x N-H), 4.12-4.09 (2H, m, $CH_3\underline{CH_2}O$), 3.51-3.41 (4H, m, 2 x -CH_2-), 1.43 (3H, s, CH_3-axial), 1.35 (3H, t, *J*= 7.2 Hz $CH_2\underline{CH_3}$), 1.21 (3H, s, CH_3-equatorial); ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.5 (C-7 & C-8), 77.4 (C-6' & C-4'), 62.2 (OCH_2), 33.9 (C-5'), 21.6 C-8'(a), 20.2 C-7'(e), 14.8 (CH_3); ^{31}P NMR (161 MHz, $CDCl_3$): δ 12.3; GCMS *m/z* (%): 276 (24) (M^+), 261 (20), 248 (45), 230 (35), 218 (21), 198 (1), 180 (16), 172 (8), 163 (39), 144 (80), 127 (70), 119 (31), 100 (31), 83(100);

2-(Benzoyloxy)-2,2-[1,3- dihydro-(3,4-1,2,5-oxadiazolediyl) diaza][5′, 5′-dimethyl-1′, 3′-propanediyl) dioxy] phosphoranes 4d: Yield 59%; m.p. 191-193 ^{0}C; Anal. Calcd for $C_{14}H_{19}O_4N_4P$: C, 49.70; H, 5.62; N, 16.56. Found: C, 49.43, H, 5.47; N, 16.49; IR (KBr, cm^{-1}): 3333 (N-H), 1483 (CH_2), 805,1044 cm^{-1} (P-O-C_{ali}); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48-6.85 (5H, m, Ar-H), 7.25 (2H, s, 2 x N-H), 4.42 (2H, s, -CH_2-), 3.93-3.84 (4H, m, 2 x -CH_2-), 1.70 (3H, s, CH_3-axial), 1.58 (3H, s, CH_3-equatorial); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.6 (C-7 & C-8), 135.6 (d, *J*=5.6 Hz, C-2", ipso carbon), 128.6 (C-4" & C-6"), 128.1 (C-5"), 127.5 (C-3" & C-7"), 78.1 (C-6' & C-4'), 65.1 (OCH_2), 31.4 (C-5'), 24.6 C-8'(a), 21.7 C-7'(e); ^{31}P NMR (161 MHz, $CDCl_3$): δ 16.9; GCMS *m/z* (%):338 (61), (M^+) 325 (58), 268 (41), 260 (21), 247 (19), 234 (75), 230 (45), 180 (19), 162 (22), 144 (99), 127 (22), 108 (27), 99 (12) 83 (100).

2-(2-chloro ethoxy)-2,2-[1,3- dihydro-(3,4-1,2,5-oxadiazolediyl) diaza][5′, 5′-dimethyl-1′, 3′-propanediyl) dioxy] phosphoranes 4e: Yield 80%; m.p. 147-149 ^{0}C; Anal. Calcd for $C_9H_{16}O_4N_4PCl$: C, 34.78; H, 5.16; N, 18.03. Found: C, 34.51, H, 5.09; N, 17.96; IR (KBr, cm^{-1}): 3382 (N-H), 1456 (CH_2), 872, 1057 cm^{-1} (P-O-C_{ali}); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (2H, s, 2 x N-H), 4.62-4.59 (2H, m, -$OC\underline{H}_2$-), 4.10 (2H, m, -$C\underline{H}_2Cl$), 3.47-3.28 (4H, m, 2 x -CH_2-), 1.36 (3H, s, CH_3-axial), 1.32 (3H, s, CH_3-equatorial); ^{31}P NMR (161 MHz, $CDCl_3$): δ 19.2.

2-(Phenoxy)-2,2-[1,3- dihydro-(3,4-1,2,5-oxadiazolediyl) diaza][5′, 5′-dimethyl-1′, 3′-propanediyl) dioxy] phosphoranes 4f: Yield 83%; m.p. 186 ^{0}C; Anal. Calcd for $C_{13}H_{17}O_4N_4P$: C, 48.18; H, 5.24; N, 17.27. Found: C, 47.90, H, 5.11; N, 17.21; IR (KBr, cm^{-1}): 3346 (N-H), 1470 (CH_2), 840, 1047cm^{-1} (P-O-C_{ali}); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (2H, s, 2 x N-H), 7.12-6.51 (5H, m, Ar-H), 3.57-3.37 (4H, m, 2 x -CH_2-), 1.30 (3H, s, CH_3-axial), 1.27 (3H, s, CH_3-equatorial); ^{13}C NMR (100 MHz,

$CDCl_3$): δ 151.5 (C-7 & C-8), 149.8 (C-1"), 126.4 (C-2" & 6"),79.0 (C-6' & C-4'), 33.7 (C-5'), 22.8 C-8'(a), 21.4 C-7'(e); ^{31}P NMR (161 MHz, $CDCl_3$): δ 18.6.

2-(4" Methyl phenoxy)-2,2-[1,3- dihydro-(3,4-1,2,5-oxadiazolediyl) diaza][5′, 5′-dimethyl-1′, 3′-propanediyl) dioxy] phosphoranes 4g: Yield 72%; m.p. 162-163 ^{0}C; Anal. Calcd for $C_{14}H_{19}O_4N_4P$: C, 49.70; H, 5.62; N, 16.55. Found: C, 49.48, H, 5.39; N, 16.49; IR (KBr, cm^{-1}): 3357 (N-H), 1468 (CH_2), 836,1038 cm^{-1} (P-O-C_{ali}); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (2H, s, 2 x N-H), 7.18-6.87 (4H, m, Ar-H), 3.64-3.46 (4H, m, 2 x -CH_2-), 2.67 (3H, s, CH_3),1.32 (3H, s, CH_3-axial), 1.25 (3H, s, CH_3-equatorial); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.8 (C-7 & C-8), 149.1 (C-1"), 125.4 (C-2" & C-6"), 129.4 (C-3" & C-5"), 130.6 (C-4"),78.3 (C-6' & C-4'), 32.8 (C-5'), 24.4 C-8'(a), 22.3C-7'(e), 20.1 (CH_3); ^{31}P NMR (161 MHz, $CDCl_3$): δ 20.1.

2-(2-Yne-propoxy)-2,2-[1,3- dihydro-(3,4-1,2,5-oxadiazolediyl) diaza][5′, 5′-dimethyl-1′, 3′-propanediyl) dioxy] phosphoranes 4h: Yield 51%; m.p. 164-166 ^{0}C; Anal. Calcd for $C_{10}H_{15}O_4N_4P$: C, 41.95; H, 5.24; N, 19.57. Found: C, 41.81, H, 5.10; N, 19.51; IR (KBr, cm^{-1}): 3361 (N-H), 1442 (CH_2), 841, 1052 cm^{-1} (P-O-C_{ali}); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 (2H, s, 2 x N-H), 4.10-4.27 (2H, m, ≡C-C$\underline{H_2}$), 3.34-3.52 (4H, m, 2 x -CH_2-), 2.72-2.70, (1H, m, ≡C$\underline{H}$) 1.44 (3H, s, CH_3-axial), 1.32 (3H, s, CH_3-equatorial); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.8 (s) (C-7 & C-8), 72.4 (C-4' & C-6'), 33.7 (C-5'), 40.5 (OCH_2-C), 75.6 ($\underline{C}\equiv CH$), 75.4 ($\underline{C}H\equiv C$), 23.9 C-8'(a), 21.0 C-7'(e); ^{31}P NMR (161 MHz, $CDCl_3$): δ 17.2.

5. Antimicrobial Activity

The Whatman No.1 filter paper disc method.[17, 18] was employed for the *in vitro* study of antibacterial and antifungal effects against *Escherichia coli, Staphylococcus aureus, Aspergillus niger* and *Helminthosporium oryzae*. The inhibitory effects of compounds **4a-h** against these organisms are given in Table 1&2 and Minimum inhibitory concentration (MIC) are given in Table 3.

5.1. Antibacterial Activity

Antibacterial activity of all the title compounds **4a-h** was assayed.[17] against the growth of *Staphylococcus aureus* (gram +Ve) and *Escherichia coli* (gram -Ve) at concentrations (100, 50, 25 ppm) (Table 1). Highlight is that majority of the compounds exhibited high activity against both the bacteria, and the compounds **4c** and **4d** were more effective than that of the standard compound.

Penicillin was tested as a standard reference compound to compare the activity of these compounds.

Table 1. Antibacterial activity of Phosphoranes **(4a-h)**

Compound	Zone of inhibition (%)					
	Escherichia coli			*Staphylococcus aureus*		
	100	**50**	**25**	**100**	**50**	**25**
4a	10	5	3	13	11	9
4b	12	6	4	9	8	--
4c	14	10	9	13	12	8
4d	8	9	8	10	9	7
4e	10	10	8	11	9	5
4f	11	7	6	12	7	8
4g	13	10	8	14	10	7
4h	10	8	7	12	10	7
Penicillin[a]	12	8	--	12	8	--

[a] Standard antibacterial compound

5.2. Antifungal activity

The compounds **4a-h** (Table 2) were screened for their antifungal activity against *Aspergillus niger* and *Helminthosporium oryzae* species along with standard fungicide Griseofulvin. Disc diffusion method.[18] was followed for screening the compounds at three different concentrations (100, 50, 25 ppm).

It is gratifying to observe that all the compounds **4a-h** were exhibited higher antifungal activity when compared with that of reference compound. The highlight is that all the compounds exhibited very high activity against fungi and the compounds **4c** and **4g** were more effective than the standard Griseofulvin.

Table 2. Antifungal activity of Phosphoranes **(4a-h)**

Compound	Zone of inhibition (%)					
	Aspergillus niger			*Helminthosporium oryzae*		
	100	**50**	**25**	**100**	**50**	**25**
4a	9	5	3	13	11	9
4b	10	6	4	9	8	--
4c	14	10	9	13	12	8
4d	13	9	8	10	9	7
4e	13	10	8	11	9	5
4f	9	7	6	12	7	8
4g	12	10	8	14	10	7
4h	10	8	7	12	10	7
Griseofulvin[a]	10	7	--	10	7	--

[a] Standard antifungal compound

Table 3. Minimum inhibitory concentration for **(4a-h)** (MIC)*

Compd.	*Aspergillus niger*	*Helminthosporium Oryzae*	*Escherichia coli*	*Staphylococcus aureus*
4a	3.6	4.0	3.3	3.5
4b	4.0	3.9	4.2	3.8
4c	3.9	5.3	4.1	4.0
4d	4.5	4.6	4.5	5.3
4e	3.2	3.8	3.8	3.0
4f	4.7	4.2	4.0	4.5
4g	3.6	3.5	2.7	3.9
4h	4.6	3.2	3.5	4.2

*μg/mL

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