Electronic supplementary information (ESI)

Synthesis and anticancer cytotoxicity with structural context of an α-hydroxy-phosphonate based compound library derived from substituted benzaldehydes

Zita Rádai[1], Tímea Windt[2], Veronika Nagy[2], András Füredi[2, 3], Nóra Zsuzsa Kiss[1], Ivan Ranđelović[4,5], József Tóvári[4,5] György Keglevich[1], Gergely Szakács[2, 3] Szilárd Tóth[2]

[1]*Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, Budapest, Hungary*

[2]*Research Centre for Natural Sciences, Hungarian Academy of Sciences, Budapest, Hungary*

e-mail: toth.szilard.enzim@ttk.mta.hu; szakacs.gergely@ttk.mta.hu

[3]*Institute of Cancer Research, Medical University Vienna, Vienna, Austria*

[4]*National Institute of Oncology, Department of Experimental Pharmacology, Budapest, Hungary*

[5]*Kineto Lab ltd., Budapest, Hungary*

Table S1 (A). Comparison of δ_P and MS value of the analogues **1**, **2** and **3** that were synthesized and published earlier.

Compound	δ_P	δ_P lit.	MS
1a	23.8	24.3 [1]	$[M + H]^+ = 217.1$
1b	23.4	–	$[M + H]^+ = 251.0$
1c	23.0	–	$[M + H]^+ = 251.0$
1d	23.2	22.1 [2]	$[M + H]^+ = 251.0$
1e	22.3	22.2 [3]	$[M + H]^+ = 262.0$
1f	22.3	21.8 [4]	$[M + H]^+ = 262.0$
1g	20.7	23.6 [5]	$[M + H]^+ = 231.1$
1h	24.1	23.8 [4]	$[M + H]^+ = 231.1$
1i	24.5	24.9 [6]	$[M + H]^+ = 247.1$
1j	23.8	–	$[M + H]^+ = 247.1$
1l	23.3	26.0 [7]	$[M + H]^+ = 235.1$
2a	21.7	19.4 [8]	$[M + H]^+ = 245.1$
2b	21.2	18.8 [9]	$[M + H]^+ = 279.1$
2c	20.8	–	$[M + H]^+ = 279.1$
2d	21.0	18.7 [8]	$[M + H]^+ = 279.0$
2e	20.1	19.3 [9]	$[M + H]^+ = 290.1$
2f	20.0	18.4 [7]	$[M + H]^+ = 290.1$
3a	22.1	22.4 [10]	$[M + H]^+ = 369.1256$
3b	21.9	21.9 [11]	$[M + H]^+ = 403.0869$
3c	22.3	22.3 [11]	$[M + H]^+ = 403.0881$
3d	21.7	22.4 [10]	$[M + H]^+ = 403.0869$
3e	21.1	21.1 [11]	$[M + H]^+ = 414.1114$
3f	20.8	20.6 [10]	$[M + H]^+ = 414.1105$
3g	22.3	22.3 [11]	$[M + H]^+ = 383.1409$
3h	22.4	22.4 [10]	$[M + H]^+ = 383.1392$
3i	22.9	22.9 [10]	$[M + H]^+ = 399.1378$

Table S1 (B). Comparison of δ_P and MS value of the analogues **4**, **5**, **6**, **7**, **8** and **9** that were synthesized and published earlier.

Compound	δ_P	δ_P lit.	MS
4a	26.2	26.0 [7]	$[M + H]^+$ = 231.1
4f	24.8	–	$[M + H]^+$ = 276.1
4k	25.4	25.6 [12]	$[M + H]^+$ = 249.1
4l	25.9	26.0 [7]	$[M + H]^+$ = 249.1
4m	25.5	26.3 [12]	$[M + H]^+$ = 309.0
4n	25.5	25.3 [3]	$[M + H]^+$ = 309.0
5f	22.5	–	$[M + H]^+$ = 304.1
6a	19.4	21.0 [13]	$[2M + H]^+$ = 377.0545
6b	18.5	16.3 [14]	–
6c	18.2	20.1 [14]	–
6d	18.6	18.9 [14]	$[2M – H]^–$ = 442.9659
6g	19.8	19.8 [11]	–
6h	18.8	18.8 [11]	$[2M – H]^–$ = 403.0751
6i	20.2	20.2 [11]	$[2M – H]^–$ = 435.0632
6o	18.4	18.4 [11]	–
7a	19.6, 35.0	19.6, 35.0 [15]	$[M + H]^+$ = 417.10146
7d	19.2, 35.3	19.2, 35.3 [15]	$[M + H]^+$ = 451.06232
7f	18.3, 36.1	18.3, 36.1 [15]	$[M + H]^+$ = 462.08590
7h	19.8, 34.9	19.8, 34.9 [15]	$[M + H]^+$ = 431.11669
8a	19.5 & 19.6, 78.6 &78.7	19.5 & 19.6, 78.6 &78.7 [15]	$[M + H]^+$ = 331.08555
8d	16.8 & 16.9, 76.9 & 77.0	16.8 & 16.9, 76.9 & 77.0 [15]	$[M + H]^+$ = 365.04651
8f	18.39 & 18.43, 80.3 & 80.4	18.39 & 18.43, 80.3 & 80.4 [15]	$[M + H]^+$ = 376.07061
8h	19.9 & 20.1, 78.7 & 78.8	19.9 & 20.1, 78.7 & 78.8 [15]	$[M + H]^+$ = 345.10145
9a	19.9, 72.7	19.9, 72.7 [15]	$[M + H]^+$ = 345.10125
9d	21.5, 75.3	21.5, 75.3 [15]	$[M + H]^+$ = 379.06235
9f	16.1, 72.1	16.1, 72.1 [15]	$[M + H]^+$ = 390.08662
9h	20.1, 72.5	20.1, 72.5 [15]	$[M + H]^+$ = 359.11697

References

1. B. J. Rowe and C. D. Spilling, *Tetrahedron: Asymmetry*, 2001, **12**, 1701-1708.
2. G. Keglevich, V. Róza Tóth and L. Drahos, 2011, **22**, 15-17.
3. H. R. Hudson, R. O. Yusuf and R. W. Matthews, *Phosphorus, Sulfur, and Silicon and the Related Elements*, 2008, **183**, 1527-1540.
4. S. R. Davies, M. C. Mitchell, C. P. Cain, P. G. Devitt, R. J. Taylor and T. P. Kee, *Journal of Organometallic Chemistry*, 1998, **550**, 29-57.
5. Q. Li, C.-J. Hou, Y.-J. Liu, R.-F. Yang and X.-P. Hu, *Tetrahedron: Asymmetry*, 2015, **26**, 617-622.
6. G. Consiglio, S. Failla and P. Finocchiaro, *Phosphorus, Sulfur, and Silicon and the Related Elements*, 1996, **117**, 37-54.
7. O. Seven, S. Polat-Cakir, M. S. Hossain, M. Emrullahoglu and A. S. Demir, *Tetrahedron*, 2011, **67**, 3464-3469.
8. A. R. Sardarian and B. Kaboudin, *Synthetic Communications*, 1997, **27**, 543-551.
9. R. M. N. Kalla, Y. Zhang and I. Kim, *New Journal of Chemistry*, 2017, **41**, 5373-5379.
10. V. D. Pawar, S. Bettigeri, S. S. Weng, J. Q. Kao and C. T. Chen, *J Am Chem Soc*, 2006, **128**, 6308-6309.
11. Z. Rádai, P. Szeles, N. Z. Kiss, L. Hegedűs, T. Windt, V. Nagy and G. Keglevich, *Heteroatom Chemistry*, 2018, **29**, e21436.
12. C. Wang, J. Zhou, X. Lv, J. Wen and H. He, *Phosphorus, Sulfur, and Silicon and the Related Elements*, 2013, **188**, 1334-1339.
13. N. S. Tulsi, A. M. Downey and C. W. Cairo, *Bioorg Med Chem*, 2010, **18**, 8679-8686.
14. G. Forlani, A. Occhipinti, L. Berlicki, G. Dziedziola, A. Wieczorek and P. Kafarski, *J Agric Food Chem*, 2008, **56**, 3193-3199.
15. Z. Rádai, V. Hodula, N. Z. Kiss, J. Kóti and G. Keglevich, *Mendeleev Commun*, 2019, **29**, 153-154.

Table S2 (A). Growth inhibition (GI) of Mes-Sa mCh and Mes-Sa/Dx5 mCh cell lines at 20 µM and at 200 µM concentrations of compounds **1**, **2**, **3**, **4** and **5**. 0 refers to no GI, while 100 refers to complete GI. Results of compounds **3** against Mes-Sa mCh were already published in a previous article.[11]

	GI at 20 µM		GI at 200 µM	
	Mes-Sa mCh	Mes-Sa/Dx5 mCh	Mes-Sa mCh	Mes-Sa/Dx5 mCh
1a	1	-3	-3	9
1b	-4	-7	-1	0
1c	-5	-13	5	8
1d	-9	14	2	10
1e	-1	-13	3	11
1f	-2	13	-3	10
1g	-4	7	7	8
1h	-9	-8	8	-2
1i	-39	-5	8	6
1j	-6	7	12	9
1l	-7	-7	11	3
2a	-30	-11	1	-4
2b	-16	-15	8	13
2c	-3	2	-5	14
2d	-16	-8	14	7
2e	-16	-12	12	8
2f	-10	-6	13	6
3a	-18	99	3	94
3b	14	99	15	97
3c	-6	99	16	97
3d	15	37	17	66
3e	30	98	30	98
3f	26	100	14	96
3g	27	99	12	95
3h	22	49	16	87
3i	23	101	16	96
4a	-4	4	-6	-5
4f	-32	5	-7	51
4k	-28	-3	7	16
4l	-19	-17	1	-8
4m	-31	-19	3	-2
4n	-35	-23	-18	-1
5f	-14	-3	-16	48

Table S2 (B). Growth inhibition (GI) of Mes-Sa mCh and Mes-Sa/Dx5 mCh cell lines at 20 µM and at 200 µM concentrations of compounds **6**, **7**, **8**, **9** and **10**. 0 refers to no GI, while 100 refers to complete GI. Results of compounds **6** against Mes-Sa mCh were already published in a previous article.[11]

	GI at 20 µM		GI at 200 µM	
	Mes-Sa mCh	Mes-Sa/Dx5 mCh	Mes-Sa mCh	Mes-Sa/Dx5 mCh
6a	33	33	0	2
6b	22	26	15	6
6c	27	31	13	15
6d	0	14	-12	11
6g	-3	-5	7	10
6h	14	6	28	28
6i	1	6	-11	4
6o	2	-3	5	-11
7a	13	70	11	92
7d	4	62	10	88
7e	6	57	1	64
7f	18	38	12	61
7h	20	96	28	97
8a	9	11	3	7
8d	9	28	-3	17
8f	-2	21	-6	-4
8h	11	14	-3	13
9a	-16	3	-4	0
9d	4	24	4	24
9f	6	31	-7	-1
9h	-2	8	6	18
10a	82	96	90	93
10c	97	98	94	95

Table S3 (A). Reaction time and yield of the products α-hydroxyphosphonic acids **6.**

Starting **3**	Reaction time (min)	Product	Yield (%)
3a	15	**6a**	80
3b	10	**6b**	85
3c	5	**6c**	76
3d	7	**6d**	88
3f	150	**6o**	50
3g	9	**6g**	77
3h	9	**6h**	90
3i	5	**6i**	72

Table S3 (B). Reaction time and yield of the products α-hydroxyphosphonates **1**, **2** and **3.** *20 mol% (300 μL instead of 150 μL) of triethylamine was used.

Product	Reaction time (min)	Yield (%)
1a	10	95
1b	10	93
1c	10	93
1d	10	90
1e	5	95
1f	5	95
1g	30*	92
1h	30*	89
1i	90	68
1j	60*	98
1l	10	96
2a	60	78
2b	60	80
2c	150	98
2d	70	79
2e	60	89
2f	45	88
3a	30	95
3b	30	93
3c	30	88
3d	30	95
3e	30	91
3f	30	99
3g	330	88
3h	330	94
3i	390	96

Table S3 (C). Reaction time and yield of the products α-hydroxyphosphonates **4** and **5.**

Product	Reaction time (h)	Yield (%)
4a	7	48
4f	2	82
4k	3	56
4l	4	38
4m	4	89
4n	3	72
5f	7	65

Table S3 (D). Reaction time and yield of the products α-phosphinoyloxiphosphonates **7**, **8** and **9** (values for **7e**, **10a** and **10c** are shown in the article).

Product	Reaction time (h)	Yield (%)
7a	48	57
7d	48	61
7f	48	70
7h	48	49
8a	24	59
8d	24	54
8f	24	72
8h	24	46
9a	24	59
9d	24	51
9f	24	80
9h	24	50