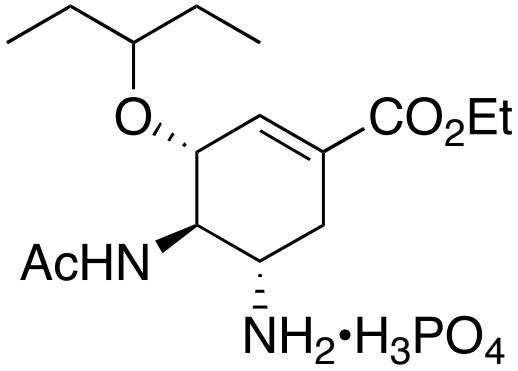
Synthèses du Tamiflu – Analyse des performances métriques de chimie verte

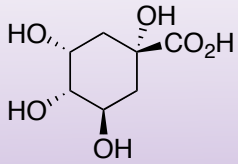
Oseltamivir Phosphate
Tamiflu™

GS-4104-02
RO0640796-002

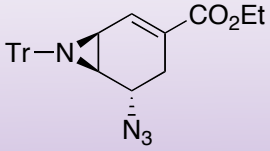
$C_{16}H_{31}N_2O_8P$
MW = 410 g

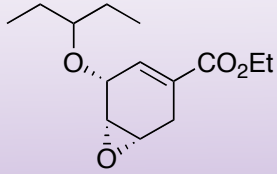


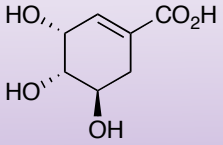
Précurseurs et intermédiaires clés :



acide (–)-quinique

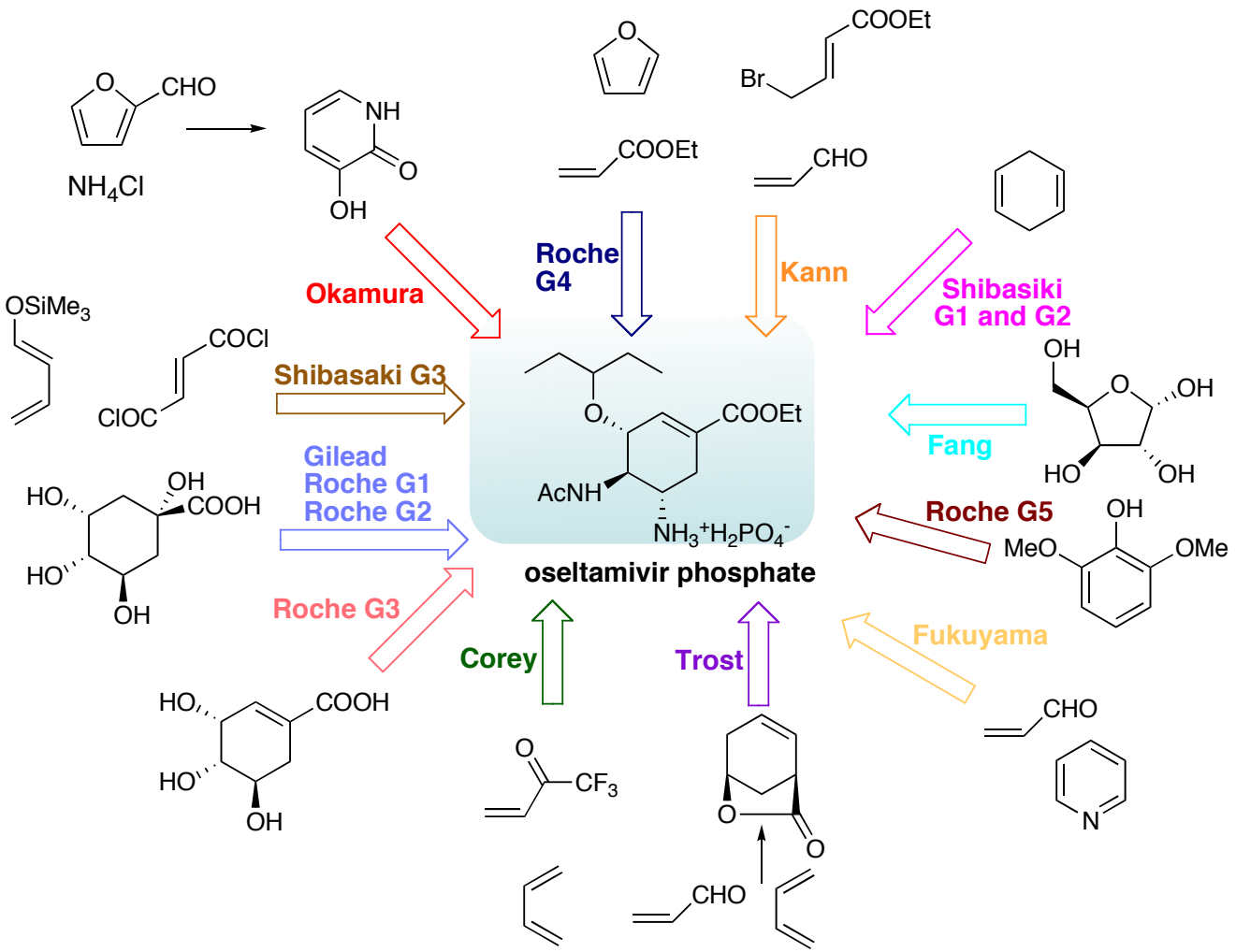






acide (-)-shiquimique

Analyse des performances synthétiques Tamiflu



"Global Green Chemistry Metrics Analysis Algorithm and Spreadsheets: Evaluation of the Material Efficiency Performances of Synthesis Plans for Oseltamivir Phosphate (Tamiflu) as a Test Case", Andraos, J., *Org. Proc. Res. Dev.* **2009**, *13*, 161–185

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Analyse des performances synthétiques (Tamiflu)

- Aspects métriques

$$E_{\text{total}} = E_{\text{byproducts\&unreactedreagents}} + E_{\text{excessreagents}} + E_{\text{auxiliaries}}$$

$$E_{\text{byproducts\&unreacted reagents}} = E_{\text{kernel}} = \frac{1}{p_n}\sum_j \left(\frac{1}{\prod_k^{n\to j}\varepsilon_k}\right)\left(\frac{p_j}{(\text{AE})_j}\right)[1-\varepsilon_j(\text{AE})_j]$$

$$E_{\text{excessreagents}} = \frac{1}{p_n}\sum_j \left(\frac{1}{\prod_k^{n\to j}\varepsilon_k}\right)\left(\frac{p_j}{(\text{AE})_j}\right)[(\text{SF})_j - 1]$$

$$E_{\text{auxiliaries}} = \frac{1}{p_n}\sum_j \left(\frac{1}{\prod_k^{n\to j}\varepsilon_k}\right)\left(\frac{c_j + s_j + \omega_j}{x_j^*}\right)$$

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Analyse des performances synthétiques (Tamiflu)

plan	year	type	N^a	M^b	I^c	$\mu_1{}^d$	β^e	δ^f	$f(\text{sac})^g$	B/M^h	HI[i]	% overall yield	% AE	% Kernel RME	kernel mass of waste (kg)[j]
Roche (shikimic acid route - G3)	1999, 2004	linear	13	13	19	−102.68	0.861	0.345	**0.457**	0.77	+0.14	**39.0**	21.0	**11.5**	**3.1**
Roche (quinic acid route - G2)	1999, 2004	linear	14	14	20	−93.57	0.868	0.338	0.467	0.71	+0.13	21.9	20.3	9.0	4.2
Trost (short)	2008	linear	**9**	**9**	**17**	−35.40	0.865	0.397	0.630	1	−0.2	29.9	16.1	5.6	6.9
Corey	2006	linear	11	11	**17**	−153.68	0.843	0.361	0.743	0.91	−3	22.4	17.2	5.5	7.2
Roche (desymmetrization route - G5)	2000	linear	11	11	24	−110.48	0.779	**0.440**	0.677	**1.36**	+1	25.6	13.8	5.3	7.3
Trost (long)	2008	linear	12	12	21	−99.92	0.892	0.397	0.690	0.83	−1.54	16.2	13.4	4.0	9.8
Roche (quinic acid route - G1)	2001	linear	12	12	21	−131.23	0.862	0.378	0.625	0.75	+0.15	7.6	18.5	3.2	12.5
Fang	2007	convergent	17	18	35	**−167.02**	0.950	0.379	0.671	0.67	+1.44	13.4	12.0	3.1	12.7
Gilead	1998	linear	12	12	21	−135.85	0.867	0.377	0.607	0.83	+0.39	6.3	20.5	2.7	15.0
Fukuyama	2007	linear	13	13	22	−133.48	0.875	0.369	0.638	0.85	−2.64	5.5	15.9	2.4	16.4
Roche (Diels−Alder route - G4)	2000	linear	**9**	**9**	17	−142.56	**0.756**	0.432	0.505	**1.11**	−0.5	1.1	**23.9**	1.5	24.4
Okamura-Corey	2008	linear	13	13	25	−124.76	0.893	0.386	0.754	0.69	−0.43	2.6	16.8	1.3	32.0
Kann	2007	linear	15	15	25	−61.26	0.880	0.363	0.788	0.60	−0.56	3.4	11.8	0.9	47.4
Shibasaki G2	2007	linear	16	16	32	**−163.86**	0.914	0.385	0.837	0.69	−0.71	4.5	10.0	0.8	47.9
Shibasaki G3	2007	linear	11	11	23	**−167.26**	0.880	0.406	0.481	**1.27**	−0.33	1.4	16.1	0.6	73.6
Shibasaki G1	2006	linear	15	15	34	−132.10	0.919	0.403	0.766	0.80	−1.19	1.4	9.6	0.3	150.3

Basé sur 1 mol de phosphate de oseltamivir obtenu (410 g)

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Analyse des performances synthétiques (Tamiflu)

plan	*E*-kernel	*E*-excess	*E*-auxiliaries	*E*-total	total mass of waste (kg)[a]
Roche (shikimic acid route - G3)	**7.7**	**24.6**	**198.6**	**230.9**	**94.7**
Roche (quinic acid route - G2)	10.1	30.0	267.7	307.9	126.2
Roche (quinic acid route - G1)	30.6	71.1	755.5	857.2	351.4
Roche (desymmetrization route - G5)	17.8	68.4	847.4	933.6	382.8
Gilead	36.7	91.5	808.6	936.7	384.0
Fang	31.0	274.8	>2275.1	>2580.9	>1058
Trost (short)[b]	16.8	141.5	>2527.1	>2685.4	>1101
Trost (long)[b]	23.8	144.5	>2690.5	>2858.7	>1172
Corey[c]	17.5	208.8	>3056.5	>3282.9	>1346
Fukuyama[d]	40.0	163.4	>3843.0	>4046.5	>1659
Roche (Diels−Alder route - G4)	66.8	181.2	>4855.6	>5103.5	>2092
Kann	115.5	285.9	>13238.0	>13639.5	>5592
Shibasaki G1[e]	366.6	3772.8	>12055.0	>16194.4	>6640
Shibasaki G2[e]	116.8	1279.9	>18817.8	>20214.5	>8288
Okamura-Corey	78.0	439.8	>21926	>22444	>9202
Shibasaki G3	179.5	1554.1	>24805.8	>26539.4	>10881

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Synthèse du Tamiflu par Roche (voie G2)