Supplementary Material

POCl3 chlorination of 4-quinazolones

Euan A. Arnott, Lai C. Chan*, Brian G. Cox, Brian Meyrick, and Andy Phillips

Kinetic Modelling

The overall reactions and the equilibrium condition between **(*O,O*)** and **(*N,O*)**] are given by eq 3, 4, 7-9 from the main text.

$$K_e = [(\boldsymbol{O,O})]/[(\boldsymbol{N,O})] = 2.8_1 \quad (3)$$

$$(\boldsymbol{O}) + Cl^- \xrightarrow{k_1} \mathbf{QCl} + (Cl)_2P(O)O^- \quad (4)$$

$$(\boldsymbol{O,O})/(\boldsymbol{N,O}) + Cl^- \xrightarrow[POCl_3]{k_2} \mathbf{QCl} + (\boldsymbol{O}) + (Cl)_2P(O)O^- \quad (7)$$

$$(\boldsymbol{O,O})/(\boldsymbol{N,O}) + (Cl)_2P(O)O^- \xrightarrow[POCl_3]{k_3} \mathbf{2}(\boldsymbol{O}) + (Cl)_2P(O)O^- \quad (8)$$

$$(\boldsymbol{N,O,O}) + Cl^-/(Cl)_2P(O)O^- \xrightarrow[POCl_3]{k_4} \mathbf{QCl} + (\boldsymbol{O,O})/(\boldsymbol{N,O}) + (\boldsymbol{O}) + (Cl)_2P(O)O^- \quad (9)$$

We may write the following rate terms.

$r1 = k_1[(\boldsymbol{O})][Cl^-]$

$r2 = k_2[(\boldsymbol{O,O})][Cl^-]$

$r3 = k_3[(\boldsymbol{O,O})][Cl_2P(O)O^-]$

$r4 = k_2[(\boldsymbol{N,O})][Cl^-]$

$r5 = k_3[(\boldsymbol{N,O})][Cl_2P(O)O^-]$

$r6 = k_4[(\boldsymbol{N,O,O})]([Cl^-] + [Cl_2P(O)O^-])$

Hence, we obtain the kinetic equations for the various species.

$d[(\boldsymbol{O})]/dt = -r1 + r2 + 2*r3 + r4 + 2*r5 + r6*[Cl_2P(O)O^-]/([Cl^-] + [Cl_2P(O)O^-])$

$d[(\boldsymbol{O,O})]/dt = -(r2 + r3) + r6*K_e/(1 + K_e)$

$d[(\boldsymbol{N,O})]/dt = -(r4 + 5r) + r6/(1 + K_e)$

$d[(\boldsymbol{N,O,O})]/dt = -r6$

$d[\mathbf{QCl}]/dt = r1 + r2 + r4 + r6*[Cl^-]/([Cl^-] + [Cl_2P(O)O^-])$

$d[Cl_2P(O)O^-]/dt = r1 + r2 + r4 + r6*[Cl^-]/([Cl^-] + [Cl_2P(O)O^-])$

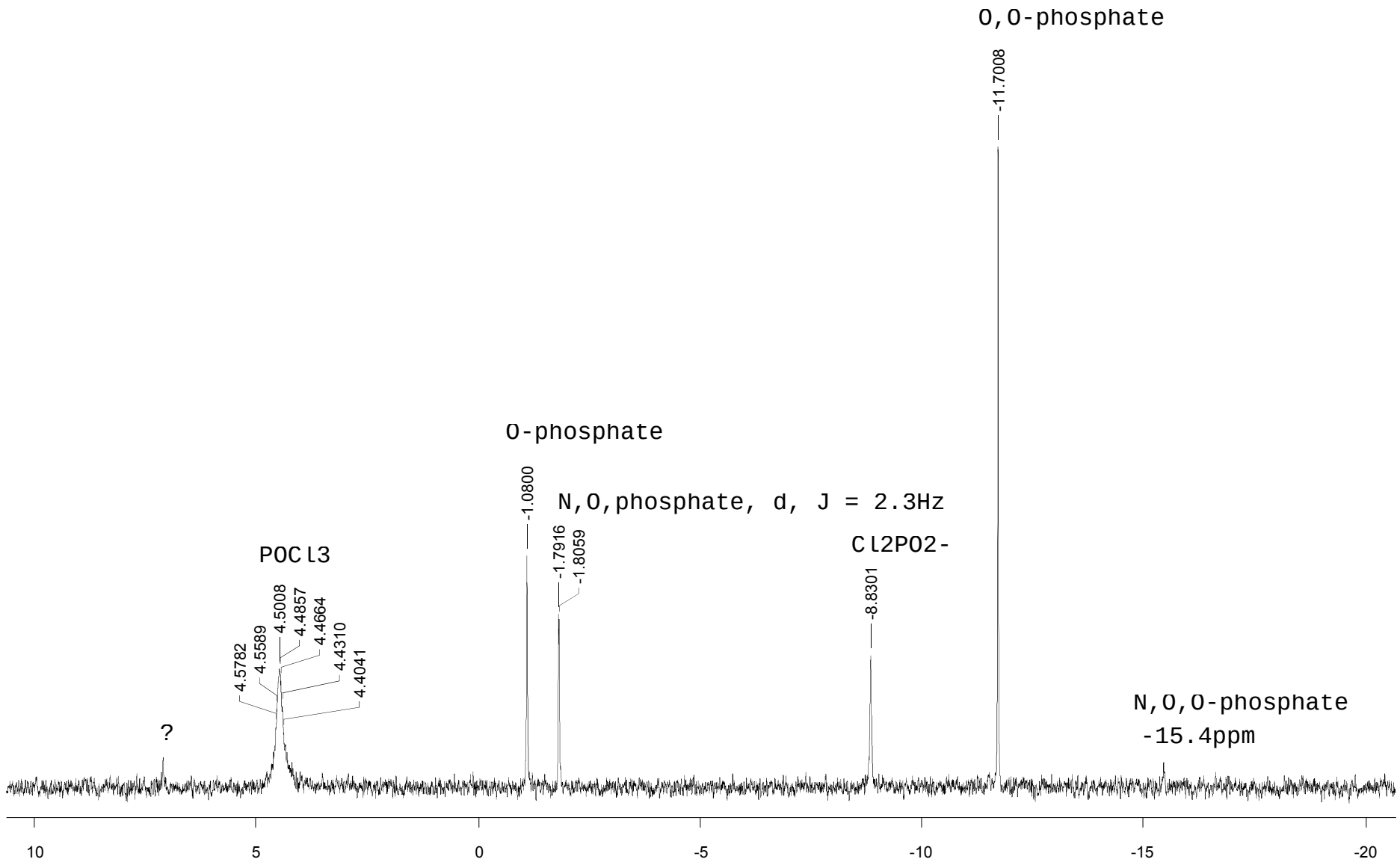
$d[POCl_3]/dt = -(r2 + r3 + r4 + r5 + r6)$

$d[Cl^-]/dt = -(r1 + r2 + r4 + r6*[Cl^-]/([Cl^-] + [Cl_2P(O)O^-]))$

In addition to the above reactions, there is a slow conversion of $Cl_2P(O)O^-$ anion to the corresponding pyrophosphate (eq 2, main text): approximately 1.5 % of $Cl_2P(O)O^-$ was converted to the pyrophosphate after 8 hr, and 4% after 20 hr. This had almost no measurable effect on the reaction profiles during the bulk of the reaction (~ 90% of product formation), but it resulted in increased chloride levels towards the end of the reaction, leading to an increased rate of consumption of **(*O*)** and **(*O,O*)/(*N,O*)**, and an increased rate of product formation. This correction term was allowed for empirically by fitting the rate of pyro formation to a polynomial, $[pyro] = at + bt^2 + ct^3$, and hence, $d[pyro]/dt = d[Cl^-]/dt = -1/2d[Cl_2P(O)O^-]/dt = a + bt + ct^2$.

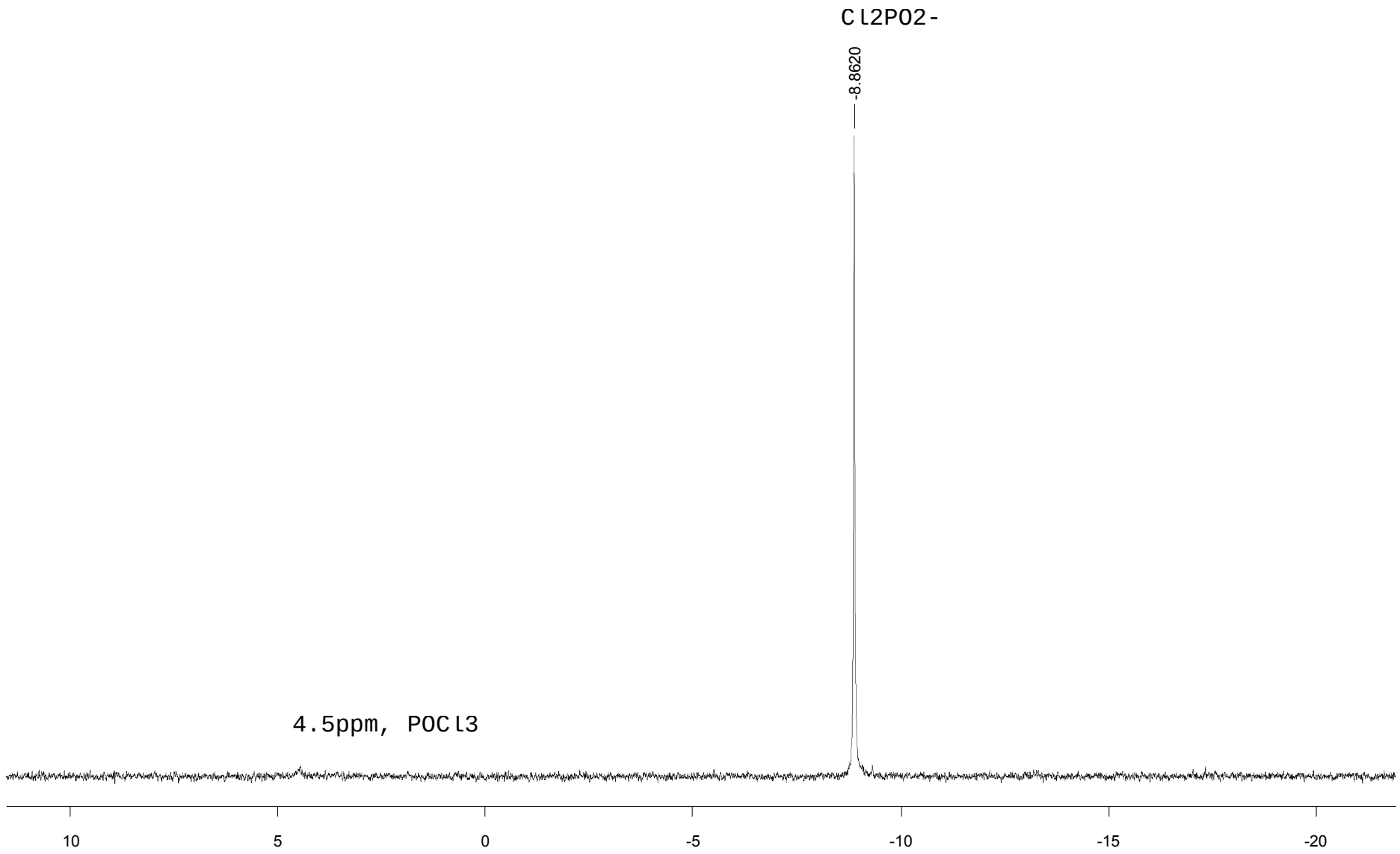
The reaction profiles, derived from the NMR measurements and shown in Figure 4 and 5, were fitted to the above equations using Micromath Scientist, to give the results listed in Table 2 and illustrated in Figure 4 and 5.

Typical 31P NMR_5-Fluoroquinazolone with POCl3 at RT 1h 15mins



JView Version 1.00 - for C&M see notebook P5676 /NMR/pdd/nmr/050308021/12/pdata/1/
Ben McKeever, 01-kbvh100-36A, 1ml 0.1ml d3MeCN 2 drops PhF
Printed by m235797 on Wed Nov 17 12:37:40 GMT 2010. nucleus: 31P, freq: 161.98 MHz, solvent: CD3CN, temperature:300K

Typical 31P NMR_5-Fluoroquinazolone with POCl3 held at 80°C for 1h



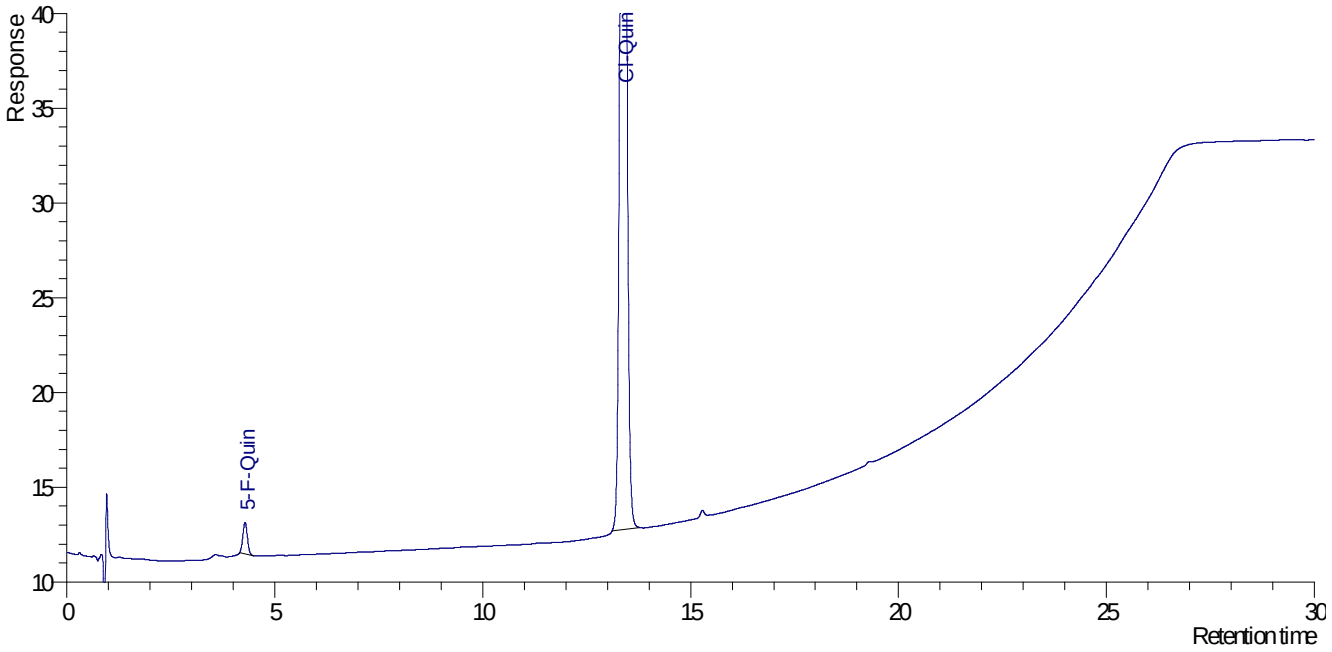
JView Version 1.00 - for C&M see notebook P5676 /NMR/pdd/nmr/050309005/12/pdata/1/
Ben McKeever, 01-kbvh100-36D, 1ml 0.1ml d3-MeCN 2drops PhF
Printed by m235797 on Wed Nov 17 12:48:14 GMT 2010. nucleus: 31P, freq: 161.98 MHz, solvent: CD3CN, temperature:300K

Area Percent Report

Workbook:	01_kkkp153_07, 10, 1	**Instrument:**	PC_051
Sample:	01-kkkp153-07G2	**Sample Type**	Sample
Project:	PC_ErbB2	**Acquired:**	06/01/2005 17:58:26

Typical HPLC chromatogram for 4-Chloro-5-fluoroquinazoline

After 90min at 87-88degC [amber solution] (1 drop / 10ml stirred diluent)



Peak	RT (mins)	Rel RT	Height	Area	Area%
5-F-Quin	4.29	0.32	1.671	12.719	1.754
Cl-Quin	13.38	1.00	74.807	712.229	98.246

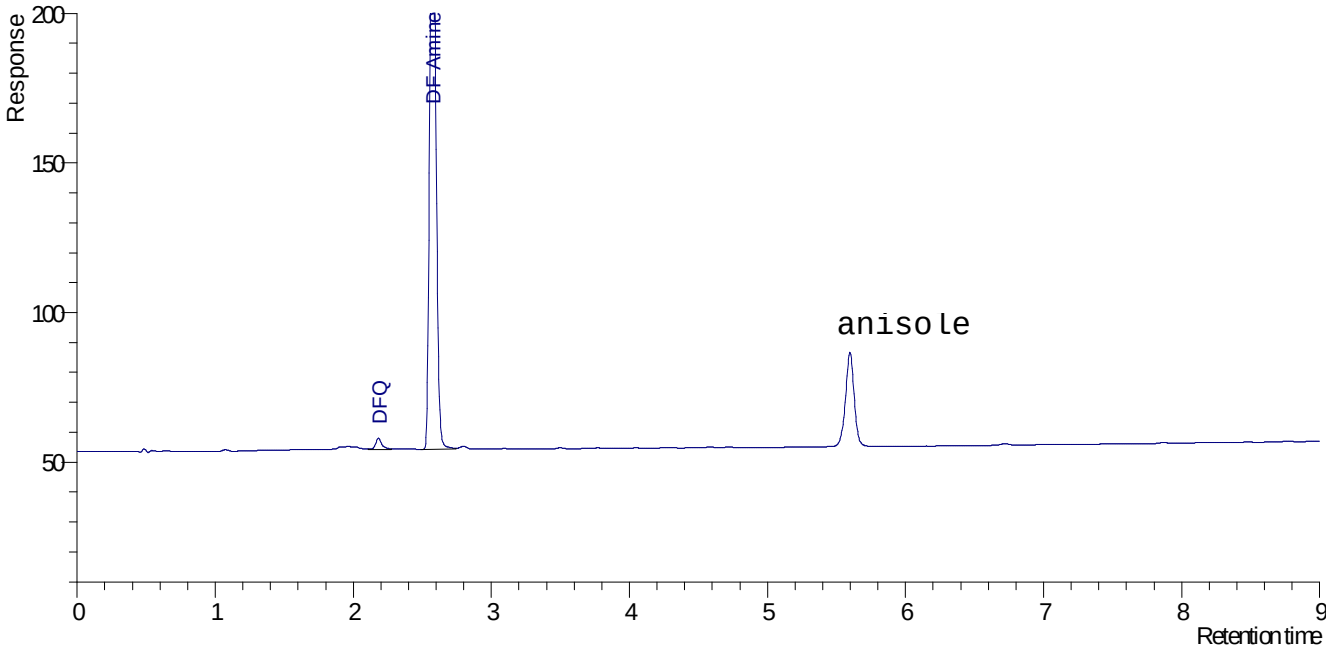
PDF created with pdfFactory trial version www.pdffactory.com

Area Percent Report

Workbook:	02-kmsb719-021, 2, 1	**Instrument:**	PC_061
Sample:	EOR 02-kmsb719-021A	**Sample Type**	Sample
Project:	PC_AZD0530	**Acquired:**	10/05/2007 09:36:46

Typical HPLC chromatogram for 4-Chloro-5,7-difluoroquinazoline quenched with pyrrolidine

EOR Check after 2.5hrs at 95C



Peak	RT (mins)	Rel RT	Height	Area	Area%
DFQ	2.18	0.00	3.778	12.159	1.836
DF Amine	2.57	0.00	218.822	650.071	98.164

PDF created with pdfFactory trial version www.pdffactory.com