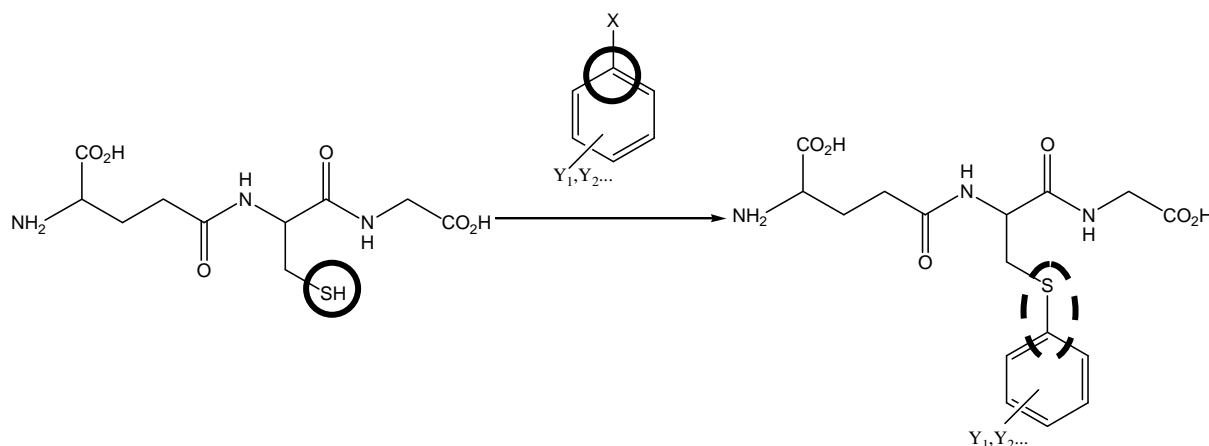


Year 2 - *In Chemico* Test Results

In Year 2 a series of compounds considered to be reactive through a substitution nucleophilic aromatic (S_NAr) reaction were tested. S_NAr is one of the major organic chemistry reaction mechanisms. It is considered to be one of the most important mechanisms for toxicological endpoints such as skin sensitisation and excess (elevated) acute toxicity. The general reaction for S_NAr reaction is:



In the reaction above the nucleophile group (SH in the solid circle on the GSH molecule on the left) is able to react with the electrophilic site of the reactive molecule (carbon in the solid circle on the molecule above the arrow). This reaction forms a strong covalent bond (shown by the dashed circle). The reaction requires, in the reactive molecule, two or more activating groups (Y) in ortho or para positions to the leaving group X.

Much is known about the *in chemico* test results for compounds that act by S_NAr reaction directly i.e. not involving transformation of the chemical by enzymatic action or oxidation in the air – the reader is referred to Schultz et al (2007).

The compounds tested in Year 2 of this project are thought to require non-enzymatic activation through an abiotic mechanism with the possibility of some metabolic activation e.g. by peroxidases. Such abiotic mechanisms are currently undefined but, for instance, include oxidation in the air.

The RC50 of reactive compounds and other results (i.e. non-reactive) are listed below. Compounds may be tested up to their saturation (in the test solution) – hence some compounds are noted as being non-reactive at saturation.

Chemical	RC50 (mM)
Nitrobenzene	not reactive
1,2-Dinitrobenzene	not reactive
1,3-Dinitrobenzene	not reactive
1,4-Dinitrobenzene	not reactive
4-Nitrobenzotrile	not reactive at 100mM
4-Nitrobenzaldehyde	not reactive at saturation
Fluorobenzene	not reactive
Chlorobenzene	not reactive
Bromobenzene	not reactive
1,2-Difluorobenzene	not reactive
1,3-Difluorobenzene	not reactive
1,4-Difluorobenzene	not reactive
1,2,3-Trifluorobenzene	not reactive
Pentafluorobenzene	not reactive
1-Fluoro-2-nitrobenzene	not reactive
1-Fluoro-3-nitrobenzene	not reactive
1-Fluoro-4-nitrobenzene	not reactive
2,4-Difluoro-1-nitrobenzene	not reactive
2,5-Difluoro-1-nitrobenzene	not reactive
1,2,3-Trifluoro-4-nitrobenzene	0.80
2,4,5-Trifluoro-1-nitrobenzene	not reactive
2,4,6-Trifluoro-1-nitrobenzene	not reactive
3,4,5-Trifluoro-1-nitrobenzene	0.9
2,3,4,5-Tetrafluoro-1-nitrobenzene	0.2
2,3,4,6-Tetrafluoro-1-nitrobenzene	0.5
1-Fluoro-2,4-dinitrobenzene	0.06
1-Chloro-2,4-dinitrobenzene	1.0
1-Bromo-2,4-dinitrobenzene	1.0
1-Iodo-2,4-dinitrobenzene	not reactive
4-Chloro-3,5-dinitro-1-benzotrifluoride	0.10
4-Chloro-3,5-dinitro-1-benzonitrile	0.06
1,5-Difluoro-2,4-dinitrobenzene	0.04
Pentafluoronitrobenzene	0.10
Pentafluorobenzaldehyde	0.5
Pentafluorobenzonitrile	0.4
Pentafluorobenzophenone	not reactive at saturation
Pentafluoroacetophenone	not reactive at saturation
Pentafluorobenzamide	not reactive at 5mM
Pentafluorophenylacetoneitrile	not reactive at saturation
Pentafluoroaniline	not reactive at saturation
Pentafluorobenzyl alcohol	not reactive at saturation
2,3,4,5-Tetrafluorobenzaldehyde	1.3
2,3,5,6-Tetrafluorobenzaldehyde	2.7
2,3,4-Trifluorobenzaldehyde	not reactive at 4mM
3,4,5-Trifluorobenzaldehyde	not reactive at 4mM
2,5-Difluorobenzaldehyde	not reactive at 15mM
5-Fluoro-2-nitrobenzaldehyde	not reactive at 5mM
2-Fluoro-5-nitrobenzaldehyde	2.5
2-Fluoro-5-nitrobenzotrile	1.2
2-Fluoro-5-nitrobenzotrifluoride	not reactive at saturation
4-Fluoro-3-nitrobenzaldehyde	0.2

4-Chloro-3-nitrobenzaldehyde	4.0
4-Chloro-3-nitrobenzotrifluoride	not reactive at saturation
4-Chloro-3-nitrobenzotrifluoride	not reactive at saturation
2,4-Dinitro-1-(trifluoromethoxy)benzene	0.2
2,4-Dinitro-1-benzonitrile	1.7
3,4-Dinitro-1-benzonitrile	0.1
3,5-Dinitro-1-benzonitrile	not reactive at saturation
2-Nitro-4-(trifluoromethyl)benzotrifluoride	not reactive at saturation
2-Nitro-4-(trifluoromethyl)benzaldehyde	not reactive at saturation

Reference

Schultz TW, Yarbrough JW, Hunter RS, Aptula AO (2007) Verification of the Structural Alerts for Michael Acceptors *Chemical Research in Toxicology* 20: 1359-1363

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