SYNTHESIS AND ANTILEUKAEMIA ACTIVITY OF N-(2,4-DIMETHYLPHENYL)HYDRAZINECARBOTHIOAMIDE AND ITS AZOMETHINE DERVIATIVES

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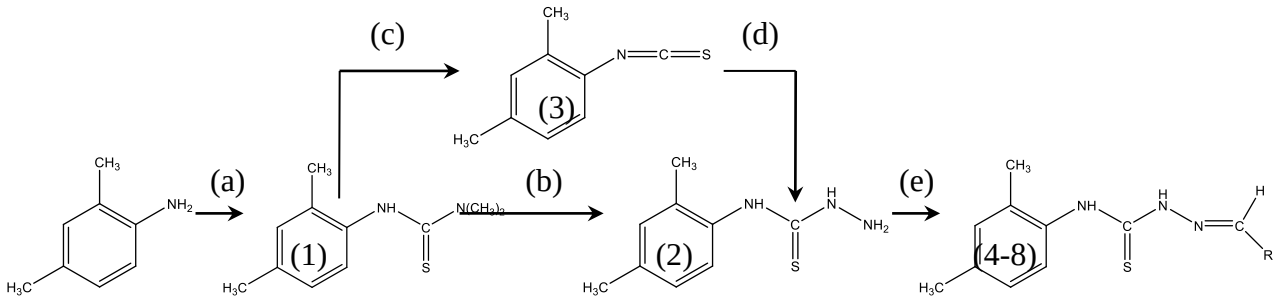
Leukaemia is a type of cancer of the blood or bone marrow characterised by an abnormal increase of immature white blood cells called "blasts". Like other cancers, it results from mutations in the DNA. Certain mutations can trigger leukaemia by activating oncogenes or deactivating tumor suppressor genes, and thereby disrupting the regulation of cell death, differentiation or division.

Since 1960s, an anthracycline antibiotic called Doxorubicin has been widely used in cancer chemotherapy. It is closely related to the natural product daunomycin, and like all anthracyclines, it works by intercalating DNA. However, Doxorubicin has a series of side-effects that strongly jeopardise patients' lives. For instance, when the cumulative dose of doxorubicin reaches 550 mg/m², the risks of developing cardiac side effects, including congestive heart failure, dilated cardiomyopathy, and death, dramatically increase. Doxorubicin cardiotoxicity is characterised by a dose-dependent decline in mitochondrial oxidative phosphorylation. Reactive oxygen species, generated by the interaction of doxorubicin with iron, can afterwards damage the myocytes, causing myofibrillar loss and cytoplasmic vacuolisation.

The synthesis of N-(2,4-dimethylphenyl) hydrazinecarbothioamide and its azomethine derivatives has been performed according to the published methods (Scheme 1), with some particular modifications:



R = (4) pyridine-3-yl; (5) pyridine-4-yl; (6) thiophene-3-yl; (7) quinoline-2-yl; and (8) 2-hydroxyphenyl.

N-(2,4-dimethylphenyl) hydrazinecarbothioamide and its five azomethine derivatives have been synthesised starting from commercially available 2,4-dimethylaniline. The composition and the structure of the synthesised compounds have been established by means of ^{1}H, ^{13}C NMR and X-ray diffraction.

Antileukaemia bioassays have shown that antiproliferative activity of the synthesised compounds is manifested mainly within the concentrations 10 μM and 1 μM and increases in the following series: **4** ≤ **5** < **7** < **2** < **6** < **8**. Therefore, the most active compounds **6** and **8** should be further studied as potential alternatives to traditional antileukaemia medicines. Also, from this study we have inferred that in order to obtain highly antiproliferative active azomethines from N-(2,4-dimethylphenyl) hydrazinecarbothioamide, we should condense it with aromatic carbocyclic or heterocyclic aldehydes or ketones, which contain donor atoms (such as O or N) in the *orto* position to the carbonyl group (e.g. salicylaldehyde, etc.).