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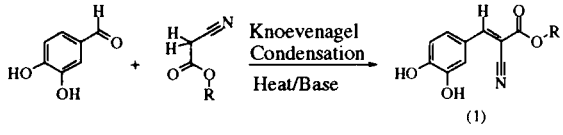
Automated synthesis of anti-cancer compounds

D. C. BILLINGTON, H. J. HUSSEY, D. L. RATHBONE, J. SIMPSON AND M. J. TISDALE

Pharmaceutical Sciences Institute, Aston University, Aston Triangle, Birmingham B4 7ET

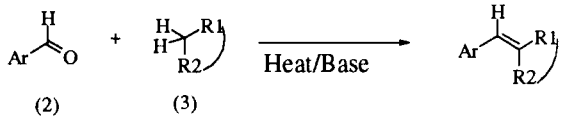
Inhibition of 12-Lipoxygenase induces tumour cell apoptosis and decreases tumour cell metastasis *in vivo*. 12-lipoxygenase may, therefore, be a critical target for intervention in tumour growth and metastasis (Hussey et al 1996).

Caffeic acid derivatives (1) synthesised by the Knoevenagel condensation have been described as potent inhibitors of 12-Lipoxygenase (Cho et al 1991). We have used automated synthesis to prepare a library of related Knoevenagel products in a purity sufficient for initial *in vitro* biological screening against two established murine colon adenocarcinomas, MAC13 and MAC16, which are generally refractive to cytotoxic agents.



(1)

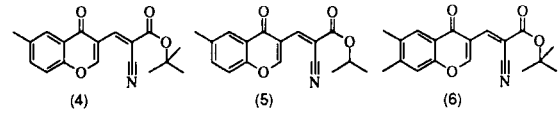
R = Simple alkyls and functionalised alkyls



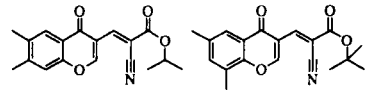
(2) (3)

R1:R2 = CN, Amides, Esters, Heterocycles

Automated parallel synthesis was used to combine a range of benzaldehydes (2) with a diverse set of active methylene substrates (3). All products were characterised by automated APCI mass spectroscopy before initial biological screening.



(4) (5) (6)



(7) (8)

The caffeic acid derivatives previously shown to have 12-Lipoxygenase inhibitory activity gave no inhibition of tumour growth. Screening of the entire diverse library, however, showed a number of compounds, with a structure resembling that of the iso-flavones, to be active. A focussed library of related compounds was then synthesised in a matrix using 12 aldehydes and 16 active methylenes as building blocks. Five products of the focussed library (compounds 4, 5, 6, 7 and 8) significantly inhibited MAC16 tumour growth when compared to a 5-Lipoxygenase inhibitor with established activity against MAC cell lines (Hussey et al 1996).

Cho H. et al (1991), Journal of Medicinal Chemistry, **34(4)**, 1503-1505

Hussey H.J. et al (1996), British Journal of Cancer, **73**, 1187-1192

Hussey H.J. et al (1996), British journal of Cancer, **74**, 683-687