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Synthesis and biological activity of simplified denoviose-coumarins related to novobiocin as potent inhibitors of heat-shock protein 90 (hsp90)

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Abstract—A new series of coumarin inhibitors of hsp90 lacking the noviose moiety as well as substituents on C-7 and C-8 positions of the aromatic ring was synthesised and their hsp90 inhibitory activity has been delineated: for example, their capacity to induce the degradation of client proteins and to inhibit estradiol-induced transcription in human breast cancer cells. In cell proliferation assay, the most active compound **5g** was ~8 times more potent than the parent novobiocin natural compound.

The aminocoumarins novobiocin and clorobiocin are well-established antibiotics agents that act as inhibitors of the bacterial ATP binding gyrase B, a type II DNA topoisomerase.[1] The natural product novobiocin (Nvb) has attracted renewed attention because of its antitumour activity.[2] The mechanism of action of novobiocin was found to inhibit the heat-shock proteins 90 (hsp90) via interaction with a previously unrecognized C-terminal ATP binding site.[3] This ATP-dependent molecular chaperone is well known to be involved in the folding of many client proteins including, among others, kinases (Akt, Raf-1, Her-2, cdk-4), transcription factors like steroid receptors and p53, that are directly associated with all six hallmarks of cancer.[4] Inhibition of hsp90 by Nvb induced the degradation of the hsp90 client proteins via the ubiquitin–proteasome pathway.[2] Consequently, hsp90 has evolved as an exciting new target in cancer drug discovery.[5]

Unfortunately, the ability of Nvb to induce degradation of hsp90 client protein (e.g., ErbB2 in SkBr3 breast cancer)[2] is relatively weak (700 μM) and requires further investigation to provide more potent compounds with improved pharmaceutical properties. Among the most active analogues, Blagg et al.[6] highlighted the crucial role of the noviose moiety at the 7-position of the coumarin ring for the biological activity, whereas the 4-hydroxy and 8-methyl groups in Nvb are not indispensable. In more recent studies,[7] 3′-descarbamoyl-4-deshydroxynovobiocin DHN2 proved to be a more effective and selective hsp90 inhibitor (Fig. 1).

As part of our research devoted to nonsugar coumarin analogues that target hsp90, we recently showed that the removal of the noviose moiety together with the introduction of a tosyl substituent at C-4 coumarins provides 4-tosylcyclonovobiocic acid (4TCNA) as a lead compound having a C-7 free-phenolic function and a C-8 methyl group.[8] Biological evaluation of 4TCNA revealed higher potency than Nvb itself to induce client-protein degradation. In our continuing structure–activity relationship (SAR) study, our aim was to determine what modifications are necessary to selectively provide more potent nonsugar coumarin com-

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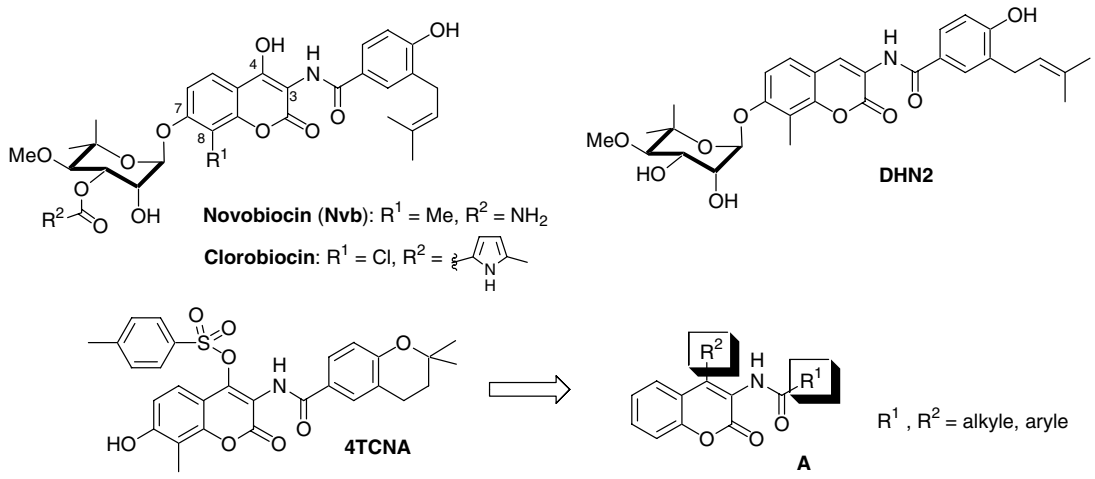
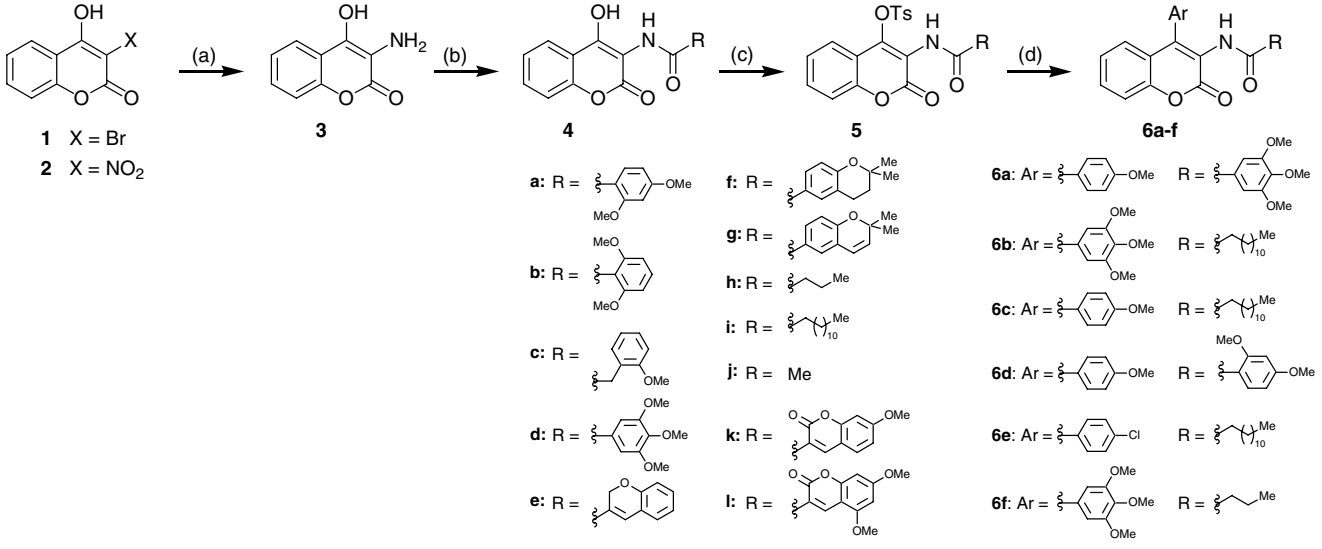


Figure 1. Hsp90 inhibitors and general structure **A** of the synthesised compounds.

pounds that target hsp90. Herein we report the synthesis of a simplified scaffold 3-(N-substituted) aminocoumarin of type **A** (Fig. 1), which includes two centres for introduction of diversity into coumarin molecule and disclose the impact of the absence of the 7-hydroxy moiety and the 8-methyl groups on the hsp90 inhibitory activity. The potencies of newly synthesised coumarins were evaluated for their capacity to inhibit estradiol (E_2)-induced transcription in human breast cancer cells, to induce the proteasome-mediated degradation of several known hsp90 client proteins, including Raf-1, the estrogen receptor α (ERα) and the progesterone receptors A and B (PRA, PRB).

Initially, the synthesis of 3-aminocoumarin derivatives **4** was examined by the palladium-catalysed C–N bond coupling reaction of known 3-bromo-4-hydroxy-coumarin **1** with a series of amide nucleophiles as we previously described.[9] All our attempts to react **1** with 2,4-dimethoxybenzamide to provide directly **4a** using various combinations of Pd/L/base mixtures (e.g., $Pd(OAc)_2$, $Pd_2(dba)_3$/Xantphos, BINAP, Xphos, dppf/Cs_2CO_3, K_3PO_4, K_2CO_3, etc.) resulted unfortunately in unsuccessful results, presumably for steric considerations. Therefore, the requisite aminocoumarins of general structure **A** were prepared by the route shown in Scheme 1. The synthesis was initiated with the reduction of the nitro function of commercially available 3-nitro-4-hydroxycoumarin **2** under Pd/C-catalysed hydrogenation to afford the corresponding 3-amino-4-hydroxycoumarin **3** in 84% yield. Further coupling with a series of aryl and alkyl carboxylic acids in the presence of PyBOP and DIEA in DMF at room temperature gave 3-acylaminocoumarin derivatives **4a**–**l** in moderate to good yields (44–91%). Because of the strong insolubility derivatives **4k** and **4l** in the usual organic solvents, their biological activity could not be delineated.



Scheme 1. Reagents and conditions: (a) H_2, Pd/C, MeOH, HCl (1%), 3 h, rt, 84%; (b) RCO_2H (1.2 equiv), PyBOP (1 equiv), DIEA (3 equiv), DMF, 18 h, rt; (c) TsCl (2 equiv), pyridine, 16 h, rt; (d) $ArB(OH)_2$ (1.3 equiv), K_3PO_4 (3 equiv), Bu_4NBr (10 mol %), $PdCl_2dppf$ (5 mol %), MeCN, 80 °C, overnight.