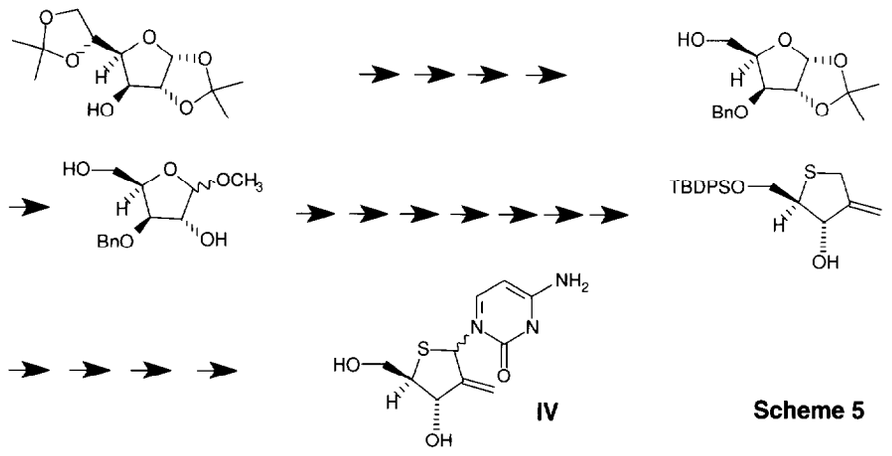

IV

Scheme 5

Synthesis of 2′-deoxy-2′substituted-4′-thiocytidines

2′-Deoxy-2′substituted-4′-thiocytidines have been previously shown to have potent antiviral and cytotoxic activities. Yoshimura, Y. and coworkers [*J. Org. Chem.* (1996) 61, 822–823] describe a novel synthesis of 4′-thiocytidines originating from D-glucose (Scheme 5) which they have utilized in the synthesis of the potent antineoplastic agent **IV** and other derivatives.

Emerging molecular targets

HIV-1 Nef protein

Nef is one of the earliest HIV proteins produced after transcriptional activation of the HIV genome. It is one of a group of 'accessory proteins' that play essential, but poorly defined, roles in the infectivity of the virus. Nef resides in the plasma membrane of the host cell where it interacts with the SH3 domains of the Hck and Lyn protein tyrosine kinases. Recent studies on the infection of monkeys with SIV reveal that if Nef is absent or inactivated, the infection does not cause the loss of CD4 lymphocytes characteristic of infection with the intact virus. Consistent with these observations, human patients infected with an HIV variant with a defective Nef were free of symptoms for long periods of time (10–14 years) with normal CD4 lymphocyte counts. Consequently, Nef may be an important target for a new class of HIV therapeutic agent.

Dr Stephan Grzesiek and coworkers at the National Institutes of Health (Bethesda, MD, USA) have just determined the solution structure of HIV-1 Nef using heteronuclear NMR spectroscopy [*Nature Structural Biology* (1996) 3, 340–345]. The overall structure is similar to the winged helix–turn–helix DNA binding proteins. The investigators mapped the region of Nef that binds the SH3 domains of tyrosine kinases. It consists of an assembly of non-contiguous amino acids that include a conserved proline-rich repeat region. The non-contiguous nature of the binding region is distinct from SH3-binding domains on mammalian proteins. Consequently, any compound that would bind to Nef and disrupt the architecture of this region might specifically block the interaction between Nef and tyrosine kinases. Assuming that this interaction is essential for Nef function in promotion of HIV infection, such a compound may have therapeutic value.

Tumor-derived cachetic factor

Cachexia, the general wasting away of muscle and weight loss associated with certain cancers, often limits chemotherapy because of the general weakened condition of the body. Few molecular targets exist for the discovery of anticachexia drugs because the molecular pathology of cancer cachexia is poorly defined. But now, Dr Penio Todorov and coworkers report that a newly discovered proteoglycan appears to play a key role in cachexia associated with adenocarcinoma [*Nature* (1996) 379, 739–742].

The proteoglycan cachetic factor (M_r, 24,000) was isolated as antigenic material from a MAAC16 tumor. The same proteoglycan was found in the urine of human cancer patients but not in samples from control patients. The factor produces a rapid weight loss in mice that could be blocked with a specific monoclonal antibody. When the factor was applied to isolated gastrocnemius muscle, it was tightly bound and there was a rapid degradation of the muscle. The cachetic factor does not correspond to any known cytokine and its receptor has not yet been identified. It may be a very important molecule to investigate for those interested in the discovery of anticachexia therapeutic agents.

AKAP79: a neuronal scaffold protein

Drug discovery scientists often view signal transduction enzymes such as protein kinases and phosphatases as poor targets for drug discovery. This is because many different cells and tissues utilize the same enzymes in distinct signaling pathways, and numerous efforts to find specific inhibitors have failed. But now an entire new approach is emerging for targeting these signaling enzymes for drug discovery. Signal transduction scientists have discovered scaffolding proteins that hold various signaling enzymes in just the right orientation for action on a particular substrate or to optimize a sequential series of reactions.

In neurons, AKAP79 is a scaffold protein in the postsynaptic densities that binds calcineurin and protein kinase A in close proximity to their substrates. Recently, Dr Theresa M. Klauck and coworkers at the Oregon Health Sciences University (Portland, OR, USA) and the W. Alton Jones Cell Science Center (Lake Placid, NY, USA) found that AKAP79 also binds protein kinase C (PKC). Their research revealed that AKAP79 contains unique binding sites for each signaling enzyme, and that a peptide corresponding to the specific domain that binds PKC blocks the interaction of PKC with AKAP79 [*Science*(1996) 271, 1589–1592]. Although much remains to be understood concerning the role of scaffold proteins in neuronal function and the regulation of binding of the various signal transduction enzymes, perturbation of such binding may be a totally new approach for the development of CNS therapeutic agents.

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