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Minor groove binders as anti-infective agents

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ABSTRACT

Minor groove binders are small molecules that form strong complexes with the minor groove of DNA. There are several structural types of which distamycin and netropsin analogues, oligoamides built from heterocyclic and aromatic amino acids, and bis-amidines separated by aromatic and heterocyclic rings are of particular pharmaceutical interest. These molecules have helical topology that approximately matches the curvature of DNA in the minor groove. Depending upon the precise structure of the minor groove binder, selectivity can be obtained with respect to the DNA base sequence to which the compound binds. Minor groove binders have found substantial applications in anti-cancer therapy but their significance in anti-infective therapy has also been significant and is growing. For example, compounds of the bis-amidine class have been notable contributors to antiparasitic therapy for many years with examples such as berenil and pentamidine being well-known. A recent growth area has been inreased sophistication in the oligoamide class. High sequence selectivity is now possible and compounds with distinct antibacterial, antifungal, antiviral, and antiparasitic activity have all been identified. Importantly, the structures of the most active compounds attacking the various infective organisms differ significantly but not necessarily predictively. This poses interesting questions of mechanism of action with many different targets involved in DNA processing being candidates. Access of compounds to specific cell types also plays a role and in some cases, can be decisive. Prospects for a range of selective therapeutic agents from this class of compounds are higher now than for some considerable time.

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1. Introduction, Minor groove binders—structural types

The term 'minor groove binder' (MGB) refers to many different classes of compound that have the property of binding, often strongly, to the minor groove of DNA. Such compounds may be natural products (Fig. 1) or synthetic compounds (Fig. 2). There are several types of natural product with minor groove binding properties and these have been recognised for many years. Among the simpler structures are the polyamides, netropsin and distamycin (Finlay et al., 1951; Arcamone et al., 1967, 1989). These compounds bind to the minor groove principally at AT rich regions (Abu-Daya et al., 1995). In the case of netropsin, a single molecule binds in the minor groove but in the case of distamycin and its analogues, it is more usual to find two molecules binding in a widened

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minor groove, face to face and antiparallel. Unless synthetic modifications have been made to introduce alkylating functional groups, distamycin and netropsin bind non-covalently to DNA. On the other hand, the duocarmycins and anthramycins typically form covalent adducts with nucleophilic groups found in the minor groove of DNA (Lemgruber et al., 1965; Hanka et al., 1978). In the case of the duocarmycins such as CC-1065, an amino group of a G base opens the cyclopropane ring in a reaction thermodynamically driven by the aromatisation of the ene-dione to which it is attached. In the case of the anthramycins, an amino group adds to the carbon–nitrogen double bond of the diazepine ring, a reaction that takes place most commonly at GC tracts of DNA (Rahman et al., 2009). If these compounds have a natural curvature that matches to a reasonable extent the curvature of the DNA minor groove to which the molecules can bind by hydrogen bonding, ionic interactions, and non-covalent bonds in addition to the specific covalent bonds mentioned above. Other naturally occurring minor groove binders have different architectures. Trabectidin (Yondelis ®) is a natural product of the ecteinascidin class and has been developed as a treatment for soft tissue sarcoma (D'Incalci & Galmarini, 2010). Its minor groove binding properties are apparently associated with the insertion of the two substructures marked with arcs into the minor groove to which they bind by hydrogen bonding and non-polar interactions.

Trabectidin is a very sophisticated structure whose activity depends upon the specific bonds and substituents. It is a synthetic challenge for the medicinal chemist and has not been the basis of extensive medicinal chemistry programmes. On the other hand, distamycin and netropsin are made up of a number pyrrole rings linked by amide bonds that lend themselves to structural variation within the pyrrole ring or on its *N*-alkyl substituent. As will be described later, a building block approach to the design of analogues of distamycin and netropsin has led to a range of very effective anti-infective compounds. The duocarmycins like CC-1065 are also made up of heterocyclic building blocks that can be varied to tune the activity and pharmacokinetic properties leading to drug candidates. A relevant example is centanamycin, which is a truncated analogue of CC-1065 with a chloroethyl group that is a latent cyclopropane; such compounds have anticancer applications (Yanow et al., 2008). Anthramycin is a highly modifiable structure provided

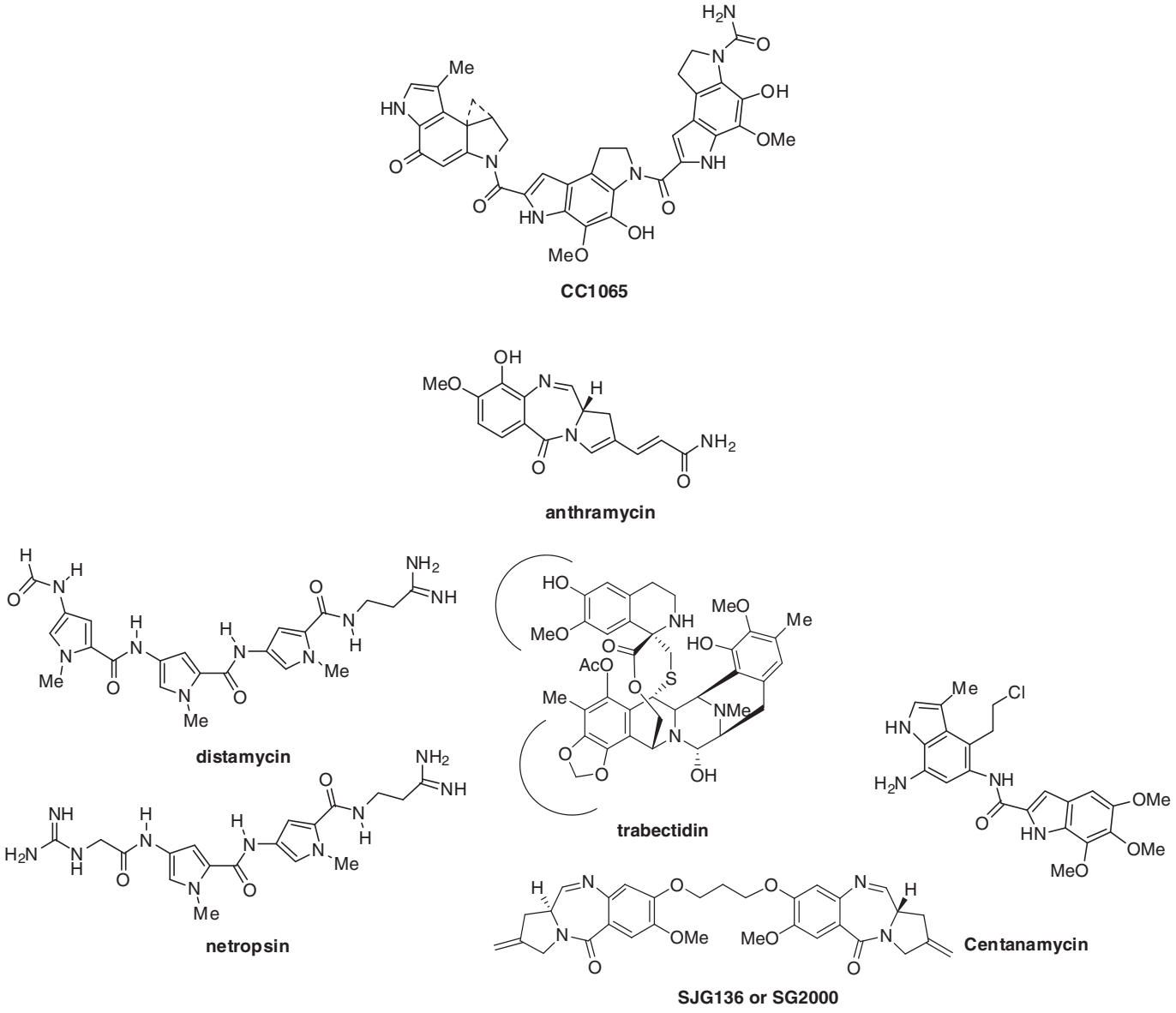

Fig. 1. The diverse structures of minor groove binders, including natural products and some synthetic derivatives.

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