

SYNTHESIS OF FUNCTIONALIZED BRIDGED BICYCLIC SULFONAMIDES WITH A BRIDGEHEAD NITROGEN ATOM

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For many years, sulfonamide-derived drugs were dramatically prevailed by aromatic derivatives. However, the recently increased interest to synthesis of their aliphatic counterparts provides an access to yet underexplored parts of pharmaceutically relevant chemical space. Although biologically active five- and six-membered alicyclic sulfonamides were reported in hundreds of papers and patents, their polycyclic analogues remain scarce in the literature. Two approaches to synthesis of functionalized bridged bicyclic sulfonamides with a bridgehead Nitrogen atom were developed.

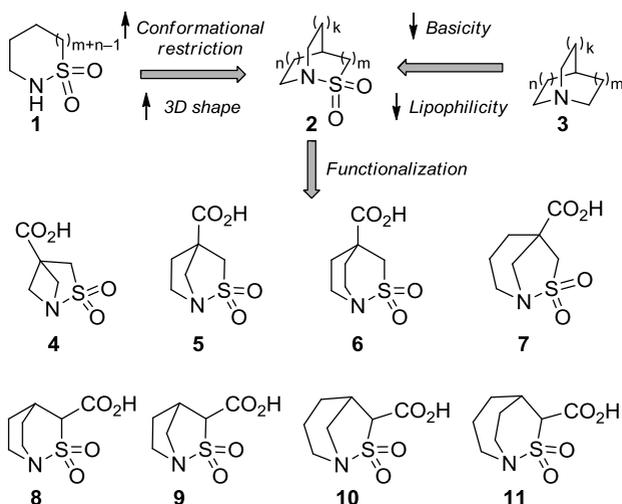


Fig. 1. Synthesized bicyclic sultams **4-11**

Synthesis of eight previously unreported functionalized bicyclic sulphonamides (**4-11**) with bridgehead Nitrogen atom was achieved on a multigram scale in up to 41 % yield over 7 steps. The target products were prepared either from monocyclic substrates containing nitrile group as a prerequisite of carboxylic acid functionality or by direct lithation–carboxylation of bicyclic non-functionalized sultams. The cyclization step used in the first approach was found to be efficient for saturated heterocyclic amino nitriles bearing $\text{CH}_2\text{SO}_2\text{F}$ group at both β -C and γ -C atoms (70–81 % yield). The key transformation of the second method, which is carboxylation at the α -position of bicyclic sulfonamide, was achieved in up to 72 % yield. However, the limitations of this approach were high ring strain in the starting substrates and presence of heteroatoms at the γ -position to sulfonamide group which promoted fragmentation of the ring. Importantly, all carboxylic acids obtained appeared to be hydrolytically stable towards long-term storage in air and can be purified by column chromatography if necessary. Overall, the developed synthetic sequences allowed to access novel and yet underexplored type of aliphatic sulfonamides which can be further used as advanced building blocks for drug discovery.