Charnwood Molecular

Excellence in Chemistry

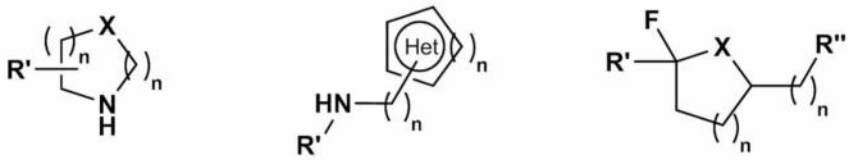
Novel Building Blocks: Providing Enhanced Structures for Your Drug Discovery Programs

Monomers to Improve Final Compound Quality

One of the most frequent requests Charnwood Molecular chemists receive from our clients is for the synthesis of novel building blocks, which are targeted at the improvement of quality and tractability of final screening compounds.

Off-the-shelf availability of such designed monomers to Discovery Chemistry groups, often spread out globally, facilitates company-wide use by synthetic chemists and enhances incorporation of these key building blocks into Medicinal Chemistry programs. This strategy has most notably been exemplified by AstraZeneca, who recently found it to both enhance and accelerate their Drug Discovery programs, with the delivery of three drug candidates containing their novel building blocks observed over a short timeframe[i].

Common building block design ideas to both introduce novelty and improve compound quality include the use of bioisosteric groups to replace commonly used functional groups, the introduction of moieties such as functionalised amines which can very effectively moderate solubility, the use of fluorinated analogues to ease metabolic liabilities and the re-introduction of 3D stereochemistry to avoid the 'flatlands' problem that has been identified to negatively affect the output of the pharmaceutical industry[ii].



X = O, CH_2, $S(O)_x$, NR

Generic Structures of Building Blocks Prepared for Medicinal Chemistry Programs

To add to industry 'rules' previously proposed for orally administered drugs[iii], to define leadlike compounds[iv] and to allow selection of fragments for lead generation[v], AstraZeneca's researchers proposed that the building blocks which were most suitable to have generally available in this regard for multiple Medicinal Chemistry programs generally fitted a 'Rule of 2' guideline. In this molecular weight (MW) was <200, clogP <2, hydrogen bond donors (HBD) ≤2 and hydrogen bond acceptors (HBA) ≤4[i]. Of course, as with the earlier proposals these criteria should be treated as guidelines rather than rules and assessed within the specific context of a particular Drug Discovery program towards specific biological targets.

Charnwood Molecular can provide synthetic chemistry services to our clients to help enhance their corporate building block collections, with the aim of accelerating both their ongoing and future Drug Discovery programs.

i. Goldberg, F. W. *et al Drug Discovery Today*, **2015**, *20* (1), 11
ii. Lovering, F.; Bikker, J.; Humblet, C. *J. Med. Chem.*, **2009**, *52*, 7652
iii. 'Rule of 5': Lipinski, C. A. *et al Adv. Drug. Deliv. Rev.*, *23*, 3.
iv. 'Rule of 4': Oprea, T. I. *et al J. Chem. Inf. Comput. Sci.*, *41*, 1308
v. 'Rule of 3': Congreve, M. *et al Drug Discov. Today*, *8*, 876

Charnwood Molecular Ltd
The Heritage Building, 7 Beaumont Court,
Prince William Road, Loughborough, UK, LE11 5DA.
www.charnwood-molecular.com
+44 (0) 1509 232007 info@charnwood-molecular.com
#charnwoodmol charnwood-molecular