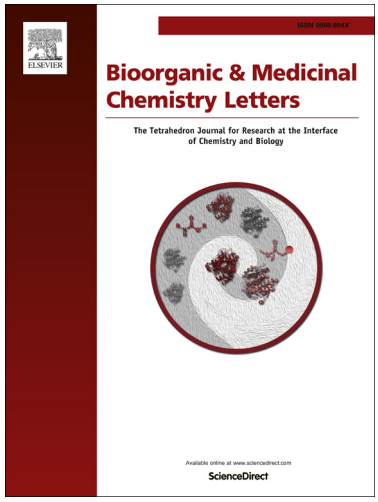

BMCL Digest

Isotope chemistry; a useful tool in the drug discovery arsenal

Charles S. Elmore, Ryan A. Bragg

PII: S0960-894X(14)01246-3
DOI: http://dx.doi.org/10.1016/j.bmcl.2014.11.051
Reference: BMCL 22206

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 29 September 2014
Revised Date: 18 November 2014
Accepted Date: 19 November 2014

Please cite this article as: Elmore, C.S., Bragg, R.A., Isotope chemistry; a useful tool in the drug discovery arsenal, *Bioorganic & Medicinal Chemistry Letters* (2014), doi: http://dx.doi.org/10.1016/j.bmcl.2014.11.051

Isotope Chemistry; a useful tool in the drug discovery arsenal.

Charles S. Elmore[a] and Ryan A. Bragg[b]

[a] Isotope Chemistry, DMPK, AstraZeneca Pharmaceuticals, 43183 Mölndal Sweden;

[b] Isotope Chemistry, DMPK, AstraZeneca Pharmaceuticals, Alderley Park, UK.

Abstract:

As Medicinal Chemists are responsible for the synthesis and optimization of compounds, they often provide intermediates for use by isotope chemistry. Nevertheless, there is generally an incomplete understanding of the critical factors involved in the labeling of compounds. The remit of an Isotope Chemistry group varies from company to company, but often includes the synthesis of compounds labeled with radioisotopes, especially H-3 and C-14 and occasionally I-125, and stable isotopes, especially H-2, C-13, and N-15. Often the remit will also include the synthesis of drug metabolites. The methods used to prepare radiolabeled compounds by Isotope Chemists have been reviewed relatively recently. However, the organization and utilization of Isotope Chemistry has not been discussed recently and will be reviewed herein.

Body:

Isotope Chemistry (IC) is a specialty function found in many large pharmaceutical companies. While the remit of IC can vary from company to company, the principal deliverable is to provide labeled compounds to the business, mostly for use by drug metabolism and pharmacokinetics (DMPK) groups for metabolism based studies. These deliveries consist primarily of H-3, C-14, and stable isotope labeled compounds, but may also encompass I-125 and S-35 as well as unlabeled compounds including metabolites and PET precursors.[1,2]

Tritium labeled compounds are used by DMPK to gather early metabolism data, to assess covalent binding of reactive metabolites (which is a key component of AstraZeneca's safety strategy)[3] for transporter efflux and uptake studies, and can also be used for quantitative whole body autoradiography (QWBA).[4] Tritium labeled compounds have many additional applications in bioscience, including receptor binding, autoradiography, and receptor occupancy studies. They are generally more easily and rapidly synthesized than C-14 labeled compounds but have a far greater potential for the loss of the label by chemical and biological processes. Tritium labeled compounds have a modest specific activity which makes them well suited for use with many receptor binding assays, while simultaneously obviating the need for a decay correction when used in metabolism studies.

As a project approaches Phase III development, IC provides C-14 labeled material for use in QWBA and mass balance studies, and ultimately C-14 labeled material for use in human absorption, distribution, metabolism, and excretion, (hADME) studies, which is prepared according to current good manufacturing practices (cGMP).[4,5] If an absolute bioavailability study is to be run, it is often conducted at the same time.[5] During Phase III and beyond, C-14 labeled material is required for environmental fate studies.[6]