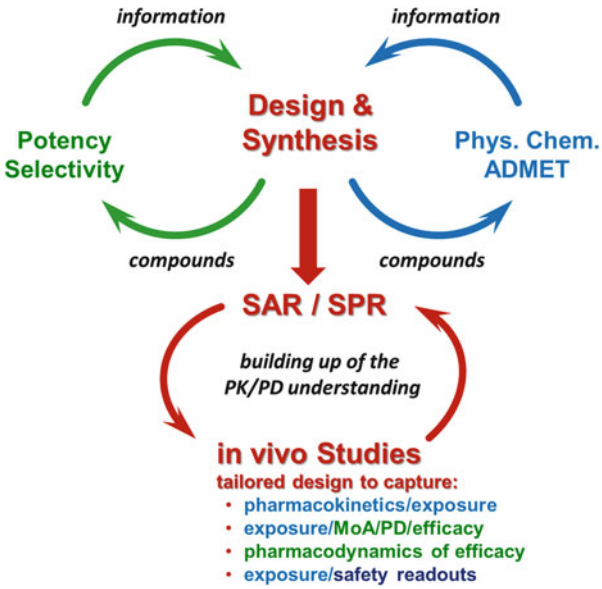

Fig. 6 Illustration of the design–make–test–analyse cycle in the LO phase. The in vitro assay in pharmacology and DMPK have to run at the same throughput and turnaround times to be able to synchronise the generation of structure–activity (SAR) and structure–property relationships (SPR) to avoid bias in the chemical synthesis. Optimised compounds are then submitted to in vivo studies (1) to examine the overall PK behaviour of the compound and (2) to evaluate the pharmacological activity in vivo in relation to unbound plasma concentrations and the in vitro potency (see Fig. 5). If possible safety readouts can be included in the in vivo studies. Depending on the level of understanding of the pharmacology of the target and the animal disease model, mode-of-action studies which can be performed after single doses or more chronic efficacy studies with repeated dosing schedules are carried out

moieties which carry the highest potential for potency and selectivity (via SAR) and optimal physicochemical, DMPK and safety properties (via SPR). It is beyond the scope of this chapter to discuss the standard ADME and safety in vitro assays which have been described extensively in the literature (Kerns and Di 2008; Meanwell 2011; Tsaioun and Kates 2011; Zhang and Surapaneni 2012; Smith et al. 2012; Wang and Urban 2014). It is important that these assays run at high throughput and with short turnaround times which are fully in line with design–make–test–analyse learning cycles (Plowright et al. 2012) that are jointly driven by medicinal chemistry, pharmacology and DMPK (Fig. 6).

A small core team with one representative from each of the three functions has been recognised to be the most efficient set-up in this process, in particular if they work along a clear hypothesis-driven way: i.e. defining a decision-related question for each compound prior to synthesising and subsequently submitting it to the relevant screening assays so to be able to rationalise their thoughts and to gradually transform the rapidly expanding amount of information into working knowledge rather than simply filling data bases very efficiently.