While it is important to keep a clear focus on the critical path and to develop a growing understanding of the relationship between pharmacokinetics/exposure and pharmacodynamics/efficacy, there are a number of pitfalls on the way to identify a viable drug candidate:

1. The potency trap. Care should be taken that the screening tree is not steering chemical synthesis into the potency trap. Highly potent compounds often carry too much lipophilicity resulting in a prohibitive ADME profile which in most cases cannot be improved without losing potency altogether. Using potency measures such as the ligand binding efficiency index, where potency gains merely by lipophilicity increase are punished, can be very useful indicators to avoid this pitfall (Reynolds et al. 2008; Hopkins et al. 2014). Also, putting due emphasis on cellular potency readouts with demonstrated relevance for in vivo efficacy rather than on potency values from biochemical assays with recombinant target proteins helps avoiding this trap. Instead, biochemical assays should be used primarily for improving the selectivity of the compounds.
2. The fast and easy way. Beyond the many easy to synthesise chemical modifications, try also to get hold of more challenging to synthesise molecules in the chemical series if they are indicated by SAR/SPR analyses. If small structural changes only bring about small improvements, larger chemical modifications might be more fruitful. They also allow exploration of the distant corners in the chemical space and may direct teams on the (unexpected) path to the ultimate development candidate (Lücking et al. 2013; Hartung et al. 2013).
3. Getting lost in too much. Attempting optimisation of all liabilities at once often proves to be overtly challenging, not so much in terms of capacity but in terms of rationalising too many SAR and SPR relationships simultaneously. It may be more satisfactory to focus on the resolution of the most crucial issues initially and address other issues once significant improvements have been achieved. The then new chemical matter might no longer suffer from other liabilities or may have other issues to take care of. The paradigm of "all compounds in all assays as early as possible" produces a lot of data and noise, and the overwhelming amount makes it difficult to extract useful knowledge for decision-making. Well-defined rational design–make–test–analyse cycles with a relevant question behind each compound and every assay the compound is submitted to turn out to be more instructive besides saving capacity (Ballard et al. 2012; Plowright et al. 2012).
4. Losing sight of the relevant issues. The validity of the screening assays in terms of delivering real improvements on the key liabilities should be repeatedly checked by in vivo studies during lead optimisation. For instance, IVIVC between solubility and/or Caco-2 permeability/efflux and oral bioavailability, and metabolic stability and total clearance should be confirmed throughout the LO phase to make sure that a significant improvement seen in vitro indeed brings about the anticipated improvement in vivo. This ensures that the screening tree is still on the right track and indicates if new issues have turned up in the current compounds which need to be taken care of in a different set of screening assays.