Development of orally available phosphodiesterase 4 (PDE4) inhibitors as anti-inflammatory drugs has been going on for decades. However, only roflumilast has received FDA approval. One key challenge has been the low therapeutic window observed in the clinic for PDE4 inhibitors, primarily due to PDE4 mediated side effects. Here we describe our approach to circumvent this issue by applying a soft-drug concept in the design of a topically acting PDE4 inhibitor for treatment of dermatological diseases. We used a fast follower approach, starting from piclamilast. In particular, simultaneous introduction of 2'-alkoxy substituents and changing an amide to a keto linker proved to be beneficial when designing potential soft-drug candidates. This effort culminated in identification of LEO 29102 (20), a potent, selective, and soft-drug PDE4 inhibitor with properties suitable for patient-friendly formulations giving efficient drug delivery to the skin. Compound 20 has reached phase 2 and demonstrated clinically relevant efficacy in the treatment of atopic dermatitis.