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Discovery of the potent non-steroidal glucocorticoid receptor modulator BAY 1003803 as clinical candidate

Markus Berger[a,*], Ekkehard May[b], Hartmut Rehwinkel[a], Heike Schäcke[c], Roland Neuhaus[d], Antje Rottmann[d], Thomas M. Zollner[c], Stefan Jaroch[e]

[a] *Medicinal Chemistry Berlin, Research & Development, Pharmaceuticals, Bayer AG, D-13353 Berlin, Germany*
[b] *Cross Indication Research, Innovation Campus Berlin, Research & Development, Pharmaceuticals, Bayer AG, D-13353 Berlin, Germany*
[c] *Therapeutic Area Endocrinology, Metabolism and Reproductive Health, Research & Development, Pharmaceuticals, Bayer AG, D-13353 Berlin, Germany*
[d] *Drug Metabolism and Pharmacokinetics, Research & Development, Pharmaceuticals, Bayer AG, D-13353 Berlin, Germany, Germany*
[e] *Open Innovation, Research & Development, Pharmaceuticals, Bayer AG, D-13353 Berlin, Germany*

Abstract:

We report on the discovery of the new clinical candidate BAY 1003803 as glucocorticoid receptor agonist for the topical treatment of psoriasis or severe atopic dermatitis. In the course of optimizing the amino alcohol series as a highly potent new non-steroidal lead structure, considerations were made as to how physicochemical properties and safety concerns relate to structural motifs. BAY 1003803 demonstrates strong anti-inflammatory activity *in vitro* paired with a pharmacokinetic profile suitable for topical application.

Keywords:
Glucocorticoid, SEGRA, Transrepression, Transactivation, Amino alcohol

For more than 70 years, glucocorticoids (GCs) have been used to treat severe inflammatory conditions,[1] such as asthma,[2] rheumatoid arthritis,[3] and eye and skin diseases including atopic dermatitis, contact eczema, and psoriasis.[4] Since long-term, high-dose treatments with orally applied GCs can cause serious adverse effects, e.g., osteoporosis, diabetes, Cushing's syndrome, glaucoma, and muscle atrophy, the last 2 decades have seen tremendous efforts to better understand the mode of action of GCs on a molecular level and thus to devise efficacious yet safer GCs. The concept that beneficial, anti-inflammatory effects are exerted through the transrepression pathway, while side-effects are triggered through the transactivation activity of GCs has served as a valuable hypothesis in the quest for novel GCs. Briefly, this concept maintains that the monomeric GC-bound glucocorticoid receptor abrogates transcription of pro-inflammatory gene products (transrepression),[5] whereas a dimeric GC-GR complex promotes *inter alia* expression of enzymes involved in catabolic processes (transactivation). This rationale showed a way forward to increase the therapeutic window of GCs by identifying compounds that act as full agonists in the transrepression pathway, yet affect the transactivation

pathway to a minor extent as partial agonists or even as antagonists.[6] This hypothesis is indeed quite simplistic and, consequently, has been refined to reflect the complexity of GC and glucocorticoid receptor (GR) biology.[7] Nevertheless, it served as a valuable paradigm for the identification of novel, non-steroidal GR agonists, and led to new selective GR (transrepression) agonists (SEGRAs).[8,9,10]

Based on our discovery of novel selective glucocorticoid receptor agonists (SEGRAs) such as quinoline **1** (Scheme 1)[11] , followed by careful inspection of the its synthetic routes, we concomitantly discovered the tetrahydronaphthalene representative **2** and super-potent glucocorticoid agonists like amino alcohol **3** [12]. Our continued optimization of the novel chemotype **3** towards the clinical candidate **BAY 1003803** for the topical treatment of atopic dermatitis and psoriasis is outlined in this paper.

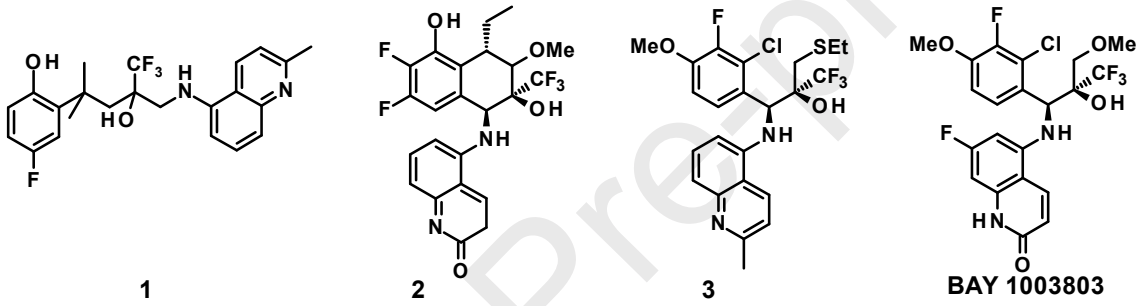


Figure 1. Overview of the structural evolution of selective glucocorticoid receptor agonist lead structures **1**, **2**, and **3** towards the clinical candidate **BAY 1003803**.

To build our understanding of the structure activity relationship (SAR) within the amino alcohol series, we could identify the 2-chloro3-fluoro-4-methoxyphenyl as the most potent substitution pattern for the benzyl amine moiety. This finding was accomplished through variation of the aromatic substitution pattern represented by compounds **3a - h** (Scheme 2 and Table 1). A major influence on potency and the relation of transactivation or transrepression behavior was found for structural changes in the remainder of the scaffold (**4 - 12**, Figure 2 and Table 1).

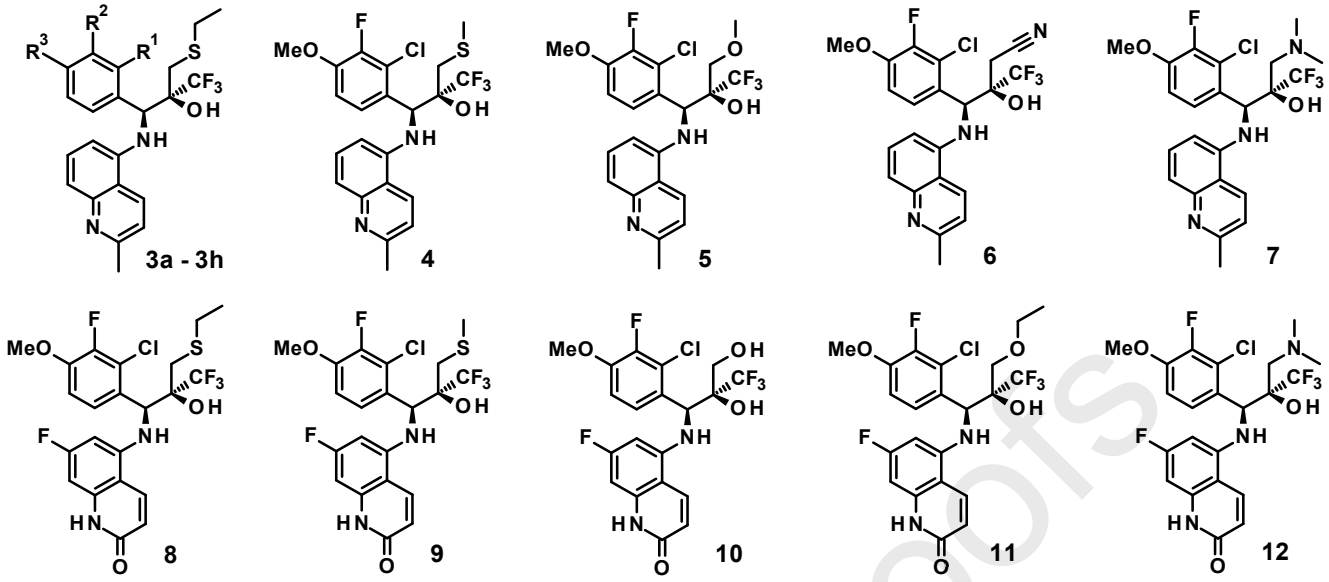


Figure 2. Chemical structures of amino alcohol derivatives.

Although the methyl thioether present in **4** and **9** guarantees for maximal potency, the switch to the methoxy group is beneficial for two reasons: 1) it slightly reduces the transrepression (198 pM for **5** compared to 118 pM for **4**) and transactivation potency (1.45 nM for **5** compared to 0.28 nM for **4**); and 2) it precludes any redox liabilities associated with the thioether group being present in a drug candidate for topical application. Introduction of a nitrile (**6**) or a dimethyl amino group (**7** and **12**) leads to a strong potency drop out of the pM-range. The free hydroxyl group (**10**) at this position can be considered as equipotent to the alkoxy-derivatives. The choice of the proper heterocyclic amine substituent was guided by physicochemical parameters in combination with safety requirements, i.e., potential genotoxicity. The parallel SAR visible from a quinoline quinolone comparison with respect to potency delivered no differentiation criterium. Differentiation was possible, however, by considering the logP[13] (Table 1) of the most potent derivatives which directly influences the aqueous solubility of the potential candidate. The switch from methylquinoline (**3**, **4** or **5**) to 7-fluoroquinolone (**8**, **9** or **BAY 1003803**) leads to a logP drop of 0.5 to 0.6 for each pair. With respect to our starting point **3** this translates into a solubility improvement of < 1 mg/ml to 12 mg/ml for **BAY 1003803**, which might ease the formulation development significantly[14].

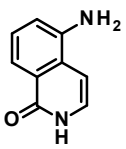
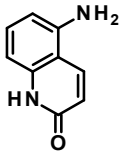
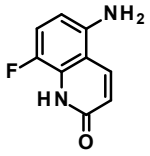
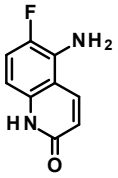
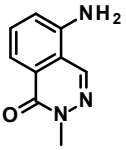
Table 1. Anti-inflammatory and immunomodulatory transactivation activity in recombinant cell assays[a].

Compound				logP[b]	Transactivation transfected HeLa, LUC readout		Transrepression monocyte inhibition of IL-8 production	
	R^1	R^2	R^3		pEC_{50}	max. efficacy [%][c]	pIC_{50}	max. efficacy [%][c]
Dexamethasone					8.1	100	8.6	100
2				3.10	8.0	29	8.2	78
3	Cl	F	OMe	4.9	9.2	87	9.8	91
3a	H	H	Me	4.8	7.9	66	8.6	87
3b	H	H	OMe	4.2	8.0	70	8.2	86
3c	OMe	F	H	4.6	8.0	47	8.7	69
3d	OMe	H	F	4.4	8.0	72	8.3	78
3e	F	H	OMe	4.4	8.3	63	8.3	85
3f	H	F	OMe	4.1	8.2	77	8.3	82
3g	OMe	F	Cl	5.3	8.9	66	8.8	82
3h	OH	F	Cl	3.4	7.6	102	7.7	107
4				4.5	9.6	89	9.9	98
5				3.8	8.8	80	9.7	97
6				3.4	8.8	80	8.9	83
7				5.3	7.4	66	8.3	77
8				4.3	8.5	92	8.8	93
9				3.9	9.4	94	10.0	100
10				2.4	9.0	88	9.2	92
11				3.8	8.8	91	9.1	99
12				4.4	8.4	62	8.1	109
BAY 1003803				3.3	9.1	85	9.4	95

[a] Ref. [15]
[b] For experimental determination of logP see supplementary data
[c] Maximal efficacy response is normalized maximum efficacy of dexamethasone (= 100%).

Since heterocyclic aniline like bicycles are potentially genotoxic[16], one objective of the lead optimization program was to explore the potential risk of the aniline motif and options for enhancing safety. Therefore, possible aniline metabolites were tested as 5-amino-quinolones in the Ames test[17] for their genotoxic potential (Table 2). The outcome of this Ames screen with only one Ames-negative amino quinolone derivative enabled the identification of the 7-fluoro-quinolone as an obvious heterocycle of choice for a safe clinical candidate.

Table 2. Ames screen on amino quinolone derivatives.

Compound						
Ames result	positive	positive	positive	negative	positive	positive

Combined evaluation of these properties lead to the identification of **BAY 1003803** as the most suitable clinical candidate. Similar to the amino quinolone fragment of this candidate compound shown in Table 2, the full parent compound **BAY 1003803** also subsequently tested Ames negative. Furthermore, the candidate compound has partial to full agonistic activity for transactivation with a slightly reduced efficacy of 85%. Extended *in vitro* characterization in relevant anti-inflammatory models was carried out to classify **BAY 1003803's** activity with respect to known highly potent steroidal glucocorticoids, which are able to inhibit the release of cytokines that are related to dermatological diseases like psoriasis and atopic dermatitis.

BAY 1003803 has been tested in parallel with two reference compounds, the very potent topical glucocorticoid, Clobetasol, and the weaker topical glucocorticoid, Dexamethasone, in primary human immune cells. **BAY 1003803** is somewhat less potent than Clobetasol, but significantly more potent than Dexamethasone, with similar efficacy for all three compounds in human peripheral blood mononuclear cells (PBMCs) stimulated with LPS or PHA (**Table 3**)[18,19].

Table 3. Inhibition of cytokine release in primary human immune cells reported as IC_{50}[nM] / Efficacy [%].

	BAY 1003803	**Clobetasol**	**Dexamethasone**
Inihbition of LPS-induced			
TNF-α	0.92 ±0.25 / 98±4	0.23±0.03 / 102±5	6.4±2.6 / 100
IL-12p40	0.75±0.28 / 96±1	0.14±0.01 / 98±4	4.3±2.3 / 100
Inhibition of PHA-induced			
IL-2	0.88±0.10 / 95±3	0.14±0.03 / 97±4	4.6±1.5 / 100
IFN-γ	0.7±0.5 / 96±6	0.16±0.07 / 101±2	3.8±2.3 / 100
IL-4	0.42±0.14 / 99±1	0.07±0.02 / 99±2	2.3±1.1 / 100

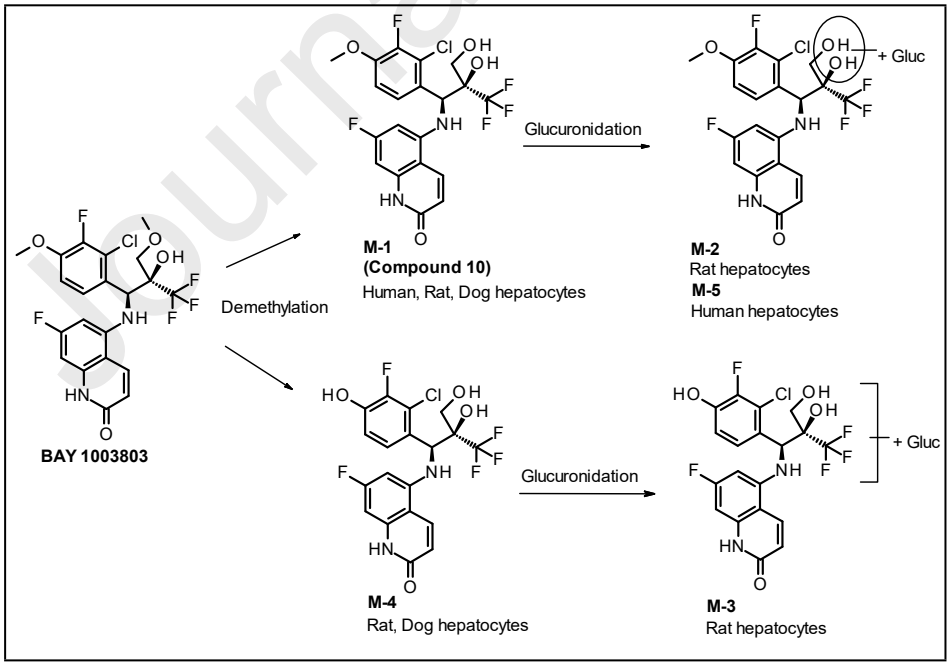
The susceptibility of **BAY 1003803** to hepatic metabolism was investigated *in vitro* using hepatocytes from different species, including human. **BAY 1003803** shows moderate CL_b in rat and dog and high CL_b in human hepatocytes. **BAY 1003803** exhibits moderate permeation and no evidence for efflux in the Caco-2 model (**Table 4**).

Table 4 *In vitro* metabolic stability and permeability of **BAY 1003803**

$CL_{b,Hep}$[a] [L/h/kg] (F_{max} [%])[b]			Caco-2 P_{app} A→B [nm/s][c] (ER)[d]
human	rat	dog	19 (0.5)
0.94 (28)	0.72 (83)	1.3 (38)	

[a] Blood clearance (CL_b) derived from hepatocytes; [b] Maximal predicted bioavailability after oral administration; [c] Apparent permeability in Caco-2 cells from apical (A) to basolateral (B) compartment; [d] efflux-ratio (ER) (P_{app} B→A divided by P_{app} A→B).

To substantiate the understanding of the hepatic clearance pathways of **BAY 1003803** the main metabolites were identified in incubations with human, rat and dog hepatocytes. In all species the *O*-demethylation to **M-1** (compound **10**) was identified as major metabolic pathway (Scheme 2). **M-1** has similar pharmacological potency compared to **BAY 1003803**. Therefore, its exposure should be taken into consideration for assessment of PK/PD correlation in preclinical pharmacological models and human *in vivo*. Furthermore, the product of demethylation of both methoxy groups (**M-4**) was found in rat and dog, but not in human hepatocytes. Subsequent glucuronidation of the demethylated metabolites was observed in the hepatocytes of humans (**M-5**) and rats (**M-2** and **M-3**).



Scheme 1 Major metabolites of **BAY 1003803** in different species. **M-1** verified by comparison with authentic compound **10** reference material.

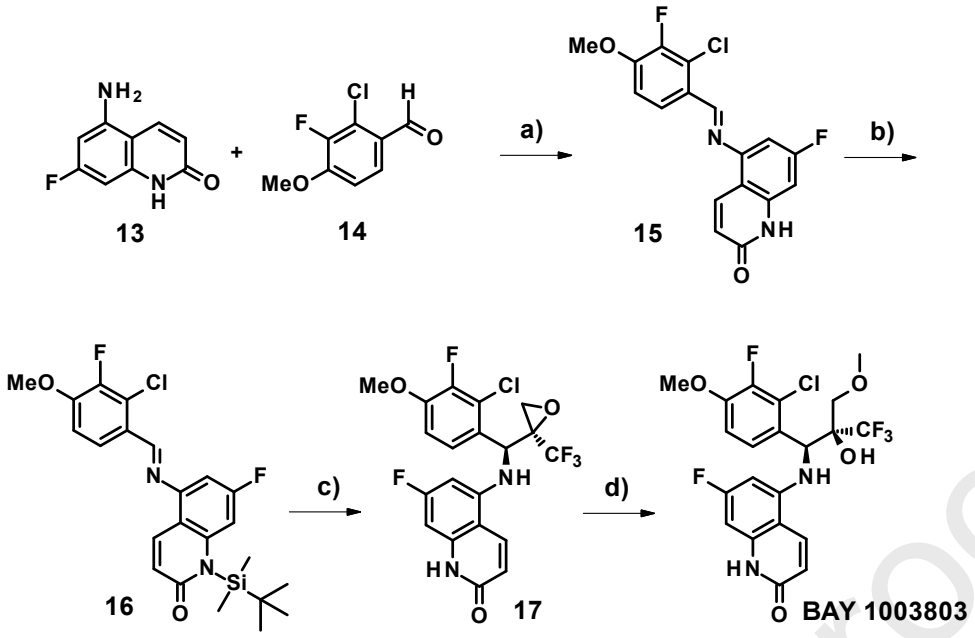
In vivo pharmacokinetics (PK) of **BAY 1003803** were determined in female rats and dogs accompanied by a PK study with separately administered metabolite **M-1** (compound **10**) in male rats. **BAY 1003803** showed a high clearance in rat which cannot be explained solely on the basis of *in vitro* clearance in rat hepatocytes indicating involvement of additional, extrahepatic clearance mechanisms. Clearance of metabolite **M-1** in rats was determined even higher compared to the parent compound. The observed moderate clearance in dogs fits well to the blood clearance predicted from dog hepatocytes. A high clearance in humans as suggested by human hepatocytes would be beneficial for a topically administered, locally acting compound helping to avoid systemic side effects. Therefore, the collected *in vivo* data gave no contraindication for advancing **BAY 1003803** to further *in vivo* studies aiming for a topical application (Table 5).

Table 5. *In vivo* pharmacokinetic data of **BAY 1003803** and metabolite M-1 (compound **10**).

Parameter	BAY 1003803 in female Wistar rat	BAY 1003803 in female Beagle dog	Metabolite **M-1** in male Wistar rat
Dose i.v. [mg/kg]	5*	1*	1**
CL_{plasma} [L/h/kg]	3.0	1.2	6.8
CL_{blood} [L/h/kg]	3.6	1.2	6.0
V_{ss} [L/kg]	7.0	2.1	18
terminal $t_{1/2, i.v.}$ [h]	1.9	1.3	2.9

Vehicle: *PEG400/saline (60/40, v/v), n=3, **PEG400/saline (70/30, v/v), n=3

To produce larger quantities of **BAY 1003803** the previously reported stereoselective synthesis of **3**[20] had to be adapted to the requirements of the presence of the fluoroquinolone and replacement of the former thioether with a methyl ether. Its synthesis started with condensation of aminoquinolone **13** and aldehyde **14** to form imine **15** *E*-selectively (**Scheme 6**). Before addition of the anion of trifluoromethyloxiran[21] to imine **15** the NH of the quinolone was exchanged *in situ* to the *tert*-butyl dimethyl silyl group by deprotonation with sodium hydride followed by addition of TBSCl. The so formed silyl compound **16** was added to the lithiated (*S*)-1,1,1-trifluoro-2,3-epoxypropane at -95°C and delivered, compound **17** with a diastereoselectivity of 4/1 towards the desired (*S*,*S*)-isomer after aqueous work up. Epoxide **17** was opened with methanol under basic conditions to yield methoxy ether **BAY 1003803**.[22]



Scheme 2. Synthesis of **BAY 1003803**: a) Acetic acid, $(t\text{-BuO})_4Ti$, toluene, 120°C, 92%; b) NaH, THF, 0°C, TBSCl, c) (*S*)-1,1,1-trifluoroepoxypropane, n-BuLi, THF, hexane, diethyl ether, -95°C to -10°C, 62%; d) Cs_2CO_3, MeOH, 56%.

In summary, we report on the discovery of the selective glucocorticoid receptor agonist **BAY 1003803** as a safe development candidate for the topical treatment of psoriasis or severe atopic dermatitis. **BAY 1003803** demonstrates strong anti-inflammatory activity *in vitro* paired with a physicochemical and pharmacokinetic profile suitable for topical application.

Declaration of Competing Interests

All authors are or have been employees of Bayer AG. The following authors are shareholders of Bayer AG: Markus Berger, Stefan Jaroch, Ekkehard May, Hartmut Rehwinkel, and Thomas M. Zollner.

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Supplementary data

Experimental procedures and spectroscopic data for **BAY 1003803** and compounds **8** to **17**.

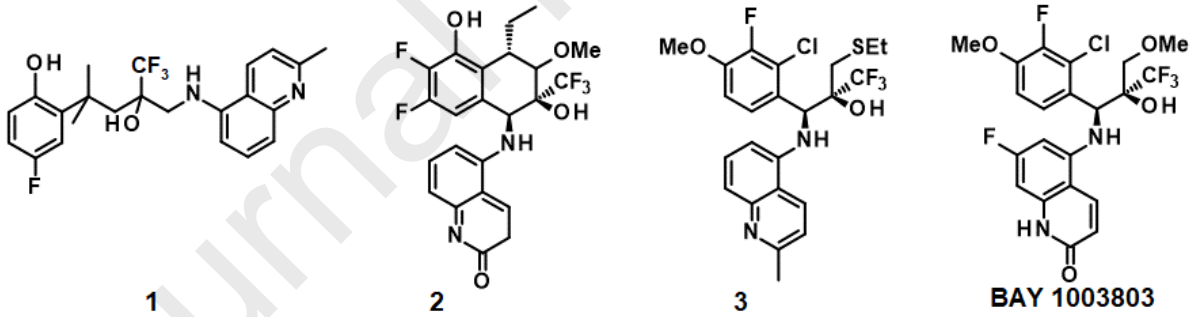
Supplementary data associated with this article can be found, at

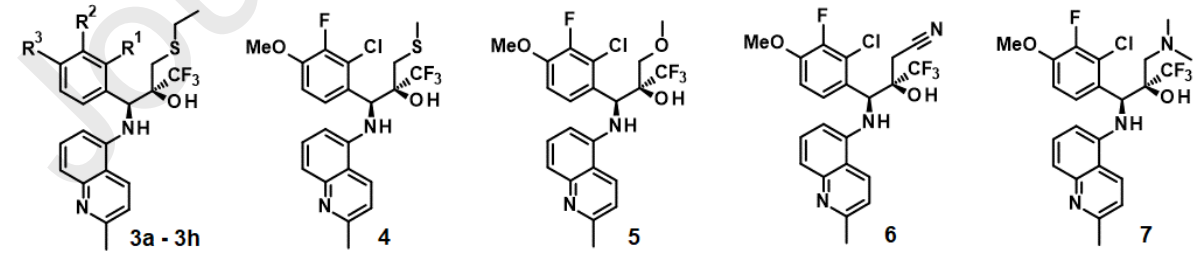
Declaration of interests

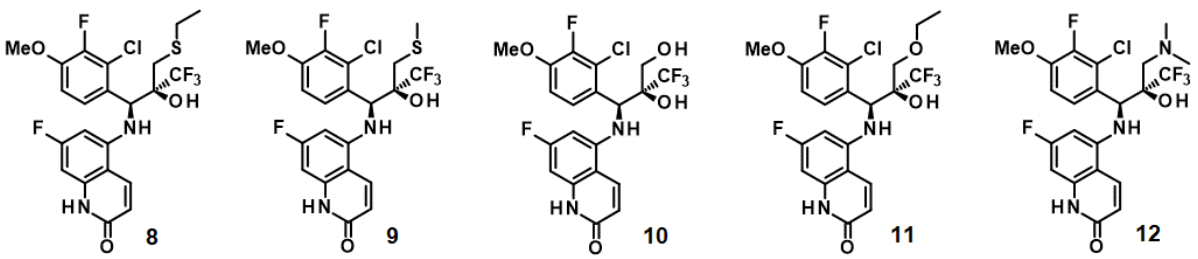
☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

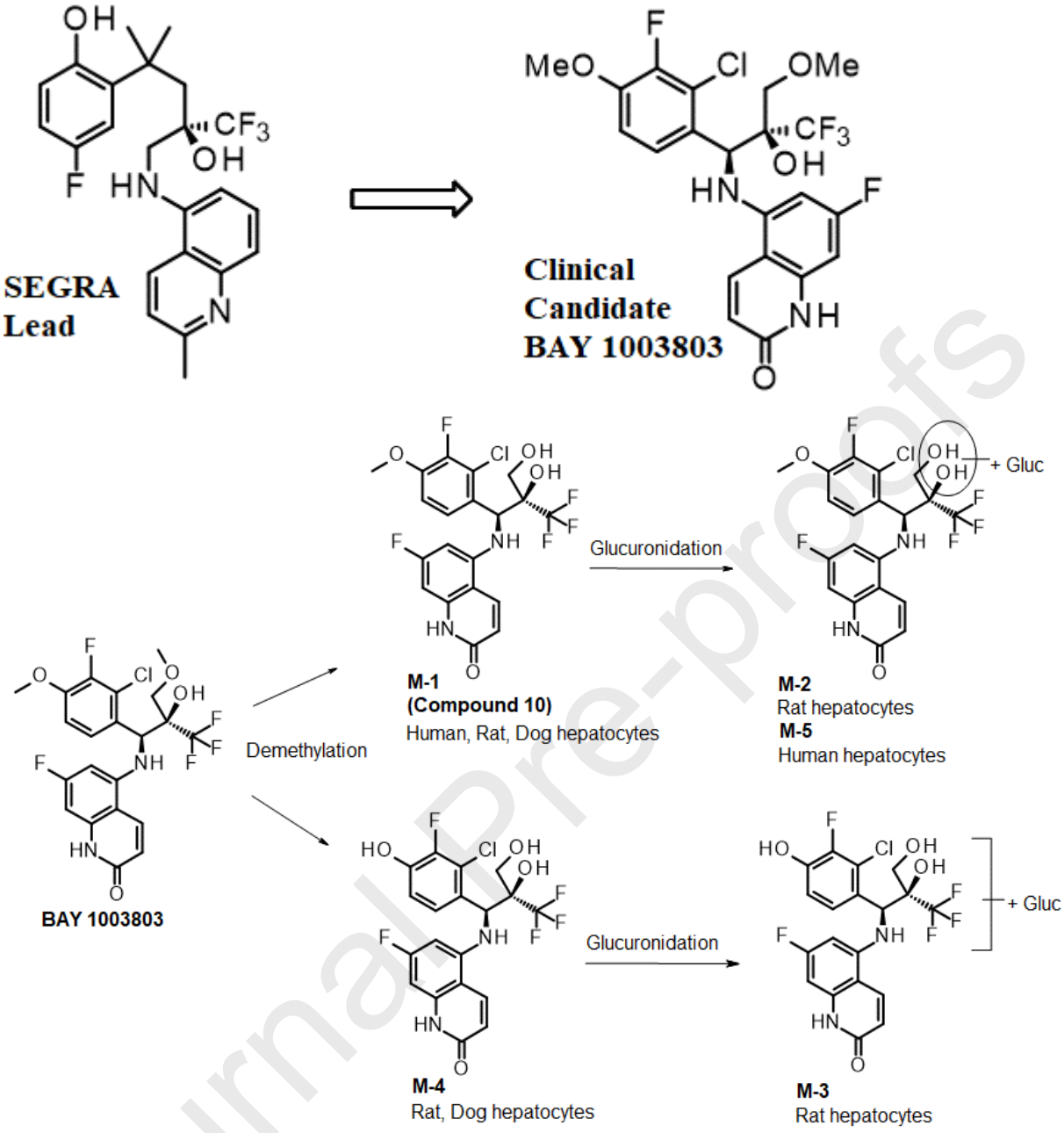
☒The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

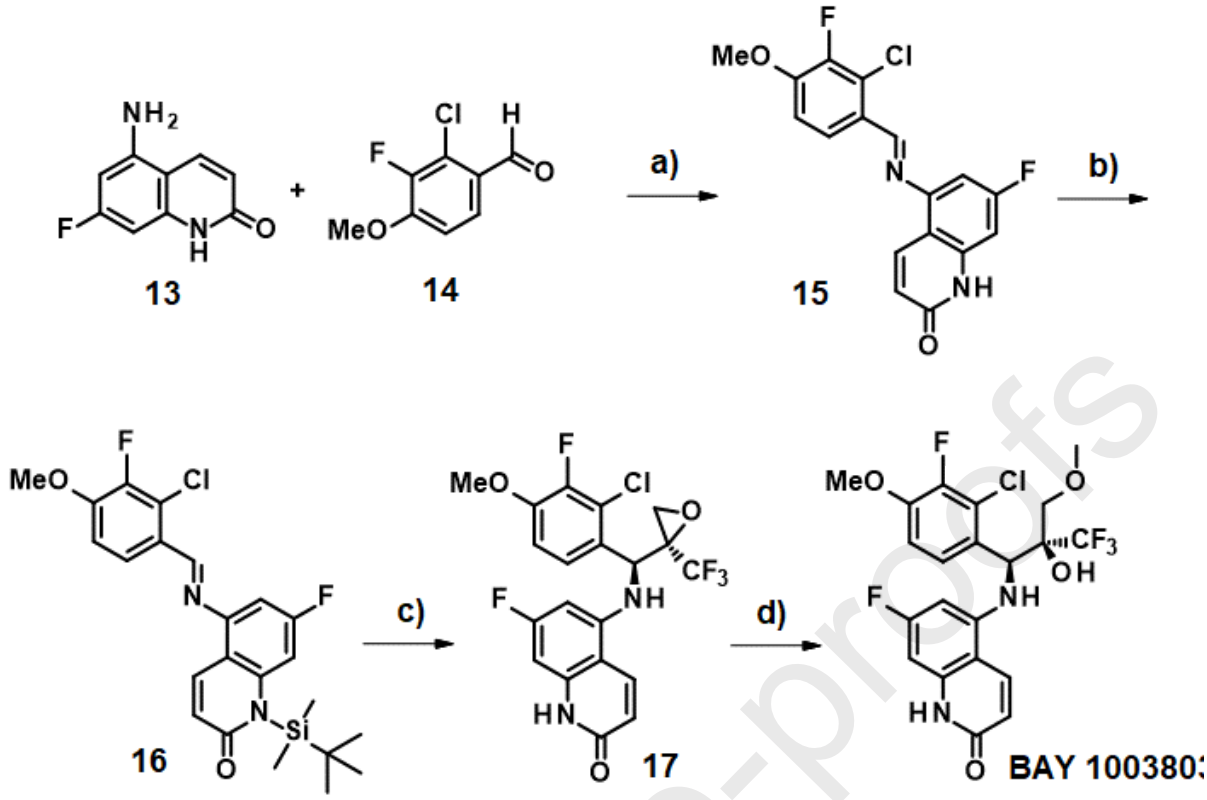
All authors are or have been employees of Bayer AG. The following authors are shareholders of Bayer AG: Markus Berger, Stefan Jaroch, Ekkehard May, Hartmut Rehwinkel, and Thomas M. Zollner.











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Graphical Abstract: