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A Career Long Effort to Discover a Drug to Treat Neurodegenerative Diseases. My Adventures with γ-Secretase for the Treatment of Alzheimer's

Rosa María Rodríguez Sarmiento[§*]

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Abstract: Neurodegenerative diseases encompass a range of chronic diseases marked by the progressive loss of structure or function of the nervous system, particularly within areas of the brain such as the neurons (or nerve cells). This degeneration leads to a decline in cognitive abilities, motor skills, and other neurological functions. The progression can be gradual, occurring over years or even decades, and often leads to significant disability and, ultimately, death. Alzheimer's disease (AD) is the most prevalent degenerative disease that affects cognition and that rises dramatically with age. It is a progressive, chronic disease that occurs when nerve cells in the brain die. Current treatments largely address symptoms without altering or reversing disease progression. However, recent advancements with amyloid-β (Aβ) antibodies validate Aβ as a therapeutic target for AD. This article details my long-term experience as a medicinal chemist and project leader working on γ-secretase, a key target in AD drug discovery. I will share initial insights from a multi-disciplinary effort to discover a disease modifying treatment for Alzheimer's disease.

Keywords: Alzheimer's disease · Amyloid-β peptide · γ-Secretase · Neurodegenerative disease

Rosa María Rodríguez Sarmiento completed her PhD under the mentorship of Prof. Julio Delgado in the University of La Laguna and the University of Sevilla winning several awards for best qualifications and best thesis. She is currently an Expert Scientist in Medicinal Chemistry at the Roche Innovation Center Basel, Pharma Research & Early Development (pRED). Rosa María is a creative drug discovery project/team leader with more than 23 years of experience in a wide array of target types, mostly in neuroscience and rare diseases. Her expertise spans all stages of drug discovery, from target evaluation to clinical candidate selection. She has made significant direct contributions to five internal Roche projects that have progressed to advanced clinical trials, including one marketed compound. Moreover, she has played a pivotal role in many projects such as the GSMs program since its inception at Roche, serving also as a project leader. Her contributions in medicinal chemistry, especially in the fields of neuroscience and rare diseases, were honoured in 2024 with the SCS Industrial Award.

1. Introduction

Alzheimer's disease (AD) is a severe neurodegenerative disease that affects memory, thinking and behaviour. It is characterized by the progressive degeneration of the nervous system, leading to a decline in cognitive function. With an aging global population, the number of affected individuals is expected to rise further in the future, representing an increasing burden on society and families.[1] γ-Secretase (GS), a multiprotein complex, is a key target for potential AD treatment. While inhibition of this enzyme causes serious side effects, its modulation offers a safe therapeutic approach. Initial efforts to obtain a novel and balanced γ-secretase modulator (GSM) with potential to be the first oral disease-modifier for early AD will be discussed.

1.1 *γ-Secretase Modulators (GSMs) for the Treatment of AD*

Alzheimer's disease (AD) is the most common form of dementia, affecting 5% of individuals over 65 years of age. Prevalence rises to 13% among those aged 75–84 and reaches 33% in people aged 85 years.[2,3] More than 55 million people worldwide are impacted, and this number is projected to double every 5 years and will increase to reach 152 million by 2050.[4] Traditionally, no cure exists for AD, making symptomatic treatment the main approach in everyday clinical practice.[5,6] Patients diagnosed with AD will experience progressive loss of cognitive function, finally affecting the independence of the patient. In histopathology, the disease is characterized by the presence of senile plaques and neurofibrillary tau tangles, respectively related to the accumulation of the amyloid-beta peptide (Aβ) and to cytoskeletal changes due to the hyperphosphorylation of microtubule-associated tau protein,

*Correspondence: Dr. R. M. Rodriguez Sarmiento, E-mail: rosa_maria.rodriguez_sarmiento@roche.com

Pharma Research and Early Development (pRED), Roche Innovation Center, Basel. F. Hoffmann-La Roche Ltd, Grenzacherstrasse 124, CH-4070.

along with neuronal and synaptic loss in regions involved in learning and memory such as the hippocampus and cortical areas.[7] Senile plaques are composed of beta amyloid (Aβ), which is a fragment of the amyloid precursor protein (APP) produced through sequential proteolytic cleavages. The main amyloidogenic Aβ species is Aβ42, which is believed to play a critical role in the initiation of AD pathogenesis.[8] Genetic and experimental evidence indicates that β-amyloid peptides (Aβ) are contributors to the pathogenesis of AD.[9] Moreover, recent results from antibodies in clinics have demonstrated the validity of reducing Aβ42 as a disease modifying therapy in AD.[10,11] Longer forms of theses peptides, particularly Aβ42 and Aβ43, are thought to be neurotoxic and more prone to aggregation,[12] while the shorter Aβ38 or Aβ37 peptides (with 38 amino acids or less) are thought to be non-toxic or even cooperatively inhibiting formation of aggregates.[13]

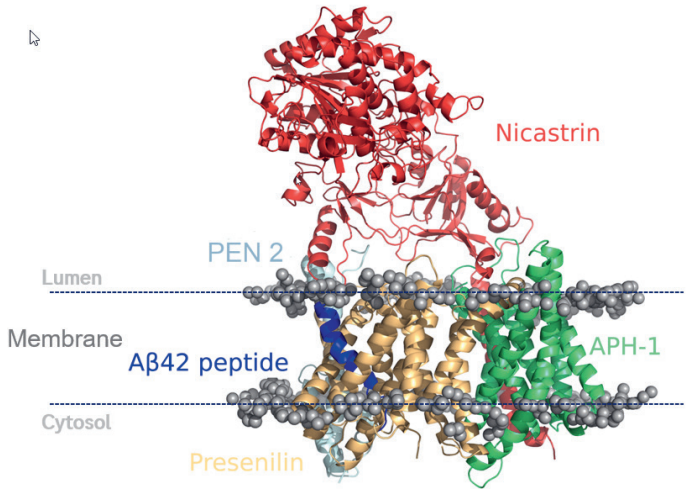
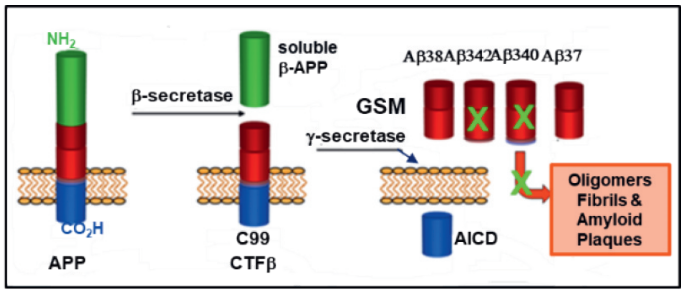


Fig.1. Structure model of human gamma-secretase complex with its 4-subunits in the endoplasmic reticulum membrane with the lumen and cytosol (lumen top and cytosol bottom). GS is responsible for the cleavage of the amyloid precursor protein (APP) to Aβ peptides such as Aβ42. In the picture, Aβ42 is modeled in blue.

γ-Secretase is a multi-enzymatic protein complex (Fig. 1) that catalyses intermembrane proteolysis of type I membrane proteins. It comprises four different subunits: presenilin (PS), nicastrin (Nc), anterior pharynx defective-1 (Aph-1) and presenilin enhancer-2 (Pen-2), each in a 1:1:1 stoichiometry with PS forming the catalytic subunit of γ-secretase.[14] It cleaves more than 90 reported substrates, of which APP and Notch are the best known to date.[15] APP cleavage results in Aβ peptides and Aβ42, while Notch is involved in gene regulation. Mutations in the APP substrate and in the PS subunit causes familial AD (FAD) with an increase of the Aβ42/Aβ40 ratio (Fig. 2).

APP is first cleaved by BACE1 to generate a 99 amino acid C-terminal fragment (C99) or CTFβ (C-terminal fragment after beta cleavage), which is then further cleaved by γ-secretase in multiple consecutive steps, to release Aβ peptides of different lengths.[14b,16]

Among several clinical γ-secretase inhibitors (GSI), two of them (Semagacestat (LY-450149) and Avagacestat (BMS-708163)), reached Phase III/II trials and were discontinued due to many liabilities (memory worsening, skin tumour and decrease in lymphocyte count) attributed to mechanism-related toxicity[17,18] and Notch.[19] They bind to the catalytic side on the PS subunit and abrogate the whole enzymatic activity, including the processing of Notch that is involved in numerous cellular processes including cell fate or cell proliferation and gene transcription or regulation.[20] GSMs also bind to presenilin (PS) but at a different side,



Abbr: APP amyloid precursor protein, **CTF** C-terminal fragment, **Aβ** amyloid β-peptide, **AICD**: APP intracellular domain.

Fig. 2. Amyloidogenic processing of APP in Alzheimer's Disease.

and shifts the cleavage pattern from amyloid beta protein towards more soluble, non-toxic shorter amyloid peptides such as Aβ37 and Aβ38 at the expense of amyloidogenic Aβ42/Aβ40, while the total Aβ levels are not affected significantly.[21]

The shorter Aβ peptides do not form aggregates and even function as Aβ42 aggregation inhibitors.[13,22] The effect of certain GSMs on Aβ peptides is in opposition to the effect of FAD PS1 mutations on APP processing, indicating potential in delaying or preventing early-onset dementia by altering Aβ42 production.[22b,23] Sensitivity of GSMs on different PS mutations can be compound dependent.[24] GSMs leave Notch-processing unaffected avoiding Notch-related side effects observed for γ-secretase inhibitors. Thus, while inhibiting γ-secretase leads to serious side effects, its modulation offers the potential to deliver a safe treatment for AD.

2. First Impressions

When I joined the GSM group at Roche in 2016, the competitive field was already populated with second generation heterocyclic non-NSAIDs (non-acids with improved brain penetration) GSM compounds.[25,26] Importantly, almost all non-NSAIDs reported, including our own initial GMSs,[27] shared privileged structural characteristics such as a high degree of aromaticity and the presence of an aryl-imidazole ring on the left hand side (LHS) that seemed to be required to achieve high potencies. This was the case with our pyrido-triazole series, that showed very high *in vitro* potency, nevertheless they suffered from limited *in vivo* efficacy (Fig. 3).[26]

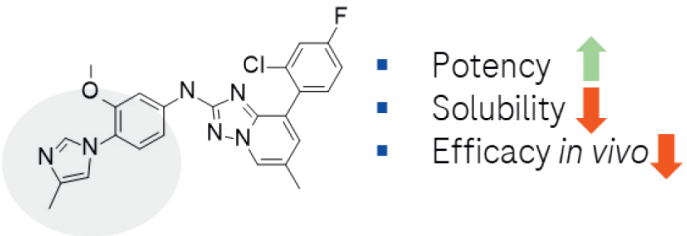


Fig. 3. Initial lead series with improved potency.

3. Adventures to Advance GSMs with Good Profiles

We made significant efforts to optimize the properties and achieved high *in vivo* potency by reducing aromaticity and by improving solubility and metabolic stability. Our differentiated GSM lead compound RO6800020 (**1**) was derived from several optimization cycles from the already patented pyrido-triazoles chemical series which were terminated due to limited *in vivo* activity together with issues such as Pgp (high Pgp efflux ratio), GSH (forming glutathione adducts) or drug-drug interactions. RO6800020 showed improved profile and exhibited promising *in vivo* efficacy in our double transgenic mice APP-Swedish

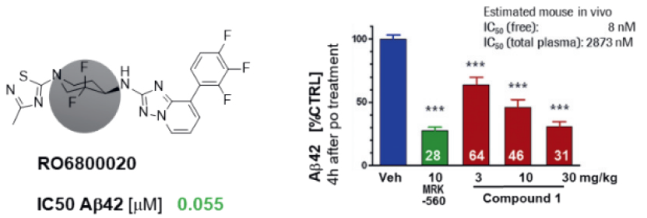


Fig. 4. First lead compound and *in vivo* potency.

mice model. We measured efficacy *via* reduction of Aβ42 in the brain. Our objective was to reduce Aβ42 by at least 50% (Fig. 4).

We confirmed that *in vitro* RO6800020, our first front runner, behaved as expected for a GSM; reducing Aβ42, Aβ40 and increasing Aβ37, Aβ38 without affecting Notch (Fig. 5).

However, RO6800020 showed several liabilities such as a phototoxicity flag, a covalent binding liability and a lack of selectivity as it inhibited phosphatidylinositol 4-kinase catalytic beta (PIK4CB) activity. The SAR in our GSH assay was not always predictive for covalent bonding (CVB) in the series (*e.g.* RO6800020 had no flag in GSH but it showed CVB measured with the radiolabelled C14 compound). We also decided to explore alternative central piperidine rings to see if the difluoro piperidine from RO6800020 could be involved in the formation of a reactive metabolite that could react with GSH, maybe *via* enamine formation.

In a 'point mutation' exercise the causative substructure for the covalent binding could be identified. Only the exchange of the thiadiazole head group led to compounds devoid of CVB (Fig. 6).

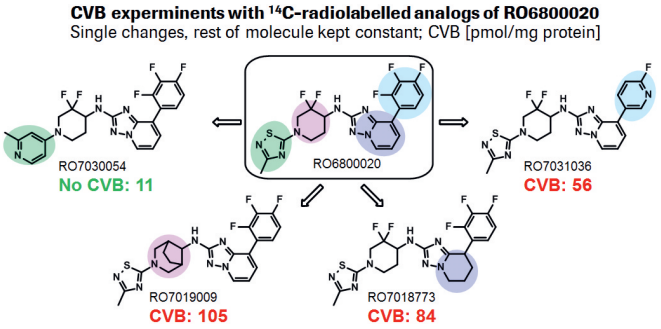


Fig. 6. 'Point mutation' of RO6800020 identified the thiadiazole as causative structural motif of CVB.

By exploring replacements for the central ring (variously bridged, bicyclic or azaspiro piperidine analogs) we revisited our previously patented bridged piperidines, and we realized that in our series the [3.2.1] bridge piperidine gave an excellent improvement in potency, without compromising the metabolic stability. We also observed that the new bridge piperidine showed a particular conformation compared with the difluoro piperidine that was 10-fold less potent. Due to the repulsion of the bridge and the lone electron pair from the piperidine nitrogen that enforces an almost linear orientation from the exit vectors, it shows a more favourable conformation (Fig. 7).[28]

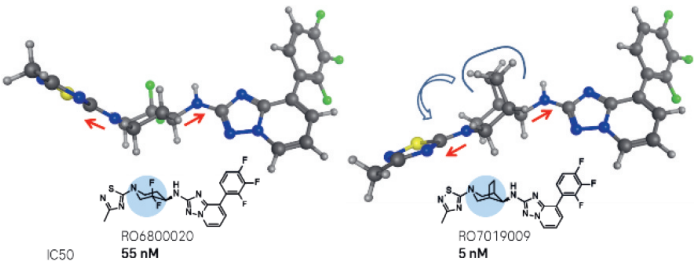


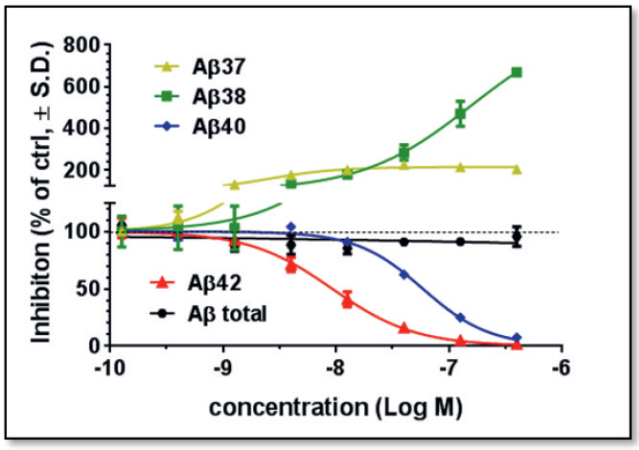
Fig 7. Favourable conformation from the bridge piperidine that enforces a more linear conformation from the exit vectors. Comparison with the less potent difluoro piperidine analog.

We recovered the original potency from pyrido triazoles using our bridge piperidine as a 'mimetic' for a phenyl ring. With the use of the bridge piperidine, we discovered our next candidate RO7019009 (compound **4**, in Fig. 8) with a much-improved potency and reduced lipophilicity along with decreased plasma protein binding (hfu: 0.4% as compared to hfu: 0.03%) and good metabolic stability that translated into a high *in vivo* efficacy.

Furthermore, compound **4**, despite having similar covalent binding to compound **3** (105 pmol/mg, measured with the radiolabelled C14 compound), shows a lower risk for idiosyncratic toxicity, due to the lower predicted human dose (7–25 mg/kg).[29] Nevertheless, compound **4** had to be discontinued due to phototoxicity.

With the introduction of a bioisosteric fluorinated alkoxy group replacing the trifluoro aromatic ring, we could avoid phototoxicity, improving solubility (Fig 8).[28] In addition, we could further improve the potency and the selectivity for PIK4CB kinase

A



B

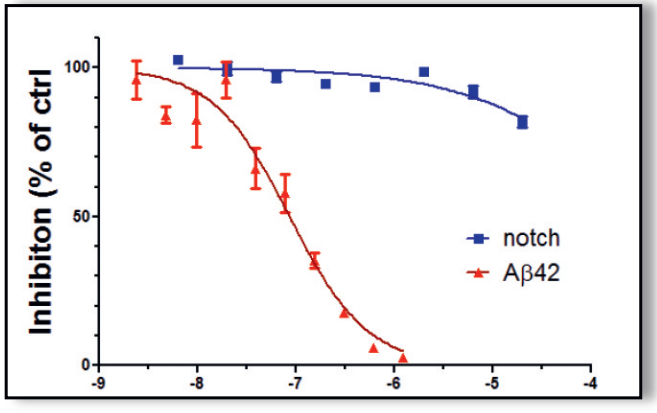


Fig. 5. A) Dose response curves on Aβ42, Aβ40 and Aβ37, Aβ38 in Hek cells. No effects of compound on total **A**β. B) Dose response of RO6800020 on Aβ42 and Notch inhibition in Hek cells.

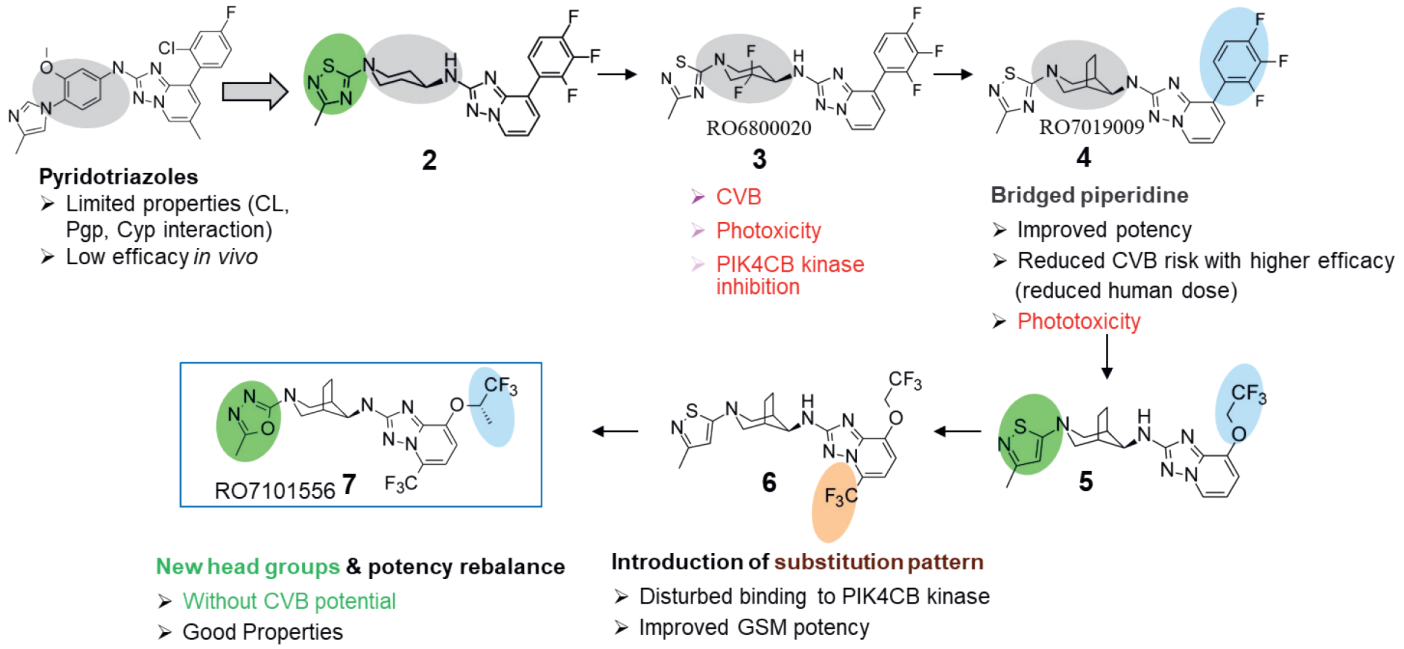


Fig. 8. Sequential changes with improvement on potency, properties and safety flags.

(from 120 nM for compound **5** to > 40 mM potency for compound **6**) by sequential changes as indicated in Fig 8.

Finally, we could replace the thiazole and isothiazole rings for different left hand side heterocycles to avoid the risk of idiosyncratic toxicity due to covalent binding. Moreover, all new compounds did not show any GSH flag or any CVB measured with radiolabelled material.[28] We selected compound **7** as our candidate for toxicological studies.

4. Securing a Leading Position After First Tox Data

From the new 'alkoxy chemical series' we evaluated compound **7** in a pharmacodynamic (PD) mice model to determine its efficacy using the double transgenic APP-Swedish mice. The compound was administered orally at single doses of 3, 10 and 20 mg/Kg which led to strong effects on Aβ reduction in a time and dose dependent manner. An *in vivo* IC_{50} of 40 nM was determined fitting the time course of exposures and the Aβ42 levels (Fig. 9). As the initial profile of compound **7** was looking promising, it was submitted for further characterization with an *in vivo* rat toxicological study.

Unfortunately compound **7** displayed low tolerability, and showed exposures lower than expected, with low separation margins (10-fold obtained, predicted 50-fold) in our minitox study in a rat (4 days treatment upon oral administration). In addition, high doses (200 mg/Kg) were needed to achieve sufficient separations, due to the medium potency and also lower exposures.

We tried to identify a backup molecule with a differentiated profile. As we did not know if the tox results were also related to the chemical class, we wanted to have chemical diversity in our back up strategy. We targeted higher potencies (IC_{50}< 20 nM) to avoid the use of high doses in the toxicological studies to achieve the desired margins of 30-fold. We also applied our learnings reducing aromaticity to avoid phototoxicity and using left hand side heterocycles to avoid CVB. Four different chemical classes were explored: the alkoxy series, the monocyclic triazole with opened ring, and the saturated series A (C-saturated) and B (N-saturated) (Fig. 10).

Within the alkoxy class we tested a compound that was more potent than compound **7** and that fulfilled the characteristics desired for a backup compound. Unfortunately, despite the higher potency and efficacy (Fig. 11) and lower doses needed in toxicological studies for compound **8**, we again saw a lack of tolerability, with low safety margins indicating a class effect.

We also identified open analogs or monocyclic triazole analogs, which posed challenges in maintaining high potency. Despite this, we successfully identified a backup candidate with favorable properties and high potency (IC_{50} for Aβ42: 10 nM). However, we discontinued profiling monocyclic triazole analogs due to the formation of a phenol, which tested positive in the AMES assay, resulting from compound hydrolysis in simulated gastric fluid at 60 °C. For this

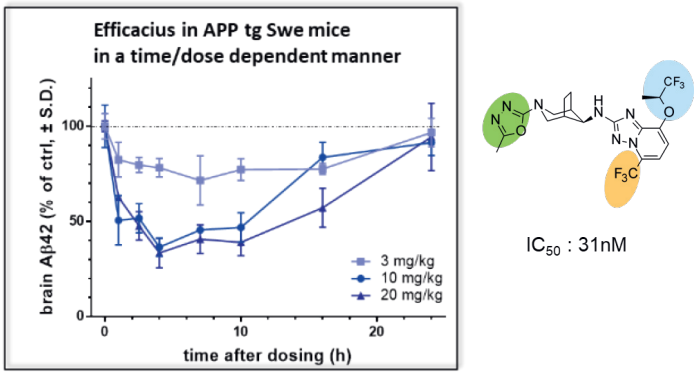


Fig. 9. Pharmacodynamic effects of compound **7** in double transgenic APP-Swedish mice.

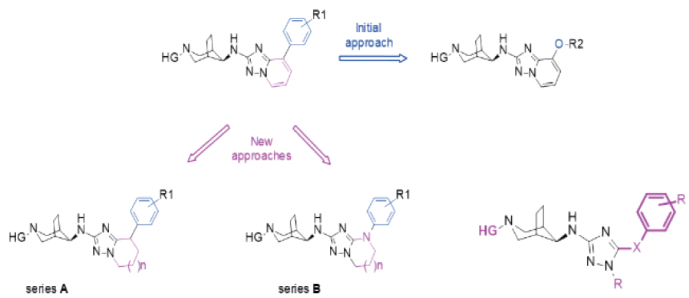
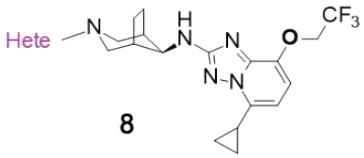


Fig. 10. Exploring chemical diversity for a backup.

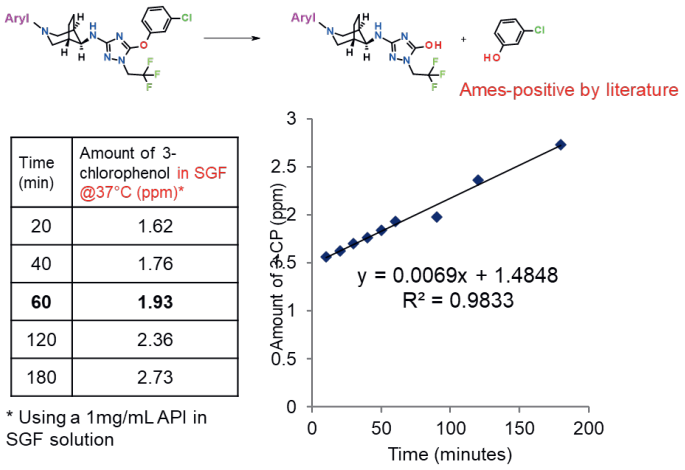


Alkoxy series **8**

In vitro [free nM]<	RO7101556	RO7187316
Hum IC_{50} H4 $A\beta_{42}$	20.4	6
Hum IC_{50} Hek293 $A\beta_{42}$	13.0	4
Mouse IC_{50} N2A $A\beta_{42}$	14.2	2.2
Mouse APP IC_{50} $A\beta_{42}$	50	3.8
Heps CI		
Hum / rat	< 1 / 6.3	7 / 12

Fig. 11. Back-up from the same chemical class as compound **7** (alkoxy series).

class, it was not feasible to develop potent compounds with desirable properties that also yielded AMES-negative alcohols (Fig. 12).



Time (min)	Amount of 3-chlorophenol in SGF @37°C (ppm)*
20	1.62
40	1.76
60	**1.93**
120	2.36
180	2.73

* Using a 1mg/mL API in SGF solution

Fig. 12. Monocyclic triazoles.

We investigated various saturated series, including the N-saturated series (B) and the C-saturated series (A) as depicted in Fig. 13. Our findings indicate that ring size affects potency, with the 6-member ring consistently exhibiting slightly higher potency when X is nitrogen for the N-saturated series. In the C-saturated series (A), the 7-member ring is the one that shows the highest potency. In this case, the effect of the ring size is more pronounced. For both series the 5-member ring is the one with the lowest potency. The effects of the ring size on potency for each subseries can be rationalized with the conformational changes for each series according to the ring size and in particular, the position of the right-hand side aromatic ring.

The potency order for N and C-saturated series agrees with the phenyl moiety being better in alignment to the aromatic ring from the potent triazolo-pyridine core RO7019009. 7-Member rings and 6-member rings are in better alignment with the trifluoro aromatic ring from RO7019009 for the C and N-saturated series respectively. This can be better observed in Fig. 14.

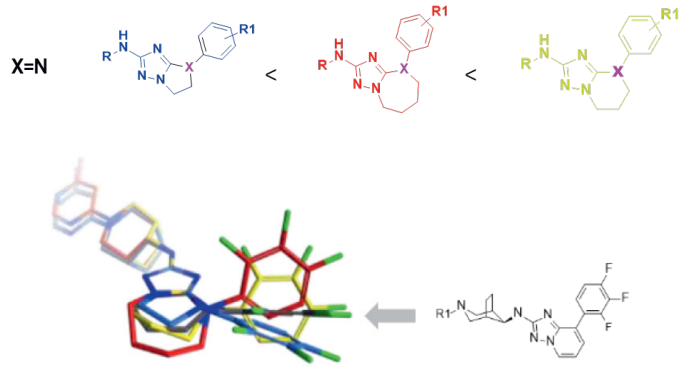


Fig. 13. Conformational effect of the ring size within sub-series B (N-saturated) & potency increases by ring size. Alignment with potent triazolo-pyridine.

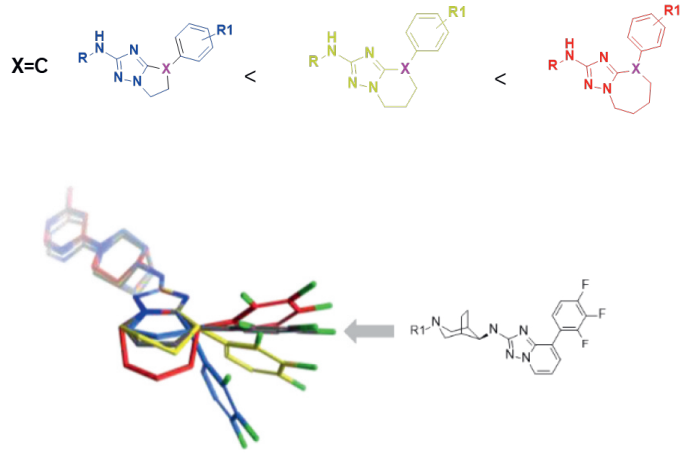


Fig. 14. Conformational effect of the ring size within sub-series A (C-saturated) & potency increases by ring size. Alignment with potent triazolo-pyridine.

For the C-saturated series the effect of ring size is stronger regarding conformation and positioning of the aromatic ring. For the N-series the effect of ring size in conformation-aromatic ring positioning is less pronounced (Figs. 14 and 15). This effect agrees with the measured potency differences for each series according to ring sizes.[30]

We focused on tetrahydro-triazolo-azepine (in red) and dihydro-triazolo-pyrimidine (in yellow) compounds for the C and N-saturated series respectively. We explored different left hand sides heterocycles R, and different substitution patterns on the phenyl moiety balancing potency, lipophilicity, Pgp, safety flags, and keeping the desired potency (< 20 nM). We discovered that for the C-saturated series the best compromise is a methyl pyrim-

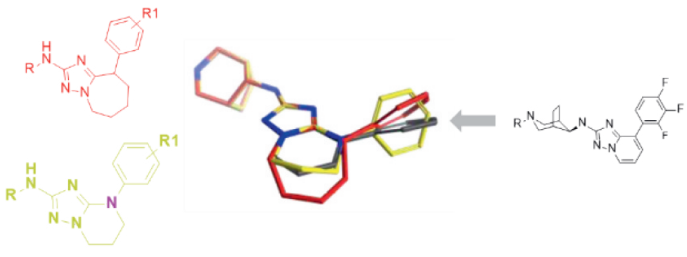


Fig. 15. Conformational effect of the ring size within C and N-saturated sub-series. Potency increases by ring size.

idine with a trifluoro substitution on the right-hand side aromatic ring. In these racemic series the *S* enantiomer is the most potent. Instead, for the N-saturated heterocycles the difluoro aromatic ring was the best on the right-hand side, in this case also a methyl pyrimidine was the best compromise in terms of properties as the left-hand side heterocycle.

We selected two compounds, **9** and **10**, with excellent *in vitro* and *in vivo* profiles for toxicity studies.[30] Both compounds were tested in 14-day toxicological studies in rodents with no serious side effects, good tolerability, and no histopathological findings. Nevertheless, they showed a different behaviour for 14-day toxicological assessment in minipigs, with compound **10** being superior compared to **9** (Fig. 16).

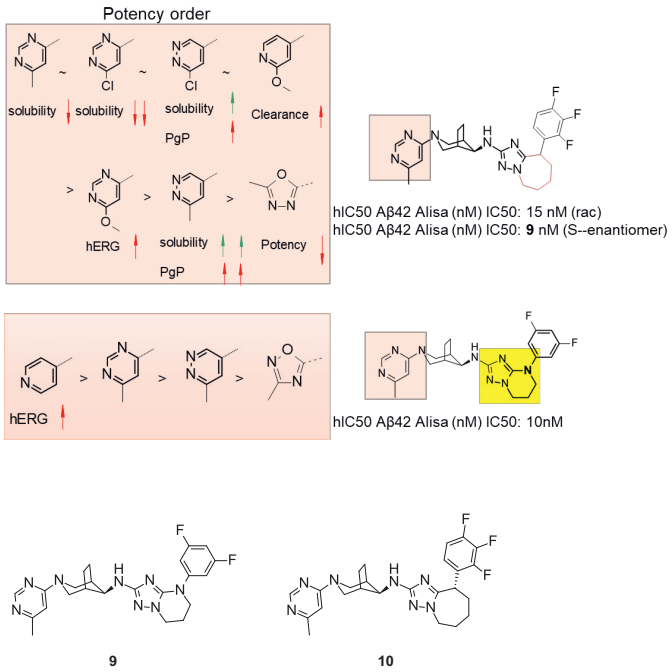


Fig. 16. Effects of substitution patterns on key properties. Final compounds **9** and **10** selected for toxicological studies.

Compound **10**, with a robust efficacy in the APP-Swedish mice (*in vivo* CSF IC_{50} Aβ42 of 2.5nM), was suitable to enter into human enabling studies. Unfortunately, after a 4 week GLP toxicology study compound **10** showed histopathology findings at exposures with low margins of separation above efficacious concentrations (Figs. 17 and 18).

5. One More Chance to Find a Better GSM

Using all the knowledge acquired during our long endeavours to find a GSM, we were able to get a further optimized compound that performed well in rodents' toxicological studies and also in GLP tox studies. RG6289 is currently in phase II clinical trials for the treatment of AD and it has the potential to become the first oral disease-modifier for early AD.[31] Further information on the compound will come in the near future. Our GSM binds at the presenilin side, nevertheless in a different pocket to GSIs which bind to the catalytic side (Fig. 19).

6. Conclusions

Drug discovery is a multi-parameter optimization problem where many properties must simultaneously be met for a new compound to fulfil the desired profile according to the indication and the target.

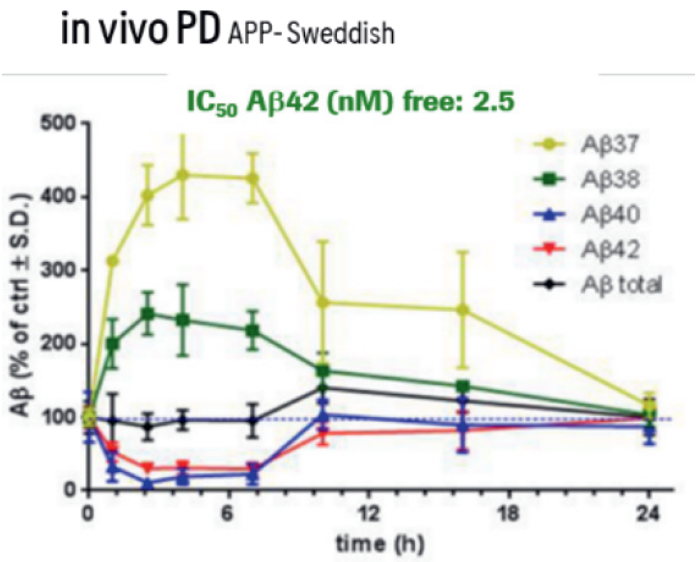
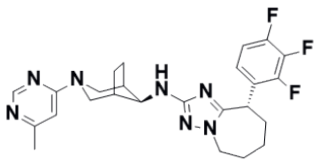


Fig. 17. *In vivo* efficacy for compound **10**.



	10
hIC50 Aβ42 Alisa (nM) total	10
Mouse IC50 Aβ42 total/free	4/2
h Notch IC50 (nM)	>10000
LogD (pH =7.4)	3.8
Cyp inh. 3A4, 2D6, 2C9 % inh. @ 10 mM	-8 / 15 / 34
Cl heps h,m,r (mL/min/Mcells)	4.5 / 6.7 / 43
Fu_{pl} h, m, r (%)	5.4 / 1.4 / 1.6
P-gp h, m (ER)	2.4 / 3.3
hERG IC_{20} patch clamp (μM) margin (IC_{20}/ 3xCss)	0.34 (22)
GSH	Neg.
AMES/MNT	Neg.

Fig. 18. Profile for compound **10**.

γ-Secretase, a target in the central nervous system (CNS), offers a unique mode of action within the refined amyloid hypothesis for Alzheimer's disease. It shifts the production of pathogenic Aβ42 towards shorter, non-amyloidogenic (non-toxic) Aβ peptides. In this context, I present my contributions to the discovery of a distinct drug for a differentiated target, aimed at treating Alzheimer's disease an area of significant unmet medical need.

Acknowledgements

We would like to extend our heartfelt thanks to our numerous colleagues at F. Hoffmann-La Roche for their invaluable contributions, in-

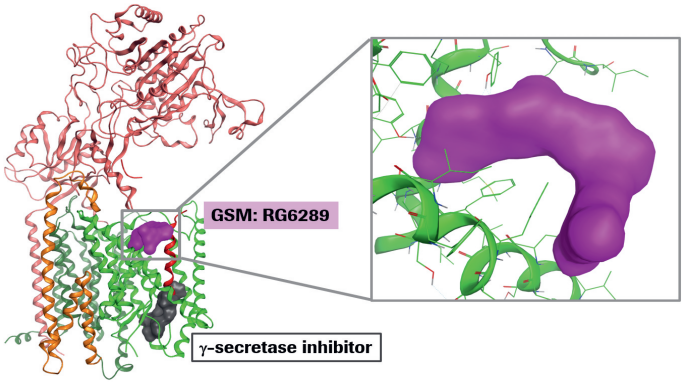


Fig. 19. PDB ID 7D8X, with GSM RG6289 modelled.

sightful discussions, and collaborative spirit over many years. We also thank the patients participating in clinical trials.

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