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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Direct syntheses of stereoisomers of 3-fluoro GABA and β-fluoroamine analogues of the calcium receptor (CaR) agonists, cinacalcet, tecalcet, fendiline and NPS R-467

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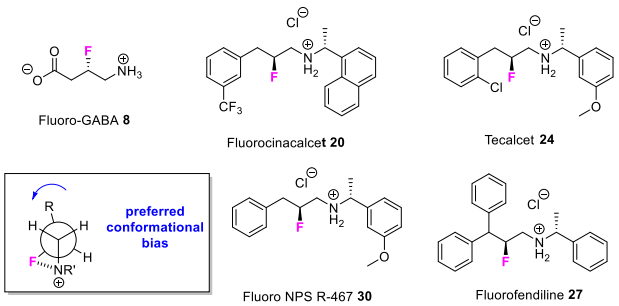
Abstract

Synthetic routes following a sequential MacMillan organocatalytic asymmetric α-fluorination protocol for aldehydes and then reductive amination, have allowed ready access to bioactive β-fluoroamines. The approach is demonstrated with a short synthesis of (*S*)-3-fluoro-γ-aminobutyric acid (3F-GABA) and was extended to β-fluoroamine stereoisomers of cinacalcet, tecalcet, fendiline and NPS R-467, all allosteric modulators of the calcium receptor (CaR). Stereoisomers of the fluorinated calcimimetic analogues were then assayed in a CaR receptor assay and a comparison of β-fluoroamine matched pair stereoisomers revealed a binding mode preference to the receptor as deduced from conformations which will be favoured as a consequence of the electrostatic *gauche* effect.



Keywords Electrostatic gauche effect · Calcimimetics · Cinacalcet · Fluorinated drugs · Calcium receptors · Asymmetric fluorination

Introduction

It is well known that fluorine can influence the electronic properties of drug candidates by modulating the pKa of neighbouring functional groups or by influencing molecular

Dedicated This study is dedicated to Dr Nicholas A. Meanwell on the occasion of his retirement who among his wide interests, also promoted applications of fluorine in medicinal chemistry.

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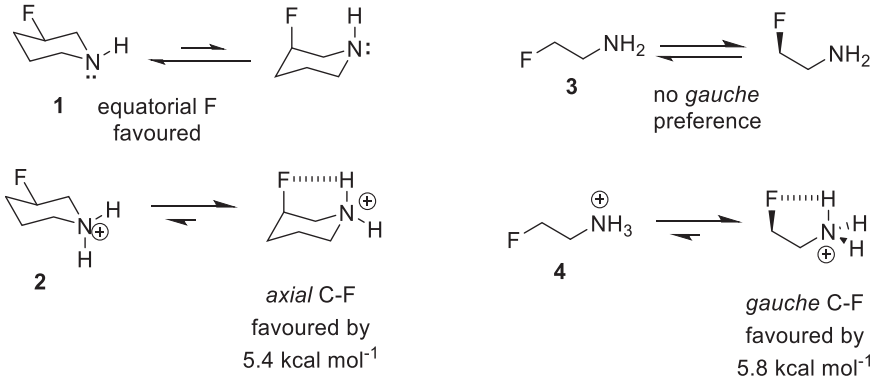
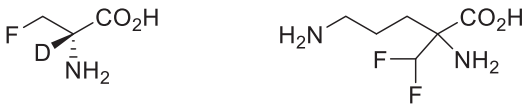


Fig. 1 The *gauche* conformation in *β*-fluoramines dominates when the amine is protonated (**2** and **4**) an effect dictated by electrostatic attraction between fluorine and the electropositive hydrogens [4–11]

conformation through the stereoelectronic preferences dictated by fluorine [1–3]. A special case in this regard is found in *β*-fluoroamines, where an attractive electrostatic interaction occurs between the carbon bound fluorine atom and the protonated amine [4]. This 'electrostatic *gauche* effect' is more significant in energy terms than the classical '*gauche* effect' in 1,2-difluoroethane, the latter of which has a *gauche* conformer around 1.0 kcal mol^{-1} lower in energy that the *anti* conformer. The phenomenon is generally considered to have an origin in weak stereoelectronic hyperconjugative interactions [5–7], whereas the electrostatic attraction between fluorine and the protonated amine is significantly stronger. The phenomenon was first discussed by Lankin and Snyder who noted an inversion of the equatorial to axial preference of the fluorine in going from 3-fluoro-piperidine **1** to the protonated piperidinium **2** ring systems as illustrated in Fig. 1 [8–11]. In the protonated case **2** the axial conformer is calculated to be stabilised by 5.4 kcal mol^{-1} and is the only conformer observed in aqueous solution. Similarly there is no obvious *gauche* preference for 2-fluoroethylamine **3** as a free base but when the amine is protonated as in **4**, then there is a very strong *gauche* preference calculated at 5.8 kcal mol^{-1} [12], and this offers another illustrative example of the significance of the electrostatic *gauche* effect [12, 13].

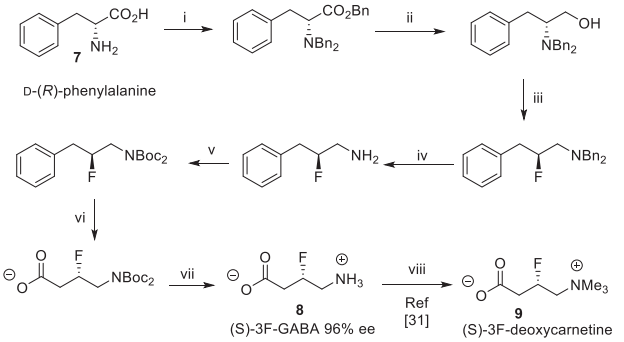
This electrostatic *gauche* preference has subsequently been described in a diversity of systems such as *β*-fluorinated N-heterocycles [14, 15] and, for example, it has been observed to influence pyrrolidine ring conformations in ligands bound to G-quadruplex DNA [16]. There are many examples where the *β*-fluoro amine motif has been incorporated into bioactives [17, 18] and although the incorporation of fluorine can have a variety of subtle effects which will influence pharmacokinetics, the electrostatic *gauche* effect is a significant one in influencing molecular conformation. Also there is a long tradition in bioorganic chemistry of using selectively fluorinated enzyme substrates as a trigger for mechanism based inhibition in enzymology including *β*-fluoroamines [19–22]. For example, *β*-fluorinated amino acids have been serially exemplified as a privileged design for mechanism based inhibitors of pyridoxal phosphate (PLP) enzymes. Examples such as fludalanine **5** [23] and eflornithine **6** [24] have become clinically significant and such approaches have been explored in 3-fluoro-γ-aminobutyric acid (3F-GABA) **8** processing enzymes [25–27].



5 **6**

In general the installation of a fluorine atom *β* to an amine requires several synthesis steps and for most situations that are useful in enzymology, then single enantiomers are required. Previously we reported a synthesis of the selectively fluorinated enantiomers of 3F-GABA **8** to explore binding affinities at the GABAα and GABAβ receptors [25–27], and we also demonstrated that the enantiomers were processed differently with the key GABA metabolising enzyme, GABA transaminase [28]. In those cases the synthesis of each enantiomer required a seven step protocol from D-(*R*)-phenylalanine **7**. This route was extended by others to prepare enantiomers of 3-fluorodeoxy carnitine **9** [29–31] as summarised in Scheme 1.

We report here a significantly shorter synthesis of the (*S*)-3F-GABA **8** using a protocol involving an asymmetric fluorination coupled to a reductive amination. The primary motivation aimed to shorten the earlier synthesis of 3F-GABA enantiomers [28], however the approach extended very easily to other bioactive *β*-fluoroamine stereoisomers, and to that end we demonstrate a direct route to stereoisomers of *β*-fluoroamine agonists of the calcium receptor (CaR) agonist cinacalcet **15**, and to other similarly derivatised stereoisomers of related calcimimetics [32, 33]. With a collection of these *β*-fluoroamine stereoisomers in hand, they were then assayed against the CaR receptor to assess the relative potency of the different stereoisomers, a comparison that should reveal preferred binding conformations

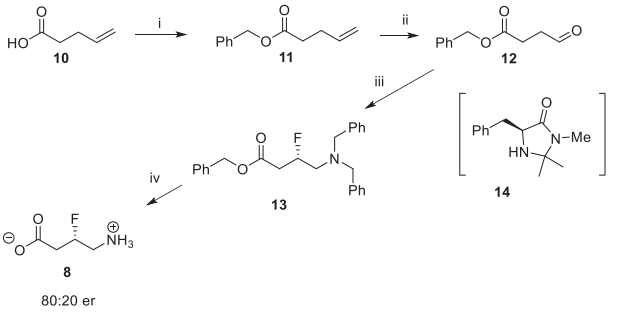


Scheme 1 Previous synthesis to (*S*)-3F-GABA and its extension to (*S*)-3F-carnitine from D-(*R*)-phenylalanine. i. BnBr, K_2CO_3, EtOH, 90%, ii. $LiAlH_4$, THF, 95%, iii. Deoxo-FluorTM, DCM, 75%, iv. $Pd(OH)_2/C$, H_2, v. Boc_2O, 4-DMAP, MeCN, 80%, vi. $NaIO_4$, $RuCl_3$, CCl_4/MeCN/H_2O, 76%, vii. HCl gas, DCM, 80%, viii. CH_3I, K_2CO_3, MeOH, quant [28, 31]

dictated by fluorine, as the electrostatic *gauche* will differentially influence the conformations of the stereoisomers. The outcomes do indeed indicate a conformational bias of the flexible chain of the calcimimetics on the receptor.

Results and discussion

A synthetic route was developed and exemplified for (*S*)-3F-GABA **8** as shown in Scheme 2. The method used the MacMillan asymmetric α-fluorination [34] protocol, one of several organocatalytic methods which have been reported for the α-fluorination of aldehydes [35, 36]. Fluorination was followed by a reductive amination to install the amine. Lyndsey et al. [37] have already demonstrated reductive aminations after such asymmetric fluorinations. That protocol focussed on piperazine and piperidine rings but did not progress to the free amines. It seemed feasible however to carry out a hydrogenolysis of a dibenzylamine product to generate the free amine for a 3F-GABA synthesis as illustrated in Scheme 2. Accordingly aldehyde **12**, which was prepared in a two-step protocol from pent-4-enoic acid **10**, was used as a substrate for organocatalytic asymmetric fluorination using organo-catalyst (*S*)-**14** and N-fluorobenzenesulfonimide (NFSI) [34]. Treatment of the product aldehyde with dibenzylamine followed by addition of sodium triacetoxyborohydride (STAB) [38] reduced the in situ formed imine, and generated amine **13**. Amine **13** was then subjected to hydrogenation (Pd/C, H_2) to remove the benzyl groups and release (*S*)-3F-GABA **8**. The enantiopurity of 3F-GABA **9** was conveniently determined by $^{19}F\{^1H\}$-NMR in $CDCl_3$ after an excess of (*S*)-lactic acid was added to the NMR tube and where the resultant diastereoisomeric *β*-fluoroammonium salts gave resolved ^{19}F-NMR signals. Although a convenient two step protocol, the stereoselective introduction of the fluorine was modest, (80:20 er) and was not easily improved.



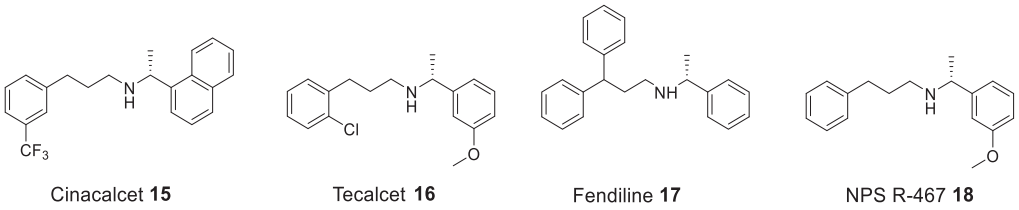
Scheme 2 Reagents i. *p*-TsOH, BnOH, Toluene, >99%, ii. O_3, DCM, 90%, iii. Catalyst **14**, NFSI, THF/*i*-PrOH; Dibenzylamine, NaB-H(OAc)$_3$, DCE, 52%, iv. Pd/C, H_2, MeOH, 93%

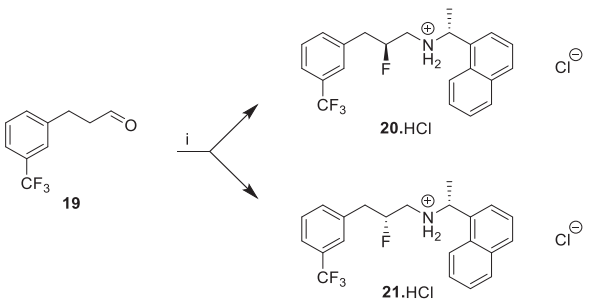
Subsequent hydrogenolysis resulted in a satisfactory preparation of (*S*)-3F-GABA **8**. This approach reduced the original seven step protocol to a four-step protocol from carboxylic acid **10** although the enantiopurity was compromised relative to the longer route.

Synthesis of *β*-fluoroamine – calcimimetic analogues

The asymmetric α-fluorination-reductive amination protocol explored above was then extended to *β*-fluoroamine analogues of the calcimimetic drugs **15**-**18** shown in Fig. 2. Cinacalcet **15** [39] tecalcet **16** [40] fendiline **17** [41] and NPS R-467 **18** [42] are agonists which act by allosteric activation of the G-coupled protein - calcium receptor (CaR) [43]. These drugs act essentially by mimicing the role of Ca^{2+} ion at the receptor. Tecalcet **16** was the first of this class to be evaluated, however it was superseded by cinacalcet **15** which received regulatory approval in 2004 and remains a daily oral therapy for patients with hyperparathyroidism. One issue with this and related drugs is to understand how they bind to the transmembrane G-protein coupled receptor, which are not well characterised structurally, certainly at the level of small molecule binding [44]. The introduction of a fluorine atom *beta* to the amine, and then comparative assays of stereoisomers which differ only in the C-F configuration, offers a tool to explore the preferred binding conformation of the parent agonists **15**-**18** on the receptor. This is because the C-F bond will prefer to adopt a *gauche* rather than *anti* peri-planar alignment to the C-N^+ bond of the protonated amines, due to a strong electrostatic attraction between the fluorine and the hydrogens of the positively charged nitrogen, a phenomenon that accounts for the 'electrostatic *gauche* effect' (Fig. 1). If both fluorinated stereoisomers of a given agonist have similar efficacies it can be assumed that both isomers adopt a similar extended zig-zag conformation. However if the matched pair isomers respond differently in assays this would imply a more biased conformation. In this study we

Fig. 2 Calcimimetic drugs **15**–**18** used in the clinic.





Scheme 3 Reagents i. Catalyst (*S*)-**14** or (*R*)-**14**, NFSI, THF/*i*-PrOH; (*R*)-1-(1-naphthyl)ethylamine, $NaBH(OAc)_3$, DCE, 28% for **20** and 50% for **21**

have prepared stereochemical pairs of several *β*-fluoro calcimimetic analogues to explore their interaction with the CaR receptor. This improved a previous study in our lab where the isomers of 3-fluorocinacalcet **20** and **21** had been prepared, however by a longer synthesis route [45], and a broader range of fluorinated analogues is prepared here.

The synthesis of the *β*-fluoroamine diastereoisomers of the cinacalcet analogues is summarised in Scheme 3. A telescoped asymmetric α-fluorination of aldehyde **19** coupled with reductive amination using (*R*)-1-(1-naphthyl) ethylamine and either organo-catalyst (*R*)-**14** or (*S*)-**14** generated diastereoisomers **20** or **21** respectively, both in good yield and high diastereoselectivities (99.5:0.5 dr) after purification.

For the synthesis of tecalcets (^{F}S)- **24** and (^{F}R)- **25**, aldehyde **23** was prepared from ester **22** after a controlled reduction with DiBAL. The asymmetric fluorination protocol was conducted with aldehyde **23** with either organo-catalyst (*R*)-**14** or (*S*)-**14** and the reductive amination was carried out after the addition of (*R*)-α-amino(3-methoxy) phenylethylamine. This generated diastereoisomers **24** (93:7 dr) or **25** (93:7 dr) respectively, as their HCl salts as illustrated in Scheme 4. An X-ray structure was solved in each case which confirmed relative stereochemistry.

For the synthesis of the fluorofendilines, each of the diastereoisomers (^{F}S)- **27** and (^{F}R)- **28** was accessible from aldehyde **26** using either catalyst (*S*)-**14** or (*R*)-**14** and then reductive amination after addition of (*R*)-*a*-phenylethylamine as illustrated in Scheme 5. Diastereoisomers **27** (90:10 dr) and **28** (95:5 dr) were isolated in good to high diastereoselectivity and an X-ray structure of the hydrochloride salt of stereoisomer **28** was solved (Scheme 5) which confirmed relative stereochemistry.

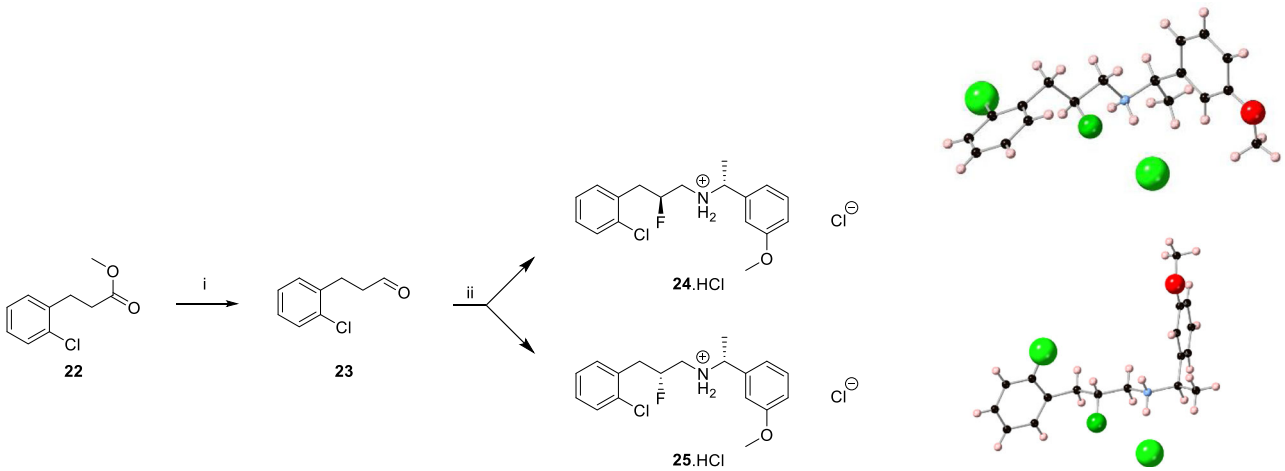
The fluorinated NPS R-467 stereoisomers (^{F}S)- **30** and (^{F}R)- **31** were prepared by the telescoped protocol. Asymmetric fluorinations of 3-phenylpropionaldehyde **29** with and either organo-catalyst (*R*)-**14** or (*S*)-**14** followed by a reductive amination with (*R*)-α-amino(3-methoxy)phenylethylamine, generated diastereoisomers **30** (88:12 dr) or **31** (84:16 dr) respectively as illustrated in Scheme 6.

In this way a collection of four pairs of diastereoisomers of *β*-fluoro calcimimetic analogues were prepared. The diastereoisomeric excesses could be improved in most cases by chromatography. The stereochemical purities before and after chromatography are summarised in Table 1.

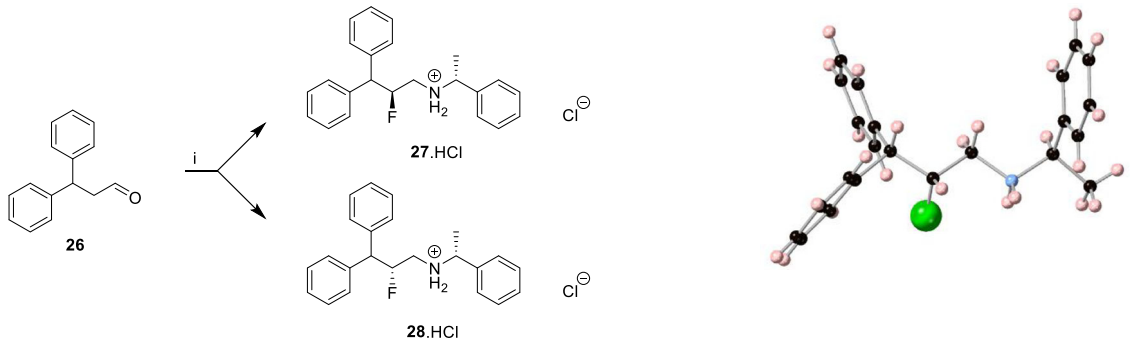
Calcium receptor (CaR) assays

The calcimimetic analogues prepared here were all assayed as agonists of the calcium receptor (CaR) [46, 47]. Assays were carried out with between $n = 4$ and $n = 6$ repeats. The outcomes of the CaR assays are reported in Table 2. All of the stereoisomers displayed agonist activity. Of the four matched sets of diastereoisomers, three sets were analysed in full and a trend in pK_B (affinity for the receptor) emerges. Those with the (^{F}S)-absolute configuration at the fluorine stereogenic centre display a consistently slightly higher level of activity than those with an (^{F}R)- absolute configuration. In the case of cinacalcet, the (^{F}S)-isomer **20** was more active than cinacalcet **15** itself and the (^{F}R)-isomer **21** had a similar level of activity. For the other two matched sets then the parent compounds **16** and **18** and the (^{F}S)-isomers **24** and **30** had similar activities respectively, and again the (^{F}R)-stereoisomers **25** and **31** had lower relative activities. It should be noted that it was only the cinacalcet stereoisomers that were stereochemically pure, the other matched sets had lower diastereoisomeric excesses (see Table 1) and thus a maximum effect will be observed in the cinacalcet cases. This is consistent with the relatively higher level of activity experienced with (^{F}S)-**20**.

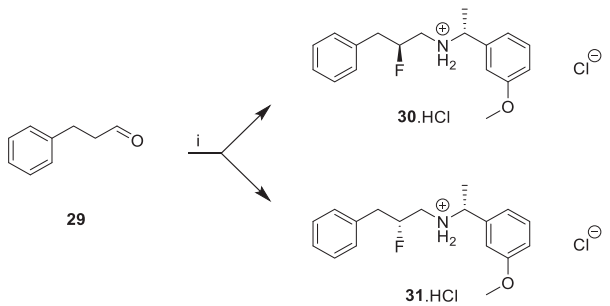
Both diastereoisomers in each matched set can access an extended *anti*-zig-zag chain conformation approximated by conformations **A** and **B** in (Fig. 3). Both of these conformations retain a stabilising electrostatic *gauche* interaction between the fluorine and the protonated nitrogen. These conformations are apparent in the X-ray



Scheme 4 Reagents i. DiBAL, Et_2O, 80%, ii. Catalyst (*S*)-**14** or (*R*)-**14**, NFSI, THF/*i*-PrOH; (*R*)-3-methoxy-α-methybenzylamine, $NaBH(OAc)_3$, DCE, 54% for **24** and 56% for **25**. X-ray crystal structures of **24**.HCl (CCDC No 2259658) and **25**.HCl (CCDC No 2259659)



Scheme 5 Reagents i. Catalyst (*S*)-**14** or (*R*)-**14**, NFSI, THF/*i*-PrOH, (*R*)-α-methybenzylamine, $NaBH(OAc)_3$, DCE, 56% for **27** and 50% for **28**. X-ray crystal structures of **28**.HCl (CCDC No 2259660)



Scheme 6 Reagents i. Catalyst (*R*)-**14** or (*S*)-**14** NFSI, THF/*i*-PrOH, (*R*)-3-methoxy-α-methybenzylamine, $NaBH(OAc)_3$, DCE, 47% for **30** and 62% for **31**

Table 1 Diastereoisomeric outcomes of telescoped syntheses of the calcimetic *β*-fluoroamine analogues, before and after chromatography

F-agonists	d.e. % (on work up)	d.e. % (after chromatography)	d.r. (after chromatography)
F-cinacalcets **20**	62	99	99.5:0.5
F-cinacalcets **21**	54	99	99.5:0.5
F-tecalcets **24**	60	86	93:7
F-tecalcets **25**	81	86	93:7
F-fendiline **27**	70	80	90:10
F-fendiline **28**	60	90	95:5
F- NPS R-467 **30**	74	76	88:12
F- NPS R-467 **31**	47	68	84:16

structures (Schemes 4 and 5) where it is clear that the amine hydrochlorides **24, 25** and **28** adopt extended *anti*-zig-zag structures with the anticipated *gauche* alignments between the C-F and C-N^+ bonds. Conformation **C** in (Fig. 3) is predicted to be higher in energy as no such *gauche* relationship is established, and it will be significantly less populated in solution relative to **A** and **B**. The data in Table 2 indicate that the (^FS)-fluoro diastereoisomers are more active than the (^FR)- fluoro diastereoisomers in each calcimimetic set. Given that this is found in all of the three cases studied it is proposed that the favoured binding conformation is biased with a chiral twist in the positioning of the R group from a perfect *anti*-zig-zag conformation. It follows from the data comparing

the different stereoisomers that the preferred binding mode is found in the (^{F}S) stereoisomers and they have the R group biased as illustrated in conformation **B** in (Fig. 3), a preference dictated by the narrower *gauche* angle between C-F and C-N^{+}. (^{F}R)-Stereoisomers conforming to **A** would have a tighter *gauche* angle of the opposite sense to **B** and orientate the R group with the opposite enantiomeric twist into a less preferred orientation and therefore adopting a higher energy binding mode. Conformation **C** is not stabilised by the electrostatic *gauche* effect as the C-F bond is *anti*-periplanar to the C-N^{+} bond, and therefore it will be higher in energy (~4–5 kcal mol^{-1}) and thus significantly less populated relative to **A** and **B**. If **C** were the preferred binding mode, then these fluorinated analogues would be unlikely to show a level of activity similar to their parent agonists, as the fluorines would influence away from conformation **C** towards conformations **A** and **B** (Fig. 3).

Conclusion

A short and convenient approach to β-fluoroamines is presented which combines the MacMillan-asymmetric α-fluorination of aldehydes with a reductive amination strategy adapted from Lyndsey. Using dibenzylamine as the amine allowed the free amine to be accessed after a straightforward hydrogenation, and this was exemplified in a synthesis of 3F-GABA. The strategy was extended to the synthesis of a series of selectively fluorinated calcimimetic agonists, as matched stereoisomeric pairs with the fluorine in a mid-chain position. In overview, both stereoisomers of each set had similar efficacies to the non-fluorinated parent agonist, although there was an apparent bias in favour of the (^{F}S)- fluoro diastereoisomers. Our hypothesis suggests that this difference in activity across three matched pairs reveals a bias in the preferred binding mode of the agonist to the CaR receptor, influenced by the electrostatic *gauche* effect. This bias suggests that the R group is not perfectly anti-periplanar to nitrogen, but that it has a chiral bias which is most stabilised by the (^{F}S)- fluoro diastereoisomers.

Table 2 Affinity (pK_B) of CaSR agonists determined in $Ca^{2+}{}_i$ mobilization assays. Data are mean ± SD from the indicated number of independent experiments (n)

Agonist	$pK_B \pm SEM$	n
Cinacalcet **15**	5.64 ± 0.11	6
(^{F}S)- **20**	6.20 ± 0.11	5
(^{F}R)- **21**	5.75 ± 0.12	4
Tecalcet **16**	5.82 ± 0.15	4
(^{F}S)- **24**	5.75 ± 0.14	4
(^{F}R)- **25**	4.19 ± 0.68	4
NPS R-467 **18**	5.57 ± 0.13	5
(^{F}S)- **30**	5.69 ± 0.14	5
(^{F}R)- **31**	4.11 ± 1.21	5

Experimental

Synthetic procedures and characterisation data

Benzyl pent-4-enoate (11)

A solution of pent-4-enoic acid (1.0 equiv, 1.02 mL, 10 mmol), *p*-toluenesulfonic acid (10%, 190 mg, 1 mmol) and benzyl alcohol (1.5 equiv, 1.55 mL, 15 mmol) in toluene (30 mL) was heated under reflux (180 °C) and then the reaction was cooled and concentrated. The product was purified over silica gel eluting with hexane/EtOAc (3:7). Ester **11** was obtained as a yellow oil in >99% yield (1.90 g). IR ν_{max}/cm^{-1} 1734, 1159, 696. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.41 (m, 5H, Ph), 5.76–5.89 (m, 1H, CH), 5.12 (s, 2H, CH_2-Ph), 4.97–5.10 (m, 2H, $=CH_2$), 2.35–2.51 (m, 4H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.0 (C = O), 136.7 (CH =), 128.7 (2 C, C_{Arom}), 128.4 (C_{Arom}), 127.9 (2 C, C_{Arom}), 127.8 (C_{Arom}), 115.7 (CH_2 =), 66.4 (CH_2-O), 33.7 (CH_2), 29.0(CH_2). ESI-MS calculated for $C_{12}H_{15}O_2$ $[M + H^+] = 191.0989$, observed $[M + H^+] = 191.0992$.

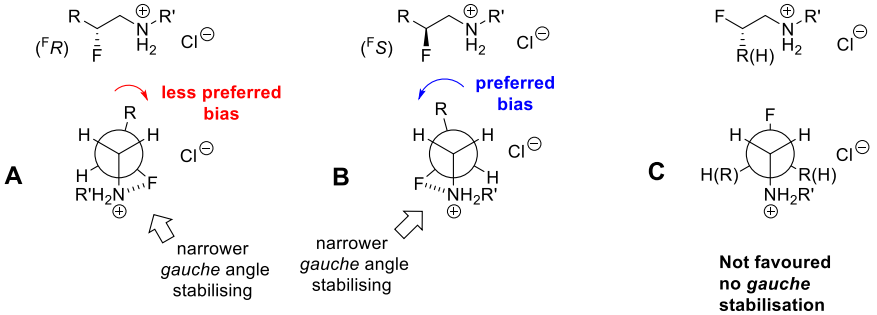


Fig. 3 The electrostatic *gauche* effect favours conformations **B** and to a lesser extent **A** but should not stabilise conformation **C**. The assay data (Table 2) is consistent with a binding conformation with an enantiomeric twist closer to conformation **B** than that of conformation **A**

Benzyl 4-oxobutanoate (12)

Ozone was passed through a solution of benzyl 4-pentenoate **11** (1.0 equiv, 461 mg, 2.47 mmol) in DCM (25 mL) at −78 °C until the solution became blue. NEt_3 (0.7 mL) was added to the reaction and it was warmed to RT. The mixture was washed with HCl (1 M, 2.25 mL), $NaHCO_3$ (5%, 1.15 mL) and dried ($MgSO_4$), filtered, and concentrated to give aldehyde **12** (90%, 427 mg). Aldehyde **12** was used without any further purification due to its previously reported instability. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.82 (s, 1H, CHO), 7.33 – 7.38 (m, 5H, Ph), 5.13 (s, 2H, OCH_2), 2.75 (m, 4H, CH_2). ESI-MS calculated for $C_{11}H_{13}O_3$ $[M + H^+] = 193.0781$, observed $[M + H^+] = 193.0789$.

General procedure for fluorination-reductive amination protocol

A 30% solution of either (*R*)-**14** or (*S*)-**14** (30%) catalyst in THF (18 mL) and *i*-PrOH (1.8 mL) was cooled to −10 °C. The aldehyde (1.0 equiv) was added followed by a slow addition of N-fluorobenzenesulfonimide (1.0 equiv, 0.60 mg, 2.0 mmol) in THF over 30 min and the reaction stirred for 12 h at –10 °C and it was then cooled to −78 °C, quenched with Et_2O (15 mL) and filtered through a pad of silica gel, eluting with Et_2O. Dimethyl sulphide (1 mL) was added and the resulting mixture was washed with saturated $NaHCO_3$ (3 × 30 mL), brine (30 mL) and dried over $MgSO_4$, filtered and concentrated. The resulting fluorinated aldehyde was dissolved in DCE (22 mL), followed by addition of the amine (1.1 equiv), and then $NaBH(OAc)_3$ (2.0 equiv, 848 mg, 4.0 mmol) was added and the reaction stirred for 18 h at RT. The reaction was quenched with saturated $NaHCO_3$ (20 mL), and the product extracted into EtOAc (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purifications were carried out with Biotage Selekt 2 automatic column chromatography. The yields are calculated on the products obtained after purifications and before moving them into salts. the products salt was obtained by addition of 1 equivalent of 1 M HCL in diethyl ether followed by a recrystallisation in DCM/Acetone.

Benzyl (*S*)-4-(dibenzylamino)-3-fluorobutanoate (13)

Prepared with **(*S*)-14** according to the general procedure from benzyl 4-oxobutanoate (1.0 equiv, 769 mg, 4.0 mmol) as aldehyde, and dibenzylamine (1.1 equiv, 560 µL, 4.4 mmol) as the amine. The product was purified by flash column chromatography with silica gel eluting with hexane/DCM using Biotage Selekt 2 (from 9:1 to 6:4 solvent ratio). The desired product (*S*)-**13** was obtained as a yellow oil in 52% yield (814 mg, ee 78%). $[\alpha]^{20}_D$ –1.02 (c 2.1, $CHCl_3$). IR ν_{max}/cm^{-1} 3030, 2802, 2360, 1735, 1170, 736, 696. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54–7.09 (m, 15H, Ph), 5.25–5.13 (m, 1H), 5.18 (s, 2H, O-CH_2-benzyl), 3.73 (qd, $J = 13.7$, 2.9 Hz, 4H, N-CH_2-benzyl), 2.79 (dddt, $J = 31.4$, 20.8, 7.2, 4.3 Hz, 4H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2 (C = O), 139.1 (C_{Arom}), 129.0 (4 C, C_{Arom}), 128.7 (2 C, C_{Arom}), 128.4 (5 C, C_{Arom}), 128.3 (2 C, C_{Arom}), 127.2 (4 C, C_{Arom}), 89.5 (d, $J = 175.6$ Hz, CHF), 66.6 (CH_2O), 59.2 (2 C, CH_2-Ph), 56.0 (d, $J = 19.5$ Hz, CH_2), 38.5 (d, $J = 28.4$ Hz, CH_2). ^{19}F NMR (376 MHz, $CDCl_3$) δ -181.4. ESI-MS calculated for $C_{25}H_{27}O_2NF$ $[M + H^+] = 392.2026$, observed $[M + H^+] = 392.2020$.

(*S*)-4-Amino-3-fluorobutanoic acid (3-F-GABA) (8)

Benzyl (*S*)-4-(dibenzylamino)-3-fluorobutanoate **13** (1.0 equiv, 65 mg, 0.16 mmol) and $Pd(OH)_2$/C 20 wt.% (2.8%, 20 mg, 0.005 mmol) were added to MeOH (5 mL) under argon. The reaction was stirred for 46 h at RT under a H_2 atmosphere (1 atm). The catalyst was filtered through a pad of Celite® and the eluant concentrated in vacuo. The residue dissolved in water (5 mL) and washed with Et_2O (5 mL) and the aqueous was submitted to reverse phase column chromatography on supported silica (C_{18}) eluting with water. The desired product **8** was obtained as a white solid in 93% yield (18 mg, ee 78%). ^{1}H NMR (400 MHz, D_2O) δ 5.05–5.30 (m, 1H, CHF), 3.18 – 3.40 (m, 2H, CH_2), 2.47–2.72 (m, 2H, CH_2). ^{13}C NMR (101 MHz, D_2O) δ 129.7 (CO_2), 129.5(CO_2), 87.3 (d, $J = 171.5$ Hz, CHF), 51.3 (d, $J = 20.6$ Hz, N-CH_2), 47.6 (d, J = 22.4 Hz, CH_2-CO_2). ^{19}F NMR (376 MHz, D_2O) δ -185.6.

(^{F}*S,R*)-F-Cinacalcet (20)

Prepared with **(*S*)-14** according to the general procedure from 3-(trifluoromethyl)benzenepropanal **19** (1.0 equiv, 340 µL, 2.0 mmol) and (*R*)-(1-naphthyl)ethylamine (1.1 equiv, 350 µL, 2.2 mmol). The product was purified by chromatography eluting with hexane/EtOAc using Biotage Selekt 2 (from 9:1 to 6:4 solvent ratio). Cinacalcet **20** was obtained as a yellow oil in 28% yield (199 mg, dr 99.5:0.5). $[\alpha]^{20}_D$ -47.0 (c 0.54, $CHCl_3$). 1H NMR (400 MHz, MeOD) δ 7.22–8.15 (m, 10H, Ph), 4.69–4.87 (m, 1H, CHF), 4.66 (q, $J = 6.7$ Hz, 1H, N-CH), 2.62–2.96 (m, 4H, CH_2), 1.47 (d, $J = 6.7$ Hz, 3H, CH_3). ^{13}C NMR (101 MHz, MeOD) δ 134.2 (2 C, C_{Arom}), 132.9 (C_{Arom}), 130.7 (C_{Arom}), 129.6 (C_{Arom}), 129.0 (2 C, C_{Arom}), 127.2 (C_{Arom}), 126.2 (C_{Arom}), 125.6 (2 C, C_{Arom}), 125.2 (C_{Arom}), 123.6 (2 C, C_{Arom}), 123.4, (C_{Arom}), 121.5 (C_{Arom}), 89.8 (d, $J = 173.0$ Hz, CHF), 53.3 (CH-N), 48.9 (d, $J = 20.6$ Hz, CH_2), 37.7 (d, $J = 19.2$ Hz, CH_2), 18.9 (CH_3). ^{19}F NMR (377 MHz, MeOD) δ -63.9 (CF_3), -186.2 (CHF). ESI-MS

calculated for $C_{22}H_{22}NF$ $[M + H^+] = 376.1688$, observed $[M + H^+] = 376.1678$.

(^{F}*R,R*)-F-Cinacalcet (21)

Prepared with **(R)-14** according to the general procedure from 3-(trifluoromethyl)benzenepropanal **19** (1.0 equiv, 340 µL, 2.0 mmol) and (*R*)-(1-naphthyl)ethylamine (1.1 equiv, 350 µL, 2.2 mmol). The product was purified by chromatography eluting with hexane/EtOAc using Biotage Selekt 2 (from 9:1 to 6:4 solvent ratio). Cinacalcet **21** was obtained as a yellow oil in 50% yield (355 mg, dr 99.5:0.5). **$[\alpha]^{20}_D$** -15.4 (c 0.37, $CHCl_3$). ^{1}H NMR (400 MHz, MeOD) δ 7.82–7.88 (m, 1H, Ph), 7.74 (d, $J = 8.2$ Hz, 1H, Ph), 7.62 (d, $J = 7.2$ Hz, 1H, Ph), 7.28–7.53 (m, 8H, Ph), 8.17 (d, $J = 8.4$ Hz, 1H, Ph), 4.64–4.86 (m, 2H, CHF, N-CH), 2.57–3.01 (m, 4H, CH_2), 1.47 (d, $J = 6.6$ Hz, 3H, CH_3). ^{13}C NMR (101 MHz, MeOD) δ 136.6 (C_{Arom}), 134.1 (C_{Arom}), 132.9 (C_{Arom}), 130.8 (C_{Arom}), 129.6 (C_{Arom}), 129.0 (2 C, C_{Arom}), 128.9 (C_{Arom}), 127.1 (2 C, C_{Arom}), 126.2 (2 C, C_{Arom}), 125.7 (C_{Arom}), 125.2 (2 C, C_{Arom}), 123.5 (C_{Arom}), 121.7 (C_{Arom}), 89.9 (d, $J = 176.6$ Hz, CHF), 53.3 (CH-N), 49.0 (d, $J = 18.1$ Hz, CH_2), 37.7 (d, $J = 18.6$ Hz, CH_2), 18.6 (CH_3). ^{19}F NMR (376 MHz, MeOD) δ -64.1 (CF_3), -185.9 (CHF). ESI-MS calculated for $C_{22}H_{22}NF$ $[M + H^+] = 376.1688$, observed $[M + H^+] = 376.1679$.

(^{F}*S,R*)-F-Tecalcet (24)

Prepared with **(*S*)-14** according to the general procedure from 3-(2-chlorophenyl)propanal **23** (1.0 equiv, 337 mg, 2.0 mmol) and (*R*)-3-methoxy-α-methylbenzylamine (1.1 equiv, 365 µL, 2.2 mmol). The product was purified by chromatography eluting with hexane/EtOAc using Biotage Selekt 2 (from 9:1 to 6:4 solvent ratio). **24** was obtained as a yellow oil in 54% yield (347 mg, dr 93:7). $[\alpha]^{20}_D + 22.6$ (c 0.67, $CHCl_3$). ^{1}H NMR (400 MHz, MeOD) δ 7.44–7.34 (m, 2H, Ph), 7.33–7.24 (m, 3H, Ph), 7.06–6.97 (m, 3H, Ph), 5.23 – 4.99 (m, 1H, CHF), 4.35 (q, $J = 6.5$ Hz, 1H, CH-N), 3.85 (s, 3H, O-CH_3), 3.21–2.93 (m, 4H, CH_2), 1.65 (dd, $J = 6.8$, 2.7 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, MeOD) δ 131.7 (2 C, C_{Arom}), 130.2 (C_{Arom}), 129.3 (C_{Arom}), 128.7 (C_{Arom}), 126.9 (2 C, C_{Arom}), 119.1 (2 C, C_{Arom}), 114.3 (C_{Arom}), 112.8 (2 C, C_{Arom}), 88.8 (d, $J = 174.7$ Hz, CHF), 58.3 (CH-N), 54.4 (CH_3-O), 48.8 (d, $J = 17.8$ Hz, CH_2), 36.0 (d, $J = 19.9$ Hz, CH_2), 19.06 (CH_3). ^{19}F NMR (377 MHz, MeOD) δ -186.8. ESI-MS calculated for $C_{18}H_{22}ONClF$ $[M + H^+] = 322.1374$, observed $[M + H^+] = 322.1365$.

(^{F}*R,R*)-F-Tecalcet (25)

Prepared with **(R)-14** according to the general procedure from 3-(2-chlorophenyl)propanal **23** (1.0 equiv, 337 mg, 2.0 mmol) and (*R*)-3-methoxy-α-methylbenzylamine (1.1 equiv, 365 µL, 2.2 mmol). The product was purified by chromatography eluting with hexane/EtOAc using Biotage Selekt 2 (from 9:1 to 6:4 solvent ratio). **25** was obtained as a yellow oil in 56% yield (360 mg, dr 93:7). $[\alpha]^{20}_D$ –27.4 (c 0.50, $CHCl_3$). ^{1}H NMR (400 MHz, MeOD) δ 7.44–7.34 (m, 3H), 7.34 – 7.15 (m, 6H), 7.07–7.00 (m, 3H), 5.07–4.87 (m, 1H, CHF), 3.84 (s, 3H, O-CH_3), 3.61 (t, $J = 6.5$ Hz, 1H, CH-N), 3.23 – 2.95 (m, 2H, CH_2), 2.90 – 2.78 (m, 2H, CH_2), 1.70 (d, $J = 6.8$ Hz, 3H, CH_3). ^{13}C NMR (101 MHz, MeOD) δ 131.7 (C_{Arom}), 130.4 (C_{Arom}), 129.3 (C_{Arom}), 129.0 (C_{Arom}), 128.8 (C_{Arom}), 127.4 (C_{Arom}), 127.2 (C_{Arom}), 126.9 (C_{Arom}), 126.7 (C_{Arom}), 119.2 (C_{Arom}), 114.7 (C_{Arom}), 113.1 (C_{Arom}), 88.8 (d, $J = 176.9$ Hz, CHF), 59.0 (N-CH), 54.5 (O-CH_3), 48.7 (d, $J = 12.2$ Hz, CH_2), 35.8 (d, $J = 16.9$ Hz, CH_2), 17.9 (CH_3). ^{19}F NMR (377 MHz, MeOD) δ -186.4. ESI-MS calculated for $C_{18}H_{22}ONClF$ $[M + H^+] = 322.1374$, observed $[M + H^+] = 322.1366$.

(^{F}*S,R*)-F-Fendiline (27)

Prepared with **(*S*)-14** according to the general procedure from 3,3-diphenylpropanal **26** (1.0 equiv, 421 mg, 2.0 mmol) and (*R*)-α-methylbenzylamine (1.1 equiv, 280 µL, 2.2 mmol). The product was purified by chromatography eluting with hexane/EtOAc using Biotage Selekt 2 (from 9:1 to 6:4 solvent ratio). Fendiline **27** was obtained as a yellow oil in 56% yield (373 mg, dr 90:10). **$[\alpha]^{20}_D$** + 17.2 (c 0.57, $CHCl_3$). ^{1}H NMR (400 MHz, MeOD) δ 7.46–7.35 (m, 5H, Ph), 7.34–7.17 (m, 10H, Ph), 5.68–5.49 (m, 1H, CHF), 4.41 (q, $J = 6.9$ Hz, 1H, CH), 4.20 (dd, $J = 16.9$, 8.2 Hz, 1H, N-CH), 3.02–2.92 (m, 2H, CH_2), 1.63 (d, $J = 6.9$ Hz, 3H, CH_3). ^{13}C NMR (101 MHz, MeOD) δ 129.3 - 128.7 (C_{Aroms}), 128.2 (C_{Arom}), 127.8 (C_{Arom}), 127.1 (C_{Arom}), 126.8 (C_{Arom}), 90.2 (d, $J = 183.5$ Hz, CHF), 58.1 (CH-N), 53.5 (d, $J = 19.5$ Hz, CH_2), 18.7 (CH_3). ^{19}F NMR (376 MHz, MeOD) δ -189.9. ESI-MS calculated for $C_{23}H_{25}NF$ $[M + H^+] = 334.1971$, observed $[M + H^+] = 334.1956$.

(^{F}*R,R*)-F-Fendiline (28)

Prepared with **(R)-14** according to the general procedure from 3,3-diphenylpropanal **26** (1.0 equiv, 421 mg, 2.0 mmol), and (*R*)-α-methylbenzylamine (1.1 equiv, 280 µL, 2.2 mmol). The product was purified by chromatography eluting with hexane/EtOAc using Biotage Selekt 2 (from 9:1 to 6:4 solvent ratio). Fendiline **28** was obtained as a yellow oil in 50% yield (333 mg, dr 95:5). $[\alpha]^{20}_D + 20.7$ (c 0.45, $CHCl_3$). ^{1}H NMR (400 MHz, MeOD) δ 7.52–7.40 (m, 7H, Ph), 7.38–7.18 (m, 9H, Ph), 5.51 (dt, $J = 50.0$, 7.9 Hz, 1H, CHF), 4.44 (m, 1H, CH), 4.24 (dd, $J = 18.4$, 7.8 Hz, 1H, N-CH), 3.26 (dt, $J = 13.8$, 10.8 Hz, 1H, CH_2), 2.92 (ddd, $J = 35.8$, 13.8, 1.9 Hz, 1H, CH_2), 1.67 (t, $J = 7.1$ Hz,

3H, CH_3). ^{13}C NMR (101 MHz, MeOD) δ 160.6 (C_{Arom}), 139.6 (C_{Arom}), 139.1 (C_{Arom}), 135.8 (C_{Arom}), 129.4 - 128.3 (C_{Aroms}), 127.7 (2 C, C_{Arom}), 127.3 -126.9 (C_{Aroms}), 90.7(d, $J = 179.1$ Hz, CHF), 58.8 (CH-N), 53.5 (d, $J = 21.1$ Hz, CH_2), 17.98 (CH_3). ^{19}F NMR (377 MHz, MeOD) δ -189.8. **ESI-MS** calculated for $C_{23}H_{25}NF$ $[M + H^+] = 334.1971$, observed $[M + H^+] = 334.1957$.

(^{F}*S,R*)-F-NPS R-467 (30)

Prepared with **(*S*)-14** according to the general procedure from 3-phenylpropanal **29** (1.0 equiv, 266 µL, 2.0 mmol), and (*R*)-3-methoxy-α-methylbenzylamine (1.1 equiv, 365 µL, 2.2 mmol). The product was purified by chromatography eluting with hexane/EtOAc using Biotage Selekt 2 (from 9:1 to 6:4 solvent ratio). **30** was obtained as a yellow oil in 47% yield (270 mg, dr 88:12). $[\alpha]^{20}_D + 28.9$ (c 0.23, $CHCl_3$). ^1H NMR (400 MHz, MeOD) δ 7.39 (t, $J = 7.9$ Hz, 1H, Ph), 7.34 – 7.16 (m, 4H, Ph), 7.09–6.97 (m, 3H, Ph), 5.08 (d, $J = 50.9$ Hz, 1H, CHF), 4.49–4.34 (m, 1H, N-CH), 3.84 (d, $J = 1.7$ Hz, 3H, O-CH_3), 3.28–2.87 (m, 4H, CH_2), 1.76–1.60 (m, 3H, CH_3). ^{13}C NMR (101 MHz, MeOD) δ 160.6 (C_{Arom}), 137.1 (C_{Arom}), 135.5 (C_{Arom}), 130.4 (C_{Arom}), 129.0 (2 C, C_{Arom}), 128.3 (2 C, C_{Arom}), 126.8 (C_{Arom}), 119.1 (C_{Arom}), 114.7 (C_{Arom}), 112.9 (C_{Arom}), 89.7 (d, $J = 168.5$ Hz, CHF), 58.5 (N-CH), 54.5 (O-CH_3), 48.5 (d, $J = 21.2$ Hz, CH_2), 38.1 (d, $J = 17.6$ Hz, CH_2), 18.4 (CH_3). ^{19}F NMR (377 MHz, MeOD) δ -186.3. ESI-MS calculated for $C_{18}H_{23}ONF$ $[M + H^+] = 288.1764$, observed $[M + H^+] = 288.1757$.

(^{F}*R,R*)-F-NPS R-467 (31)

Prepared with **(*R*)-14** according to the general procedure from 3-phenylpropanal **29** (1.0 equiv, 266 µL, 2.0 mmol) and (*R*)-3-methoxy-α-methylbenzylamine (1.1 equiv, 365 µL, 2.2 mmol). The product was purified by chromatography eluting with hexane/EtOAc using Biotage Selekt 2 (from 9:1 to 6:4 solvent ratio). **31** was obtained as a yellow oil in 62% yield (356 mg, dr 84:16). $[\alpha]^{20}_D + 42.6$ (c 0.96, $CHCl_3$). ^1H NMR (400 MHz, MeOD) δ 7.40–7.34 (m, 1H, Ph), 7.33–7.18 (m, 6H, Ph), 7.04–6.94 (m, 3H, Ph), 4.87–4.77 (m, 1H, CHF), 4.27 (q, $J = 6.8$ Hz, 1H, CH-N), 3.83 (d, $J = 2.2$ Hz, 3H, O-CH_3), 3.15 (td, $J = 13.3$, 9.7 Hz, 1H, CH_2), 3.04–2.85 (m, 3H, CH_2), 1.62 (d, $J = 6.8$ Hz, 3H, CH_3). ^{13}C NMR (101 MHz, MeOD) δ 160.4 (C_{Arom}), 138.8 (C_{Arom}), 135.5 (C_{Arom}), 130.1 (C_{Arom}), 129.0 (2 C, C_{Arom}), 128.2 (2 C, C_{Arom}), 126.7 (C_{Arom}), 119.1 (C_{Arom}), 114.2 (C_{Arom}), 112.8 (C_{Arom}), 90.8 (d, $J = 174.5$ Hz, CHF), 58.74 (CH-N), 54.42 (O-CH_3), 49.0 (d, $J = 20.0$ Hz, CH_2), 38.4 (d, $J = 20.0$ Hz, CH_2), 18.85 (CH_3). ^{19}F NMR (377 MHz, MeOD) δ -185.9. ESI-MS calculated for $C_{18}H_{23}ONF$ $[M + H^+] = 288.1764$, observed $[M + H^+] = 288.1756$.

CaR receptor assays

Cell lines

Generation of DNA and FlpIn HEK TREx cells which are stable in expressing c-myc-tagged wild type CaSR in pcDNA5/frt/TO has been described previously [46]. FlpIn HEK TREx CaSR cells were maintained in DMEM cell culture medium, containing 5% FBS, 200 µg/mL hygromycin B and 5 µg/mL blasticidin S HCl.

Ca^{2+}_i mobilization assay in FlpIn HEK293 TRex-expressing CaSR cells

FlpIn HEK293 TRex-expressing CaR cells were seeded in clear 96-well plates coated with poly-D-lysine (50 µg mL^{-1}, 80,000 cells/well) and incubated overnight in the presence of tetracycline (100 ng mL^{-1}) to induce CaR expression. The following day, cells were washed with the assay buffer (150 mM NaCl, 2.6 mM KCl, 1.18 mM $MgCl_2$, 10 mM D-Glucose, 10 mM HEPES, 0.1 mM $CaCl_2$, 0.5 % BSA and 4 mM probenecid at pH 7.4) and loaded with Fluo-8 AM (1 µM in assay buffer) for 1 h at 37 °C. Cells were washed once with assay buffer and fresh buffer was added to wells. Extracellular calcium (Ca^{2+}_o) and the calcimimetic compounds were co-added to wells and measurements of Ca^{2+}_i elevations were performed at 37 °C using a Flexstation (Molecular Devices). Fluorescence was detected for 60 s at 490 nm excitation and 520 nm emission and peak fluorescence was used as a readout of the agonist response. Relative peak fluorescence units were normalised to the fluorescence stimulated by 1 µM ionomycin to account for differences in cell number and loading efficiency.

Data availability

The data sets generated during the current study are available from the author on reasonable request.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1007/s00044-023-03103-0.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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