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# Synthesis and biological evaluation of (–)-kainic acid analogues as phospholipase D-coupled metabotropic glutamate receptor ligands†

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(–)-Kainic acid potently increases stretch-induced afferent firing in muscle spindles, probably acting through a hitherto uncloned phospholipase D (PLD)-coupled mGlu receptor. Structural modification of (–)-kainic acid was undertaken to explore the C-4 substituent effect on the pharmacology related to muscle spindle firing. Three analogues **1a–c** were synthesised by highly stereoselective additions of a $CF_3$, a hydride and an alkynyl group to the *Re* face of the key pyrrolidin-4-one intermediate **5a** followed by further structural modifications. Only the 4-(1,2,3-triazolyl)-kainate derivative **1c** retained the kainate-like agonism, increasing firing in a dose-dependent manner. Further modification of **1c** by introduction of a PEG-biotin chain on the 1,2,3-triazole fragment afforded compound **14** which retained robust agonism at 1 μM and appears to be suitable for future use in pull-down assays and far western blotting for PLD-mGluR isolation.

## Introduction

Muscle spindles are skeletal muscle sensory organs (or mechanoreceptors) that play a key role in motor control and in the regulation of muscle length during movement. Recently, we presented evidence[1] that the glutamate receptor in mechanically sensitive nerve terminals of the muscle spindle is pharmacologically distinct from any of the cloned receptors but its pharmacology strongly resembles that of the uncloned phospholipase D (PLD)-coupled mGluR described in the hippocampus.[2] A similar receptor seems to be present in the blood pressure sensors (baroreceptors) of the cardiovascular system, where it may prove a useful drug target for treating high blood pressure (hypertension). We therefore aimed to produce ligands that could be used to isolate and localise the receptor, with a view to sequencing, cloning and characterising it.

(–)-Kainic acid (Fig. 1), which selectively activates the kainate family of ionotropic channels but has no known activity at any metabotropic receptors (mGluRs), potently increases muscle spindle stretch-induced afferent firing at 1 μM concentration ($n$ = 7, $p$ < 0.01). (–)-Kainic acid is not acting through the classical kainate group of glutamate receptors, as the kainate receptor-specific antagonist NBQX (2,3-dioxo-6-nitro-1,2,3,4-tetrahydrobenzo[*f*]quinoxaline-7-sulfonamide) had no effect either alone ($n$ = 4) or on the (–)-kainic acid-mediated increase in afferent firing ($n$ = 7). However, the enhancement by (–)-kainic acid was inhibited by PCCG13 [(2*R*,1′*S*,2′*R*,3′*S*)-2-(2′-carboxy-3′-phenylcyclopropyl)glycine], a selective competitive antagonist of the PLD-coupled mGluR, ($n$ = 4, $p$ > 0.05).[3] Thus, the enhancement by (–)-kainic acid seemed to be through activation of the PLD-mGluR.

The aim of the current study was the synthesis of (–)-kainic acid analogues suitable to be used as tools for characterising and isolating the enigmatic PLD-mGluR in future studies.

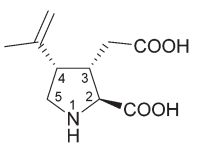


**Fig. 1** (–)-Kainic acid.

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†Electronic supplementary information (ESI) available: Experimental methods and characterisation of compounds **1–14**, biological tests on compounds **1a–c** and **14**, and copies of the NOESY and HOESY NMR experiments. CCDC 1019225. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4ob02002b

## Results and discussion

Most mGluR ligands, both cyclic and acyclic, feature a glutamate-like structural framework, incorporating one amino group and two free acidic functions.[4] We therefore hypothesised that the positions 1 to 3 of the (−)-kainic acid scaffold could be very important for binding to the target PLD-mGluR, in analogy with other mGluR ligands. Based on these considerations, it was decided to focus on the modification of the position 4 of (−)-kainic acid (Fig. 1), to explore the influence of the C4 substituent – which is a prop-2-ene group in native (−)-kainic acid – on the pharmacology related to muscle spindle firing.

Since (−)-kainic acid is an expensive chemical, it was deemed not to be an ideal starting substrate for the synthesis of analogues for the present structure–activity relationship (SAR) study, therefore we synthesised from inexpensive *trans*-4-hydroxy-L-proline a common precursor or key intermediate (Scheme 1) which could be easily transformed into our target kainic acid analogues **1a**, **1b** and **1c**.

### Synthesis

This work took advantage of the efficient chemistry developed by Baldwin *et al.*[5] to convert, in good yield and on a multigram scale (Scheme 2), *trans*-4-hydroxy-L-proline into ketone **2** through a three step synthesis: Fisher esterification, N-benzoylation under standard Schotten–Baumann conditions and ruthenium tetroxide Sharpless oxidation.

In order to obtain compound **3**, Baldwin's pathway envisaged the formation of an enamine from ketone **2** and subsequently a diastereoselective alkylation to install the substituent in position 3. Since the yields reported in the literature for the latter step were rather modest,[5] it was decided to alkylate directly the ketone **2** using the conditions previously reported by Greene[6] and Schafmeister.[7] Disappointingly, the enolisation of compound **2** with *n*-BuLi in THF-HMPA at −78 °C, followed by treatment with *tert*-butyl-bromoacetate at −40 °C, provided a mixture of mono- and di-alkylated products. Although the desired compound **3** was obtained as single diastereoisomer having the desired *R* configuration at C3, the yield was still too low (30%).

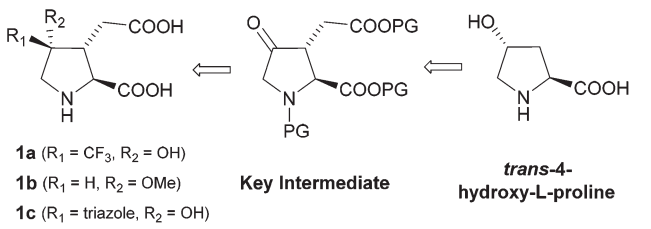
After this explorative attempt, we changed strategy and decided to replace the benzoyl protecting group with a *N*-phenylfluorenyl group (Pf), which had been previously employed on the same substrate giving excellent results.[6–8]

Therefore, the *N*-Pf protected ketone **4** was synthesised starting from *trans*-4-hydroxy-L-proline (Scheme 3) through Fischer esterification, *N*-Pf protection and Swern oxidation (that provided a simplified work-up procedure in comparison with the Ruthenium tetroxide oxidation).

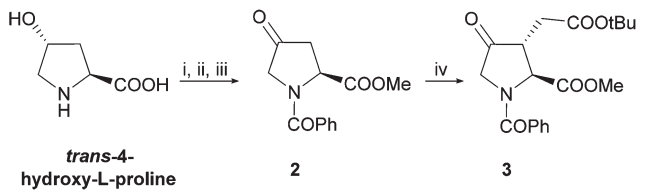
As expected,[7] the alkylation of ketone **4** gave **5a** in a good yield (80%) and excellent diastereoselectivity (dr 16 : 1).

After silica gel chromatography separation of the two diastereoisomers **5a** and **5b**, the stereochemistry of each ketone was confidently assigned by comparing the respective $^1$H NMR spectra, and specifically the chemical shifts and the coupling constants between H2 and H3 in **5a,b** with those reported previously in the literature for similar *trans*/*cis* derivarives[6,7,8b] (**5a**: H2 appears as a doublet at 3.50 ppm with $J_{H2\beta-H3\alpha}$ = 6.1 Hz; **5b**: H2 appears as doublet at 4.02 ppm with $J_{H2\beta-H3\beta}$ = 8.2 Hz). This assignment was subsequently confirmed by X-ray analysis of the derivative **9** (see Fig. 5).

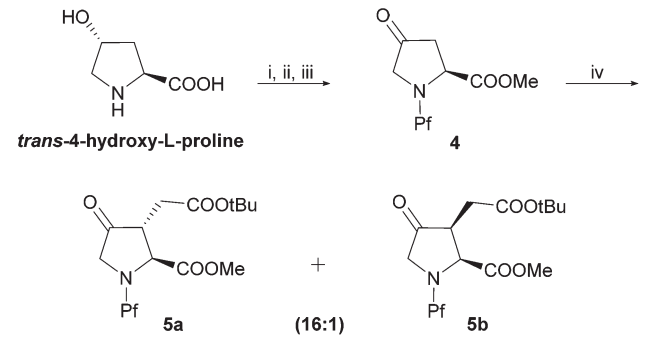
With the ketone precursor **5a** in hand, we proceeded with the synthesis of the target analogues. The synthesis of compound **1a** (Scheme 4) started with a trifluoromethylation reaction using the Ruppert–Prakash reagent[9] which afforded the alcohol **6** as a single diastereoisomer in moderate yield (48%). Next, the Pf group was removed *via* hydrogenolysis (Pd/C, $H_2$, in EtOAc at rt, quantitative yield) and, using the procedure reported by Baldwin *et al.* (HCl 6 N in water at reflux for



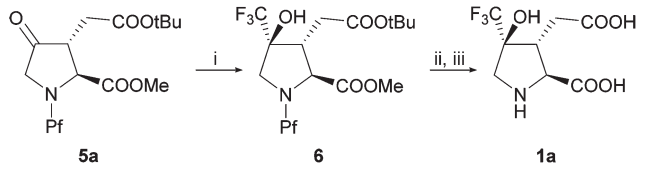

**Scheme 1** Retrosynthetic approach to the target analogues **1a–c**.




**Scheme 2** First synthetic approach to a candidate key intermediate **3**. *Reagents and conditions*: (i) $SOCl_2$, MeOH, 45 °C, overnight, (90%); (ii) BzCl, $NaHCO_3$, $H_2O$/THF, rt, 1.5 h, (98%); (iii) $RuCl_3{\cdot}H_2O$, $NaIO_4$, $CH_3CN$/$CCl_4$/$H_2O$, rt, 4 h, (80%); (iv) *n*BuLi, THF/HMPA at −78 °C, 30 min then NaI, $BrCH_2COOtBu$ from −60 °C to −42 °C, 1 h, (30% as single diastereoisomer).




**Scheme 3** Second synthetic approach: synthesis of the key intermediate **5a**. *Reagents and conditions*: (i) $SOCl_2$, MeOH, 45 °C, overnight, (90%); (ii) $Me_3SiCl$, TEA, DCM, reflux 1 h then MeOH, DCM, rt, 1 h then PfBr, $Pb(NO)_3$, rt, 96 h, (90%); (iii) DMSO, $(COCl)_2$, DCM, −78 °C, 1 h, (90%); (iv) *n*BuLi, THF/HMPA at −78 °C, 30 min then NaI, $BrCH_2COOtBu$ from −60 °C to −42 °C, 1 h, (80%, dr 16 : 1).




**Scheme 4** Synthesis of the analogue **1a**. *Reagents and conditions*: (i) $Me_3SiCF_3$, $Cs_2CO_3$, DMF, rt, 2 h then TBAF, rt, 30 min (48% as a single diastereoisomer); (ii) $H_3PO_4$ 85% wt in $H_2O$, toluene, rt, 2 h; (iii) LiOH 0.5N in $H_2O$, rt, 6 h (48% in two steps).

16 h),[10] both the carboxylic acidic functions were deprotected. Unfortunately the C2 stereocenter underwent epimerization during the acidic hydrolysis. To circumvent this undesired event, we opted to use a milder hydrolytic strategy consisting in the removal of the acid-labile protecting group (Pf and *t*-butyl ester) with aqueous $H_3PO_4$,[11] while the methyl ester was cleaved using aqueous LiOH which delivered the unprotected $CF_3$-derivative **1a** in stereopure form.

The stereochemical configuration of compound **1a** at C4 was assigned by performing a $^1$H NOESY NMR experiment[12] on the alcohol precursor **6** (Scheme 4). The NOE peaks for H2 and H3, and their corresponding integration values (Fig. 2A), are in accordance with the already established configuration of these two stereocenters, since the observed coupling signals are stronger when the two protons are in *cis* (α–α and β–β) and weaker if they are in *trans* (α–β) relationship. Analysing the relative intensity of the OH coupling signals (Fig. 2B) it was noticed that they are weaker in the case of the couplings with Hβ protons (H2 and H5β) while they are stronger for the couplings with Hα (H3 and H5α). This evidence allowed the assignment of an *S* configuration to the newly formed stereocenter at C4 (OHα and $CF_3$β).

To support this stereochemical assignment, a heteronuclear $^{19}$F–$^1$H HOESY NMR experiment[12] was performed on the same compound **6** for confirming the spatial arrangement between $CF_3$ and non-bonded nuclei around the fluorine atoms. As shown in Fig. 3, the coupling between fluorides and H5α has a weaker intensity (β–α) than that with H5β (β–β): this is consistent with the NOESY experiment and supports the previous stereochemical assignment.

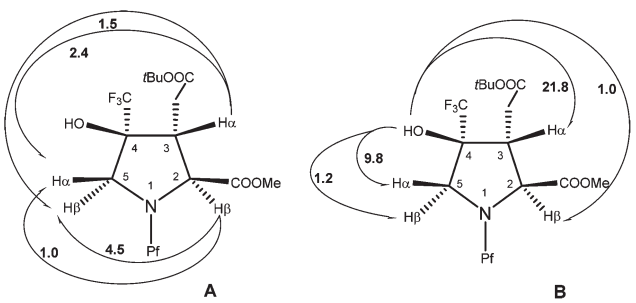



**Fig. 2** 2D NOESY spectroscopic data for compound **6** showing the relative intensity of through-space coupling signals: (A) couplings among H2, H3 and H5 and (B) the same protons with the OH in 4.

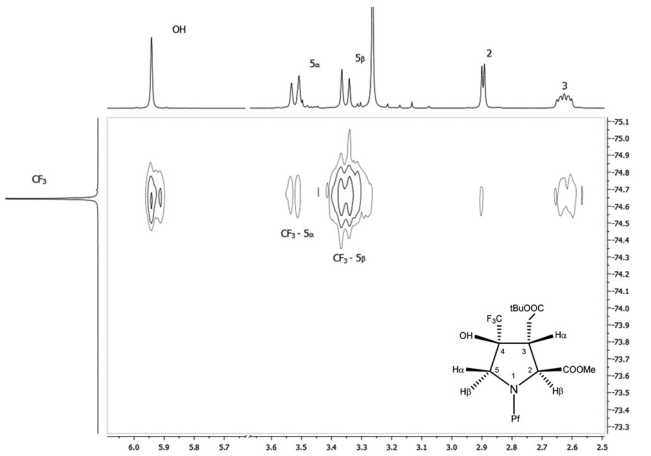
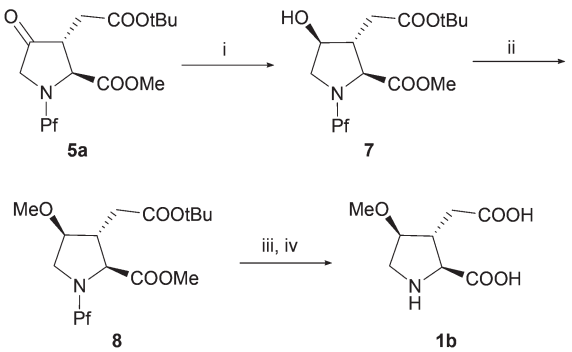



**Fig. 3** $^{19}$F–$^1$H HOESY spectrum of compound **6**.




**Scheme 5** Synthesis of analogue **1b**. *Reagents and conditions*: (i) $NaBH_4$, MeOH, rt, 2 h, (90% as a single diastereoisomer); (ii) NaH, DMF, 0 °C, 30 min then MeI, rt, 3 h, (70%); (iii) $H_3PO_4$ 85% wt in $H_2O$, toluene, rt, 2 h; (iv) LiOH 0.5N in $H_2O$, rt, 4 h (60% in two steps).

The synthesis of the 4-methoxy analogue **1b** (Scheme 5) also started from the key ketone **5a**. Hydride reduction ($NaBH_4$ in MeOH) afforded the alcohol 7 as a single diastereoisomer in excellent yield (90%). Subsequently, *O*-methylation with NaH/MeI gave the ether **8** that was subjected to the previously used (see Scheme 4) acidic-basic deprotection sequence of the ester groups to give compound **1b**.

Although the stereochemical outcome of the reduction from ketone **5a** to alcohol 7 could be confidently predicted based on literature reports on structurally related compounds,[8b,13] a NOESY spectrum of the alcohol 7 was performed to confirm its configuration. The intensity of the coupling peaks integrals for H3 and H2 is consistent with the stereochemistry of C3 and C2 (Fig. 4A). The OH in C4 (Fig. 4B) displays stronger signals for α–α couplings (with H5α and H3) and weaker signals for the α–β coupling with H5β, while H4 (Fig. 4C) shows similarly low signals for the interactions with H3 and H5α (which are both in a *trans* correlation) and a stronger coupling with H5β (in a *cis* correlation). From this NMR experiment, supported by literature data, an *S* configuration at the C4 of compound **1b** could be therefore safely assigned.

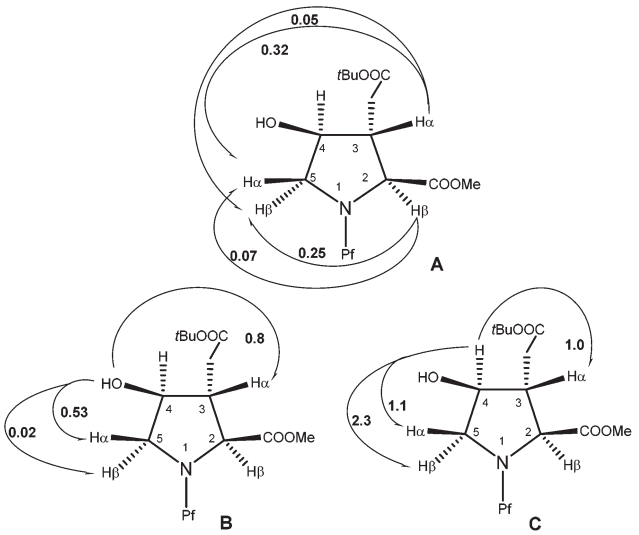
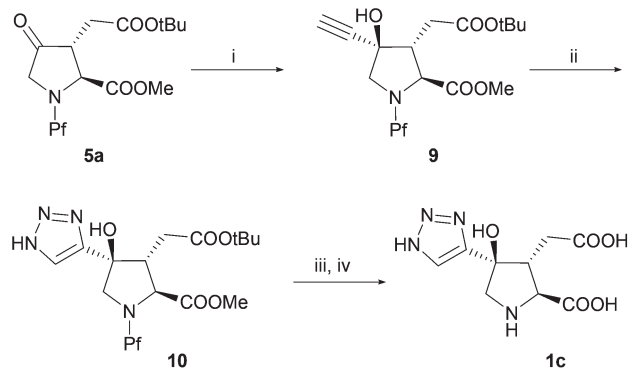



Fig. 4 2D NOESY spectroscopic data for compound **7** showing the relative intensity of through-space coupling signals: (A) coupling among H3, H2 and H5, (B) the same protons with the OH in 4 and (C) the same proton with the H in 4.




**Scheme 6** Synthesis of analogue **1c**. *Reagents and conditions*: (i) $SiMe_3CH$, *n*BuLi, THF, −10 °C, 1 h, (70% as a single diastereoisomer); (ii) $Me_3SiN_3$, $CuSO_4$, Na ascorbate, DMF/$H_2O$, microwave at 120 °C for 30 min, (70%); (iii) $H_3PO_4$ 85% wt in $H_2O$, toluene, rt, 2 h; (iv) LiOH 0.5N in $H_2O$, rt, 6 h (65% in two steps).

The 4-(1,2,3-triazolyl) kainic analogue **1c** was obtained (Scheme 6) through the alkynylation[14] of ketone **5a** using (trimethylsilyl)acetylene to give the alkyne **9**. The triazole moiety was then installed by means of a copper-catalysed azide-alkyne cycloaddition[15] employing trimethylsilylazide under microwave irradiation. The newly formed triazole diester **10** was transformed into the final unprotected compound **1c** *via* the usual deprotection steps.

In order to establish the stereochemical configuration at C4 of the analogue **1c**, a crystallographic analysis on the alkyne **9** (Fig. 5) was performed. The configurations of atoms C2 (*S*), C3 (*R*) and C4 (*R*) were established by refinement of the Flack

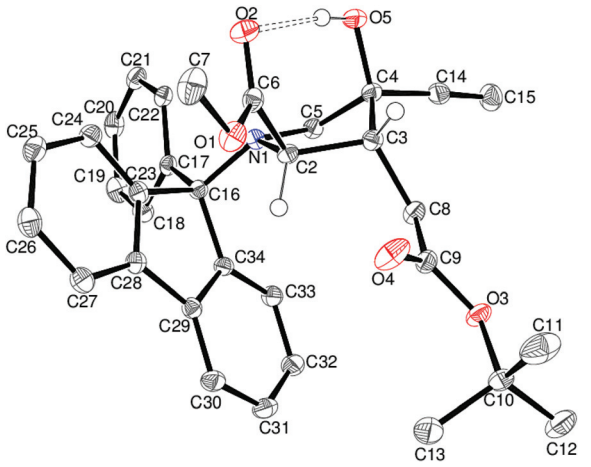



Fig. 5 ORTEP of compound **9**.[16]

absolute structure parameter. The conformation of the five-membered ring is an envelope with the C4-carbon atom bearing the OH group as the flap. This facilitates the formation of an intramolecular O–H···O hydrogen bond, featuring an H···O distance = 2.083 (17) A.

The synthesis of a number of additional kainic acid derivatives modified in position 4 was also unsuccessfully attempted. For example, dehydroxy-fluorination of **7**, as well as of other protected 4-hydroxy analogues, failed to produce the corresponding 4-fluoro-kainic derivatives under a range of conditions (DAST, Deoxofluor, mesylation followed by treatment with TBAF) affording either no reaction or complex reaction mixtures. Attempts to perform reductive amination on **2a** for installing a 4-amino group also failed under a variety of conditions. Analogously, attempts to achieve alkynylation of **5a** with lithiated phenyl-acetylene afforded only complex reaction mixtures. Finally, attempts to achieve copper-catalysed azide-alkyne cycloaddition from **9** using alkyl azides, such as methyl azide, failed too. Due to the above described synthetic difficulties, the pool of kainic acid analogues available for biological studies was limited to compounds **1a–c**.

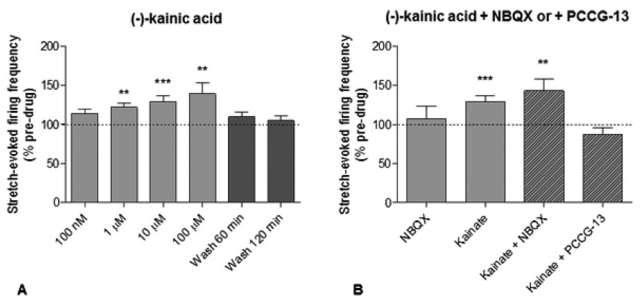



Fig. 6 Kainate increases stretch-induced afferent firing in muscle spindles by acting at the PLD-mGluR and not the kainate receptor. (A) Kainate at 1 μM 10 μM and 100 μM increases stretch-induced afferent firing in muscle spindles. (B) This effect is blocked by PCCG-13 but not NBQX, showing kainate's actions are mediated by the PLD-mGluR and not the iGluR kainate receptor.

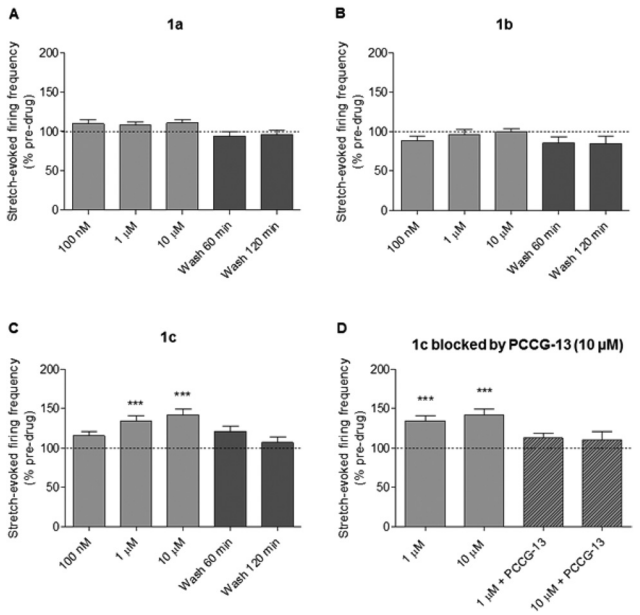
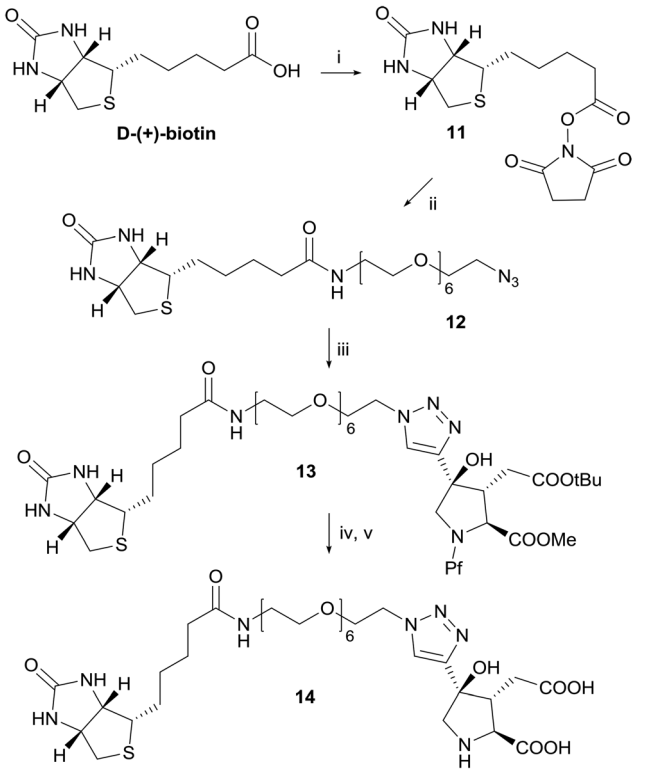



**Fig. 7** Compound **1c** increases stretch-induced afferent firing in muscle spindles by acting at the PLD-mGluR. (A) and (B) Neither compound 1a or 1b are pharmacologically active on muscle spindle stretch-evoked activity. (C) In contrast, 1c increases firing at 1 μM and above. (D) Even at 10 μM, the enhancement by 1c is blocked by PCCG-13.




**Scheme 7** Synthesis of biotinylated compound **14**. *Reagents and conditions*: (i) *N*-hydroxysuccinimide, EDC·HCl, DMF, rt, 24 h; (ii) *O*-(2-aminoethyl)-*O*′-(2-azidoethyl)pentaethylene glycol, TEA, DMF, rt, 24 h (98% in two steps); (iii) alkyne **9**, *t*BuOH/$H_2O$/THF, $CuSO_4$, Na ascorbate, rt, 36 h, (83%); (iv) $H_3PO_4$ 85% wt in $H_2O$, toluene, rt, 2 h; (v) LiOH 0.5N in $H_2O$, rt, 12 h (50% in two steps).

## Biological evaluation

As shown in Fig. 6, and discussed above, (−)-kainic acid potently increases stretch induced afferent firing in muscle spindles. This action is not inhibited by the ionotropic kainic acid receptor agonist NBQX, but is inhibited by the specific PLD mGluR antagonist PCCG-13. These data suggest (−)-kainic acid is acting *via* the PLD mGluR in muscle spindles to increase afferent firing.

Fig. 7 shows that compounds **1a** ($n$ = 8) (Fig. 7A) and **1b** ($n$ = 8) (Fig. 7B) are completely inactive in muscle spindles while compound **1c** has a potency similar to that of (−)-kainic acid ($n$ = 8) (Fig. 7C). Like (−)-kainic acid the ability of **1c** to increase stretch-induced afferent firing is inhibited by PCCG-13 ($n$ = 6) (Fig. 7D), suggesting it also acts *via* the PLD mGluR.

## Further development

To achieve further insight into the pharmacological properties of the most active analogue **1c**, with the idea of using it for a pull-down experiment on the target mGlu receptor, we synthesised a biotinylated version **14** (Scheme 7) of compound **1c** carrying a PEG chain as a spacer between the biotin and the triazole fragments. The synthesis started with the formation of the activated biotin ester **11** (*N*-hydroxysuccinimide and EDC·HCl)[17] that was directly coupled with the amino linker, affording the azide **12**. The following click reaction[18] provided the 1,2,3-triazole **13** that was fully deprotected to give the target biotinylated compound **14**.

Compound **14**'s biological activity differed slightly from that of **1c**, as it had a bell-shaped response curve, perhaps reflecting receptor desensitisation or internalisation at higher concentrations. Thus, firing rates increased significantly at 1 μM ($n$ = 8) but not at 10 μM ($n$ = 8) (Fig. 8). This retention of pharmacological action at modest ligand concentrations means that compound **14** will be a useful tool in further investigations into the receptor.

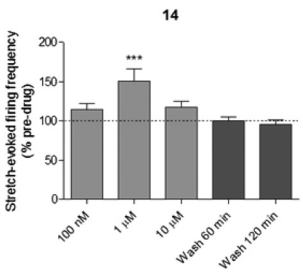



**Fig. 8** Compound **14** reversibly enhances stretch-evoked spindle firing. There is a bell-shaped response, with 1 μM producing a robust enhancement. Increasing concentration further to 10 μM returned firing to baseline.

## Conclusions

To investigate the pharmacology of the hitherto uncloned phospholipase D-coupled mGlu receptor, we undertook a modification of the C4 position of (−)-kainic acid, which is known to selectively and potently increase muscle spindle stretch-induced afferent firing. Highly stereoselective trifluoromethylation, hydride reduction/*O*-methylation and alkynylation/"click" reaction, all occurring from the *Re*-face of the key common C4-oxo intermediate **5a**, produced the three kainic analogues **1a–c**. Only the triazole compound **1c** retained the kainate-like agonism, increasing firing in a dose-dependent manner. The further modification of **1c** by introduction of a PEG-biotin chain on the C4-1,2,3-triazole fragment afforded compound **14** which retains robust agonism at 1 μM, although care must be taken at higher concentrations, due to the bell-shaped response. However, notably biotinylation did not destroy the receptor binding capabilities, meaning compound **14** is suitable for use in pull-down and other assays, such as far western blotting, for PLD-mGluR isolation.

## Acknowledgements

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