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Structure–activity relationships for the linker in a series of pyridinyl-alkynes that are antagonists of the metabotropic glutamate receptor 5 (mGluR5)

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Abstract—Studies of structure–activity relationships for the linker in a new series of metabotropic glutamate receptor 5 antagonists are presented together with in vitro and in vivo pharmacokinetic data.

We recently disclosed[1] that a number of compounds having the common structure **1** (Fig. 1) showed good to excellent affinity towards the cloned human metabotropic glutamate receptor 5 (mGluR5).

The aim of the present study was to examine the SAR around the linker (L) with optional variation of the aryl B ring under the restriction that the 6-methyl-pyridine ring (A) and the triple bond are retained (Fig. 2). X could be, for example, CH_2, S, O, or NH (optionally substituted), while R′ could be alkyl branches or part of a bicycle with the B ring.

All compounds were screened in a FLIPR assay and IC_{50} values of potent ($IC_{50} < 10{,}000$ nM) compounds were determined as means of triplicate measurements.[2]

To synthesize analogues with X being O, S, or NH and R′ being H or small alkyl, the procedures described in Scheme 1 were employed. Thus, Sonogashira cross-coupling[3] of 2-bromo-6-methyl-pyridine **2** with a propargylic alcohol by route a[4] with subsequent mesylation gave

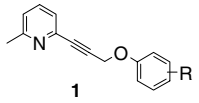

Figure 1.

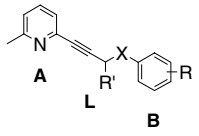

Figure 2.

3. The mesylate **3** was then reacted with a number of phenols, thiophenols, and anilines by route c to form a series of compounds **4**. Compound **31** was made like compound **21** in 34% yield, **19** like **22** in 38% yield. The synthesis of **20** is previously described.[1] A different route had to be employed in those cases where an appropriately branched alcohol for step a (e.g., R′ = *i*-Pr) was not commercially available. Thus, **2** was reacted with TMS-alkyne and the product **5** was desilylated with base to give terminal alkyne **6**. Reaction of **6** with an aldehyde gave **7** which after mesylation was reacted in situ with thiophenols to give **8**. Low yields for the f–g

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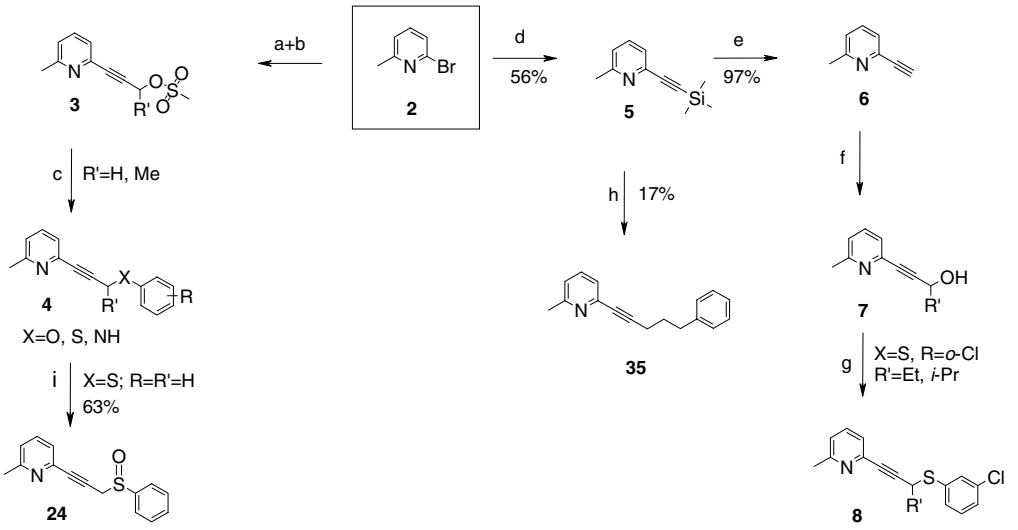


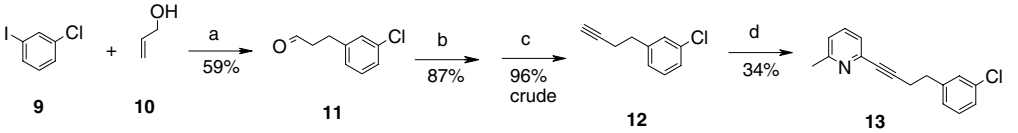
Scheme 1. Reagents and conditions: (a) HC≡CCH(R′)OH, $(PPh_3)_2PdCl_2$, CuI, NEt_3, 60 °C, 3.5–4 h (R′ = H: 56%; R′ = Me: 67%); (b) MsCl, NEt_3, DCM, −20 °C, 1 h (R′ = H or R′ = Me: quant.); (c) compound **21**: R = *o*-Cl, R′ = H, X = S: Ar-SH, NEt_3, DCM, rt, 24 h (44%); compound **22**: R = R′ = H, X = NH: $ArNH_2$, NEt_3, rt, 1.5 h (40%); compound **23**: R = R′ = H, X = S: Ar-SH, NEt_3, THF, rt, 1 h (39%); compound **25**: R = R′ = H, X = N–Me: ArNHMe, K_2CO_3, DMF, 70 °C, 3 days (38%); compound **29**: R = *o*-Cl, R′ = Me, X = NH: $ArNH_2$, $LiN(SiCH_3)_2$, THF, 0 °C, 20 min, then rt, 20 h (14%); compound **30**: R = *o*-Cl, R′ = Me, X = O: ArOH, NaH, THF, 0 °C, 20 min, then rt, 24 h (46%); (d) HC≡C$(Si(CH_3)_3)$, $(PPh_3)_2PdCl_2$, CuI, NEt_3, 60 °C, 2 h then rt, 16 h; (e) K_2CO_3, DCM/MeOH, rt, 2 h; (f) compound **33**: R = *o*-Cl, R′ = *i*-Pr, X = S: $LiN(Si(CH_3)_3)_2$, 2-methylpropanal, THF, −78 °C to rt, elute through SCX column, concentrate and continue in (g) MsCl, NEt_3, DCM, rt, 3 h, concentrate, then add Ar-SH, NEt_3, DCM, rt, 16 h (4%); (h) $Br(CH_2)_3Ph$, $(n\text{-}Bu)_4NF_2SiPh_3$, 60 °C, 24 h; (i) R = R′ = H, X = S: *m*-CPBA, 1.4 equiv, DCM, −50 to 0 °C over 1.5 h.

sequence was ascribed to instability of the mesylate. The chain-elongated product **35** was obtained from **5**, however in low yield, by using a fluorosilicate.[5] Sulfoxide **24** was made by simple oxidation.

Alkyne **12** to be used for Sonogashira coupling was not commercially available and was synthesized from the corresponding aldehyde **11** by the Corey–Fuchs method[6] followed by elimination and hydro-dehalogenation (Scheme 2).[7] Branched compound **36** (Table 1) was made by the same method, starting with 3-phenyl-butyraldehyde. Aldehyde **11** was obtained by coupling of the iodobenzene **9** with allyl alcohol **10**.[8] Compound **34** was made by Sonogashira coupling from commercial starting materials in 69% yield, according to procedure d in Scheme 2.

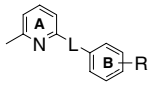
The 2,2-dibromoalkene **15** (Scheme 3) was prepared by the Corey–Fuchs method from aldehyde **14** and subsequently converted into terminal lithium alkyne that was reacted in situ with phenyl isocyanate to give amide **26**. Alternatively, **15** was converted into the 1-bromo alkyne**16** which was used for a Suzuki coupling to obtain the heterocyclic **37**. To obtain chain-elongated amides and ureas, the mesylate **3** was reacted with ammonia to give amine **17** which could be easily reacted with an acid chloride or an isocyanate to give amide **27** and urea **28**, respectively.

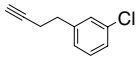
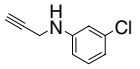
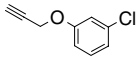
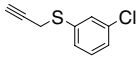
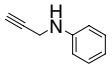
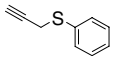
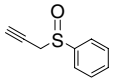
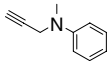
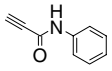
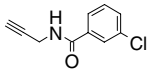
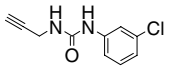
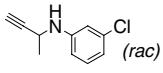
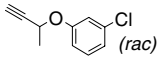
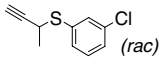
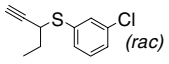
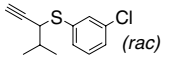
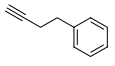
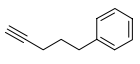
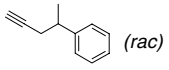
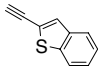
Development of structure–activity relationships for the linker was done with compounds having 6-methyl-pyridine as the A ring and with phenyl or *m*-chlorophenyl as the B ring (see Table 1). A clear trend in the SAR of the linker was the increase in affinity in the series N < O < S < C (**18**–**21** and **29**–**31**). Compounds from each of these series were tested against mGluR1, which has the highest sequence homology to mGluR5 among the mGluRs, and found to be inactive. Further, compounds **18** and **34** were tested against the mGluRs 3, 4, and 8 and found to be inactive. Interestingly, compound **20** when lacking the Cl-substituent showed no activity in our assay towards mGluR5;[1] nothing similar was observed for the analogous compounds with N, S, or C in the linker (compare pairs **19/22**, **21/23**, and **18/34**). In the N-series, N-methylation dramatically decreased potency (**25**) while amides and ureas were either of low or no potency (**26**–**28**). Branching with a methyl at the α-C somewhat reduced potency (**29**–**31**); however, compounds **29**–**31** were racemates. By further branching with ethyl or *iso*-propyl (**32** and **33**) the potency clearly decreased. Branching at the β-C with a methyl group was allowed (**36**). Further chain elongation or incorpo-



Scheme 2. Reagents and conditions: (a) $Pd(OAc)_2$, $(n\text{-}Bu)_4NCl$, $NaHCO_3$, DMF, rt, 16 h, then 50 °C, 16 h; (b) CBr_4, PPh_3, Zn, DCM, rt, 14 h; (c) $LiN(Si(CH_3)_3)_2$, 1.5 equiv, THF, −78 °C, 0.5 h, then *n*-BuLi, 2.5 equiv, −78 °C, 1 h, then rt, 1 h, then quench with H_2O; (d) **2**, $(PPh_3)_2PdCl_2$, CuI, NEt_3, 60 °C, 12 h.

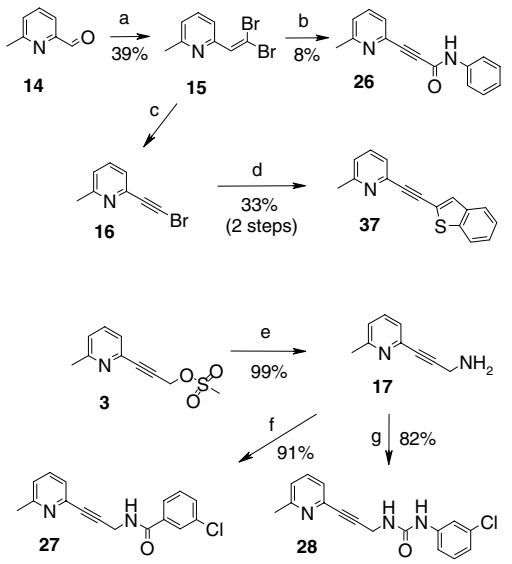
Table 1. Variations of the linker (L) and aryl group B



Compound	L-B	IC_{50} (nM)	SEM
18		5	1.1
19		174	6
20		100[a]	0.6
21		43	5.2
22		223	17
23		589	195
24		>10,000	—
25		6728	1391
26		>10,000	—
27		2614	193
28		>10,000	—
29		709	28
30		281	3
31		118	7
32		862	18
33		461	25
34		78	6.6
35		258	142
36		59	10.8
37		306	40

The alkyne is connected to the 6-methyl-pyridine.

[a] Value from Ref. 1, included for comparison.



Scheme 3. Reagents and conditions: (a) CBr_4, PPh_3, 0 °C, 0.5 h; (b) $LiN(Si(CH_3)_3)_2$, THF, −78 °C, 10 min, then add BuLi, −78 °C, 1.5 h, then add PhNCO, −78 °C, 2 h, then −10 °C, 1.5 h; (c) $LiN(Si(CH_3)_3)_2$, 1.1 equiv, THF, −78 °C, 1 h; continue in (d) 1-benzothien-2-ylboronic acid, $Pd(PPh_3)_4$, Na_2CO_3, rt, 3 days, then 110 °C, 3 h; (e) excess NH_3 (conc, aq), rt, 5 min; (f) *m*-Cl-Ph–COCl, NEt_3, DCM, 16 h, rt; (g) *m*-Cl-Ph–NCO, DCM, 2 h, rt.

ration of a bicycle resulted in some loss of potency (**35** and **37**).

In vitro metabolic stability of compound **18** in rat liver microsomes showed a CL_{int} = 197 μL/min/mg. Pharmacokinetic properties in vivo (dog) of compound **18** were CL = 66 mL/min/kg, V_{ss}=3.2 L/kg, and $T_{1/2}$ = 2 h. Transient lower esophageal sphincter relaxations (TLESRs) are defined as a complete relaxation of the lower esophageal sphincter in the absence of swallowing and are the main mechanism behind gastro-esophageal reflux. mGluR5 antagonists are useful for the inhibition of TLESRs and thereby for the treatment of gastro-esophageal reflux disease (GERD).[9] In dog (N = 4), compound **18** at dose 3.9 μmol/kg (iv) reduced the TLESRs with 31% (SEM = 13).[2] As a comparison, the known mGluR5-selective antagonists 2-methyl-6-(phenyl-ethynyl) pyridine (MPEP) in dog (N = 3) at dose 8.7 μmol/kg (iv) reduced the TLESRs with 59% (SEM = 11).[9]

In conclusion, structure–activity relationships around the linker in a series of pyridinyl-alkynes as mGluR5 antagonists have been presented together with demonstration of in vivo effect of one selected compound.

Acknowledgment

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References and notes

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