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A Linker for Amidines in Solid Phase Synthesis

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Abstract: A range of linkers for the important amidine pharmacophore, cleavable using acid or light have been developed for use in library synthesis. The utility of these linkers is demonstrated by the solid phase synthesis of the Novartis (ex-Ciba) phase II compound CGS-25019C.

The majority of linkers used to date in solid phase and combinatorial chemistry have their origins in solid phase peptide chemistry allowing controlled compound release at a price, that being the relatively limited range of termini generated upon linker cleavage. For example the widely utilised acid cleavable Rink[1] and Wang linkers[2] giving rise to primary amide and carboxyl functionalities respectively. These 'traditional linkers' have recently seen a new lease of life with their use in a variety of new solid phase chemistries, allowing free amines and phenols to be generated upon cleavage: for example the use of the Rink linker as a component in the multi component Ugi reaction[3] and the Wang linker in the generation of a range of benzodiazapenes[4]. Other linkers have also come to the fore including the use of trityl based linkers for a range of heteroatoms (e.g. amines)[5] again derived from original use in peptide chemistry, allyl based linkers,[6] the light cleavable nitrobenzyl linkers[7] again originally used in peptide chemistry as well as the more exotic "traceless" silicon based linkers,[8] the olefin generating linker using a "Horner-Wadsworth-Emmons" cleavage strategy[9] and the isoquinone generating linker of Kurth.[10] We now report the use of a "Wang" type linker for the immobilisation of the amidine moiety.

The amidine moiety is an important pharmacophore in medicinal chemistry. It has been widely used in a number of research areas and is found in a number of pharmaceutical products for example the fibrinogen receptor antagonist lamifiban which is currently in clinical development as an injectable antithrombic,[11] the LTB_4 antagonist (CGS-25019C)[12] which is now in phase II clinical trials and the Daiichi compound DX9065[13] which is a potent and selective factor Xa inhibitor (figure 1). Compounds containing amidines have also been used in the preparation of muscarinic receptor agonists and in inhibitors of S-adenosylmethionine decarboxylase.[14]

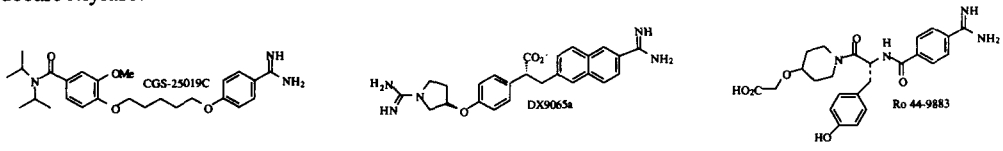
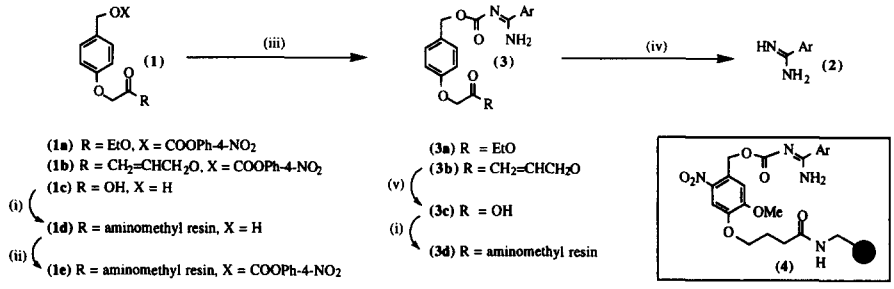


Figure 1: Some Important Amidine Containing Compounds

The strategy for the solid phase attachment of amidines to the solid phase was based on linkers previously designed for polyamine chemistry.[15] Thus amidines were coupled to the solid support by an amidoxime (**3**) prepared by the reaction of amidines (**2**) with 4-nitrophenylcarbonates (**1a,b,e**). Trial reactions of carbonate (**1a**) and benzamidine (**2a**) gave the expected product (**3a**) in good yield (Scheme 1). Cleavage of the amidoxime with TFA/DCM/Water (10/9/1) gave excellent recovery of the amidine showing the practicality of the approach for amidine chemistry. Interestingly saponification of the ethyl ester of (**3a**) was successful but acidic work up was complicated by the acid lability of the amidoxime linkage resulting in extensive degradation of the linker-amidine bond. To overcome this problem the allyl ester (**3b**) was cleaved using Pd(0) and the product (**3c**)[16] purified by column chromatography, without work up. (**3c**) was then immediately coupled to aminomethyl polystyrene resin (0.9 mmol/g) to give (**3d**). An alternative method of synthesis was the preparation of the resin-linked carbonate (**1e**) followed by reaction with 5 equivalents of amidine. This method was slow (as monitored by nitrophenol release) requiring between 24 and 72 hours but gave high amidine loadings.



Scheme 1: (i) Aminomethyl resin, DIC, HOBt, DCM; (ii) *p*O_2N-PhO-CO-Cl, pyridine, DCM; (iii) Amidines (5 eq., HN=C(NH_2)-Ar), dioxane, K_2CO_3 or NEt_3; (iv) 50% TFA, 5% water, DCM; (v) Pd(0), dimedone, DCM.

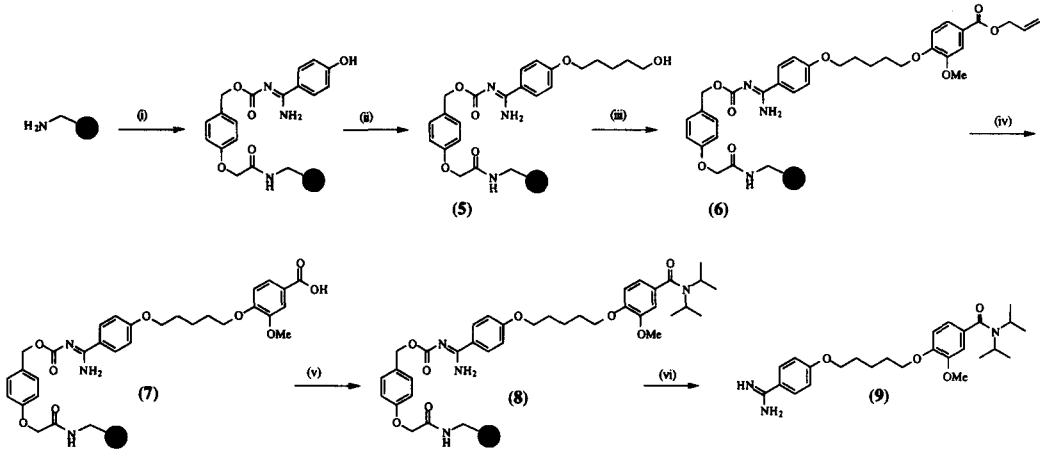
HPLC analysis of the cleaved amidines (**2**) showed them to be 66-99% pure and recovery was reasonable (41-71%) (table 1). There was little difference to choose between the two methods of attachment. The light cleavable linker (**4**) was also investigated. Cleavage of the amidine (**2a**) from (**4**) was accomplished by irradiation using a 100 watt medium pressure mercury lamp (λ_{max}350 nm) in degassed dioxane in poor yield (20%) but reasonable purity 65-70%. (It should be noted that no special precautions were needed when using this linker under standard laboratory lighting).

Table 1: Cleavage Efficiency of a Range of Resin Linked Amidines (**3d**).

amidines	R	Yield[a]	% purity[b]
(2a)	Ph	41%	66%
(2b)	4-amide-Ph	71%	98%
(2c)	3-nitro-Ph	52%	97%
(2d)	4-chloro-Ph	64%	96%
(2e)	4-hydroxy-Ph	60%	99%

[a] From initial substitution of aminomethyl resin and using internal HPLC calibrants. Measures both loading and cleavage efficiency. [b] % Area of integration.

The suitability of this amidine linker for solid phase chemistry was shown by the synthesis of the Ciba phase II LTB_4 antagonist CGS-25019C. This was prepared, as shown in scheme 2, in a total of eight steps. All reactions were monitored by HPLC, MALDI-TOF MS and ES MS. Thus immobilisation of the amidinophenol (**2e**) (60% recovery of (**2e**) from (**1c**) over 4-steps, 99% purity) was followed by Mitsunobu coupling with 1,5-pentanediol.[17] A second Mitsunobu coupling with allyl (3-methoxy-4-hydroxy-benzoate) (HPLC: 98% conversion and 55% purity) and finally an allyl ester deprotection (HPLC: 94% conversion and 57% purity) and amide coupling (PyBroP) gave CGS-25019C. The final amide coupling with PyBrop and diisopropylamine proceeded poorly as anticipated due to the hindered amine while the resin became very discolored. This is a problem we have previously encountered with PyBrop[18] and other electron-rich aromatic acids and suggests other coupling reagents should be used for such sluggish couplings. However the acid (**7**) was totally consumed and CGS-25019C (14%) and the related pyrrolidine amide (from the PyBrop) (21%) were isolated as pure products by reverse phase HPLC and gave the expected spectroscopic data.[19]
This solid-phase approach to CSG-25019C is obviously readily amenable to the generation of combinatorial diversity and highlights the scope of the developed linker methodology.



Scheme 2: (i) (a), (**1c**), DIC, HOBt, DCM; (b), *p*-O_2N-PhO-CO-Cl, pyridine, DCM; (c), (**2e**), Et_3N, dioxane; (ii) TMAD, Bu_3P, 1,5-pentanediol, dry (DCM/THF: 1/1); (iii) TMAD, Bu_3P, allyl- 3-methoxy-4-hydroxy-benzoate, dry (DCM/THF: 1/1); (iv) Pd(0), dimedone, DCM; (v) iPr_2NH, PyBrop, DCM; (vi) 50% TFA, 5% water, DCM.

In summary we have developed what we believe is an efficient linker system for amidines for solid phase and combinatorial chemistry. We have demonstrated the applicability of this linker strategy with a range of amidines and have shown its utility in the total synthesis of a compound already in clinical development with Novartis.

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16. **(3c)**: δ_H (300MHz, $(CD_3)_2SO$): 9.10 (1H, s, $CO_2\underline{H}$), 8.00 (2H, d, *J* 7, <u>H</u>-2,6 amidine), 7.55 (1H, t, *J* 7, <u>H</u>-3,5 amidine), 7.47 (2H, t, *J* 7, <u>H</u>-4 amidine), 7.35 and 6.90 (4H, 2xd, AB system, *J* 7, H-2,3,5 and 6 linker), 5.08 (2 H, s, Ph-$\underline{CH_2}$-O), 4.68 (2 H, s, O-$\underline{CH_2}$-CO_2); δ_C (75.5MHz, $(CD_3)_2SO$): 170.4 (CO_2H), 166.7 and 163.8 (OCON and $CNH(NH_2)$), 157.6 (C-1 linker), 134.3 (C-1 amidine), 132.0, 129.8, 129.2, 127.7 and 114.3 (linker and amidine Ar<u>C</u>H), 128.0 (C-4 linker), 66.9 (Ph-$\underline{C}H_2$-O), 65.5 (O-$\underline{C}H_2$-CO_2H); m/z (ESI +ve): 657.2 (dimer, $[M_2+ H]^+$, 28.7%), 329.2 ($[M+H]^+$, 69%); HRMS FAB, calculated ($[M+H]^+$ = 329.1137), found ($[M+H]^+$ = 329.1169).
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19. **(9)**: δ_H (360MHz, $(CD_3)_2SO$): 9.22 and 8.82 (4 H, 2xs, 2 $N\underline{H}_2$-amidine), 7.91 and 7.26 (4H, 2xd AB system *J* 9, amidine H-2,3,5,6), 7.06 (1H, d, ^3J 8, H-5), 6.92 (1H, d, ^4J 2, H-2), 6.89 (1H, dd, ^3J 8 and ^4J 2, H-6), 4.22 (2H, t *J* 6, CH_2-$C\underline{H}_2$-O), 4.10 (2H, t, *J* 6, CH_2-$C\underline{H}_2$-O), 3.85 (3H, s, O-$C\underline{H}_3$), 2.56 (signals overlapped by DMSO, N-$C\underline{H}$-Me_2), 1.92 (4H, m, O-CH_2-$C\underline{H}_2CH_2C\underline{H}_2$), 1.67 (2H, q, *J* 7, CH_2-$C\underline{H}_2$-CH_2), 1.45-1.30 (12H, overlapping signals, $N(CH(C\underline{H}_3)_2)_2$); m/z (ESI +ve): 456.2 ($[M+H]^+$, 100%), 478.2 ($[M + Na]^+$, 6.2%); HRMS FAB, calculated ($[M+H]^+$ = 456.2862), found ($[M+ H]^+$ = 456.2877).

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