Okuyama M, Gardiner SM, Kaup SS, Bennett T, Baker D, Selwood DL, Hiley CR (2007), Br J Pharmacol 152:751-764).

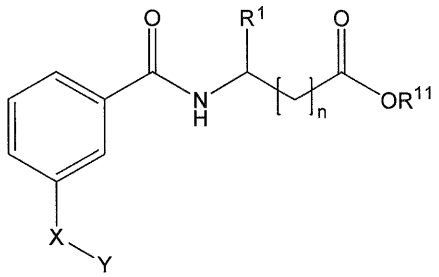
VSN-16 was first disclosed in WO 2005/080316 (in the name of University College London). Initial studies demonstrated that VSN16 exhibits a marked effect on spasticity in CREAE mice, providing strong evidence that a selective inhibition of spasticity is achieved without producing significant adverse CNS effects.

With regard to the involvement of glycine in spasticity mechanisms, mutations in the glycine receptor demonstrate an important role in the control of muscle tone as shown by studies in mouse strains (*Oscillator*, *Spasmodic* and *Spastic*). The archetypal glycine antagonist, strychnine causes severe muscle cramps. A hyperekplexic response (an exaggerated startle response to tactile or acoustic stimuli) is observed in humans with similar mutations. Similar responses have now been shown in humans with mutations in the glycine transporter GlyT2a (Rees MI, Harvey K, Pearce BR, Chung SK, Duguid IC, Thomas P, Beatty S, Graham GE, Armstrong L, Shiang R, Abbott KJ, Zuberi SM, Stephenson JB, Owen MJ, Tijssen MA, van den Maagdenberg AM, Smart TG, Supplisson S, Harvey RJ (2006), Nat Genet 38:801-806).

The present invention seeks to provide new compounds that have therapeutic applications in the treatment of muscular disorders, particularly for controlling spasticity and/or tremors.

STATEMENT OF INVENTION

A first aspect of the invention relates to a compound of formula I, or a pharmaceutically acceptable salt thereof,



I

wherein:

n is 0 or 1;

R^1 is selected from H, alkyl and aralkyl, wherein said alkyl and aralkyl groups may be optionally substituted by one or more OH groups;

X is a group selected from

$-C\equiv C-(CH_2)_p-$;

$-C(R^5)=C(R^6)-(CH_2)_q-$; and

$-C(R^5)(R^6)C(R^7)(R^8)-(CH_2)_r-$;

where each of R^5, R^6, R^7 and R^8 is independently H or alkyl, and each of p, q and r is independently 1, 2, 3, 4 or 5;

Y is $CONR^3R^4$,

where each of R^3 and R^4 is independently H or alkyl; or R^3 and R^4 are linked, together with the nitrogen to which they are attached, to form a 5 or 6-membered heterocycloalkyl or heterocycloalkenyl group, said heterocycloalkyl or heterocycloalkenyl group optionally containing one or more further groups selected from O, N, CO and S; and R^{11} is independently H or alkyl.

Advantageously, a number of the presently claimed compounds exhibit one or more of the following properties: improved potency/activity, improved selectivity, improved distribution, improved aqueous solubility or decreased lipophilicity and/or reduced rates of metabolism.

Also disclosed is a compound of formula I, or a pharmaceutically acceptable salt thereof, for use in treating a muscular disorder.

Also disclosed is a compound of formula I, or a pharmaceutically acceptable salt thereof, for use in controlling spasticity and tremors, or for treating bladder spasticity.

Also disclosed is a compound of formula I, or a pharmaceutically acceptable salt thereof, for use in treating pain.

A second aspect of the invention relates to a pharmaceutical composition comprising a compound of formula I as defined above admixed with a pharmaceutically acceptable diluent, excipient or carrier.

A third aspect of the invention relates to a compound as disclosed herein for use in medicine.

A fourth aspect of the invention relates to a compound as disclosed herein for use in the prevention or treatment of a muscular disorder, or for treating or controlling spasticity and tremors.

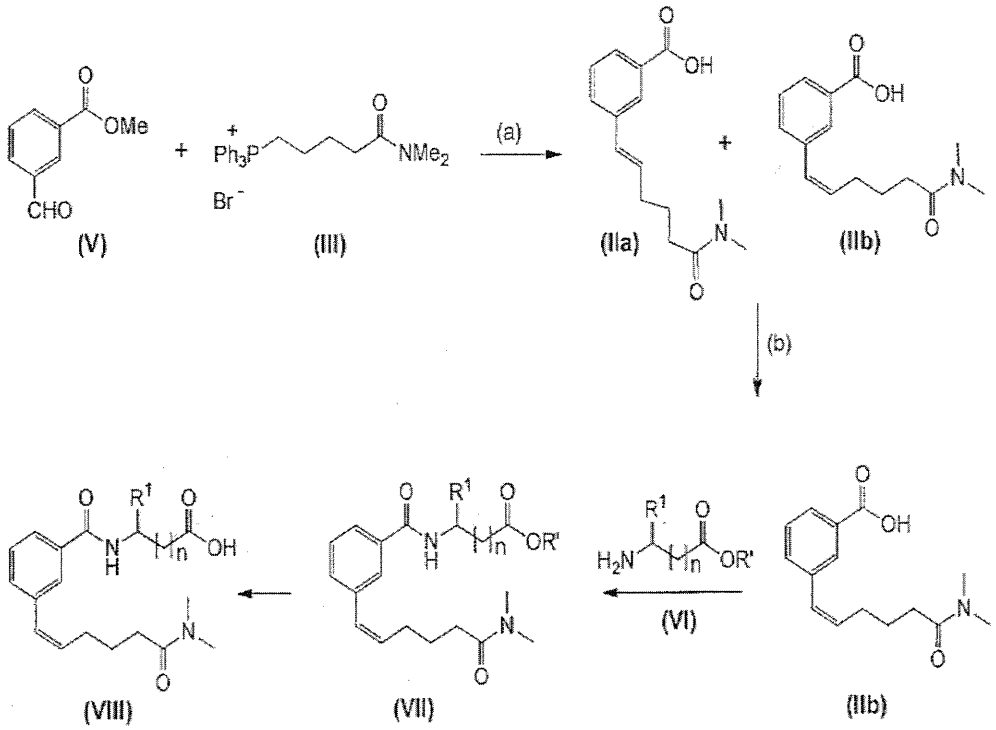
A fifth aspect of the invention relates to a compound as disclosed herein for use in the treatment of spasticity in MS.

A sixth aspect of the invention relates to compound as disclosed herein for use in the treatment of pain.

A seventh aspect of the invention relates to use of a compound as disclosed herein for in the preparation of a medicament for the prevention or treatment of a muscular disorder, or for treating or controlling spasticity and tremors, or for treating bladder spasticity, or for treating pain, or for treating asthma.

Also disclosed is a process for preparing compounds of formula I.

A eight aspect of the invention relates to a process for preparing a compound of formula I as disclosed herein which is of formula (VIII), wherein R^1 and n are as defined herein, said process comprising the steps of:



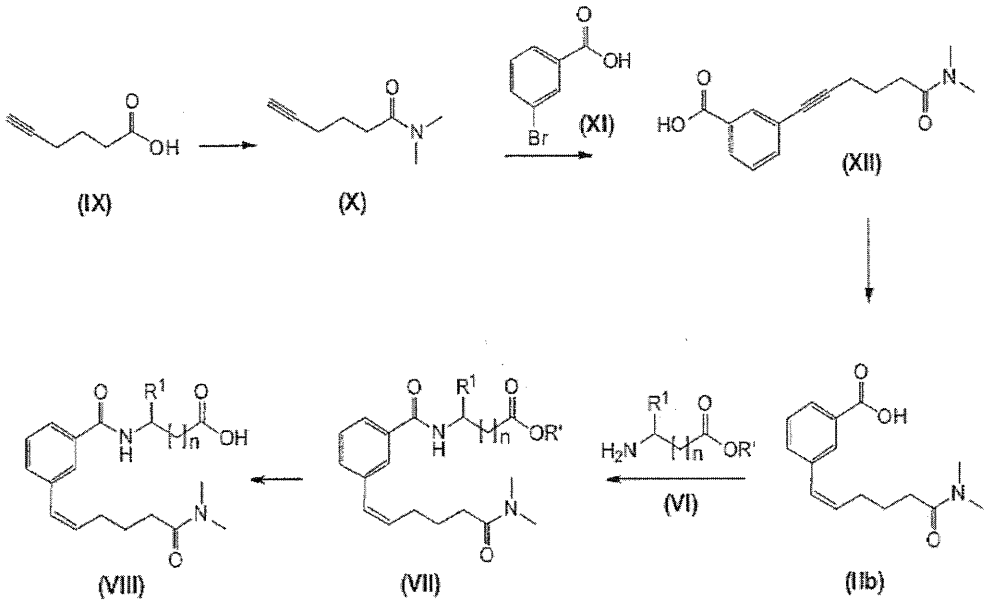
(i) coupling a compound of formula (V) with a compound of formula (III) to form a mixture comprising compounds of formulae (IIa) and (IIb);

(ii) separating said compound of formula (IIb) from the mixture obtained in step (i);

(iii) treating the compound of formula (IIb) obtained in step (ii) with a compound of formula (VI), where R^1 and n are as defined in claim 1, and R' is alkyl, to form a compound of formula (VII); and

(iv) converting said compound of formula (VII) to a compound of formula (VIII).

A ninth aspect of the invention relates to a process for preparing a compound as disclosed herein which is of formula (VIII), wherein R^1 and n are as defined herein, said process comprising the steps of:



(i) treating a compound of formula (IX) with dimethylamine to form a compound of formula (X);

(ii) reacting said compound of formula (X) with a compound of formula (XI) to form a compound of formula (XII);

(iii) hydrogenating said compound of formula (XII) to form a compound of formula (IIb);

(iv) treating said compound of formula (IIb) with a compound of formula (VI), where R^1 and n are as defined in claim 1, and R' is alkyl, to form a compound of formula (VII); and

(v) converting said compound of formula (VII) to a compound of formula (VIII)

DETAILED DESCRIPTION

COMPOUNDS

The present invention relates to compounds of formula I as defined herein, and pharmaceutically acceptable salts and prodrugs thereof.

As used herein, the term "alkyl" includes both saturated straight chain and branched alkyl groups which may be substituted (mono- or poly-) or unsubstituted. Preferably, the alkyl group is a C_{1-20} alkyl group, more preferably a C_{1-15}, more preferably still a C_{1-}

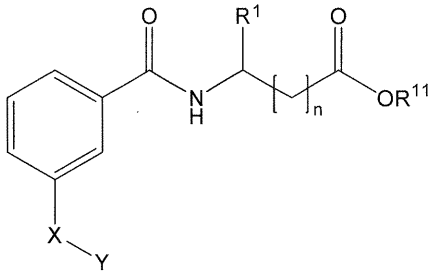
$_{10}$ alkyl group, more preferably still, a C_{1-6} alkyl group or a C_{1-4} alkyl group. Particularly preferred alkyl groups include, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl and hexyl. Suitable substituents include, for example, alkyl, hydroxy, halo-, alkoxy-, nitro-, COOH, CO_2-alkyl, alkenyl, CN, NH_2 and CF_3.

As used herein, the term "cycloalkyl" refers to a cyclic alkyl group which may be substituted (mono- or poly-) or unsubstituted. Preferably, the cycloalkyl group is a C_{3-6}-cycloalkyl group. Suitable substituents include, for example, alkyl, hydroxy, halo-, alkoxy-, nitro-, COOH, CO_2-alkyl, alkenyl, CN, NH_2 and CF_3.

As used herein, the term "alkenyl" refers to group containing one or more double bonds, which may be branched or unbranched, and substituted (mono- or poly-) or unsubstituted. Preferably the alkenyl group is a C_{2-20} alkenyl group, more preferably a C_{2-15} alkenyl group, more preferably still a C_{2-10} alkenyl group, or preferably a C_{2-6} alkenyl group. Suitable substituents include, for example, alkyl, hydroxy, halo-, alkoxy-, nitro-, COOH, CO_2-alkyl, alkenyl, CN, NH_2 and CF_3.

CLAIMS

1. A compound of formula I, or a pharmaceutically acceptable salt thereof,



I

wherein:

n is 0 or 1;

R^1 is selected from H, alkyl and aralkyl, wherein said alkyl and aralkyl groups may be optionally substituted by one or more OH groups;

X is a group selected from

$-C\equiv C-(CH_2)_p-$;

$-C(R^5)=C(R^6)-(CH_2)_q-$; and

$-C(R^5)(R^6)C(R^7)(R^8)-(CH_2)_r-$;

where each of R^5, R^6, R^7 and R^8 is independently H or alkyl, and each of p, q and r is independently 1, 2, 3, 4 or 5;

Y is $CONR^3R^4$,where each of R^3 and R^4 is independently H or alkyl; or R^3 and R^4 are linked, together with the nitrogen to which they are attached, to form a 5 or 6-membered heterocycloalkyl or heterocycloalkenyl group, said heterocycloalkyl or heterocycloalkenyl group optionally containing one or more further groups selected from O, N, CO and S; and R^{11} is independently H or alkyl.

2. A compound according to claim 1 wherein R^1 is selected from H, Me, Et, ^{n}Pr, ^{i}Pr, CH_2-phenyl, CH_2-[4-(OH)-phenyl], CH_2OH, $CH(OH)CH_3$, $CH(CH_3)CH_2CH_3$ and $CH_2CH(CH_3)_2$.

3. A compound according to claim 1 or claim 2 wherein Y is selected from $CON(Me)_2$, CONHMe, CONHEt, CO-piperidinyl, CO-pyrrolidinyl, more preferably, $CON(Me)_2$.

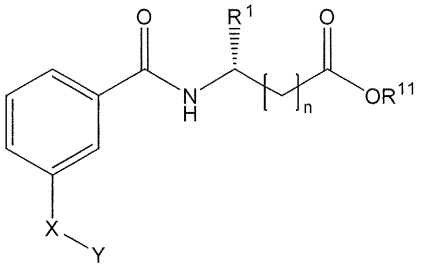
4. A compound according to any preceding claim wherein X- is *cis* $-C(R^5)=C(R^6)-(CH_2)_q-$ and q is 2, 3 or 4.

5. A compound according to claim 4 wherein X is $-CH=CH-(CH_2)_q-$ and q is 2 or 3.

6. A compound according to any one of claims 1 to 3 wherein X is $-C(R^5)(R^6)C(R^7)(R^8)-(CH_2)_r-$ and r is 2, 3 or 4.

7. A compound according to claim 6 wherein X is $-CH_2-CH_2-(CH_2)_r-$ and r is 2 or 3.

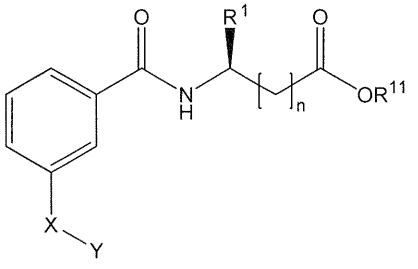
8. A compound according to any preceding claim which is of formula Ia, or a pharmaceutically acceptable salt thereof,



Ia

wherein R^1, R^{11}, X, Y and n are as defined in claim 1.

9. A compound according to any one of claims 1 to 7 which is of formula Ib, or a pharmaceutically acceptable salt thereof,



Ib

wherein R^1, R^{11}, X, Y and n are as defined in claim 1.

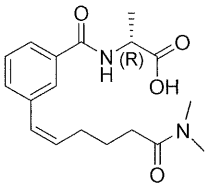
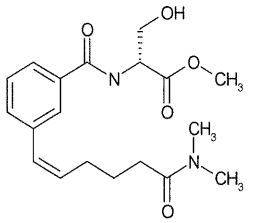
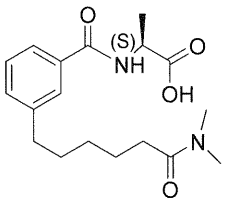
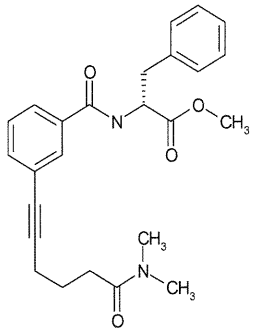
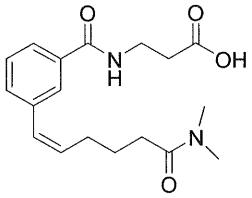
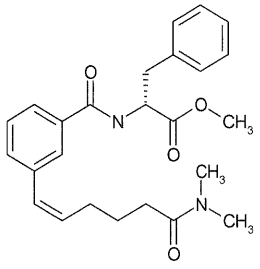
10. A compound according to any preceding claim wherein n is 0.

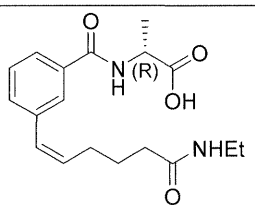
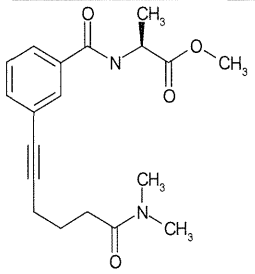
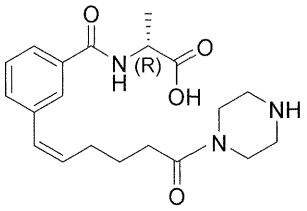
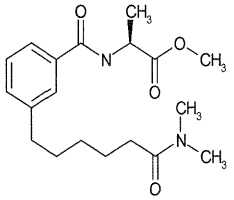
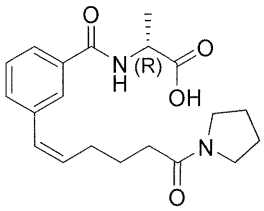
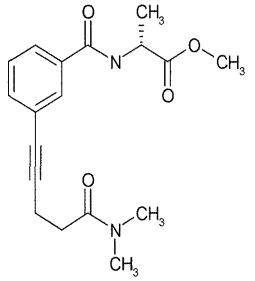
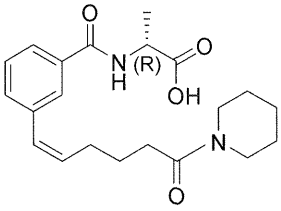
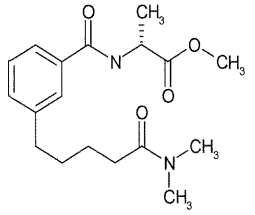
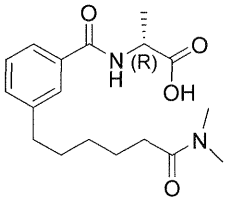
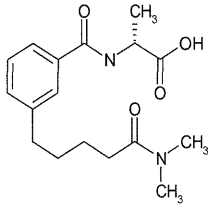
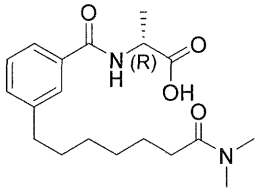
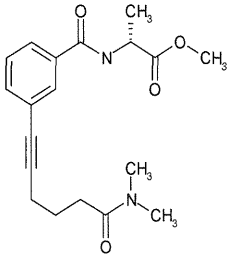
11. A compound according to any preceding claim wherein R^1 is Me.

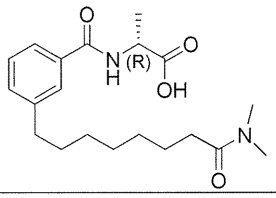
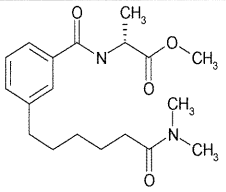
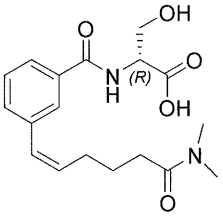
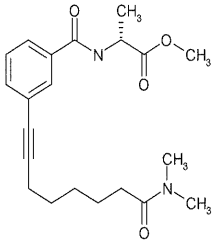
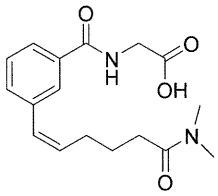
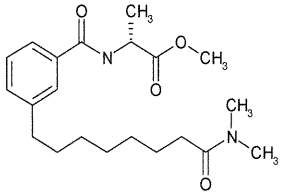
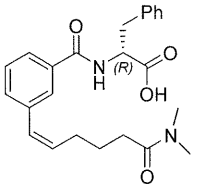
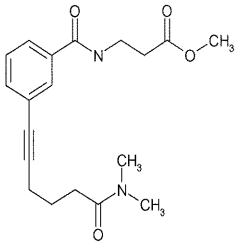
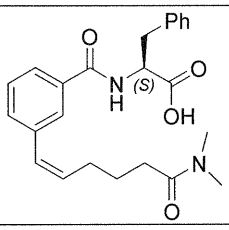
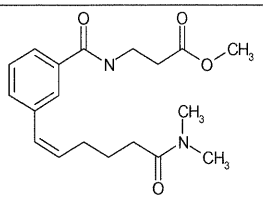
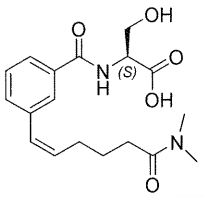
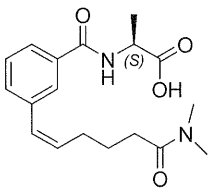
12. A compound according to claim 8 wherein n is 0, R^1 is Me and X is –CH=CH–$(CH_2)_3$– or –CH_2-CH_2-$(CH_2)_3$–.

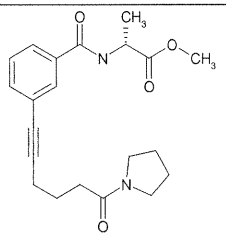
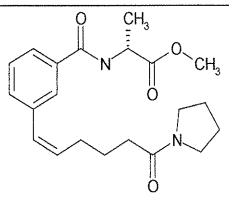
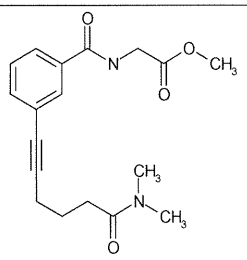
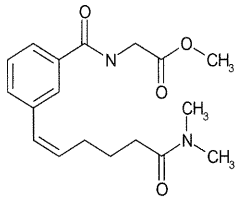
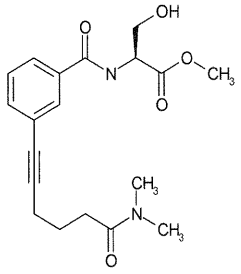
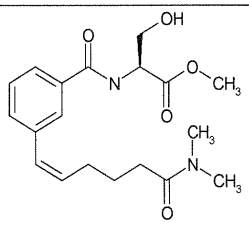
13. A compound according to any one of claims 1 to 9 wherein n is 1 and R^1 is H.

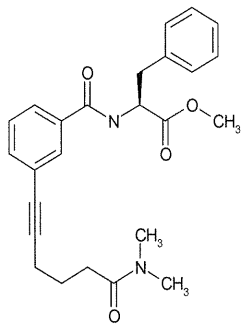
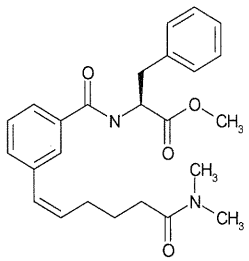
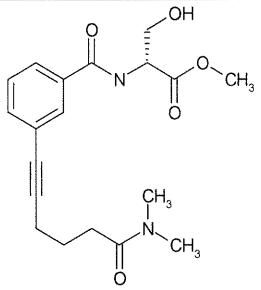
14. A compound according to any preceding claim which is selected from the following:

[1]		[29]	
[4]		[30]	
[5]		[31]	

[7]		[32]	
[8]		[33]	
[9]		[34]	
[10]		[35]	
[11]		[36]	
[12]		[37]	

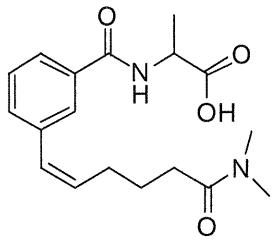
[13]		[38]	
[14]		[39]	
[15]		[40]	
[16]		[41]	
[17]		[42]	
[18]			
[19]			

[20]			
[21]			
[22]			
[23]			
[24]			
[25]			

[26]			
[27]			
[28]			

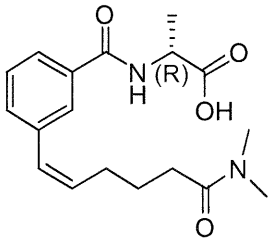
and pharmaceutically acceptable salts and enantiomers thereof.

15. A compound according to claim 1 which is of the formula [1], or a pharmaceutically acceptable salt thereof:

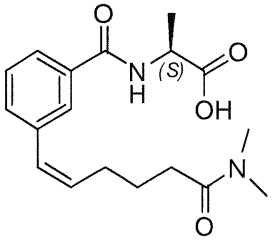


[1]

16. A compound according to claim 1 which is of the formula [1a] or formula [1b], or a pharmaceutically acceptable salt thereof:



[1a]



[1b]

17. A pharmaceutical composition comprising a compound according to any one of claims 1 to 16 admixed with a pharmaceutically acceptable diluent, excipient or carrier.

18. A compound according to any one of claims 1 to 16 for use in medicine.

19. A compound according to any one of claims 1 to 16 for use in the prevention or treatment of a muscular disorder, or for treating or controlling spasticity and tremors.

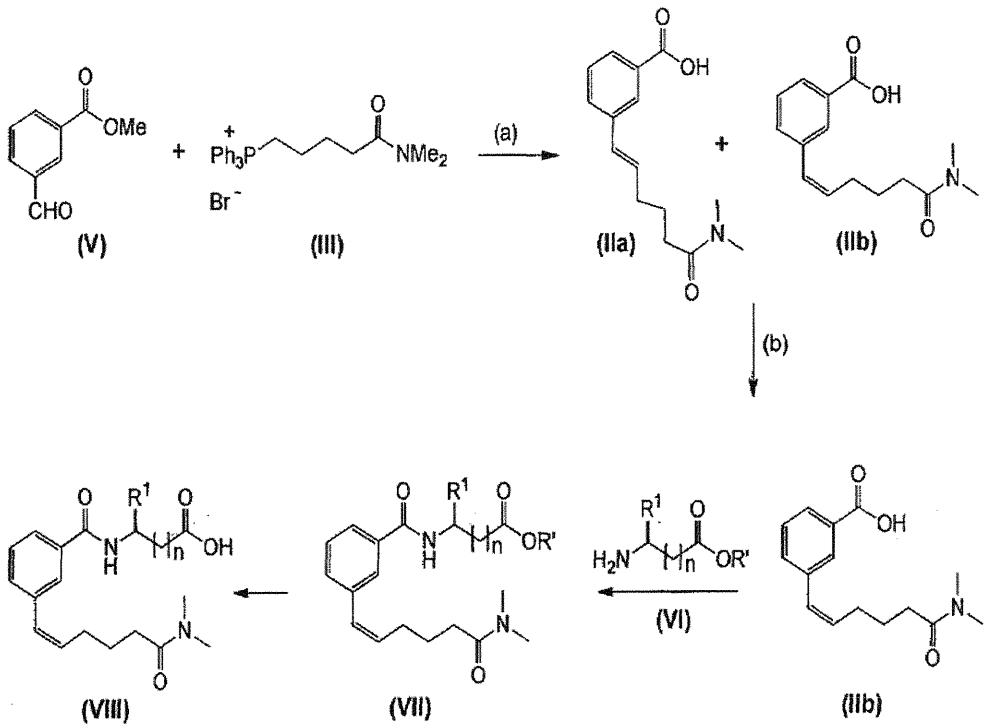
20. A compound for use according to claim 19 wherein the disorder is a neuromuscular disorder.

21. A compound according to any one of claims 1 to 16 for use in the treatment of spasticity in MS.

22. A compound according to any one of claims 1 to 16 for use in the treatment of pain.

23. Use of a compound according to any one of claims 1 to 16 for use in the preparation of a medicament for the prevention or treatment of a muscular disorder, or for treating or controlling spasticity and tremors, or for treating bladder spasticity, or for treating pain, or for treating asthma.

24. A process for preparing a compound of formula I as defined in claim 1 which is of formula (VIII), wherein R^1 and n are as defined in claim 1, said process comprising the steps of:



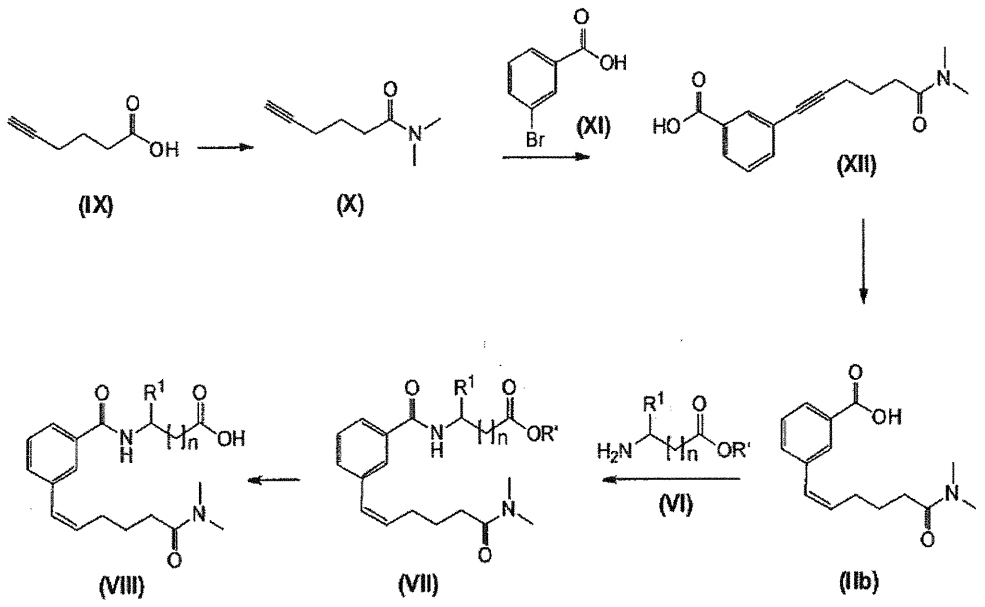
(i) coupling a compound of formula (V) with a compound of formula (III) to form a mixture comprising compounds of formulae (IIa) and (IIb);

(ii) separating said compound of formula (IIb) from the mixture obtained in step (i);

(iii) treating the compound of formula (IIb) obtained in step (ii) with a compound of formula (VI), where R^1 and n are as defined in claim 1, and R' is alkyl, to form a compound of formula (VII); and

(iv) converting said compound of formula (VII) to a compound of formula (VIII).

25. A process for preparing a compound of formula I as defined in claim 1 which is of formula (VIII), wherein R^1 and n are as defined in claim 1, said process comprising the steps of:



(i) treating a compound of formula (IX) with dimethylamine to form a compound of formula (X);

(ii) reacting said compound of formula (X) with a compound of formula (XI) to form a compound of formula (XII);

(iii) hydrogenating said compound of formula (XII) to form a compound of formula (IIb);

(iv) treating said compound of formula (IIb) with a compound of formula (VI), where R^1 and n are as defined in claim 1, and R' is alkyl, to form a compound of formula (VII); and

(v) converting said compound of formula (VII) to a compound of formula (VIII).