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**Hiestand et al.**

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(54) **S1P RECEPTOR MODULATORS FOR TREATING RELAPSING-REMITTING MULTIPLE SCLEROSIS**

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**Christian Schnell**, Helsingue (FR)

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**Christian Schnell**, Helsingue (FR)

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(73) Assignee: **Novartis AG**, Basel (CH)

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(\* ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

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(21) Appl. No.: **14/257,342**

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(22) Filed: **Apr. 21, 2014**

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(65) **Prior Publication Data**

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**Related U.S. Application Data**

(60) Division of application No. 13/149,468, filed on May 31, 2011, now Pat. No. 8,741,963, which is a continuation of application No. 12/303,765, filed as application No. PCT/EP2007/005597 on Jun. 25, 2007, now abandoned.

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(30) **Foreign Application Priority Data**

Jun. 27, 2006 (GB) ..... 0612721.1

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(51) **Int. Cl.**

**A61K 31/13** (2006.01)  
**C07C 215/08** (2006.01)  
**A61K 31/137** (2006.01)  
**A61K 31/397** (2006.01)

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(52) **U.S. Cl.**

CPC ..... **C07C 215/08** (2013.01); **A61K 31/137** (2013.01); **A61K 31/397** (2013.01); **A61K 31/13** (2013.01)

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(58) **Field of Classification Search**

CPC ..... **A61K 31/13**; **A61K 31/137**  
USPC ..... **514/667**, **903**  
See application file for complete search history.

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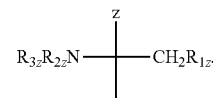
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(57) **ABSTRACT**

The present invention relates uses of an S1P receptor modulator such as 2-substituted 2-amino-propane-1,3-diol or 2-amino-propanol derivatives, e. g. a compound comprising a group of formula X



for the treatment or prevention of neo-angiogenesis associated with a demyelinating disease, e.g. multiple sclerosis.

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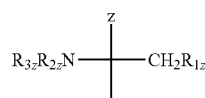
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## S1P RECEPTOR MODULATORS FOR TREATING RELAPSING-REMITTING MULTIPLE SCLEROSIS

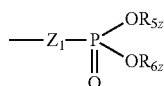
The present invention relates to the use of an S1P receptor modulator in the treatment or prevention of neo-angiogenesis associated with a demyelinating disease, e.g. multiple sclerosis.

S1P receptor modulators are typically sphingosine analogues, such as 2-substituted 2-amino-propane-1,3-diol or 2-amino-propanol derivatives, e.g. a compound comprising a group of formula X.

Sphingosine-1 phosphate (hereinafter "S1P") is a natural serum lipid. Presently there are eight known S1P receptors, namely S1P1 to S1P8. S1P receptor modulators are typically sphingosine analogues, such as 2-substituted 2-amino-propane-1,3-diol or 2-amino-propanol derivatives, e.g. a compound comprising a group of formula X



wherein Z is H, C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl, C<sub>2-6</sub>alkynyl, phenyl, phenyl substituted by OH, C<sub>1-6</sub>alkyl substituted by 1 to 3 substituents selected from the group consisting of halogen, C<sub>3-8</sub>cycloalkyl, phenyl and phenyl substituted by OH, or CH<sub>2</sub>-R<sub>4z</sub> wherein R<sub>4z</sub> is OH, acyloxy or a residue of formula (a)



wherein Z<sub>1</sub> is a direct bond or O, preferably O; each of R<sub>5z</sub> and R<sub>6z</sub>, independently, is H, or C<sub>1-4</sub>alkyl optionally substituted by 1, 2 or 3 halogen atoms;

R<sub>1z</sub> is OH, acyloxy or a residue of formula (a); and each of R<sub>2z</sub> and R<sub>3z</sub>, independently, is H, C<sub>1-4</sub>alkyl or acyl.

Group of formula X is a functional group attached as a terminal group to a moiety which may be hydrophilic or lipophilic and comprise one or more aliphatic, alicyclic, aromatic and/or heterocyclic residues, to the extent that the resulting molecule wherein at least one of Z and R<sub>1z</sub> is or comprises a residue of formula (a), signals as an agonist at one of more sphingosine-1-phosphate receptor.

S1P receptor modulators are compounds which signal as agonists at one or more sphingosine-1 phosphate receptors, e.g. S1P1 to S1P8. Agonist binding to a S1P receptor may e.g. result in dissociation of intracellular heterotrimeric G-proteins into Gα-GTP and Gβγ-GTP, and/or increased phosphorylation of the agonist-occupied receptor and activation of downstream signaling pathways/kinases.

The binding affinity of S1P receptor modulators to individual human S1P receptors may be determined in following assay:

S1P receptor modulator activities of compounds are tested on the human S1P receptors S1P<sub>1</sub>, S1P<sub>2</sub>, S1P<sub>3</sub>, S1P<sub>4</sub> and S1P<sub>5</sub>. Functional receptor activation is assessed by quantifying

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bly expressing the appropriate human S1P receptor. The assay technology used is SPA (scintillation proximity based assay). Briefly, DMSO dissolved compounds are serially diluted and added to SPA-bead (Amersham-Pharmacia) immobilised S1P receptor expressing membrane protein (10-20 μg/well) in the presence of 50 mM Hepes, 100 mM NaCl, 10 mM MgCl<sub>2</sub>, 10 μM GDP, 0.1% fat free BSA and 0.2 nM GTP [γ-<sup>35</sup>S] (1200 Ci/mmol). After incubation in 96 well microtiterplates at RT for 120 min, unbound GTP [γ-<sup>35</sup>S] is separated by a centrifugation step. Luminescence of SPA beads triggered by membrane bound GTP [γ-<sup>35</sup>S] is quantified with a TOPcount plate reader (Packard). EC<sub>50</sub>s are calculated using standard curve fitting software. In this assay, the S1P receptor modulators preferably have a binding affinity to S1P receptor <50 nM.

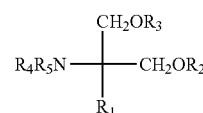
Preferred S1P receptor modulators are e.g. compounds which in addition to their S1P binding properties also have accelerating lymphocyte homing properties, e.g. compounds which elicit a lymphopenia resulting from a re-distribution, preferably reversible, of lymphocytes from circulation to secondary lymphatic tissue, without evoking a generalized immunosuppression. Nave cells are sequestered; CD4 and CD8 T-cells and B-cells from the blood are stimulated to migrate into lymph nodes (LN) and Peyer's patches (PP).

The lymphocyte homing property may be measured in following Blood Lymphocyte Depletion assay:

A S1P receptor modulator or the vehicle is administered orally by gavage to rats. Tail blood for hematological monitoring is obtained on day -1 to give the baseline individual values, and at 2, 6, 24, 48 and 72 hours after application. In this assay, the S1P receptor agonist or modulator depletes peripheral blood lymphocytes, e.g. by 50%, when administered at a dose of e.g. <20 mg/kg.

Examples of appropriate S1P receptor modulators are, for example:

Compounds as disclosed in EP627406A1, e.g. a compound of formula I



wherein R<sub>1</sub> is a straight- or branched (C<sub>12-22</sub>) chain which may have in the chain a bond or a hetero atom selected from a double bond, a triple bond, O, S, NR<sub>6</sub>, wherein R<sub>6</sub> is H, C<sub>1-4</sub>alkyl, aryl-C<sub>1-4</sub>alkyl, acyl or (C<sub>1-4</sub>alkoxy)carbonyl, and carbonyl, and/or which may have as a substituent C<sub>1-4</sub>alkoxy, C<sub>2-4</sub>alkenyl-oxo, C<sub>2-4</sub>alkynyl-oxo, aryl-C<sub>1-4</sub>alkyl-oxo, acyl, C<sub>1-4</sub>alkylamino, acylamino, (C<sub>1-4</sub>alkoxy)carbonyl, (C<sub>1-4</sub>alkoxy)-carbonylamino, acyloxy, (C<sub>1-4</sub>alkyl) carbamoyl, nitro, halogen, amino, hydroxyimino, hydroxy or carboxy; or

R<sub>1</sub> is  
 a phenylalkyl wherein alkyl is a straight- or branched (C<sub>6-20</sub>)carbon chain; or  
 a phenylalkyl wherein alkyl is a straight- or branched (C<sub>1-30</sub>)carbon chain wherein said phenylalkyl is substituted by  
 a straight- or branched (C<sub>6-20</sub>)carbon chain optionally substituted by halogen,

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a straight- or branched (C<sub>6-20</sub>)alkenyloxy, phenyl-C<sub>1-4</sub>alkoxy, halophenyl-C<sub>1-4</sub>alkoxy, phenyl-C<sub>1-4</sub>alkoxy-C<sub>1-4</sub>alkyl, phenoxy-C<sub>1-4</sub>alkoxy or phenoxy-C<sub>1-4</sub>alkyl, cycloalkylalkyl substituted by C<sub>6-20</sub>alkyl, heteroarylalkyl substituted by C<sub>6-20</sub>alkyl, heterocyclic C<sub>6-20</sub>alkyl or heterocyclic alkyl substituted by C<sub>2-20</sub>alkyl,

and wherein

the alkyl moiety may have

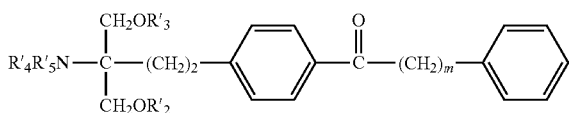
in the carbon chain, a bond or a heteroatom selected from a double bond, a triple bond, O, S, sulfinyl, sulfonyl, or NR<sub>6</sub>, wherein R<sub>6</sub> is as defined above, and

as a substituent C<sub>1-4</sub>alkoxy, C<sub>2-4</sub>alkenyloxy, C<sub>2-4</sub>alkynyl, aryl/C<sub>1-4</sub>alkyloxy, acyl, C<sub>1-4</sub>alkylamino, C<sub>1-4</sub>alkylthio, acylamino, (C<sub>1-4</sub>alkoxy)carbonyl, (C<sub>1-4</sub>alkoxy)carbonylamino, acyloxy, (C<sub>1-4</sub>alkyl)carbamoyl, nitro, halogen, amino, hydroxy or carboxy, and

each of R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub>, independently, is H, C<sub>1-4</sub>alkyl or acyl

or a pharmaceutically acceptable salt or hydrate thereof;

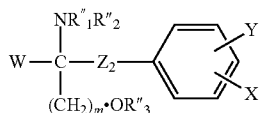
Compounds as disclosed in EP 1002792A1, e.g. a compound of formula II



wherein m is 1 to 9 and each of R'<sub>2</sub>, R'<sub>3</sub>, R'<sub>4</sub> and R'<sub>5</sub>, independently, is H, C<sub>1-6</sub>alkyl or acyl,

or a pharmaceutically acceptable salt or hydrate thereof;

Compounds as disclosed in EP0778263 A1, e.g. a compound of formula III



wherein W is H; C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl or C<sub>2-6</sub>alkynyl; unsubstituted or by OH substituted phenyl; R'<sub>4</sub>O(CH<sub>2</sub>)<sub>n</sub>; or C<sub>1-6</sub>alkyl substituted by 1 to 3 substituents selected from the group consisting of halogen, C<sub>3-8</sub>cycloalkyl, phenyl and phenyl substituted by OH;

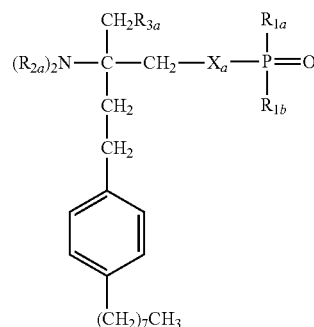
X is H or unsubstituted or substituted straight chain alkyl having a number p of carbon atoms or unsubstituted or substituted straight chain alkoxy having a number (p-1) of carbon atoms, e.g. substituted by 1 to 3 substituents selected from the group consisting of C<sub>1-6</sub>alkyl, OH, C<sub>1-6</sub>alkoxy, acyloxy, amino, C<sub>1-6</sub>alkylamino, acylamino, oxo, haloC<sub>1-6</sub>alkyl, halogen, unsubstituted phenyl and phenyl substituted by 1 to 3 substituents selected from the group consisting of C<sub>1-6</sub>alkyl, OH, C<sub>1-6</sub>alkoxy, acyl, acyloxy, amino, C<sub>1-6</sub>alkylamino, acylamino, haloC<sub>1-6</sub>alkyl and halogen; Y is H, OH, C<sub>1-6</sub>alkoxy, acyl, acyloxy, amino, C<sub>1-6</sub>alkylamino, acylamino, haloC<sub>1-6</sub>alkyl or halogen, Z<sub>2</sub> is a single bond or a straight chain alkylene having a number or carbon atoms of q,

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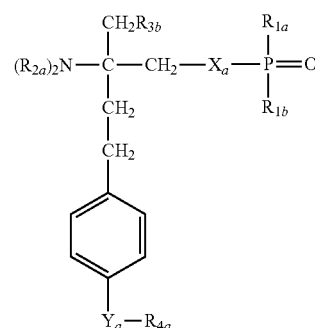
each of R''<sub>1</sub>, R''<sub>2</sub>, R''<sub>3</sub> and R''<sub>4</sub>, independently, is H, C<sub>1-4</sub>alkyl or acyl,

or a pharmaceutically acceptable salt or hydrate thereof,

5 Compounds as disclosed in WO02/18395, e.g. a compound of formula IVa or IVb



IVa

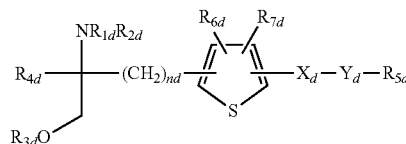


IVb

wherein X<sub>a</sub> is O, S, NR<sub>1a</sub> or a group —(CH<sub>2</sub>)<sub>n<sub>a</sub></sub>—, which group is unsubstituted or substituted by 1 to 4 halogen; n<sub>a</sub> is 1 or 2, R<sub>1a</sub> is H or (C<sub>1-4</sub>)alkyl, which alkyl is unsubstituted or substituted by halogen; R<sub>1a</sub> is H, OH, (C<sub>1-4</sub>)alkyl or O(C<sub>1-4</sub>)alkyl wherein alkyl is unsubstituted or substituted by 1 to 3 halogen; R<sub>1b</sub> is H, OH or (C<sub>1-4</sub>)alkyl, wherein alkyl is unsubstituted or substituted by halogen; each R<sub>2a</sub> is independently selected from H or (C<sub>1-4</sub>)alkyl, which alkyl is unsubstituted or substituted by halogen; R<sub>3a</sub> is H, OH, halogen or O(C<sub>1-4</sub>)alkyl wherein alkyl is unsubstituted or substituted by halogen; and R<sub>3b</sub> is H, OH, halogen, (C<sub>1-4</sub>)alkyl wherein alkyl is unsubstituted or substituted by hydroxy, or O(C<sub>1-4</sub>)alkyl wherein alkyl is unsubstituted or substituted by halogen; Y<sub>a</sub> is —CH<sub>2</sub>—, —C(O)—, —CH(OH)—, —C(=NOH)—, O or S, and R<sub>4a</sub> is (C<sub>4-14</sub>)alkyl or (C<sub>4-14</sub>)alkenyl;

or a pharmaceutically acceptable salt or hydrate thereof;

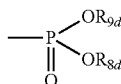
Compounds as disclosed in WO02/06268A1, e.g. a compound of formula V



V

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$R_{3d}$  is hydrogen, a hydroxy-protecting group or a residue of formula



$R_{4d}$  is  $C_{1-4}$ alkyl;

$n_d$  is an integer of 1 to 6;

$X_d$  is ethylene, vinylene, ethynylene, a group having a formula  $-D-CH_2-$  (wherein D is carbonyl,  $-\text{CH}(\text{OH})-$ , O, S or N), aryl or aryl substituted by up to three substituents selected from group a as defined hereinafter;

$Y_d$  is single bond,  $C_{1-10}$ alkylene,  $C_{1-10}$ alkylene which is substituted by up to three substituents selected from groups a and b,  $C_{1-10}$ alkylene having O or S in the middle or end of the carbon chain, or  $C_{1-10}$ alkylene having O or S in the middle or end of the carbon chain which is substituted by up to three substituents selected from groups a and b;

$R_{5d}$  is hydrogen,  $C_{3-6}$ cycloalkyl, aryl, heterocyclic group,  $C_{3-6}$ cycloalkyl substituted by up to three substituents selected from groups a and b, aryl substituted by up to three substituents selected from groups a and b, or heterocyclic group substituted by up to three substituents selected from groups a and b;

each of  $R_{6d}$  and  $R_{7d}$ , independently, is H or a substituent selected from group a;

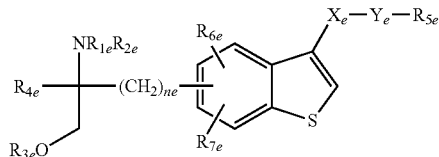
each of  $R_{8d}$  and  $R_{9d}$ , independently, is H or  $C_{1-4}$ alkyl optionally substituted by halogen;

<group a> is halogen, lower alkyl, halogeno lower alkyl, lower alkoxy, lower alkylthio, carboxyl, lower alkoxy-carbonyl, hydroxy, lower aliphatic acyl, amino, mono-lower alkylamino, di- $C_{1-4}$ alkylamino, acylamino, cyano or nitro; and

<group b> is  $C_{3-6}$ cycloalkyl, aryl or heterocyclic group, each being optionally substituted by up to three substituents selected from group a;

with the proviso that when  $R_{5d}$  is hydrogen,  $Y_d$  is a either a single bond or linear  $C_{1-10}$  alkylene, or a pharmacologically acceptable salt, ester or hydrate thereof;

Compounds as disclosed in JP-14316985 (JP2002316985), e.g. a compound of formula VI

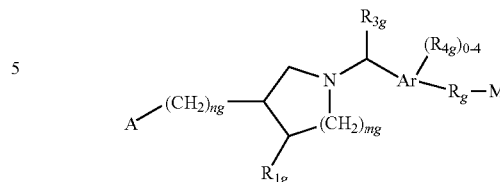


wherein  $R_{1e}$ ,  $R_{2e}$ ,  $R_{3e}$ ,  $R_{4e}$ ,  $R_{5e}$ ,  $R_{6e}$ ,  $R_{7e}$ ,  $n_e$ ,  $X_e$  and  $Y_e$  are as disclosed in JP-14316985;

or a pharmacologically acceptable salt, ester or hydrate thereof;

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VII

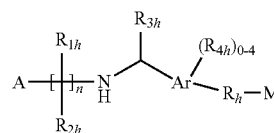


wherein

Ar is phenyl or naphthyl; each of  $m_g$  and  $n_g$  independently is 0 or 1; A is selected from  $\text{COOH}$ ,  $\text{PO}_3\text{H}_2$ ,  $\text{PO}_2\text{H}$ ,  $\text{SO}_3\text{H}$ ,  $\text{PO}(\text{C}_{1-3}\text{alkyl})\text{OH}$  and 1H-tetrazol-5-yl; each of  $R_{1g}$  and  $R_{2g}$  independently is H, halogen, OH,  $\text{COOH}$  or  $C_{1-4}$ alkyl optionally substituted by halogen;  $R_{3g}$  is H or  $C_{1-4}$ alkyl optionally substituted by halogen or OH; each  $R_{4g}$  independently is halogen, or optionally halogen substituted  $C_{1-4}$ alkyl or  $C_{1-3}$ alkoxy; and each of  $R_g$  and M has one of the significances as indicated for B and C, respectively, in WO03/062252A1;

or a pharmacologically acceptable salt, solvate or hydrate thereof;

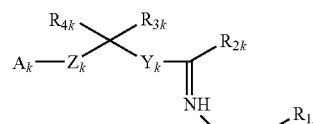
Compounds as disclosed in WO 03/062248A2, e.g. a compound of formula VIII



wherein Ar is phenyl or naphthyl; n is 2, 3 or 4; A is  $\text{COOH}$ , 1H-tetrazol-5-yl,  $\text{PO}_3\text{H}_2$ ,  $\text{PO}_2\text{H}_2$ ,  $-\text{SO}_3\text{H}$  or  $\text{PO}(\text{R}_{5h})\text{OH}$  wherein  $R_{5h}$  is selected from  $C_{1-4}$ alkyl, hydroxy $C_{1-4}$ alkyl, phenyl,  $-\text{CO}-C_{1-3}$ alkoxy and  $-\text{CH}(\text{OH})$ -phenyl wherein said phenyl or phenyl moiety is optionally substituted; each of  $R_{1h}$  and  $R_{2h}$  independently is H, halogen, OH,  $\text{COOH}$ , or optionally halogeno substituted  $C_{1-6}$ alkyl or phenyl;  $R_{3h}$  is H or  $C_{1-4}$ alkyl optionally substituted by halogen and/OH; each  $R_{4h}$  independently is halogeno, OH,  $\text{COOH}$ ,  $\text{S}(\text{O})_0, 1 \text{ or } 2$   $C_{1-3}$ alkyl,  $C_{1-3}$ alkoxy,  $C_{3-6}$ cycloalkoxy, aryl or aralkoxy, wherein the alkyl portions may optionally be substituted by 1-3 halogens; and each of  $R_h$  and M has one of the significances as indicated for B and C, respectively, in WO03/062248A2

or a pharmacologically acceptable salt, solvate or hydrate thereof.

Compounds as disclosed in WO 04/103306A, WO 05/000833, WO 05/103309 or WO 05/113330, e.g. compounds of formula IXa or IXb



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Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

## Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

## API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

## LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

## FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

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Sync your system to PACER to automate legal marketing.