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[Continued on next page]

(54) Title: IMPROVED INHIBITORS OF GRB7

(57) Abstract: Disclosed herein is a compound of formula (I), or a pharmaceutically acceptable salt or prodrug thereof: ((Formula (I))).

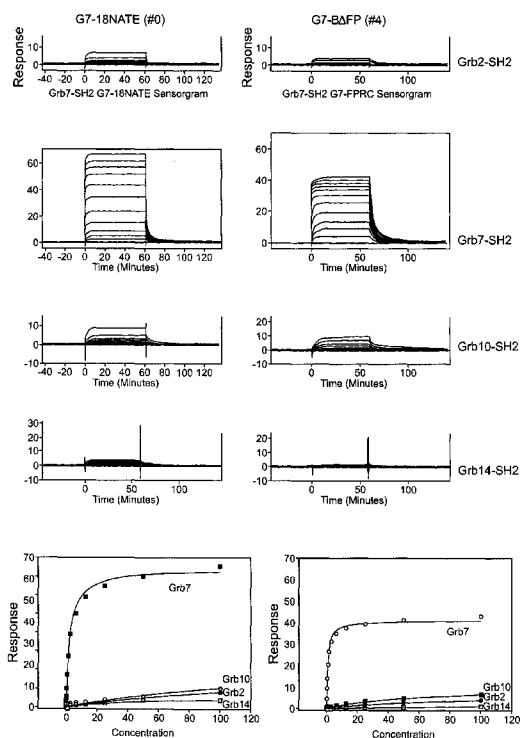
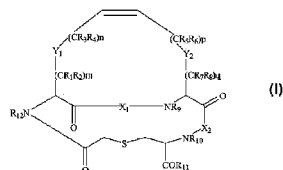


Figure 6



(I)



BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

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IMPROVED INHIBITORS OF GRB7

PRIORITY DOCUMENT

[0001] The present application claims priority from Australian Provisional Patent Application No. 2012905067 titled "IMPROVED INHIBITORS OF GRB7" and filed on 20 November 2012, the contents of which are hereby incorporated by reference in their entirety.

TECHNICAL FIELD

[0002] The present invention relates to inhibitors of growth factor receptor bound protein 7 (GRB7) and their use in the prevention or treatment of disorders associated with abnormal interaction of GRB7 to a signalling factor such as a GRB7 ligand.

BACKGROUND

[0003] Human growth factor receptor bound protein 7 ("GRB7") is an adapter protein that is prevalent in breast and other cancers where it is co-overexpressed with the well-known propagator of cancerous cell growth, the erbB-2 receptor (also known as HER2). GRB7 is activated upon phosphorylation through association with focal adhesion kinase (FAK) upon which it plays a role in cell migration, contributing to the metastatic potential of the cell. In addition, when overexpressed, GRB7 is found aberrantly associated with erbB-2, and is thus also implicated in dysregulated cell growth (Stein *et al.* 1994). GRB7 has been identified as a therapeutic target against these cancers (Pero *et al.* 2003; Nadler *et al.* 2010).

[0004] GRB7 is a 532 amino acid protein that interacts with upstream phosphorylated tyrosine kinases in the propagation of signal transduction pathways. GRB7 is a member of a family of proteins that includes two other homologous proteins, GRB10 (Ooi *et al.* 1995) and GRB14 (Daly *et al.* 1996). These proteins share a conserved multi-domain structure with domains that mediate both protein-protein and protein-lipid interactions. These domains include an N-terminal proline rich domain, a Ras-associating-like (RA) domain, a pleckstrin homology (PH) domain, a C-terminal src-homology 2 (SH2) domain and a region between the PH and SH2 domains termed the BPS domain (Han *et al.* 2001).

[0005] GRB7 upstream binding partners include the members of the erbB (also known as HER) receptor family and focal adhesion kinase (FAK) whose activities play a critical role in

the regulation of cell proliferation and migration. Interactions with other tyrosine kinases have also been reported (Stein *et al.* 1994; Yokote *et al.* 1996; Han and Guan 1999; Han *et al.* 2001; Holt and Daly 2005). The downstream proliferative activity of GRB7 overexpressing cells is mediated via the recruitment of RasGTPases and subsequent phosphorylation of ERK1/2 leading to cell proliferation (Chu *et al.* 2010). The way in which the GRB7/FAK interaction impacts on migration in human cancer cells is not yet determined, but there is evidence to suggest that the phosphorylation of GRB7 by FAK impacts at the level of translational regulation (Tsai *et al.* 2007; Tsai *et al.* 2008).

[0006] GRB7 has also been shown to be involved in cancer cell progression. Although GRB7 normally binds to the cytoplasmic domain of the erbB-3 receptor, in cancer cells it has been found in tight association with the erbB-2 receptor that plays a major role in cancer cell proliferation (Stein *et al.* 1994). The erbB-2 receptor is the target of anti-cancer proliferation drugs already in clinical use (Arteaga *et al.* 2012). GRB7 is tightly co-amplified with erbB-2 in approximately 20-25% of breast cancer cell lines, and there is also a strong correlation between erbB-2 and GRB7 over-expression in oesophageal, gastric and ovarian cancers (Kishi *et al.* 1997; Tanaka *et al.* 1997; Wang *et al.* 2010). In studies to directly determine the role of GRB7, it has been shown that the removal of GRB7 from breast cancer cells (using RNAi) reduces breast cancer cell viability and increases the activity of the anti-erbB-2 cancer therapeutic lapatinib (Kao and Pollack 2006; Nencioni *et al.* 2010). Conversely, GRB7 overexpression in breast cancer cells promotes their growth (Bai and Luoh 2008). GRB7 inhibition can also enhance the antiproliferative effect of the erbB-2 antibody drug, Herceptin (Pero *et al.* 2007). There is also compelling evidence that implicates GRB7 in cancer cell migration (and hence metastasis of cancer cells). GRB7 is found in focal adhesions in association with FAK (Han *et al.* 2000) and plays a key role in integrin-mediated signal transduction in cell migration (Shen and Guan 2001). Overexpression of GRB7 has been shown to enhance cell migration, whereas inhibition of GRB7 (by overexpression of the GRB7 SH2 domain acting as a dominant negative inhibitor) resulted in the inhibition of cell migration (Han and Guan 1999). Knockdown of GRB7 in hepatocellular carcinoma cells lowered their invasive potential in vitro and delayed the onset of tumours in mice (Itoh *et al.* 2007). Furthermore, disruption of the GRB7:FAK interaction significantly attenuates the migratory potential of pancreatic cancer cells (Tanaka *et al.* 2006) and several breast cancer cell lines (Gircz *et al.* 2011). GRB7 thus plays a significant role in cancer progression and is an important new therapeutic target (Pero *et al.* 2003; Nadler *et al.* 2010).

[0007] The interaction between GRB7 and its partners is mediated by the SH2 domain (residues 416-532) of GRB7 (Stein *et al.* 1994). Approximately 100 amino acids in length, SH2 domains are small, modular domains which bind to phosphorylated tyrosine residues in a sequence-dependent manner. The SH2 domain is able to recognize the 3-6 residues immediately C-terminal to the phosphotyrosine (pTyr). The SH2 domain forms a specific binding site for pTyr motifs within the erbB-2 receptor and within FAK leading to unwanted downstream events. The GRB7-SH2 domain is thus the prime target for specific inhibition since blocking its interaction with receptor would obliterate the downstream pathways.

[0008] Several molecules (peptide and non-peptide) have been discovered that bind to the GRB7-SH2 domain. These include a small molecule that binds to the GRB7-SH2 domain but not with high affinity (Ambaye *et al.* 2011) and a GRB2-SH2 peptide-based inhibitor (mAZ-pTyr-(α Me)pTyr-Asn-NH₂) that also binds with good affinity to the GRB7-SH2 domain (Luzy *et al.* 2008).

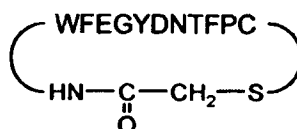
[0009] It has been shown that the GRB7 SH2 domain interaction with upstream binding partners can be antagonized by a mimetic of the pTyr containing target site. Both pTyr containing and non-phosphorylated peptides have been discovered that have the ability to bind to the GRB7-SH2 domain and inhibit its interaction with binding partners (Pero *et al.*, 2002; Luzy *et al.*, 2008; Spuches *et al.*, 2007). The non-phosphorylated class of inhibitor tends to bind with lower affinity than pTyr-containing peptide due to their reduced potential for ionic interactions in the pTyr binding site of the SH2 domain. These inhibitors are of particular importance, however, because they are more amenable to studies of biological activity due to phosphate group instability and lack of cell membrane permeability.

[0010] Non-phosphorylated inhibitors of the SH2 domain of GRB7 thus provide a means of inhibiting the GRB7 protein from interacting with its upstream binding partners and instigating its downstream effects in cells.

[0011] A non-phosphorylated inhibitor of GRB7 that was found to bind with specificity to the GRB7-SH2 domain (i.e. binding with lower affinity to the closest SH2 homologues found in GRB 10, 14, and 2) was discovered by Pero *et al.*, 2002. Cyclised non-phosphorylated peptides were developed via phage display using strategically placed cysteines and oxidizing conditions to form disulphide bonds. This cyclisation was found necessary for binding to GRB7-SH2. Subsequent chemical modification of the lead peptide to a thioether cyclised form (that would

be maintained in the reducing environment of the cell) lead to G7-18NATE, an 11 residue peptide of sequence WFEGYDNTFPC that is cyclised via the formation of a thioether bond between the N-terminus and the C-terminal cysteine side chain.

[0012]



G7-18NATE

[0013] With the addition of a cell permeability sequence (that would allow the peptide to cross cell membranes) it was found that the G7-18NATE peptide was able to enter cells and exert biological activity in various cancer cell lines. Both reduction in cell proliferation and cell migration were observed consistent with the inhibition of GRB7 signalling pathways (Pero *et al.*, 2007; Tanaka *et al.*, 2006; Giricz *et al.*, 2012).

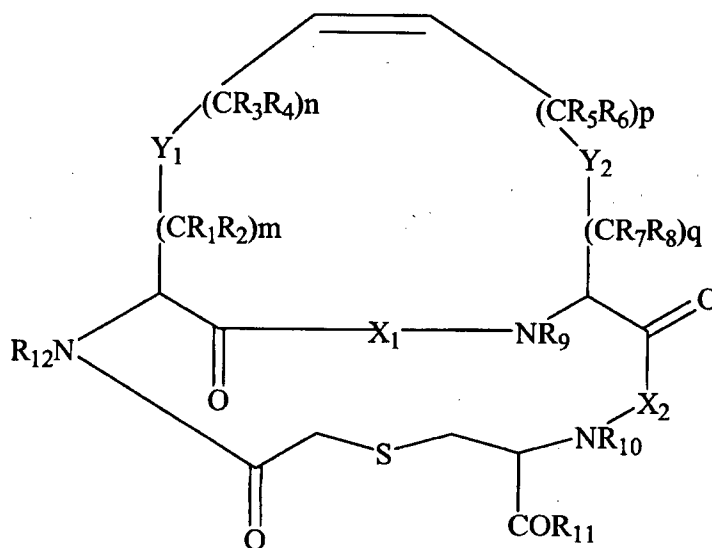
[0014] Other specific inhibitors of GRB7 include non-phosphorylated peptides that were discovered to bind to the GRB7-SH2 domain using a yeast-two hybrid system. Binding was not observed for the GRB14-SH2 domain, implying a degree of specificity (Zhang *et al.* 2012).

[0015] There is a need for improved inhibitors that selectively bind to GRB7 SH2 domain and/or provide an alternative to known inhibitors.

SUMMARY

[0016] The present invention arises from our previous studies into the basis for the affinity and specificity of G7-18NATE for the GRB7-SH2 domain (Gunzburg *et al.*, 2011). In that study, biophysical testing of G7-18NATE revealed it binds to the GRB7-SH2 domain with an affinity of $K_d = 4.2 \mu\text{M}$. Structural studies of the GRB7-SH2 domain in complex with G7-18NATE revealed the structural basis for the interaction (Ambaye *et al.*, 2011). The key amino acid residues forming contacts with the surface of the protein, and the precise conformation of the backbone fold were elucidated in that study. The present invention provides derivatives of the G7-18NATE peptide.

[0017] In a first aspect, the present invention provides a compound of formula I, or a pharmaceutically acceptable salt or prodrug thereof:



I

[0018] wherein:

[0019] X_1 is a moiety having binding affinity for the SH2 domain of GRB7;

[0020] X_2 is selected from the group consisting of a bond, an amino acid, and a dipeptide;

[0021] Y_1 and Y_2 are each independently selected from the group consisting of $(CR_{13}R_{14})$, O, S, and N;

[0022] each R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_{13} and R_{14} is independently selected from the group consisting of: H, halogen, OH, NO_2 , CN, NH_2 , optionally substituted C_1 - C_{12} alkyl, optionally substituted C_2 - C_{12} alkenyl, optionally substituted C_2 - C_{12} alkynyl, optionally substituted C_2 - C_{12} heteroalkyl, optionally substituted C_3 - C_{12} cycloalkyl, optionally substituted C_2 - C_{12} heterocycloalkyl, optionally substituted C_2 - C_{12} heterocycloalkenyl, optionally substituted C_6 - C_{18} aryl, optionally substituted C_1 - C_{18} heteroaryl, optionally substituted C_1 - C_{12} alkyloxy, optionally substituted C_2 - C_{12} alkenyloxy, optionally substituted C_2 - C_{12} alkynyloxy, optionally substituted C_2 - C_{12} heteroalkyloxy, optionally substituted C_3 - C_{12} cycloalkyloxy, optionally

substituted C₃-C₁₂cycloalkenyloxy, optionally substituted C₁-C₁₂heterocycloalkyloxy, optionally substituted C₂-C₁₂heterocycloalkenyloxy, optionally substituted C₆-C₁₈aryloxy, optionally substituted C₁-C₁₈heteroaryloxy, optionally substituted C₁-C₁₂alkylamino, SR₁₅, SO₃H, SO₂NH₂, SO₂R₁₅, SONH₂, SOR₁₅, COR₁₅, COOH, COOR₁₅, CON R₁₅R₁₆, NR₁₅COR₁₆, NR₁₅COOR₁₆, NR₁₅SO₂R₁₆, N R₁₅CON R₁₅R₁₆, N R₁₅R₁₆, and acyl;

[0023] each m, n, p, and q is an integer which is independently selected from the group consisting of: 0, 1, 2, and 3;

[0024] R₁₁ is selected from the group consisting of: NR₁₇R₁₈, wherein each R₁₇ and R₁₈ is independently selected from the group consisting of: H, optionally substituted C₁-C₁₂alkyl, amino acid, peptide, a toxin, a radioactive agent, a chemotherapeutic agent, an anti-angiogenic agent, an immunomodulatory agent, and a translocation agent; and

[0025] each R₉, R₁₀, R₁₂, R₁₅ and R₁₆ is independently selected from the group consisting of: H, optionally substituted C₁-C₁₂alkyl, optionally substituted C₂-C₁₂alkenyl, optionally substituted C₂-C₁₂alkynyl, optionally substituted C₂-C₁₂heteroalkyl, optionally substituted C₃-C₁₂cycloalkyl, optionally substituted C₃-C₁₂cycloalkenyl, optionally substituted C₂-C₁₂heterocycloalkyl, optionally substituted C₂-C₁₂heterocycloalkenyl, optionally substituted C₆-C₁₈aryl, and optionally substituted C₁-C₁₈heteroaryl.

[0026] In embodiments, X₁ comprises a peptide or derivative thereof comprising 4 to 12 amino acids. In more specific embodiments, X₁ comprises a peptide or derivative thereof comprising 5 to 7 amino acids. X₁ preferably comprises an amino acid sequence that binds to the SH2 domain of GRB7. The examples provided herein enable the skilled person to determine whether a peptide has binding affinity for the SH2 domain of GRB7. In embodiments, the peptide of X₁ comprises a Y-Xaa-N (SEQ ID No: 1) motif wherein Y is tyrosine, N is asparagine and Xaa is selected from the group consisting of alanine (A), aspartic acid (D), and glutamic acid (E). In specific embodiments, X₁ comprises a six amino acid peptide comprising a Y-Xaa-N (SEQ ID No: 1) motif wherein Y is tyrosine, N is asparagine and Xaa is selected from the group consisting of alanine (A), aspartic acid (D), and glutamic acid (E), or a derivative thereof.

[0027] In some embodiments, X₁ comprises a six amino acid peptide comprising a YDN (SEQ ID No: 2) motif. In embodiments, X₁ comprises a six amino acid peptide comprising

Xaa1Xaa2Xaa3YDN (SEQ ID No: 3). In embodiments, Xaa1 is phenylalanine (F). In embodiments, Xaa2 is glutamic acid (E). In embodiments, Xaa3 is glycine (G).

[0028] In some embodiments, X_1 comprises a six amino acid peptide comprising a YAN (SEQ ID No: 4) motif. In embodiments, X_1 comprises a six amino acid peptide comprising Xaa1Xaa2Xaa3YAN (SEQ ID No: 5). In embodiments, Xaa1 is phenylalanine (F). In embodiments, Xaa2 is glutamic acid (E). In embodiments, Xaa3 is glycine (G).

[0029] In some embodiments, X_1 comprises a six amino acid peptide comprising a YEN (SEQ ID No: 6) motif. In embodiments, X_1 comprises a six amino acid peptide comprising Xaa1Xaa2Xaa3YEN (SEQ ID No: 7). In embodiments, Xaa1 is phenylalanine (F). In embodiments, Xaa2 is glutamic acid (E). In embodiments, Xaa3 is glycine (G).

[0030] In embodiments, X_2 comprises a bond. In these embodiments, the carbonyl group (C=O) is bonded directly to the NR_{10} group.

[0031] In other embodiments, X_2 is a dipeptide. In these embodiments, the dipeptide preferably comprises non-polar amino acids. In embodiments, the dipeptide comprises amino acids selected from the group consisting of alanine (A), glycine (G), isoleucine (I), leucine (L), phenylalanine (F), proline (P), and valine (V). In specific embodiments, the dipeptide comprises phenylalanine (F) and proline (P). In specific embodiments, the dipeptide is FP.

[0032] In still other embodiments, X_2 is a single amino acid. In these embodiments, the amino acid is preferably a non-polar amino acid. The non-polar amino acid may be selected from the group consisting of alanine (A), glycine (G), isoleucine (I), leucine (L), phenylalanine (F), proline (P), and valine (V). In specific embodiments, the amino acid is proline (P).

[0033] In embodiments, Y_1 and Y_2 are each independently selected from the group consisting of O, S, and N. In specific embodiments, Y_1 and Y_2 are O.

[0034] In embodiments, R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , and R_8 are selected from the group consisting of H and F. In specific embodiments, R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , and R_8 are H.

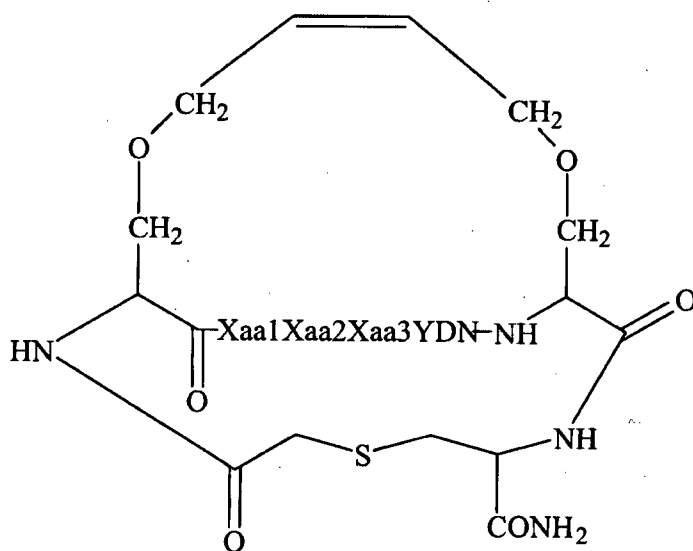
[0035] In embodiments, n and p are integers which are independently selected from the group consisting of: 1 and 2. In embodiments, n and p are 1.

[0036] In embodiments, m and q are integers which are independently selected from the group consisting of: 1 and 2. In embodiments, m and q are 1.

[0037] In embodiments, R_{11} is NH_2 . In other embodiments, R_{11} is NHR_{18} , wherein R_{18} is selected from the group consisting of: a toxin, a radioactive agent, a chemotherapeutic agent, an anti-angiogenic agent, an immunomodulatory agent, and a translocation agent. In specific embodiments, R_{18} is a translocation agent.

[0038] In embodiments, R_9 , R_{10} , and R_{12} are H.

[0039] In specific embodiments, X_1 comprises a six amino acid residue peptide comprising Xaa1Xaa2Xaa3YDN (SEQ ID No: 3), X_2 is a bond, Y_1 and Y_2 are O, R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , and R_{12} are H, R_{11} is NH_2 , and n, p, m, and q are 1. This provides compounds of formula II.



II

[0040] In a second aspect, the present invention provides a pharmaceutical composition comprising a compound according to the first aspect of the invention and a pharmaceutically acceptable diluent, excipient or carrier.

[0041] In a third aspect, the present invention provides a method of inhibiting binding of growth receptor bound (GRB) 7 protein to a GRB7 ligand, the method comprising exposing a cell expressing GRB7 or a fragment or complex thereof or a functional equivalent thereof to an effective amount of a compound according to the first aspect of the invention. The method may be performed *in vivo* or *in vitro*.

[0042] In a fourth aspect, the present invention provides a method of treating or preventing a condition in a mammal in which inhibition of binding of growth receptor bound (GRB) 7 protein to a GRB7 ligand prevents, inhibits or ameliorates a pathology or a symptomology of the condition, the method including administration of a therapeutically effective amount of a compound according to the first aspect of the invention.

[0043] In a fifth aspect, the present invention provides use of a compound according to the first aspect of the invention in the preparation of a medicament for treating a condition in a mammal in which inhibition of binding of growth receptor bound (GRB) 7 protein to a GRB7 ligand prevents, inhibits or ameliorates a pathology or a symptomology of the condition.

[0044] In a sixth aspect, the present invention provides use of a compound according to the first aspect of the invention in the treatment of a condition in which inhibition of binding of growth receptor bound (GRB) 7 protein to a GRB7 ligand prevents, inhibits or ameliorates a pathology or a symptomology of the condition.

[0045] In a seventh aspect, the present invention provides a method for inhibiting a metastasis in a subject, the method including administration of a therapeutically effective amount of a compound according to the first aspect of the invention.

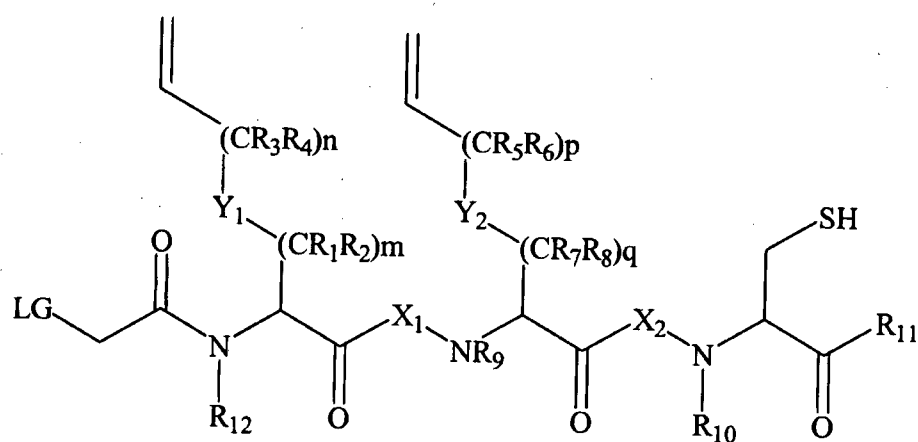
[0046] In an eighth aspect, the present invention provides a method for the prevention or treatment of a proliferative condition associated with abnormal interaction of GRB7 with a GRB7 ligand in a subject, the method including administration of a therapeutically effective amount of a compound according to the first aspect of the invention.

[0047] In a ninth aspect, the present invention provides use of a compound according to the first aspect of the invention in the preparation of a medicament for treating a proliferative condition associated with abnormal interaction of GRB7 with a GRB7 ligand in a subject.

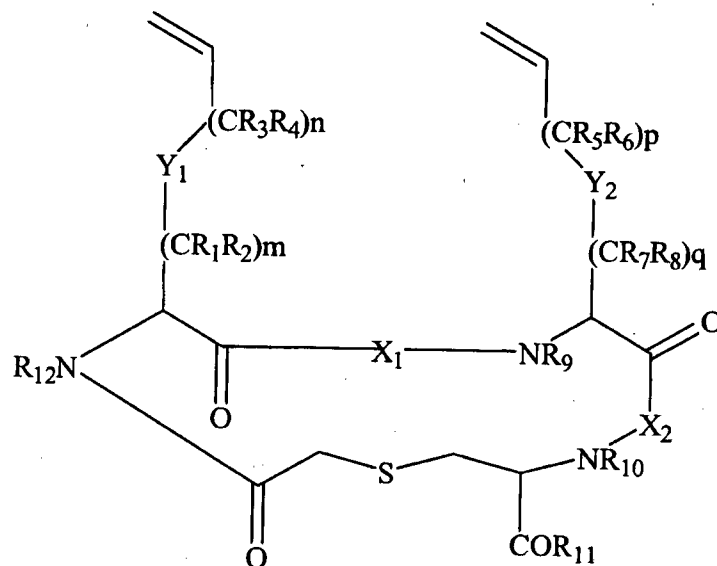
[0048] In embodiments, the proliferative condition is a cancer characterized by overexpression of GRB7.

[0049] In a tenth aspect, the present invention provides a method for preparing a compound of the first aspect, the method comprising:

(i) cyclising a compound of formula (a) to form a thioether cyclised compound of formula (b)



(a)



(b)

(ii) cyclising a compound of formula (b) to form a compound of formula (I)

[0050] wherein LG is a leaving group and X_1 , X_2 , Y_1 , Y_2 , and R_1 - R_{16} are as defined previously.

BRIEF DESCRIPTION OF THE ACCOMPANYING FIGURES

[0051] Illustrative embodiments of the present invention will be discussed with reference to the accompanying figures wherein:

[0052] Figure 1 shows an ITC thermogram obtained for the binding of the G7-B peptide to the GRB7-SH2 domain. The upper panel shows raw data obtained from 10 μ l injections of peptides at 25 °C. The lower panel shows a plot of integrated total energy exchanged (as kcal/mol of injected peptides) as a function of molar ratio of the peptides to the GRB7 SH2 domain;

[0053] Figure 2 shows SPR sensorgrams obtained for the binding of G7- Δ FPC to the GRB7-SH2 domain. The top panel shows sensorgrams obtained for a series of SPR experiments at a range of peptide concentrations. The lower panel shows the equilibrium binding curve used to derive a K_d for the peptide interaction with GRB7-SH2 domain;

[0054] Figure 3 shows SPR sensorgrams obtained for the binding of G7-BΔF to the GRB7-SH2 domain. The top panel shows sensorgrams obtained for a series of SPR experiments at a range of peptide concentrations. The lower panel shows the equilibrium binding curve used to derive a K_d for the peptide interaction with GRB7-SH2 domain;

[0055] Figure 4 shows SPR sensorgrams obtained for the binding of G7-BΔFP to the GRB7-SH2 domain. The top panel shows sensorgrams obtained for a series of SPR experiments at a range of peptide concentrations. The lower panel shows the equilibrium binding curve used to derive a K_d for the peptide interaction with GRB7-SH2 domain;

[0056] Figure 5 shows SPR sensorgrams obtained for the binding of G7-TEΔFP to the GRB7-SH2 domain. The top panel shows sensorgrams obtained for a series of SPR experiments at a range of peptide concentrations. The lower panel shows the equilibrium binding curve used to derive a K_d for the peptide interaction with GRB7-SH2 domain;

[0057] Figure 6 shows SPR sensorgrams obtained for the binding of G7-18NATE and G7-BΔFP to the SH2 domains of Grb2, 7, 10 and 14. The top panels show sensorgrams obtained for a series of SPR experiments at a range of peptide concentrations. The bottom panels show the equilibrium binding curve used to derive K_d s for the peptide interaction with SH2 domains;

[0058] Figure 7 shows binding curves derived from SPR sensorgrams showing the relative binding of G7-TEM to Grb7-SH2 domain in different buffers. The highest binding is seen in low phosphate solutions;

[0059] Figure 8 shows binding curves derived from SPR sensorgrams showing G7-TEM binds with higher affinity than G7-18NATE to Grb7-SH2 domain in conditions of low phosphate concentration in the buffer; and

[0060] Figure 9 shows binding curves derived from SPR sensorgrams showing binding of G7-TEM is much higher to Grb7-SH2 domain than to Grb2 and Grb10 SH2 domains under conditions of low phosphate concentration in the buffer.

DETAILED DESCRIPTION

[0061] In this specification a number of terms are used which are well known to a skilled addressee. Nevertheless for the purposes of clarity a number of terms will be defined.

[0062] As used herein, the term "unsubstituted" means that there is no substituent or that the only substituents are hydrogen.

[0063] The term "optionally substituted" as used throughout the specification denotes that the group may or may not be further substituted or fused (so as to form a condensed polycyclic system), with one or more non-hydrogen substituent groups. In certain embodiments the substituent groups are one or more groups independently selected from the group consisting of halogen, =O, =S, -CN, -NO₂, -CF₃, -OCF₃, alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, haloalkynyl, heteroalkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, heteroarylalkyl, arylalkyl, cycloalkylalkenyl, heterocycloalkylalkenyl, arylalkenyl, heteroarylalkenyl, cycloalkylheteroalkyl, heterocycloalkylheteroalkyl, arylheteroalkyl, heteroarylheteroalkyl, hydroxy, hydroxyalkyl, alkyloxy, alkyloxyalkyl, alkyloxycycloalkyl, alkyloxyheterocycloalkyl, alkyloxyaryl, alkyloxyheteroaryl, alkyloxycarbonyl, alkylaminocarbonyl, alkenyloxy, alkynyloxy, cycloalkyloxy, cycloalkenyloxy, heterocycloalkyloxy, heterocycloalkenyloxy, aryloxy, phenoxy, benzyloxy, heteroaryloxy, arylalkyloxy, amino, alkylamino, acylamino, aminoalkyl, arylamino, sulfonylamino, sulfinylamino, sulfonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, sulfinyl, alkylsulfinyl, arylsulfinyl, aminosulfinylaminoalkyl, -C(=O)OH, -C(=O)R^a, -C(=O)OR^a, C(=O)NR^aR^b, C(=NOH)R^a, C(=NR^a)NR^bR^c, NR^aR^b, NR^aC(=O)R^b, NR^aC(=O)OR^b, NR^aC(=O)NR^bR^c, N R^aC(=N R^b) N R^cR^d, NR^aSO₂R^b, -SR^a, SO₂NR^aR^b, -OR^a, OC(=O)NR^aR^b, OC(=O)R^a and acyl,

[0064] wherein R^a, R^b, R^c and R^d are each independently selected from the group consisting of H, C₁-C₁₂alkyl, C₁-C₁₂haloalkyl, C₂-C₁₂alkenyl, C₂-C₁₂alkynyl, C₂-C₁₀ heteroalkyl, C₃-C₁₂cycloalkyl, C₃-C₁₂cycloalkenyl, C₂-C₁₂heterocycloalkyl, C₂-C₁₂heterocycloalkenyl, C₆-C₁₈aryl, C₂-C₁₈heteroaryl, and acyl, or any two or more of R^a, R^b, R^c and R^d, when taken together with the atoms to which they are attached form a heterocyclic ring system with 3 to 12 ring atoms.

[0065] In embodiments each optional substituent is independently selected from the group consisting of: halogen, =O, =S, -CN, -NO₂, -CF₃, -OCF₃, alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, haloalkynyl, heteroalkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, hydroxy, hydroxyalkyl, alkyloxy, alkyloxyalkyl, alkyloxyaryl, alkyloxyheteroaryl, alkenyloxy, alkynyloxy, cycloalkyloxy, cycloalkenyloxy, heterocycloalkyloxy, heterocycloalkenyloxy, aryloxy, heteroaryloxy, arylalkyl, heteroarylalkyl, arylalkyloxy, amino, alkylamino, acylamino, aminoalkyl, arylamino, sulfonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, aminoalkyl, -COOH, -SH, and acyl.

[0066] Examples of particularly suitable optional substituents include F, Cl, Br, I, CH₃, CH₂CH₃, OH, OCH₃, CF₃, OCF₃, NO₂, NH₂, and CN.

[0067] Alternatively, two optional substituents on the same moiety when taken together may be joined to form a fused cyclic substituent attached to the moiety that is optionally substituted. Accordingly the term optionally substituted includes a fused ring such as a cycloalkyl ring, a heterocycloalkyl ring, an aryl ring or a heteroaryl ring.

[0068] In the definitions of a number of substituents below it is stated that "the group may be a terminal group or a bridging group". This is intended to signify that the use of the term is intended to encompass the situation where the group is a linker between two other portions of the molecule as well as where it is a terminal moiety. Using the term alkyl as an example, some publications would use the term "alkylene" for a bridging group and hence in these other publications there is a distinction between the terms "alkyl" (terminal group) and "alkylene" (bridging group). In the present application no such distinction is made and most groups may be either a bridging group or a terminal group.

[0069] "Acyl" means an R-C(=O)- group in which the R group may be an alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl group as defined herein. Examples of acyl include acetyl and benzoyl. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the carbonyl carbon.

[0070] "Acylamino" means an R-C(=O)-NH- group in which the R group may be an alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl group as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the nitrogen atom.

[0071] "Alkenyl" as a group or part of a group denotes an aliphatic hydrocarbon group containing at least one carbon-carbon double bond and which may be straight or branched preferably having 2-12 carbon atoms, more preferably 2-10 carbon atoms, most preferably 2-6 carbon atoms, in the normal chain. The group may contain a plurality of double bonds in the normal chain and the orientation about each is independently E or Z. Exemplary alkenyl groups include, but are not limited to, ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl and nonenyl. The group may be a terminal group or a bridging group.

[0072] "Alkenyloxy" refers to an alkenyl-O- group in which alkenyl is as defined herein. Preferred alkenyloxy groups are C₂-C₆ alkenyloxy groups. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the oxygen atom.

[0073] "Alkyl" as a group or part of a group refers to a straight or branched aliphatic hydrocarbon group, preferably a C₁-C₁₂ alkyl, more preferably a C₁-C₁₀ alkyl, most preferably C₁-C₆ alkyl unless otherwise noted. Examples of suitable straight and branched C₁-C₆ alkyl substituents include methyl, ethyl, n-propyl, 2-propyl, n-butyl, sec-butyl, t-butyl, hexyl, and the like. The group may be a terminal group or a bridging group.

[0074] "Alkylamino" includes both mono-alkylamino and dialkylamino, unless specified. "Mono-alkylamino" means an Alkyl-NH- group, in which alkyl is as defined herein. "Dialkylamino" means a (alkyl)₂N- group, in which each alkyl may be the same or different and are each as defined herein for alkyl. The alkyl group is preferably a C₁-C₆ alkyl group. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the nitrogen atom.

[0075] "Alkylaminocarbonyl" refers to a group of the formula (Alkyl)_x(H)_yNC(=O)- in which alkyl is as defined herein, x is 1 or 2, and the sum of X+Y =2. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the carbonyl carbon.

[0076] "Alkyloxy" refers to an alkyl-O- group in which alkyl is as defined herein. Preferably the alkyloxy is a C₁-C₆ alkyloxy. Examples include, but are not limited to, methoxy and ethoxy. The group may be a terminal group or a bridging group.

[0077] "Alkyloxyalkyl" refers to an alkyloxy-alkyl- group in which the alkyloxy and alkyl moieties are as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the alkyl group.

[0078] "Alkyloxyaryl" refers to an alkyloxy-aryl- group in which the alkyloxy and aryl moieties are as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the aryl group.

[0079] "Alkyloxycarbonyl" refers to an alkyl-O-C(=O)- group in which alkyl is as defined herein. The alkyl group is preferably a C₁-C₆ alkyl group. Examples include, but are not limited to, methoxycarbonyl and ethoxycarbonyl. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the carbonyl carbon.

[0080] "Alkyloxycycloalkyl" refers to an alkyloxy-cycloalkyl- group in which the alkyloxy and cycloalkyl moieties are as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the cycloalkyl group.

[0081] "Alkyloxyheteroaryl" refers to an alkyloxy-heteroaryl- group in which the alkyloxy and heteroaryl moieties are as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the heteroaryl group.

[0082] "Alkyloxyheterocycloalkyl" refers to an alkyloxy-heterocycloalkyl- group in which the alkyloxy and heterocycloalkyl moieties are as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the heterocycloalkyl group.

[0083] "Alkylsulfinyl" means an alkyl-S-(=O)- group in which alkyl is as defined herein.. The alkyl group is preferably a C₁-C₆ alkyl group. Exemplary alkylsulfinyl groups include, but not limited to, methylsulfinyl and ethylsulfinyl. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the sulfur atom.

[0084] "Alkylsulfonyl" refers to an alkyl-S(=O)₂- group in which alkyl is as defined above. The alkyl group is preferably a C₁-C₆ alkyl group. Examples include, but not limited to methylsulfonyl and ethylsulfonyl. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the sulfur atom.

[0085] "Alkynyl" as a group or part of a group means an aliphatic hydrocarbon group containing a carbon-carbon triple bond and which may be straight or branched preferably having from 2-12 carbon atoms, more preferably 2-10 carbon atoms, more preferably 2-6 carbon atoms in the normal chain. Exemplary structures include, but are not limited to, ethynyl and propynyl. The group may be a terminal group or a bridging group.

[0086] "Alkynyloxy" refers to an alkynyl-O- group in which alkynyl is as defined herein. Preferred alkynyloxy groups are C₂-C₆ alkynyloxy groups. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the oxygen atom.

[0087] "Amino acid" and variations of that term used herein includes the twenty naturally occurring amino acids shown in the table below; those amino acids often modified post-translationally *in vivo*, including, for example, hydroxyproline, phosphoserine and phosphothreonine; and other non-natural amino acids. Furthermore, the term "amino acid" includes both D- and L-amino acids.

Alanine	Ala	A
Arginine	Arg	R
Asparagine	Asn	N
Aspartic acid	Asp	D
Cysteine	Cys	C
Glutamine	Gln	Q

Glutamic Acid	Glu	E
Glycine	Gly	G
Histidine	His	H
Isoleucine	Ile	I
Leucine	Leu	L
Lysine	Lys	K
Methionine	Met	M
Phenylalanine	Phe	F
Proline	Pro	P
Serine	Ser	S
Threonine	Thr	T
Tryptophan	Trp	W
Tyrosine	Tyr	Y
Valine	Val	V

[0088] "Aminoalkyl" means an NH_2 -alkyl- group in which the alkyl group is as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the alkyl group.

[0089] "Aminosulfonyl" means an $\text{NH}_2\text{-S(=O)}_2\text{-}$ group. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the sulfur atom.

[0090] "Aryl" as a group or part of a group denotes (i) an optionally substituted monocyclic, or fused polycyclic, aromatic carbocycle (ring structure having ring atoms that are all carbon) preferably having from 5 to 12 atoms per ring. Examples of aryl groups include phenyl, naphthyl, and the like; (ii) an optionally substituted partially saturated bicyclic aromatic carbocyclic moiety in which a phenyl and a $\text{C}_5\text{-C}_7$ cycloalkyl or $\text{C}_5\text{-C}_7$ cycloalkenyl group are fused together to form a cyclic structure, such as tetrahydronaphthyl, indenyl or indanyl. The group may be a terminal group or a bridging group. Typically an aryl group is a $\text{C}_6\text{-C}_{18}$ aryl group.

[0091] "Arylalkenyl" means an aryl-alkenyl- group in which the aryl and alkenyl are as defined herein. Exemplary arylalkenyl groups include phenylallyl. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the alkenyl group.

[0092] "Arylalkyl" means an aryl-alkyl- group in which the aryl and alkyl moieties are as defined herein. Preferred arylalkyl groups contain a $\text{C}_1\text{-C}_6$ alkyl group. Exemplary arylalkyl groups include benzyl, phenethyl, 1-naphthalenemethyl and 2-naphthalenemethyl. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the alkyl group.

[0093] "Arylalkyloxy" refers to an aryl-alkyl-O- group in which the alkyl and aryl are as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the oxygen atom.

[0094] "Arylamino" includes both mono-arylamino and di-arylamino unless specified. Mono-arylamino means a group of formula arylNH- , in which aryl is as defined herein, di-arylamino means a group of formula $(\text{aryl})_2\text{N-}$ where each aryl may be the same or different and are each as defined herein for aryl. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the nitrogen atom.

[0095] "Arylheteroalkyl" means an aryl-heteroalkyl- group in which the aryl and heteroalkyl moieties are as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the heteroalkyl group.

[0096] "Aryloxy" refers to an aryl-O- group in which the aryl is as defined herein. Preferably the aryloxy is a C₆-C₁₈aryloxy, more preferably a C₆-C₁₀aryloxy. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the oxygen atom.

[0097] "Arylsulfonyl" means an aryl-S(=O)₂- group in which the aryl group is as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the sulfur atom.

[0098] A "bond" is a linkage between atoms in a compound or molecule. The bond may be a single bond, a double bond, or a triple bond.

[0099] "Cycloalkenyl" means a non-aromatic monocyclic or multicyclic ring system containing at least one carbon-carbon double bond and preferably having from 5-10 carbon atoms per ring. Exemplary monocyclic cycloalkenyl rings include cyclopentenyl, cyclohexenyl or cycloheptenyl. The cycloalkenyl group may be substituted by one or more substituent groups. A cycloalkenyl group typically is a C₃-C₁₂ alkenyl group. The group may be a terminal group or a bridging group.

[00100] "Cycloalkyl" refers to a saturated monocyclic or fused or spiro polycyclic, carbocycle preferably containing from 3 to 9 carbons per ring, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like, unless otherwise specified. It includes monocyclic systems such as cyclopropyl and cyclohexyl, bicyclic systems such as decalin, and polycyclic systems such as adamantane. A cycloalkyl group typically is a C₃-C₁₂ alkyl group. The group may be a terminal group or a bridging group.

[00101] "Cycloalkylalkyl" means a cycloalkyl-alkyl- group in which the cycloalkyl and alkyl moieties are as defined herein. Exemplary monocycloalkylalkyl groups include cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl and cycloheptylmethyl. The group

may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the alkyl group.

[00102] "Cycloalkylalkenyl" means a cycloalkyl-alkenyl- group in which the cycloalkyl and alkenyl moieties are as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the alkenyl group.

[00103] "Cycloalkylheteroalkyl" means a cycloalkyl-heteroalkyl- group in which the cycloalkyl and heteroalkyl moieties are as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the heteroalkyl group.

[00104] "Cycloalkyloxy" refers to a cycloalkyl-O- group in which cycloalkyl is as defined herein. Preferably the cycloalkyloxy is a C₁-C₆ cycloalkyloxy. Examples include, but are not limited to, cyclopropanoxy and cyclobutanoxy. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the oxygen atom.

[00105] "Cycloalkenyloxy" refers to a cycloalkenyl-O- group in which the cycloalkenyl is as defined herein. Preferably the cycloalkenyloxy is a C₃-C₈ cycloalkenyloxy. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the oxygen atom.

[00106] "Haloalkyl" refers to an alkyl group as defined herein in which one or more of the hydrogen atoms has been replaced with a halogen atom selected from the group consisting of fluorine, chlorine, bromine and iodine. A haloalkyl group typically has the formula C_nH_(2n+i-m) wherein each X is independently selected from the group consisting of F, Cl, Br and I. In groups of this type n is typically from 1 to 10, more preferably from 1 to 6, most preferably 1 to 3. m is typically 1 to 6, more preferably 1 to 3. Examples of haloalkyl include fluoromethyl, difluoromethyl and trifluoromethyl.

[00107] "Haloalkenyl" refers to an alkenyl group as defined herein in which one or more of the hydrogen atoms has been replaced with a halogen atom independently selected from the group consisting of F, Cl, Br and I.

[00108] "Haloalkynyl" refers to an alkynyl group as defined herein in which one or more of the hydrogen atoms has been replaced with a halogen atom independently selected from the group consisting of F, Cl, Br and I.

[00109] "Halogen" refers to chlorine, fluorine, bromine or iodine.

[00110] "Heteroalkyl" refers to a straight- or branched-chain alkyl group preferably having from 2 to 12 carbons, more preferably 2 to 6 carbons in the chain, in which one or more of the carbon atoms (and any associated hydrogen atoms) are each independently replaced by a heteroatomic group selected from S, O, P and NR' where R' is selected from the group consisting of H, optionally substituted C₁-C₁₂alkyl, optionally substituted C₃-C₁₂cycloalkyl, optionally substituted C₆-C₁₈aryl, and optionally substituted C₁-C₁₈heteroaryl. Exemplary heteroalkyls include alkyl ethers, secondary and tertiary alkyl amines, amides, alkyl sulfides, and the like. Examples of heteroalkyl also include hydroxyC₁-C₆alkyl, C₁-C₆alkyloxy C₁-C₆alkyl, amino C₁-C₆alkyl, C₁-C₆alkylaminoC₁-C₆alkyl, and di(C₁-C₆alkyl)amino C₁-C₆alkyl. The group may be a terminal group or a bridging group.

[00111] "Heteroalkyloxy" refers to a heteroalkyl-O- group in which heteroalkyl is as defined herein. Preferably the heteroalkyloxy is a C₂-C₆heteroalkyloxy. The group may be a terminal group or a bridging group.

[00112] "Heteroaryl" either alone or part of a group refers to groups containing an aromatic ring (preferably a 5 or 6 membered aromatic ring) having one or more heteroatoms as ring atoms in the aromatic ring with the remainder of the ring atoms being carbon atoms. Suitable heteroatoms include nitrogen, oxygen and sulphur. Examples of heteroaryl include thiophene, benzothiophene, benzofuran, benzimidazole, benzoxazole, benzothiazole, benzisothiazole, naphtho[2,3-b]thiophene, furan, isoindolizine, xantholene, phenoxatine, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, 1,3,5-triazene, tetrazole, indole, isoindole, 1 H-indazole, benzotriazole, purine, quinoline, isoquinoline, phthalazine, naphthyridine, quinoxaline, cinnoline, carbazole, phenanthridine, acridine, phenazine, thiazole, isothiazole, phenothiazine, oxazole, isooxazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,3-triazole, 1,2,4-triazole, 1,2,4-thiadiazole, 1,3,4-thiadiazole, furazane, phenoxazine, 2-, 3- or 4- pyridyl, 2-, 3-, 4-, 5-, or 8- quinolyl, 1-, 3-, 4-, or 5-isoquinoliny 1-, 2-, or 3- indolyl, and 2-, or 3-thienyl. A heteroaryl group is typically a C₁-C-18 heteroaryl group. The group may be a terminal group or a bridging group.

[00113] "Hétéroarylalkyl" means a heteroaryl-alkyl group in which the heteroaryl and alkyl moieties are as defined herein. Preferred heteroarylalkyl groups contain a lower alkyl moiety. Exemplary heteroarylalkyl groups include pyridylmethyl. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the alkyl group.

[00114] "Heteroarylalkenyl" means a heteroaryl-alkenyl- group in which the heteroaryl and alkenyl moieties are as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the alkenyl group.

[00115] "Heteroarylheteroalkyl" means a heteroaryl-heteroalkyl- group in which the heteroaryl and heteroalkyl moieties are as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the heteroalkyl group.

[00116] "Heteroaryloxy" refers to a heteroaryl-O- group in which the heteroaryl is as defined herein. Preferably the heteroaryloxy is a C₁-C₁₈ heteroaryloxy. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the oxygen atom.

[00117] "Heterocyclic" refers to saturated, partially unsaturated or fully unsaturated monocyclic, bicyclic or polycyclic ring system containing at least one heteroatom selected from the group consisting of nitrogen, sulfur and oxygen as a ring atom. Examples of heterocyclic moieties include heterocycloalkyl, heterocycloalkenyl and heteroaryl.

[00118] "Heterocycloalkenyl" refers to a heterocycloalkyl group as defined herein but containing at least one double bond. A heterocycloalkenyl group typically is a C₂-C₁₂ heterocycloalkenyl group. The group may be a terminal group or a bridging group.

[00119] "Heterocycloalkyl" refers to a saturated monocyclic, bicyclic, or polycyclic ring containing at least one heteroatom selected from nitrogen, sulfur, oxygen, preferably from 1 to 3 heteroatoms in at least one ring. Each ring is preferably from 3 to 10 membered, more preferably 4 to 7 membered. Examples of suitable heterocycloalkyl substituents include pyrrolidyl, tetrahydrofuryl, tetrahydrothiofuranyl, piperidyl, piperazyl, tetrahydropyranyl,

morphilino, 1,3-diazapane, 1,4-diazapane, 1,4-oxazepane, and 1,4-oxathiapane. A heterocycloalkyl group typically is a C₂-C₁₂ heterocycloalkyl group. The group may be a terminal group or a bridging group.

[00120] "Heterocycloalkylalkyl" refers to a heterocycloalkyl-alkyl- group in which the heterocycloalkyl and alkyl moieties are as defined herein. Exemplary heterocycloalkylalkyl groups include (2-tetrahydrofuryl)methyl, (2-tetrahydrothiofuranyl) methyl. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the alkyl group.

[00121] "Heterocycloalkylalkenyl" refers to a heterocycloalkyl-alkenyl- group in which the heterocycloalkyl and alkenyl moieties are as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the alkenyl group.

[00122] "Heterocycloalkylheteroalkyl" means a heterocycloalkyl-heteroalkyl- group in which the heterocycloalkyl and heteroalkyl moieties are as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the heteroalkyl group.

[00123] "Heterocycloalkyloxy" refers to a heterocycloalkyl-O- group in which the heterocycloalkyl is as defined herein. Preferably the heterocycloalkyloxy is a C₁-C₆heterocycloalkyloxy. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the oxygen atom.

[00124] "Heterocycloalkenyloxy" refers to a heterocycloalkenyl-O- group in which heterocycloalkenyl is as defined herein. Preferably the heterocycloalkenyloxy is a C₁-C₆ heterocycloalkenyloxy. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the oxygen atom.

[00125] "Hydroxyalkyl" refers to an alkyl group as defined herein in which one or more of the hydrogen atoms has been replaced with an OH group. A hydroxyalkyl group typically has the formula C_nH_(2n+1-x)(OH)_x. In groups of this type n is typically from 1 to 10, more preferably from 1 to 6, most preferably 1 to 3. x is typically 1 to 6, more preferably 1 to 3.

[00126] "Sulfinyl" means an R-S(=O)- group in which the R group may be OH, alkyl, cycloalkyl, heterocycloalkyl; aryl or heteroaryl group as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the sulfur atom.

[00127] "Sulfinylamino" means an R-S(=O)-NH- group in which the R group may be OH, alkyl, cycloalkyl, heterocycloalkyl; aryl or heteroaryl group as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the nitrogen atom.

[00128] "Sulfonyl" means an R-S(=O)₂- group in which the R group may be OH, alkyl, cycloalkyl, heterocycloalkyl; aryl or heteroaryl group as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the sulfur atom.

[00129] "Sulfonylamino" means an R-S(=O)₂-NH- group. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the nitrogen atom.

[00130] Some of the compounds of the disclosed embodiments may exist as single stereoisomers, racemates, and/or mixtures of enantiomers and/or diastereomers. All such single stereoisomers, racemates and mixtures thereof, are intended to be within the scope of the subject matter described and claimed. The isomeric forms such as diastereomers, enantiomers, and geometrical isomers can be separated by physical and/or chemical methods known to those skilled in the art.

[00131] Additionally, formula I is intended to cover, where applicable, solvated as well as unsolvated forms of the compounds. Thus, each formula includes compounds having the indicated structure, including the hydrated as well as the non-hydrated forms.

[00132] The term "pharmaceutically acceptable salts" refers to salts that retain the desired biological activity of the above-identified compounds, and include pharmaceutically acceptable acid addition salts and base addition salts. Suitable pharmaceutically acceptable acid addition salts of compounds of formula I may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, sulfuric, and phosphoric acid.

Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, heterocyclic carboxylic and sulfonic classes of organic acids, examples of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, fumaric, maleic, alkyl sulfonic, arylsulfonic. Additional information on pharmaceutically acceptable salts can be found in Remington's Pharmaceutical Sciences, 19th Edition, Mack Publishing Co., Easton, PA 1995. In the case of agents that are solids, it is understood by the skilled person that the compounds, agents and salts may exist in different crystalline or polymorphic forms, all of which are intended to be within the scope of the present invention and specified formulae.

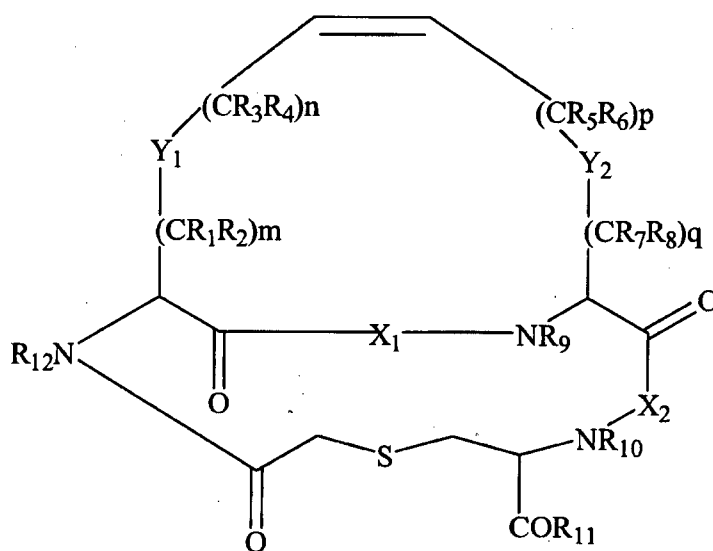
[00133] "Prodrug" means a compound that undergoes conversion to a compound of formula I within a biological system, usually by metabolic means (e.g. by hydrolysis, reduction or oxidation). For example an ester prodrug of a compound of formula I containing a hydroxyl group may be convertible by hydrolysis *in vivo* to the parent molecule. Suitable esters of compounds of formula I containing a hydroxyl group, are for example acetates, citrates, lactates, tartrates, malonates, oxalates, salicylates, propionates, succinates, fumarates, malates, methylene-bis-P-hydroxynaphthoates, gestisates, isethionates, di-p-toluoyltartrates, methanesulphonates, ethanesulphonates, benzenesulphonates, p-toluenesulphonates, cyclohexylsulphamates and quinate. As another example an ester prodrug of a compound of formula I containing a carboxy group may be convertible by hydrolysis *in vivo* to the parent molecule. Examples of ester prodrugs are those described by Leinweber, 1987. Similarly, an acyl prodrug of a compound of formula I containing an amino group may be convertible by hydrolysis *in vivo* to the parent molecule. Examples of prodrugs for these and other functional groups, including amines, are provided in Borchardt *et al.*, 2007.

[00134] The term "therapeutically effective amount" or "effective amount" is an amount sufficient to effect beneficial or desired clinical results. An effective amount can be administered in one or more administrations. An effective amount is typically sufficient to palliate, ameliorate, stabilize, reverse, slow or delay the progression of the disease state.

[00135] The term "functional equivalent" is intended to include variants of the specific peptides or proteins described herein. It will be understood that peptides and proteins may have isoforms, such that while the primary, secondary, tertiary or quaternary structure of a given peptide or protein isoform is different to the prototypical peptide or protein, the molecule maintains biological activity. Isoforms may arise from normal allelic variation within a population and include mutations such as amino acid substitution, deletion, addition, truncation,

or duplication. Also included within the term "functional equivalent" are variants generated at the level of transcription.

[00136] As discussed, the present invention provides, in a first aspect, a compound of formula I, or a pharmaceutically acceptable salt or prodrug thereof:



I

[00137] wherein:

[00138] X_1 is a moiety having binding affinity for the SH2 domain of GRB7;

[00139] X_2 is selected from the group consisting of a bond, an amino acid, and a dipeptide;

[00140] Y_1 and Y_2 are each independently selected from the group consisting of $(CR_{13}R_{14})$, O, S, and N;

[00141] each R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_{13} and R_{14} is independently selected from the group consisting of: H, halogen, OH, NO_2 , CN, NH_2 , optionally substituted C_1 - C_{12} alkyl, optionally substituted C_2 - C_{12} alkenyl, optionally substituted C_2 - C_{12} alkynyl, optionally substituted C_2 - C_{12} heteroalkyl, optionally substituted C_3 - C_{12} cycloalkyl, optionally substituted C_2 -

C₁₂heterocycloalkyl, optionally substituted C₂-C₁₂heterocycloalkenyl, optionally substituted C₆-C₁₈ aryl, optionally substituted C₁-C₁₈heteroaryl, optionally substituted C₁-C₁₂alkyloxy, optionally substituted C₂-C₁₂alkenyloxy, optionally substituted C₂-C₁₂alkynyloxy, optionally substituted C₂-C₁₂heteroalkyloxy, optionally substituted C₃-C₁₂cycloalkyloxy, optionally substituted C₃-C₁₂cycloalkenyloxy, optionally substituted C₁-C₁₂heterocycloalkyloxy, optionally substituted C₂-C₁₂heterocycloalkenyloxy, optionally substituted C₆-C₁₈aryloxy, optionally substituted C₁-C₁₈heteroaryloxy, optionally substituted C₁-C₁₂alkylamino, SR₁₅, SO₃H, SO₂NH₂, SO₂R₁₅, SONH₂, SOR₁₅, COR₁₅, COOH, COOR₁₅, CON R₁₅R₁₆, NR₁₅COR₁₆, NR₁₅COOR₁₆, NR₁₅SO₂R₁₆, N R₁₅CON R₁₅R₁₆, N R₁₅R₁₆, and acyl;

[00142] each m, n, p, and q is an integer which is independently selected from the group consisting of: 0, 1, 2, and 3;

[00143] R₁₁ is selected from the group consisting of: NR₁₇R₁₈, wherein each R₁₇ and R₁₈ is independently selected from the group consisting of: H, optionally substituted C₁-C₁₂alkyl, amino acid, peptide, a toxin, a radioactive agent, a chemotherapeutic agent, an anti-angiogenic agent, an immunomodulatory agent, and a translocation agent; and

[00144] each R₉, R₁₀, R₁₂, R₁₅ and R₁₆ is independently selected from the group consisting of: H, optionally substituted C₁-C₁₂alkyl, optionally substituted C₂-C₁₂alkenyl, optionally substituted C₂-C₁₂alkynyl, optionally substituted C₂-C₁₂heteroalkyl, optionally substituted C₃-C₁₂cycloalkyl, optionally substituted C₃-C₁₂cycloalkenyl, optionally substituted C₂-C₁₂heterocycloalkyl, optionally substituted C₂-C₁₂heterocycloalkenyl, optionally substituted C₆-C₁₈aryl, and optionally substituted C₁-C₁₈heteroaryl.

[00145] Compounds of formula (I) may show improved binding to the SH2 domain of GRB7 relative to G7-18NATE and/or they may provide a useful alternative to known inhibitors of GRB7. In order to develop higher affinity or alternative GRB7 inhibitors we undertook to rigidify the G7-18NATE peptide in its bound conformation based upon the principle of reducing entropic loss upon binding. Specifically, W1 and T8, which our structural studies revealed were not important to the interaction, were substituted with O-ally-Ser residues. Ring closure metathesis was then used to form a covalent linker tethering the peptide across the middle. This peptide, named G7-B (B= bicyclic), was found to have improved affinity over G7-18NATE with a K_d= 1.9 μM. The fact that good binding was still observed confirmed our prediction that W1 and T8 were not required for binding.

[00146] Upon crystallization and structure determination of the G7-B peptide in complex with the GRB7-SH2 domain, however, it was discovered that the peptide interacts with the GRB7-SH2 domain in an unexpected mode. Whilst the FEGYDN (SEQ ID No: 8) portion of the molecule interacts identically with the recognition surface of the GRB7-SH2 domain, the FPC portion no longer forms contacts with the protein. Instead, the tethered alkene group is positioned against the surface of the protein. It forms Van der Waals contacts with a hydrophobic surface of the molecule where F9 previously had this role. This finding raised the question as to whether the FPC portion was required for binding. To answer this, a peptide named G7- Δ FPC was prepared that lacks the FPC portion (and thus no longer contains a thioether bond). This peptide was found to have no measurable binding affinity for the GRB7-SH2 domain, and thus it was established that the connection formed by this thioether link was required. Importantly, although the G7-B peptide binds in a different mode to the G7-18NATE peptide, it is anticipated to also possess specificity for GRB7. It maintains all of the contacts previously established as the basis for recognition.

[00147] By the same logic as previously applied, we considered that the FPC-thioether linker could be shortened to rigidify the molecule and thus enhance its binding affinity to better than what was achieved with G7-B (i.e. $K_d = 1.9 \mu\text{M}$). Thus a series of peptides were prepared with a shorter thioether linked portion. The G7-B Δ F peptide, in which F9 was removed, showed slightly reduced binding with $K_d = 3.9 \mu\text{M}$. The G7-B Δ FP peptide, in which both F9 and P10 were removed, however, showed enhanced binding with $K_d = 0.75 \mu\text{M}$. This represents the highest affinity non-phosphorylated ligand of GRB7-SH2 domain discovered to date. Notably, it binds with higher or similar affinity to GRB7-SH2 domain as ligands that possess a pTyr group (Luzy *et al.*, 2008; Spuches *et al.*, 2007). As one further check to ascertain whether this shortened peptide still required the covalent link, the precursor to the molecule, named G7-TE Δ FP, in which the covalent link between the O-allyl-Ser residues is not formed, was tested for binding. This peptide bound with a $K_d = 4.9 \mu\text{M}$. This represents a lower affinity than the G7-B Δ FP and thus established that the covalent link contributes to binding for the shortened peptide.

[00148] The G7-B Δ FP peptide was anticipated to bind with the FEGYDN (SEQ ID No: 8) forming specific contacts with the recognition surface of the GRB7-SH2 domain, and the covalent link forming contacts as observed for G7-B. X-ray crystallographic data showed that the binding was in the anticipated mode. We also ascertained that G7-B Δ FP still binds with

specificity to the GRB7-SH2 domain over other closely related SH2 domains (Table 3 and Figure 6).

[00149] In the compounds of formula (I), X_1 may be any peptide which binds to GRB7 and thereby interferes with GRB7 binding to a GRB7 ligand. Suitable peptides can be identified by conventional screening methods such as phage display procedures. Peptides that bind selectively to the SH2 domain of GRB7, are obtained by selecting those phages which express on their surface an amino acid sequence which recognizes and binds to the SH2 domain of GRB7. Preferably, the peptides bind specifically to GRB7-SH2 domains and not to the other SH2 domains. Thus, prescreening of phage to GRB2-SH2 or GRB14-SH2 domains or mutant GRB7 domains can enrich for phage of interest.

[00150] In embodiments, X_1 comprises a peptide or derivative thereof comprising 4 to 12 amino acids. In more specific embodiments, X_1 comprises a peptide or derivative thereof comprising 5 to 7 amino acids. In embodiments, the peptide of X_1 comprises a Y-Xaa-N (SEQ ID No: 1) motif wherein Y is tyrosine, N is asparagine and Xaa is selected from the group consisting of alanine (A), aspartic acid (D), and glutamic acid (E). In specific embodiments, X_1 comprises a six amino acid peptide comprising a Y-Xaa-N (SEQ ID No: 1) motif wherein Y is tyrosine, N is asparagine and Xaa is selected from the group consisting of alanine (A), aspartic acid (D), and glutamic acid (E), or a derivative thereof.

[00151] In some embodiments, X_1 comprises a six amino acid peptide comprising a YDN (SEQ ID No: 2) motif. In embodiments, X_1 comprises a six amino acid peptide comprising Xaa1Xaa2Xaa3YDN (SEQ ID No: 3). In embodiments, Xaa1 is phenylalanine (F). In embodiments, Xaa2 is glutamic acid (E). In embodiments, Xaa3 is glycine (G).

[00152] In some embodiments, X_1 comprises a six amino acid peptide comprising a YAN (SEQ ID No: 4) motif. In embodiments, X_1 comprises a six amino acid peptide comprising Xaa1Xaa2Xaa3YAN (SEQ ID No: 5). In embodiments, Xaa1 is phenylalanine (F). In embodiments, Xaa2 is glutamic acid (E). In embodiments, Xaa3 is glycine (G).

[00153] In some embodiments, X_1 comprises a six amino acid peptide comprising a YEN (SEQ ID No: 6) motif. In embodiments, X_1 comprises a six amino acid peptide comprising Xaa1Xaa2Xaa3YEN (SEQ ID No: 7). In embodiments, Xaa1 is phenylalanine (F). In embodiments, Xaa2 is glutamic acid (E). In embodiments, Xaa3 is glycine (G).

[00154] In embodiments, X_2 comprises a bond. In these embodiments, the carbonyl group ($C=O$) is bonded directly to the NR_{10} group.

[00155] In other embodiments, X_2 is a dipeptide. In these embodiments, the dipeptide preferably comprises non-polar amino acids. In embodiments, the dipeptide comprises amino acids selected from the group consisting of alanine (A), glycine (G), isoleucine (I), leucine (L), phenylalanine (F), proline (P), and valine (V). In specific embodiments, the dipeptide comprises phenylalanine (F) and proline (P). In specific embodiments, the dipeptide is FP.

[00156] In still other embodiments, X_2 is a single amino acid. In these embodiments, the amino acid is preferably a non-polar amino acid. The non-polar amino acid may be selected from the group consisting of alanine (A), glycine (G), isoleucine (I), leucine (L), phenylalanine (F), proline (P), and valine (V). In specific embodiments, the amino acid is proline (P).

[00157] Conservative amino acid substitutions may also be made in X_1 and/or X_2 to provide functionally equivalent variants. As used herein, a "conservative amino acid substitution" refers to an amino acid substitution which does not alter the relative charge or size characteristics of the peptide or protein in which the amino acid substitution is made. Variants can be prepared according to methods for altering peptide sequence known to one of ordinary skill in the art such as are found in references which compile such methods, e.g. *Molecular Cloning: A Laboratory Manual*, J. Sambrook, et al., eds., Second Edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1989, or *Current Protocols in Molecular Biology*, F. M. Ausubel, et al., eds., John Wiley & Sons, Inc., New York. Conservative substitutions of amino acids include substitutions made amongst amino acids within the following groups: (a) M, I, L, V; (b) F, Y, W; (c) K, R, H; (d) A, G; (e) S, T; (f) Q, N; and (g) E, D.

[00158] Other amino acids which may be incorporated into the compound of the invention include the non-naturally occurring amino acids α -aminobutyric acid, L-N-methylalanine, α -amino- α -methylbutyrate, L-N-methylarginine, aminocyclopropane, L-N-methylasparagine carboxylate, L-N-methylaspartic acid, aminoisobutyric acid, L-N-methylcysteine, aminonorbornyl, L-N-methylglutamine carboxylate, L-N-methylglutamic acid, cyclohexylalanine, L-N-methylhistidine, cyclopentylalanine, L-N-methylisoleucine, D-alanine, L-N-methylleucine, D-arginine, L-N-methyllysine, D-aspartic acid, L-N-methylmethionine, D-cysteine, L-N-methylnorleucine, D-glutamine, L-N-methylnorvaline, D-glutamic acid, L-N-methylornithine, D-histidine, L-N-methylphenylalanine, D-isoleucine, L-N-methylproline, D-

leucine, L-N-methylserine, D-lysine, L-N-methylthreonine, D-methionine, L-N-methyltryptophan, D-ornithine, L-N-methyltyrosine, D-phenylalanine, L-N-methylvaline, D-proline, L-N-methylethylglycine, D-serine, L-N-methyl-t-butylglycine, D-threonine, L-norleucine, D-tryptophan, L-norvaline, D-tyrosine, α -methyl-aminoisobutyrate, D-valine, α -methyl- γ -aminobutyrate, D- α -methylalanine, α -methylcyclohexylalanine, D- α -methylarginine, α -methylcyclopentylalanine, D- α -methylasparagine, α -methyl- α -naphthylalanine, D- α -methylaspartate, α -methylpenicillamine, D- α -methylcysteine, N-(4-aminobutyl)glycine, D- α -methylglutamine, N-(2-aminoethyl)glycine, D- α -methylhistidine, N-(3-aminopropyl)glycine, D- α -methylisoleucine, N-amino- α -methylbutyrate, D- α -methylleucine, α -naphthylalanine, D- α -methyllysine, N-benzylglycine, D- α -methylmethionine, N-(2-carbamylethyl)glycine, D- α -methylornithine, N-(carbamylmethyl)glycine, D- α -methylphenylalanine, 4-carboxymethyl phenylalanine, N-(2-carboxyethyl)glycine, D- α -methylproline, N-(carboxymethyl)glycine, D- α -methylserine, N-cyclobutylglycine, D- α -methylthreonine, N-cycloheptylglycine, D- α -methyltryptophan, N-cyclohexylglycine, D- α -methyltyrosine, N-cyclodecylglycine, D- α -methylvaline, N-cyclododecylglycine, D- α -methylalnine, N-cyclooctylglycine, D- α -methylarginine, N-cyclopropylglycine, D- α -methylasparagine, N-cycloundecylglycine, D- α -methylaspartate, N-(2,2-diphenylethyl)glycine, D- α -methylcysteine, N-(3,3-diphenylpropyl)glycine, D-N-methylleucine, N-(3-indolylyethyl) glycine, D-N-methyllysine, N-methyl- γ -aminobutyrate, N-methylcyclohexylalanine, D-N-methylmethionine, D-N-methylornithine, N-methylcyclopentylalanine, N-methylglycine, D-N-methylphenylalanine, N-methylaminoisobutyrate, D-N-methylproline, N-(1-methylpropyl)glycine, D-N-methylserine, N-(2-methylpropyl)glycine, D-N-methylserine, N-(2-methylpropyl)glycine, D-N-methylthreonine, D-N-methyltryptophan, N-(1-methylethyl)glycine, D-N-methyltyrosine, N-methyl- α -naphthylalanine, D-N-methylvaline, N-methylpenicillamine, γ -aminobutyric acid, N-(p-hydroxyphenyl)glycine, L-t-butylglycine, N-(thiomethyl)glycine, L-ethylglycine, penicillamine, L-homophenylalanine, L- α -methylalanine, L- α -methylarginine, L- α -methylasparagine, L- α -methylaspartate, L- α -methyl-t-butylglycine, L- α -methylcysteine, L-methylethylglycine, L- α -methylglutamine, L- α -methylglutamate, L- α -methylhistidine, L- α -methylhomo phenylalanine, L- α -methylisoleucine, N-(2-methylthioethyl)glycine, D-N-methylglutamine, N-(3-guanidinopropyl)glycine, D-N-methylglutamate, N-(1-hydroxyethyl)glycine, D-N-methylhistidine, N-(hydroxyethyl)glycine, D-N-methylisoleucine, N-(imidazolylethyl)glycine, D-N-methylleucine, N-(3-indolylyethyl)glycine, D-N-methyllysine, N-methyl- γ -aminobutyrate, N-methylcyclohexylalanine, D-N-methylmethionine, D-N-methylornithine, N-methylcyclopentylalanine, N-methylglycine, D-N-methylphenylalanine, N-

methylaminoisobutyrate, D-N-methylproline, N-(1-methylpropyl)glycine, D-N-methylserine, N-(2-methylpropyl)glycine, D-N-methylthreonine, D-N-methyltryptophan, N-(1-methylethyl)glycine, D-N-methyltyrosine, N-methyl- α -naphthylalanine, D-N-methylvaline, N-methylpenicillamine, γ -aminobutyric acid, N-(p-hydroxyphenyl)glycine, L-t-butylglycine, N-(thiomethyl)glycine, L-ethylglycine, penicillamine, L-homophenylalanine, L- α -methylalanine, L- α -methylarginine, L- α -methylasparagine, L- α -methylaspartate, L- α -methyl-t-butylglycine, L- α -methylcysteine, L-methylethylglycine, L- α -methylglutamine, L- α -methylglutamate, L- α -methylhistidine, L- α -methylhomophenylalanine, L- α -methylisoleucine, N-(2-methylthioethyl)glycine, L- α -methylleucine, L- α -methyllysine, L- α -methylmethionine, L- α -methylnorleucine, L- α -methylnorvaline, L- α -methylornithine, L- α -methylphenylalanine, L- α -methylproline, L- α -methylserine, L- α -methylthreonine, L- α -methylvaline, L- α -methyltyrosine, L- α -methylleucine, L-N-methylhomophenylalanine, N-(N-(2,2-diphenylethyl) N-(N-(3,3-diphenylpropyl) carbamylmethyl-glycine, carbamylmethylglycine, and 1-carboxy-1-(2,2-diphenyl Nmbc ethylamino)cyclopropane.

[00159] In other embodiments, the peptide of X_1 comprises a Y^* -Xaa-N motif wherein Y^* is a tyrosine phosphomimetic, N is asparagine and Xaa is selected from the group consisting of alanine (A), aspartic acid (D), and glutamic acid (E). In specific embodiments, X_1 comprises a six amino acid peptide comprising a Y^* -Xaa-N motif wherein Y^* is a tyrosine phosphomimetic, N is asparagine and Xaa is selected from the group consisting of alanine (A), aspartic acid (D), and glutamic acid (E), or a derivative thereof. The tyrosine phosphomimetic (Y^*) may be 4-carboxymethyl phenylalanine. We have established that by replacing tyrosine with the tyrosine phosphomimetic 4-carboxymethylphenylalanine, we are able to maintain low micromolar binding affinity at physiologically relevant concentrations of phosphate in the buffer (~ 1 mM). It should be noted that previous measurements of high peptide binding affinity were found to be dependent on the presence of phosphate (~ 50 mM) in the buffer (Gunzburg *et al.*, 2012).

[00160] Tyrosine phosphomimetics have been used previously for enhancing the binding of peptides to SH2 domains (Burke *et al.*, 2003). We have found that, in the present case, the Y/Y^* substitution enhances the binding of the G7 peptide to the Grb7-SH2 domain but not to the Grb2- and Grb10-SH2 domains. i.e. binding specificity of the peptide for its target is maintained. This substitution would be expected to enhance the binding of the other G7-series of peptides for Grb7-SH2 domain, but not to other SH2 domains.

[00161] In embodiments, Y_1 and Y_2 are each independently selected from the group consisting of O, S, and N. In specific embodiments, Y_1 and Y_2 are O.

[00162] In embodiments, R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , and R_8 are H.

[00163] In embodiments, n and p are integers which are independently selected from the group consisting of: 1 and 2. In embodiments, n and p are 1.

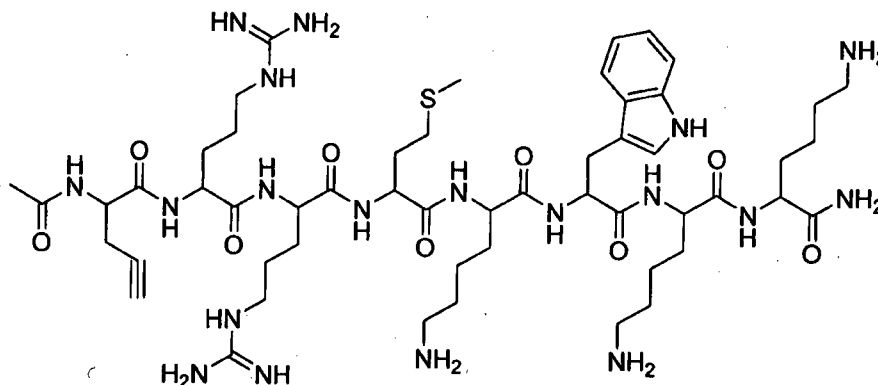
[00164] In embodiments, m and q are 1.

[00165] In embodiments, R_{11} is NH_2 .

[00166] In other embodiments, R_{11} is NHR_{18} , wherein R_{18} is selected from the group consisting of: a toxin, a radioactive agent, a chemotherapeutic agent, an anti-angiogenic agent, an immunomodulatory agent, and a translocation agent. In specific embodiments, R_{18} is a translocation agent. The translocation agent may be a short peptide or peptidomimetic that is capable of spontaneously crossing cell membranes and translocating covalently attached molecules with it to reach an intracellular target (i.e. a "cell permeability" peptide, peptidomimetic or agent). Such peptidic translocating peptides tend to be Arg/Lys rich or hydrophobic in character. Examples of suitable translocation agents include, but are not limited to, Penetratin™ (i.e. RQIKIWFQNRRMKWKK- NH_2 ; available commercially from Innovagen) and truncated versions thereof, the Tat peptide and Transportan (i.e. GWTLNSAGYLLGKINLKALAALAKKIL; available commercially from EGT Group). Details of other translocation agents can be found in Jones and Sayers, 2012.

[00167] In other embodiments, R_{18} is a translocation agent that is covalently bonded to the compound of the invention after cyclisation. In these embodiments, R_{11} may be a lysine residue that can be selectively deprotected and functionalised with an azide group. This azide group then permits "click chemistry" to be used to couple the compound of the invention to a cell permeability peptide that has a propargyl group incorporated. This may be a preferable way to form a cell permeability peptide. i.e. rather than synthesising the cell permeable portion with the inhibitor peptide portion in one continuous chain, the parts can be made separately and then connected. This modularity provides flexibility and allows several different cell permeability peptides to be attached to compare their relative effectiveness.

[00168] In embodiments, the translocation agent is PrgylPenNat ("PEN"):

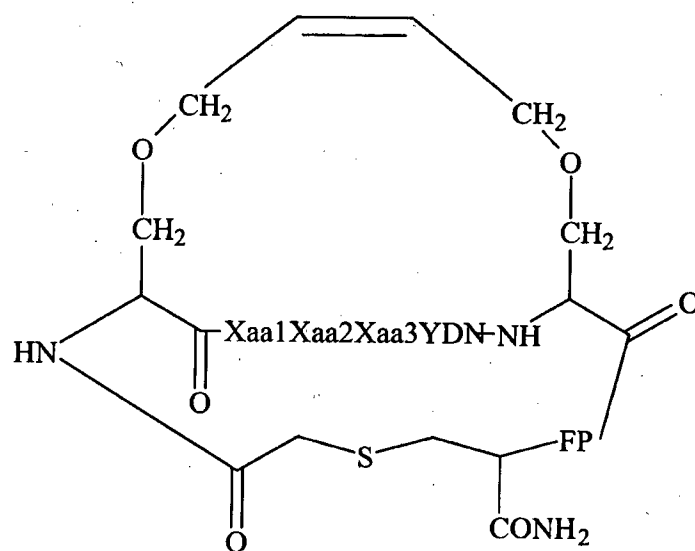


[00169] As described, the propargyl group of PEN can conveniently be bonded to the compound of the invention in which R_{18} contains an azide group using "click chemistry". For example, the "click" reaction may be carried out by combining the azide containing compound of the invention and the propargyl containing cell permeability peptide in the presence of a Cu(II) catalyst and ascorbate, as is known in the art (Thirumurugan *et al.*, 2013).

[00170] In embodiments, R_9 , R_{10} , and R_{12} are H.

[00171] In specific embodiments, X_1 comprises a six amino acid residue peptide comprising Xaa1Xaa2Xaa3YDN (SEQ ID No: 3), X_2 comprises a dipeptide comprising FP, Y_1 and Y_2 are O, R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , and R_{12} are H, R_{11} is NH_2 , and n , p , m , and q are 1. This provides compounds of formula II.

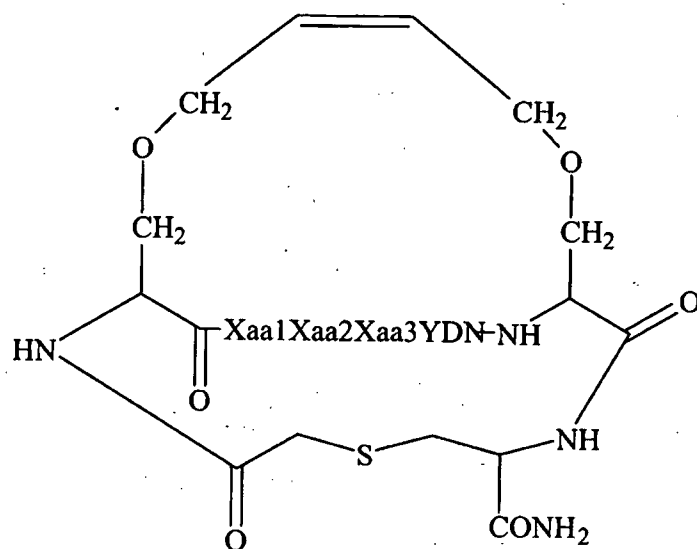
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II

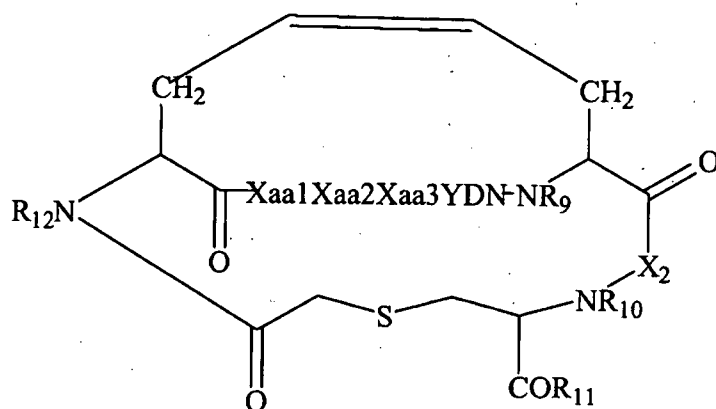
[00172] In preferred embodiments, X₁ comprises a six amino acid residue peptide comprising Xaa1Xaa2Xaa3YDN (SEQ ID No: 3), X₂ is a bond, Y₁ and Y₂ are O, R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₉, R₁₀, and R₁₂ are H, R₁₁ is NH₂, and n, p, m, and q are 1. This provides compounds of formula III.

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III

[00173] As discussed, we found that the G7-B peptide was found to have improved affinity over G7-18NATE. However, a large improvement in binding was not observed with the G7-B peptide and it was considered that the only moderately enhanced affinity was due to the fact that the covalent linker was not short enough in length (9 bonds between α carbons) to effectively tether the peptide between residues 1 and 8 the ideal distance of 5 Å. Therefore, the present invention also provides a compound of formula IV.



IV

[00174] wherein X_2 is a dipeptide comprising non-polar amino acids. In embodiments, the dipeptide comprises phenyl alanine (ie. F) and proline (ie. P). In specific embodiments, the dipeptide is FP.

[00175] The compounds of formulae (I) to (IV) may be conjugated to an agent. The agent may be selected from the group consisting of a toxin, a radioactive molecule, a chemotherapeutic agent, an anti-angiogenic agent, an immunomodulatory agent, and a translocation agent. Conveniently, the agent may be conjugated to the compounds of formulae (I) to (IV) via the C-terminal CONH₂ group. Thus, in some embodiments R_{11} is a group of the type -NH-agent.

[00176] In embodiments, the compound is conjugated to a translocation agent that promotes the translocation of the compound to various cellular locations, such as the cytoplasm or the nucleus. The translocation agent may be a membrane translocating agent which effects the transfer of the compounds from the extracellular environment to the intracellular environment or a nuclear translocation agent which effects the transfer of the compounds from the cytoplasm to the nucleus. The translocation agent may be selected from the group consisting of a membrane translocating sequence, a transportan sequence, an Antennapedia sequence, a cyclic integrin-binding peptide, and a Tat-mediated peptide, or modified versions thereof.

[00177] Administration of compounds of formula I to humans can be by any of the accepted modes for enteral administration such as oral or rectal, or by parenteral administration such as subcutaneous, intramuscular, intravenous and intradermal routes. Injection can be bolus or via constant or intermittent infusion. The compound is typically included in a pharmaceutically acceptable carrier or diluent and in an amount sufficient to deliver to the patient a therapeutically effective dose.

[00178] In using the compounds they can be administered in any form or mode which makes the compound bioavailable. One skilled in the art of preparing formulations can readily select the proper form and mode of administration depending upon the particular characteristics of the compound selected, the condition to be treated, the stage of the condition to be treated and other relevant circumstances. We refer the reader to Remingtons Pharmaceutical Sciences, 19th edition, Mack Publishing Co. (1995) for further information.

[00179] The compounds can be administered alone or in the form of a pharmaceutical composition in combination with a pharmaceutically acceptable carrier, diluent or excipient. Thus, in a second aspect, the present invention provides a pharmaceutical composition comprising a compound according to the first aspect of the invention and a pharmaceutically acceptable diluent, excipient or carrier.

[00180] Other embodiments provide a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions. The pack or kit may comprise a container having a unit dosage of the agent(s). The kits can include a composition comprising the compounds of the first aspect of the invention either as concentrates (including lyophilized compositions), which can be diluted further prior to use or they can be provided at the concentration of use, where the containers may include one or more dosages. Conveniently, in the kits, single dosages can be provided in sterile vials so that the physician can employ the vials directly, where the vials will have the desired amount and concentration of agent(s). Associated with such container(s) can be various written materials such as instructions for use, or a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

[00181] The compounds may be used or administered in combination with one or more additional drug(s) for the treatment of the disorder/diseases mentioned. For example, the compounds may be used in conjunction with other anti-cancer agents in order to inhibit more than one cancer signalling pathway simultaneously and/or inhibit cell migration via Grb7 inhibition to make cancer cells more susceptible to anti-proliferative agents. The components can be administered in the same formulation or in separate formulations. If administered in separate formulations the compounds may be administered sequentially or simultaneously with the other drug(s).

[00182] In addition to being able to be administered in combination with one or more additional drugs, the compounds may be used in a combination therapy. When this is done the compounds are typically administered in combination with each other. Thus one or more of the compounds may be administered either simultaneously (as a combined preparation) or sequentially in order to achieve a desired effect. This is especially desirable where the therapeutic profile of each compound is different such that the combined effect of the two drugs provides an improved therapeutic result.

[00183] For example, in cancer cells GRB7 has been found in tight association with the erbB-2 receptor (Stein *et al.* 1994). The erbB-2 receptor is the target of anti-cancer proliferation drugs already in clinical use (Arteaga *et al.* 2012). Therefore, the compounds of the first aspect of the invention may be used in combination of any of these anti-cancer proliferation drugs. Furthermore, it has been shown that the removal of GRB7 from breast cancer cells (using RNAi) increases the activity of the anti-erbB-2 cancer therapeutic lapatinib (Kao and Pollack 2006; Nencioni *et al.* 2010). Therefore, the compounds of the first aspect of the invention may be used in combination with lapatinib. GRB7 inhibition can also enhance the antiproliferative effect of the erbB-2 antibody drug, herceptin (Pero *et al.* 2007). Therefore, the compounds of the first aspect of the invention may be used in combination with Herceptin.

[00184] Pharmaceutical compositions for parenteral injection comprise pharmaceutically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions as well as sterile powders for reconstitution into sterile injectable solutions or dispersions just prior to use. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils (such as olive oil), and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

[00185] These compositions may also contain adjuvants such as preservative, wetting agents, emulsifying agents, and dispersing agents. Prevention of the action of micro-organisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents such as sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents that delay absorption such as aluminium monostearate and gelatin.

[00186] If desired, and for more effective distribution, the compounds can be incorporated into slow release or targeted delivery systems such as polymer matrices, liposomes, and microspheres.

[00187] The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid

compositions that can be dissolved or dispersed in sterile water or other sterile injectable medium just prior to use.

[00188] As discussed, the inhibition of abnormal signal transduction pathways involving GRB7 using inhibitors or antagonists that bind to the SH2 domain of GRB7 thereby preclude or diminish binding of GRB7 to its endogenous ligands, thereby modulating signal transduction pathways involving GRB7.

[00189] Thus, in a third aspect, the present invention provides a method of inhibiting binding of growth receptor bound (GRB) 7 protein to a GRB7 ligand, the method comprising exposing a cell expressing GRB7 or a fragment or complex thereof or a functional equivalent thereof to an effective amount of a compound according to the first aspect of the invention. The method may be performed *in vivo* or *in vitro*.

[00190] In embodiments, the GRB7 ligand is a tyrosine kinase. The tyrosine kinase may be selected from the group consisting of ErbB2 (HER2), ErbB3, ErbB4, PDGFR, epidermal growth factor receptor (EGFR), and Ret proto-oncogene.

[00191] In other embodiments, the GRB7 ligand is a phosphatase. The phosphatase may be Syp/SHPTP2.

[00192] In other embodiments, the GRB7 ligand is an adaptor protein. The adaptor protein may be SHC or GRB10.

[00193] In other embodiments, the GRB7 ligand is an Fc epsilon receptor.

[00194] In a fourth aspect, the present invention provides a method of treating or preventing a condition in a subject in which inhibition of binding of growth receptor bound (GRB) 7 protein to a GRB7 ligand prevents, inhibits or ameliorates a pathology or a symptomology of the condition, the method including administration of a therapeutically effective amount of a compound according to the first aspect of the invention.

[00195] In a fifth aspect, the present invention provides use of a compound according to the first aspect of the invention in the preparation of a medicament for treating a condition in a subject in which inhibition of binding of growth receptor bound (GRB) 7 protein to a GRB7 ligand prevents, inhibits or ameliorates a pathology or a symptomology of the condition.

[00196] In a sixth aspect, the present invention provides use of a compound according to the first aspect of the invention in the treatment of a condition in which inhibition of binding of growth receptor bound (GRB) 7 protein to a GRB7 ligand prevents, inhibits or ameliorates a pathology or a symptomology of the condition.

[00197] As discussed, GRB7 has been shown to be involved in cancer cell progression. In cancer cells it has been found in tight association with the erbB-2 receptor that plays a major role in cancer cell proliferation (Stein *et al.* 1994). Thus, the condition in which inhibition of binding of growth receptor bound (GRB) 7 protein to a GRB7 ligand of the fourth to sixth aspects may be cancer.

[00198] Likewise, GRB7 is also active in cancer cell migration (and hence metastasis of cancer cells). Overexpression of GRB7 has been shown to enhance cell migration, whereas inhibition of GRB7 (by overexpression of the GRB7 SH2 domain acting as a dominant negative inhibitor) resulted in the inhibition of cell migration (Han and Guan 1999). Thus, the condition in which inhibition of binding of growth receptor bound (GRB) 7 protein to a GRB7 ligand of the fourth aspect may be metastasis of cancer cells. Thus, in a seventh aspect, the present invention provides a method for inhibiting a metastasis in a subject, the method including administration of a therapeutically effective amount of a compound according to the first aspect of the invention.

[00199] In an eighth aspect, the present invention provides a method for the prevention or treatment of a proliferative condition associated with abnormal interaction of GRB7 with a GRB7 ligand in a subject, the method including administration of a therapeutically effective amount of a compound according to the first aspect of the invention.

[00200] In a ninth aspect, the present invention provides use of a compound according to the first aspect of the invention in the preparation of a medicament for treating a proliferative condition associated with abnormal interaction of GRB7 with a GRB7 ligand in a subject.

[00201] As used herein, a subject is a human, non-human primate, cow, horse, pig, sheep, goat, dog, cat or rodent.

[00202] The subject to be treated may be at risk of developing a disorder associated with abnormal interaction of GRB7 with a GRB7 ligand, or alternatively, the subject may have such

a disorder. The term "associated with abnormal interaction of GRB7 with a GRB7 ligand" refers to and increased interaction of GRB7 with one or more of its ligands, increased signal transduction through GRB7, or interaction of GRB7 with a signalling factor which GRB7 normally does not interact with.

[00203] The disorder to be treated may result from increased levels of GRB7 ligands, or increased accessibility of these ligands to GRB7, thereby saturating GRB7 binding sites and precluding interaction with other ligands.

[00204] Abnormal levels of GRB7, GRB7 ligands or of GRB7 interaction are defined as levels higher than those observed in a control normal population.

[00205] The therapeutically effective amount of the compounds of the first aspect or the compositions of the second aspect will depend upon the mode of administration, the particular condition being treated, and the desired outcome. It will also depend upon the stage and severity of the condition, the subject to be treated including the age and physical condition of the subject, the nature of concurrent therapy, if any, and like factors well-known to the medical practitioner. For prophylactic applications, it is generally that amount sufficient to delay the onset of, inhibit the progression of, or halt altogether the particular condition sought to be prevented. For therapeutic applications, it is generally that amount sufficient to achieve a medically desirable result.

[00206] The disorders to be prevented or treated may occur in tissues in which GRB7 is known to be expressed, such as liver, kidney, and gonads, including the testes, ovary, and uterus (in mouse), and pancreas, kidney, prostate, small intestine, and placenta (in humans). Tissues in which GRB7 is expressed at lower levels include (in humans) lung, liver, testis, and colon. However, disorders to be prevented or treated may also occur in tissues in which GRB7 expression has not been detected normally (e.g., heart, breast, brain, esophagus, skeletal muscle, spleen, thymus, and peripheral blood leukocytes).

[00207] It will be evident from the foregoing discussion that a proliferative disorder being diagnosed or treated may be cancer. The methods of the invention are intended to be used to in the prevention and treatment of primary tumors and secondary tumors (i.e., metastases). Examples of cancers to be diagnosed, prevented, and/or treated include: biliary tract cancer; brain cancer, including glioblastomas and medulloblastomas; breast cancer; cervical cancer;

choriocarcinoma; colon cancer; endometrial cancer; esophageal cancer; gastric cancer; hematological neoplasms, including acute lymphocytic and myelogenous leukemia; chronic lymphocytic and myelogenous leukemia; multiple myeloma; AIDS-associated leukemias and adult T-cell leukemia lymphoma; intraepithelial neoplasms, including Bowen's disease and Paget's disease; liver cancer; lung cancer; lymphomas, including Hodgkin's disease and lymphocytic lymphomas; neuroblastomas; oral cancer, including squamous cell carcinoma; ovarian cancer, including those arising from epithelial cells, stromal cells, germ cells, and mesenchymal cells; pancreas cancer; prostate cancer, colorectal cancer; sarcomas, including leiomyosarcoma, rhabdomyosarcoma, liposarcoma, fibrosarcoma, and osteosarcoma; skin cancer, including melanoma, Kaposi's sarcoma, basocellular cancer, and squamous cell cancer; testicular cancer, including germinal tumors (seminoma, non-seminoma teratomas, and choriocarcinomas), stromal tumors, and germ cell tumors; thyroid cancer, including thyroid adenocarcinoma and medullar carcinoma; and renal cancer including adenocarcinoma and Wilms' tumor.

[00208] In embodiments, the cancer is an ErbB2 expressing cancer. ErbB2 expressing cancers include breast cancer, lung cancer, ovarian cancer, gastric cancer and bladder cancer.

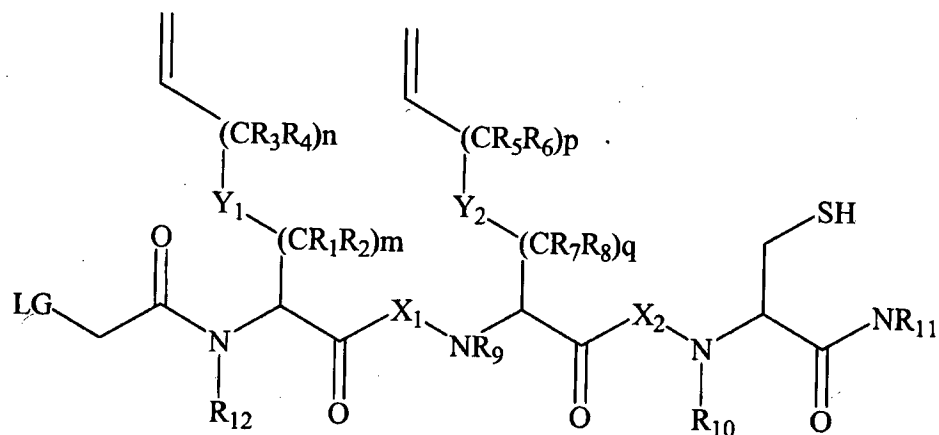
[00209] Inhibition of GRB7 interaction with PDGF can be used for the prevention and/or treatment of disorders involving PDGF such as atherosclerosis, myelofibrosis as well as some cancers.

[00210] The compounds of the first aspect of the invention can also be used to prevent or inhibit metastasis. The term "metastasis" as used herein refers to the invasion and migration of tumor cells away from the primary tumor site.

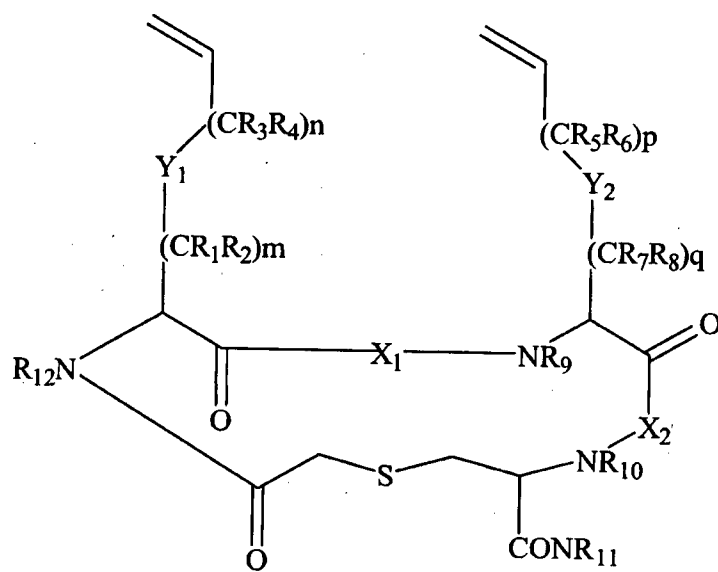
[00211] The prophylactic methods of the invention are directed to subjects who are at risk of developing the disorder. A subject at risk may be one who exhibits an abnormal level of GRB7 or signalling factor expression products or one who exhibits an abnormal level of interaction of GRB7 with a signalling factor. Other subjects at risk of developing such a disorder may be those with a family history of such disorders.

[00212] In a tenth aspect, the present invention provides a method for preparing a compound of the first aspect, the method comprising:

(i) cyclising a compound of formula (a) to form a thioether cyclised compound of formula (b)



(a)



(b)

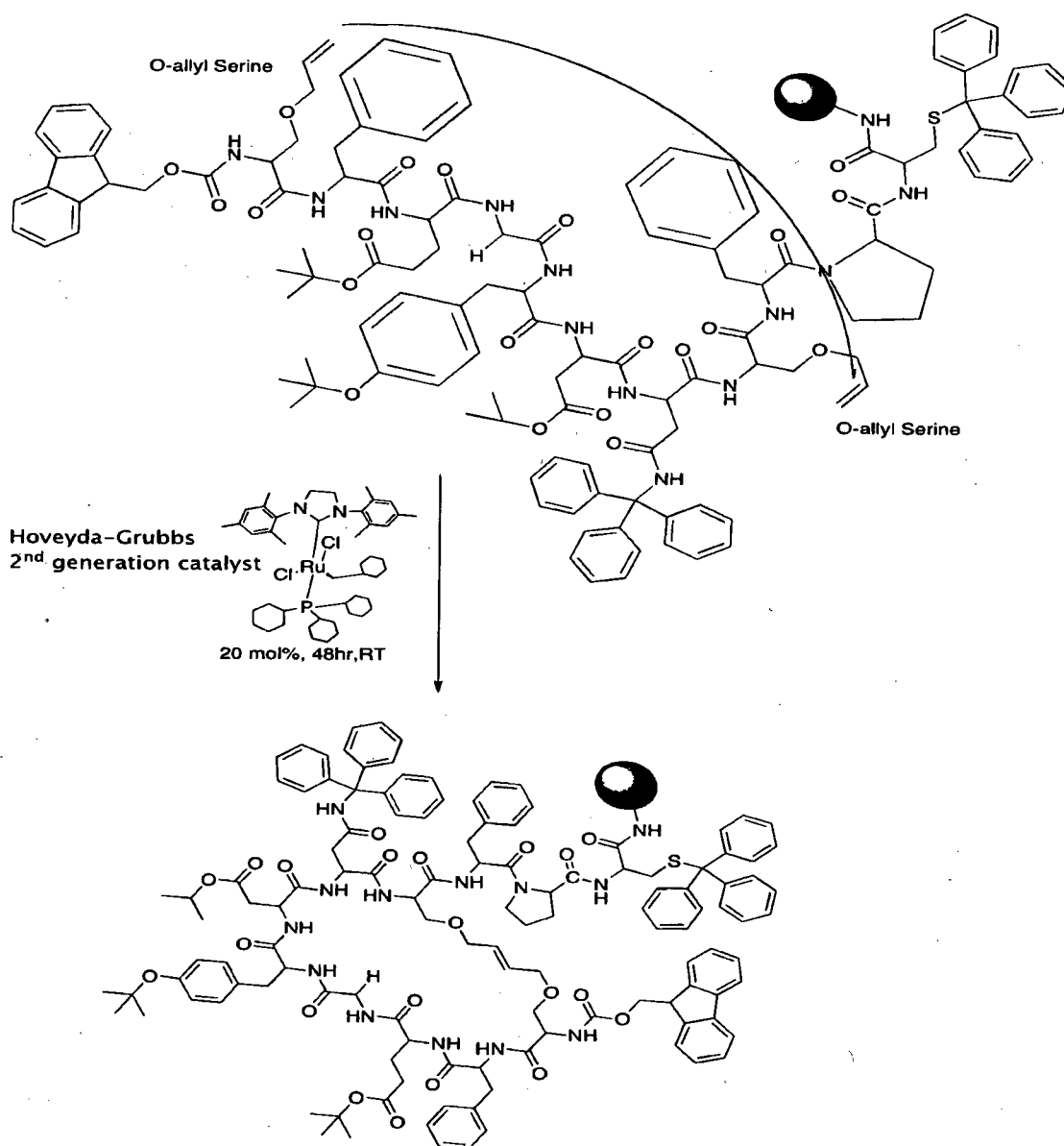
(ii) cyclising a compound of formula (b) to form a compound of formula (I)

[00213] wherein LG is a leaving group and X_1 , X_2 , Y_1 , Y_2 , and R_1 - R_{16} are as defined previously.

EXAMPLES

[00214] **Example 1 – Synthesis of G7-B**

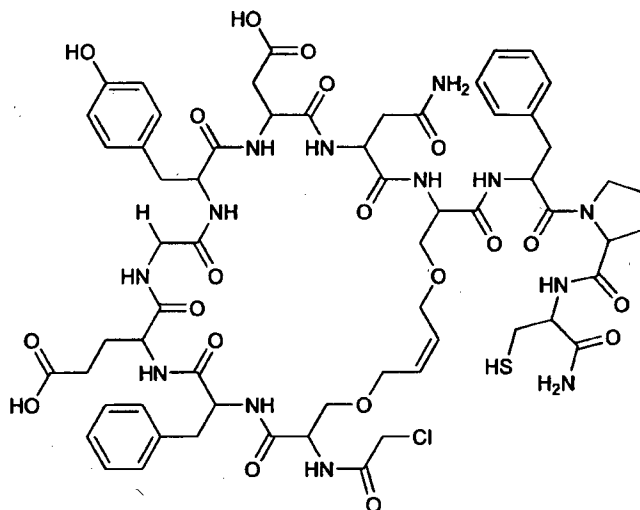
[00215] G7-B was synthesised with the ring closure metathesis conducted on resin.



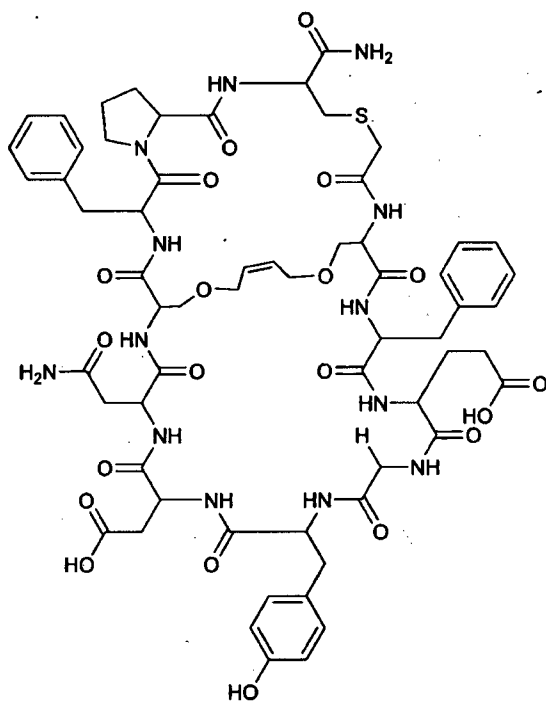
[00216] The bicyclic peptide used for co-crystallization (sequence: XFEGYDNXFPC where X=allyl-serine) was prepared using solid phase synthesis as a peptide amide using the Fmoc based tactic on a rink amide resin (1.0 mmole/g). The synthesis was carried out manually at room temperature. The 9-fluorenyl methoxy carbonyl protecting group on the resin and the amino acids was removed with 20% v/v piperidine/DMF in 45 min. The Kaiser test (Kaiser *et al.*, 1970) was employed to check the success of Fmoc removal. The coupling and activating agents used were *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HBTU) and di-isopropyl ethylamine (DIPEA). Residue coupling reactions were carried out for 45 min and, in cases where less than efficient coupling was noted, as indicated by the Kaiser's colour reaction, the coupling time was increased up to 1 hr and a more effective coupling agent 2-(7-Aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluoro phosphate (HATU) was employed. Double couplings were employed for residues Phe, Tyr and Asn and the coupling time was doubled.

[00217] Ring closing metathesis (RCM) was employed to form the first ring as follows (Jacobsen *et al.*, 2010): 20 mol % second-generation Grub-Hoveyda catalysts in DCM was applied to the resin-bound crude peptide. The metathesis reaction was effected on the fully protected resin bound crude peptide for 48 hours. After successful RCM, the N-terminal Fmoc group was removed with 20% piperidine/DMF and chloroacetylation on the freed N-terminal amino moiety was carried out using chloroacetic acid anhydride (171 mg, 2 ml DMF, 100 μ l DIPEA, 45 min). The resin was then dried for 1 hr and the peptide cleavage effected using a cocktail consisting of 94.5% trifluoroacetic acid (TFA) /2.5% triisopropylsilane (TIPS)/2.5% H_2O / 0.5% ethanedithiothreitol (EDT) for 3 hours. TFA evaporation and resin drying was effected with a stream of nitrogen gas. This was followed by precipitation of the peptide in ice-cold diethyl ether. Finally the crude peptides were dissolved and extracted with successive small volumes of 50%ACN/ H_2O and were lyophilized overnight. Thioether formation was achieved by dissolving the crude, deprotected, lyophilized peptide at 2 mg/ml in 50 mM NH_4HCO_3 in 50% ACN/ H_2O of pH 8.0 for 11/2 hrs. The cyclized peptides were freeze-dried overnight and purified using preparative RP HPLC. Final peptide homogeneity and identity as well as the success of capping, RCM and thioether formation reactions were monitored by analytical reverse phase HPLC and electrospray ionization mass spectroscopy.

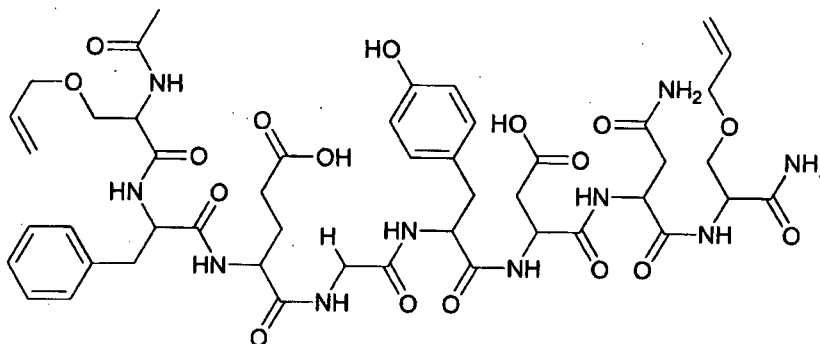
[00218] G7-B before thioether formation



[00219] G7-B after thioether formation

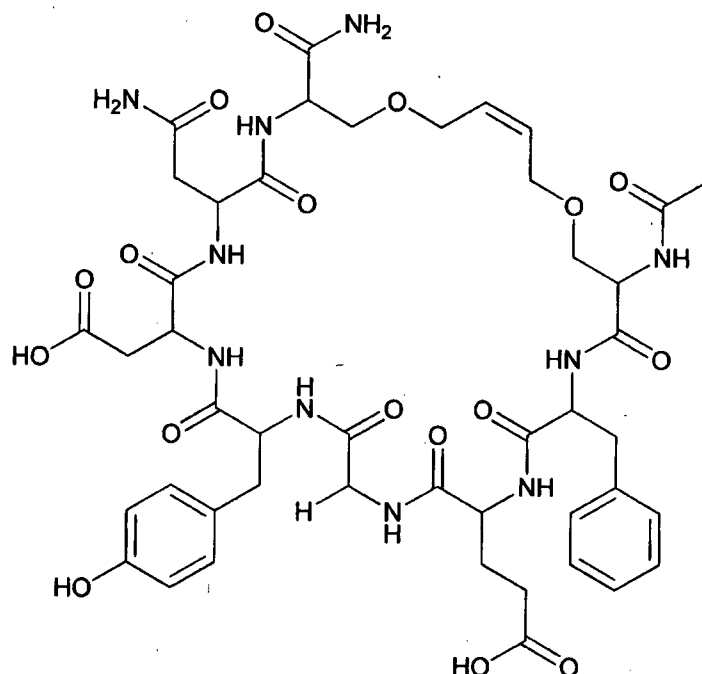


[00220] **Example 2 - Synthesis of G7-ΔFPC**



[00221] The peptide was synthesised on a 0.9 mmol scale using standard Fmoc chemistry on a Rink amide resin (1 mmol/g loading). The Rink amide resin (900 mg, 0.9 mmol) was split into three equal batches (300 mg, 0.3 mmol) and chemistry was performed on each batch as follows. The amide resin (300 mg, 0.3 mmol) was washed with DMF (3 x 5 mL). The Fmoc protecting group on the resin was removed with 2 washes of 20 % piperidine in DMF (5 mL) for 15 min each. The resin was thoroughly washed (3 x 30 s) with DMF (5 mL) and then soaked in Fmoc-protected amino acid (3.1 eq. to resin loading), dissolved in DMF (4 mL) along with HBTU (3 eq. to resin loading), HoBt (3 eq. to resin loading) and DIPEA (4.5 eq. to resin loading), for 45 min. The amino acid coupling cycle was then repeated. The resin was washed (3 x 30 s) with DMF (5 mL), and Kaiser test was performed on a few beads of the resin to confirm complete coupling. The terminal Fmoc protecting group on the amino acid was removed with 2 washes of 20 % piperidine in DMF (5 mL) for 15 min each. Peptide elongation cycle was then repeated until the peptide sequence was complete. After removing the terminal Fmoc protecting group on the peptide, the resin was treated with (2 x 20 min) 10 % v/v acetic anhydride and 1 % v/v DIPEA in DMF (4 mL) to afford an acetyl-capped N-terminus. The resin was subsequently washed (3 x 30 s) with DMF (5 mL), (2 x 30 s) CH₂Cl₂ (1 mL), (3 x 30 s) Et₂O (1 mL), and dried for 20 min. Cleavage was performed on 0.3 mmol of the resin, by treating the resin with a cleavage solution (10 mL) comprising of 250 μL of distilled water (2.5 % v/v), 250 μL of triisopropylsilane (2.5 % v/v), 50 μL of ethanedithiol (0.5 % v/v) in TFA, for 180 min. TFA was then evaporated under a stream of N₂ and the peptide was precipitated by addition of Et₂O (50 mL). The precipitate was filtered and redissolved in H₂O/CH₃CN (1:1) for lyophilisation.

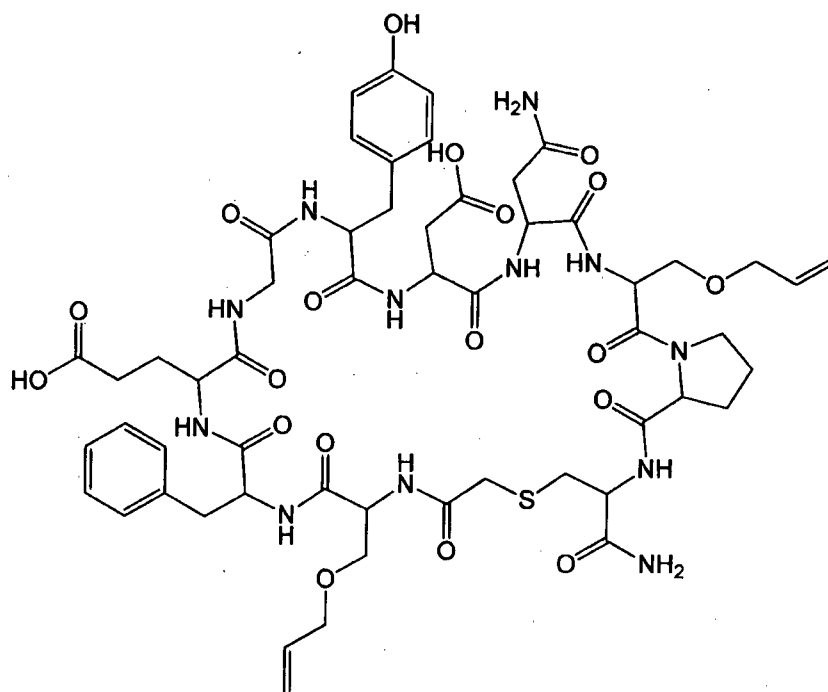
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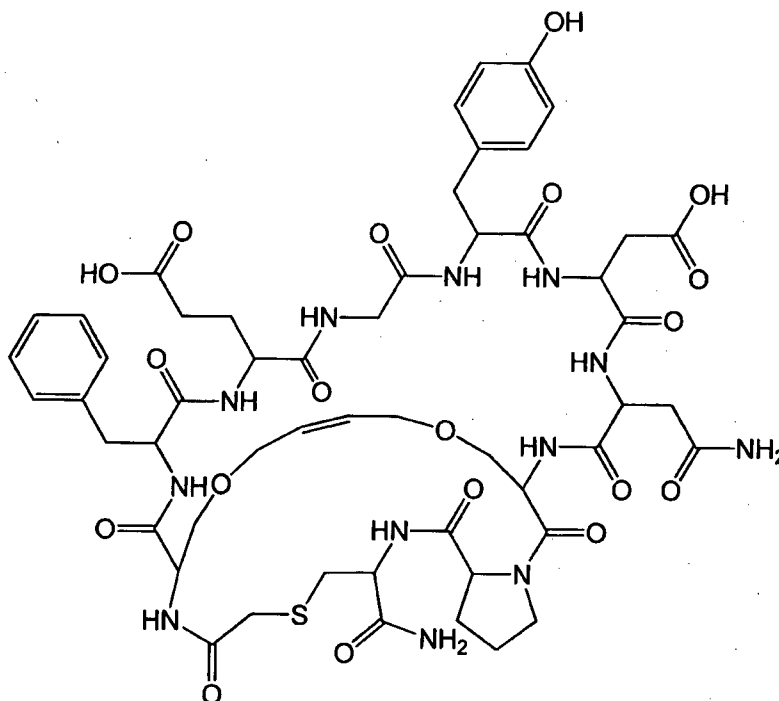
[00222] Ring closing metathesis (RCM) of the acetyl capped peptide (30 mg, 28.9 μmol) was performed in solution, using 2,2,2-trifluoroethanol and CH_2Cl_2 as the solvent in 4:1 ratio (3 mL), at approximately 10 mM concentration, with Hoveyda-Grubbs II generation as the catalyst (35 mol %, 6.3 mg), under microwave irradiation, for 3 hours at 65 °C. Solvent was then evaporated under reduced pressure and the crude peptide was purified using a Hewlett-Packard 1200 series HPLC system (Agilent Technologies, CA), by injecting the sample onto a reverse-phase preparative (C18, 300 Å, 5 μm , 10 mm x 250 mm) column, eluted over a 50 min gradient from 0 to 60 % solvent B, (solvent A: 0.1 % TFA/ H_2O ; solvent B: 0.1 % TFA/ CH_3CN) with a flow rate of 6 mL/min. The fractions were collected and then analysed with liquid chromatography and mass spectrometry. The pure fractions were lyophilised to afford the cyclic peptide.

[00223] Purified peptide was analysed using a Hewlett-Packard 1100 series HPLC system (Agilent Technologies, CA). The samples were injected onto a reverse-phase Vydac™ analytical (C18, 300 Å, 5 μm , 4.6 mm x 150 mm) column and eluted over a 45 min gradient from 0 to 50 % solvent B, (solvent A: 0.1 % TFA/ H_2O ; solvent B: 0.1 % TFA/ CH_3CN) with a flow rate of 1 mL/min. The mass spectrum was acquired using an Agilent 1100 MSD SL ion trap mass spectrometer [$M_{\text{calculated}}=1009.4$; $M_{\text{observed}}=1009.3$].

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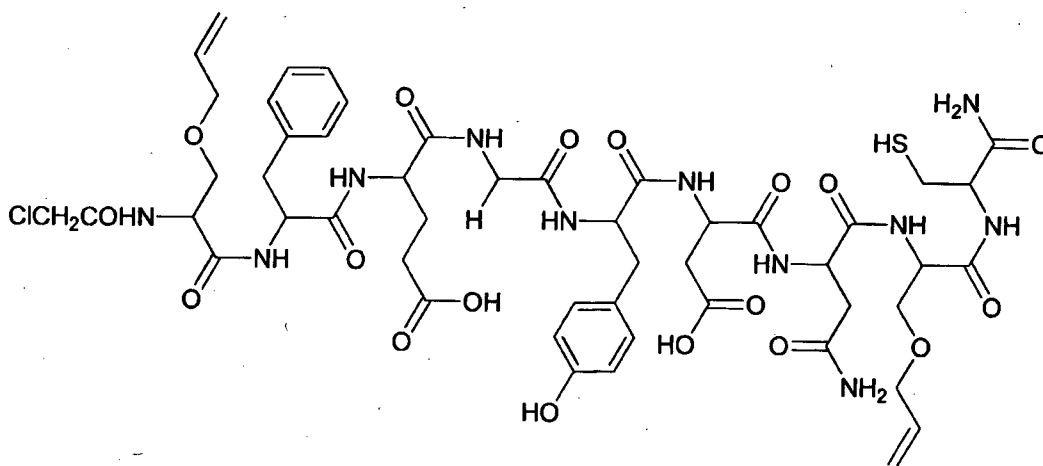
[00226] After lyophilisation, thioether formation was effected by dissolving the peptide (2 mg/mL concentration) in 50 mM NH₄HCO₃ solution (made up in 50% CH₃CN/H₂O), at pH 8.0, for 1.5 h at room temperature. The success of cyclisation was confirmed using an Agilent 1100 MSD SL ion trap mass spectrometer. The cyclised peptide was then lyophilised and purified using a Hewlett-Packard 1200 series HPLC system (Agilent Technologies, CA), by injecting the sample onto a reverse-phase preparative (C18, 300 Å, 5 µm, 10 mm x 250 mm) column, eluted over a 50 min gradient from 0 to 60 % solvent B, (solvent A: 0.1 % TFA/H₂O; solvent B: 0.1 % TFA/CH₃CN) with a flow rate of 6 mL/min. The fractions were collected and then analysed with liquid chromatography and mass spectrometry. The pure fractions were lyophilised to afford the cyclised peptide.



[00227] Ring closing metathesis (RCM) of the cyclised peptide (34 mg, 27.5 μ mol) was performed in solution, using 2,2,2-trifluoroethanol and CH_2Cl_2 as the solvent in 4:1 ratio (3 mL), at approximately 10 mM concentration, with Hoveyda-Grubbs II generation as the catalyst (35 mol %, 6 mg), under microwave irradiation, for 3 hours at 65 $^\circ\text{C}$. Solvent was then evaporated under reduced pressure and the crude peptide was purified using a Hewlett-Packard 1200 series HPLC system (Agilent Technologies, CA), by injecting the sample onto a reverse-phase preparative (C18, 300 $\text{\AA}$, 5 μm , 10 mm x 250 mm) column, eluted over a 50 min gradient from 0 to 60 % solvent B, (solvent A: 0.1 % TFA/ H_2O ; solvent B: 0.1 % TFA/ CH_3CN) with a flow rate of 6 mL/min. The fractions were collected and then analysed with liquid chromatography and mass spectrometry. The pure fractions were lyophilised to afford the bicyclic peptide.

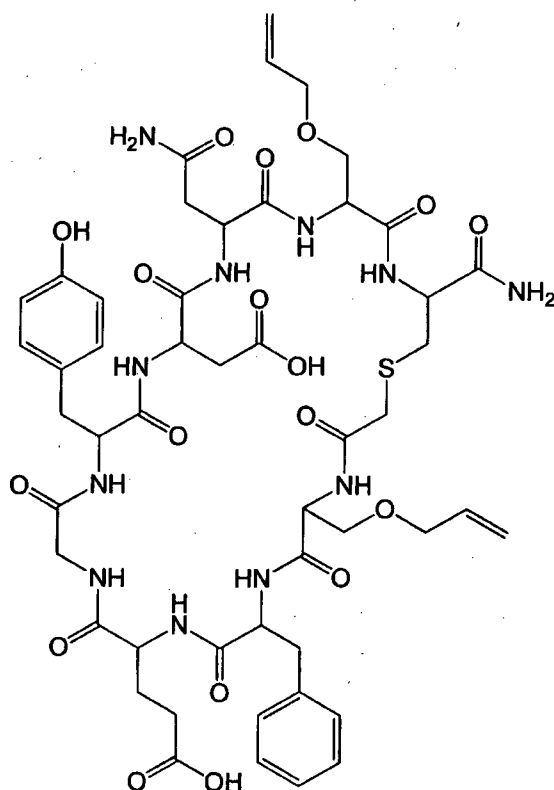
[00228] Purified peptide was analysed using a Hewlett-Packard 1100 series HPLC system (Agilent Technologies, CA). The samples were injected onto a reverse-phase VydacTM analytical (C18, 300 $\text{\AA}$, 5 μm , 4.6 mm x 150 mm) column and eluted over a 45 min gradient from 0 to 50 % solvent B, (solvent A: 0.1 % TFA/ H_2O ; solvent B: 0.1 % TFA/ CH_3CN) with a flow rate of 1 mL/min. The mass spectrum was acquired using an Agilent 1100 MSD SL ion trap mass spectrometer. [$M_{\text{calculated}}=1207.44$; $M_{\text{observed}}=1207.3$].

[00229] **Example 4 – Synthesis of G7-BΔFP**

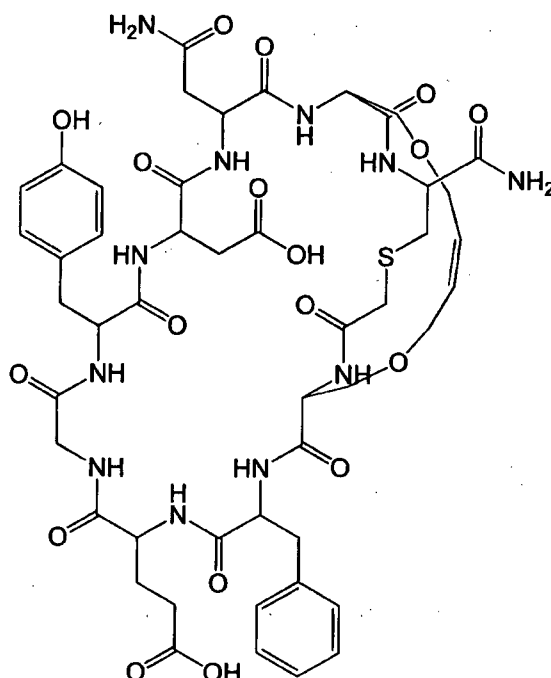


[00230] The peptide was synthesised on a 0.9 mmol scale using standard Fmoc chemistry on a Rink amide resin (1 mmol/g loading). The Rink amide resin (900 mg, 0.9 mmol) was split into three equal batches (300 mg, 0.3 mmol) and chemistry was performed on each batch as follows. The amide resin (300 mg, 0.3 mmol) was washed with DMF (3 x 5 mL). The Fmoc protecting group on the resin was removed with 2 washes of 20 % piperidine in DMF (5 mL) for 15 min each. The resin was thoroughly washed (3 x 30 s) with DMF (5 mL) and then soaked in Fmoc-protected amino acid (3.1 eq. to resin loading), dissolved in DMF (4 mL) along with HBTU (3 eq. to resin loading), HoBt (3 eq. to resin loading) and DIPEA (4.5 eq. to resin loading), for 45 min. The amino acid coupling cycle was then repeated. The resin was washed (3 x 30 s) with DMF (5 mL), and Kaiser test was performed on a few beads of the resin to confirm complete coupling. The terminal Fmoc protecting group on the amino acid was removed with 2 washes of 20 % piperidine in DMF (5 mL) for 15 min each. Peptide elongation cycle was then repeated until the peptide sequence was complete. After removing the terminal Fmoc protecting group on the peptide, the resin was treated with chloroacetic anhydride (171 mg, 1 mmol) and DIPEA (100 μ L) in DMF (2 mL) for 30 min to afford a chloroacetyl-capped N-terminus. The resin was subsequently washed (3 x 30 s) with DMF (5 mL), (2 x 30 s) CH_2Cl_2 (1 mL), (3 x 30 s) Et_2O (1 mL), and dried for 20 min. Cleavage was performed on 0.3 mmol of the resin, by treating the resin with a cleavage solution (10 mL) comprising of 250 μ L of distilled water (2.5 % v/v), 250 μ L of triisopropylsilane (2.5 % v/v), 50 μ L of ethanedithiol (0.5 % v/v) in TFA, for 180 min. TFA was then evaporated under a stream of N_2 and the peptide

was precipitated by addition of Et₂O (50 mL). The precipitate was filtered and redissolved in H₂O/CH₃CN (1:1) for lyophilisation.



[00231] After lyophilisation, thioether formation was effected by dissolving the peptide (2 mg/mL concentration) in 50 mM NH_4HCO_3 solution (made up in 50% $\text{CH}_3\text{CN}/\text{H}_2\text{O}$), at pH 8.0, for 1.5 h at room temperature. The success of cyclisation was confirmed using an Agilent 1100 MSD SL ion trap mass spectrometer. The cyclised peptide was then lyophilised and purified using a Hewlett-Packard 1200 series HPLC system (Agilent Technologies, CA), by injecting the sample onto a reverse-phase preparative (C18, 300 Å, 5 µm, 10 mm x 250 mm) column, eluted over a 50 min gradient from 0 to 60 % solvent B, (solvent A: 0.1 % TFA/ H_2O ; solvent B: 0.1 % TFA/ CH_3CN) with a flow rate of 6 mL/min. The fractions were collected and then analysed with liquid chromatography and mass spectrometry. The pure fractions were lyophilised to afford the cyclised peptide.

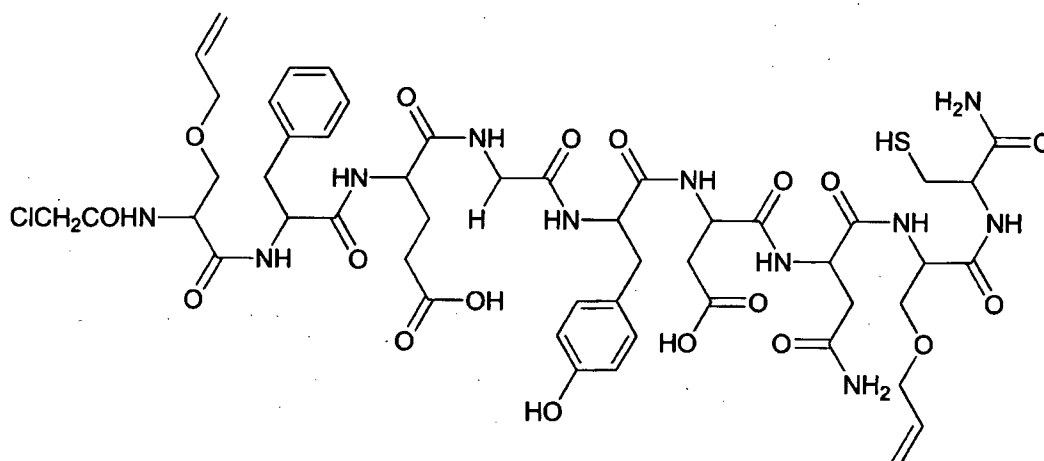


[00232] Ring closing metathesis (RCM) of the cyclised peptide (30 mg, 26.3 μ mol) was performed in solution, using 2,2,2-trifluoroethanol and CH_2Cl_2 as the solvent in 4:1 ratio (3 mL), at approximately 10 mM concentration, with Hoveyda-Grubbs II generation as the catalyst (35 mol %, 5.8 mg), under microwave irradiation, for 3 hours at 65 $^\circ\text{C}$. Solvent was then evaporated under reduced pressure and the crude peptide was purified using a Hewlett-Packard 1200 series HPLC system (Agilent Technologies, CA), by injecting the sample onto a reverse-phase preparative (C18, 300 $\text{\AA}$, 5 μm , 10 mm x 250 mm) column, eluted over a 50 min gradient from 5 to 60 % solvent B, (solvent A: 0.1 % TFA/ H_2O ; solvent B: 0.1 % TFA/ CH_3CN) with a flow rate of 6 mL/min. The fractions were collected and then analysed with liquid chromatography and mass spectrometry. The pure fractions were lyophilised to afford the bicyclic peptide.

[00233] Purified peptide was analysed using a Hewlett-Packard 1100 series HPLC system (Agilent Technologies, CA). The samples were injected onto a reverse-phase VydacTM analytical (C18, 300 $\text{\AA}$, 5 μm , 4.6 mm x 150 mm) column and eluted over a 45 min gradient from 0 to 50 % solvent B, (solvent A: 0.1 % TFA/ H_2O ; solvent B: 0.1 % TFA/ CH_3CN) with a flow rate of 1 mL/min. The mass spectrum was acquired using an Agilent 1100 MSD SL ion trap mass spectrometer. [$M_{\text{calculated}}=1110.38$; $M_{\text{observed}}=1110.3$].

[00234]

Example 5 – Synthesis of G7-TE Δ FP



[00235] The peptide was synthesised on a 0.9 mmol scale using standard Fmoc chemistry on a Rink amide resin (1 mmol/g loading). The Rink amide resin (900 mg, 0.9 mmol) was split into three equal batches (300 mg, 0.3 mmol) and chemistry was performed on each batch as follows. The amide resin (300 mg, 0.3 mmol) was washed with DMF (3 x 5 mL). The Fmoc protecting group on the resin was removed with 2 washes of 20 % piperidine in DMF (5 mL) for 15 min each. The resin was thoroughly washed (3 x 30 s) with DMF (5 mL) and then soaked in Fmoc-protected amino acid (3.1 eq. to resin loading), dissolved in DMF (4 mL) along with HBTU (3 eq. to resin loading), HoBt (3 eq. to resin loading) and DIPEA (4.5 eq. to resin loading), for 45 min. The amino acid coupling cycle was then repeated. The resin was washed (3 x 30 s) with DMF (5 mL), and Kaiser test was performed on a few beads of the resin to confirm complete coupling. The terminal Fmoc protecting group on the amino acid was removed with 2 washes of 20 % piperidine in DMF (5 mL) for 15 min each. Peptide elongation cycle was then repeated until the peptide sequence was complete. After removing the terminal Fmoc protecting group on the peptide, the resin was treated with chloroacetic anhydride (171 mg, 1 mmol) and DIPEA (100 μ L) in DMF (2 mL) for 30 min to afford a chloroacetyl-capped N-terminus. The resin was subsequently washed (3 x 30 s) with DMF (5 mL), (2 x 30 s) CH_2Cl_2 (1 mL), (3 x 30 s) Et_2O (1 mL), and dried for 20 min. Cleavage was performed on 0.3 mmol of the resin, by treating the resin with a cleavage solution (10 mL) comprising of 250 μ L of distilled water (2.5 % v/v), 250 μ L of triisopropylsilane (2.5 % v/v), 50 μ L of ethanedithiol (0.5 % v/v) in TFA, for 180 min. TFA was then evaporated under a stream of N_2 and the peptide

[00239] The binding thermodynamics of G7-B (#1) was determined by calorimetry on a VP-ITC Microcalorimeter (Microcal, Northampton, MA, USA) at 25 °C [32] [27]. Grb7 SH2 domain was dialyzed against 2 litres of 100 mM sodium phosphate, pH 6.0, and 1 mM DTT at 4 °C overnight. The peptide was dissolved in the filtered dialysis buffer to make 1.15 mM solution. The concentration of Grb7 SH2 was determined by absorbance measurement at 280 nm. The peptide and protein solutions were degassed and thermostated at 20 °C for 5 min using the ThermoVac of the VP-ITC Microcalorimeter. The reference power of the experiment was set to 20 μ Cal/sec and the cell contents were stirred continuously at 307 rpm throughout the titrations. The reference cell was filled with MQ water. The peptide was titrated into Grb7 SH2 solutions of 70 μ M concentrations in 10 μ L injections. A binding isotherm was generated by plotting the heat change evolved per injection against the molar ratio of peptides to Grb7 SH2 domain receptor. The heat generated by the last titration was used to estimate the heats of dilution and mixing which was then subtracted from the binding data. The corrected data was then employed to fit to a single binding site model using a non-linear least squares with the Origin (Microcal Software, Northampton, MA, USA). All of the ITC fitting parameters were kept floating during the fitting procedure.

[00240] Table 1. Thermodynamic binding parameters of G7-B (#1)

Binding Parameter	N	K(10^5)	ΔH (Kcal/mol)	-T ΔS (Kcal/mol)	ΔG (Kcal/mol)	K _d (μ M)
Value	1.08+0.01	5.16+0.29	-6.53+0.05	-1.26+0.11	-7.79+0.16	1.94

[00241] **Binding affinity determined using Surface Plasmon Resonance (SPR)**

[00242] SPR was performed using a BIAcore T100. Polyclonal anti-GST-antibody (GE Life Science) was immobilised on the active and reference flow cell of a BIAcore CM5 series S sensor chip (GE Life Science), using a GST capture kit (GE Life Science) and amine coupling kit. GST-Grb2-SH2, GST-Grb14-SH2, GST-Grb10-SH2, and/or GST-Grb7-SH2 were immobilised on active flow cells and recombinant GST was immobilised on a control flow cell by injecting each protein at a concentration of 0.7 μ M as previously described (Gunzburg *et al.*, 2010). Triplicate or duplicate samples of 0-632 μ M G7-peptide were injected for 60 seconds at 30 μ L per minute, with a 3 minute dissociation. The data was analysed using Scrubber2 (BioLogic Software, Australia) and SigmaPlot version 11.0 (Systat Software, Inc.).

[00243] Table 2. Summary of binding data for G7 peptides #2, #3, #4 and #5 to the GRB7-SH2 domain.

Peptide	K_D (μ M)	B_{max} (RU)
G7- Δ FPC	-	-
G7-B Δ F	3.93 $\pm$ 0.09	55.9 $\pm$ 0.3
G7-B Δ FP	0.76 $\pm$ 0.01	47.4 $\pm$ 0.1
G7-TE Δ FP	4.930 $\pm$ 0.007	34.7 $\pm$ 0.01

[00244] Table 3. Summary of binding data for G7-18NATE and G7-B Δ FP peptides to the SH2 domains of Grb2, 7, 10 and 14.

Protein-SH2 domain	G7-18NATE (#0)	G7-B Δ FP (#4)
Grb2	261 μ M	56.4 μ M
Grb7	2.9 μ M	0.838 μ M
Grb10	148 μ M	52.7 μ M
Grb14	43 μ M	Negligible

[00245] **Example 7 – Synthesis and binding studies of a phosphotyrosine mimetic of G7-B Δ FP**

[00246] The procedure of Example 4 was followed but with substitution of the tyrosine residue in the former procedure with 4- caromethoxyphenylalanine to produce G7-TEM (i.e. ThioEther Mimetic).

SPR was used to measure the binding affinity of G7-TEM (Figures 7 to 9). The data show that by replacing tyrosine with carboxymethylphenylalanine, we are able to maintain low micromolar binding affinity at physiologically relevant concentrations of phosphate in the buffer ($\sim$ 1mM). It should be noted that previous measurements of high peptide binding affinity were

found to be dependent on the presence of phosphate (~50 mM) in the buffer (Gunzburg *et al.*, 2012).

[00247] It will be appreciated by persons skilled in the art that numerous variations and/or modifications may be made to the invention as shown in the specific embodiments without departing from the spirit or scope of the invention as broadly described. The present embodiments are, therefore, to be considered in all respects as illustrative and not restrictive.

[00248] Throughout this specification the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps.

[00249] The following amino acid sequences are disclosed herein:

[00250] SEQ ID No: 1: YXaaN

[00251] SEQ ID No: 2: YDN

[00252] SEQ ID No: 3: Xaa1Xaa2Xaa3YDN

[00253] SEQ ID No: 4: YAN

[00254] SEQ ID No: 5: Xaa1Xaa2Xaa3YAN

[00255] SEQ ID No: 6: YEN

[00256] SEQ ID No: 7: Xaa1Xaa2Xaa3YEN

[00257] SEQ ID No: 8: FEGYDN

REFERENCES

[00258] All publications mentioned in this specification are herein incorporated by reference. Any discussion of documents, acts, materials, devices, articles or the like which has been included in the present specification is solely for the purpose of providing a context for the present invention. It is not to be taken as an admission that any or all of these matters form part of the prior art base or were common general knowledge in the field relevant to the present invention as it existed in Australia or elsewhere before the priority date of each claim of this application.

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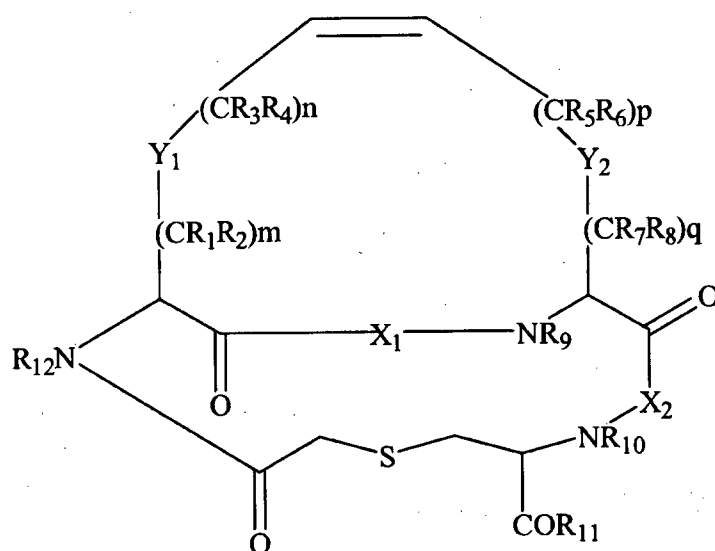
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CLAIMS

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



I

wherein:

X_1 is a moiety having binding affinity for the SH2 domain of GRB7;

X_2 is selected from the group consisting of a bond, an amino acid, and a dipeptide;

Y_1 and Y_2 are each independently selected from the group consisting of $(CR_{13}R_{14})$, O, S, and N;

each R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_{13} and R_{14} is independently selected from the group consisting of: H, halogen, OH, NO_2 , CN, NH_2 , optionally substituted C_1 - C_{12} alkyl, optionally substituted C_2 - C_{12} alkenyl, optionally substituted C_2 - C_{12} alkynyl, optionally substituted C_2 - C_{12} heteroalkyl, optionally substituted C_3 - C_{12} cycloalkyl, optionally substituted C_2 - C_{12} heterocycloalkyl, optionally substituted C_2 - C_{12} heterocycloalkenyl,

optionally substituted C₆-C₁₈ aryl, optionally substituted C₁-C₁₈heteroaryl, optionally substituted C₁-C₁₂alkyloxy, optionally substituted C₂-C₁₂alkenyloxy, optionally substituted C₂-C₁₂alkynyloxy, optionally substituted C₂-C₁₂heteroalkyloxy, optionally substituted C₃-C₁₂cycloalkyloxy, optionally substituted C₃-C₁₂cycloalkenyloxy, optionally substituted C₁-C₁₂heterocycloalkyloxy, optionally substituted C₂-C₁₂heterocycloalkenyloxy, optionally substituted C₆-C₁₈aryloxy, optionally substituted C₁-C₁₈heteroaryloxy, optionally substituted C₁-C₁₂alkylamino, SR₁₅, SO₃H, SO₂NH₂, SO₂R₁₅, SONH₂, SOR₁₅, COR₁₅, COOH, COOR₁₅, CON R₁₅R₁₆, NR₁₅COR₁₆, NR₁₅COOR₁₆, NR₁₅SO₂R₁₆, N R₁₅CON R₁₅R₁₆, N R₁₅R₁₆, and acyl;

each m, n, p, and q is an integer which is independently selected from the group consisting of: 0, 1, 2, and 3;

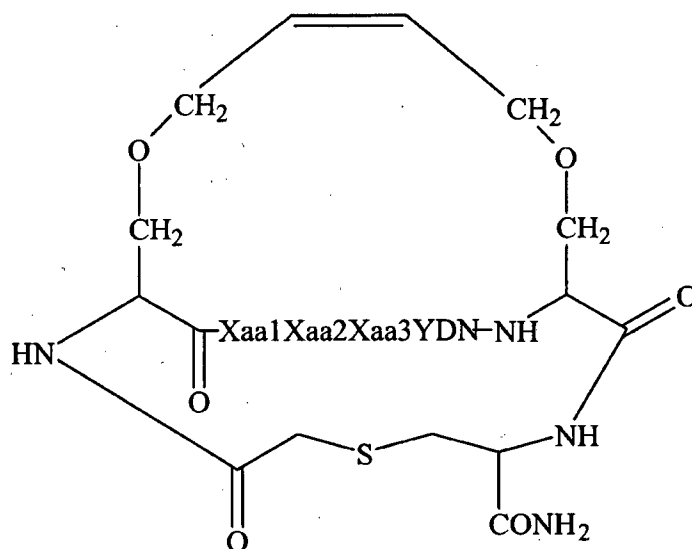
R₁₁ is selected from the group consisting of: NR₁₇R₁₈, wherein each R₁₇ and R₁₈ is independently selected from the group consisting of: H, optionally substituted C₁-C₁₂alkyl, amino acid, peptide, a toxin, a radioactive agent, a chemotherapeutic agent, an anti-angiogenic agent, an immunomodulatory agent, and a translocation agent; and

each R₉, R₁₀, R₁₂, R₁₅ and R₁₆ is independently selected from the group consisting of: H, optionally substituted C₁-C₁₂alkyl, optionally substituted C₂-C₁₂alkenyl, optionally substituted C₂-C₁₂alkynyl, optionally substituted C₂-C₁₂heteroalkyl, optionally substituted C₃-C₁₂cycloalkyl, optionally substituted C₃-C₁₂cycloalkenyl, optionally substituted C₂-C₁₂heterocycloalkyl, optionally substituted C₂-C₁₂heterocycloalkenyl, optionally substituted C₆-C₁₈aryl, and optionally substituted C₁-C₁₈heteroaryl.

2. The compound of claim 1, wherein X₁ comprises a six amino acid peptide comprising a YXaaN (SEQ ID No: 1) motif wherein Y is tyrosine, N is asparagine and Xaa is selected from the group consisting of alanine (A), aspartic acid (D), and glutamic acid (E), or a derivative thereof.
3. The compound of claim 2, wherein X₁ comprises a six amino acid peptide comprising a YDN (SEQ ID No: 2) motif.
4. The compound of claim 3, wherein X₁ comprises FEGYDN (SEQ ID No: 8).

5. The compound of any one of the preceding claims, wherein X_2 comprises a bond.
6. The compound of any one of claims 1 to 4, wherein X_2 comprises a dipeptide.
7. The compound of claim 6, wherein the dipeptide is FP.
8. The compound of any one of the preceding claims, wherein Y_1 and Y_2 are each independently selected from the group consisting of O, S, and N.
9. The compound of claim 8, wherein Y_1 and Y_2 are O.
10. The compound of any one of the preceding claims, wherein $R_1, R_2, R_3, R_4, R_5, R_6, R_7$, and R_8 are selected from the group consisting of H and F.
11. The compound of claim 10, wherein $R_1, R_2, R_3, R_4, R_5, R_6, R_7$, and R_8 are H.
12. The compound of any one of the preceding claims, wherein n and p are 1.
13. The compound of any one of the preceding claims, wherein m and q are 1.
14. The compound of any one of the preceding claims, wherein R_9, R_{10} , and R_{12} are H.
15. The compound of any one of the preceding claims, wherein R_{11} is NH_2 .
16. The compound of any one of claims 1 to 14, wherein R_{11} is NHR_{18} and R_{18} is a translocation agent.

17. A compound of formula II:



II

wherein Xaa1, Xaa2 and Xaa3 are amino acids.

18. A pharmaceutical composition comprising a compound of any one of claims 1 to 17 and a pharmaceutically acceptable diluent, excipient or carrier.
19. A method of inhibiting binding of growth receptor bound (GRB) 7 protein to a GRB7 ligand, the method comprising exposing a cell expressing GRB7 or a fragment or complex thereof or a functional equivalent thereof to an effective amount of a compound of any one of claims 1 to 17.
20. A method of treating or preventing a condition in a mammal in which inhibition of binding of growth receptor bound (GRB) 7 protein to a GRB7 ligand prevents, inhibits or ameliorates a pathology or a symptomology of the condition, the method including administration of a therapeutically effective amount of a compound of any one of claims 1 to 17.
21. Use of a compound of any one of claims 1 to 17 in the preparation of a medicament for treating a condition in a mammal in which inhibition of binding of growth receptor bound

(GRB) 7 protein to a GRB7 ligand prevents, inhibits or ameliorates a pathology or a symptomology of the condition.

22. Use of a compound of any one of claims 1 to 17 in the treatment of a condition in which inhibition of binding of growth receptor bound (GRB) 7 protein to a GRB7 ligand prevents, inhibits or ameliorates a pathology or a symptomology of the condition.

23. A method for inhibiting a metastasis in a subject, the method including administration of a therapeutically effective amount of a compound of any one of claims 1 to 17.

24. A method for the prevention or treatment of a proliferative condition associated with abnormal interaction of GRB7 with a GRB7 ligand in a subject, the method including administration of a therapeutically effective amount of a compound of any one of claims 1 to 17.

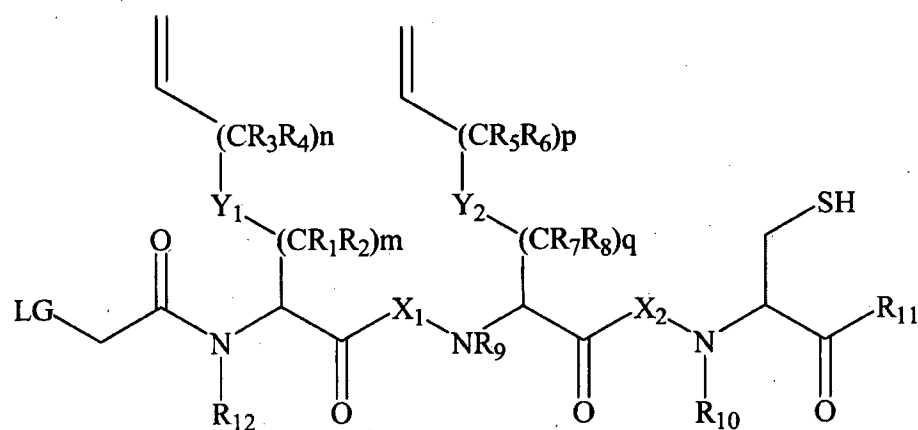
25. Use of a compound of any one of claims 1 to 17 in the preparation of a medicament for treating a proliferative condition associated with abnormal interaction of GRB7 with a GRB7 ligand in a subject.

26. The use of claim 25, wherein the proliferative condition is a cancer characterised by overexpression of GRB7.

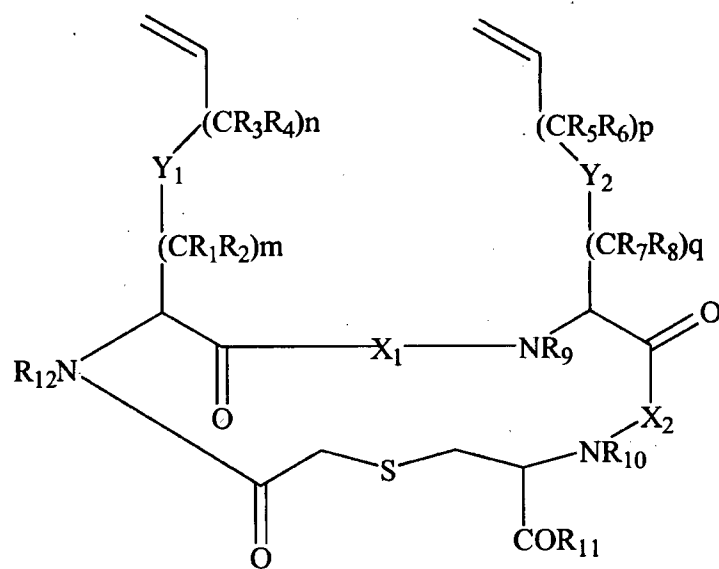
27. A method for preparing a compound of the first aspect, the method comprising:

(i) cyclising a compound of formula (a) to form a thioether cyclised compound of formula (b).

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(a)

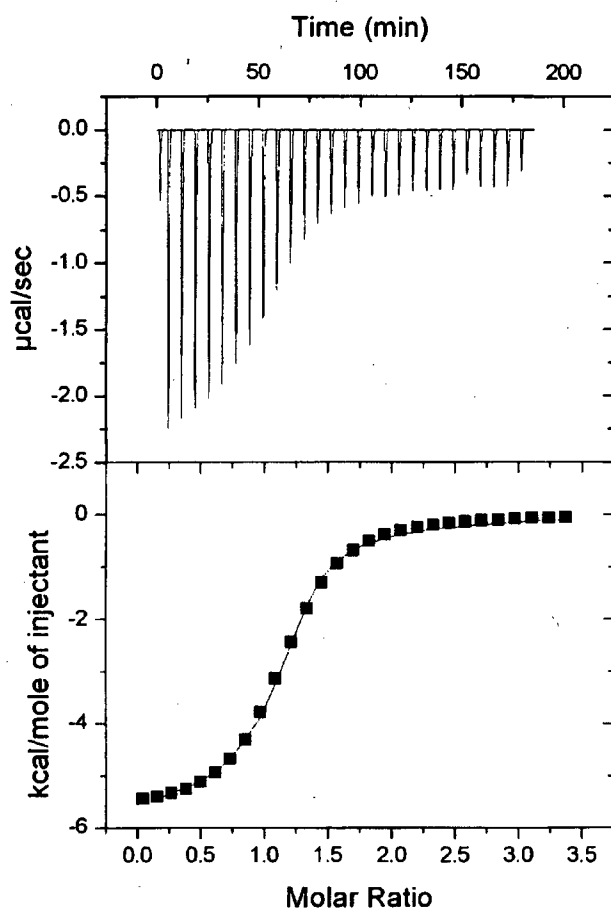


(b)

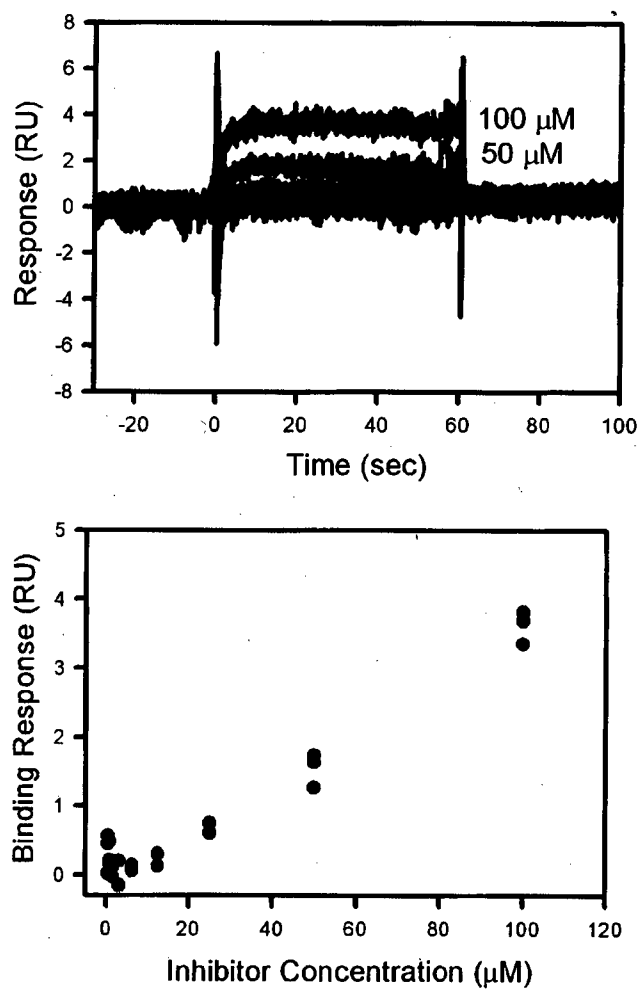
(ii) cyclising a compound of formula (b) to form a compound of formula (I)

wherein LG is a leaving group and X_1 , X_2 , Y_1 , Y_2 , and R_1 - R_{16} are as defined previously.

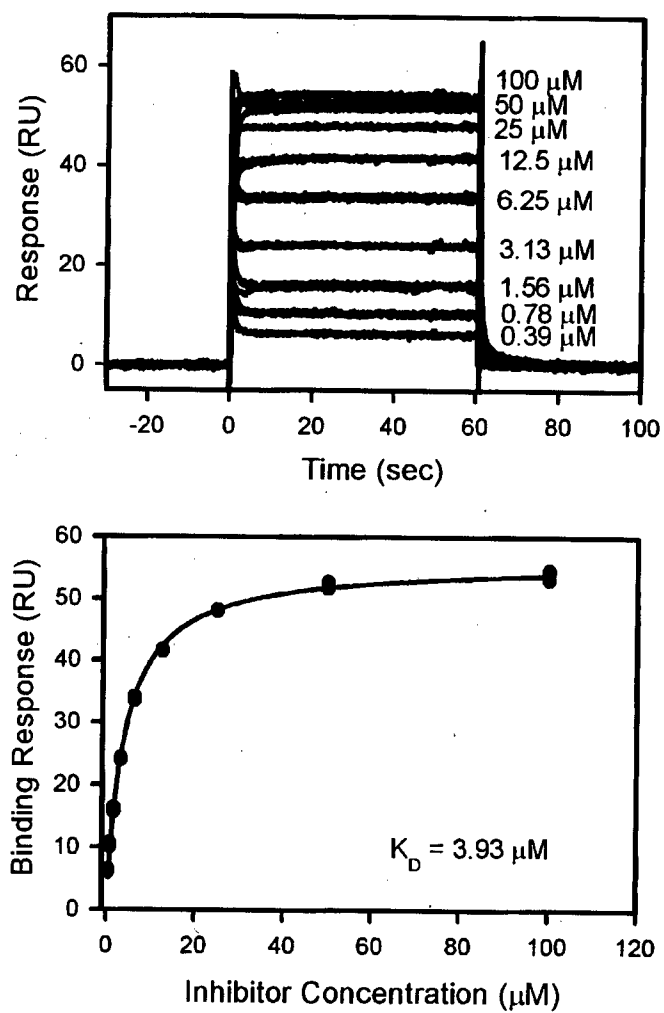
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**Figure 1**

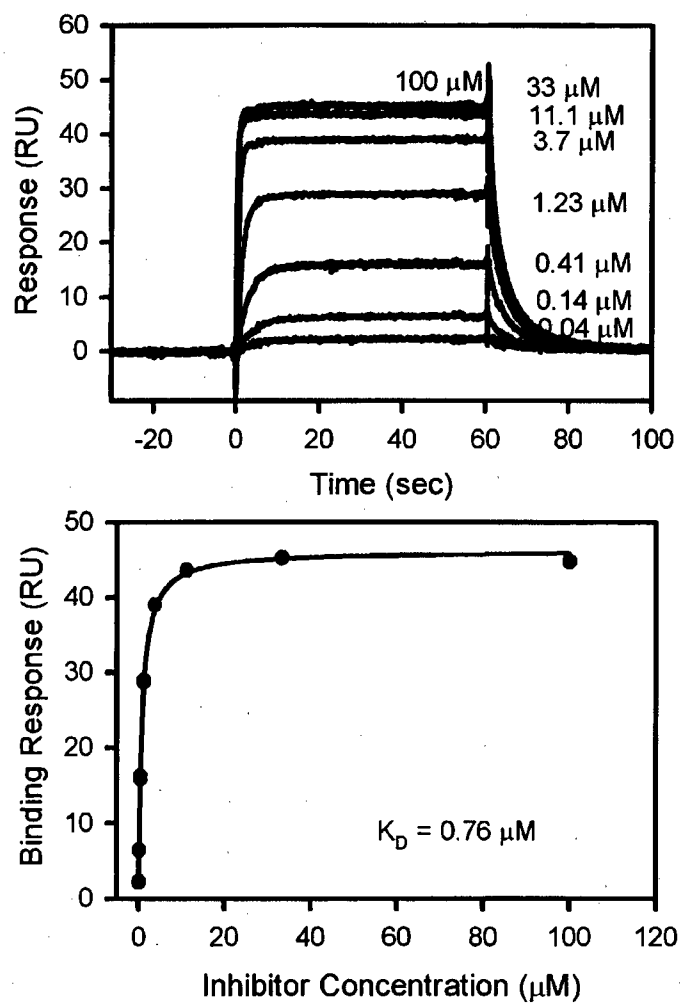
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**Figure 2**

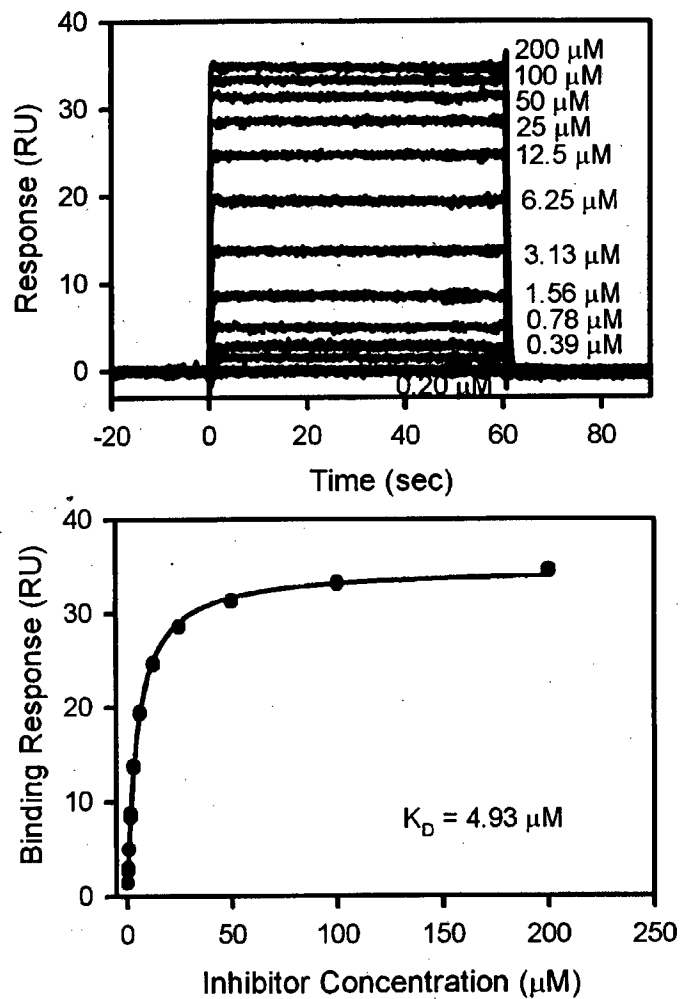
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**Figure 3**

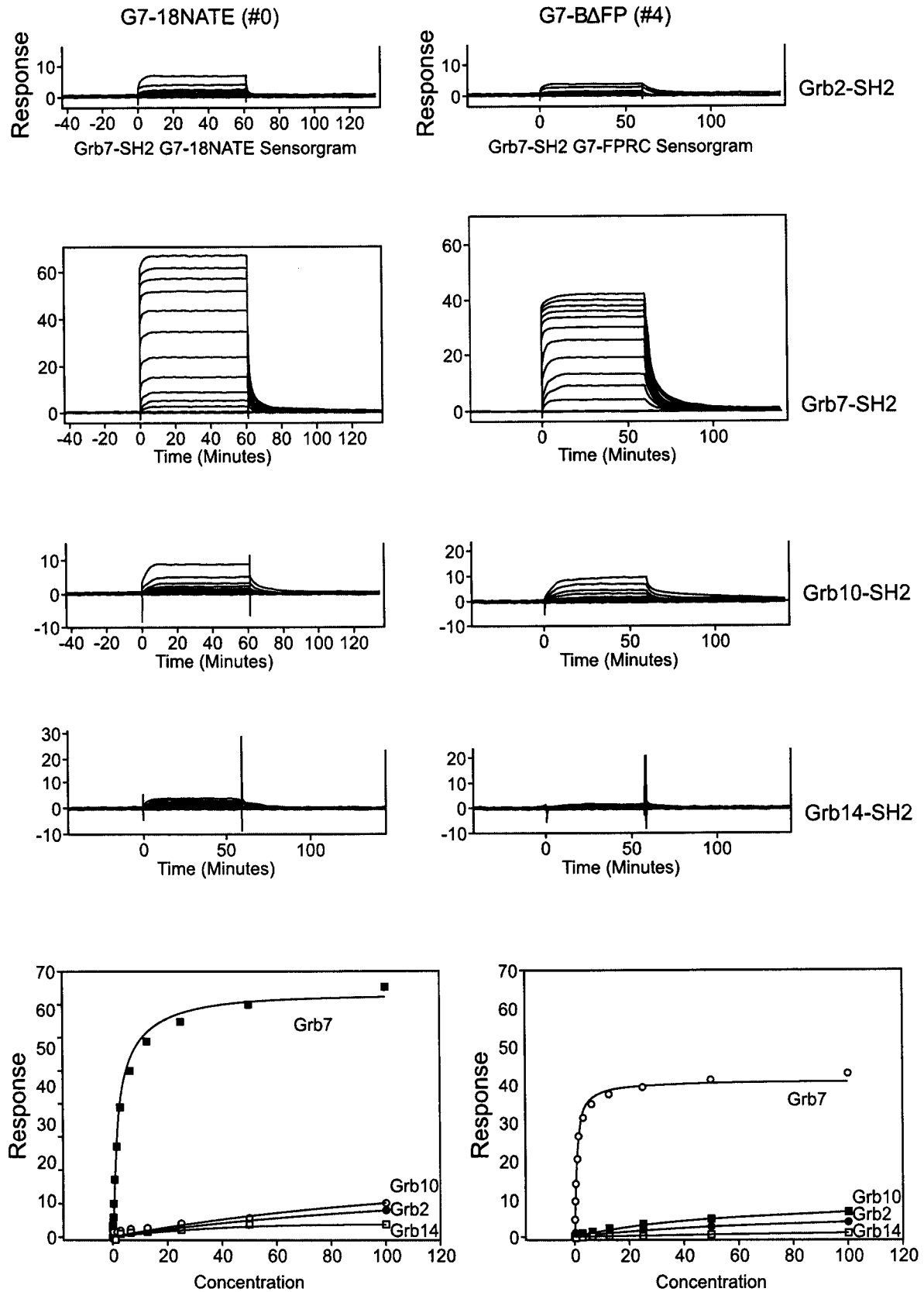
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**Figure 4**

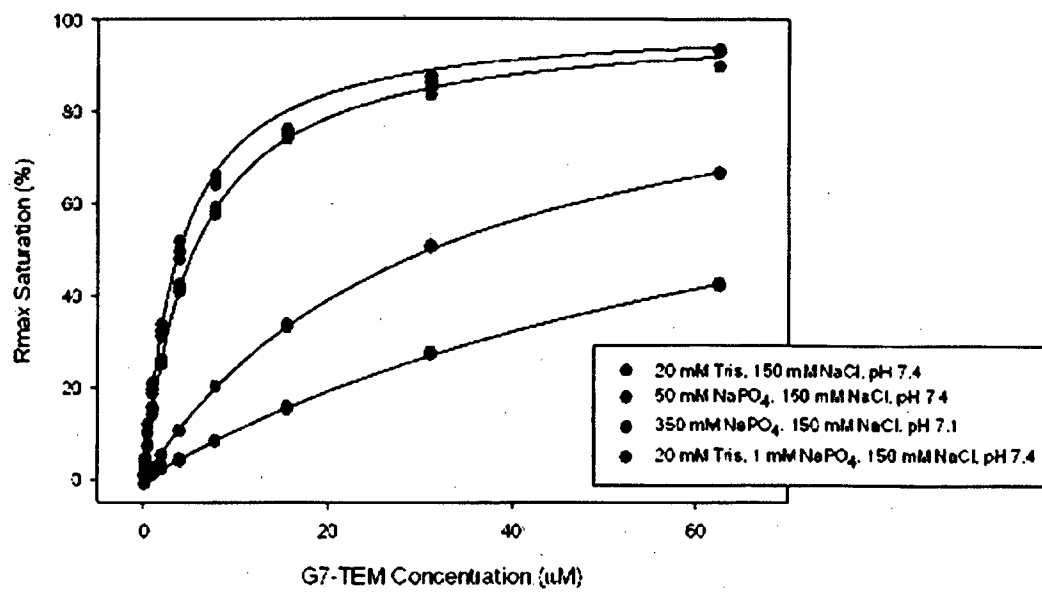
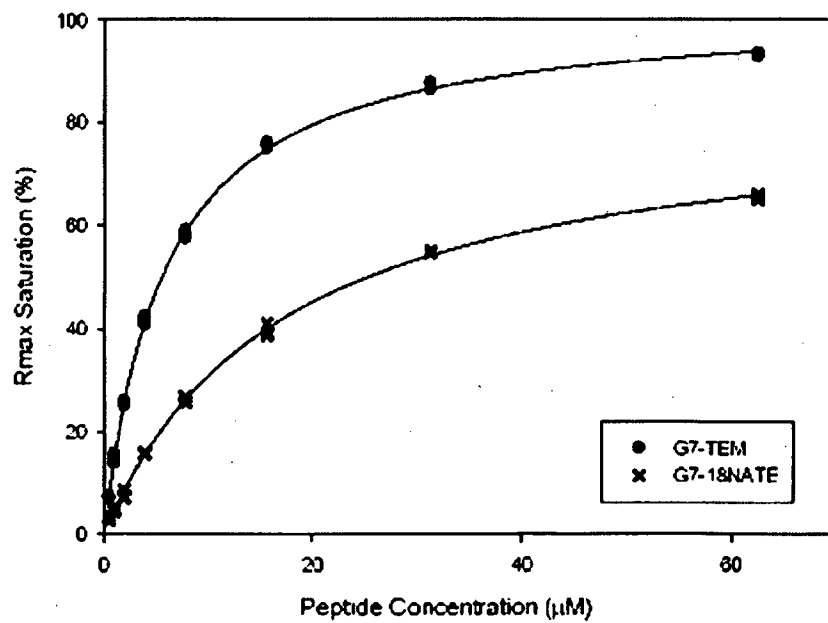
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**Figure 5**

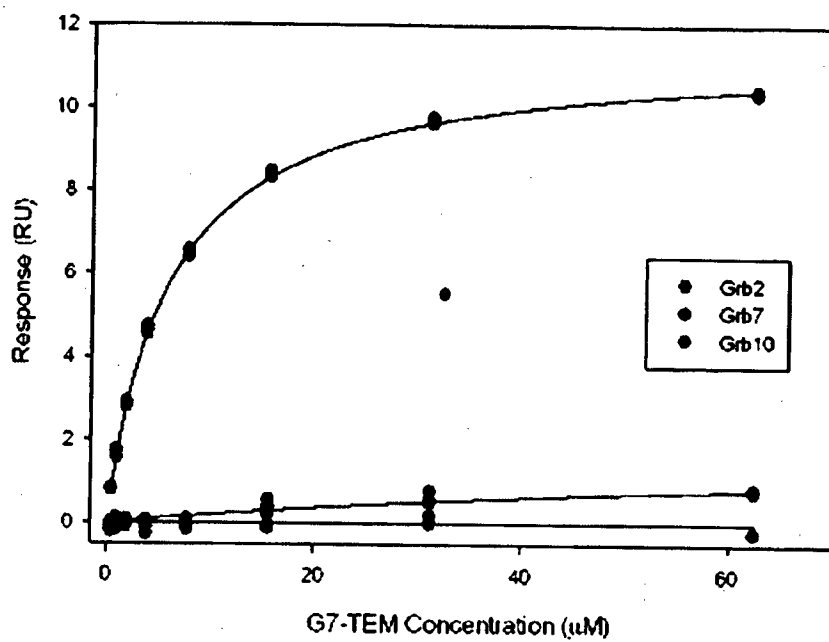
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**Figure 6**

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**Figure 7****Figure 8**

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**Figure 9**

INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU2013/001332

A. CLASSIFICATION OF SUBJECT MATTER

C07K 7/06 (2006.01) A61K 38/08 (2006.01) A61P 35/00 (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Registry, CAplus: structure search based on compound of formula 1

Medline, CAplus, Wpids, Biosis, Biotechabs: keywords: metathesis, rcm, olefin, allyl, thioether, bicyclic, SH2, grb, peptide and like terms

PubMed: inventor search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	



Further documents are listed in the continuation of Box C



See patent family annex

* Special categories of cited documents:	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier application or patent but published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search
28 February 2014Date of mailing of the international search report
28 February 2014

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INTERNATIONAL SEARCH REPORT		International application No.
C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		PCT/AU2013/001332
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	AMBAYE, N.D. et al. 'Structural basis of binding by cyclic nonphosphorylated peptide antagonists of Grb7 implicated in breast cancer progression', Journal of Molecular Biology. 2011, vol. 412, pages 397-411 See Abstract; Figure 5, page 406; pages 399-401; Conclusion, page 407; Figure 2, page 402; page 398, right column, first complete paragraph; page 398, left column; page 407, left column	1-16, 18-27
Y	QUARTARARO, J.S. et al. 'Peptide bicycles that inhibit the Grb2 SH2 domain', ChemBioChem. 2012, vol. 13, pages 1490-1496 (published online 11 June 2012) See Abstract; Figure 1, page 1491; page 1491, right column; page 1492, first complete paragraph; Figure 2, page 1492; Figure 3, page 1493; pages 1491-1495	1-16, 18-27
A	PEREZ de VEGA, M.J. et al. 'A role for ring-closing metathesis in medicinal chemistry: Mimicking secondary architectures in bioactive peptides', Medicinal Research Reviews. 2011, vol. 31, pages 677-715 See Abstract; pages 701-703; Scheme 2, page 688	1-27
P,X	GUNZBURG, M.J. et al. 'Design and testing of bicyclic inhibitors of Grb7 - Are two cycles better than one?', Biopolymers (Peptide Science). 2013, vol. 100, pages 543-549 (published online 15 March 2013) See Figure 1, page 546; Discussion, page 547-549	1-4, 6-16, 18-27
Form PCT/ISA/210 (fifth sheet) (July 2009)		