(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
28 March 2013 (28.03.2013)

WIPO | PCT

(10) International Publication Number
WO 2013/042065 A2

(51) International Patent Classification:
A61K 31/52 (2006.01) *A61P 39/02* (2006.01)
A61K 31/7052 (2006.01)

(21) International Application Number:
PCT/IB2012/054999

(22) International Filing Date:
20 September 2012 (20.09.2012)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2011/06840 20 September 2011 (20.09.2011) ZA

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, 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, IS, JP, KE, KG, KM, 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, 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.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, 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, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

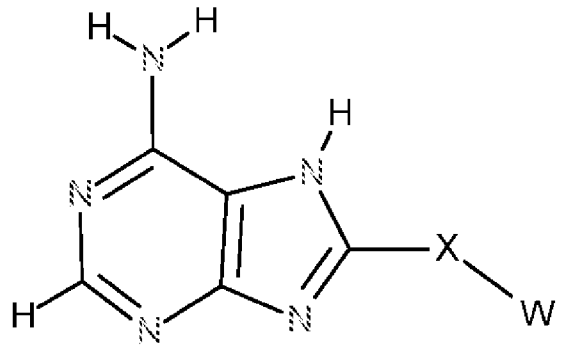
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *of inventorship (Rule 4.17(iv))*

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

(54) Title: INHIBITORS OF TYPE II RIBOSOME INACTIVATING PROTEINS



(I)

(57) Abstract: The invention provides compounds which are inhibitor of ricin, abrin, Shiga or saporin and which have a bipartite configuration comprising an aromatic heterocyclic structure resembling an adenine moiety in size and shape connected at the C8 position to an aromatic or non- aromatic cyclic ring structure resembling a ribose moiety in size and shape. More particularly, the inhibitors have the formula (I): (I) where X = -S-, -O-, -CH 2 -, -NH-, -PH-, -O-Y-, -CH 2 -Y-, -NH-Y-, -PH-Y, or -S-Y; Y = -S-, -O-, -CH 2 -, -NH-, or -PH-; and W = a 5- or 6-membered aromatic or non-aromatic cyclic ring. Uses of these compounds in manufacturing a medicament and in treating a subject are also described, as is a method of identifying suitable inhibitors.

WO 2013/042065 A2

INHIBITORS OF TYPE II RIBOSOME INACTIVATING PROTEINS

FIELD OF THE INVENTION

This invention relates to compounds which are capable of inhibiting ribosome inactivating protein (RIP) type II lectins and to the use of these compounds in pharmaceutical compositions for treating or preventing diseases or infections.

BACKGROUND TO THE INVENTION

Ribosome inactivating proteins (RIPs) are protein synthesis inhibitors that act at the ribosome. Members of the family include Shiga and Shiga-like toxins, trichosanthin, luffin, saporin, ricin, agglutinin and abrin.

Ricin, from the castor oil plant *Ricinus communis*, is a very toxic type II ribosome inactivating protein (RIP). A dose as small as 1.76 mg can kill an adult.

Ricin has been investigated for its military potential by at least the United States, Canada and the Soviet Union. The toxin has been involved in a number of incidents, including the high-profile “umbrella-tip” assassination of Georgi Markov in 1978. More recently, there have been press reports of extremist groups and individuals planning to use ricin in terrorist attacks.

Ricin also has the potential to be a therapeutic protein or immunotoxin for use in, for example, the treatment of autoimmune diseases, psoriasis, cancer, HIV infection or AIDS. However, due to non-specific cytotoxicity and immunogenicity which result when ricin is administered, repeat dosing is prevented and the therapeutic use of ricin has not yet been approved.

Abrin is a toxalbumin found in the seeds of a plant called the lucky bean (or the rosary pea or jequirity pea). Although it is far more deadly than ricin, it has some potential uses, such as in treatment to kill cancer cells.

Another RIP is Shiga. The most common sources for Shiga toxin are the bacteria *S. dysenteriae* and the Shigatoxigenic group of *Escherichia coli* (STEC), which includes serotypes O157:H7, O104:H4, and other enterohemorrhagic *E. coli* (EHEC). It is estimated that at least 90 people die each year from coming into contact with *E. coli* that make Shiga or Shiga-like toxins, and thousands more are hospitalized.

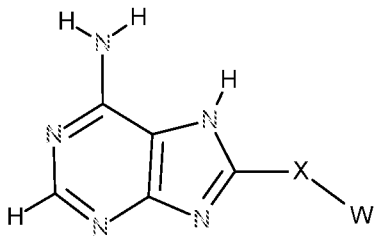
Saporin, from the seeds of *Saponaria officinalis* (soapwort), is another RIP. It has been used in research as an immunotoxin for leukaemia and lymphoma and to target and eliminate neuronal populations.

To date no effective antidote is known for ricin or its related family members. There is therefore a need for a compound or composition which can inhibit ricin or its related toxins, such as Shiga, saporin and abrin.

SUMMARY OF THE INVENTION

According to a first embodiment of the invention, there is provided a compound which is a ricin, abrin, Shiga or saporin inhibitor, wherein the compound has a bipartite configuration comprising an aromatic heterocyclic structure that resembles an adenine moiety in size and shape connected at the C8 position to an aromatic or non-aromatic cyclic ring structure that resembles a ribose moiety in size and shape.

The compound may be of formula (I):

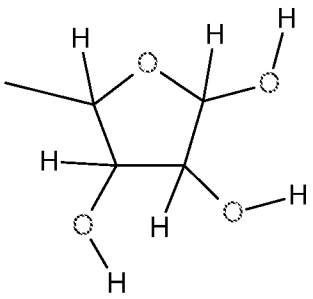


(I)

where X = -S-, -O-, -CH_2-, -NH-, -PH-, -O-Y-, -CH_2-Y-, -NH-Y-, -PH-Y, or -S-Y;

Y = -S-, -O-, -CH_2-, -NH-, or -PH-; and

W = a 5- or 6-membered aromatic or non-aromatic cyclic ring selected from any one of formulae (II) to (XX), or a derivative thereof:



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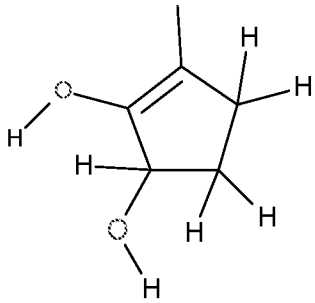

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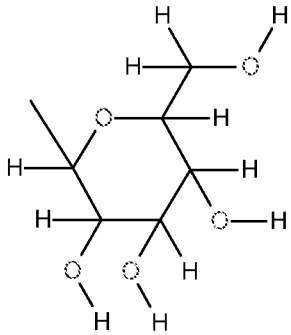

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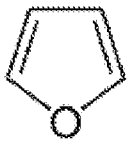

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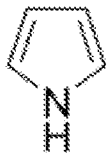

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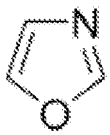

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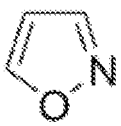

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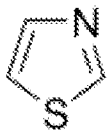

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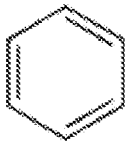

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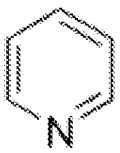

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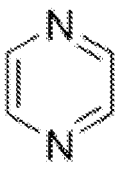

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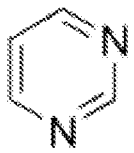

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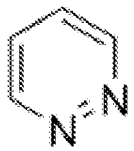

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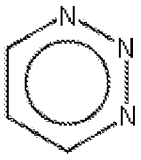

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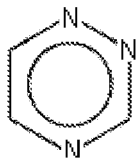

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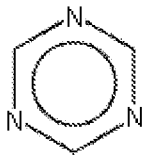
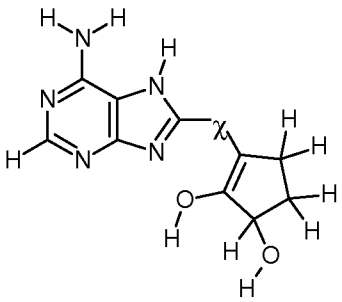


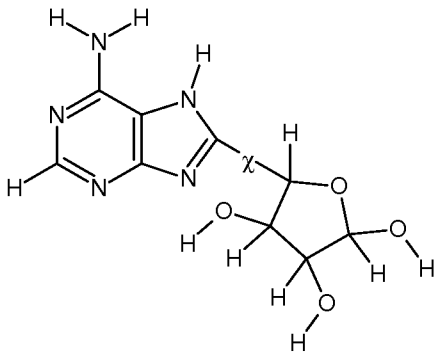
(XX)

or isomers, tautomers, pharmaceutically acceptable salts, esters or prodrugs thereof, for use as an inhibitor of ricin, abrin, Shiga or saporin.

More particularly, the compound of formula (I) may be selected from compounds of the formulae (XXI), (XXII), (XXIII) or (XXIV):



(XXI)



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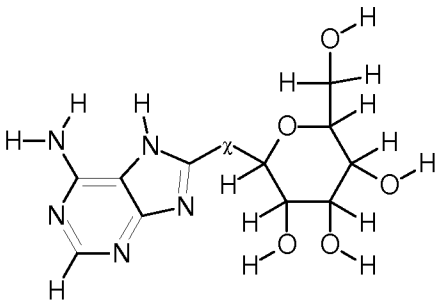

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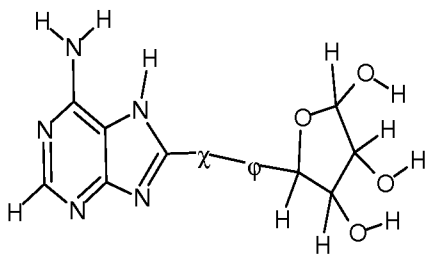


(XXIV)

where

χ is selected from any one of -(S)-, -(O)-, -(CH_2)-, –(NH)-, or –(PH); and

φ is selected from any one of -(S)-, -(O)-, -(CH_2)-, –(NH)-, or –(PH),

or any isomers, tautomers, pharmaceutically acceptable salts, esters or prodrugs thereof.

The compound may be for use in controlling non-specific cytotoxicity due to ricin, abrin, Shiga or saporin, and more particularly for treating diseases or conditions such as psoriasis, autoimmune diseases or cancer, HIV infection or AIDS.

According to a second embodiment of the invention, there is provided the use of a compound substantially as described above in a method of manufacturing a medicament for use in a method of for use in a method of inhibiting ricin, abrin, Shiga or saporin and/or of treating non-specific cytotoxicity, and in particular of treating psoriasis, autoimmune diseases or cancer, HIV infection and AIDS.

According to a third embodiment of the invention, there is provided a pharmaceutical composition comprising a compound substantially as described above and a pharmaceutically acceptable excipient or additive.

According to a fourth embodiment of the invention, there is provided a method for identifying a compound which is effective for inhibiting ricin, abrin, Shiga or saporin, the method comprising the step of identifying a test compound which:

i) has an adenine resembling moiety and a ribose resembling moiety which are connected to each other via the C8 of the adenine resembling moiety;

ii) resembles the shape, size and binding pattern of the transition state structure of the ricin-catalyzed reaction; and

iii) resembles the electrostatic surface potential of the transition state structure of the ricin-catalyzed reaction;

and measuring the effect of the test compound on ricin-, abrin-, Shiga- or saporin-mediated protein synthesis inhibition, wherein a reduction of ricin-, abrin-, Shiga- or saporin-mediated protein synthesis inhibition in the presence of the test compound indicates that the test compound is a ricin, abrin, Shiga or saporin inhibitor.

According to a fifth embodiment of the invention, there is provided a method of inhibiting ricin, abrin, Shiga or saporin or of controlling non-specific cytotoxicity due to ricin, abrin,

Shiga or saporin when using it as a therapeutic agent, such as for treating psoriasis, autoimmune diseases, cancer, HIV infection or AIDS, the method comprising the step of administering a therapeutically effective amount of a compound substantially as described above along with the ricin, abrin, Shiga or saporin to a subject in need of such treatment.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows binding of a natural substrate (a 12-mer RNA) loop to ricin. The ricin backbone is shown in blue; the RNA loop is shown in green and the target adenine is highlighted in a liquorish representation;

Figure 2 shows the ricin transition state ESP;

Figure 3 shows transition state analogues identified herein as potential new inhibitors of ricin;

Figure 4 shows binding of the newly identified ricin inhibitors to RTA;

Figure 5 shows a comparison of binding sites of abrin, Shiga, saporin and ricin;

Figure 6 shows docking results of the newly identified inhibitors to abrin;

Figure 7 shows docking results of the newly identified inhibitors to Shiga; and

Figure 8 shows docking results of the newly identified inhibitors to saporin.

DETAILED DESCRIPTION OF THE INVENTION

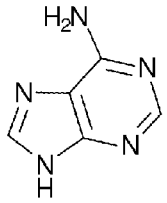
Inhibitors of type II ribosome inactivating proteins (RIPs) such as ricin, abrin, Shiga and saporin are described herein.

The identified inhibitors can be used as antidotes to these toxins or to facilitate immunotoxin treatment by controlling non-specific cytotoxicity. More specifically, it is anticipated that the

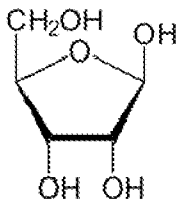
inhibitors could be used for the treatment or prevention of diseases or conditions such as psoriasis, autoimmune diseases, cancers, HIV infection or AIDS[8].

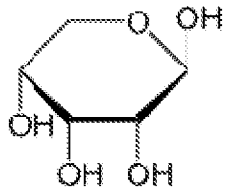
Methods of identifying suitable inhibitors of ricin and its related toxins are also described, using computer simulations to elucidate the mechanism of the ricin reaction and using its transition state as a model to design and identify transition state analogue inhibitors for ricin.

Inhibitors have been identified which have a bipartite configuration comprising an aromatic heterocyclic structure resembling an adenine moiety in size and shape connected at the C8 position to an aromatic or non-aromatic cyclic ring structure resembling a ribose moiety in size and shape.



Adenine

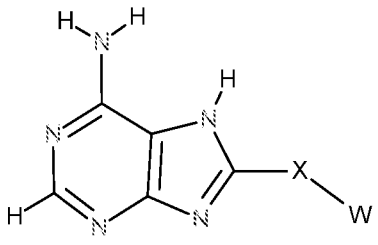




Ribose

Adenine and ribose moieties will be well-known to those skilled in the art of the present invention. Structures resembling a ribose moiety are 5- or 6-membered cyclic rings, with the ring atoms generally being selected from C, O, N or S and the side groups or atoms attached to the ring generally being OH or H.

In particular, the inhibitors are compounds of formula (I):

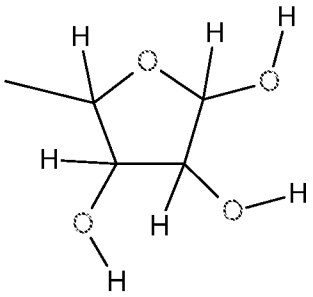


(I)

where X = -S-, -O-, -CH_2-, -NH-, -PH-, -O-Y-, -CH_2-Y-, -NH-Y-, -PH-Y, or -S-Y;

Y = -S-, -O-, -CH_2-, -NH-, or -PH-; and

W = a 5- or 6-membered aromatic or non-aromatic cyclic ring selected from any one of formulae (II) to (XX) or a derivative thereof:



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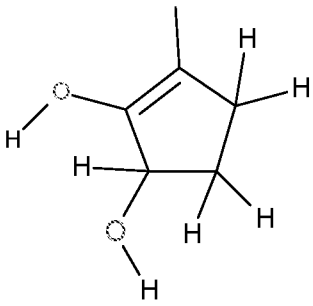

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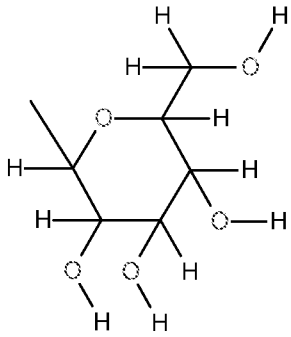

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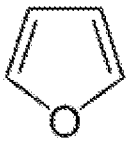

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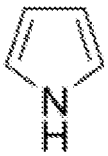

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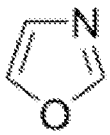

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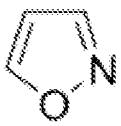

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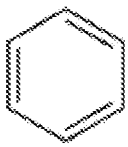

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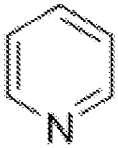
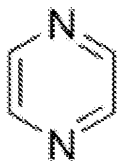
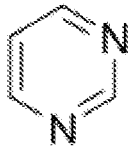


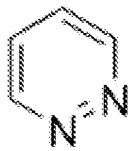
(XIV)



(XV)



(XVI)



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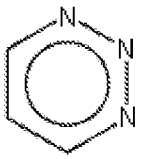
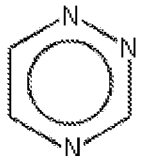


(XVIII)



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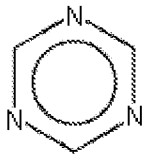
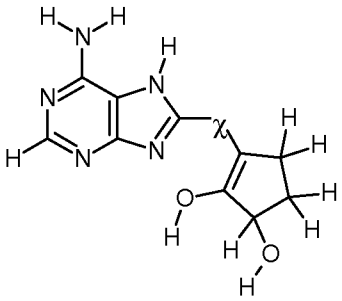


(XX)

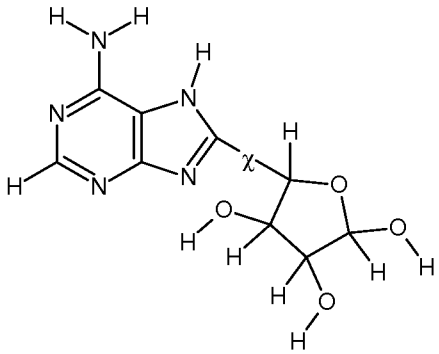
or isomers, tautomers, pharmaceutically acceptable salts, esters or prodrugs thereof.

Derivates could be derived by replacing one or more ring atoms and/or by replacing one or more ring hydrogens with any atom or group of atoms.

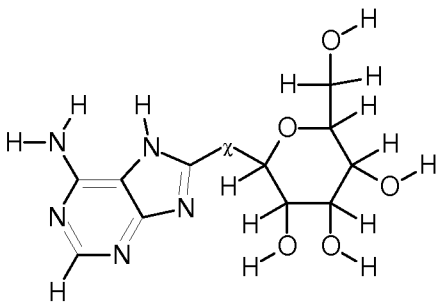
For example, suitable compounds of formula (I) include compounds of formulae (V), (VI), (VII) or (VIII):



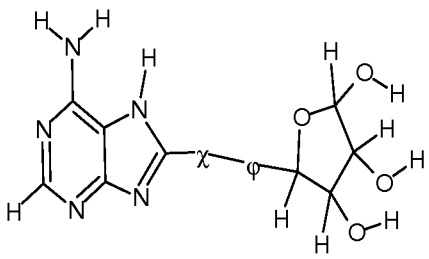
(V)



(VI)



(VII)



(VIII)

where

χ is selected from any one of -(S)-, -(O)-, -(CH_2)-, –(NH)-, and –(PH)-; and

φ is selected from any one of -(S)-, -(O)-, -(CH_2)-, –(NH)-, and –(PH)-,

or any isomers, tautomers, pharmaceutically acceptable salts, esters or prodrugs thereof.

All RIPs are structurally related and the RIP active site is preserved. Ricin is classified as a type II RIP. Whereas type I RIPs consist of a single enzymatic protein chain, type II RIPs are heterodimeric glycoproteins. Type II RIPs consist of an A chain that is functionally equivalent to a type I RIP and is catalytically active, and which is covalently connected by a single disulfide bond to a B chain that is catalytically inactive, but serves to mediate entry of the A-B protein complex into the cytosol. Both type I and type II RIPs are functionally active against ribosomes *in vitro*, but only type II RIPs display cytoxicity due to the lectin properties of the B chain. In order to display its ribosome inactivating function, the ricin disulfide bond must be reductively cleaved.

The tertiary structure of ricin is a globular, glycosylated heterodimer of approximately 60-65 kDA[7]. Ricin toxin A chain and ricin toxin B chain are of similar molecular weight, approximately 32 kDA and 34 kDA respectively.

- **Ricin A Chain** (RTA) is an N-glycoside hydrolase composed of 267 amino acids.[1] It has three structural domains with approximately 50% of the polypeptide arranged into alpha-helices and beta-sheets. The three domains form a pronounced cleft that is the active site of RTA.
- **Ricin B Chain** (RTB) is a lectin composed of 262 amino acids that is able to bind terminal galactose residues on cell surfaces[2,6]. RTB form a bilobal, barbell-like structure lacking alpha-helices or beta-sheets where individual lobes contain three subdomains. At least one of these three subdomains in each homologous lobe possesses a sugar-binding pocket that gives RTB its functional character.

Ricin inactivates 60S ribosomal subunits by an N-glycosidic cleavage which releases the adenine base at position 4324 (A4324) from the sugar-phosphate backbone of the 28S rRNA, but leaves the phosphodiester backbone of the RNA intact. A4324 is contained in a highly conserved sequence of 12 nucleotides universally found in eukaryotic ribosomes. The sequence, 5'-AGUACGAGAGGA-3', termed the sarcin-ricin loop, is important in binding

elongation factors during protein synthesis. The depurination event rapidly and completely inactivates the ribosome, resulting in toxicity from inhibited protein synthesis. A single RTA molecule in the cytosol is capable of depurinating approximately 1500 ribosomes per minute.

Not only is the structure for all RIPs similar, but the RIP active site is also preserved and the RIPs catalyse the same depurination reaction. Specifically, abrin, Shiga, saporin and ricin have the same set of catalytic residues. The corresponding residue numbers for the catalytic sets of abrin, Shiga, saporin and ricin are shown in Table 1.

Table 1: Common catalytic residues of RIP proteins

Catalytic Site Residues	**Abrin**	**Shiga**	**Saporin**	**Ricin**
ARG	ARG167	ARG170	ARG177	ARG180
GLU	GLU164	GLU167	GLU174	GLU177
TYR	TYR74	TYR77	TYR73	TYR80
TYR	TYR113	TYR114	TYR123	TYR123

As there is a considerable amount of published data relating to the inhibition of ricin, this compound was selected as the main candidate for the study into potential inhibitors of RIPs. However, it will be apparent to a person skilled in the art that the information described herein could equally apply to other RIPs, such as abrin, Shiga and saporin.

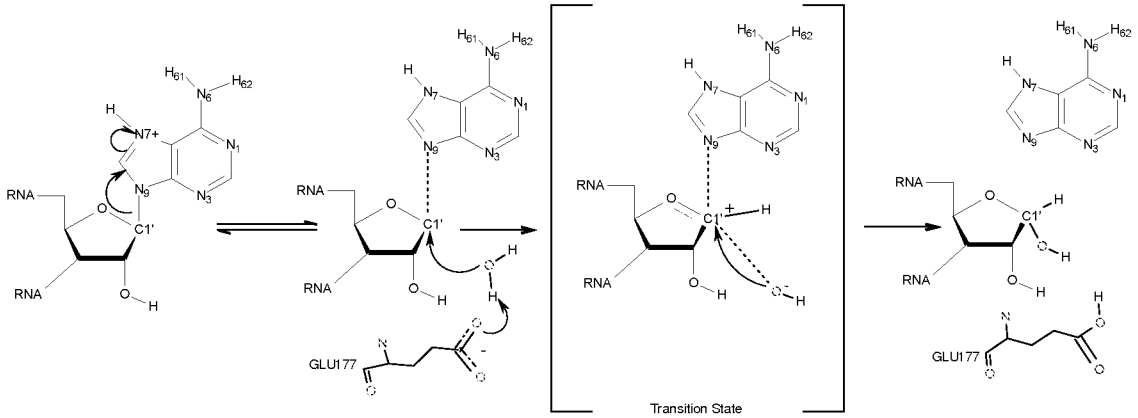
The reaction simulation was carried out using the hybrid Quantum Mechanical-Molecular Mechanical (QM/MM) approach with an in-house computer software program named Free Energies from Adaptive Reaction Coordinate Forces (FEARCF).[3,4,9,10] This approach allows the reacting system to dynamically sample the high energy regions (including the transition state) of the reaction potential energy surface by using a biasing potential that is generated by the system's own dynamics. The contents of these publications are also specifically incorporated herein. All simulations were carried out using the CHARMM program with the SCC-DFTB[5] level of theory.

Examples:

The starting structure for ricin was obtained from the PDB file 1FMP, wherein ricin is bound to formycin monophosphate (FMP), a substrate analogue for ricin. The initial substrate structure was obtained from high resolution NMR studies of the ricin-saricin target loop (PDB ID : 1ZIG). The parent RNA loop was reduced to a total of 12 nucleic acid bases including the ricin target GAGA tetra loop. It was found that the model must have at least 12 bases to maintain the integrity of the RNA loop during the simulations.

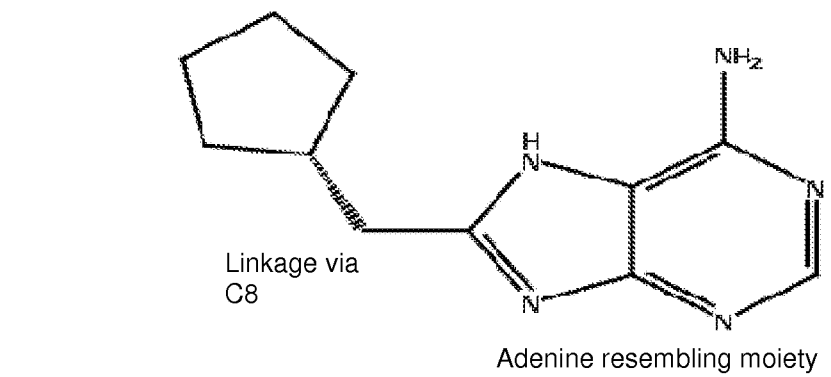
The target adenine in this loop was manually flipped (as proposed by various base flipping mechanisms) to facilitate its docking to the RTA binding site. Subsequently, the substrate loop was manually docked to the RTA binding site as guided by the binding of FMP. After a few nanoseconds of classical Molecular Dynamics (MD) simulation of the substrate: ricin complex, a snap shot of this system was taken as the starting structure for a QM/MM dynamics simulation. After a few hundred picoseconds of QM/MM equilibration, reaction simulations were carried out as mentioned earlier. The length of the C1'-N9 bond (susceptible glycosidic bond) and the length of the forming bond between the incoming OH^- nucleophile and C1' were used as the reaction coordinates in the reaction simulations. The starting structure of the substrate: ricin complex is shown in Figure 1.

The mechanism proposed in this study for the ricin-catalysed RNA depurination reaction is shown below. The major steps in the reaction mechanism are: (i) reversible cleavage of the C1'-N9 bond, (ii) activation of the catalytic water molecule and generation of the OH^- nucleophile, (iii) formation of the transition state (TS), (iv) permanent departure the adenine base, attack by the OH^- at C1' and formation of the final products.



Mechanism of the ricin-catalysed adenine hydrolysis reaction as elucidated by computer simulations

From the reaction simulations, a reaction-surface was obtained and this was used to identify the transition state. Based on this knowledge, a molecular core that resembles the transition state structure in size, shape, functional groups/molecular descriptors, binding pattern and electrostatic surface potential was designed to identify transition state analogue inhibitors for ricin. The transition state structure with its electrostatic surface potential (ESP) mapped to the electron density is shown in Figure 2. Unlike possible transition state structures which have previously been described for ricin, which exclude the incoming hydroxyl that displaces the adenine base that is leaving, the transition state structure of the present invention includes the sugar, base and hydroxyl group. This molecular triad (of the transition state) was used to calculate the electron density distribution of the transition state and the ESP. It was hypothesized that compounds having this structure should be able to bind to the active site of ricin with a very high affinity.



Schematic representation of the newly designed molecular core

The molecular core is bipartite and has an adenine resembling moiety and a ribose resembling moiety. It was found that any linkage via the N9 position of the adenine resembling moiety to the sugar resembling moiety jeopardizes the preferred (matching to the transition state) ESP of the new molecule. Therefore, in this molecular core, the connection between the adenine resembling moiety and the sugar resembling moiety was designed to be via the C8 of the adenine resembling moiety, so as to preserve the desired ESP. The molecular core described herein is far less reactive than previously suggested structures as it does not have any kind of linkage between C1' and N9. This C8 linkage is not found in any of the previously proposed bipartite ricin inhibitors.

A pharmacophore was then designed based on the molecular core and chemical databases were searched to identify potential ricin inhibitors. The identified molecules were docked to the ricin binding site using extra precision docking algorithms (Schrodinger molecular modelling package). Strong-binding conformations of these molecules that mimic the geometry of the transition state were then subjected to an ESP test. It was found that the compounds identified herein (Figure 3) have higher binding affinities than even the best known ricin inhibitor, 9OG (Table 2).

Table 2: Docking results for known ricin inhibitors

Known Inhibitors	Docking Score	IC 50 (nM)
FMP	-9.69	
9OG	-5.54	4.00E+05
Guanine	-4.28	9.00E+05
7DG	-2.30	2.80E+06

Figure 4 depicts the binding of the new inhibitors to RTA. Each 2D ligand interaction diagram depicts each ligand in the RTA binding site. Binding of the adenine moiety of these ligands is identical to the binding of the leaving (adenine) group in the transition state structure to RTA. Depending on its structure, each ligand shows a unique binding pattern to RTA for its ribose resembling moiety.

The X-ray crystal structures of other RIPs (abrin, Shiga and saporin) were obtained from the protein data bank and their binding sites were compared with that of ricin (Figure 5).

The ricin inhibitors identified above were docked to abrin, Shiga and saporin and the pose that was most similar to the pose of the transition state in the ricin binding site was selected for each inhibitor. In some cases, no similar pose was obtained. However, a person skilled in the art will realise that this does not necessarily mean that a ricin-TS-like-pose is not possible. It might be the case that binding sites of these enzymes were “pre-defined” for another inhibitor or for the apo enzyme, but not for the transition state. The initial docking results are presented in Figures 6 to 8. These promising initial results show the potency of the compounds identified herein as new inhibitors against abrin, saporin and Shiga toxins.

The methodology described herein differs from conventional high throughput screening (HTS), where millions of compounds are analyzed to identify potential leads. This is usually performed using a pharmacophore that is designed based on the structure of the active site (structure-based-design). In the present strategy, the pharmacophore was designed based on a molecular core that mimics the transition state of the reaction, and a combined-screening (pharmacophore and ESP) strategy was used to search for and/or design transition state analogue inhibitors which could be potential ricin, abrin, Shiga or saporin

inhibitors. Furthermore, the present strategy also requires the inhibitors to have the 8th position of the base moiety connected to the sugar-like moiety, whereas previously proposed inhibitors use the 9th position of the base for this purpose.

References

(1) Olsnes, S.; Pihl, A. *Biochemistry* 1973, *12*, 3121-3126.

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(6) Wales R.; Richardson, P. T.; Robers, L. M.; Woodland, H. R.; et al. *J Biol Chem.* 1991, *266*, 19172–79.

(7) Aplin PJ; Eliseo T. *Med. J. Aust.* 1997, *167(5)*: 260–261. PMID 9315014.

(8) Fodstad, O.; Olsnes, S.; Pihl, A. *Cancer Res.* 1977, *37,* 4559-4567.

(9) Naidoo, K. J. *Physical Chemistry Chemical Physics* **14**, 9026-9036, doi:10.1039/c2cp23802k (2012).

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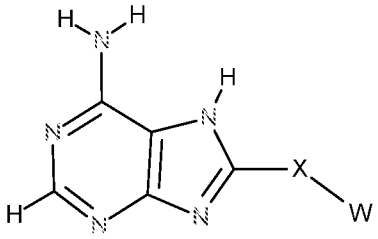
CLAIMS

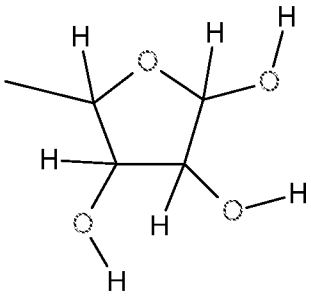
1. A compound for use in inhibiting ricin, abrin, Shiga or saporin, which has a bipartite configuration comprising an aromatic heterocyclic structure resembling an adenine moiety in size and shape connected at the C8 position to a non-aromatic cyclic ring structure resembling a ribose moiety in size and shape.

2. A compound according to claim 1, which has the formula (I):

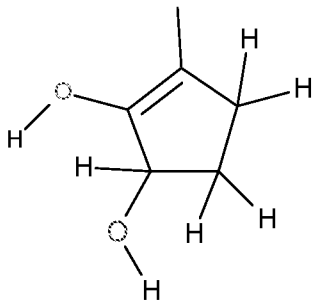


(I)

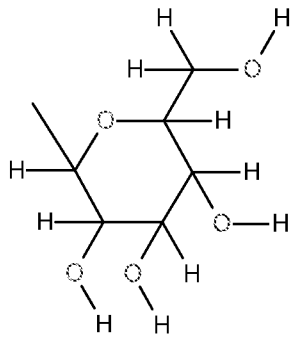
where X = -S-, -O-, -CH_2-, -NH-, -PH-, -O-Y-, -CH_2-Y-, -NH-Y-, -PH-Y, or -S-Y;
Y = -S-, -O-, -CH_2-, -NH-, or -PH-; and
W = a 5- or 6-membered aromatic or non-aromatic cyclic ring selected from any one of formulae (II) to (XX) or a derivative thereof:



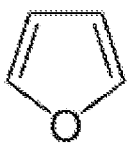
(II)



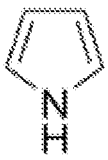
(III)



(IV)



(V)



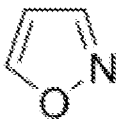
(VI)

(VII)

(VII)

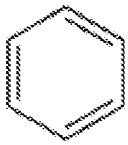
(IX)

(X)



(XI)

(XII)



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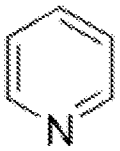
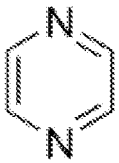
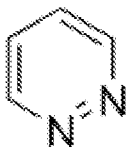


(XIV)

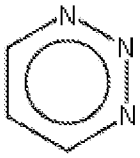


(XV)

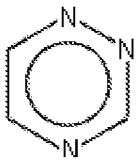
(XVI)



(XVII)



(XVIII)



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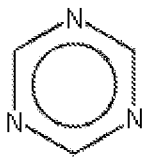
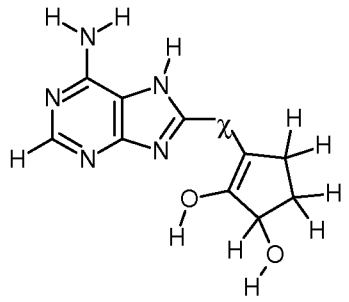


(XX)

or an isomer, tautomer, pharmaceutically acceptable salt, ester or prodrug thereof.

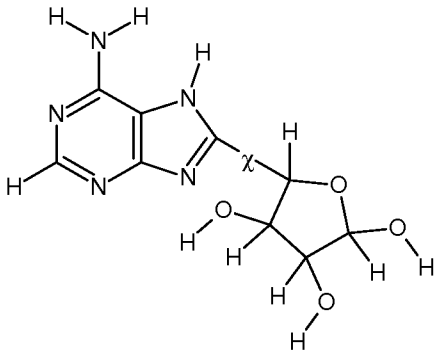
3. A compound according to claim 2, which has the formula (XXI):



(XXI)

where χ is selected from any one of -(S)-, -(O)-, -(CH_2)-, –(NH)-, or –(PH);
or an isomer, tautomer, pharmaceutically acceptable salt, ester or prodrug thereof.

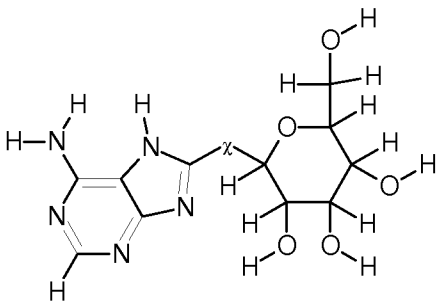
4. A compound according to claim 2, which has the formula (XXII):



(XXII)

where χ is selected from any one of -(S)-, -(O)-, -(CH_2)-, –(NH)-, or –(PH);
or an isomer, tautomer, pharmaceutically acceptable salt, ester or prodrug thereof.

5. A compound according to claim 2, which has the formula (XXIII):

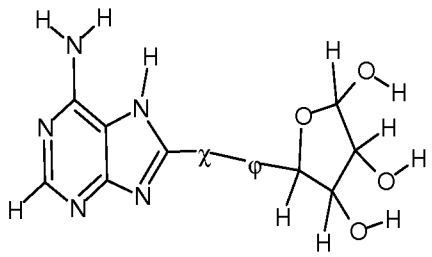


(XXIII)

where χ is selected from any one of -(S)-, -(O)-, -(CH_2)-, –(NH)-, or –(PH);

or an isomer, tautomer, pharmaceutically acceptable salt, ester or prodrug thereof.

6. A compound according to claim 2, which has the formula (XXIV):



(XXIV)

where

χ is selected from any one of -(S)-, -(O)-, -(CH_2)-, –(NH)-, or –(PH); and

φ is selected from any one of -(S)-, -(O)-, -(CH_2)-, –(NH)-, or –(PH),

or an isomer, tautomer, pharmaceutically acceptable salt, ester or prodrug thereof.

7. A compound according to any one of claims 1 to 6, for use in controlling non-specific cytotoxicity due to ricin, abrin, Shiga or saporin.

8. A compound according to claim 7, for use in a method of treating psoriasis, autoimmune diseases, cancer or HIV infection, wherein the method of treatment comprises administering ricin, abrin, Shiga or saporin and the compound to a patient.

9. A compound according to claim 8, wherein the method of treatment comprises administering the compound and ricin, abrin, Shiga or saporin simultaneously, sequentially or separately.

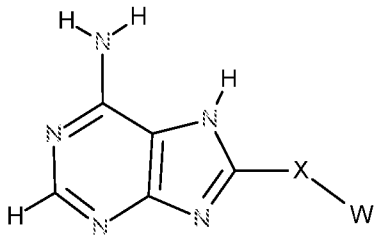
10. The use of a compound having a bipartite configuration comprising an aromatic heterocyclic structure resembling an adenine moiety in size and shape connected at the C8 position to an aromatic or non-aromatic cyclic ring structure resembling a ribose moiety in size and shape, in a method of manufacturing a medicament for use in a method of inhibiting ricin, abrin, Shiga or saporin.

11. The use of a compound having a bipartite configuration comprising an aromatic heterocyclic structure resembling an adenine moiety in size and shape connected at the C8 position to an aromatic or non-aromatic cyclic ring structure resembling a

ribose moiety in size and shape, in a method of manufacturing a medicament for use in a method of treating non-specific cytotoxicity.

12. The use according to claim 11, wherein the non-specific cytotoxicity is from treating psoriasis, autoimmune diseases, cancer or HIV/AIDS with ricin, abrin, Shiga or saporin.

13. The use according to any one of claims 10 to 12, wherein the compound is a compound of formula (I):

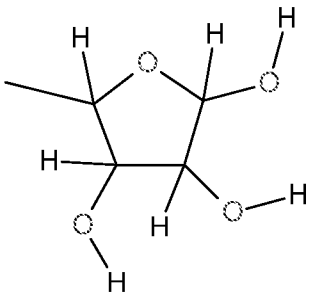


(I)

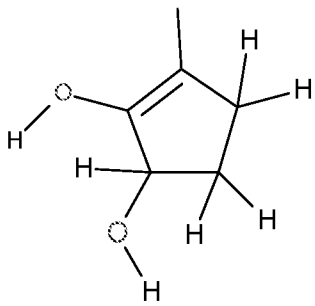
where X = -S-, -O-, -CH_2-, -NH-, -PH-, -O-Y-, -CH_2-Y-, -NH-Y-, -PH-Y, or -S-Y;

Y = -S-, -O-, -CH_2-, -NH-, or -PH-; and

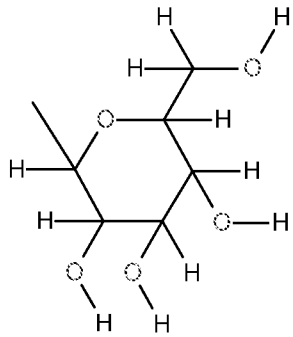
W = a 5- or 6-membered aromatic or non-aromatic cyclic ring selected from any one of formulae (II) to (XX) or a derivative thereof:



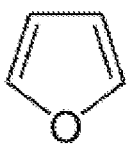
(II)



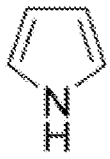
(III)



(IV)



(V)



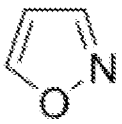
(VI)

(VII)

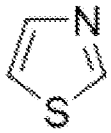
(VII)

(IX)

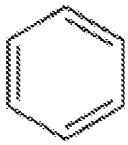
(X)



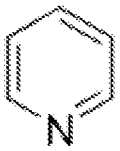
(XI)



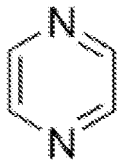
(XII)



(XIII)

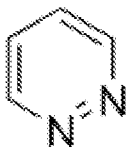


(XIV)

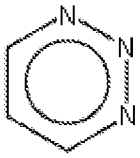


(XV)

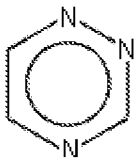
(XVI)



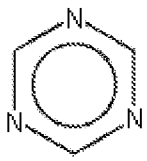
(XVII)



(XVIII)



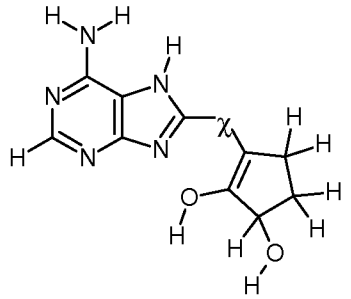
(XIX)



(XX)

or an isomer, tautomer, pharmaceutically acceptable salt, ester or prodrug thereof.

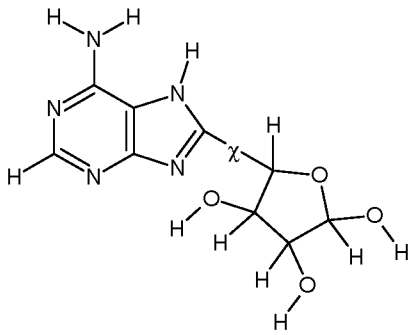
14. The use according to claim 13, wherein the compound is a compound of formula (XXI):



(XXI)

where χ is selected from any one of -(S)-, -(O)-, -(CH_2)-, –(NH)-, or –(PH),
or an isomer, tautomer, pharmaceutically acceptable salt, ester or prodrug thereof.

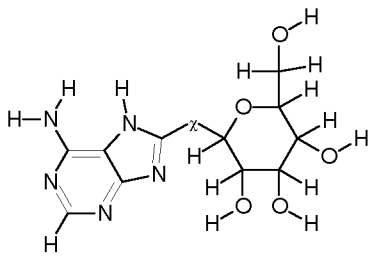
15. The use according to claim 13, wherein the compound is a compound of formula (XXII):



(XXII)

where χ is selected from any one of -(S)-, -(O)-, -(CH_2)-, –(NH)-, or –(PH),
or an isomer, tautomer, pharmaceutically acceptable salt, ester or prodrug thereof.

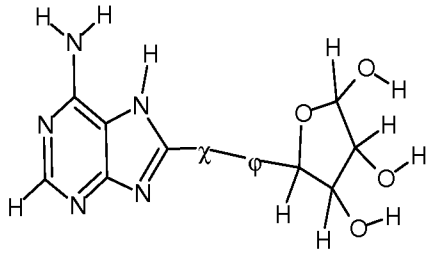
16. The use according to claim 13, wherein the compound is a compound of formula (XXIII):



(XXIII)

where χ is selected from any one of -(S)-, -(O)-, -(CH_2)-, –(NH)-, or –(PH),
or an isomer, tautomer, pharmaceutically acceptable salt, ester or prodrug thereof.

17. The use according to claim 13, wherein the compound is a compound of formula (XXIV):



(XXIV)

where

χ is selected from any one of -(S)-, -(O)-, -(CH_2)-, –(NH)-, or –(PH); and

φ is selected from any one of -(S)-, -(O)-, -(CH_2)-, –(NH)-, or –(PH),

or an isomer, tautomer, pharmaceutically acceptable salt, ester or prodrug thereof.

18. A method for identifying a compound which is effective for inhibiting ricin, abrin, Shiga or saporin, the method comprising the step of identifying a test compound which:

i) has an adenine resembling moiety and a ribose resembling moiety which are connected to each other via the C8 of the adenine resembling moiety;

ii) resembles the shape, size and binding pattern of the transition state structure of the ricin-catalyzed reaction; and

iii) resembles the electrostatic surface potential of the transition state structure of the ricin-catalyzed reaction;

and measuring the effect of the test compound on ricin-, abrin-, Shiga- or saporin-mediated protein synthesis inhibition, wherein a reduction of ricin-, abrin-, Shiga- or saporin-mediated protein synthesis inhibition in the presence of the test compound indicates that the test compound is a ricin, abrin, Shiga or saporin inhibitor.

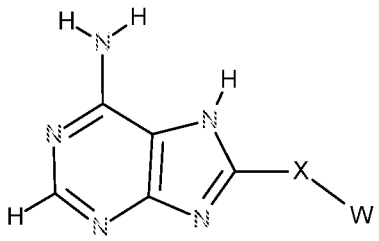
19. A pharmaceutical composition comprising a compound of any one of claims 1 to 9 and a pharmaceutically acceptable excipient or additive.

20. A pharmaceutical composition according to claim 19, for use in inhibiting ricin, abrin, Shiga or saporin toxicity in a subject.

21. A pharmaceutical composition according to either of claims 19 or 20, for use in treating psoriasis, an autoimmune disease, cancer, HIV infection or AIDS.

22. A method of inhibiting ricin, abrin, Shiga or saporin in a subject, the method comprising the step of administering to the subject a therapeutically effective amount of a compound which has a bipartite configuration comprising an aromatic heterocyclic structure resembling an adenine moiety in size and shape connected at the C8 position to a non-aromatic cyclic ring structure resembling a ribose moiety in size and shape, and wherein the compound is an inhibitor of ricin, abrin, Shiga or saporin.

23. A method according to claim 22, wherein the compound is of formula (I):

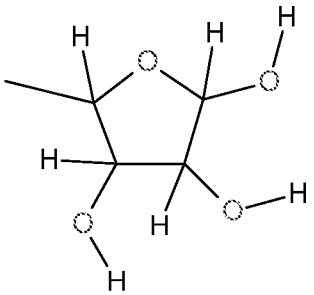


(I)

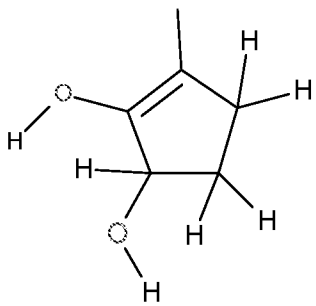
where X = -S-, -O-, -CH_2-, -NH-, -PH-, -O-Y-, -CH_2-Y-, -NH-Y-, -PH-Y, or -S-Y;

Y = -S-, -O-, -CH_2-, -NH-, or -PH-; and

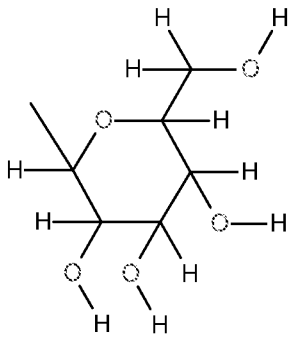
W = a 5- or 6-membered aromatic or non-aromatic cyclic ring selected from any one of formulae (II) to (XX) or a derivative thereof:



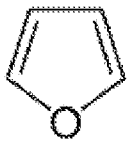
(II)



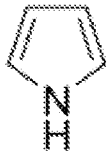
(III)



(IV)



(V)

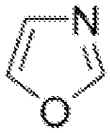


(VI)

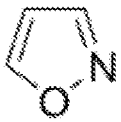
(VII)

(VII)

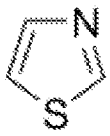
(IX)



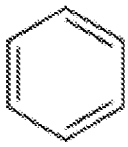
(X)



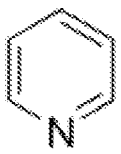
(XI)



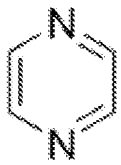
(XII)



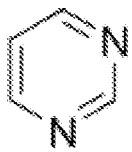
(XIII)



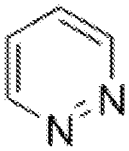
(XIV)



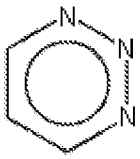
(XV)



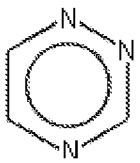
(XVI)



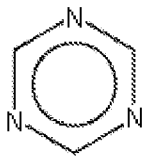
(XVII)



(XVIII)



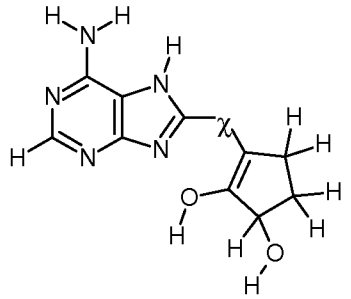
(XIX)



(XX)

or an isomer, tautomer, pharmaceutically acceptable salt, ester or prodrug thereof.

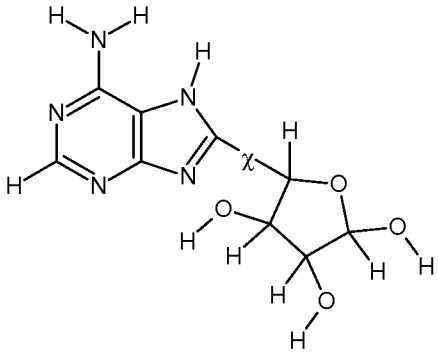
24. A method according to claim 23, wherein the compound has the formula (XXI):



(XXI)

where χ is selected from any one of -(S)-, -(O)-, -(CH_2)-, –(NH)-, or –(PH).

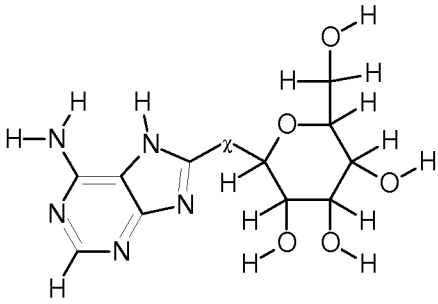
25. A method according to claim 23, wherein the compound has the formula (XXII):



(XXII)

where χ is selected from any one of -(S)-, -(O)-, -(CH_2)-, –(NH)-, or –(PH).

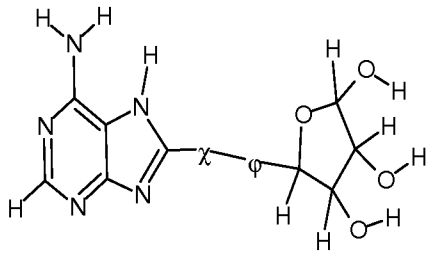
26. A method according to claim 23, wherein the compound has the formula (XXIII):



(XXIII)

where χ is selected from any one of -(S)-, -(O)-, -(CH_2)-, –(NH)-, or –(PH).

27. A method according to claim 23, wherein the compound has the formula (XXIV):



(XXIV)

where

χ is selected from any one of -(S)-, -(O)-, -(CH_2)-, –(NH)-, or –(PH); and

φ is selected from any one of -(S)-, -(O)-, -(CH_2)-, –(NH)-, or –(PH).

28. A method according to any one of claims 22 to 27, wherein ricin, abrin, Shiga or saporin is additionally administered to the subject.

29. A method according to claim 28, wherein the ricin, abrin, Shiga or saporin is administered to treat psoriasis, an autoimmune disease, cancer, HIV infection or AIDS.

30. A method according to either of claims 28 or 29, wherein the compound and ricin, abrin, Shiga or saporin are administered simultaneously, sequentially or separately.

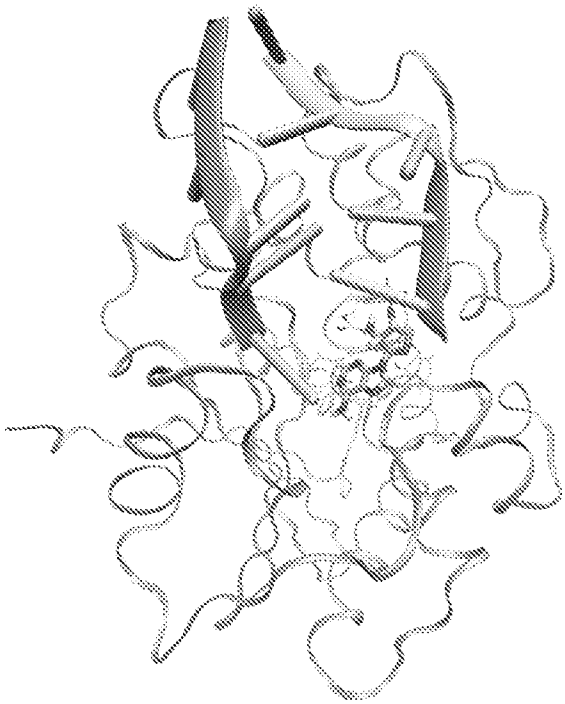


Figure 1

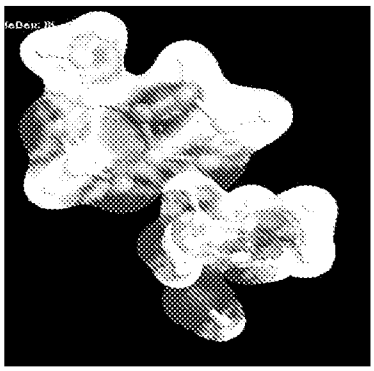


Figure 2

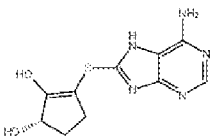
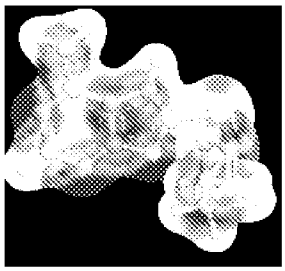
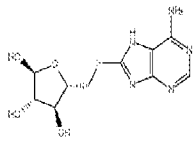
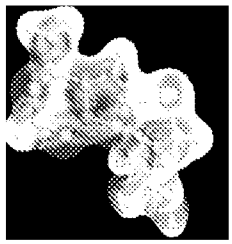
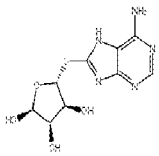
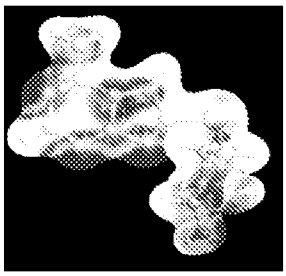
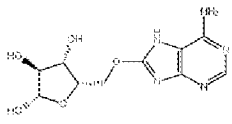
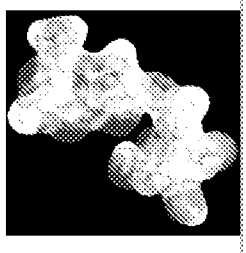
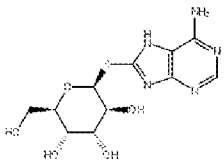
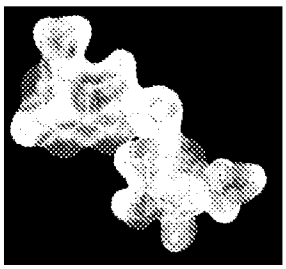
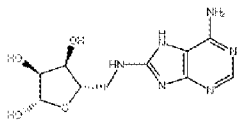
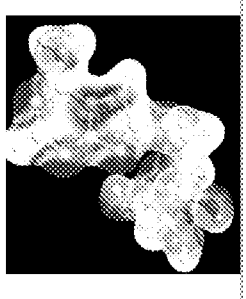
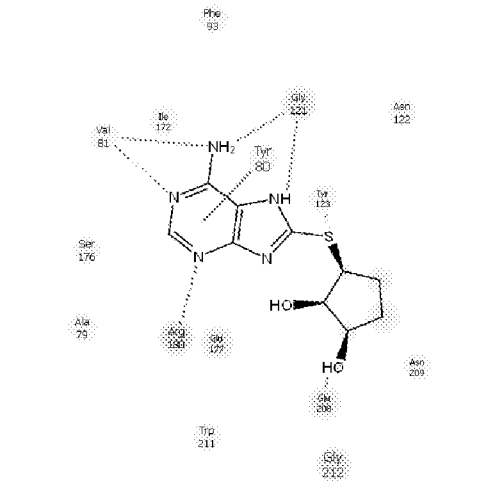
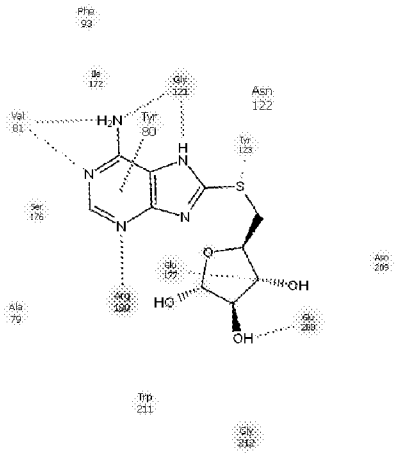
New Inhibitor	ESP	Score	New Inhibitor	ESP	Score
 SCRU-RTAI- 1		-11.33	 SCRU-RTAI- 4		-12.34
 SCRU-RTAI- 2		-11.66	 SCRU-RTAI- 5		-12.26
 SCRU-RTAI- 3		-12.05	 SCRU-RTAI- 6		-11.00

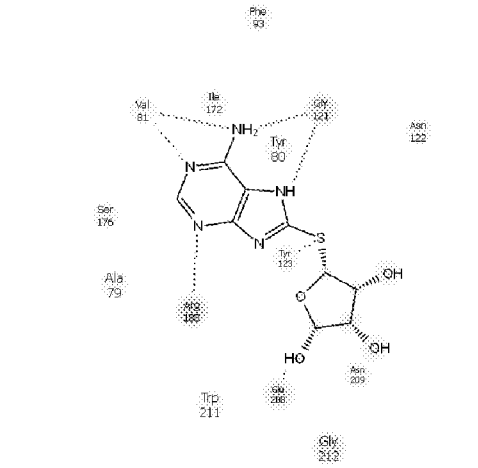
Figure 3



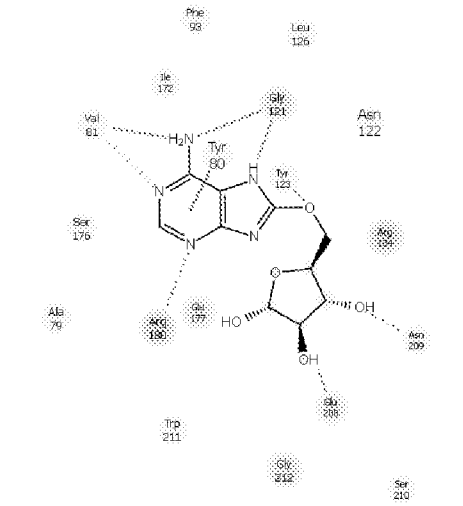
SCRU-RTAI- 1



SCRU-RTAI- 4



SCRU-RTAI- 2



SCRU-RTAI- 5

Figure 4A

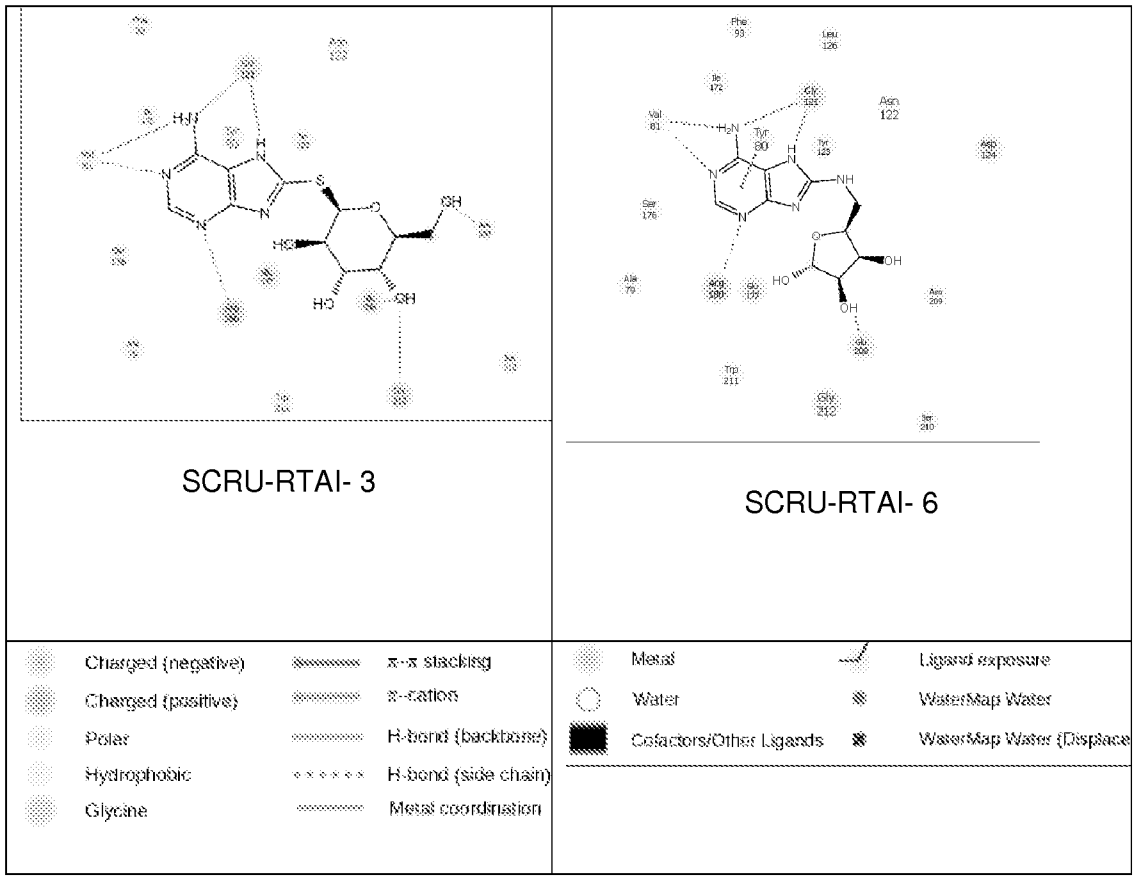

SCRU-RTAI- 3
SCRU-RTAI- 6
Charged (negative)
Charged (positive)
Polar
Hydrophobic
Glycine
π-π stacking
π-cation
H-bond (backbone)
H-bond (side chain)
Metal coordination
Metal
Water
Cofactors/Other Ligands
Ligand exposure
WaterMap Water
WaterMap Water (Displace

Figure 4B

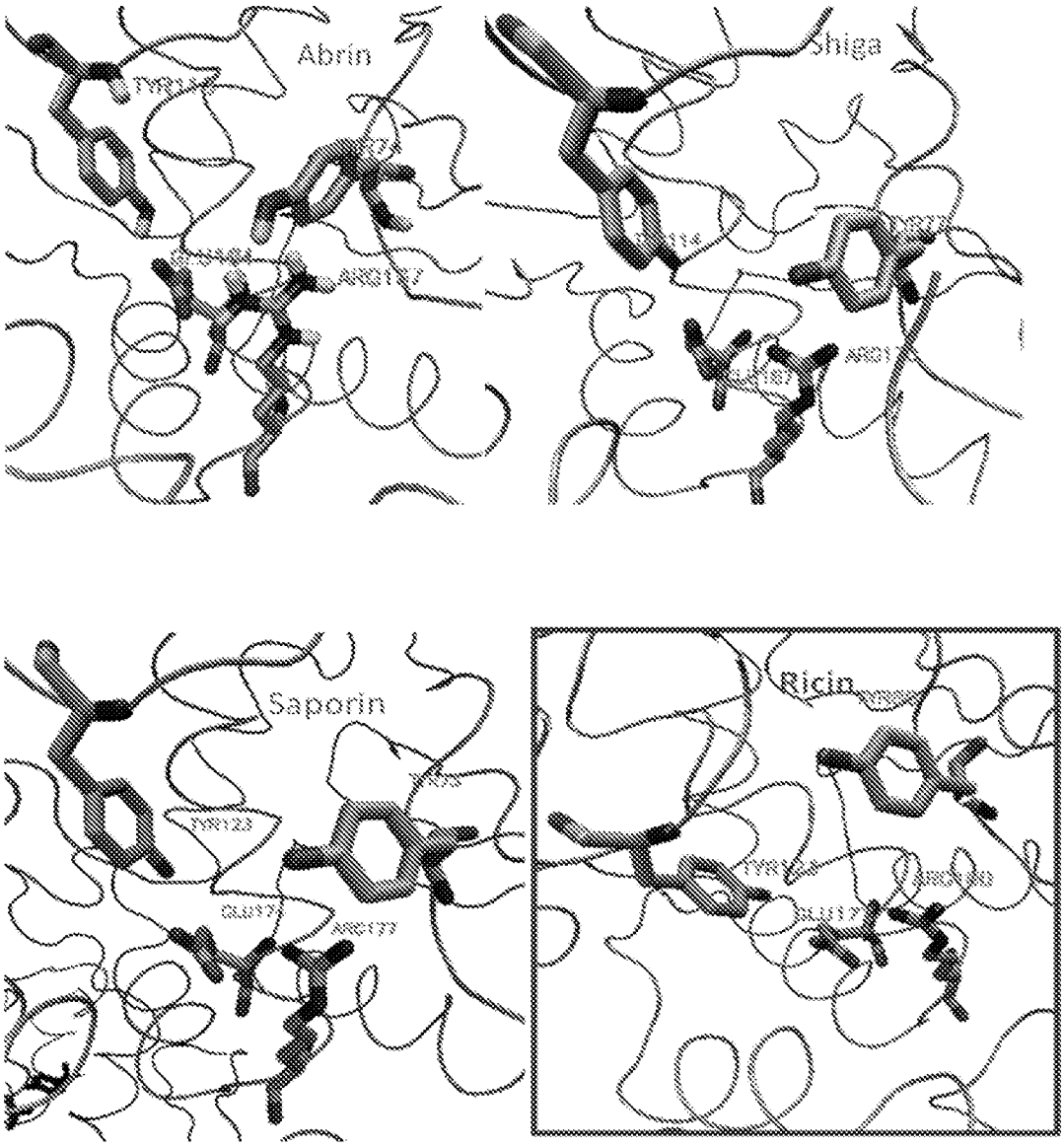
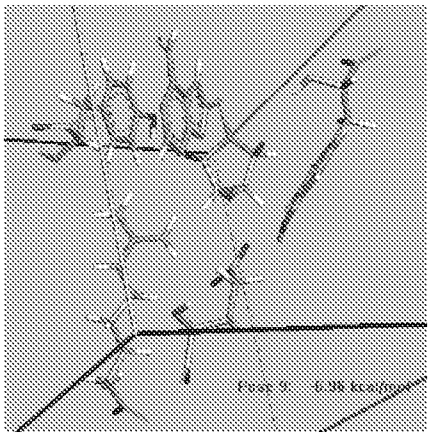
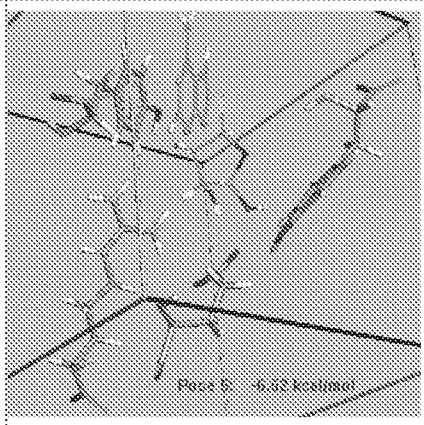

Abrin
TYR114
ARG177
Shiga
TYR114
ARG177
Saporin
TYR123
GLU177
ARG177
Ricin
TYR80
GLU177

Figure 5

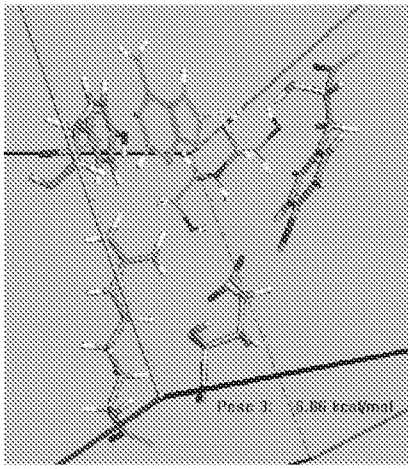
ABRIN



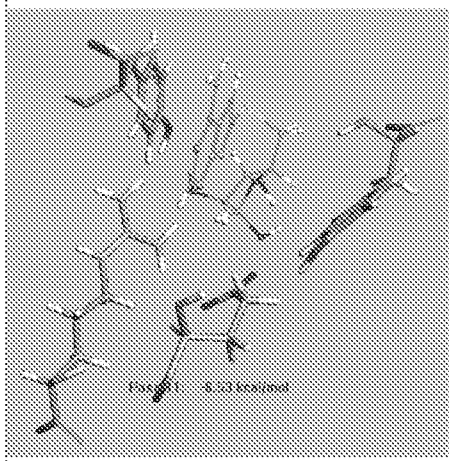
SCRU-1 -6.96



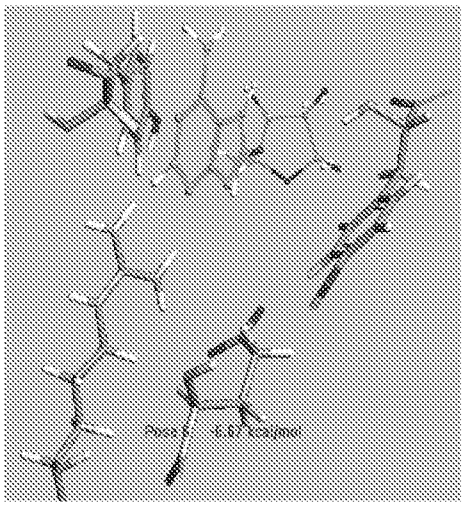
SCRU-2 -6.62



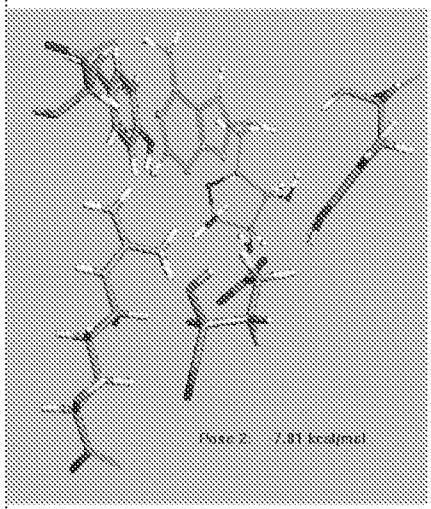
SCRU-3 -6.86



SCRU-4 -6.53



SCRU -5 -6.67



SCRU- 6 -7.01

Figure 6

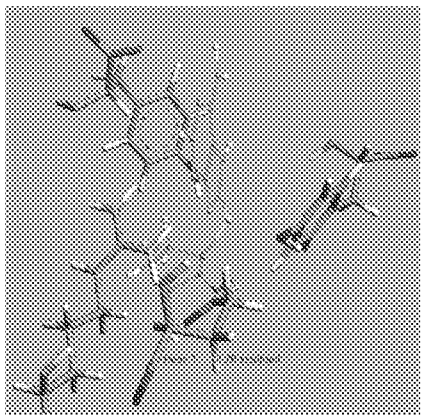
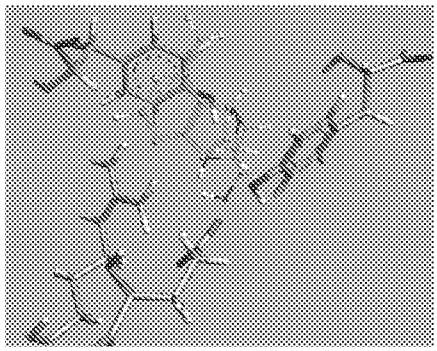
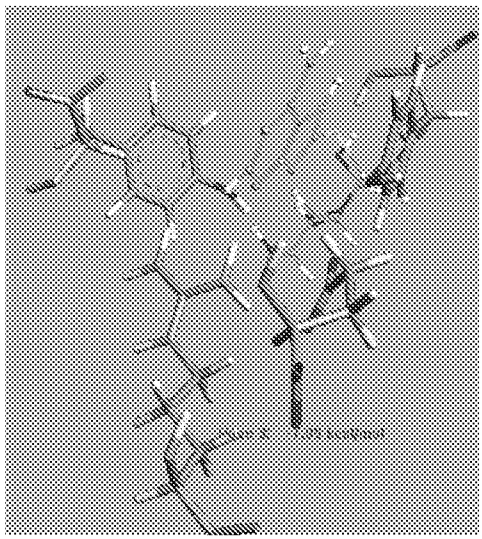
SHIGA			
SCRU-1	 -8.70 kcal/mol	**SCRU-4**	No similar pose
SCRU-2	 -7.73 kcal/mol	**SCRU-5**	No similar pose
SCRU-3	 -7.09 kcal/mol	**SCRU-6**	No similar pose

Figure 7

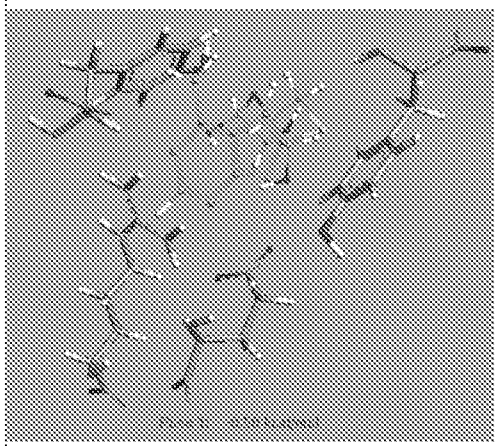
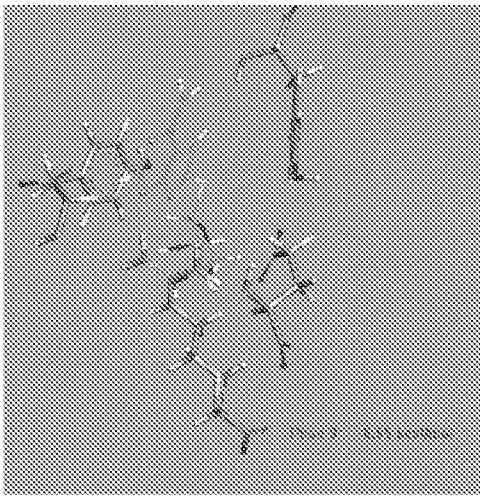
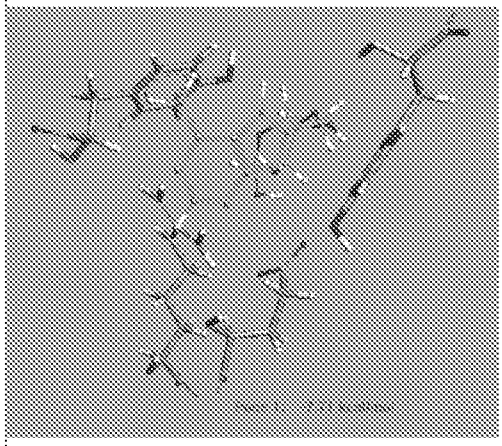
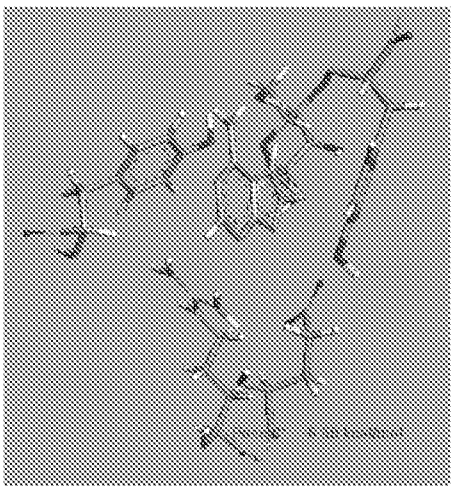
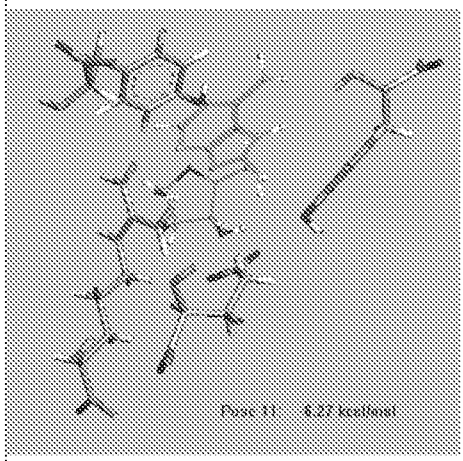
Saporin			
SCRU-1	No similar pose	**SCRU-4**	 -8.50 kcal/mol
SCRU-2	 -6.55 kcal/mol	**SCRU-5**	 -7.71 kcal/mol
SCRU-3	 -6.60 kcal/mol	**SCRU-6**	 -6.27 kcal/mol

Figure 8