NATURAL
PRODUCT
DISCOVERY
SYSTEM

NADI©

rapid
no-fuss
cost-effective
natural product
drug discovery

Leveraging Malaysia's Biodiversity towards Value Creations using Bioinformatics

Habibah A Wahab, PhD
Malaysian Institute of Pharmaceuticals and Nutraceuticals,
Ministry of Science, Technology and Innovation
SAINS@USM, 11900, Penang
habibah@ipharm.gov.my

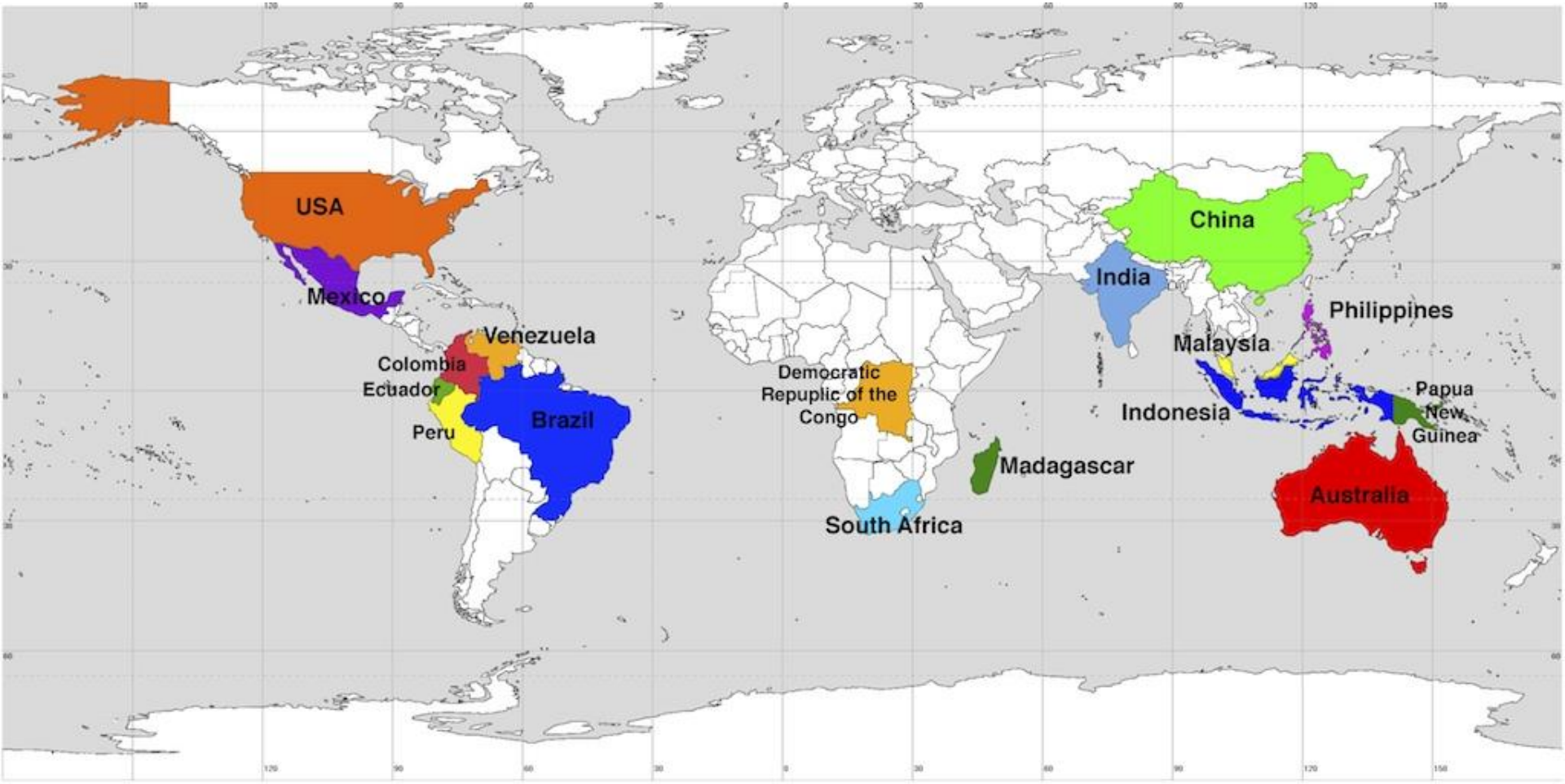
Pharmaceutical Design and Simulation Laboratory,
School of Pharmaceutical Sciences, USM
habibahw@usm.my

Shaharum Shamsuddin *D. Phil (Oxon.)*
Advance Molecular and Cellular Biology Laboratory
Deputy Dean
School of Health Sciences, USM
shaharum@kb.usm.my

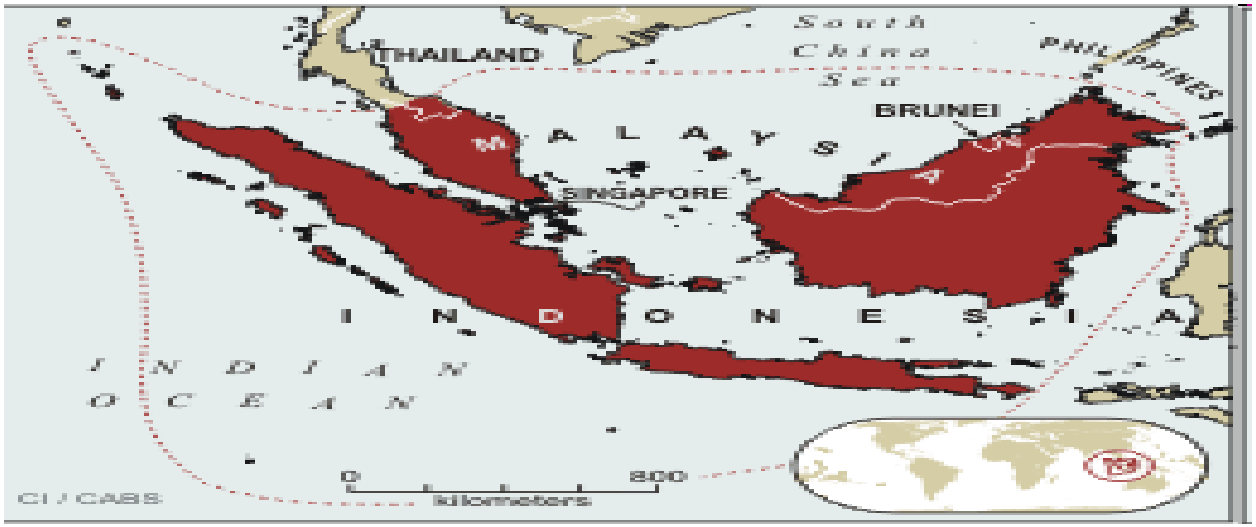
Institut Farmaseutikal dan Nutraseutikal Malaysia

Kementerian Sains, Teknologi dan Inovasi

World's Megadiversity



Biodiversity hotspot: Sundaland



Taxonomic Group	Species	Endemic Species	Percent Endemism
Plants	25,000	15,000	60.0
Mammals	380	172	45.3
Birds	769	142	18.5
Reptiles	452	243	53.8
Amphibians	244	196	80.3
Freshwater Fishes	950	350	36.8

Country	Mammals	Birds	Plants
Malaysia	337	746	15500

http://www.biodiversityhotspots.org/xp/hotspots/sundaland/Pages/biodiversity.aspx

Malaysia Biodiversity and National Biotechnology Policy

Mission Statement

- Innovation to create wealth by utilising and advancing biotechnology for socio-economic benefits of the nation in accordance with established social and ethical norms

Vision

- Position biotechnology as the new economic engine to enhance prosperity and wellness of the nation by 2020
- Through Healthcare, Industrial and Agriculture
- Enhance R&D and Tech Acquisition, Human Capital Development, Legal and Financial Structure

To optimise economic benefits from sustainable utilisation of the components of biological diversity;

IPHARM

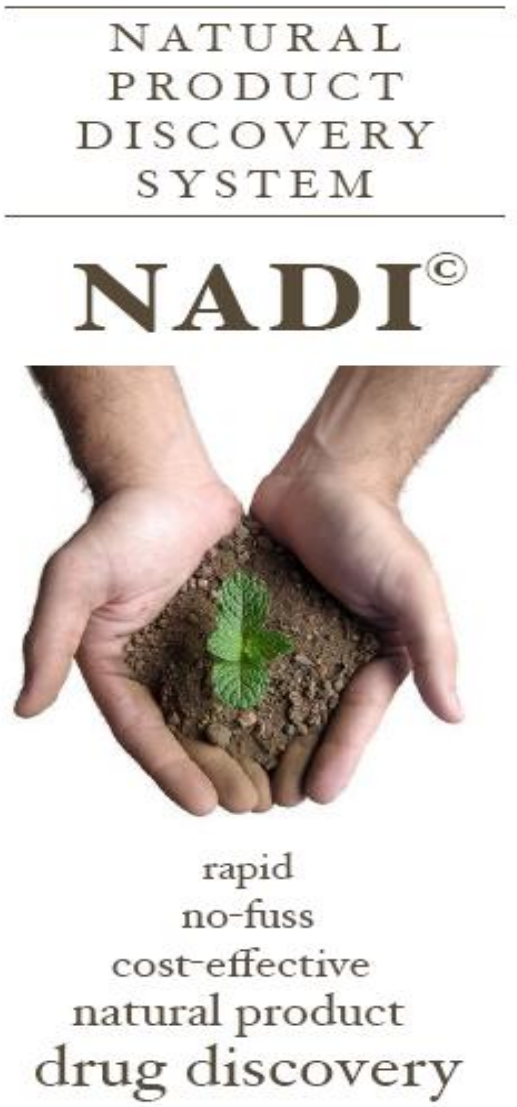
- Identification and Development of Bioactive Compounds
- Bioprocessing
- Pre-formulation for Product Development
- Screening of Bioactive Compounds
- Advanced Drug Delivery Systems

Wealth from plant biodiversity

- Food (through agriculture and harvest of natural population)
  - Crops, livestock, forestry and fish
  - Food products: fruits, vegetables, nuts
  - Food Additives: colourings, flavourings, preservatives
- Medicine
  - ~ 119 pure chemicals are extracted from < 90 species of higher plants and used as medicines throughout the world, for example caffeine, quinine, vincristine, vinblastin.
- Industry
  - Fibers for clothing; wood for shelter and warmth
  - Source of energy (biomass);
  - Industrial products: oils, lubricants, perfumes, fragrances, dyes, paper, waxes, rubber, latexes, resins, poisons
  - All these can be derived from various plant species.
- Tourism & Recreation
  - Biodiversity is a source of economical wealth for many regions of the world
  - Nature reserves, parks and forests
  - Ecotourism, National park, wetland resort

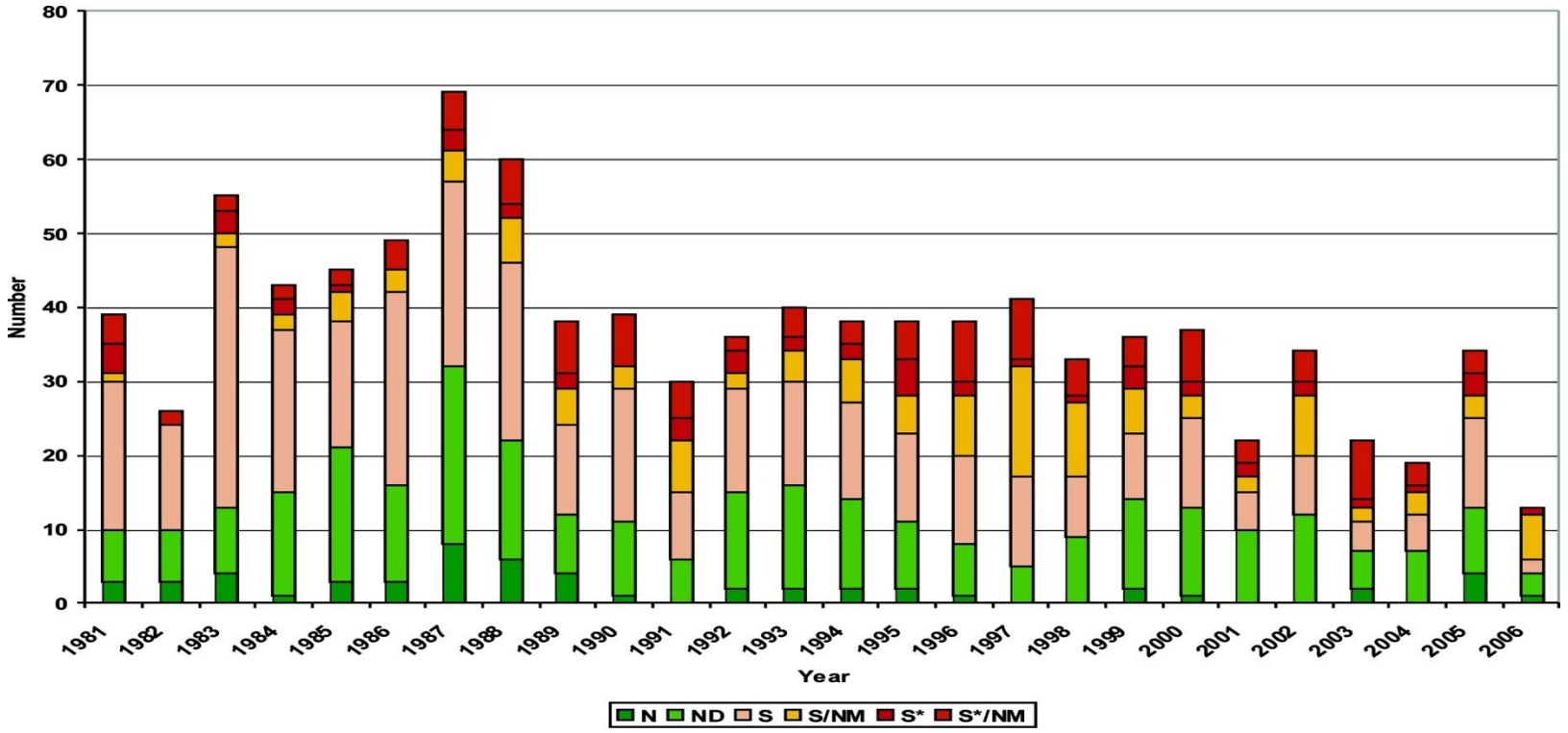
Natural Products **Di**scovery System (NADI) & Value creations

- Natural products
- Value creations
  - Pharmaceuticals
  - Nutraceuticals
  - Cosmeceuticals
  - Specialty chemicals



Natural product based pharmaceutical discovery

- The global pharmaceutical markets worth $770 billion in 2008 and expected to grow 4 to 6% in 2010 exceeding $825 billion following stable demand in 2009 (IMS report, June 2009).
- Natural products are established and long source of drug. 61% of the 877 small molecule new chemical entities introduced as drugs worldwide during 1981-2006 can be traced to or were inspired by natural products.



David J. Newman; Gordon M. Cragg; *J. Nat. Prod.* **2007,** 70, 461-477.

Natural Products: Source of Drugs (& medications)

COVER STORY
October 13, 2003
Volume 81, Number 41
CENEAR 81 41 pp. 77-78, 82-83, 86, 88-91
ISSN 0009-2347

REDISCOVERING NATURAL PRODUCTS

Cast aside for years, natural products drug discove appears to be reclaiming attention and on the verge comeback

A. MAUREEN ROUHI, C&EN WASHINGTON

The pharmaceutical industry's productivity continues to be disma state of affairs is due to many factors, and one may have been th diminished interest in natural products drug discovery as the indu embraced promising and exciting new technologies, particularly combinatorial chemistry.

However, the tide may be turning, for three reasons. First, combinatorial chemistry's promise to fill drug

Welcome to Science Online

The abstract or summary of the article you requested is below. By joining AAAS and becom receive member benefits, and support our mission to advance science and serve society. Clic pay-per-view

Science, Vol 310, Issue 5747, 451-453 , 21 October 2005
[DOI: 10.1126/science.1116364]

Perspectives

CHEMISTRY:

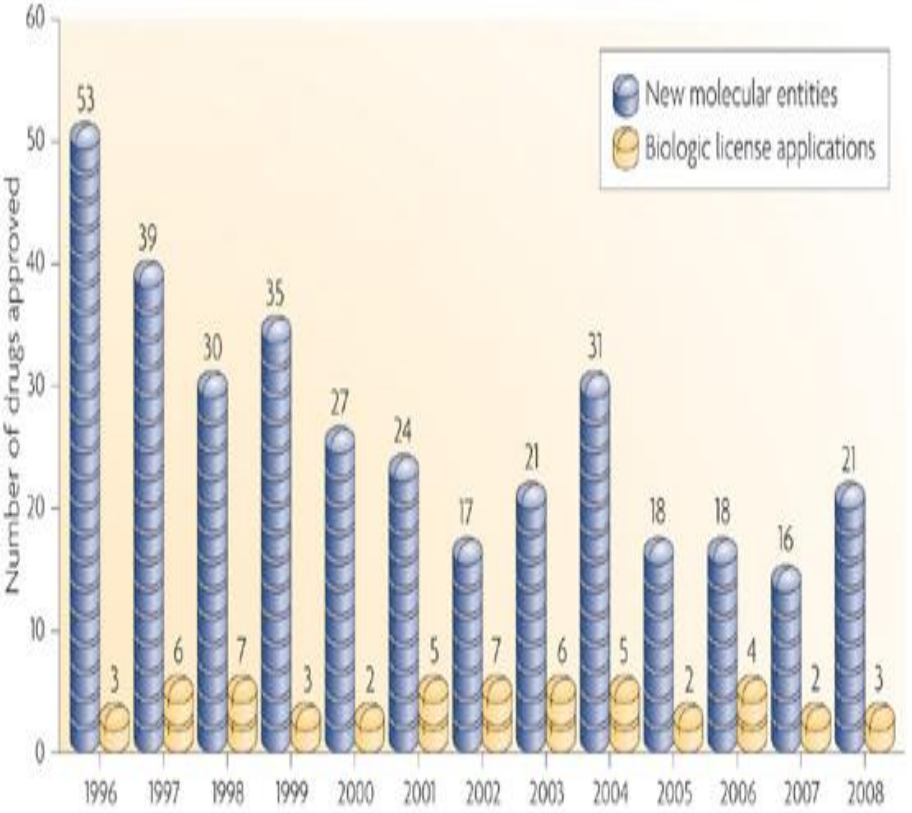
The Renaissance of Natural Products as Drug Candidat

Ian Paterson and Edward A. Anderson

In recent years, the use of natural products for drug discovery has declined in favor of combinatorial methods and the rapid generation of large libraries of potential lead compounds.

Done

Natural Product Drug Discovery: Opportunity



- ~250,000 flowering plant known , ~ 125K found in the tropical forests.
- Only ~1% of tropical species have been studied for their pharmaceutical potential.
- 2002-2006, 26 are plant derived.

Nature Reviews | Drug Discovery

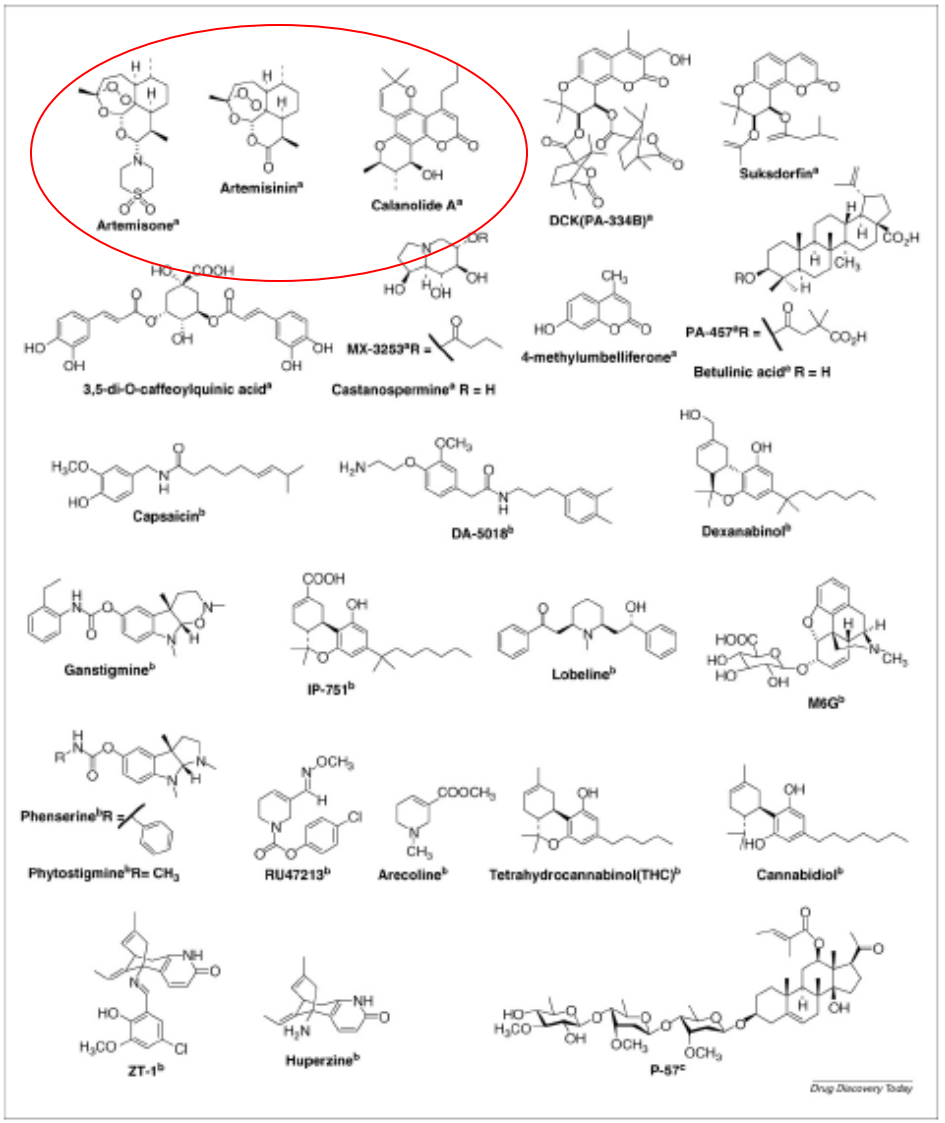


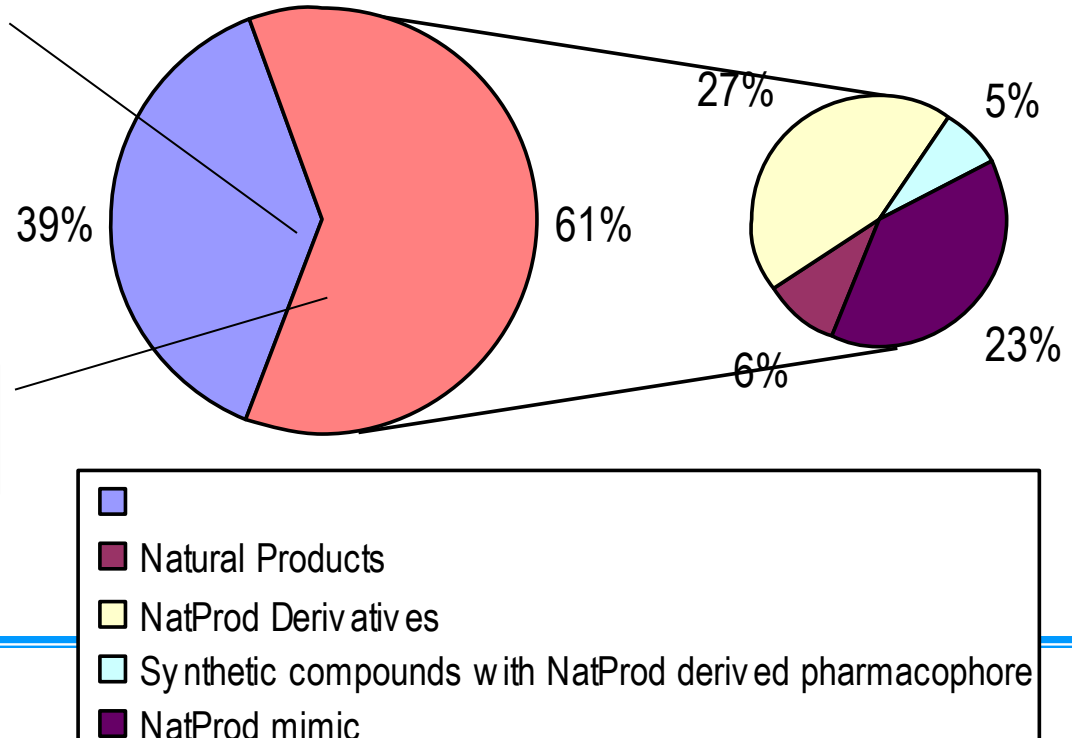
FIGURE 1
Plant-derived compounds launched in clinical trials. **(a)** Infectious and parasitic disease application, **(b)** pain and neurological disease application, **(c)** cardiovascular and metabolic disease application.

Natural Product Discovery: Opportunity

- Malaysia has > 15000 flowering species, 2000 with medicinal values
- Many compounds (vincristine, vinblastine, reserpine) in Malaysian natural products are current drugs in the market though not discovered in Malaysia.
- Herbal industry in Malaysia, RM8 billion/year – growing at 10% per year.

Used to treat 87% (48/55) of human diseases

Antibacterials 78%
Anticancer 74%



David J. Newman* and Gordon M. Cragg *J. Nat. Prod.*, **70** (3), 461 -477, 2007"

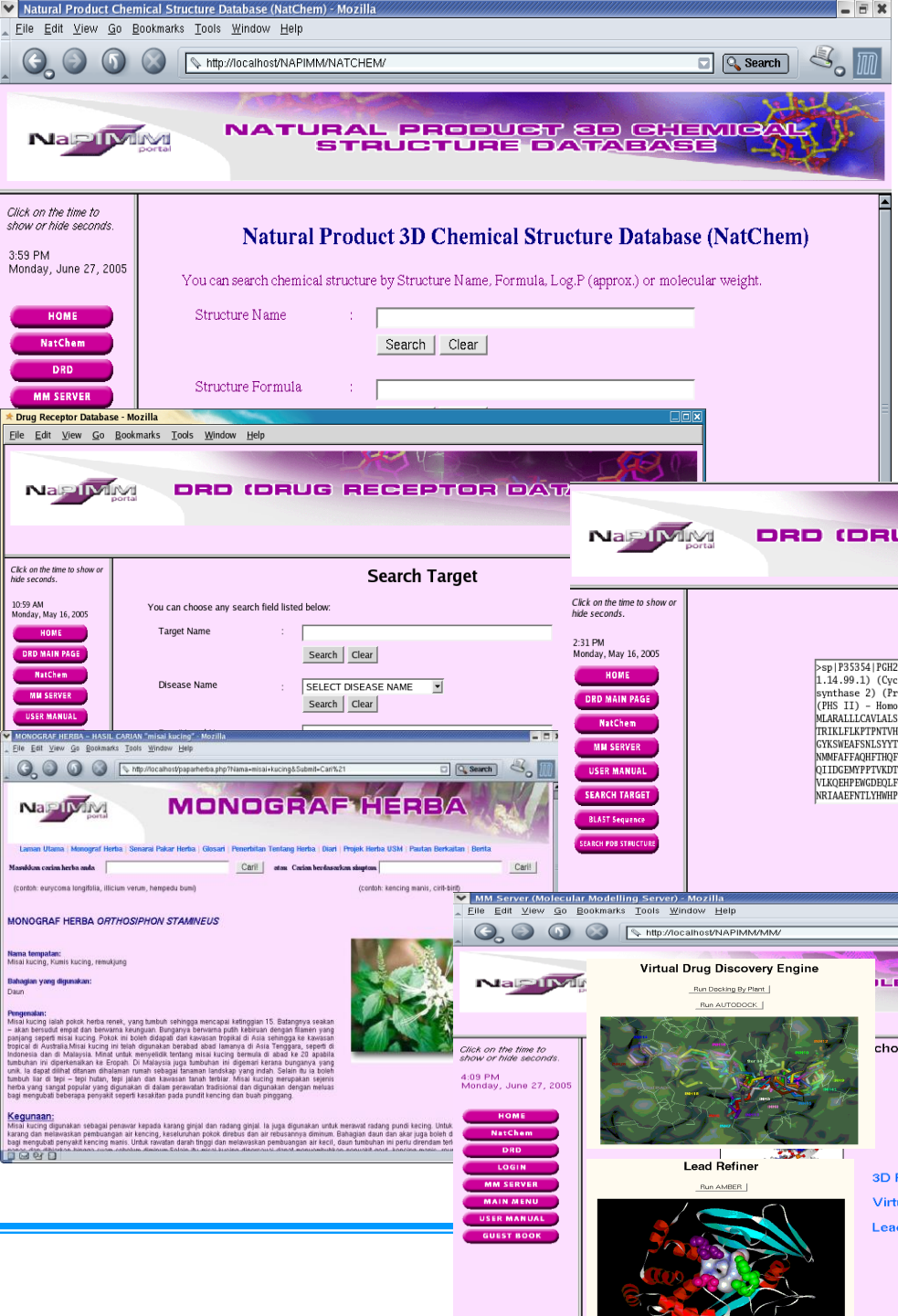
Challenges

- Approaches to natural discovery:
  - random selection followed by chemical screening,
  - random selection followed by one or more biological assays, follow-up of biological activity reports,
  - follow-up of ethnomedical (traditional medicine) use of plants

- Challenges:
  - Tedious isolation and characterization of natural products and heavy reliance on good screening and bioassays
  - The discovery of compounds that are cytotoxic or have other unsuitable properties.
  - Reinventing the wheels
- Problems:
  - not enough availability. can be overcome by semi-synthesis/synthesis or using tissue-culture techniques
  - Isolated bioactive compounds are known compounds

NADI: Bioinformatic approach to complementing Natural Product Research

- NADI applications:
  - One stop centre for information
  - Plant selections
    - Ethnopharmological basis & Follow-on research
    - Systematic evaluation
    - Modelling?
  - Assay selections
    - Ethnomedical basis
    - Random/systematic screening
    - Virtual Screening?



NADI:

Bioinformatic databases: small molecules, receptor databases, plant monographs

Bioinformatic tools: Blast, Protein Structure Prediction, Molecular Docking etc.

NADI: Information Centre for Malaysian Herbs

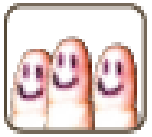
NADI® empowers:

40 monographs — rapid retrievals of enthnomedical information across 40 monographs.

4000 compounds — searches over 4000 natural product compounds. and the list is growing...

645 targets — interrogation of 645 validated drug targets with over 4000 natural product compounds.

NADI® features:


user-friendly interface.

? search using plant's name and traditional uses, receptors, diseases and ligand/drug name.


search substructures, formula, Log P, molecular weight ranges.

ONE click — just one click to dock a compound or a group of compounds into a receptor of your choice.

2D structures — structures for cheminformatics purposes.

3D structures — ready for rapid *in silico* drug screening.

Ethnomedical/follow-on basis

MONOGRAF HERBA ~ HASIL CARIAN "eurycoma" - Mozilla Firefox

File Edit View History Bookmarks Tools Help

http://phd.usm.my/paparherba.php?Nama=eurycoma&Submit=Cari!

NaDI Resources
Nature Based Drug Discovery Intelligent Resources

NADI-HERBS

Keyword Search: Plant's name

Keyword Search: Symptom

Laman Utama | Monograf Herba | Senarai Pakar Herba | Glosari | Penerbitan Tentang Herba | Diari | Projek Herba USM | Pautan Berkaitan | Berita

Masukkan carian herba anda Cari! **atau** **Carian berdasarkan simptom**

(contoh: eurycoma longifolia, illicium verum, hempedu bumi) (contoh: kencing manis, cirit-bi

MONOGRAF HERBA *EURYCOMA LONGIFOLIA JACK*

Nama tempatan:
Payong ali, tongkat ali, tongkat baginda, petala bumi, setunjang bumi, penawar pahit ; pasak bumi(Indonesia)

Plant's name

Bahagian yang digunakan:

Plant's part used

Akar.

Introduction about the plant

Pengenalan:
Eurycoma longifolia ataupun lebih dikenali sebagai Tongkat Ali adalah daripada famili Simaraubaceae terkenal sebagai ramuan ubatan tradisional. Ianya didapati tumbuh dalam hutan di Malaysia, Indochina, Sumatra dan Borneo. Tongkat Ali adalah sejenis tumbuhan renek hutan yang berbatang kurus berwarna merah dan tumbuh tanpa ranting. Ia boleh mencapai ketinggian sehingga 4.6 meter. Pelepah daunnya boleh memanjang sehingga 1 meter dan mempunyai 30 sehingga 40 daun runcing yang

MONOGRAF HERBA ~ HASIL CARIAN "eurycoma" - Mozilla Firefox

File Edit View History Bookmarks Tools Help

http://phd.usm.my/paparherba.php?Nama=eurycoma&Submit=Cari!

Traditional Uses of the plant

Kegunaan:

Didalam perubatan tradisional orang ☐ orang Melayu, pokok Tongkat Ali adalah sangat terkenal sebagai ramuan ubatan tradisional. Ekstrak air bahagian tumbuhan ini digunakan untuk rawatan pelbagai penyakit. Sebut sahaja berkenaan dengan Tongkat Ali ianya terkenal sebagai aprodisiak dan merangsangkan tenaga batin bagi kaum lelaki dan Tongkat Ali juga boleh diminum sebagai tonik untuk ibu - ibu yang baru bersalin.

Daun Tongkat Ali pula boleh digunakan untuk mengubat luka dan kecederaan di kepala. Selain daripada itu, campuran tongkat Ali, buah keras dan beras biasanya dijadikan minyak untuk mengurangkan demam dan sakit perut. Air rebusan kulit akar tongkat Ali boleh diminum seperti teh untuk meredakan demam panas, ulser, luka ☐ luka, gusi berdarah, hipertensi, gatal ☐ gatal di badan.Tumbuhan ini juga digunakan untuk rawatan pelbagai penyakit seperti kurap dan akar tumbuhan ini juga digunakan untuk rawatan disentri dan bengkak kelenjar. Herba ini juga dipercayai berkesan untuk mengubati sakit kepala, sakit perut, kesakitan yang disebabkan oleh syphilis dan juga beberapa sakit biasa. Tongkat Ali bukan sahaja berfungsi sebagai tonik seks, tetapi di dalam perubatan tongkat Tongkat Ali digunakan lebih meluas sebagai ubat sakit jantung, strok, kanser prostat dan lenguh otot dan sendi. Selain itu, sebagai ubat Osteoporosis dan retak pangkal paha dan ubat untuk lemah ingatan dan kepupusan fungsi otak seperti penyakit Alzheimer di kalangan orang lanjut usia.

Pada masa ini, tongkat Ali sudah pun dijadikan bahan komersil yang laris dengan kehadiran teh tongkat Ali di pasaran. Walaupun harganya agak mahal berbanding teh biasa, tetapi khasiatnya melebihi harga yang ditawarkan.

Tiada maklumat.

Penggunaan yang disyorkan ialah diantara 100mg sehingga 400mg serbuk akar dimakan dua kali setiap hari. Penggunaan yang biasa ialah 300mg serbuk akar dimakan dua kali setiap hari.

Fakta Saintifik Mengenai Bioaktiviti:

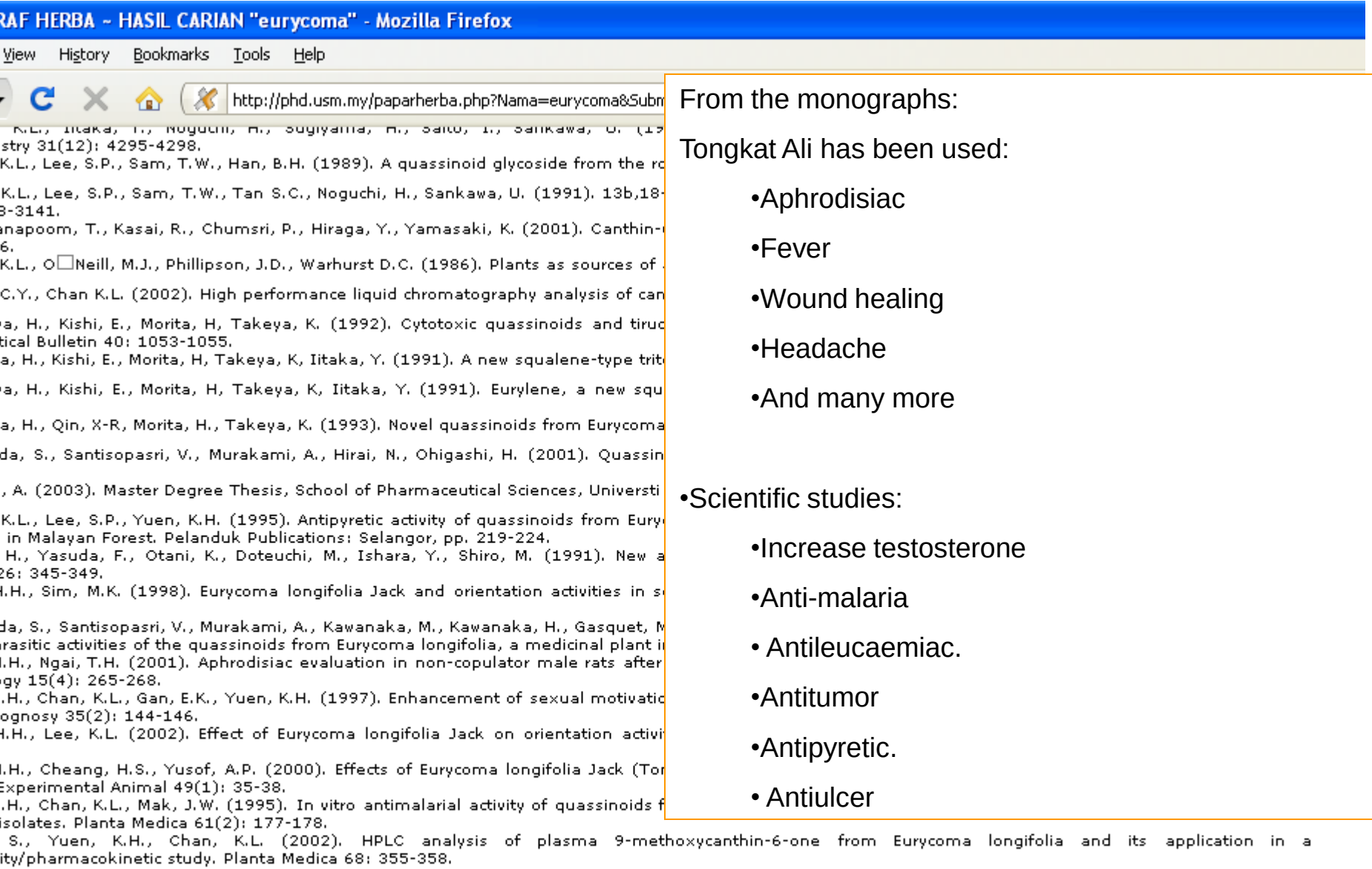
Scientific Studies on Bioactivities

- Meningkatkan paras testosterone (29).
- Anti-malaria (30).
- Antileukemik (2).
- Antitumor (25).
- Antipiretik (22).
- Antiulser (23).

Rujukan:

References

1. Suong, N.-N., Bhatnagar, S., Polonsky, J. (1982). Structure of laurycolactone A and B, new C18 - quassinoids from Eurycoma longifolia and revised structure of eurycomalactone (X-ray analysis). Tetrahedron Letters 23(49): 5159-5162.
2. Morita, H., Kishi, E., Takeya, K., Itokawa, H., Tanaka, O. (1990). New quassinoids from the roots of Eurycoma longifolia. Chemistry Letters 749-752.
3. Morita, H., Kishi, E., Takeya, K., Itokawa, H., Iitaka, Y. (1993). Squalene-derivatives from Eurycoma longifolia. Phytochemistry 34(3): 765-771.
4. Ang, H.H., Hitotsuyanagi, Y., Fukaya, H., Takeya, K. (2002). Quassinoids from Eurycoma longifolia. Phytochemistry 59(8): 833-837.
5. Ang, H.H., Hitotsuyanagi, Y., Takeya, K. (2000). Euyrcolactones A-C, novel quassinoids from Eurycoma longifolia. Tetrahedron Letters 41: 6849-6853.
6. Morita, H., Kishi, E., Takeya, K., Itokawa, H., Iitaka, Y. (1993). Highly oxygenated quassinoids from Eurycoma longifolia. Phytochemistry 33(3): 691-696.
7. Morita, H., Kishi, E., Takeya, K., Itokawa, H. (1992). Biphenylneolignans from wood of Eurycoma longifolia. Phytochemistry 31(11): 3993-3995.
8. Mitsunaga, K., Koike, K., Tanaka, T, Ohkawa, Y., Kobayashi, Y., Sawaguchi, T., Ohmoto, T. (1994). Canthin-6-one alkaloids from Eurycoma longifolia. Phytochemistry 35(3): 799-802.



From the monographs:

Tongkat Ali has been used:

- Aphrodisiac
- Fever
- Wound healing
- Headache
- And many more

- Scientific studies:
  - Increase testosterone
  - Anti-malaria
  - Antileucaemiac.
  - Antitumor
  - Antipyretic.
  - Antiulcer

Live search on the PubMed on the related references

Systematic Evaluation

Who's doing what?

PENYELIDIK TEMPATAN DALAM BIDANG HERBA

Nama	Institusi	Bidang Penyelidikan
Dr. Azlina Abdul Aziz	Universiti Malaya	*Eurycoma langifolia*(Tongkat ali
Dr. Johari Mohd Ali	Universiti Malaya	*Centella asiatica*(Pegaga)
Dr. Nornisah Mohamed	Universiti Sains Malaysia	*Blumea balsamifera*(Sembong)
Prof. Chan Kit Lam	Universiti Sains Malaysia	*Typhonium flagelliforme*(Keladi tikus), *Eurycoma langifolia*(To
Prof. Dato' Dzulkifli Abdul Razak	Universiti Sains Malaysia	*Goniothalamus macrophyllus*(Selayak hitam), *Mitragyna speci*
Prof. Madya Dr. Abas Hj Hussin	Universiti Sains Malaysia	*Kaempferia galanga*(Cekur), *Gynura procumbens*(Sambung ny
Prof. Madya Dr. Amirin Sadikun	Universiti Sains Malaysia	*Mimosa pudica*(Semalu), *Gynura procumbens*(Sambung nyaw *galanga*(Cekur), *Tinospora crispa*(Patawali)


Bookmarks Tools Help
http://phd.usm.my/NADI/main.php
Google
NADI
Nature-Based Drug Discovery Intelligent
Search drug-like compounds
Search!
Search compounds by plant.
Search only drug-like compounds or all compounds in selected plant.
Please select plant
Select plant name
Citrus clementina
Citrus hystrix
Citrus limon
Citrus reticulata
Clausena excavate
Cucurbita moschata
Curcuma longa
Curcuma xanthorrhiza
Curcuma zedoaria
Cymbopogon nardus
Cyperus rotundus
Erythroxylum cuneatum
Eugenia cumini
Eugenia jambos
Eugenia michelii
Eurycoma longifolia
Garcinia atroviridis
Garcinia mangostana
Harrisonia perforate
Jasminum officinale
Structure Name
Structure Formula
Log. P (approx.)
Molecular Weight (g/mol)
Investigated activity
Search
Clear
>> Substructure search
All Copyrights Reserved.
Any question or enquiries please contact:
Last Updated: 31 March 2008

Bookmarks Tools Help

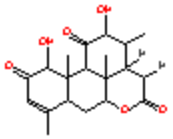
http://phd.usm.my/NADI/main.php

Google

NADI

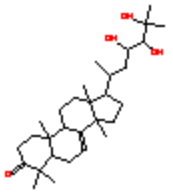
Nature-Based Drug Discovery Intelligent

List of chemical structure:



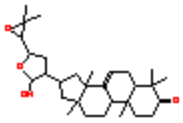
Structure name:
12-epi-11-Dehydroklaineanone

Molecular formula: C20H26O6



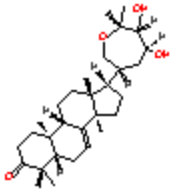
Structure name:
Piscidinol

Molecular formula: C30H50O4



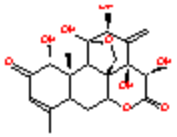
Structure name:
Melianone

Molecular formula: C30H46O4



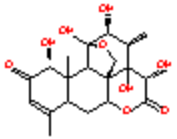
Structure name:
Hispidone

Molecular formula: C30H48O



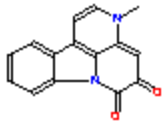
Eurycomanone

Molecular formula: C20H24O9



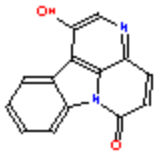
Structure name:
Iandonone

Molecular formula: C20H26O9



Structure name:
Picrasidine L

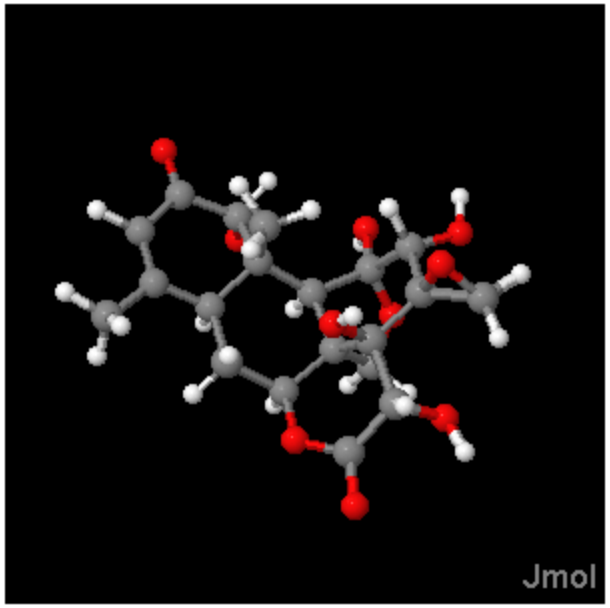
Molecular formula: C15H10N2O

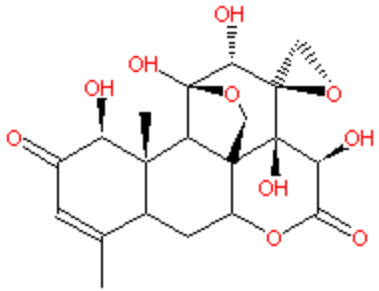


Structure name:
1-hydroxycanthin-6-one

Molecular formula: C14H8N2O2

Total results displayed **73**





Structure Code	: MSC566
Structure Name	: Pasakbumin B
Synonym	:
Molecular Formula	: C20H24O10
Molecular Weight	: 424.39856
Log. P (approx.)	: -2.45
H-Bond Acceptors	: 10
H-Bond Donors	: 5
Chemotype	: Quassinoid

Plant source:

Scientific name	Local names
Eurycoma longifolia	- Tongkat Ali

Structure references:

- Guo, Z., et. al. (2005). Bioloqically Active Quassinoids and Their Chemistry: Potential Leads for Driq Desiqn. Journal of Medicinal Chemistry, 12, p. 173-190

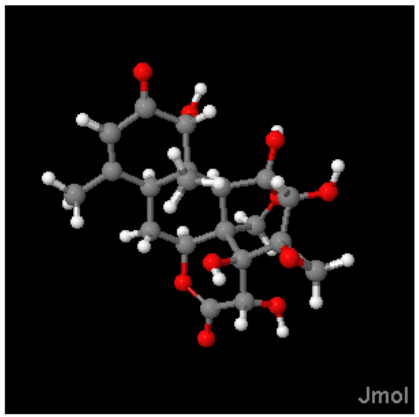
Investigated Activities:

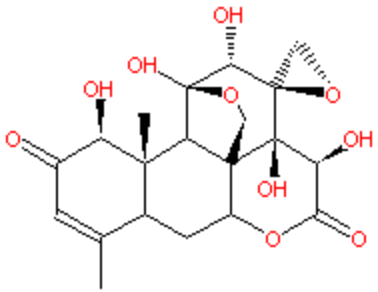
- Exhibited strong cytotoxicity toward human breast cancer (1)

Structure Code	: MSC566
Structure Name	: Pasakbumin B
Synonym	:
Molecular Formula	: C20H24O10
Molecular Weight	: 424.39856
Log. P (approx.)	: -2.45
H-Bond Acceptors	: 10
H-Bond Donors	: 5
Chemotype	: Quassinoid

References:

1 . Guo, Z., et. al. (2005). Biologically Active Quassinoids and Their Chemistry: Potential Leads for Drig Design. Journal of Medicinal Chemistry, 12, p. 173-190.





Structure Code : MSC566
Structure Name : Pasakbumin B
Synonym :
Molecular Formula : C20H24O10
Molecular Weight : 424.40
Log. P (approx.) : -2.45
H-Bond Acceptors : 10
H-Bond Donors : 5

Plant source:

Scientific name	Local names	Plant parts
Eurycoma longifolia	- Tongkat Ali	- Root

Structure references:

- Guo, Z., et. al. (2005). Biologically Active Quassinoids and Their Chemistry: Potential Leads for Drig Design. Journal of Medicinal Chemistry, 12, p. 173-190

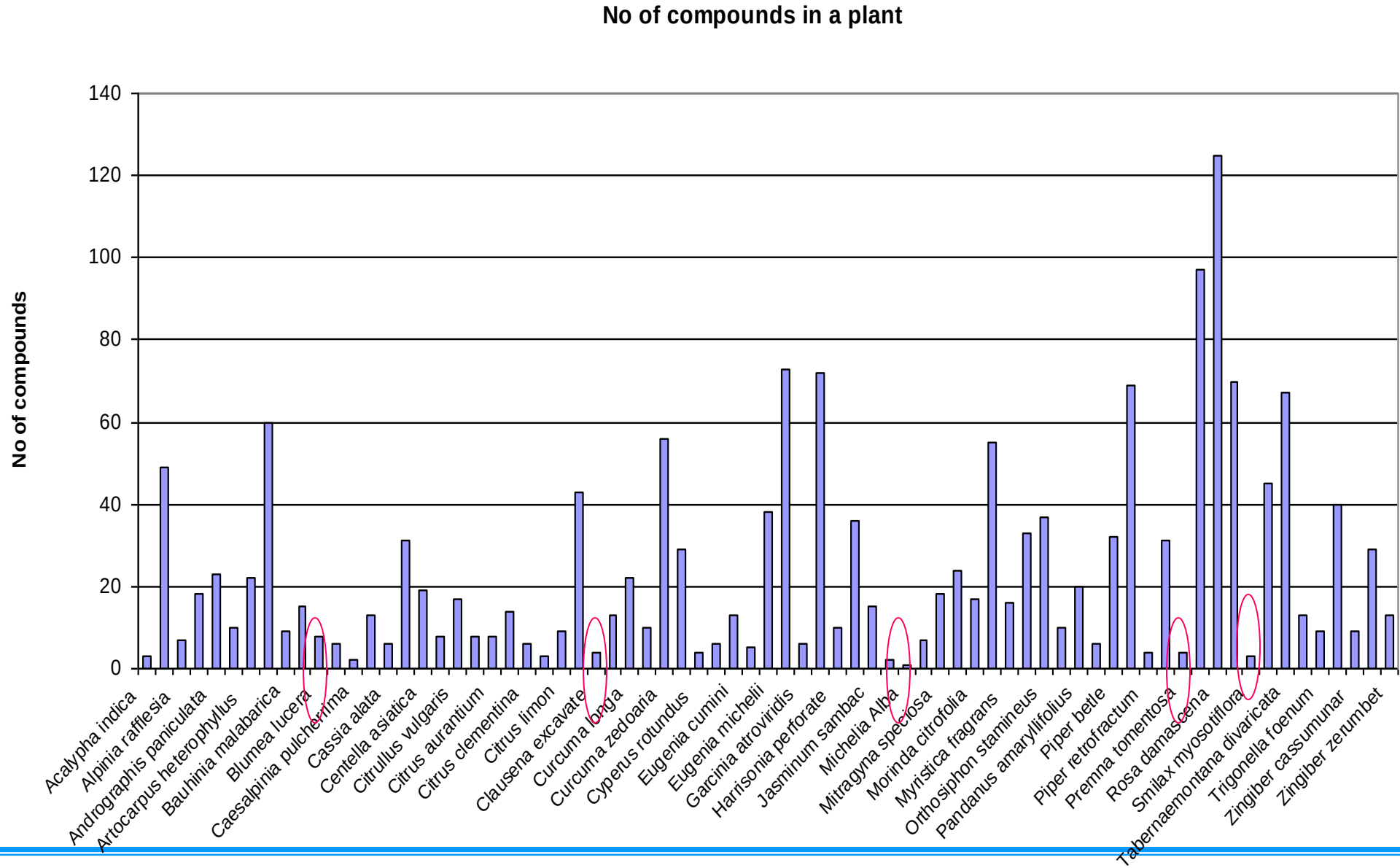
Investigated Activities:

- Exhibited strong cytotoxicity toward human breast cancer (1)

References:

1 . Guo, Z., et. al. (2005). Biologically Active Quassinoids and Their Chemistry: Potential Leads for Drig Design. Journal of Medicinal Chemistry, 12, p. 173-190.

- What has been done?
- Do we need to reinvent the wheel?



http://phd.usm.my/NADI/main.php

NADI

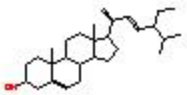
Nature-Based Drug Discovery Inte

lick on the time to show or hide econds.

02 AM
Wednesday, November 2, 2008

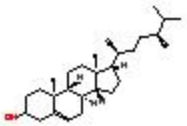
- ::HOME
- ::NADI-CHEM
- ::NADI-DIRECT
- ::NADI-EXPERT
- ::NADI-PUBS
- ::RECEPTOR DATABASE
- ::NADI-HERBS
- ::MNATCHEM
- ::NAPIMM
- ::NADI-VISAGE
- ::AMEXg
- ::PUBCHEM
- ::NCI CHEMICAL DATABASES
- ::USM HERBAL RESOURCES
- ::USM-HERBAL PROJECT

List of chemical structure:



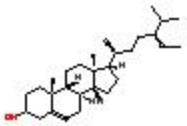
Structure name:
Stigmasterol

Molecular formula: C29H48O



Structure name:
Campesterol

Molecular formula: C28H48O



Structure name:
Sitosterol

Molecular formula: C29H50O

Total results displayed **3**

Rational Selection – Assays

- When a novel compound identified, how do I know it has potential as a drug?
- NADI provides link to USM's Reverse Docking for prediction of potential receptor(s) to target….

AUTOMATED REVERSE DOCKING SYSTEM

Reverse Docking Server & Drug Receptor Database

Wed, Nov 12 2008
8:10:01 AM

Information

- Home
- Sitemap
- User guide
- Disclaimer
- Links
- Contact

Related Links

- Universiti Sains Malaysia
- School of Pharmaceutical Sciences
- School of Computer Sciences
- NADI
- vPHDs Lab

Reverse Docking Server

LOGIN TO REVERSE DOCKING SERVER

Introduction to Ligand-Receptors Docking

Docking is an approach to "rational drug design that aims to predict the structure and binding free energy of a ligand-receptor complex". It involves the development of computer algorithms that evaluate the binding modes of ligands in receptor sites (1). The example of a computer program or algorithm being used for automated docking and scoring is AutoDock (2). For more information on using this utility, please refer to User Guide.

AutoDock

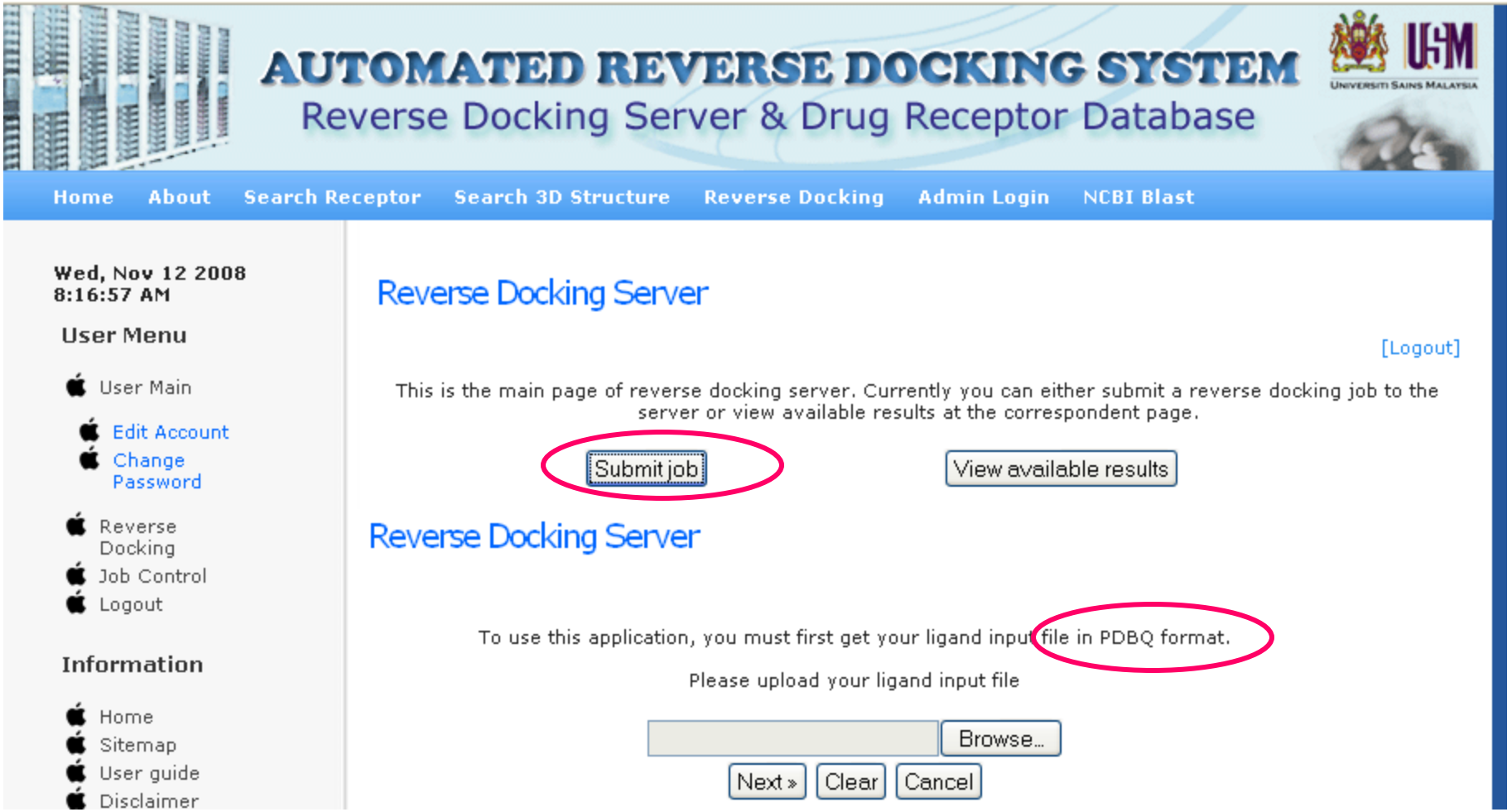
AutoDock (2) is a suite of automated docking tool. It is one of the docking programs mostly used in this area, which suitable for docking small molecule libraries and structures and also for high-throughput screening (3). AutoDock consists of three programs: AutoTors to set up which bonds will treated as rotatable in the ligand; AutoGrid to pre-calculates grids of target protein and AutoDock to performs the docking of the ligand to a set of grids describing the target protein. It is an efficient program, which produce high quality predictions of the ligand conformations, and good correlations between predicted inhibition constants with the experimental ones (4,5).

References:

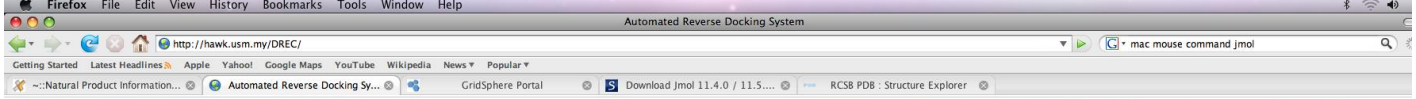
1. Jones, G. and Willett, P. (1995). Docking small-molecule ligands into active sites. *Current Opinion in Biotechnology*, **6**, 652-656.

2. Morris, G.M., Goodsell, D.S., Halliday, R.S., Huey, R., Hart, W.E., Belew, R.K. and Olson, A.J. (1998). Automated Docking Using a Lamarckian Genetic Algorithm and an Empirical Binding Free Energy Function. *Journal of Computational Chemistry*, **19**(4), 1639-1662.

3. Oprea, T.I. and Matter, H. (2004). Integrating virtual screening in lead discovery. *Current Opinion in Chemical Biology*, **8**, 349-358.


AUTOMATED REVERSE DOCKING SYSTEM
Reverse Docking Server & Drug Receptor Database
USM
Universiti Sains Malaysia
Home
About
Search Receptor
Search 3D Structure
Reverse Docking
Admin Login
NCBI Blast
Wed, Nov 12 2008
8:16:57 AM
User Menu
User Main
Edit Account
Change Password
Reverse Docking
Job Control
Logout
Information
Home
Sitemap
User guide
Disclaimer
Reverse Docking Server
[Logout]
This is the main page of reverse docking server. Currently you can either submit a reverse docking job to the server or view available results at the correspondent page.
Submit job
View available results
Reverse Docking Server
To use this application, you must first get your ligand input file in PDBQ format.
Please upload your ligand input file
Browse...
Next »
Clear
Cancel


Firefox File Edit View History Bookmarks Tools Window Help
Automated Reverse Docking System
http://hawk.usm.my/DREC/
mac mouse command jmol
Getting Started Latest Headlines Apple Yahoo! Google Maps YouTube Wikipedia News Popular
~::Natural Product Information...
Automated Reverse Docking Sy...
GridSphere Portal
Download Jmol 11.4.0 / 11.5....
A Jmol Tutorial: Introduction
AUTOMATED REVERSE DOCKING SYSTEM
Reverse Docking Server & Drug Receptor Database
Prepared by: Nur Hannani Che Mat
Tuesday, 17th Jun 2008
[Logout]
4:20:57 PM MYT
Reverse Docking Tool
Home
Site Map
User Guide
Search Receptor
Search 3D Structure
Reverse Docking
NCBI Blast
To use this application, you must first get your ligand input file in PDBQ format.
Please upload your ligand input file
Browse...
Next >> Clear Cancel
File Upload
Desktop
search
DEVICES
SHARED
PLACES
MEDIA
Draft Agen...90408.doc
GoogleEarthMac.dmg
gutachterform_fg.rtf
JCIM
junk
logotaip.gif
MGCC
mgltools_i..._1.4.6.dmg
mgltools_i..._1.5.1.dmg
MSC366.pdb
NADI-description.doc
NADI-Disclosure.doc
NCI-Divers...-0.1.tar.gz
nlReader.dll
NT2007
PDB
Name MSC366.pdb
Size 8 KB
Kind PDB file
Created Today at 4:16 PM
Modified Today at 4:16 PM
Last opened Today at 4:16 PM
Cancel
Open
Copyrights © Reserved
Last Updated: 17th 2007.
NADI : School of Pharmaceutical Sciences : USM : About Us : Disclaimer : Quick Links : Admin Login : Contact
Done



AUTOMATED REVERSE DOCKING SYSTEM

Reverse Docking Server & Drug Receptor Database

Tuesday, 17th Jun 2008

8:06:05 AM MYT

[Home][Logout]

Results for reverse docking with MSC366

Home
Site Map
User Guide
Search Receptor
Search 3D Structure
Reverse Docking
NCBI Blast

PDB ID	Final Docked Energy (kcal/mol)**	Receptor Name	DLG File
2SDF	-175.25	Stromal cell-derived factor 1	Download File
1QLY	-90.96	Tyrosine-protein kinase BTK	Download File
6COX	-11.54	Prostaglandin G/H synthase 2	Download File
1A0J	-10.92	Trypsin	Download File
4COX	-10.68	Prostaglandin G/H synthase 2	Download File
1HWI	-9.85	3-hydroxy-3-methylglutaryl-coenzyme A reductase	Download File
5COX	-9.72	Prostaglandin G/H synthase 2	Download File
2C5T	-9.70	Cell-division protein kinase 2	Download File
1PYN	-9.51	Protein Tyrosine Phosphatase 1B	Download File
1KE6	-9.43	Cell-division protein kinase 2	Download File
1KMV	-9.40	Dihydrofolate reductase (DHFR)	Download File
1A25	-9.39	Protein kinase C	Download File
1H1S	-9.26	Cell-division protein kinase 2	Download File
1RC4	-9.14	Dihydrofolate reductase (DHFR)	Download File
1A31	-9.10	DNA topoisomerase I	Download File

Tuesday, 17th Jun 2008

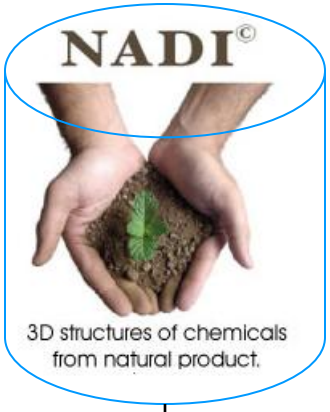
8:10:27 AM MYT

Home
Site Map
User Guide
Search Receptor
Search 3D Structure
Reverse Docking
NCBI Blast

Copyrights © Reserved
Last Updated: 17th June 2007.

1GX1	-8.75	2C-Methyl-D-erythritol 2,4-cyclodiphosphate synthase	Download File
1UZE	-8.73	Angiotensin converting enzyme-like protein	Download File
2VPF	-8.71	Vascular endothelial growth factor	Download File
2FJM	-8.71	Protein Tyrosine Phosphatase 1B	Download File
1QBS	-8.71	HIV-1 protease	Download File
1QBU	-8.70	HIV-1 protease	Download File
1DMP	-8.70	HIV-1 protease	Download File
1QBT	-8.69	HIV-1 protease	Download File
1YKR	-8.62	Cell-division protein kinase 2	Download File
1IRB	-8.59	Phospholipase A2	Download File
1A52	-8.58	Estrogen receptor	Download File
1H07	-8.57	Cell-division protein kinase 2	Download File
1A9M	-8.52	HIV-1 protease	Download File
1HWR	-8.51	HIV-1 protease	Download File
110L	-8.49	T4 lysozyme	Download File
1R31	-8.41	3-hydroxy-3-methylglutaryl-coenzyme A reductase	Download File
109L	-8.40	T4 lysozyme	Download File
1ODX	-8.35	HIV-1 protease	Download File
1A8K	-8.34	HIV-1 protease	Download File
2EXM	-8.31	Cell-division protein kinase 2	Download File
1MES	-8.25	HIV-1 protease	Download File
1HFQ	-8.19	Dihydrofolate reductase (DHFR)	Download File
1G7F	-8.14	Protein Tyrosine Phosphatase 1B	Download File
1XKK	-8.09	Epidermal growth factor receptor	Download File
1VPF	-8.09	Vascular endothelial growth factor	Download File
1GIJ	-8.08	Cell-division protein kinase 2	Download File
1AI4	-8.05	Penicillin amidohydrolase	Download File
1YM7	-8.03	Beta-1 adrenergic receptor	Download File
1A30	-8.00	HIV-1 protease	Download File

NADI Drug Design Workflow



Literature review

Validated target Identified

Molecular Dynamics Simulation

*

Molecular Docking

Virtual Hits Identified

*

In vitro assay

Hit Identified

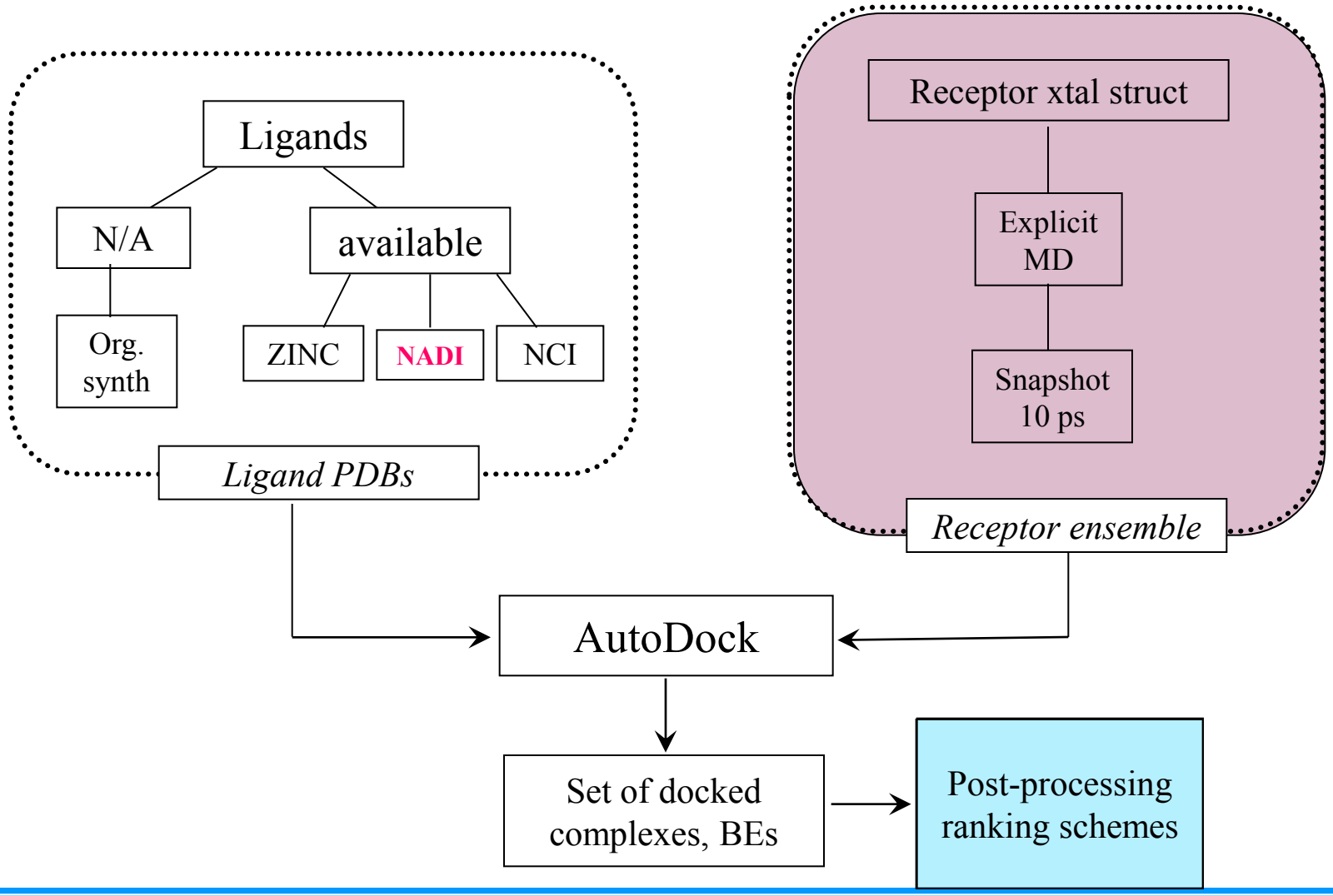
Pharmacophore - Modelling

Virtual Lead Identified

Lead Identified

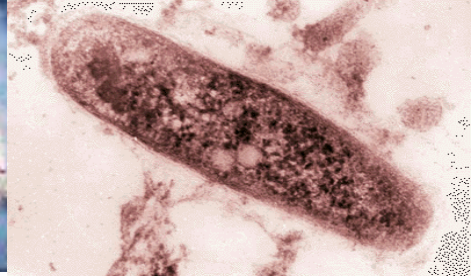
Further tests

Ensemble Based Docking



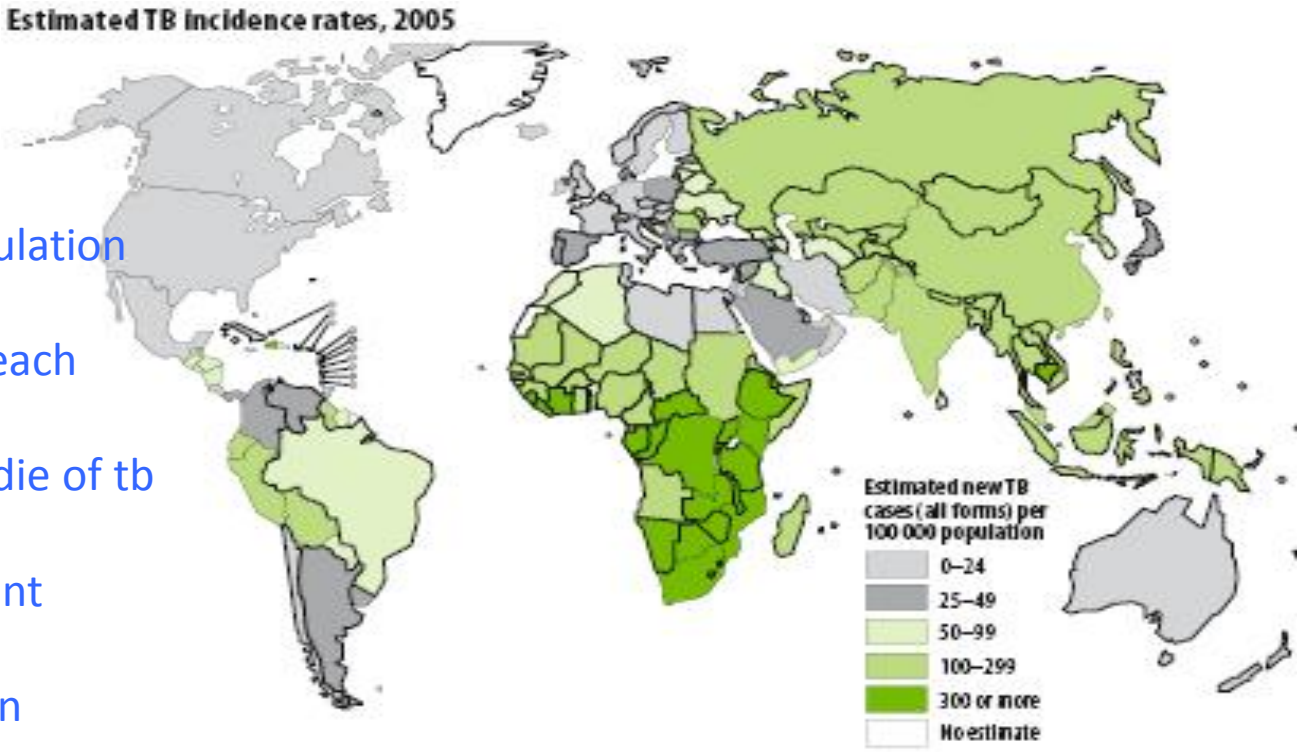
R. Amaro, JACS, 2008

NADI example: TB



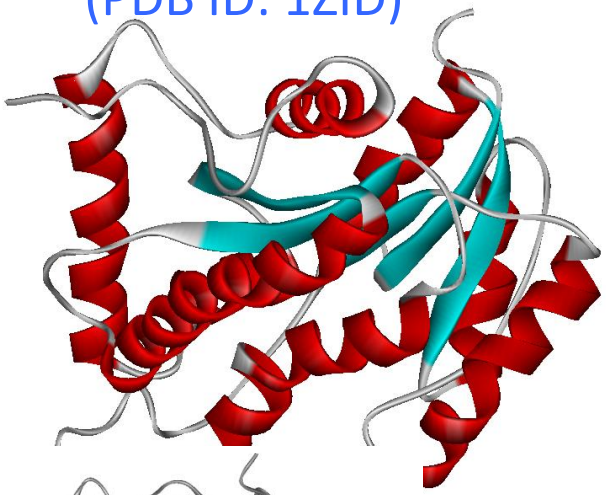
- Caused by *Mycobacterium tuberculosis*
- One third of the world population is infected
- WHO: 8 million new cases each year

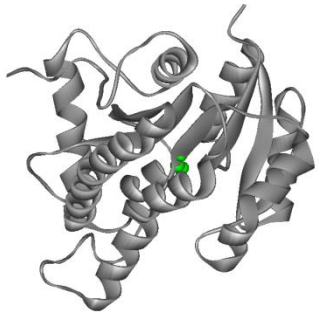
  : 30 million people will die of tb this decade
- As much as 30% INH resistant strain TB
- Multi-drug resistant strain in HIV/AIDS patients



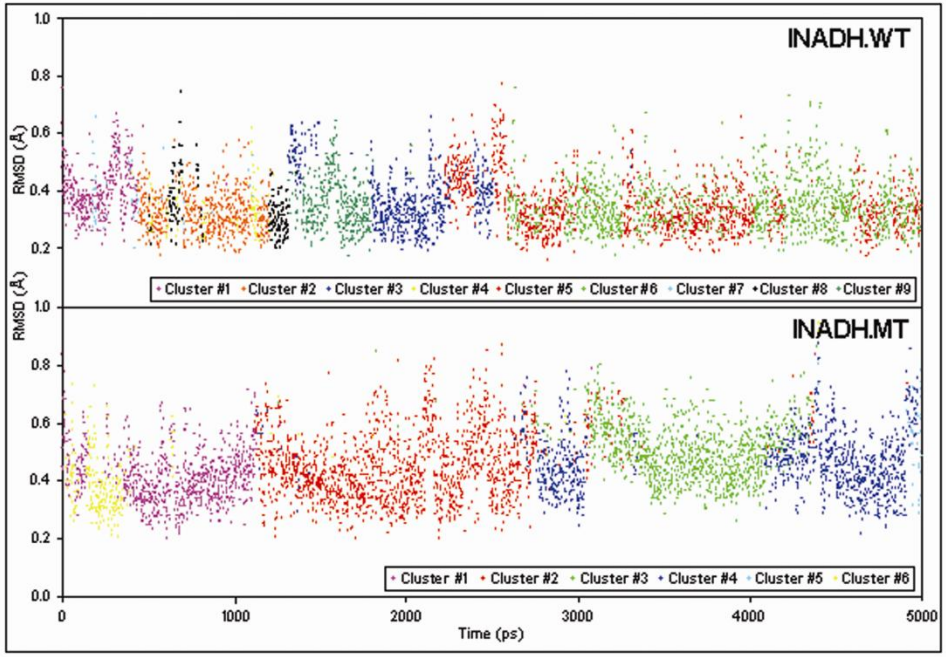
Drug Target: InhA

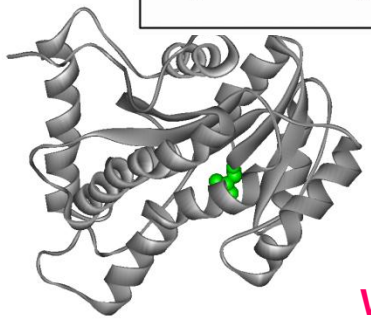
(PDB ID: 1ZID)



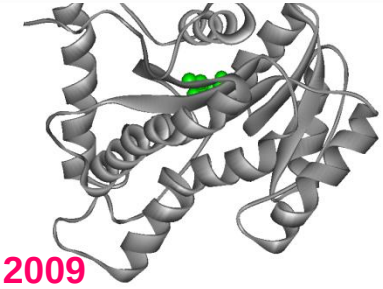


S94A MT InhA (PDB ID: 1ENZ)



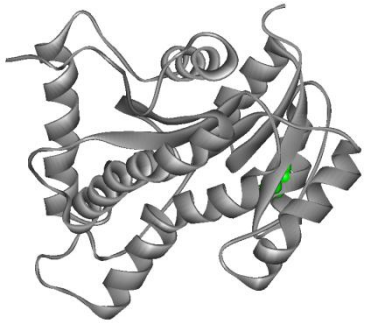


I16

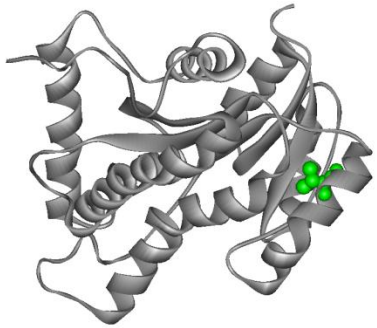


I21

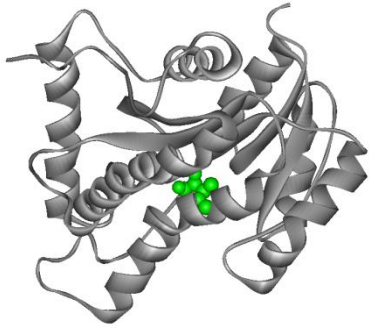
Wahab, JCIM, 2009



I47



V78



I95

in-silico screening using NADI

[Docking] [Results] [Logout]

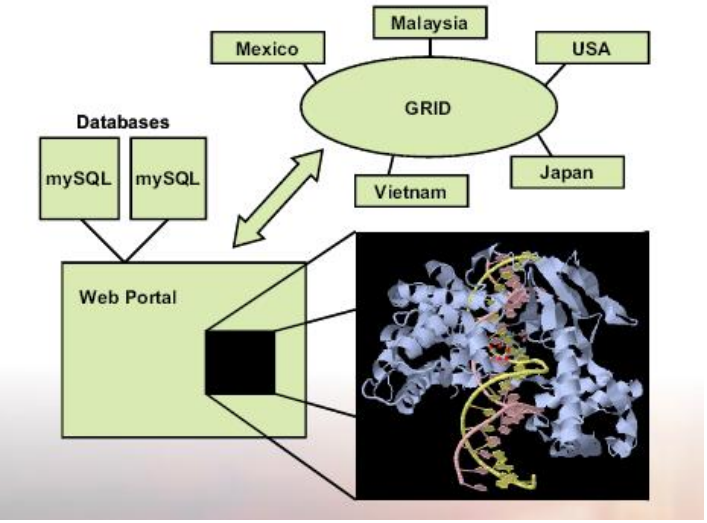
NADI-VISAGE

Login

user name

password

login reset



[Docking] [Results] [Logout]

Docking

Receptor

Receptor name: Adenylate cyclase, type II

Disease name: Blood vessel disorders

PDB file name: select

Upload

select
1ab8
1azs
1cjk
1cjt
1cju
1cjv
1cs4
1cu1

Compound

Structure name

or

Plant name: Ajuga decumbens

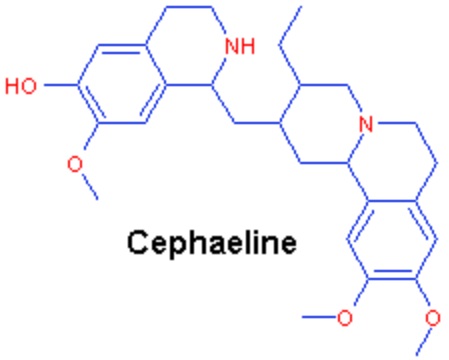
Option

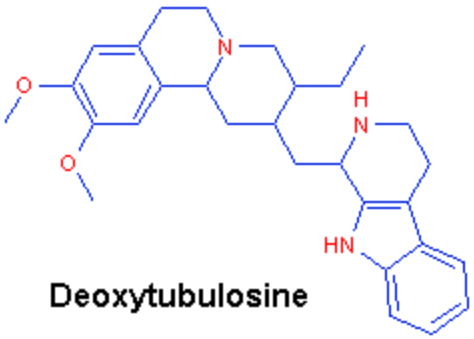
E-mail

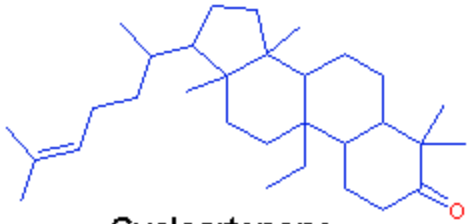
~400 plants,

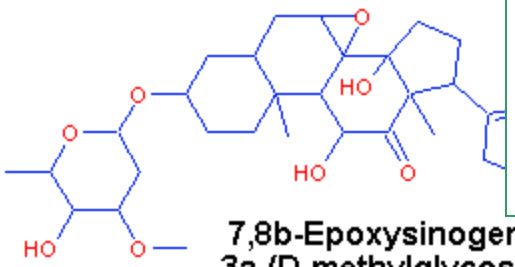
~4000 compounds

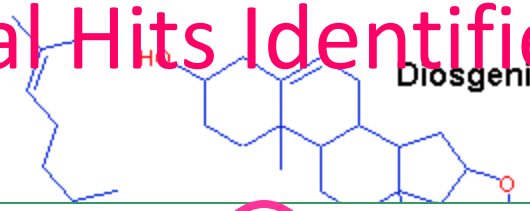
Virtual Hits Identified

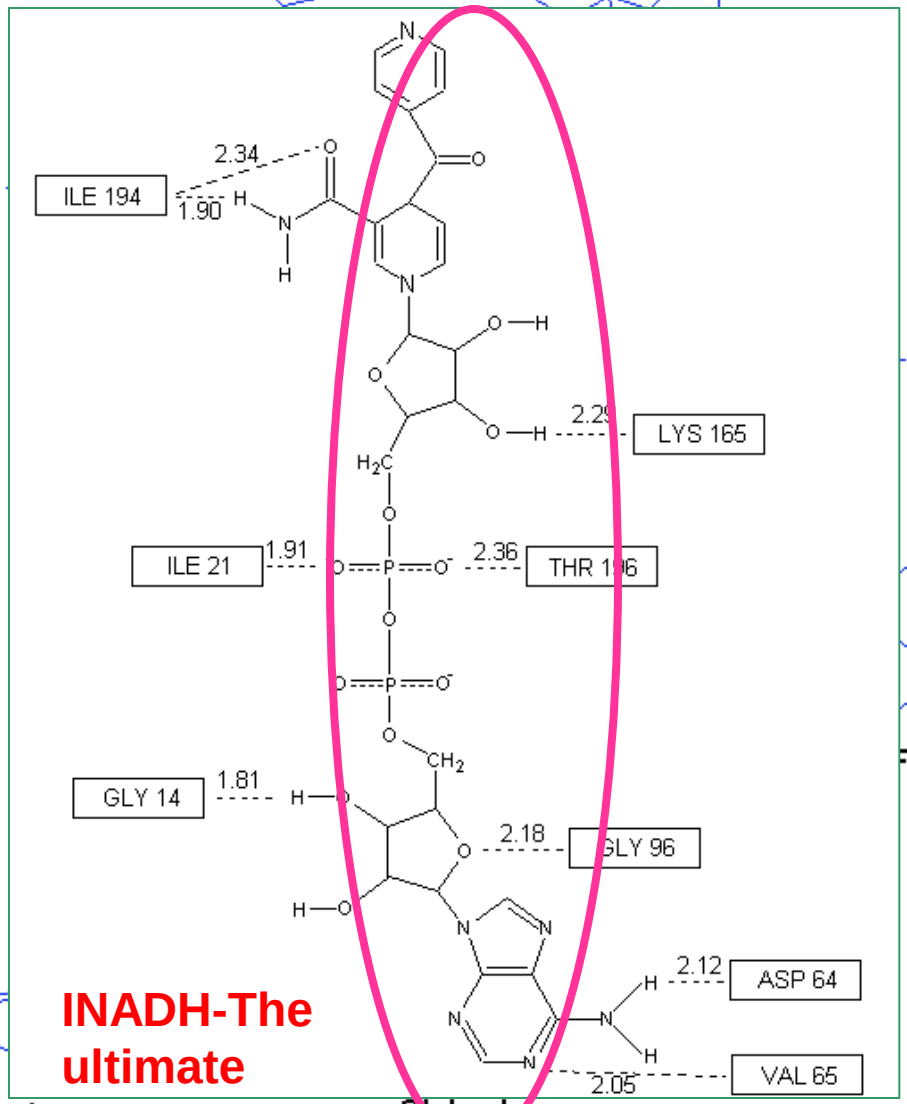




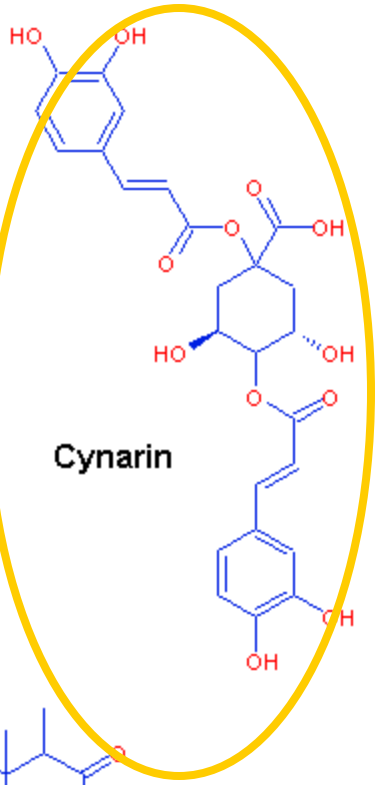


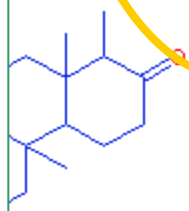


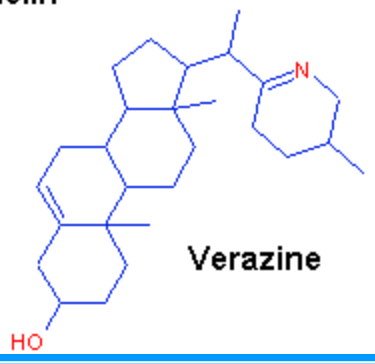




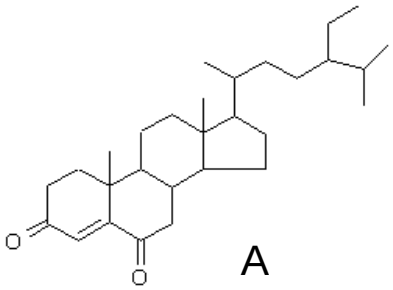
INADH-The ultimate inhibitor



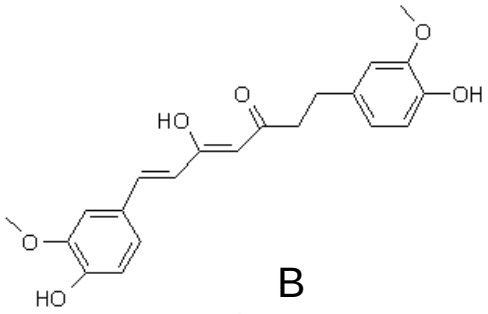




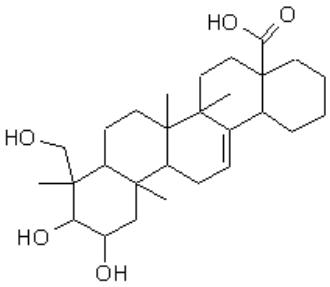
Plants Identified



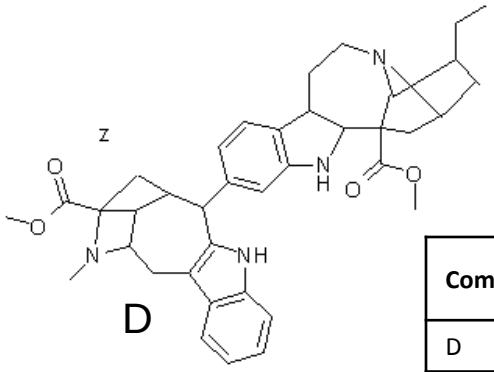
A



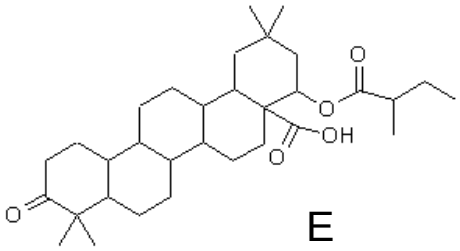
B



C



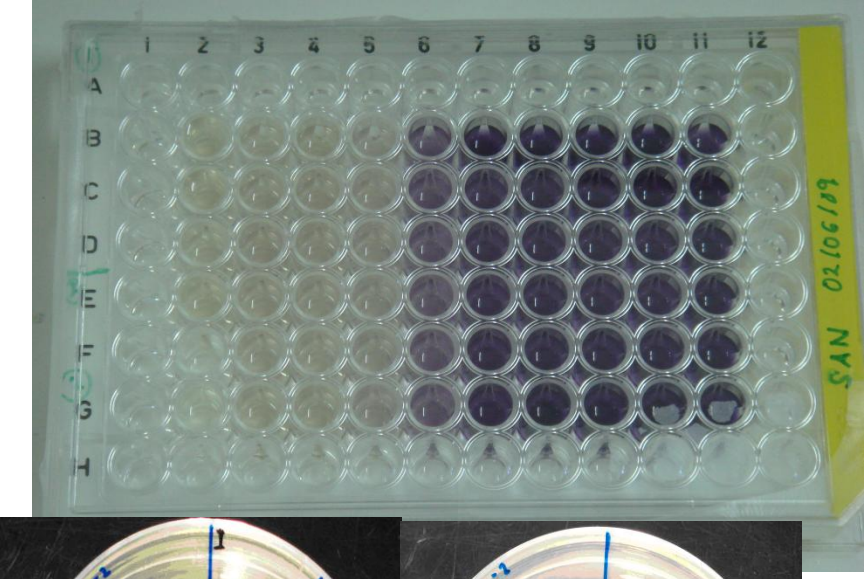
D

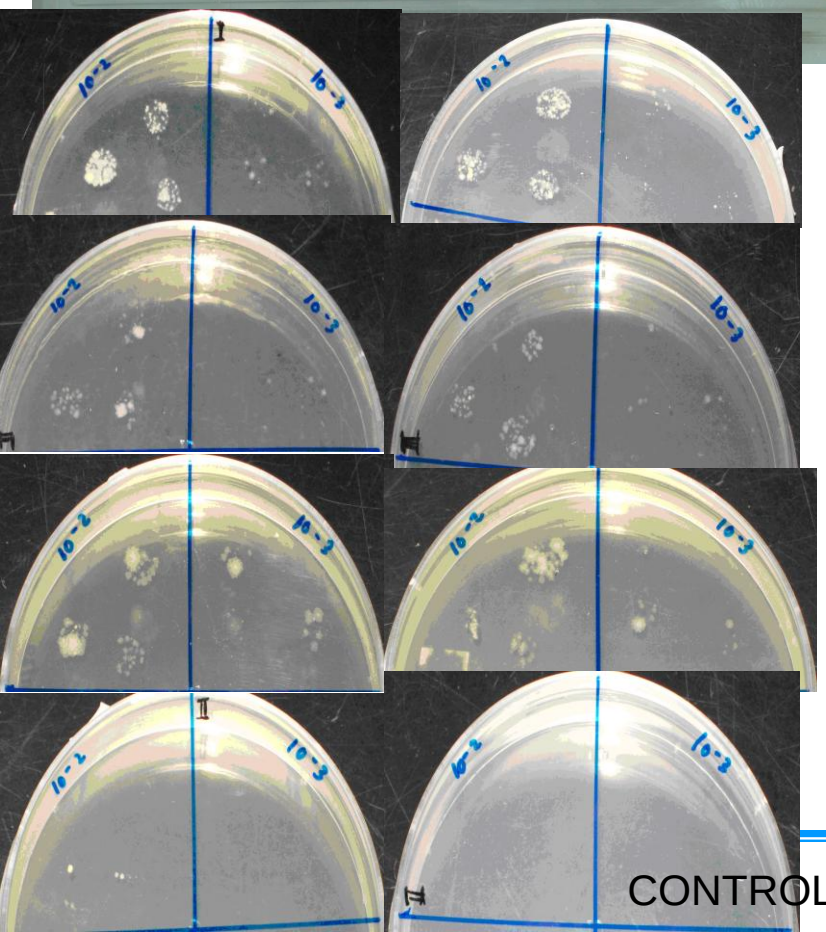


E

Table 1: The predicted activities of chemical compounds reportedly to be isolated from Malaysian plants

Compounds	Plant source	Predicted Inhibition Constant (Ki)
D	Pegaga	5.78E-17
B	Akar susun kelapa	4.73E-16
C	Sireh	4.13E-16
E	Kunyit	1.5E-16
A	Bunga tahi ayam	1.05E-16
Isoniazid (INADH)	Synthetic molecule	3.795E-13





Minimum inhibitory concentration (MIC) determinations

No.	Plants	Plant parts	Extracts	MIC (µg/ml)
1	*Lantana camara* (Bunga tahi ayam)	leaves	Methanol	25
2	*Centella asiatica* (Pegaga)	whole plant	Methanol	25
3	*Psidum guajava* (Jambu batu)	leaves	Methanol	200
		fruits	Methanol	50
4	*Tabernaemontana coronaria* (Jasmin)	leaves	Methanol	50
5	*Phyllanthus niruri* (Dukung anak)	whole plant	Methanol	≥ 200
6	*Murraya paniculata* (Kemuning)	leaves	Methanol	50
7	*Piper betle* (sireh)	whole plant	Ethanol	100
			Chloroform	50
			Petroleum ether	50
			Ethanol:water	50
8	Isoniazid			0.31

NADI example 2 : Avian Influenza

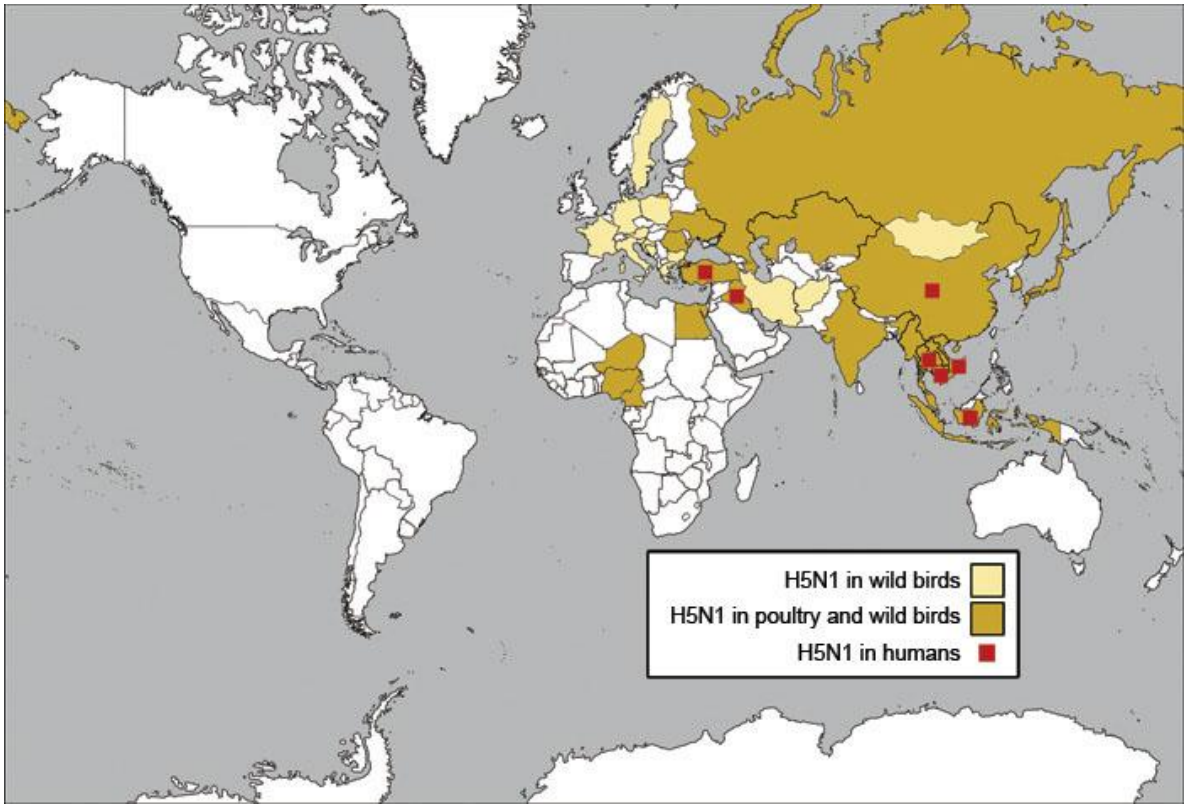
•Major outbreak began 2003. Affected countries:

•The Republic of Korea, Viet Nam, Japan, Thailand, Cambodia, The Lao People's Democratic Republic, Indonesia, China, and Malaysia.

•2005, the virus spread to the Russian Federation, Kazakhstan, Mongolia, Turkey, Romania, Croatia, Ukraine and the Netherland.

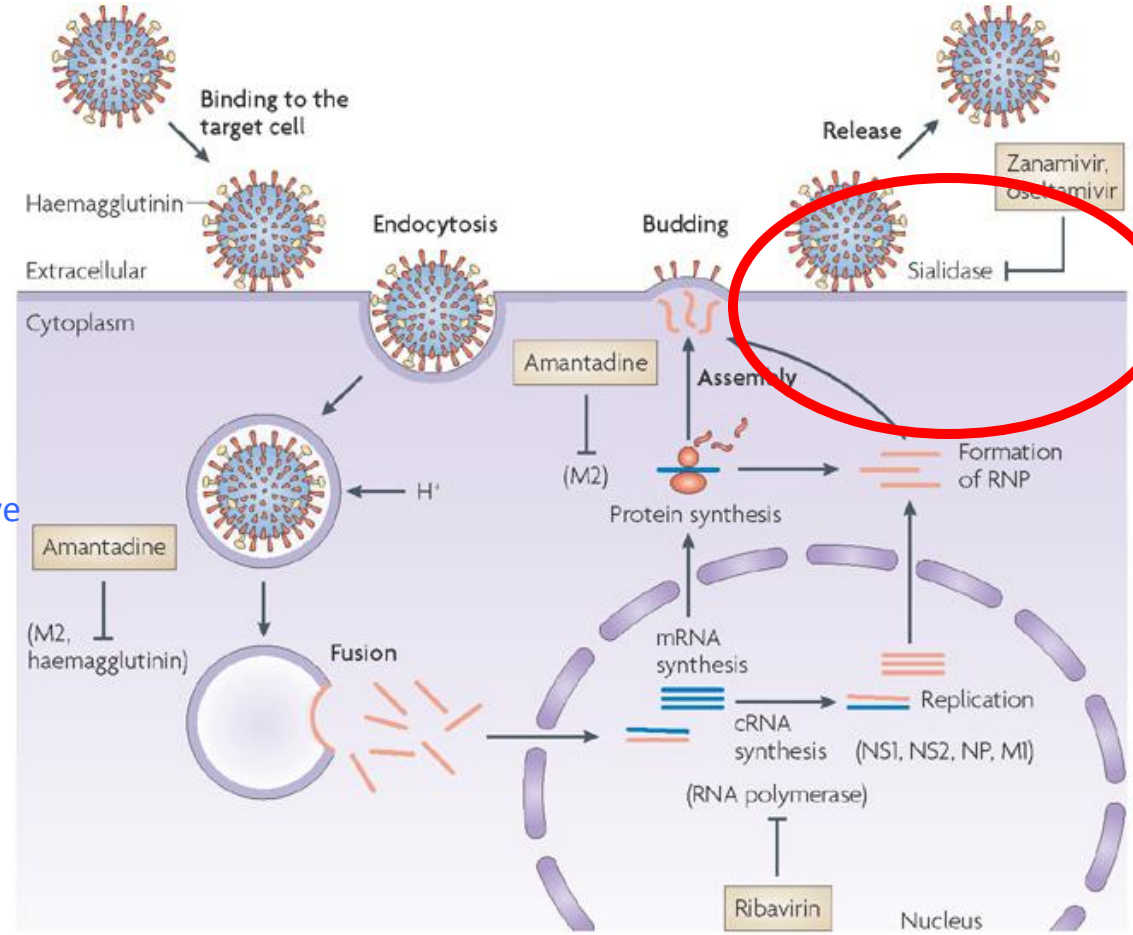
•Japan, the Republic of Korea, and Malaysia have controlled their outbreaks and are now considered free of the disease. Elsewhere in Asia, the virus has become endemic in several of the initially affected countries.

•Source: WHO



viral replication and drug targets

- Influenza virus membranes contain two glycoproteins: haemagglutinin and neuraminidase.
- 2 groups of neuraminidase subtypes:
  - group-1 contains the subtypes N1, N4, N5 and N8 (Avian Flu is of N1 subtype).
  - group-2 contains the subtypes N2, N3, N6, N7 and N9.
- The enzyme facilitates the spread of virus during an infection, thus becomes an attractive target for antiviral drugs. E.g. of drugs inhibit its activity are oseltamivir and zanamivir.
- These inhibitors were originally developed using crystal structures of neuraminidase subtypes N9 and N2 and another neuraminidase from the type B genus of influenza viruses.
- Other drug targets include M2, H2 and RNA polymerase.



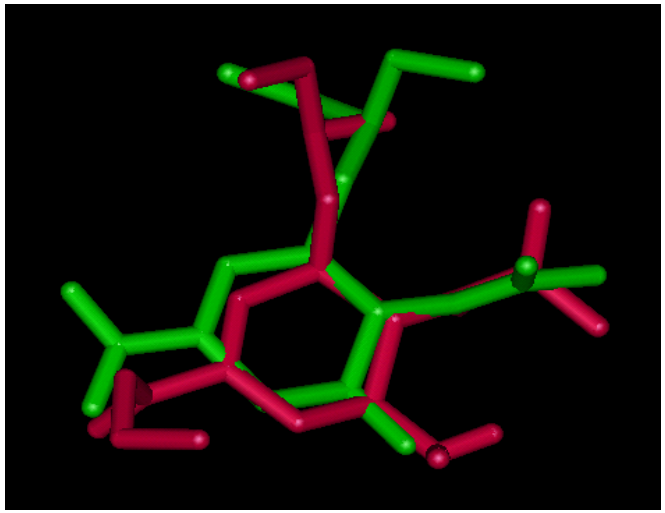
Nature Reviews | Drug Discovery

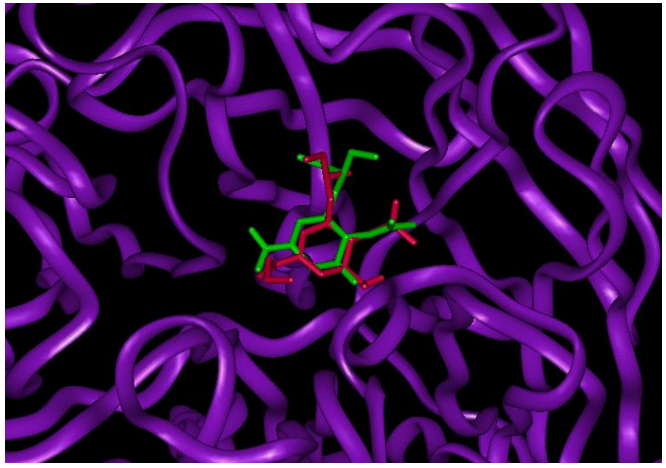
in-silico screening using NADI

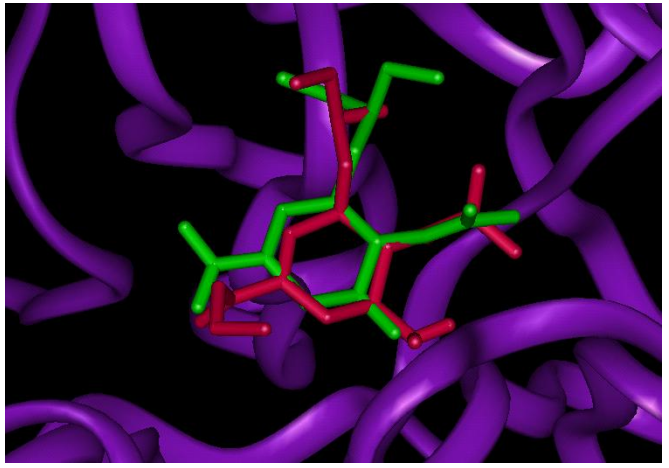
Total: 208 plants
3500 cpds

Docking of Oseltamivir onto H5N1 Neuraminidase

- RMSD: 1.3 Å
- Predicted Ki = 0.13 nM (exp Ki ranging from 0.073 – 0.37 nM, AAC, Aug. 2006)

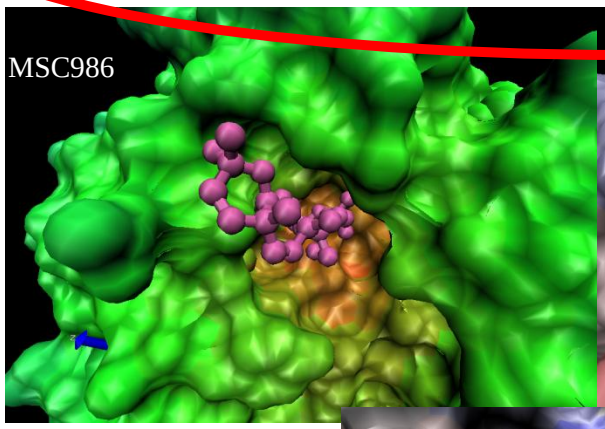


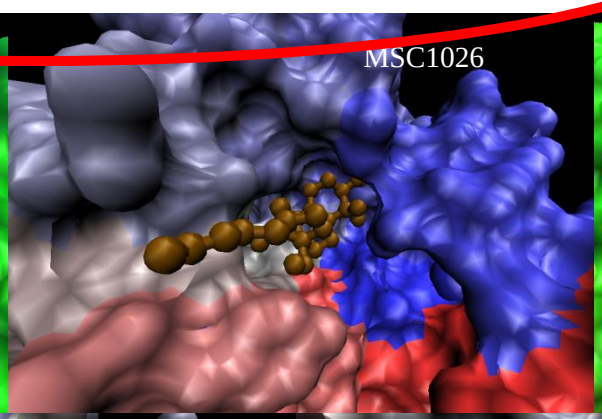


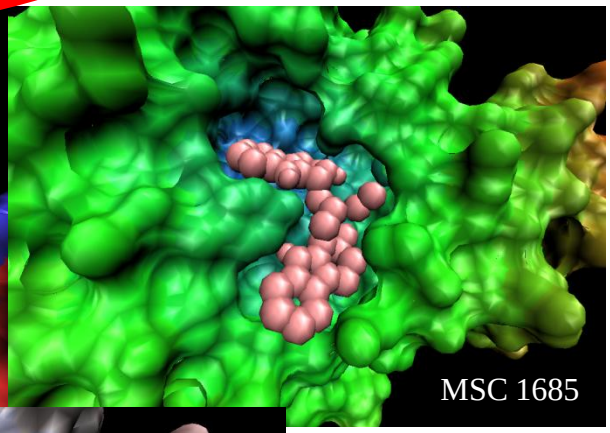


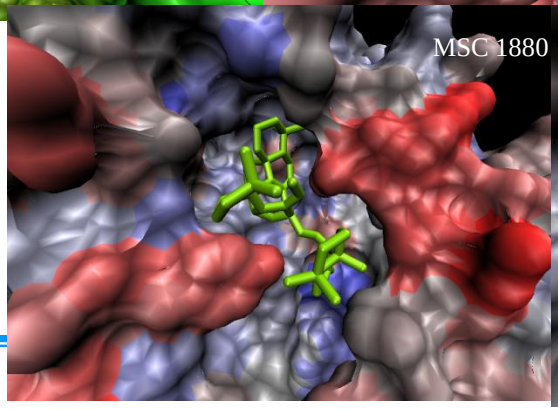
Top 5 compounds screened from MD trajectories of neuraminidase

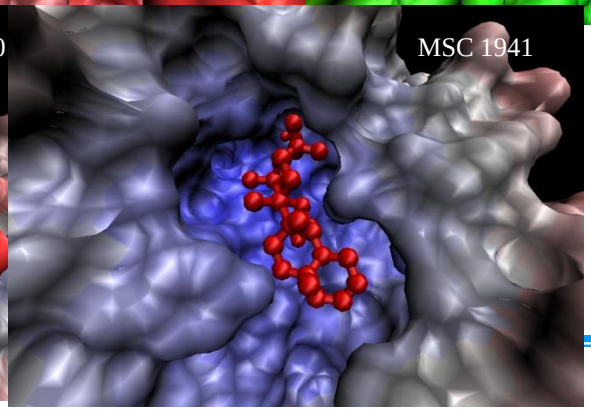
Compound name	Final Docked energy, kcal/mol	Inhibition constant, Ki
MSC 986	-11.27	5.35E-09
MSC 1026	-12.54	3.45E-09
MSC 1685	-12.71	6.29E-09
MSC 1880	-15.55	8.58E-10
MSC 1941	-12.22	9.42E-10



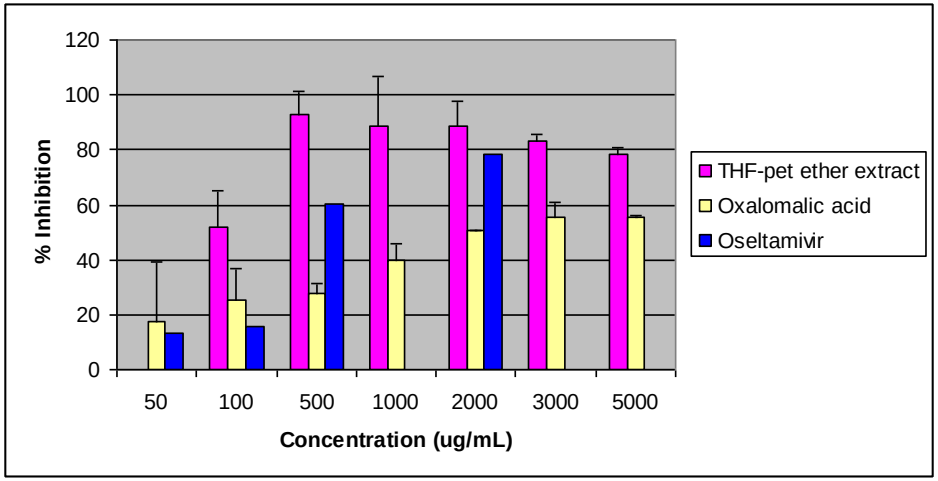


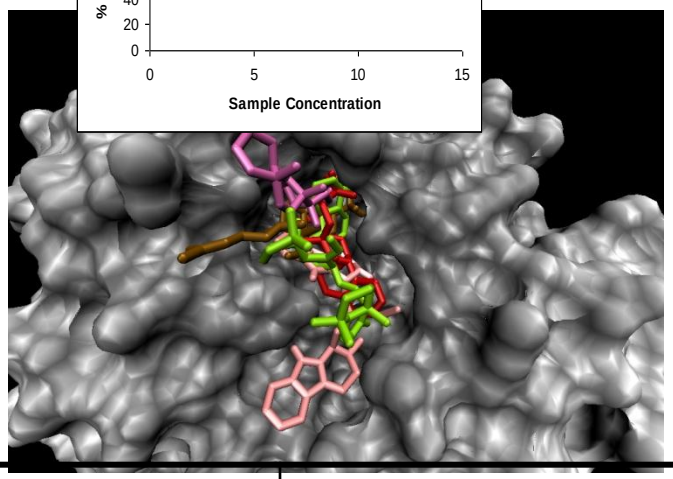






Preliminary results of enzyme Inhibition Studies

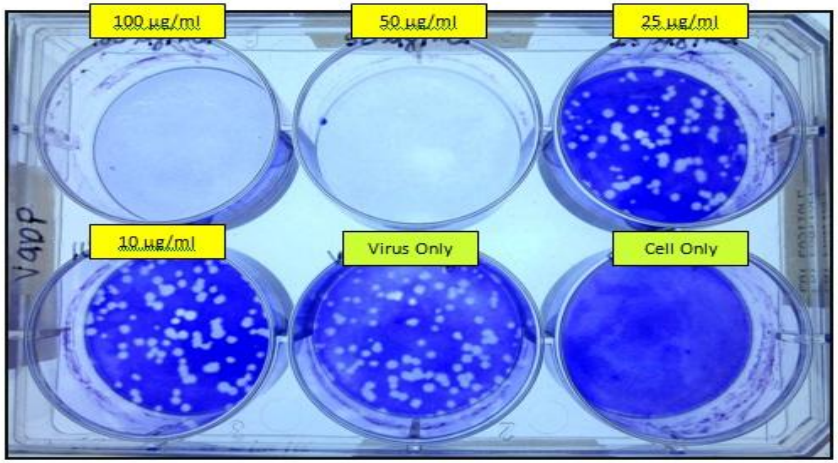




Sample Concentration (µg/ml)	% inhibitory i	% inhibitory ii	Average
12.00	95.50	95.80	95.65
3.00	83.20	84.90	84.55
1.50	59.80	77.10	68.45
0.75	67.80	72.10	69.95
0.05	47.60	49.70	48.65

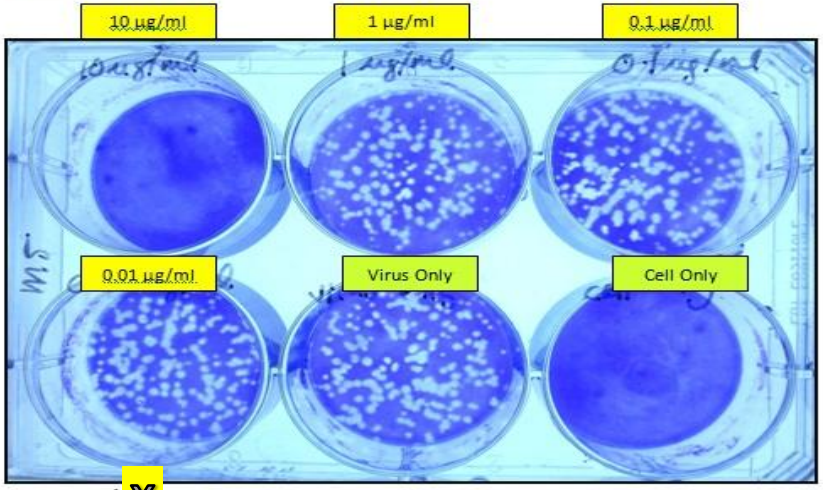
Plaque assay experiment : Testing the compound againts live H1N1 virus

Figure 5.



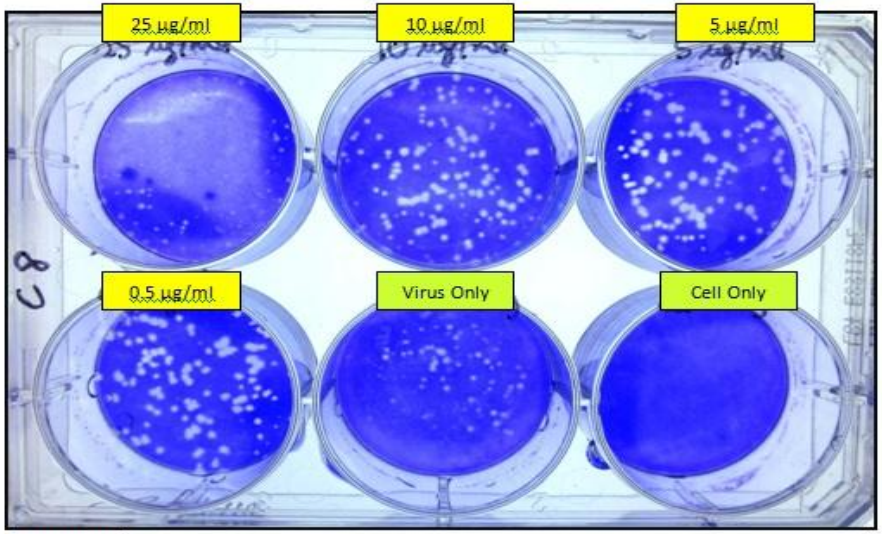
Compound VADP.

Figure 6.



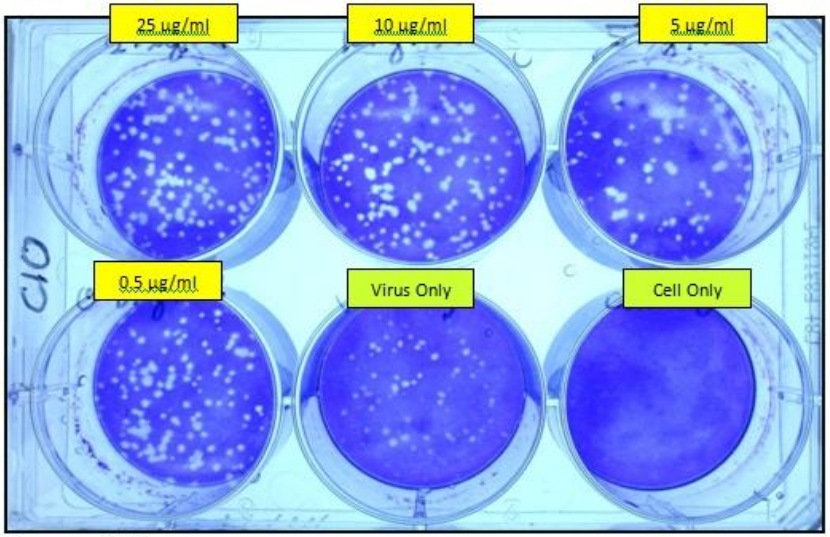
Compound X

Figure 7.



Compound C8.

Figure 8.



Compound C10.

NADI, Herbals, Cosmetics and Specialty Chemicals

Pharmaceutical

Nutraceutical

Natural Product Discovery: Way Forward

- NADI database and bioinformatics approach important and have values to:
  - the rational selection of plants for further studies
  - survey new chemical structures found in various classes of natural compounds
  - predict compounds with new pharmacological activity (compounds only have value if they act differently or on new targets relative to known structures)
  - utilise natural products derived structures as guiding principle for new chemical library for synthesis.
    - Analogues of natural products can be more potent than the parent compounds, or possess superior drug-like properties.
    - New biological activities not even seen with the parent molecule.
    - Intensified search for new natural product derived molecules.
- Collaboration efforts from different disciplines – rapid and cost-effective discovery
- Safeguard our natural treasure (wealth, security)

Acknowledgement

NADI Developers:

NAPIMM:

- Yam Wai Keat, Nurul Bahiyyah, Suhaini Ahmad

NADI-RA

- Nur Hanani Che Mat

NADI-HERBS

- Nornisah Mohamed

NADI-CHEM

- Suhaini Ahmad, Ezatul E Kamarulzaman, Ros Fatihah Halim, Nur Faezah Abdullah

NADI-VISAGE

- Suhaini Ahmad,
- Junya Seo (PhD, Osaka U)
- Mitsuru Jikeya (MSc, Osaka U)
- Masafumi Tominaga (MSc, Osaka U)

BIRD FLU RESEARCH GROUP

Academic PI

•Dr. Aisyah Saad Abdul Rahim
•Dr. Hasnah Osman
•Dr. Shafida Abdul Hamid
•Dr. Nornisah Mohamed
•Dr. Razip Samian
•Dr. Normi Yusuf
•Dr. Rashidah Abdul Rahim
•Dr. Shaharum Shamsuddin
•Dr. Sharifah Syed Hassan

Funding
USM Research University Grant

TB Drug Discovery
•Dr. Shaida Fariza Sulaiman
•Suriyati Muhamad
•Dr. Pazilah Ibrahim
•Dr. Choong Yee Siew
Funding
MOSTI-EScience

Post Doctoral Fellow
Dr. Hassan Abdullah
Dr Muhamad TM Al Dajani

Postgraduates:

- Mohd Razip Asaruddin (PhD)
- Suhaini Ahmad (MSc)
- Nurul Izzah (MSc)
- Noor Hamdah Musa (MSc)
- Siti Marina Maidin (MSc)
- Sharizan Abdullah (MSc)
- Fauziah Hanim (MSc)
- Fauziahanim Zakaria (MSc)

Internship Students:

- Vicky Yang (BSc, UCSD)
- Cindy Trans (BSc, UCSD)
- Ranmali Varahenage (BSc, UC San Diego)

Thank You