African Medicinal Plants: Natural Product Database Development, Lead Discovery and Toxicity Assessment

Dr. Fidele Ntie-Kang[1,2]

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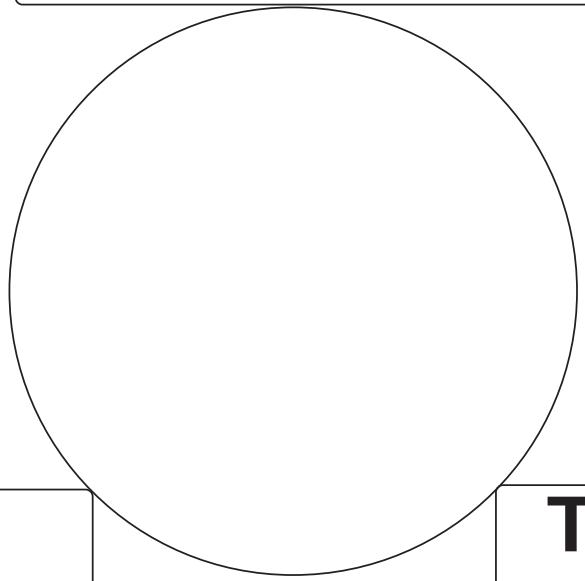
12 June 2018

Concept



NP Databases

-p-ANAPL
-NANPDB
-Afrocancer
-AfroDb
-ConMedNP, etc.

Lead Discovery

-Virtual screening
-Modeling of drug-target interactions
-Nature-inspired lead discovery
-DMPK profiling

Toxicity Prediction

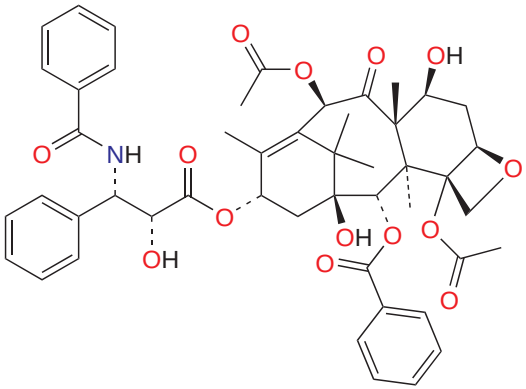
-Knowledgbase development
-Eco-Derek (chemical alerts)
-Tox Prediction

Outline

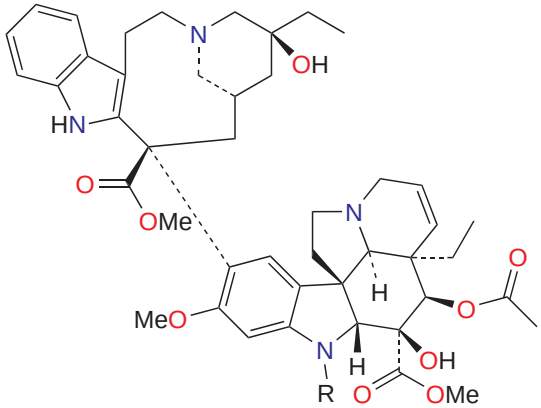
1. Natural Product Databases
   - Focus on African sources
2. Lead Compound Discovery
   - Lead Compounds Discovery by Virtual Screening and Biological Testing
3. Toxicity Prediction
   - Develoment of Toxicity Prediction Knowledgbase

Outline

Natural Products
Preamble

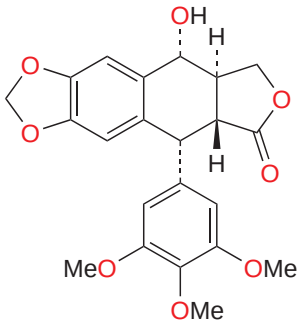


Paclitaxel or Taxol (**1**)

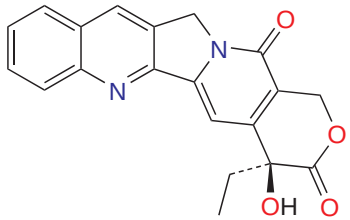


Vinblastine or vincaleukoblastine (**2**): R = CH_3

Vincristine or leurocristine (**3**) : R = CHO



Podophyllotoxin (**4**)



Camptothecin (**5**)

2D structures of selected naturally occurring NP anticancer drug leads.

Natural Products

Some statistics

Table: Natural products *versus* synthetic drugs

Newman and Cragg. *J. Nat. Prod.* **2016**, 79:629-661

Property	NPs	SDs
Samples	Limited quantities (time consuming extraction processes)	Readily available
Drug-likeness	Weaker bioavailability (poor DMPK)	More bioavailable
Chemistry	Complex scaffolds, more stereogenic centres	Less O atoms, less aromatics, etc.
Marketed drugs	- 6% (unaltered),	
	-26% (NP derivatives),	
	-32% (NP mimics) or from NP ph4s	
	-73% of small molecule antibacterials	
	-50% of anticancer drugs (e.g. taxol)	

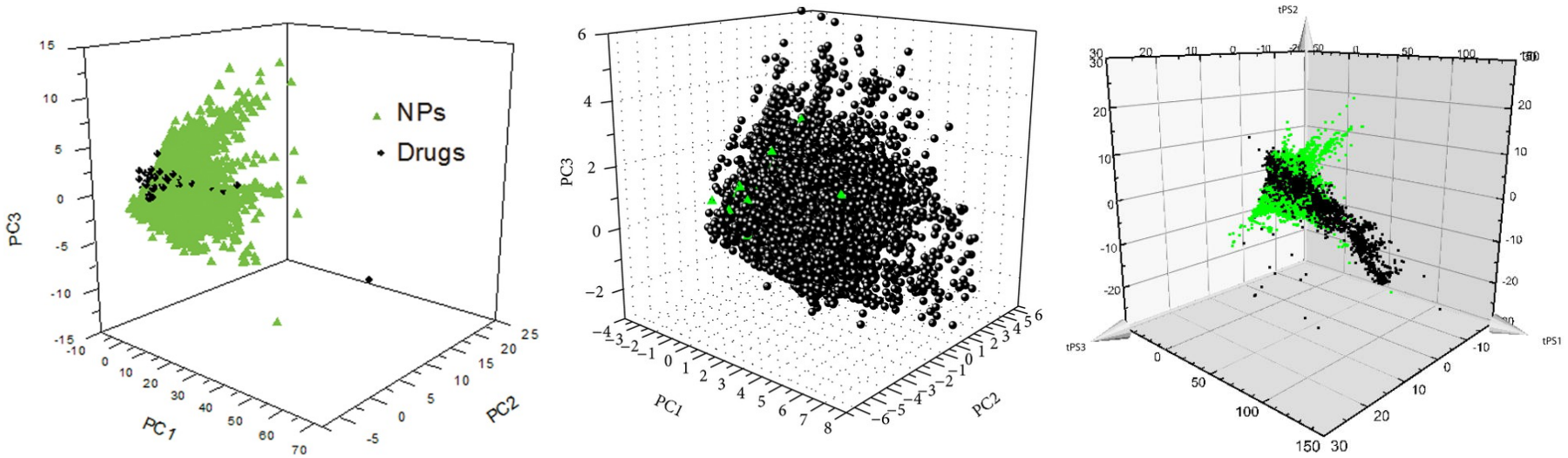
Natural Products

Some recent assesments I

- *~10% of known NP chemical space is purchasable*
- *Much more on demand (outsourcing services, collaborations, etc.)*
- Chen *et al*., Data resources for the computer-guided discovery of bioactive natural products. *J. Chem. Inf. Model*. **2017**, 57(9):2099-2111

Natural Products

Chemical space of natural products



(left) NPs (green) in the UNPD and FDA-approved drugs (black):
Lachance *et al.*, *J. Med. Chem.*, **2012**, 55:5989-6001.
(middle) NPs in MPs (black) and 25 FDA-approved drugs against T2DM (green):
Rosén *et al.*, *J. Med. Chem.*, **2009**, 52:1953-1962.
(right) Predicted score (tPS) plots of NPs (green) and bioactive med chem cpds from the WOMBAT database (black):

Feher & Schmidt. *J. Chem. Inf. Comput. Sci.*, **2003**, 43:218-227.

Assessment Criteria

Drug-likeness *versus* natural product-likeness assessment

'Drug-likeness': Lipinski *et al.* (2001)

- Likely OA if: $MW \leq 500$ Da; $\log P \leq 5$; $HBA \leq 10$; $HBD \leq 5$

'Lead-likeness': Teague *et al.* (1999)

- Likely LC if: $150 \leq MW \leq 350$ Da; $\log P \leq 4$; $HBA \leq 6$; $HBD \leq 3$

'NP-likeness': Ertl *et al.* (2008)

- Likely an NP if:

$$f_i = \log\left(\frac{A_i}{B_i} \cdot \frac{B_{tot}}{A_{tot}}\right)$$

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Natural Products from African Medicinal Plants II

General objectives

- Generate electronically accessible 3D models for molcular modeling research.
- Valorise the use of medicinal plants in Africa in traditional medicine.
- Identify lead compounds from medicinal plants by using computer modeling (e.g. *via in silico* docking and ph4 modeling).
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Natural Products from African Medicinal Plants IV

Our contributions I.

RSC Advances

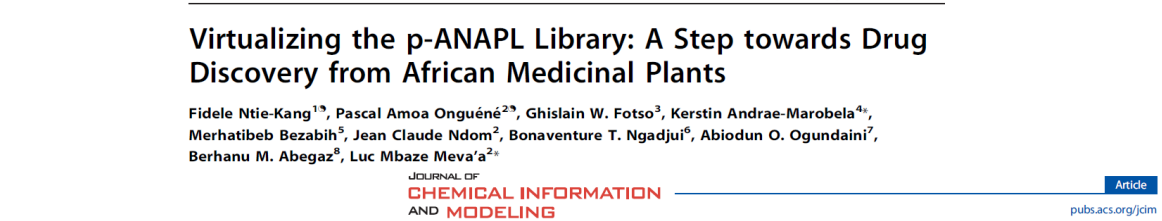
COMMUNICATION

ConMedNP: a natural product library from Central African medicinal plants for drug discovery†

Cite this: *RSC Adv.*, 2014, 4, 409

Received 19th July 2013
Accepted 24th October 2013

Fidele Ntie-Kang,*[abc] Pascal Amoa Onguéné,[d] Michael Scharfe,[c] Luc C. Owono Owono,[e] Eugene Megnassan,[f] Luc Meva'a Mbaze,[d] Wolfgang Sippl[c] and Simon M. N. Efange[b]



OPEN ACCESS Freely available online

PLOS ONE

Virtualizing the p-ANAPL Library: A Step towards Drug Discovery from African Medicinal Plants

Fidele Ntie-Kang[1☯], Pascal Amoa Onguéné[2☯], Ghislain W. Fotso[3], Kerstin Andrae-Marobela[4*], Merhatibeb Bezabih[5], Jean Claude Ndom[2], Bonaventure T. Ngadjui[6], Abiodun O. Ogundaini[7], Berhanu M. Abegaz[8], Luc Mbaze Meva'a[2*]

JOURNAL OF CHEMICAL INFORMATION AND MODELING

Article

pubs.acs.org/jcim

Molecular Modeling of Potential Anticancer Agents from African Medicinal Plants

Fidele Ntie-Kang,*[,†,‡,#] Justina Ngozi Nwodo,[§,#] Akachukwu Ibezim,[§] Conrad Veranso Simoben,[†] Berin Karaman,[‡] Valery Fuh Ngwa,[∥] Wolfgang Sippl,[‡] Michael Umale Adikwu,[⊥] and Luc Meva'a Mbaze*[,⊗]

JOURNAL OF NATURAL PRODUCTS

Article

pubs.acs.org/jnp

NANPDB: A Resource for Natural Products from Northern African Sources

Fidele Ntie-Kang,*[,†,‡,#] Kiran K. Telukunta,[§,#] Kersten Döring,[§] Conrad V. Simoben,[†] Aurélien F. A. Moumbock,[‡] Yvette I. Malange,[‡] Leonel E. Njume,[∥] Joseph N. Yong,[‡] Wolfgang Sippl,[†] and Stefan Günther*[,§,⊥]

http://african-compounds.org/about/

Natural Products from African Medicinal Plants VI

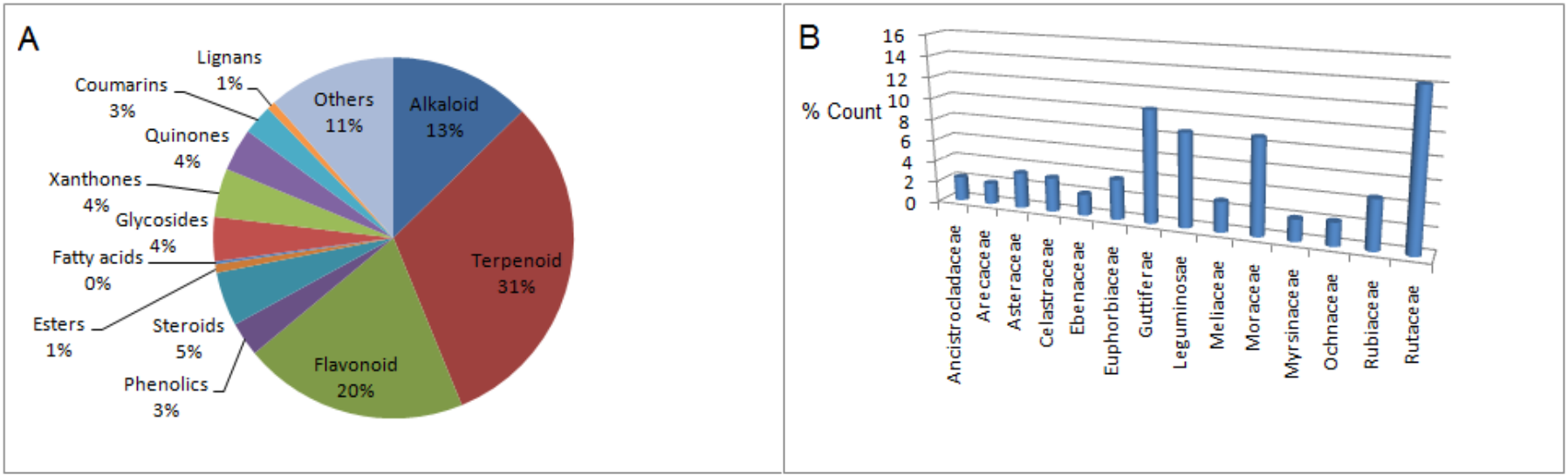
Our contributions III.

Summary of electronic databases developed within this work.

Library name	***Library size***	***Source organisms***	***Families***
CamMedNP	1,859	224	55
ConMedNP	3,177	376	79
AfroDb	986	–	–
AfroCancer	390	–	–
AfroMalariaDb	511	131	45
Afrotryp	321	–	22
p-ANAPL	534	ND	ND
NANPDB	4,928	751	155

Natural Products from African Medicinal Plants IV

Modeling AfroCancer compounds.



Ntie-Kang *et al. J. Chem. Inf. Model.*, **2014**, 54(9):2433–2450

Natural Products from African Medicinal Plants IV

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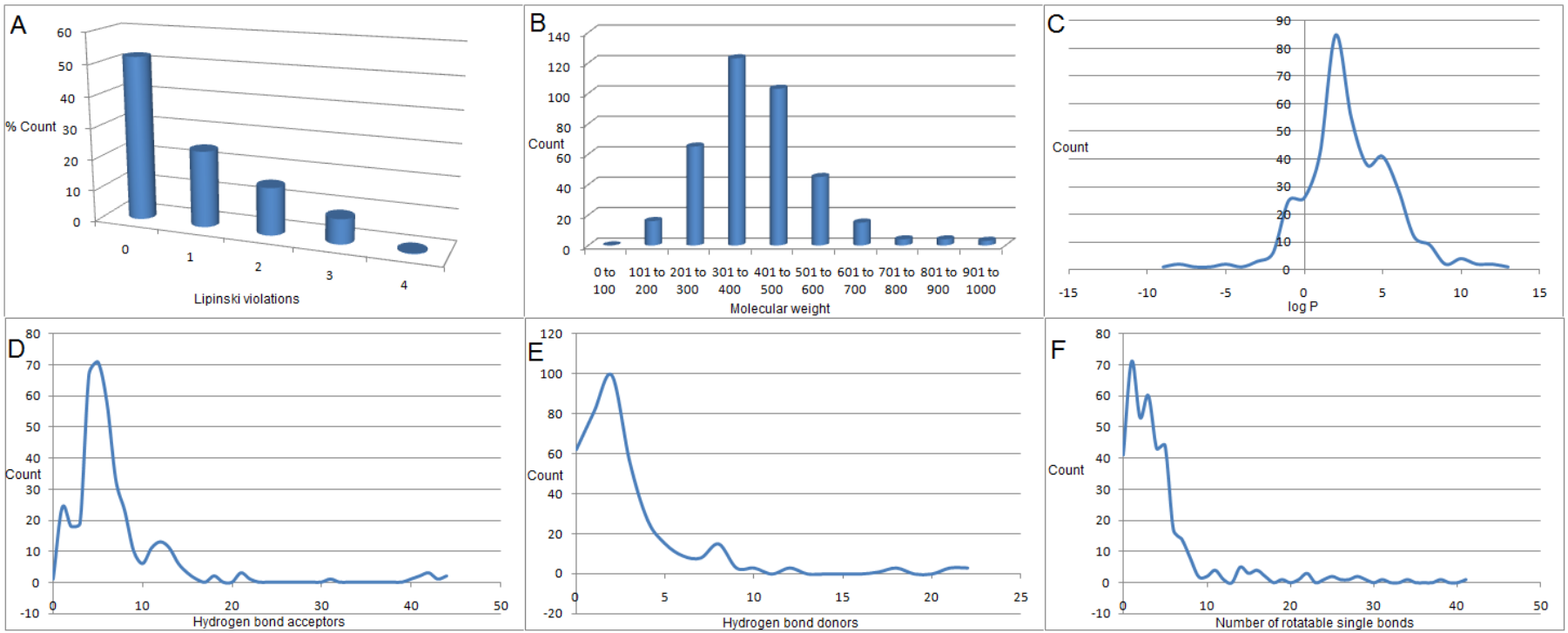

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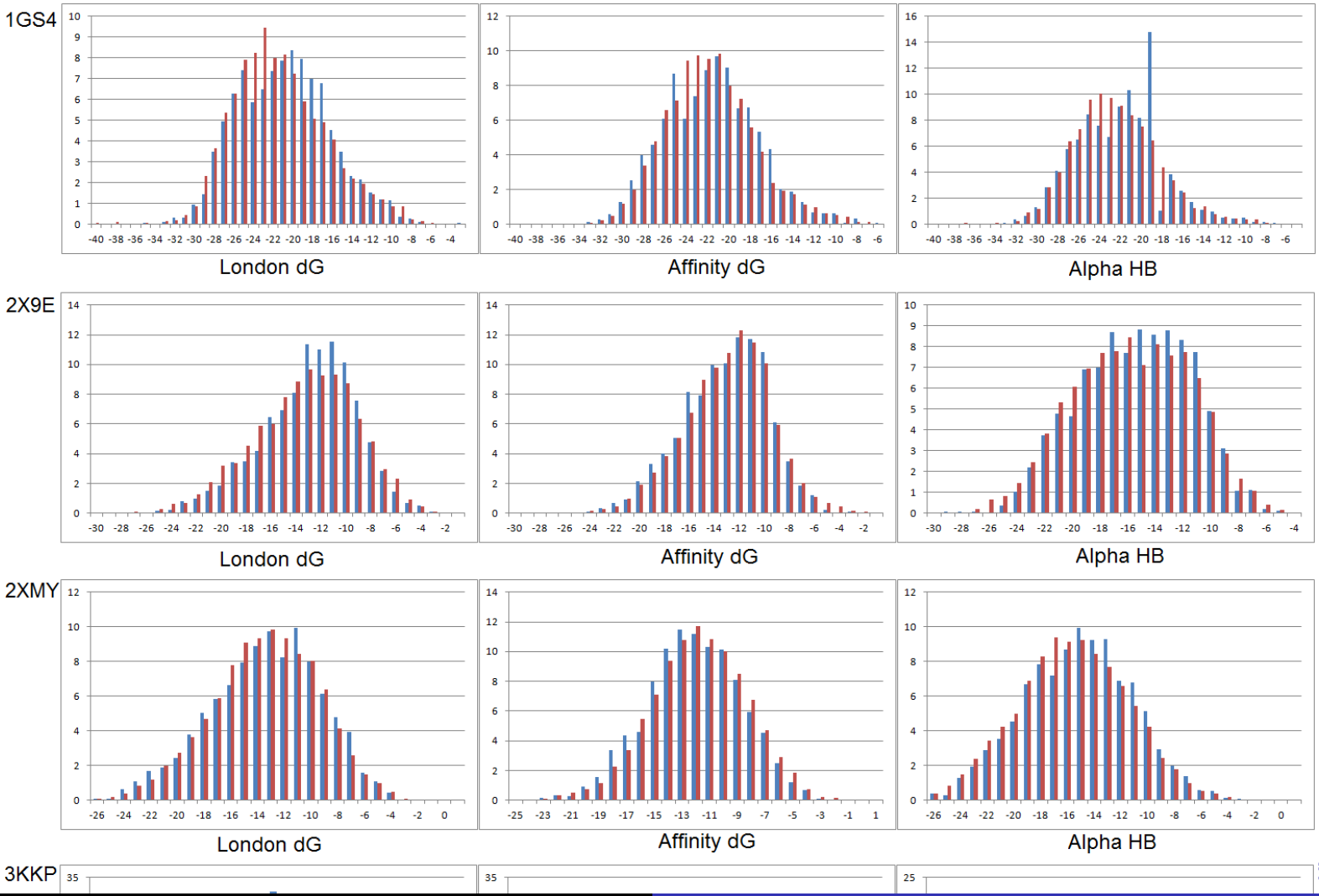

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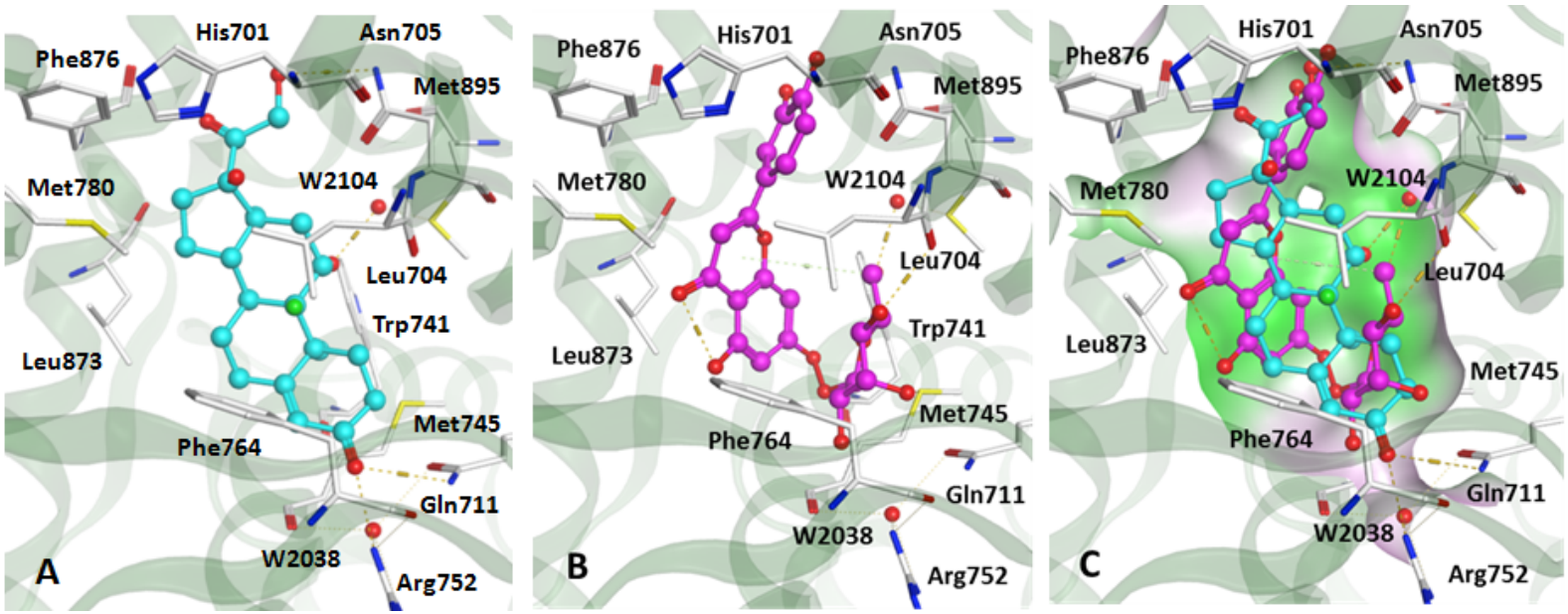
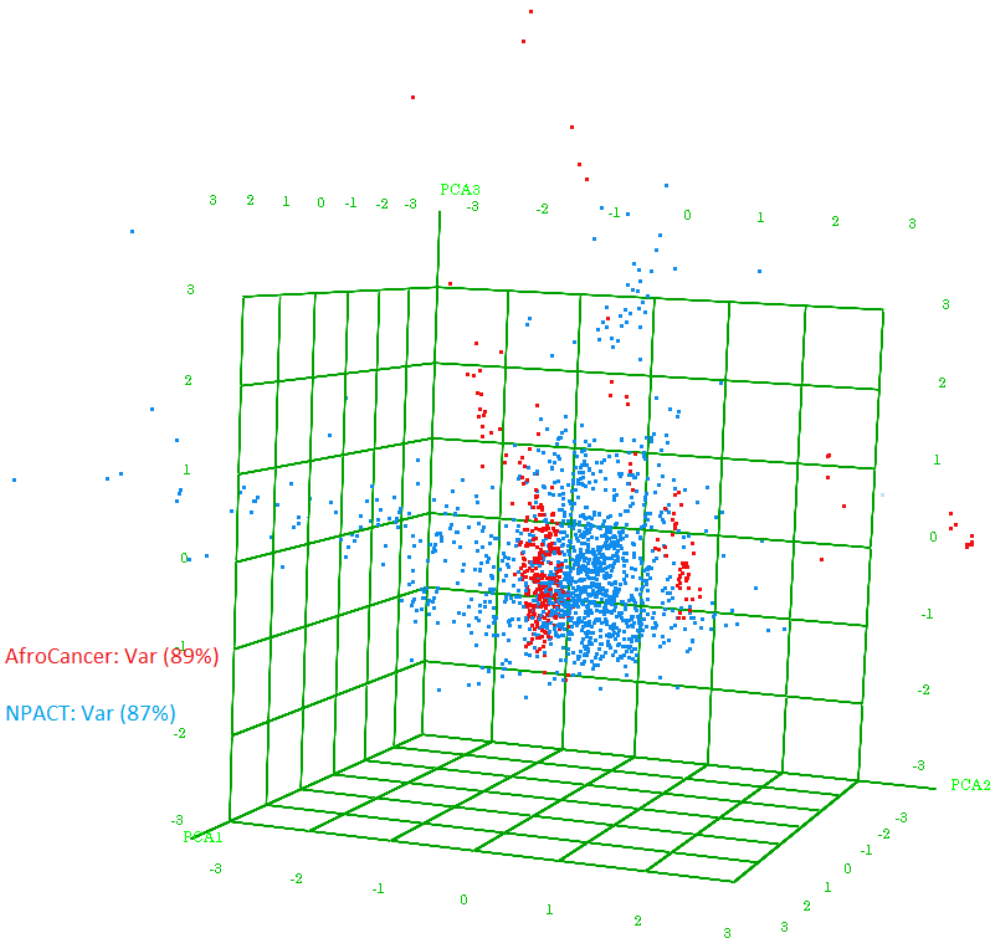


Top scoring pose for Glide docking of AfroCancer for modeling of the androgen receptor: (A) crystal structure the drug target (1GS4) in complex with cocrystallized 9α-fluorocortisol. (B) in complex with docked luteolin-7-O-β-glucopyranoside (from the Egyptian medicinal plant, *Livistona australis*). (C) Comparison of binding modes of docking pose of the luteolin-7-O-β-glucopyranoside with co-crystallized 9α-fluorocortisol. Polar regions are shown in magenta, hydrophobic regions in green.

Natural Products from African Medicinal Plants IV

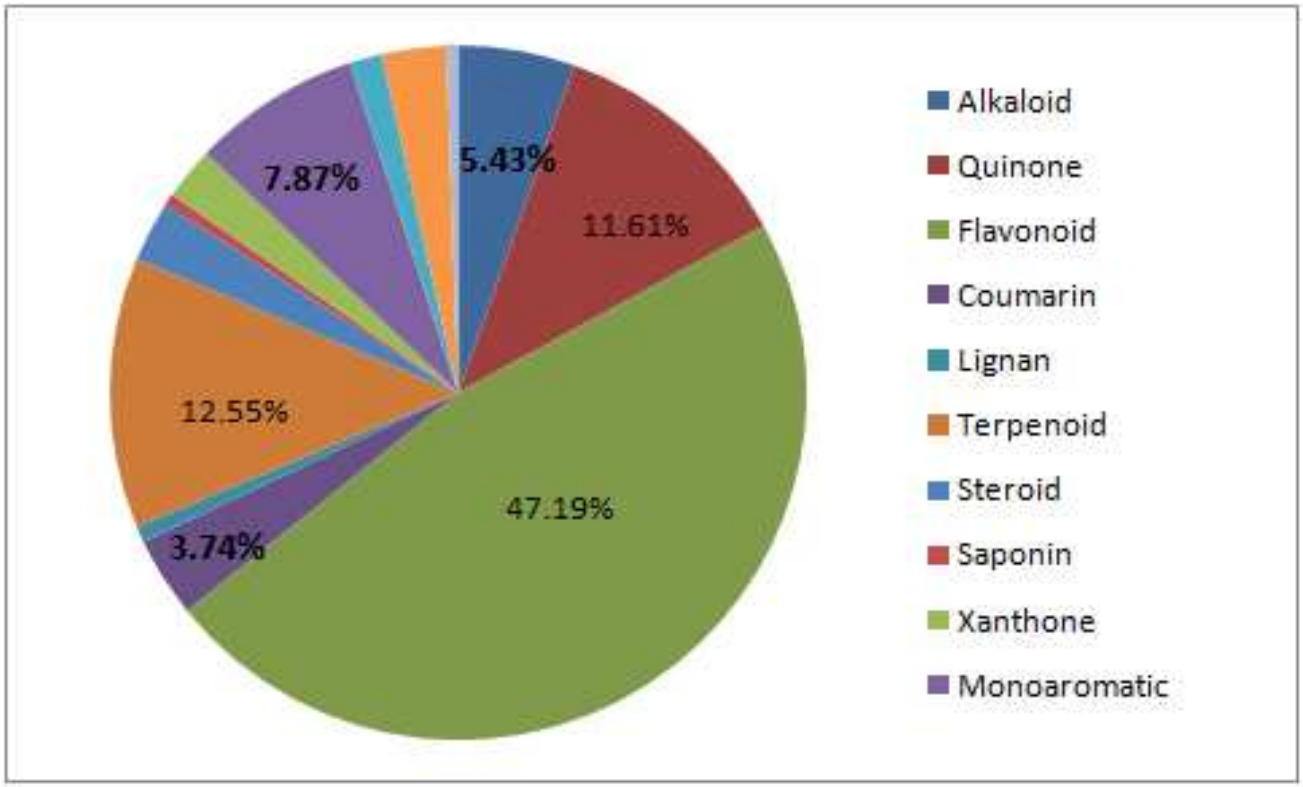
Modeling AfroCancer compounds.



Ntie-Kang *et al.* *Drug Design Dev Therapy.*, **2016**, 10:2137-2154

Natural Products from African Medicinal Plants V

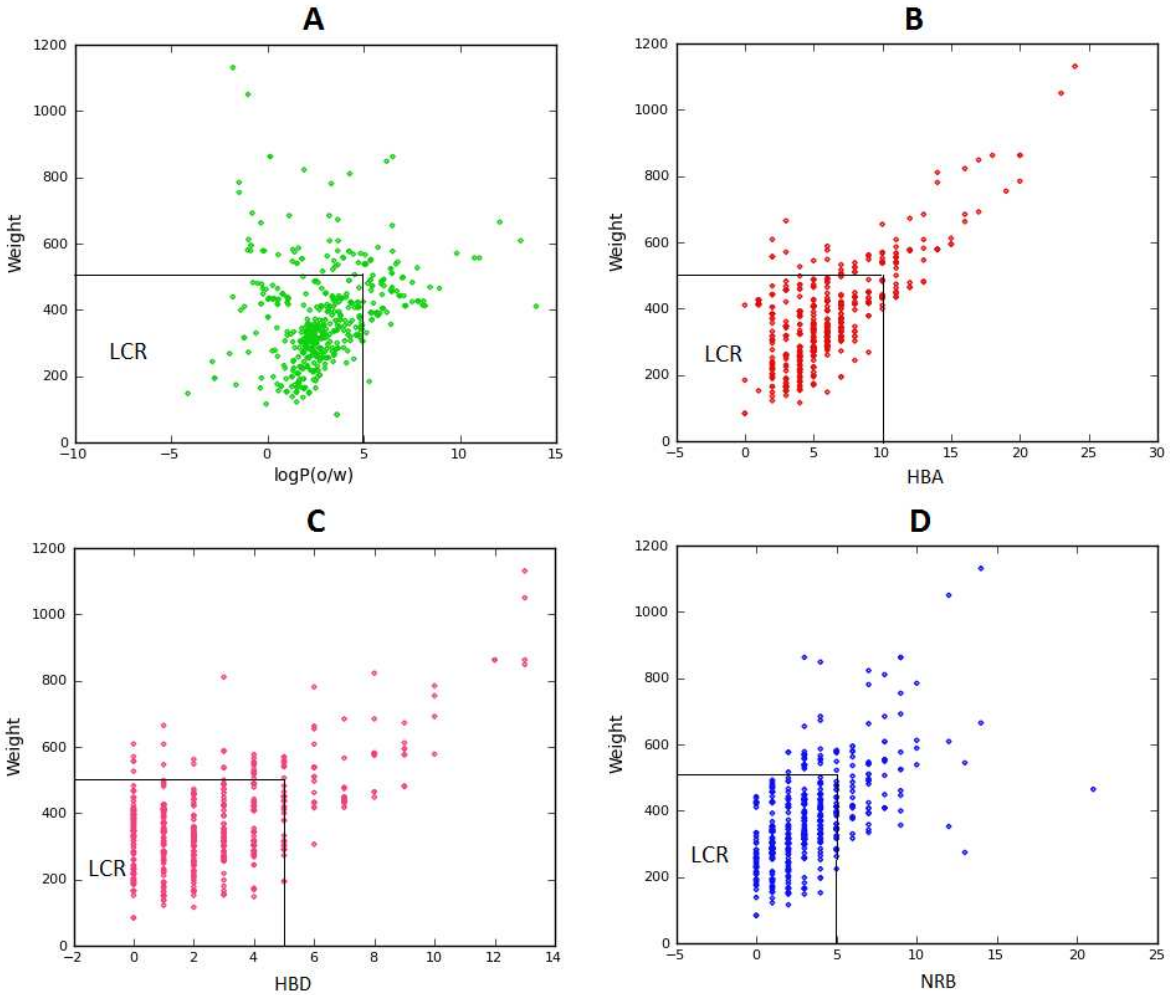
The p-ANAPL project.



Ntie-Kang *et al.* *PLoS ONE*, **2014**, 9(3): e90655.

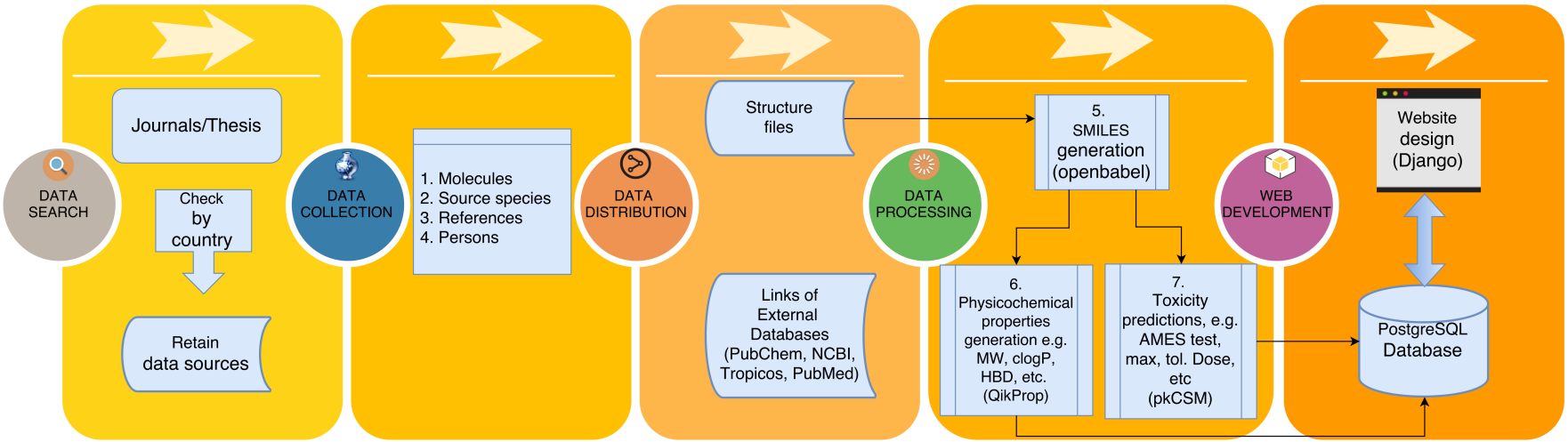
Natural Products from African Medicinal Plants V

The p-ANAPL project.



Natural Products from African Medicinal Plants V

The NANPDB project.



Ntie-Kang *et al. J. Nat. Prod.*, **2017**, 80(7):2067-2076.

Natural Products from African Medicinal Plants V

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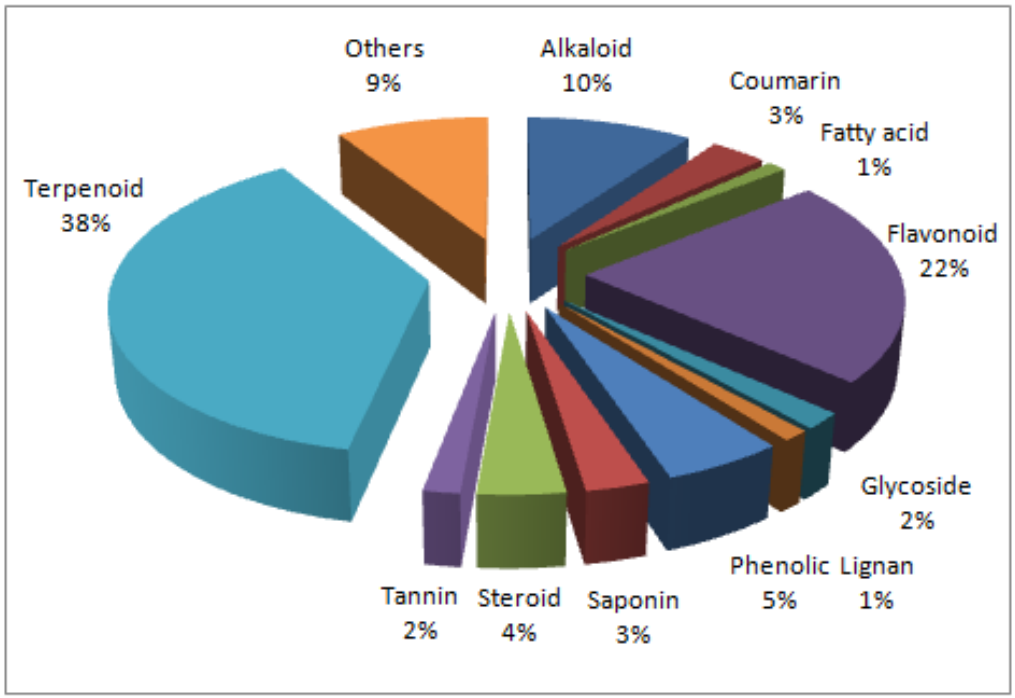
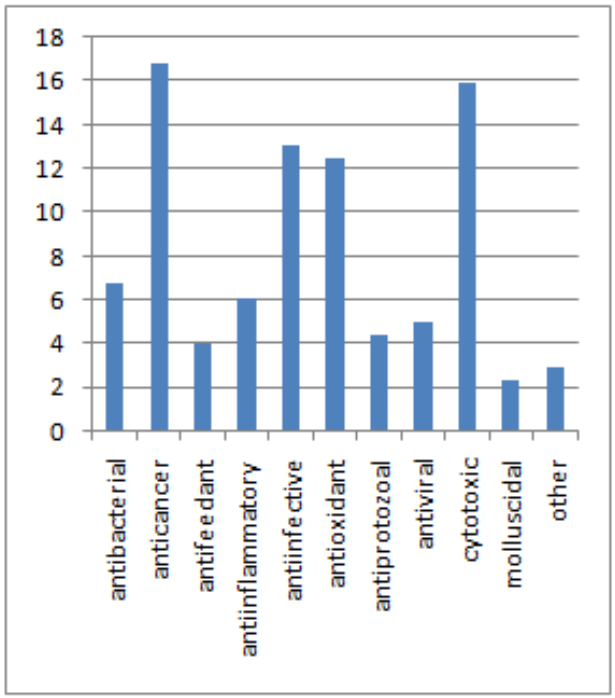
A



B



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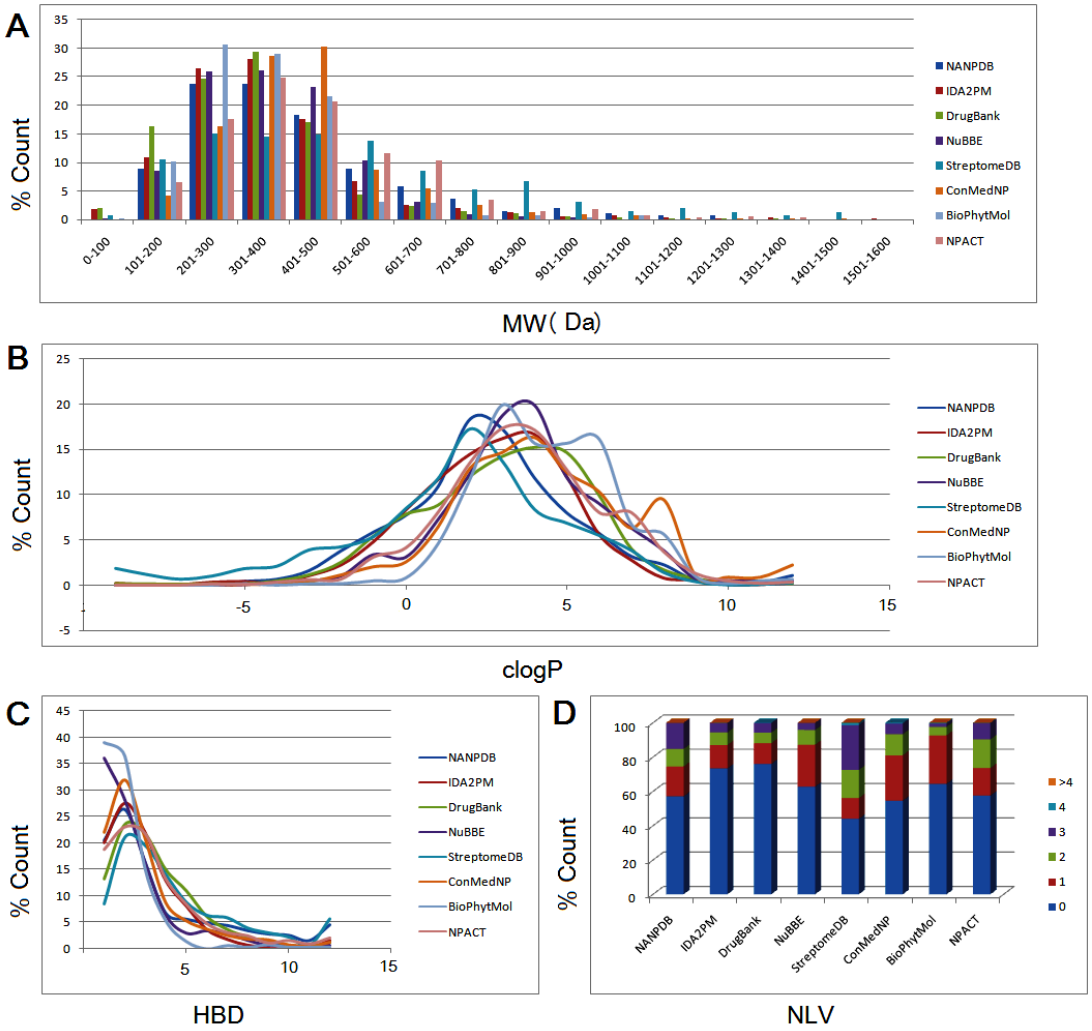

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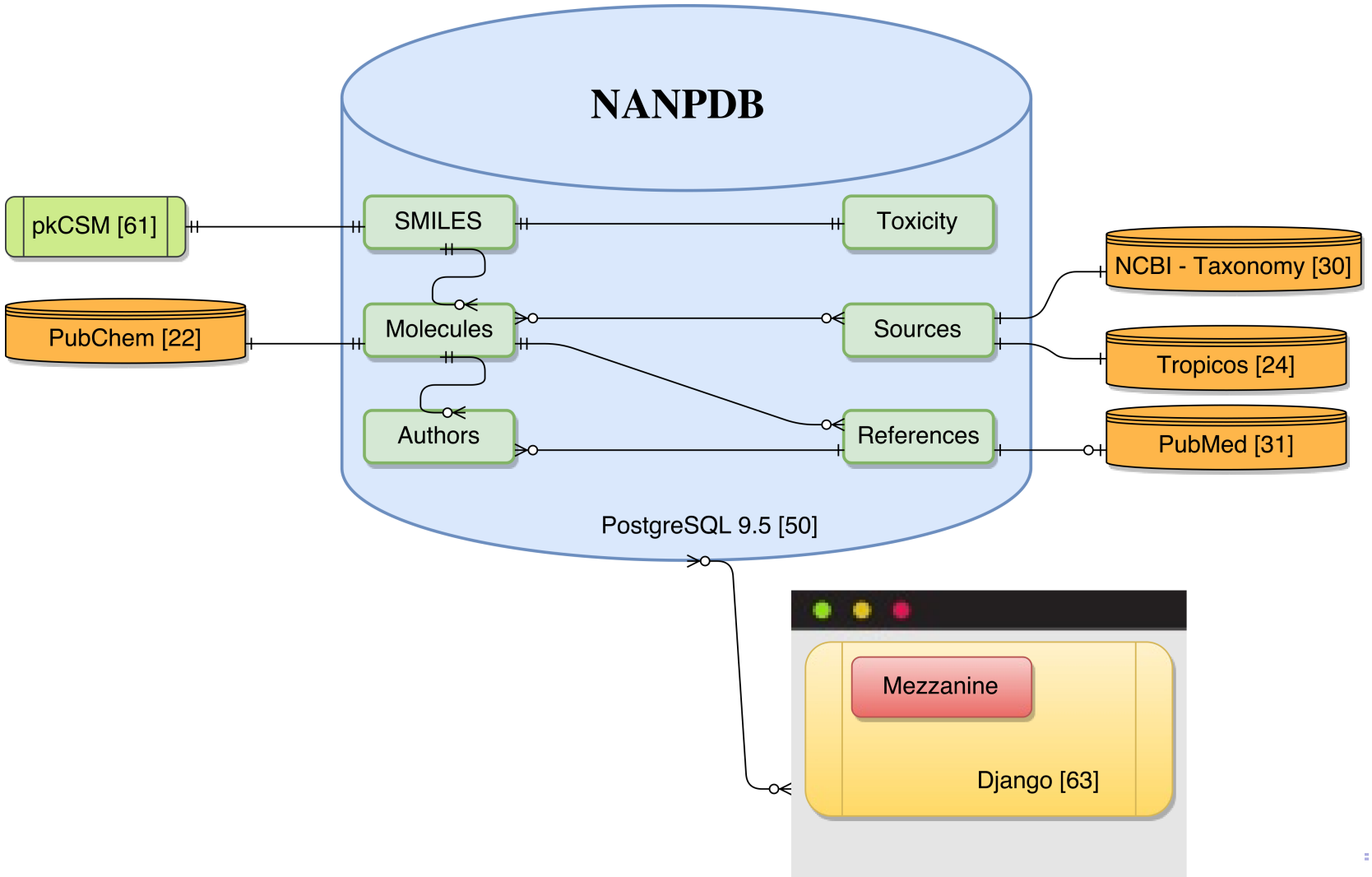

Outline

Pharmacophore-based Virtual Screening

Background and motivation

- Currently, no licensed ARVs target the accessory proteins of HIV-1.
- Vpu is an 81–82 amino acid transmembrane protein that is found in HIV-1.
- Vpu enhances viral replication through multiple functions, e.g. by downregulating CD4 and the host restriction factor BST2/CD317/tetherin. Vpu is also reported by some to have ion channel activity
- HIV-1 viruses with defective Vpu generally display reduced spread, defects in viral budding, and accumulation at the surface of infected cells.
- Thus, effective replication of HIV *in vivo* requires a functional Vpu protein, which makes it a promising drug target.

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Pharmacophore-based Virtual Screening

Literature

Anal Bioanal Chem (2010) 396:2559–2563
DOI 10.1007/s00216-010-3498-x

SHORT COMMUNICATION

Ligand-protein docking studies of potential HIV-1 drug compounds using the algorithm FlexX

George Patargias · Gary Ewart · Carolyn Luscombe · Wolfgang B. Fischer

ELSEVIER

Biochimica et Biophysica Acta 1512 (2001) 291–298

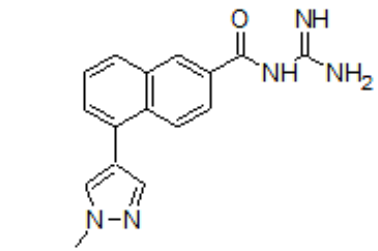
www.bba-direct.com

The structure of the HIV-1 Vpu ion channel: modelling and simulation studies

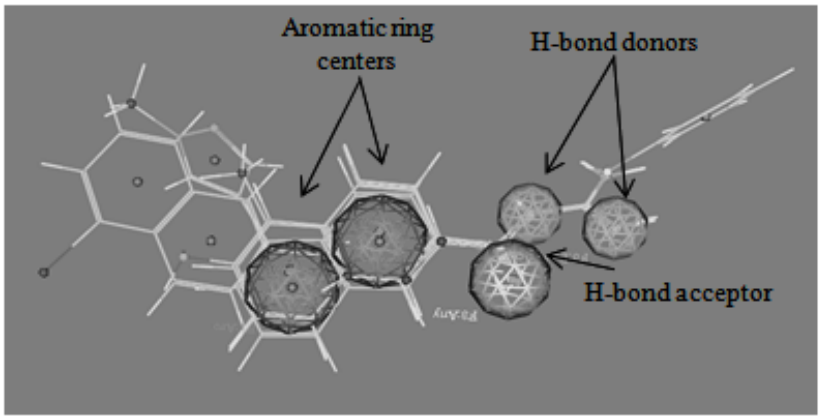
F.S. Cordes [a], A. Kukol [1,b], L.R. Forrest [a], I.T. Arkin [2,b], M.S.P. Sansom [a], W.B. Fischer [a,*]

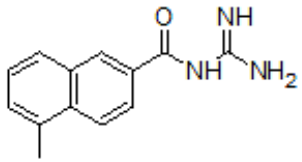
Pharmacophore-based Virtual Screening

Our contribution

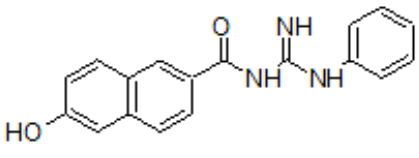


N-(5-(1-methyl-1H-pyrazol-4-yl)naphthalene-2-carbonyl)guanidine (BIT-225)

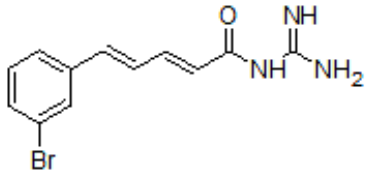




5-methyl-2-napthoylguanidine



N-(6-hydroxy-2-napthoyl)-N'-phenylguanidine

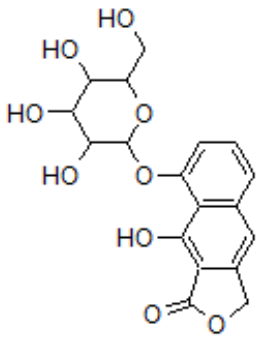


5-(3'-bromophenyl)penta-2,4-dienoylguanidine

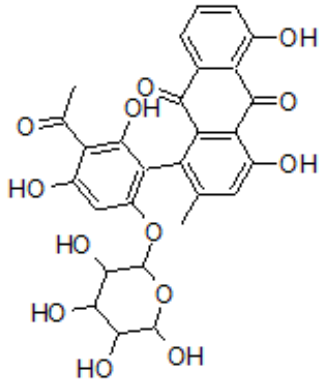
Tietjen I, Ntie-Kang F, *et al.*, *PLos ONE*, **2015**, 10(4): e0121099.

Pharmacophore-based Virtual Screening

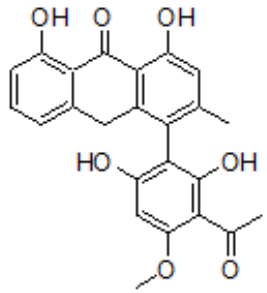
Virtual hits



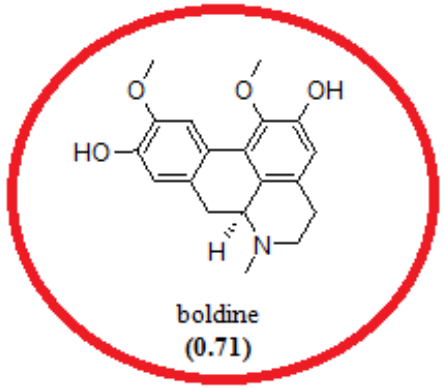
geshoidin
(0.84)



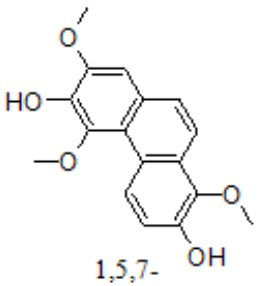
1-(3-acetyl-2,4-dihydroxy-6-((3,4,5,6-tetrahydroxytetrahydro-2H-pyran-2-yl)oxy)phenyl)-4,5-dihydroxy-2-methylanthracene-9,10-dione (2MA)
(0.74)



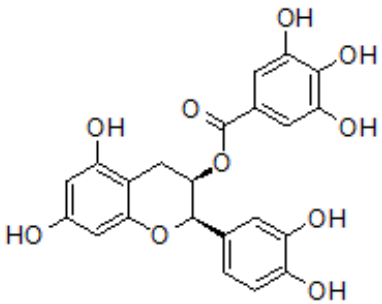
knipholone anthrone (KA)
(0.74)



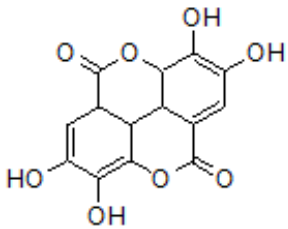
boldine
(0.71)



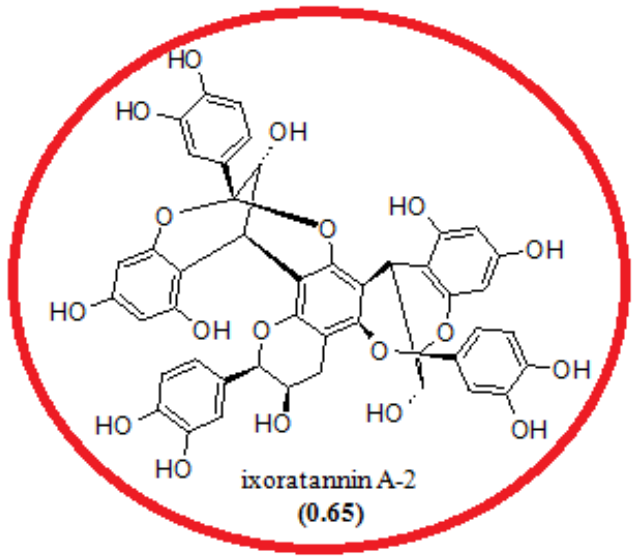
1,5,7-trimethoxyphenanthrene-2,6-diol (PA)
(0.70)



epicatechin gallate (ECG)
(0.67)



ellagic acid (EA)
(0.65)



ixoratannin A-2
(0.65)

Pharmacophore-based Virtual Screening

Virtual hits

Table 1. Cell toxicity and inhibition of HIV-1_{NL4-3} in CEM-GXR cells by p-ANAPL compounds.

Compound	Cell toxicity (CC50, μM)	HIV-1_{NL4-3} inhibition (EC50, μM)
BIT-225	10.7	n/d
geshoidin	>10	>100
2MA	50.9	>100
KA	0.9	n/d
boldine	>100	50.2
PA	26.8	n/d
ECG	>100	>100
EA	52.3	>100
ixoratannin A-2	57.5	34.4

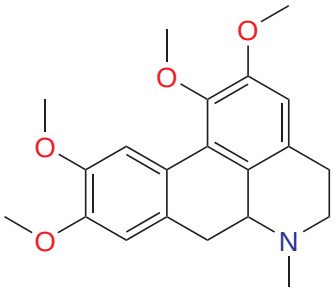
n/d, not determined.

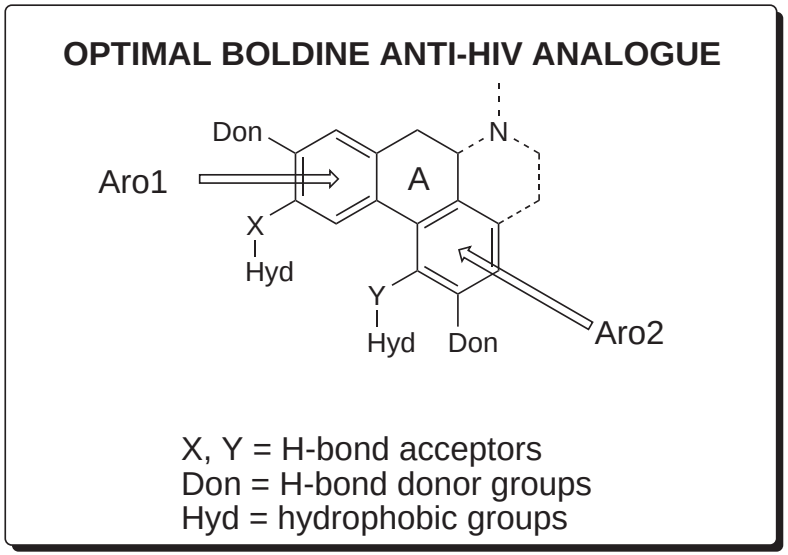
doi:10.1371/journal.pone.0121099.t001

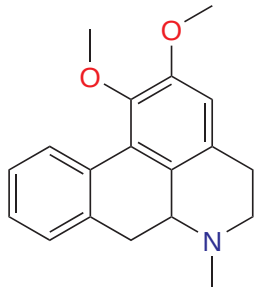
Tietjen I, Ntie-Kang F, *et al.*, *PLos ONE*, **2015**, 10(4): e0121099.

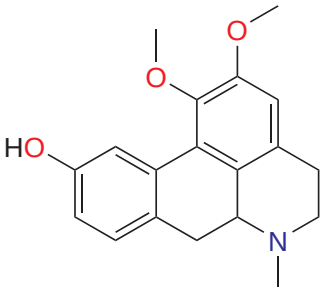
Pharmacophore-based Virtual Screening

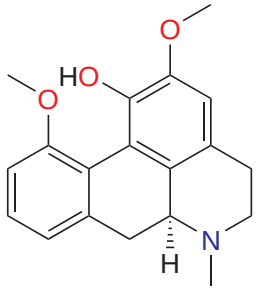
Ideas for Boldine analogues

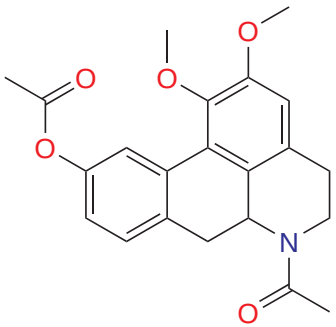


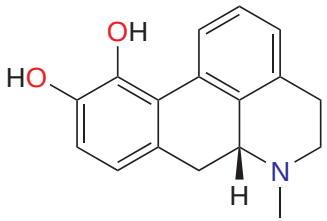












Structure-based Virtual Screening

Background on sirtuins

- Sirt = silent information regulator, belonging to a highly conserved family of drug targets.
- In the category of epigenetic drug targets, they are referred to as "erasers".
- Sirts are nicotinamide adenine dinucleotide (NAD^+)-dependent class III histone deacetylases.
- Sirts are linked to the pathogenesis of numerous diseases, e.g. HIV, metabolic disorders, neurodegeneration (including Alzheimer's disease and Parkinson's disease), aging and cancer.

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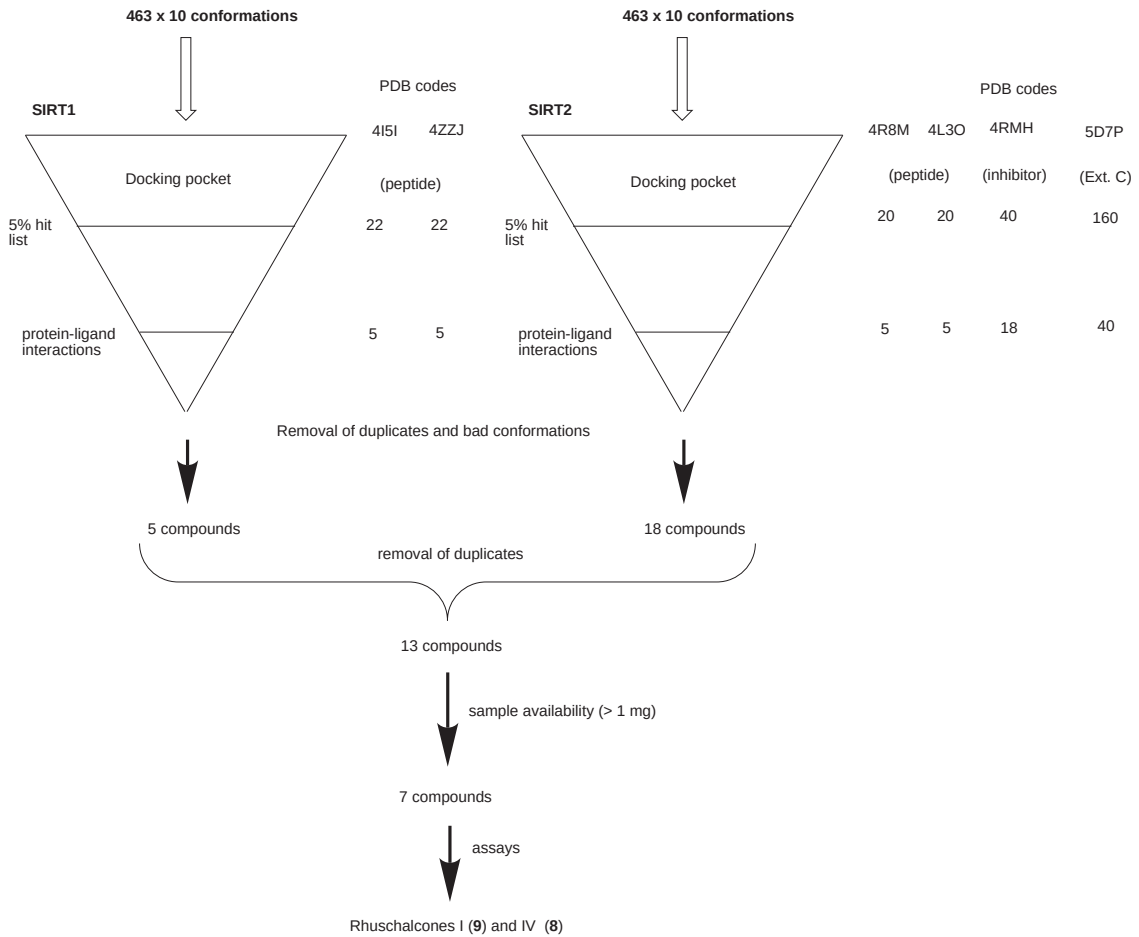
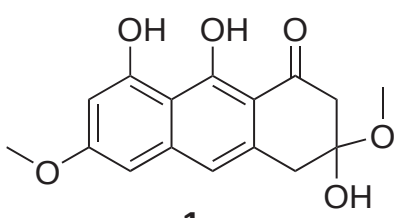
Structure-based Virtual Screening

Discovery of sirtuin inhibitors

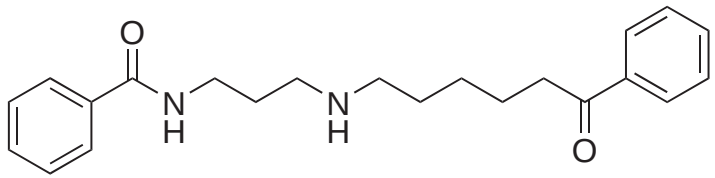


Structure-based Virtual Screening

Discovery of sirtuin inhibitors



1



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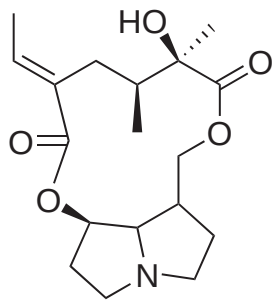
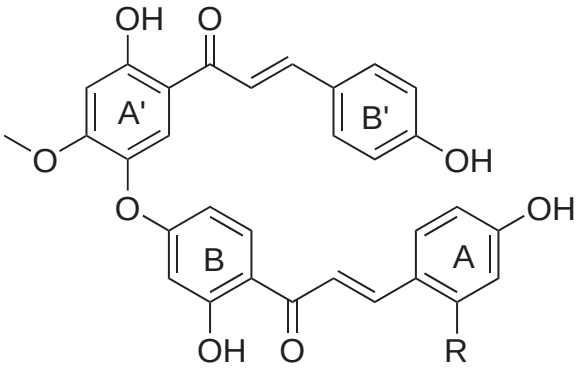
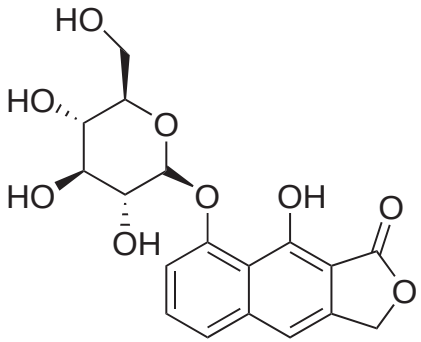


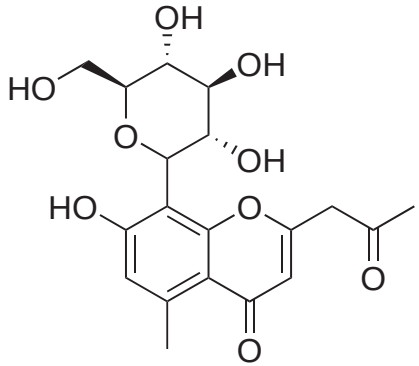
Manduresin (**10**)



Rhuschalcone IV (**8**): R = H,
Rhuschalcone I analogue (**9**): R = OH



Geshoidin (**12**)



13

Structure-based Virtual Screening

Discovery of sirtuin inhibitors

Table 1. IC_{50} or percentage inhibitions at 50% of tested pan-African Natural Products Library (p-ANAPL) compounds against sirt1, 2 and 3.

Compound Number	Sirt 1 (μM)	Sirt 2 (μM)	Sirt 3 (μM or % Inhibition)
1 [b]	n.d. [c]	n.d. [c]	n.d. [c]
2	n.i. [a]	n.i. [a]	n.i. [a]
8	46.7 ± 6.0	48.5 ± 39.5	38%
9	40.8 ± 8.5	44.8 ± 5.1	23%
10	n.i. [a]	n.i. [a]	n.i. [a]
12 [b]	n.d.	n.d.	n.d.
13	n.i. [a]	n.i. [a]	n.i. [a]
NA	142.4 ± 9.1	49.8 ± 4.6	67.9 ± 3.3
EX-527	1.4 ± 0.1	10.6 ± 1.1	19%

[a] n.i. = no inhibition (<10%). [b] autofluorescence. [c] n.d. = not detectable. Note that activity was not detectable due to the autofluorescence. NA = nicotinamide, EX-527 = sirt inhibitor in clinical trials.

Structure-based Virtual Screening

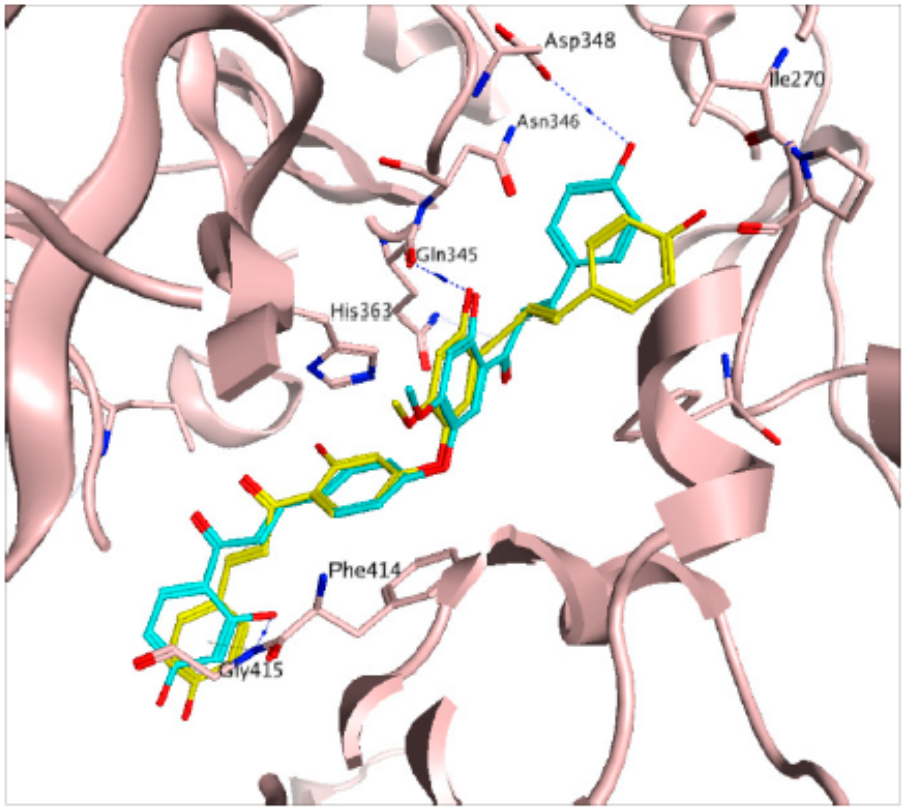
Discovery of sirtuin inhibitors

-*Rhus pyroides* (Anacardiaceae)
-Tree from Eastern Botswana
-Antifeedant properties

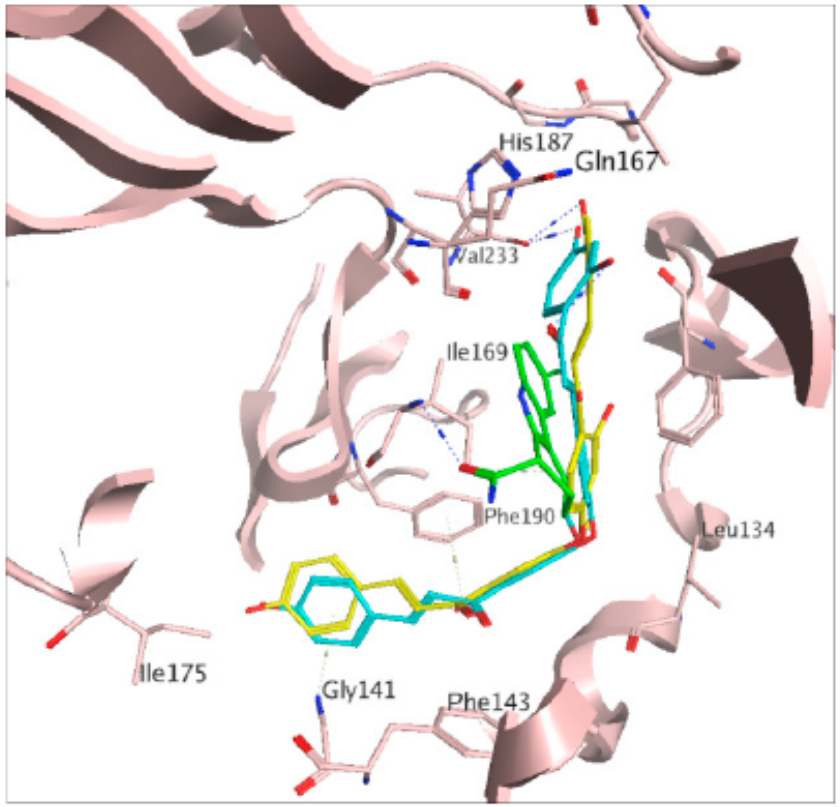
-Rich source of O-linked and C-C
-Coupled bischalcones and biflavonoids

Structure-based Virtual Screening

Discovery of sirtuin inhibitors



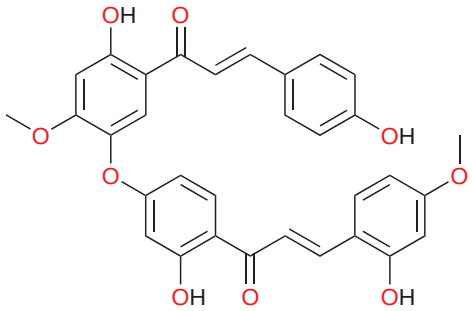
(a)



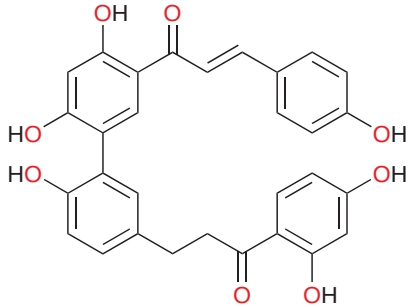
(b)

Structure-based Virtual Screening

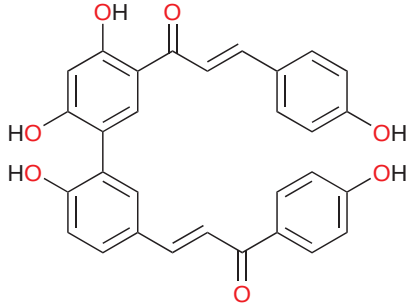
Some suggestions



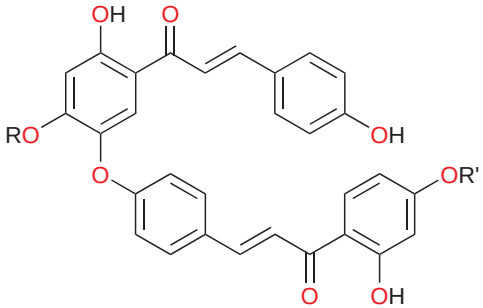
Rhuschalcone I



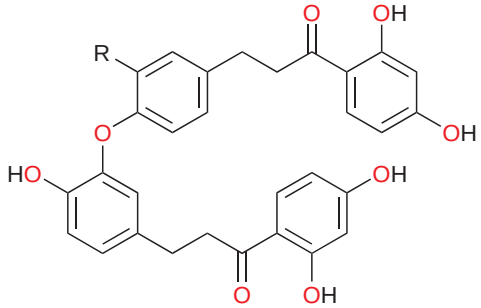
Rhuschalcone V



Rhuschalcone VI



Rhuschalcone II : R = R' = H
Rhuschalcone III: R = Me, R' = H



Littorachalcone: R = H
Verbenachalcone: R = OMe

Outline

Knowledgbase for Toxicity Prediction

Eco-Derek Background

- Toxicity model: 40 hour static flow growth inhibition assay ($\log(1/IGC_{50})$ values) for the ciliated protozoan *Tetrahymena pyriformis*, from Schultz *et al*. Toxicol. Methods 1997, 7: 289-309.
- Published data on over 1200 chemicals, from Xue *et al*. Chem. Res. Toxicol. 2006, 19:1030-1039.
- $\log(1/IGC_{50})$ was predicted as a function of log P, e.g. log $(1/IGC_{50}50$ NPN$) = 0.78$ log P - 2.01 ($n = 87$, $r^2 = 0.96$).

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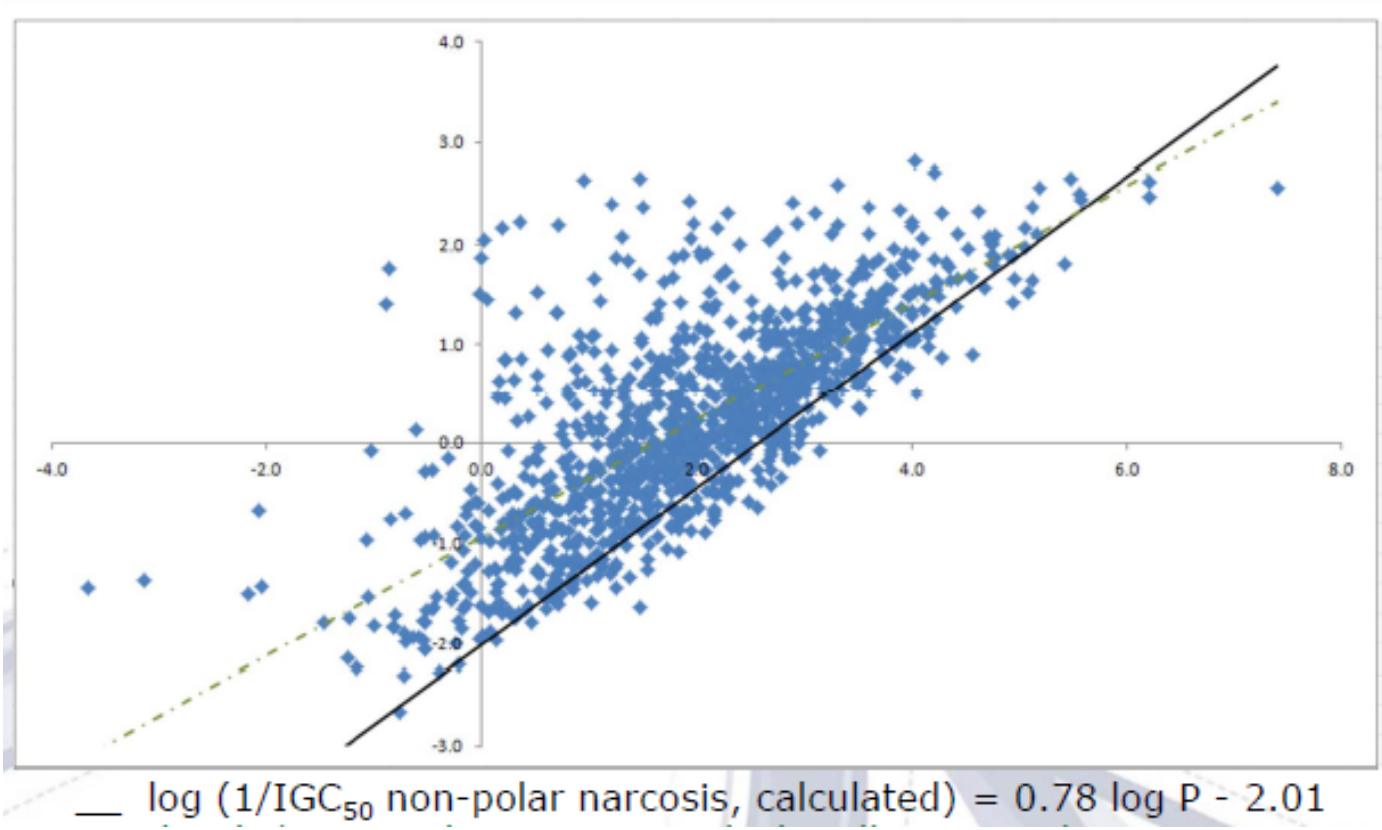

Xue *et al*. dataset. Regression equations reported in Ellison *et al*. *SAR QSAR Environ. Res*. **2008**:19, 751-783 for non-polar narcosis and Schultz *et al*. *Sci. Total Environ*. **1991**, 109-110:569-580 for polar narcosis.

Highlights

- Computer modeling was used to valorise of the medicinal potential of African medicinal plants (databases, lead compounds, etc.).
- New databases were developed and published in the web.
- Identification NP lead molecules via LBVS and SBVS were carried out.
- NP mimics with potent activities were synthesized and tested.
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Thanks for your kind attention !

Department of Informatics and Chemistry
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www.african-compounds.org