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Foreword

For a reader of this thesis, who is not familiar with the German research system, the term "habilitation" refers to a postdoctoral degree awarded in order to qualify a person to officially teach (*venia legendi*), hold a research group leader position or professorship at a university or higher education institution and eventually supervise Ph.D. students and postdocs. In Martin-Luther University Halle-Wittenberg (MLU), the guidelines regulating the examination and award of a "habilitation" by the Faculty I of Natural Science are contained in the "Habilitationsordnung" (http://www.natfak1.uni-halle.de/dekanat/habilitationen/). In order to obtain this qualification, a candidate must have demonstrated teaching and research abilities (usually in the form of publications), officially presented the research results and demonstrated teaching aptitudes before a panel or commission of professors (Habilitationskommission) in order to earn the title *doctor habilitatus* (Dr. habil.). In principle, the "habilitation" is no longer a must in most German universities, as a researcher could be considered as having obtained an "habilitation's equivalent" (after proven research and teaching aptitudes, e.g. *via* a "junior professorship" or "junior research group leader" position).

In order to obtain a "habilitation", the applicant must submit a written report (or "Habilitationsschrift" with accompanying documents, e.g. the candidate's CV and previous degrees, evidence of teaching and student supervisions, etc.). This report should contain the main results or research findings, which should be different from the results obtained in the Ph.D. thesis. The candidate has the open choice to write a full-length report, showing details of the obtained results or simply provide a summary of the main research findings, in this case, a cumulative thesis. This goes through a normal peer review process (3 peer reviewers). If successful, the candidate is invited to openly give two presentations of about 45 minutes each, followed by question and answer sessions of equal duration. One of these presentations is a typical teaching lesson drawn from 3 topics proposed by the applicant, from which the commission selects 1 topic. Besides, the candidate is often expected to have taught at the given faculty for a period of at least two years prior to submission of the application. In the second presentation, the candidate is expected to show the main research findings after the doctoral thesis. In both cases, the commission seeks to assess the candidate's ability to teach and mentor younger researchers within a specific discipline. Unlike in some other countries where the "habilitation" is granted by a national commission, in Germany, this is the responsibility of each university (specifically each Faculty's "Habilitationskommission").

Abstract

The work presented in this thesis focuses on new natural product database tools and datasets for the discovery of lead compounds from African floral matter. Prior to the investigations, data regarding compounds which had been identified from the aforementioned sources were scattered in literature sources, some of which were inaccessible to the wider community of scientists. The resulting investigation has led to a collection of data on the constituent metabolites, their biological activities, as well as the uses of the source organisms in traditional medicine, which have been made available *via* the web. Moreover, the investigations have led to the identification (assisted and non assisted by molecular modeling) of lead compounds with anti-HIV, anti-*Onchocerca*, antiplasmodial, protease inhibitory and sirtuin inhibitory properties, beginning from plants with popular uses in African traditional medicine. The results presented in this thesis constitute the first outcome of computer-based investigation of the potential of African medicinal plants for drug discovery.

Keywords: African flora, compound libraries, docking, *in silico*, lead compounds, natural product database, pharmacophore, QSAR, virtual screening.

Kurzfassung

Die vorliegende Arbeit befasst sich mit neuen Naturproduktdatenbank-Tools und Datensätzen zur Entdeckung von Leitstrukturen aus afrikanischer Blütenmasse. Vor den Untersuchungen waren Daten zu Verbindungen, die aus den oben genannten Quellen identifiziert worden waren, in Literaturquellen verstreut, von denen einige für die breitere Gemeinschaft von Wissenschaftlern unzugänglich waren. Die daraus resultierende Untersuchung hat zu einer Sammlung von Daten über die Metaboliten der Inhaltsstoffe, ihre biologischen Aktivitäten sowie über die Verwendung der Quellen in der traditionellen Medizin geführt, die über das Internet zur Verfügung gestellt wurden. Darüber hinaus haben die Untersuchungen zur Identifizierung (unterstützt und nicht unterstützt durch molekulares Modellieren) von Bleiverbindungen mit anti-HIV-, anti-*Onchocerca*, Antiplasmodien-, Proteasehemmungs- und Sirtuin-hemmenden Eigenschaften geführt, beginnend mit Pflanzen, die in der traditionellen afrikanischen Medizin populär sind. Die in dieser Arbeit vorgestellten Ergebnisse sind das erste Ergebnis einer computergestützten Untersuchung des Potenzials afrikanischer Arzneipflanzen für die Wirkstoffforschung.

Schlüsselwörter: Afrikanische Pflanzen, Verbundbibliotheken, Docking, *in silico*, Leitverbindungen, Naturstoffdatenbank, Pharmakophor, QSAR, virtuelles Screening.

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This work could not have been feasible without the initial contributions of my parents (who laid the foundational education and provided the necessary trigger and encouragements to move to the top). I truly acknowledge the company and assistance of my wife and daughter, along with the encouraging words of my parents-in-law, my brothers and sisters.

Financial support for the realization of the projects whose results are presented herein, particularly from CBIC, the DAAD and the Alexander von Humboldt Foundation, is acknowledged.

Dedication

To the three women who matter the most in my life; my mum, my wife and my daughter.

I consider an intimate knowledge of the BIBLE an indispensable quality of a well educated man (Robert A. Milikan, Nobel Laureat Physics, 1923)

I have seen something else under the sun: The race is not to the swift or the battle to the strong, nor does food come to the wise or wealth to the brilliant or favor to the learned; but time and chance happen to them all.(Ecclesiastes 9:11, NIV)

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List of Abbreviations and Acronyms

ADMET: absorption, distribution, metabolism, excretion and toxicity

CamMedNP: Cameroonian Medicinal chemistry and Natural Products database

CBIC: Chemical Bioactivity Information Centre (www.cbic-africa.org)

ConMedNP: Congo Basin Medicinal plants and Natural Products database

DAAD: Deutscher Akademischer Austausch Dienst (German Academic Exchange Service)

DMPK: drug metabolism and pharmacokinetics

DNA: deoxyribonucleic acid

DNP: Dictionary of Natural Products

FDA: United States Food and Drug Administration

HBA: hydrogen bond acceptors

HBD: hydrogen bond donors

HIV: human immunodeficiency virus

log $P_{o/w}$: logarithm of the *n*-octanol/water partition coefficient

MMFF: Merck Molecular Forcefield

MOE: Molecular Operating Environment

MW: molecular weight

NAD: nicotinamide adenine dinucleotide

NMR: Nuclear Magnetic Resonance

NP: natural product

NRB: number of rotatable bonds

p-ANAPL: pan-African Natural Products Library

PBMs: plant-based metabolites

PCA: principal component analysis

PDB: protein databank

QSAR: quantitative structure-activity relationship

RMSD: root mean square deviation

ro5: “Rule of Five”

ro3: “Rule of Three”

SDs: synthetic drugs

SMs: synthetic molecules

T2DM: type II diabetes mellitus

UNPD: Universal Natural Products Database

VS: virtual screening

WOMBAT: World of Molecular Bioactivity database

Original Peer-reviewed Contributions after the Ph.D. Thesis

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Additional publications could be consulted on the author's ORCID profile,[1] personal web page,[2] on ResearchGate[3] or on Google Scholar[4]

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[4]Google Scholar Profile of Dr. Fidele Ntie-Kang: https://scholar.google.de/citations?user=XvORr_kAAAAJ&hl=de

CHAPTER ONE

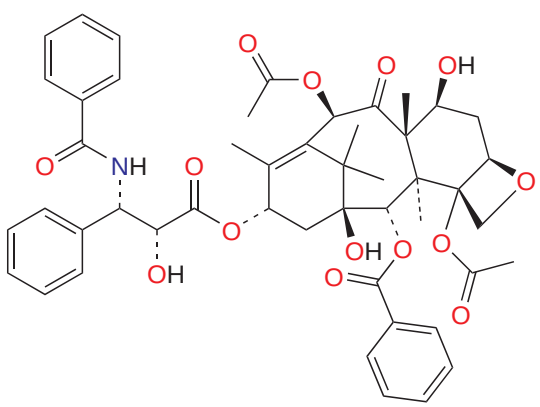
GENERAL INTRODUCTION AND OBJECTIVES

1.1 General introduction

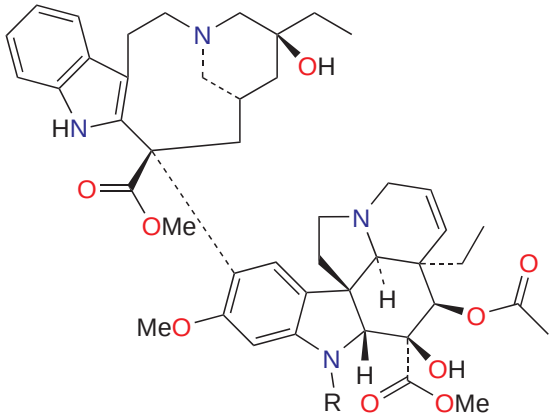
1.1.1 Natural products

Natural products (NPs) are known to play an important role in drug discovery, as they often provide scaffolds as starting points for hit/lead discovery [1, 2]. Several known drugs, e.g. the anticancer compounds (**1** to **5**, Fig. 1.1), are known to be derived from natural sources [3]. Of major importance is that NPs continue to play a role as drugs [4], as biological probes, and as study targets for synthetic and analytical chemists [5]. In fact, it was shown that about half of all approved drugs between 1981 and 2010 were NP-based [6]. What makes NPs unique, when compared with synthetic drugs (SDs) is that they often contain more complex scaffolds and chiral centres, with more O-atoms and aromatic groups [7]. In addition, a study involving a comparison of SDs *versus* NPs showed that drugs derived from NP-based structures display greater chemical diversity and occupy wider regions of chemical space [4]. This is because drugs which are synthesized based on NP pharmacophores often exhibit lower hydrophobicity and greater stereochemical content when compared with drugs which are completely of synthetic origin. The aforementioned study showed that, of all approved drugs, NPs constituted 6% (unaltered), 26% (NP derivatives), 32% (NP mimics) or from NP pharmacophores, 73% of small molecule antibacterials and 50% of anticancer drugs (including taxol, vinblastine, vincristine, topotecan, etc.). This implies that if structural features provided by nature are successfully incorporated into SDs, this would increase the chemical diversity available for small-molecule drug discovery [4]. Howbeit, the reasons for the decline of interest by the pharmaceutical industry during the last two decades range from the time factor involved in the search for NP lead compounds to the labour intensiveness of the whole process [8]. This has now been rendered much easier within industrial settings by streamlined screening procedures and enhanced organism sourcing mechanisms [9].

Despite their evolving role in drug discovery [10, 11], a recent chemoinformatic study involving a dataset of all published microbial and marine-derived compounds since the 1940s (comprising 40,229

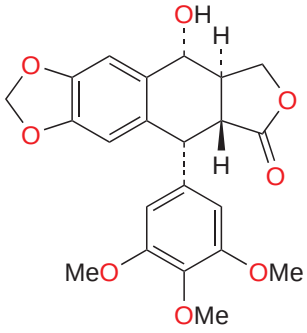


Paclitaxel or Taxol (**1**)

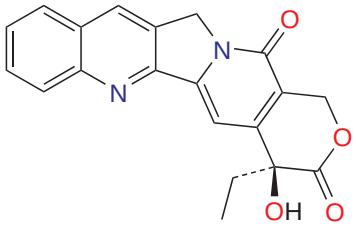


Vinblastine or vincaleukoblastine (**2**): R = CH_3

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



Podophyllotoxin (**4**)



Camptothecin (**5**)

Figure 1.1: 2D structures of selected naturally occurring NP anticancer drug leads.

NPs) showed that most NPs being published today bear close similarity[1] to previously published structures, with a plateau being observed since the mid-1990s [12]. This study had, thus, suggested that the range of scaffolds readily accessible from nature is limited, i.e. scientists are now close to having described all of the chemical space covered by NPs, even though appreciable numbers of NPs with no structural precedents continue to be discovered. A reproduction of the previous study on another dataset of 32,380 NPs, also showed the same trend [13]. By carrying out a similar analysis on a dataset of randomnly selected compounds from the ZINC database having overall lower structural similarity, the authors of the latter study further proved that such trends may be a feature of any growing database of chemical structures, rather than reflecting trends specific to NP discovery. Besides, it was also shown that since 1990, the rate of structurally novel compound discovery has dramatically outpaced random expectation[2] [13]. This means that NPs discovered within the last three decades have been characterized by unprecedented chemical diversity,[3] suggesting that the dream of continuously discovering new chemical structures from nature remains positive.

[1]Two compounds were considered to be dissimilar by taking a Tanimoto cutoff of $T_c < 0.4$.
[2]By use of the Kolmogorov–Smirnov test, $P = 6.2 \times 10^{-14}$.
[3]The median maximum T_c has declined relative to random expectation, with $P = 7.6 \times 10^{-11}$.

1.1.2 Natural product libraries

Renewed interest in drug discovery from natural sources has ignited the development of several database resources and compound libraries, some of which are more comprehensive, including compounds from terrestrial, marine and microbial organisms, while other databases focus on particular disease types or on compounds from specific geographical regions or organism types. Moreover, several companies specialized in the commercialisation of NP compound samples are currently in the market [14], while other general sample suppliers include both NPs and SDs in their catalogues. A comprehensive list of useful databases for NP lead discovery and dereplication has been made available by the OMICs group (https://omictools.com/natural-products-category). A very recent study carried out by Chen *et al.* on 25 virtual libraries and 41 physical sample collections, revealed that of the ~250,000 NPs included in the investigated virtual library collections, about 10% have readily purchasable samples [14]. A summary of the most interesting NP resources (excluding the author's own contributions) is provided in Table 1.1.

The contrast between 'general' *versus* 'focused' libraries

Several libraries include NPs from diverse sources and having diverse biological activities. The so-called 'inclusive' libraries would include the commercial Dictionary of Natural Products [24], the open access SuperNatural [38], the Universal Natural Products Database (UNPD [44]) and the most recently published open access Natural Product Activity and Species Source (NPASS [29]), along with the NP subsets included in PubChem [33], Reaxys [34], and ZINC [45]. The most well developed 'exclusive' database resources based on compounds from a specific biosphere include those from marine and microbial sources [15, 16, 23, 27]. In contrast to marine and microbial sources, a universal plant-based NP database has not yet been developed [12]. Most databases of plant-based metabolites (PBMs) are from diverse source organisms and could be classified according to their geographical origin, i.e. by regions (e.g. from North East [39] and South East [43] Asia) or by countries (e.g. Brazil [31], South Africa [35], etc.). PBM and diverse databases could also be classified according to source organisms (e.g. NPs from *Rauvolfia serpentina* [36]), according to the compound classes (e.g. the caretenoids [19]) or according to the disease type or drug target (e.g. cancer [21, 26, 28, 30], mycobacterial infections [18], cardiovascular diseases [22], etc.). A majority of recent databases of PBMs focus of components of traditional medicines, e.g. Ayurveda [17, 25, 32], traditional Chinese medicine [20, 21, 28, 40, 41, 42] and African traditional medicine [35].

1.1.3 Drug-likeness *versus* natural product-likeness assessment

According to Lipinski's "Rule of Five" (ro5), an orally bioavailable drug should respect a set of rules ($MW \leq 500$; $\log P_{o/w} \leq 5$; HBD ≤ 5; HBA ≤ 10), and must not violate more than 2 of the "rules" [46]. While Lipinski initially hypothesized that NPs do not generally comply to the popular

Table 1.1: Summary of currently available natural product database resources.

Database	***Description***	***Web accessibility***	[a]***Cpd. #***	[b]***S. Org. #***	[c]***CAI***	[d]***Ref.***
AntiBase	Microbial and higher fungal sources	https://omictools.com/antibase-tool/	> 40 k	-	yes	[15]
AntiMarin	Merger of AntiBase and MarinLit	https://omictools.com/marinlit-tool/				[16]
Ayurveda	From traditional Ayurvedic medicine	https://omictools.com/ayurveda-tool/	~950	~50		[17]
BioPhytoMol	Possess antimycobacterial activities	http://ab-openlab.csir.res.in/biophytmol/	> 600	~800	yes	[18]
Carotenoids Database	Natural carotenoids	http://carotenoiddb.jp/	> 1.1 k	~700	yes	[19]
Chem-TCM	From traditional Chinese medicine	http://www.chemtcm.com/				[20]
CHMIS-C	Bind to anticancer targets	http://sw16.im.med.umich.edu/chmis-c/	> 9 k		yes	[21]
CVDHD	Related to cardiovascular diseases	http://pkuxxj.pku.edu.cn/CVDHD/	> 35 k		yes	[22]
DMNP	Dictionary of marine NPs	dmnp.chemnetbase.com/	> 55 k		yes	[23]
[e]DNP	Diverse sources and activities	dnp.chemnetbase.com/	> 230 k		yes	[24]
InPACdb	Indian plant anticancer compounds	http://www.inpacdb.org/				[25]
MAPS Database	From Indian sources	http://www.mapsdatabase.com/			yes	[26]
MarinLit	From marine sources	http://pubs.rsc.org/marinlit/	> 29 k		yes	[27]
NPACT	Possess anticancer properties	http://crdd.osdd.net/raghava/npact/	~1500		yes	[28]
NPASS	Diverse sources and activities	http://bidd2.nus.edu.sg/NPASS/	~32 k	~25k	yes	[29]
NPCARE	For cancer regulation	http://silver.sejong.ac.kr/npcare/	~6.5 k	~2 k	no	[30]
$NuBBE_{DB}$	From Brazilian sources	[f]See below	~3 k		yes	[31]
Phytochemica	From Himalayan medicinal plants	[g]See below	~ 1 k	5	yes	[32]
PubChem NPs	Diverse sources and activities	https://pubchem.ncbi.nlm.nih.gov/	~ 3 k		yes	[33]
Reaxys	Diverse sources and activities	https://new.reaxys.com/	> 220 k		yes	[34]
SANCDB	From South African sources	https://sancdb.rubi.ru.ac.za/	~600		yes	[35]
SerpentinaDB	From the plant *Rauvolfia serpentina*	[h]See below				[36]
StreptomeDB	From bacteria (*Streptomyces* sp.)	[i]See below	> 4 k	~2.5 k	yes	[37]
SuperNatural	Diverse sources and activities	[j]See below	> 325 k		yes	[38]
TM-MC	From Northeast Asian sources	http://informatics.kiom.re.kr/compound/				[39]
TCM-ID	From traditional Chinese medicine	http://www.megabionet.org/tcmid/	> 13 k	~8.2 k	no	[40]
TCM database@Taiwan	From traditional medicine in Taiwan	http://tcm.cmu.edu.tw/	> 50 k	~450	yes	[41]
TCMSP	From traditional Chinese medicine	http://sm.nwsuaf.edu.cn/lsp/tcmsp.php/	> 29 k	~500		[42]
TIPdb	From indigenous plants in Taiwan	http://cwtung.kmu.edu.tw/tipdb/	~9 k		no	[43]
UNPD	Universal natural products database	http://pkuxxj.pku.edu.cn/UNPD/	> 229 k		no	[44]
[h]ZINC NPs (UEFS)	Diverse sources and activities	http://zinc.docking.org/catalogs/uefsnp/	....	~500	yes	[45]

[a]Cpd. # = Approximate number of compounds, [b]S. Org. # = Approximate number of source organisms, [c]CAI = Chemistry aware interface, [d]Ref. = References, [e]Dictionary of natural products, [f]https://nubbe.iq.unesp.br/portal/nubbedb.html, [g]home.iitj.ac.in/bagler/webservers/Phytochemica, [h]http://home.iitj.ac.in/bagler/webservers/SerpentinaDB/, [i]http://www.pharmaceutical-bioinformatics.org/streptomedb/, [j]http://bioinf-applied.charite.de/supernatural_new/, [h]NP subset in ZINC database.

ro5 [46], it has been recently shown that a large majority of known approved drugs are either NPs or NP mimics [4]. Thus, NPs have the huge potential to be developed into drugs, often ascribed to as 'lead-like' molecules [47]. Several metrics have been used to assess the 'drug-likeness' [48], the 'lead-likeness' (respecting the "Rule of 3.5": $150 \leq MW \leq 350$; $\log P_{o/w} \leq 4$; HBD ≤ 3; HBA ≤ 6), [49] and the 'natural product-likeness' [50] of a molecule. The concept of 'natural product-likeness' (NP-likeness), a Bayesian measure which allows for the determination of how molecules are similar to the structural space covered by natural products, was originally developed by Ertl *et al.* [50] and has now been has been implemented in several open-source, open-data tools [51]. The NP-likeness score is an efficient approach to separate NPs from synthetic molecules (SMs), with possible applications in virtual screening, prioritization of compound libraries toward NP-likeness, and design of building blocks for the synthesis of 'NP-like' libraries [50]. The NP-likeness score (ranging from -5 to 5) is computed for a whole molecule, as a sum of contributions of fragments, f_i, (considered to be independent of each other, Eqn. 1.1) in the molecule, normalized relative to the molecule size:

$$f_i = \log\left(\frac{A_i}{B_i} \cdot \frac{B_{tot}}{A_{tot}}\right) \tag{1.1}$$

where A_i is the number of NPs which contain fragment i, B_i is the number of SMs which contain fragment i, A_{tot} is the total number of NPs, and B_{tot} is the total number of SMs in the training set.

A property distribution of three investigated datasets consisting of 3,287 NPs, 10,968 drug molecules and 13,506 randomnly selected combinatorially-derived lead candidates, respectively, led to the analysis of the number of chiral centres, rotatable bonds, aromatic rings, complex ring systems, degrees of saturation, as well as the ratios of different heteroatoms (O, N, etc.). [52]. This study showed that the main structural differences between NPs and combinatorially-derived libraries arise from properties introduced during the synthetic process in order to render combinatorial synthesis more efficient. Moreover, it was shown that, since drug molecules originate from both natural and synthetic sources, they occupy a joint area of chemical space spread between NPs and combinatorially-derived compounds.

1.1.4 Chemical space of natural products

Several investigations of the three-dimensional (3D) chemical space, occupied by compounds of synthetic and natural origins, using principal component analysis (PCA) have been published [4, 44, 52, 53, 54, 55, 56, 57, 58, 59]. It was generally observed that, when compared with FDA-approved drugs and SDs, the distribution of NPs in chemical space cover regions that lack representation in synthetic medicinal chemistry compounds (Fig. 1.2), thus showing that NPs have a much wider coverage of chemical space. The unexplored areas appear to contain lead-like NPs that could subsequently be of interest in drug discovery. This indicates that these areas have not yet been investigated in drug discovery.

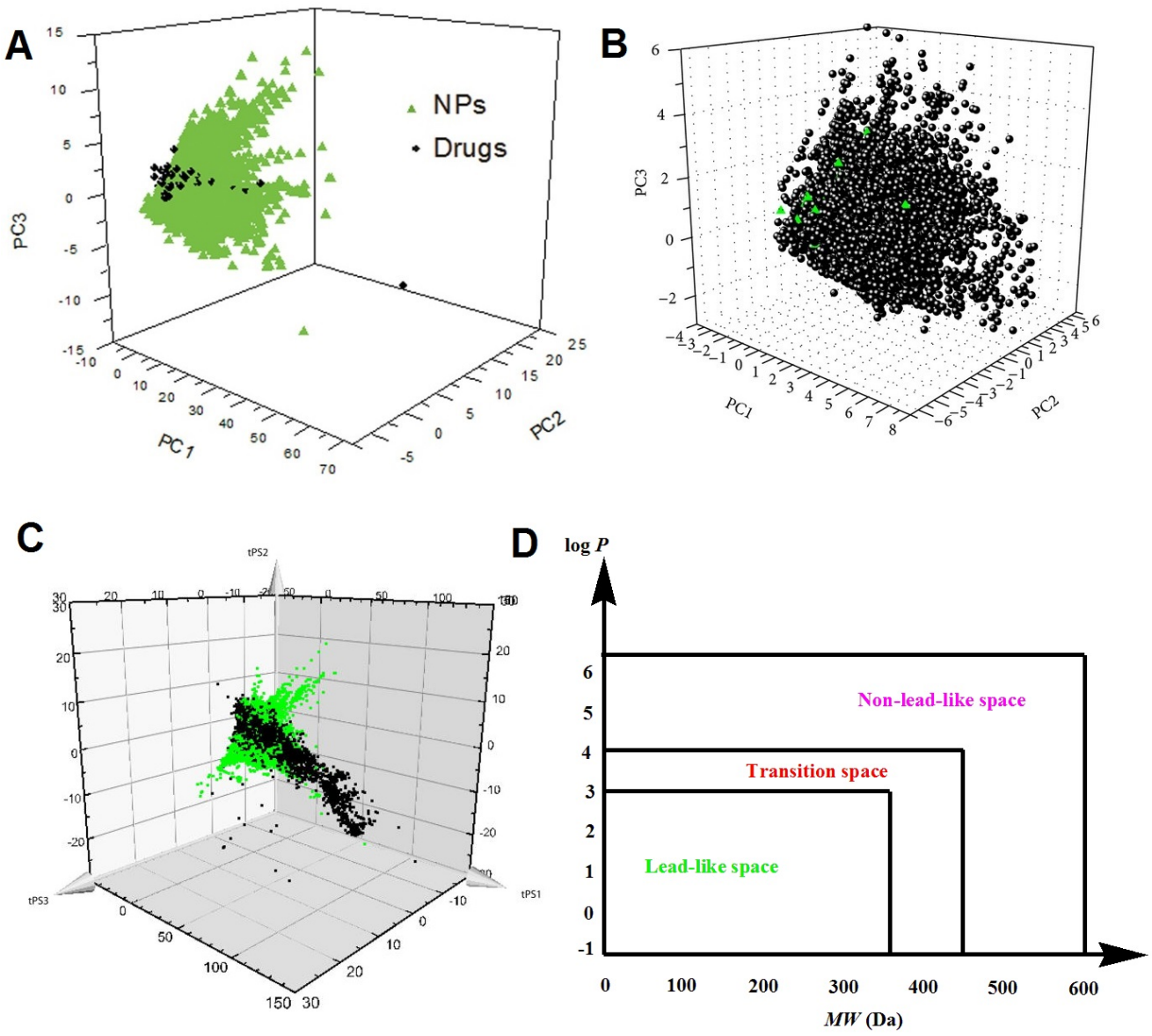


Figure 1.2: The distribution of biologically relevant chemical space of NPs, when compared with SDs: (A) PCA analysis of NPs in the Universal Natural Products Database (UNPD) and FDA-approved drugs. The green triangles and black dots represent natural products and FDA-approved drugs, respectively [44]; (B) PCA analysis of NPs contained in medicinal plants and 25 FDA-approved drugs for the treatment of type II diabetes mellitus (T2DM). The black dots and green triangles represent natural products and FDA-approved drugs, respectively [54]; (C) Predicted score (tPS) plots of NPs (in green) and bioactive medicinal chemistry compounds from the World of Molecular Bioactivity (WOMBAT) database (in black) [53]; (D) Property space representation for lead-like molecules of some selected chemical libraries [60]. Figures adapted by permission.

1.1.5 Nature-inspired drug discovery

Classical natural product drug discovery is only able to undertake drug-likeness analysis after the compounds are isolated and their structures elucidated. However, there are success stories using approaches that address front-loading of both extracts and subsequent fractions with desired physicochemical properties prior to screening for drug discovery [60]. If NPs are often referred to as 'sources of inspiration', it simply implies that 'lead-like' libraries could be designed, starting from NP scaffolds, with many examples available in the literature [60, 61, 62, 63, 64]. However, when an NP is used as the guiding structure for the creation of 'NP-like' libraries, controlling certain molecular descriptors (e.g. *MW*, log $P_{o/w}$, etc.) during the synthetic process is of major importance for the generation of 'lead-like' libraries [60]. This simply means preparing a ro5-compliant library can ensure the timely development of natural product lead compounds at a reasonable rate.

1.1.6 Virtual screening

In the quest to identify new and/or promising lead compounds from the plants, *in silico* (computer-based) modeling is often employed since this approach has proven to accelerate the process and cuts down the cost of identifying lead compounds [65]. Virtual screening methods are useful because, in principle, they narrow down the number of compounds to be actually tested in biological assays. This is practicable when the *in silico* scoring methods are sufficiently able to discriminate between active compounds and inactive ones. The approaches of structure-based methods, e.g. docking [66, 67, 68], or ligand-based methods, e.g. quantitative structure-activity relationship (QSAR) and pharmacophore searching [69, 70, 71] or a combination of several approaches within the same workflow [72] have been recently employed with relative success within several lead generation programs from NP libraries.

1.1.7 Computer-based prediction of drug metabolism and pharmacokinetics

Many drugs often fail to enter the market as a result of poor pharmacokinetic profiles [73]. Thus, it has become imperative nowadays to design lead compounds which can be easily orally absorbed, easily transported to their desired site of action, not easily metabolised into toxic metabolic products before reaching the targeted site of action and easily eliminated from the body before accumulating in sufficient amounts that may produce adverse side effects. The sum of the above-mentioned properties is often referred to as ADME (absorption, distribution, metabolism and elimination) properties, or better still ADMET, ADME/T or ADMETox (when considerations are given to toxicity issues). The inclusion of pharmacokinetic considerations at earlier stages of drug discovery programs [74, 75] using computer-based methods has become sufficiently popular [45, 76, 77]. The rationale behind *in silico* approaches are the relatively lower cost and the time factor involved, when compared to standard experimental approaches for ADMET profiling [73, 78]. As an example, it only takes a minute in an *in*

silico model to screen 20,000 molecules, when compared with 20 weeks in the "wet" laboratory to do the same exercise [74]. Due to the accumulated ADMET data in the late 1990s, many pharmaceutical companies are now using computational models that, in some cases, are replacing the "wet" screens [74]. This paradigm shift has therefore spurred up the development of several theoretical methods for the prediction of ADMET parameters. A host of these theoretical models have been implemented in a number of software programs currently available for drug discovery protocols [79, 80, 81, 82], even though some of the predictions could be disappointing [83]. The software tools currently used to predict the ADMET properties of potential drug candidates often make use of QSAR [83, 84] or knowledge-based methods [85, 86, 87]. A promising lead compound may, therefore, be defined as one which combines potency with an attractive ADMET profile. As such, compounds with uninteresting predicted ADMET profiles may be completely dismissed from the list of potential drug candidates early enough (even if these prove to be highly potent). Otherwise, the DMPK properties are "fine-tuned" in order to improve their chances of making it to clinical trials [88].

1.2 Objectives of the work

This thesis intends to valorise the African flora as both a rich source of secondary metabolites and a valuable starting point for nature-inspired drug discovery. At the unset of our investigations, there were no database resources for NPs which have been identified in medicinal plants growing in Africa, despite the long history of the use of their source organisms in traditional medicine, which dates back to prehistoric and pharaonic times [89, 90]. Moreover, data for the use of the compound sources, collection points of compound sources, biological activities of tested isolates, access to compound samples for screening purposes, among others, are often unavailable and/or scattered in the literature. Some of these data are inaccessible to a majority of scientists. A smaller proportion of these literature sources includes M.Sc. and Ph.D. theses, which are often stored as hard copies in university libraries and inaccessible to the wider community of scientists working on natural products drug discovery.

1.2.1 General objectives

The main objectives of this work were, among others, to:

- generate electronically accessible 3D models, which could be used by research groups focusing on the modeling of biomolecular interactions,
- valorise the use of medicinal plants in Africa in traditional medicine,
- identify compounds from plants used in traditional medicine for drug discovery by using computer modeling (e.g. *via in silico* docking and pharmacophore modeling) and to
- assess the toxicity profiles of metabolites from African sources.

1.2.2 Specific objectives

The aforementioned goals were achieved through the:

- development of molecular databases of natural products, including source organisms, biological activities and literature information, which cover the entire continent of Africa,
- building and updating an electronic library for the pan-African Natural Products Library (p-ANAPL), rendering it a useful and effective starting point for lead discovery,
- identification of natural products with anti-HIV activity, antiplasmodial, anti-*Onchocerca*, kinase inhibitory and sirtuin inhibitory activities, whose potencies have been validated experimentally.
- modeling the medicinally-relevant properties of compounds isolated from selected species (e.g. *Dacryodes edulis*, *Cyperus articulatus*, *Scleria striatinux* and *Helichrysum* sp.), hence predicting their drug metabolism and pharmacokinetic properties and drug-target interactions in an attempt to explain their binding properties to known targets,
- natural product-inspired synthesis of new antimalarial and sigma-binding compounds.
- development of a knowledge base for predicting the toxicity of chemicals and assessing the toxicity profiles of natural product libraries generated.

In this thesis, chapters 2, 3 and 4 focus on the main results, while chapter 5 contains the conclusions and perspectives. Chapter 6 describes the methods, while chapter 7 includes the appendices.

CHAPTER TWO

COMPOUND DATABASE RESOURCES GENERATED

2.1 Objectives of the chapter

In this chapter, the contributions are towards the development of databases and datasets of natural compounds from African flora and related sources are presented.

2.2 CamMedNP and ConMedNP

2.2.1 Composition of CamMedNP and main results

Within my Ph.D. thesis, Cameroonian medicinal chemistry and natural products database (CamMedNP) - a new database beginning with more than 2,500 compounds of natural origin, along with some of their derivatives which were obtained through hemisynthesis, was developed [91]. These are pure compounds which have been previously isolated and characterized using modern spectroscopic methods and published by several research teams spread across Cameroon. A total of 224 distinct medicinal plant species belonging to 55 plant families were considered (Fig. 2.1). This was later extended to cover compounds from 10 countries in Central Africa, now known as the Congo Basin Medicinal Plant and Natural Products (ConMedNP) database library [92]. About 80 % of the compounds have been previously published and/or referenced in internationally recognized journals, with the rest of the data referenced in Ph.D. and M.Sc. theses and conference presentations. For each compound, the optimized 3D structure, drug-like properties, plant source, collection site and currently known biological activities are given, as well as literature references. We have evaluated the "drug-likeness" of this database using Lipinski's ro5. A diversity analysis has been carried out in comparison with the ChemBridge diverse database. CamMedNP could be highly useful for database screening and natural product lead generation programs.

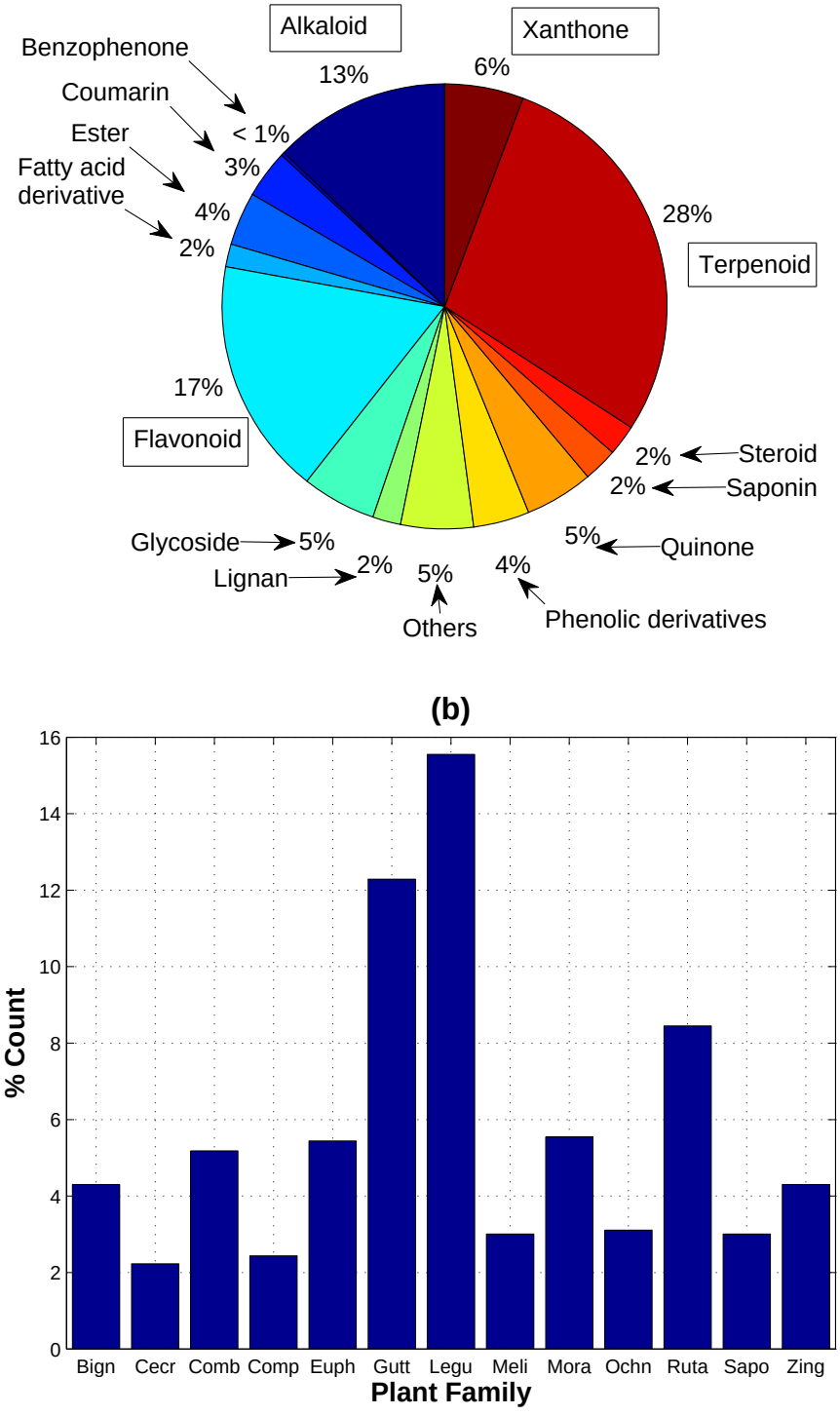


Figure 2.1: (a) Pie chart showing the classification of compound types currently within the CamMedNP database, (b) Bar chart showing % counts of compounds currently within the CamMedNP database (for which % composition ≥ 2%), classified by plant family of origin. Each plant family is represented by the first 4 letters of its name (e.g., Bign = Bignioniaceae, . . .). Figures reproduced by permission.

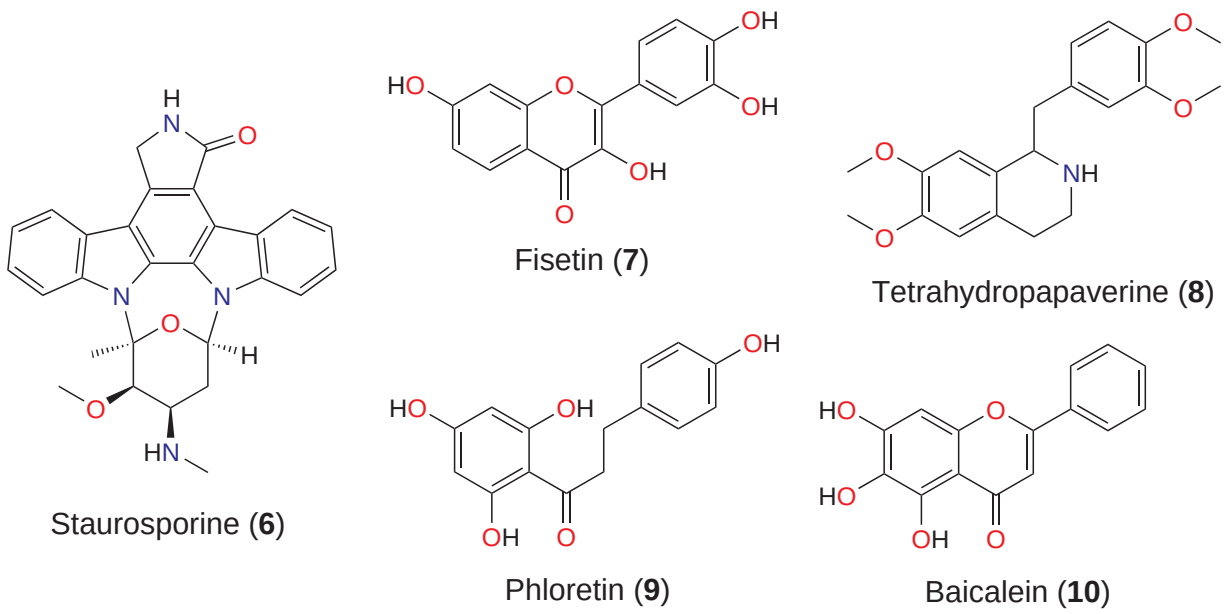


Figure 2.2: Kinase inhibitors identified by in silico and in vitro screening campaigns in which CamMedNP is included in the screening set.

2.2.2 Impact of the Central African natural product databases

Successful virtual screening campaigns, by including CamMedNP in the screening library, have led to the identification of kinase inhibitors (Fig. 2.2, Table 2.1), e.g. the protein kinase C (PKC), which plays a key role in neurotransmission in the central nervous system [93]. The targeting of PKC domain has, therefore, been considered as a strategy to modulate the anaesthetic effects. The 100 top scoring hits were tested, among which 12 showed inhibitory potencies against PKC. Among the identified *in vitro* hits were the promiscuous kinase inhibitor staurosporine (**6**, IC_{50} = 64 nM), together with fisetin (**7**) and tetrahydropapaverine (**8**), which both showed inhibitory potencies within the nanomolar range (IC_{50} = 370 and 190, respectively). Another virtual screening campaign led to the identification of Rho kinase inhibitors, with a potential for the development of drugs against pulmonary hypertension [94]. These are phloretin (**9**) and baicalein (**10**), with IC_{50} values of 0.22 and 0.95 μM, respectively.

Table 2.1: *Summary of kinase inhibitors identified from virtual campaigns in which CamMedNP was included in the screening set.*

Compound name (#)	***PubChem ID***	***Source organism***	***Target***	***IC_{50} (μM)***	[a]***Ref.***
Staurosporine (**6**)	44259	*Streptomyces* sp. B5136	PKC	0.06	[95]
Fisetin (**7**)	5281614	diverse fruits and vegetables	PKC	0.37	[96]
Tetrahydropapaverine (**8**)	5418	*Glaucium flavum* GFLOMT2	PKC	0.19	[97]
Phloretin (**9**)	4788	*Afzelia bipendensis*	Rho	0.22	[98]
Baicalein (**10**)	5281605	*Scutellaria lateriflora*	Rho	0.95	[99]

[a]*Ref. = References.*

2.2.3 Composition of ConMedNP and main results

The medicinal value and "drug-likeness" of ~3200 compounds of natural origin, along with some of their derivatives which were obtained through hemisynthesis, was assessed [92]. In this study, 376 distinct medicinal plant species belonging to 79 plant families from the Central African flora have been considered, based on data retrieved from literature sources. For each compound, the optimised 3D structure has been used to calculate physico-chemical properties which determine oral availability on the basis of the ro5. A comparative analysis has been carried out with the "drug-like", "lead-like", and "fragment-like" subsets, containing 1726, 738 and 155 compounds, respectively. ConMedNP was also compared with our smaller previously published CamMedNP library and the Dictionary of NPs. A diversity analysis has been carried out in comparison with the DIVERSet™ Database (containing 48,651 compounds) from Chem-Bridge. Our results prove that drug discovery, beginning with natural products from the Central African flora, could be promising. The 3D structures are available and could be useful for virtual screening and natural product lead generation programs. The contents of both datasets have been summarised in Table 2.2.

Table 2.2: *Summary of property distributions and comparison of the ConMedNP library, with it's various subsets.*

Library name	***Library size***	***Totaumers***	$\overline{M_w}$ ***(Da)***	$\overline{log\ P}$	$\overline{HBA}$	$\overline{HBD}$	$\overline{NRB}$
ConMedNP	3,177	7,838	426.70	4.18	5.85	2.39	5.31
Drug-like	1,726	3,900	326.16	2.87	4.97	1.79	2.96
Lead-like	738	1,610	269.58	2.48	4.17	1.49	2.01
Fragment-like	155	355	192.12	1.74	3.31	1.08	1.14
CamMedNP	1,859	5,286	421.63	4.07	6.00	2.40	5.51

$\overline{M_w}$: average molar weight; $\overline{log\ P}$: average logarithm of the octan-1-ol/water partition coefficient; $\overline{HBA}$: average number of hydrogen bond acceptors; $\overline{HBD}$: average number of hydrogen bond donors ; $\overline{NRB}$: average number of rotatable bonds.

The results in this section are based on the following article:

Ntie-Kang, F.;* Onguéné, P. A.; Scharfe, M.; Mbaze, L. M.; Owono, L. C. O.; Megnassan, E.; Sippl, W.; Efange, S. M. N. ConMedNP: a natural product library from Central African medicinal plants for drug discovery. *RSC Advances*, **2014**, *4*, 409–419.

2.3 AfroDb

AfroDb is a select highly potent and diverse natural product library from African medicinal plants, which we collected from different regions of the continent, based on literature information and information from traditional healers [100]. This is a dataset of ~1,000 compounds from African medicinal

plants, which have been tested and proven a wide range of biological activities. For each isolated compound, the 3D structure has been used to calculate physico-chemical properties used in the prediction of oral bioavailability on the basis of Lipinski's ro5. A comparative analysis has been carried out with the "drug-like", "lead-like", and "fragment-like" subsets, as well as with the Dictionary of Natural Products [24]. A diversity analysis has been carried out in comparison with the ChemBridge diverse database. Furthermore, descriptors related to absorption, distribution, metabolism, excretion and toxicity (ADMET) have been used to predict the pharmacokinetic profile of the compounds within the dataset. Our results prove that drug discovery, beginning with natural products from the African flora, could be highly promising. The 3D structures are available and could be used for virtual screening and natural product lead generation programs. AfroDb has now been included as a subset of the ZINC database [101].

2.4 AfroCancer

Naturally occurring anticancer compounds represent about half of the chemotherapeutic drugs which have been put on the market against cancer until date. Computer-based or *in silico* virtual screening methods are often used in lead/hit discovery protocols. In this study, the "drug-likeness" of ~400 compounds from African medicinal plants that have shown *in vitro* and/or *in vivo* anticancer, cytotoxic, and antiproliferative activities has been explored [102]. To verify potential binding to anticancer drug targets, the interactions between the compounds and 14 selected targets (including an androgen receptor, a mitotic regulator for chromosomal alignment and segregation, human protein kinases, a protein farnesyltransferase, a cyclin-dependent kinase (CDK) responsible for regulating transcription, a class I histone deacetylase and tubulin) have been analysed by *in silico* modeling. Docking and binding affinity calculations were carried out, in comparison with known anticancer agents comprising ~1,500 published naturally occurring plant-based compounds from around the world. The results reveal that African medicinal plants could represent a good starting point for the discovery of anticancer drugs. The small data set generated (named AfroCancer) has been made available for research groups working on virtual screening. Our results showed that, for five scoring methods, a significant number of the identified compounds within our dataset had docking scores comparable with those of the bound inhibitors within the X-ray structures of the drug targets, implying the presence of potential binders within this dataset. In addition, the docking pose of the antiproliferative luteolin-7-β-glucopyranoside, isolated from the Egyptian medicinal plant, *Livistona australis* [103],[1] showed similar binding interactions as the native ligand (9α-fluorocortisol), co-crystallized in the androgen receptor (PDB code: 1GS4, Fig. 2.3). This revealed that African medicinal plants could represent a good starting point for the discovery of anticancer drugs.

Molecular modeling has been employed in the search for lead compounds of chemotherapy to fight cancer. In a related study, pharmacophore models have been generated and validated for use in vir-

[1]This plant is used locally in treating various tumors, and the isolated metabolite showed *in vitro* cytotoxicities when assayed against liver carcinoma HEPG2, breast carcinoma MCF7 and colon carcinoma HCT116 cell lines.

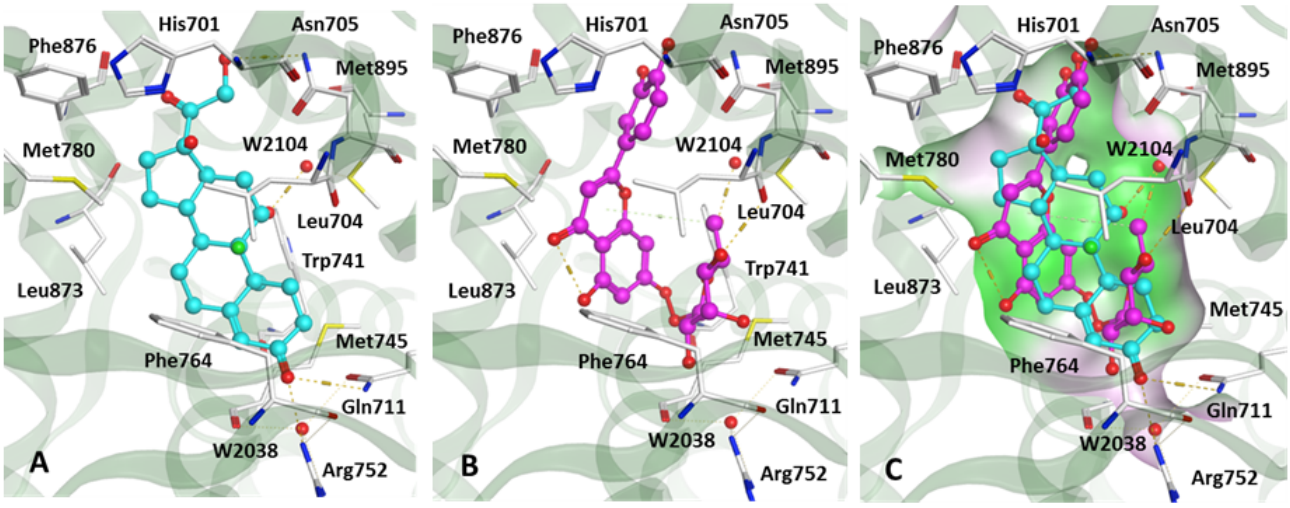


Figure 2.3: (A) crystal structure of the androgen receptor (1GS4) in complex with co-crystallized 9α-fluorocortisol; (B) in complex with docked luteolin-7-O-β-glucopyranoside; (C) docking pose of the luteolin-7-O-β-glucopyranoside (C-atoms colored pink) compared with the co-crystallized 9α-fluorocortisol (C-atoms colored cyan). The molecular surface of the binding pocket is displayed and colored according to the hydrophobicity. Polar regions are shown in magenta, hydrophobic regions in green. Figures reproduced by permission.

tual screening protocols for eight known anticancer drug targets, including tyrosine kinase, protein kinase B β, cyclin-dependent kinase, protein farnesyltransferase, human protein kinase, glycogen synthase kinase, and indoleamine 2,3-dioxygenase 1 [104]. Pharmacophore models were validated through receiver operating characteristic and Güner–Henry scoring methods, indicating that several of the models generated could be useful for the identification of potential anticancer agents from natural product databases. The validated pharmacophore models were used as 3D search queries for virtual screening of the newly developed AfroCancer database (~400 compounds from African medicinal plants), along with the Naturally Occurring Plant-based Anticancer Compound-Activity-Target dataset (comprising ~1,500 published naturally occurring plant-based compounds from around the world). Additionally, an *in silico* assessment of toxicity of the two datasets was carried out by the use of 88 toxicity end points predicted by the Lhasa's expert knowledge-based system (Derek), showing that only an insignificant proportion of the promising anticancer agents would be likely showing high toxicity profiles. A diversity study of the two datasets, carried out using the analysis of principal components from the most important physico-chemical properties often used to access drug-likeness of compound datasets, showed that the two datasets do not occupy the same chemical space.

The results in this section are based on the following articles:

1. **Ntie-Kang, F.;**[†*] Nwodo, J. N.;[†] Ibezim, A.; Simoben, C. V.; Karaman, B.; Ngwa, V. F.; Sippl, W.; Adikwu, M. U.; Mbaze, L. M. Molecular modeling of potential anticancer agents from African medicinal plants. *Journal of Chemical Information and Modeling*, **2014**, *54*, 2433–2450.

2. **Ntie-Kang, F.;**[†*] Simoben, C. V.;[†] Karaman, B.; Ngwa, V. F.; Judson, P. N.; Sippl, W.; Mbaze,

L. M.* Pharmacophore modeling and *in silico* toxicity assessment of potential anticancer agents from African medicinal plants. *Drug Design, Development and Therapy*, **2016**, *10*, 2137–2154.

2.5 AfroMalariaDb

Malaria is an endemic disease affecting many countries in Tropical regions. In the search for compound hits for the design and/or development of new drugs against the disease, many research teams have resorted to African medicinal plants in order to identify lead compounds. In this study, 3D molecular models were generated for antimalarial compounds of African origin (from 'weakly' active to 'highly' active), which were identified from literature sources [105]. Selected computed molecular descriptors related to the ADMET properties of the phytochemicals have been analysed and compared with those of known drugs in order to access the 'drug-likeness' of these compounds. More than 500 antimalarial compounds identified from 131 distinct medicinal plant species belonging to 44 plant families from the African flora have been considered. On the basis of Lipinski's ro5, about 70% of the compounds were predicted to be orally bioavailable, while on the basis of Jorgensen's 'Rule of Three' (ro3), a corresponding >80% were compliant. An overall drug-likeness parameter indicated that approximately 55% of the compounds could be potential leads for the development of drugs. From the above analyses, it could be estimated that >50% of the compounds exhibiting antiplasmodial/antimalarial activities, derived from the African flora, could be starting points for drug discovery against malaria. The 3D models of the compounds have been included as an accompanying file and could be employed in virtual screening.

The results in this section are based on the following article:

Onguéné, P. A;† **Ntie-Kang, F.;**†* Mbah, J. A.; Lifongo, L. L.; Ndom, J. C.; Sippl, W.; Mbaze, L. M. The potential of anti-malarial compounds derived from African medicinal plants, part III: An *in silico* evaluation of drug metabolism and pharmacokinetics profiling. *Organic and Medicinal Chemistry Letters*, **2014**, *4*, 6.

2.6 Afrotryp

This is a relatively small dataset (~350 compounds) of NPs from African flora with known activities against the human African trypanosomiasis (HAT) parasite [106]. Apart from the computer-based predictions for pharmacokinetic properties of the library a docking study was conducted, using 3 docking/scoring methods, in order to assess the affinity of the library dataset towards the binding site of 6 selected validated anti-*Trypanosoma* drug targets. It was observed that about 42% of the compounds contained in the Afrotryp dataset were predicted to show a good overall performance in terms of predicted parameters for absorption, distribution, metabolism, elimination and toxicity

properties. Docking calculations identified 15 compounds with lowest theoretical binding energies toward the studied proteins, 9 of which are suited for the treatment of stage 2 HAT, due to their low polar surface area. Analysis of their binding modes gave a basis for the observed unique molecular interactions which exist between the Afrotryp dataset and the 6 studied drug targets. The results lay the foundations for the rational development of novel trypanocidal drugs with improved potency.

The results in this section are based on the following article:

Ibezim, A.; Debnath, B.; **Ntie-Kang, F.;**[*] Mbah, C. J.; Nwodo, N. J. Binding of anti-*Trypanosoma* natural products from African flora against selected drug targets: a docking study. *Medicinal Chemistry Research*, **2017**, *26*, 562–579.

2.7 p-ANAPL

The pan-African natural products library (p-ANAPL) is a consortium of natural product collections isolated from African biota and owned by scientists and/or groups of scientists working in African institutions. Based the limited quantities of available samples for screening, we prepared a virtual library of 3D structures of p-ANAPL compounds to ease *in silico* identification of lead compounds, to be complemented with experimental assays. A current collection of physical samples of > 500 compound derived from African medicinal plants aimed at screening for drug discovery has been made by donations from several researchers from across the continent to be directly available for drug discovery programs. A virtual library of 3D structures of compounds has been generated and Lipinski's ro5 has been used to evaluate likely oral availability of the samples. A majority of the compound samples are made of flavonoids and about two thirds (2/3) are compliant to the ro5. The pharmacological profiles of thirty six (36) selected compounds in the collection were described in the paper [107]. The p-ANAPL library is the largest physical collection of natural products derived from African medicinal plants directly available for screening purposes. The virtual library is also available and could be employed in virtual screening campaigns.

The results in this section are based on the following article:

Ntie-Kang, F.;[†] Onguéné, P. A.;[†] Fotso, G. W.; Andrae-Marobela, K.; Bezabih, M.; Ndom, J. C.; Ngadjui, B. T.; Ogundaini, A. O.; Abegaz, B. M.; Mbaze, L. M. Virtualizing the p-ANAPL compound library: a step towards drug discovery from African medicinal plants. *PLoS ONE*, **2014**, *9*, e90655.

2.8 NANPDB

Our most recently built the Northern African Natural Products Database (NANPDB) was an initial collection of ~4500 (currently ~5000) NPs, now covering literature data for the period from 1962

to 2017 [108]. The data cover compounds isolated mainly from plants, with contributions from some endophyte, animal (e.g., coral), fungal, and bacterial sources, which currently constitute 751 source species from 155 families. Computed physico-chemical properties, often used to predict drug metabolism and pharmacokinetics, as well as predicted toxicity information, were included for each compound in the data set. This was the largest collection of annotated natural compounds produced by native organisms from Northern Africa. Additional search features have been included, also giving users the possibility to make contributions to update the data. Moreover, NANPDB is the most comprehensive database of NPs from the Northern Africa region. For each compound, the details of its chemical structure, biological and physico-chemical properties, source species, and literature information are provided. The importance of the database is also demonstrated by the low number of compounds already annotated in the PubChem database and the relatively few references common with PubMed. The bioactive compounds can be further investigated for modes of action and alternative biological activities, while the untested molecules are a valuable resource for future drug discovery efforts. While the database includes well-known drugs and drug leads, the medical potential of a majority of the molecules is yet to be investigated. The database could be useful for drug discovery efforts, analysis of the bioactivity of selected compounds, or the discovery of synthesis routes toward secondary metabolites. The additional advantage of NANPDB is its web accessibility (http://african-compounds.org/nanpdb/) and its chemistry aware interface.

The results in this section are based on the following article:

Ntie-Kang, F.;[†*] Telukunta, K. K.;[†] Döring, K.; Simoben, C. V.; Moumbock, A. F. A.; Malange, Y. I.; Njume, L. E.; Yong, J. N.; Sippl, W.; Günther, S.[*] NANPDB: a resource for natural products from Northern African sources. *Journal of Natural Products*, **2017**, *80*, 2067−2076.

2.9 Ongoing

Data on NPs from East and West Africa have been collected and are in the process being published. Updates of ConMedNP, p-ANAPL and AfroDb are also being prepared, along with advanced search options of NANPDB.

2.10 Chapter summary

This chapter was intended to provide the author's contributions towards providing electronically accessible datasets and databases which could enhance drug discovery from African medicinal plants, along with some promising preliminary results in the literature. Table 2.3 provided a summary of the state-of-the-art of the each of the aforementioned databases.

Table 2.3: *Summary of electronic databases developed within this work.*

Library name	[a]***Library size***	[b]***Source organism***	[c]***Families***	***Web Accessibility***	***Reference***
CamMedNP	1,859	224	55	http://african-compounds.org/about/cammednp/	[91]
ConMedNP	3,177	376	79	http://african-compounds.org/about/conmednp/	[92]
AfroDb	986	–	–	http://african-compounds.org/about/afrodb/	[100, 101]
AfroCancer	390	–	–	http://african-compounds.org/about/afrocancer/	[102, 104]
AfroMalariaDb	511	131	45	http://african-compounds.org/about/afromalariadb/	[105]
Afrotryp	321	–	22	http://african-compounds.org/about/afrotryp/	[106]
p-ANAPL	534	[d]ND	[d]ND	http://african-compounds.org/about/p-anapl/	[107]
NANPDB	4,928	751	155	http://african-compounds.org/nanpdb/	[108]

[a]*Library size = number of compounds,* [b]*Source organism = number of source organisms,* [c]*Families = number of source families,* [d]*ND = not determined.*

CHAPTER THREE

MOLECULAR MODELING AND LEAD COMPOUND IDENTIFICATION

3.1 Objectives of the chapter

In this chapter, the contributions towards the identification of NPs, NP mimics and NP derivatives as lead compounds are summarised. This has been in several national and international collaborative projects, within which the main contribution has been providing the relevant molecular modeling support and/or carrying out the modeling and interpreting the results.

3.2 Assessment of DMPK profiles of externally generated natural product libraries

3.2.1 StreptomeDB

Computer-aided drug design (CADD) often involves virtual screening (VS) of large compound datasets and the availability of such is vital for drug discovery protocols. An assessment of the "drug-likeness" and pharmacokinetic profile of > 2,400 compounds of natural origin, available in the StreptomeDB database had been conducted [109], using 46 computed physico-chemical properties or molecular descriptors often used to predict ADMET properties. This survey demonstrated that, of the computed molecular descriptors, about 28% of the compounds were compliant, having properties which fell within the range of ADMET properties of 95% of currently known drugs, while about 44% of the compounds had ≤ 2 violations. Moreover, about 50% of the compounds within the corresponding "drug-like" subset showed compliance, while >83% of the "drug-like" compounds had ≤ 2 violations. In addition to the previously verified range of measured biological activities, the compounds in the StreptomeDB database showed interesting DMPK profiles and hence could represent an important starting point for hit/lead discovery from natural sources. The generated data are available and could be highly useful for natural product lead generation programs.

3.2.2 NPACT

In a similar analysis, an investigation of how 'drug-like' naturally occurring NPs with anticancer properties are, was carried out [110]. An attempted answer consisted in investigating the compliance of ~1500 anticancer NPs from the NPACT dataset [28] to Lipinski's ro5 and Jorgensen's ro3 as assessment criteria for oral availability. This analysis made use of popular parameters like molecular weights, predicted lipophilicities, number of hydrogen bond donors/acceptors, predicted aqueous solubilities, number of primary metabolites and Caco-2 permeabilities. Meanwhile, 24 descriptors have been used to predict properties related to the ADMET properties. The ADMET profiles of the anticancer natural products have been analysed in comparison with the range of properties for 95% of known drugs. It was shown that the computed parameters fall within the recommended range for about 42% of the studied compounds, while respectively 63% and 69% of the corresponding 'drug-like' and 'lead-like' subsets had properties predicted to fall within the recommended range for 95% of known drugs. The aim of giving a picture of how drug-like they are and bring out the need to return to natural sources in searching for anticancer lead compounds.

The results in this section are based on the following article:

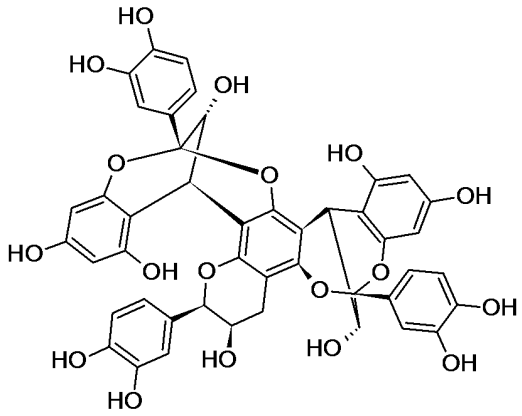
Ntie-Kang, F.;* Lifongo, L. L.; Judson, P. N.; Sippl, W.; Efange, S. M. N. How "drug-like" are naturally occurring anticancer compounds? *Journal of Molecular Modeling*, **2014**, *20*, 2069.

3.3 Naturally occurring plant metabolites identified by virtual screening

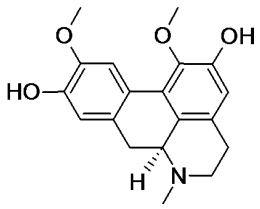
Both structure-based and ligand-based virtual screening experiments were employed to identify lead compounds with potencies against the human immunodeficiency virus (HIV), sirtuins and cancer.

3.3.1 Anti-HIV metabolites identified by pharmacophore-based filtering

The continued burden of HIV in resource-limited regions such as parts of sub-Saharan Africa, combined with adverse effects and potential risks of resistance to existing antiretroviral therapies, emphasize the need to identify new HIV inhibitors. A combined pharmacophore model, based on active ligands and scoring the p-ANAPL compounds, the largest collection of medicinal plant-derived pure compounds on the African continent [107] in a virtual screen led to the identification of Vpu interactors. Eight molecules with structural similarity to reported interactors of Vpu, an HIV-1 accessory protein with reported ion channel activity, were identified [111]. Using *in vitro* HIV-1 replication assays with a CD4+ T cell line and peripheral blood mononuclear cells, we confirmed antiviral activity and minimal cytotoxicity for two compounds, ixoratannin A-2 (**11**) and boldine (**12**), Fig. 3.1.



Ixoratannin A-2 (**11**)



Boldine (**12**)

Figure 3.1: Anti-HIV compounds identified from the p-ANAPL library.

Notably, ixoratannin A-2 retained inhibitory activity against recombinant HIV-1 strains encoding patient-derived mutations that confer resistance to protease, non-nucleoside reverse transcriptase, or integrase inhibitors. Moreover, ixoratannin A-2 was less effective at inhibiting replication of HIV-1 lacking Vpu, supporting this protein as a possible direct or indirect target. In contrast, boldine was less effective against a protease inhibitor-resistant HIV-1 strain. Both ixoratannin A-2 and boldine also inhibited *in vitro* replication of hepatitis C virus (HCV). However, BIT-225, a previously-reported Vpu inhibitor, demonstrated antiviral activity but also cytotoxicity in HIV-1 and HCV replication assays. Thus, pure compounds derived from African plants with potential novel activities against viruses that disproportionately afflict resource-limited regions of the world were identified.

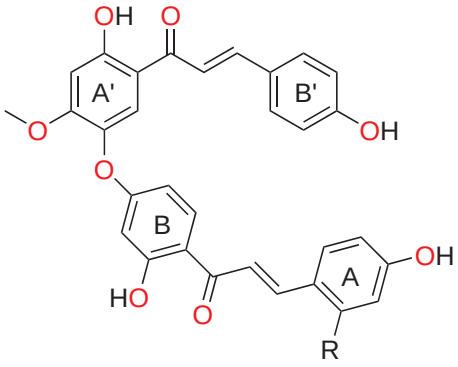
The results in this section are based on the following article:

Tietjen, I.; **Ntie-Kang, F.;** Mwimanzi, P.; Onguéné, P. A.; Scull, M. A.; Idowu, T. O.; Ogundaini, A. O.; Mbaze, L. M.; Abegaz, B. M.; Rice, C. M.; Andrae-Marobela, K.; Brockman, M. A.; Brumme, Z. L.; Fedida, D. Screening of the pan-African natural product library identifies ixoratannin A-2 and boldine as novel HIV-1 inhibitors. *PLoS ONE*, **2015**, *10*, e0121099.

3.3.2 Naturally occurring Sirtuin inhibitors identified by docking

Docking of the virtual pan-African natural products library (p-ANAPL), followed by *in vitro* assays, resulted in the identification of two inhibitors of Sirtuin 1, 2 and 3 (Sirt1-3) [112]. Sirtuins are nicotinamide adenine dinucleotide (NAD^+)-dependent class III histone deacetylases, which have been linked to the pathogenesis of numerous diseases such as HIV [113], aging [114], metabolic disorders [115], inflammation [116, 117], neurodegeneration (including Alzheimer's disease and Parkinson's disease) [118, 119], and cancer [120]. Bichalcones (Fig. 3.2); rhuschalcone IV (**13**) and an analogue of rhuschalcone I (**14**), previously isolated from the medicinal plant *Rhus pyroides* [121, 122], were shown to be active. The rhuschalcone I analogue showing the best activity against Sirt1, having

an IC_{50} of 40.8 μM. Based on the docking experiments, suggestions for improving the biological activities of the newly identified hit compounds have been provided.



Rhuschalcone IV (**13**): R = H,
Rhuschalcone I analogue (**14**): R = OH

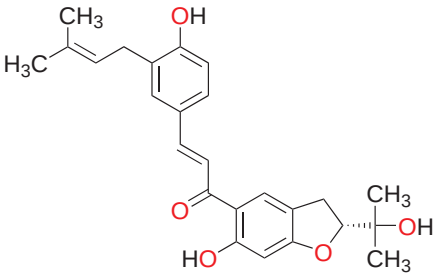
Figure 3.2: Chemical structures of rhuschalcones identified by in silico and in vitro screening.

The results in this section are based on the following article:

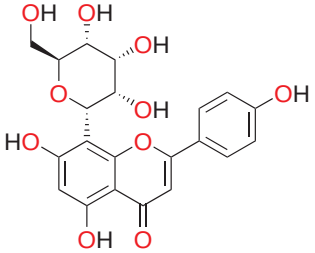
Karaman, B.;[†] Alhalabi, Z.;[†] Swyter, S.; Mihigo, S. O.; Andrae-Marobela, K.; Jung, M.; Sippl, W.; **Ntie-Kang, F.**[*] Identification of bichalcones as sirtuin inhibitors by virtual screening and *in vitro* testing. *Molecules*, **2018**, *23*, 416.

3.3.3 Anticancer metabolites with predicted kinase inhibitory properties by QSAR

Inhibitors of Myt1 kinase and PRK were also identified from the p-ANAPL library using structure-based docking, coupled with QSAR. While *in vitro* screening for potential inhibitors of Myt1 kinase is ongoing (results unpublished), the initial results on the application of on lead discovery (including new NP scaffolds, Fig. 3.3) against an interesting anticancer drug target, the protein kinase C-related kinase (PRK1), has been published [123].



Bartericin B (**15**)



Vitexin or apigenin-8-C glucoside (**16**)

Figure 3.3: Chemical structures of PRK1 in silico hits.

One of the *in silico* hits is bartericin B (**15**; PubChem CID: 12136210), originally derived from *Dorstenia barteri* [124]. The binding mode of compound **15** is shown in Fig. 3.4A. The compound is predicted to interact with hinge region residue Ser704 with one H-bond. The phenol ring forms an additional H-bond with the backbone of Asp764 from the DFG-motif.

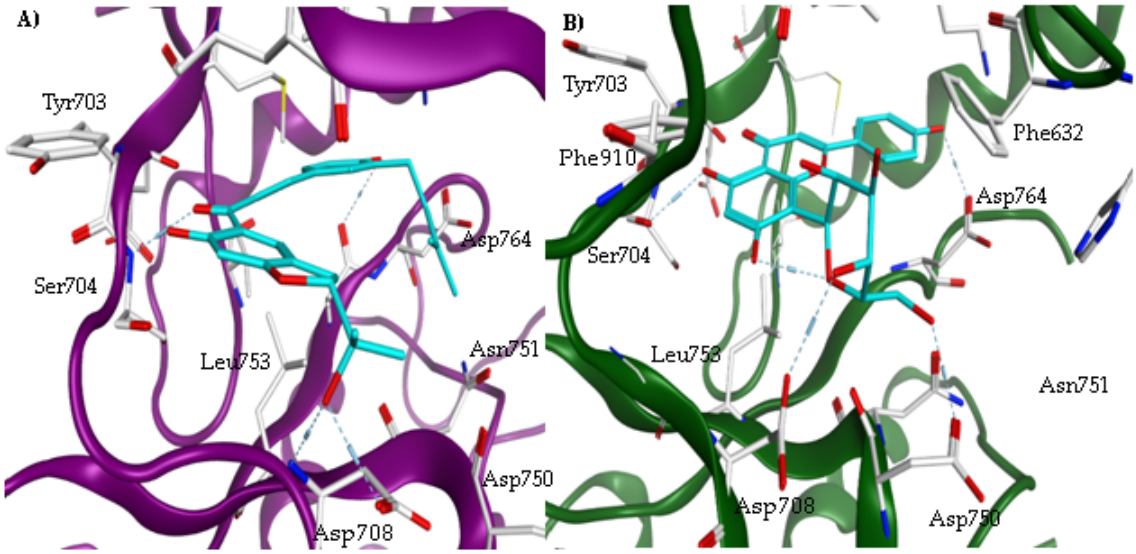


Figure 3.4: Docking poses of the selected hits in PRK1 binding pocket: A) Docking poses of bartericin B in the binding pocket of PRK1 structure 4OTG; B) Docking pose of vitexin in PRK1 structure 4OTH. Figures reproduced by permission.

The interaction with the front polar pocket and the ribose binding pocket is mediated by two H-bonds between Asp708 and propanol substituent in the compound. The calculated pIC_{50} values ranged from 7.45 to 7.85, using the generated QSAR models. The second hit (P87), vitexin or apigenin-8-C glucoside (**16**; PubChem CID: 5280441), is a flavonoid glycoside from diverse sources, e.g. *Hyparrhenia hirta* [125]. The binding mode of this compound (Fig. 3.4B) shows that it might form one H-bond with the hinge region residue Ser704. Additionally, the substituents on the oxane ring are targeting the front polar pocket and forming two H-bonds with Asp708 and Asp750. The phenyl ring interacts with the back hydrophobic pocket and further forms an H-bond with Asp764 in the DFG-motif. Moreover, vitexin was predicted to be a highly potent compound, with a predicted $pIC_{50} > 7$, using the aforementioned QSAR models. Bartericin B and vitexin are only 2 examples of promising NPs which could target PRK1. In further investigations, the selected compounds will be submitted for biological assay to figure out their ability to bind to PRK1. Bartericin B is known to exhibit antimicrobial activities against *Trichomonas gallinarum*, with minimum lethal concentrations (MLCs) of 0.244 and 0.121 μg/mL after 24 H and 48 H, respectively [124], while its analogue (bartericin A from *Dorstenia angusticornis*), is known to be very active against some bacteria and yeasts associated with human pathologies [126]. Both compounds are known to also have potential antiprotozoal activities [127], e.g. against *Plasmodium falciparum* [128]. Vitexin, on the other hand, is known for its antioxidative and [129], spasmolytic effects [130]. The biological activities of vitexin and isovitexin have been reviewed, including but not limited to antioxidant, anticancer, anti-inflammatory, anti-hyperalgesic, and

neuroprotective effects [131]. Meanwhile, isovitexin (apigenin-6-C-glucoside), an isomer of vitexin, generally purified together with vitexin, also exhibits diverse biological activities. The compound is known to be abundant in plants of the genus *Vitex* (Verbenaceae), which are known to exert insect antifeeding activities, amongst others [132]. These compounds could now be tested in biological assays for potential PRK1 inhibition.

The results in this section are based on the following article:

Najjar, A.; **Ntie-Kang, F.;*** Sippl, W. *Application of computer modeling to drug discovery: case study of PRK1 kinase inhibitors as potential drugs in prostate cancer treatment*. ***In*** Unique Aspects of Anti-cancer Drug Development. Latosińska, J.; Latosińska, M. (Editors); Rijeka: InTech: ISBN 978-953-51-5240-8, **2017**, pp. 17–47.

3.4 Isolated and synthesized compounds further investigated by computer-based methods

3.4.1 Antimalarial compounds from *Dacryodes edulis* (Burseraceae)

The aims of this study were to identify the compounds responsible for the antimalarial activity of *Dacryodes edulis* (Burseraceae) and to investigate their suitability as leads for the treatment of drug-resistant malaria [133]. Five compounds (Fig. 3.5) were isolated from ethyl acetate and hexane extracts of *D. edulis* stem bark and tested against 3D7 (chloroquine-susceptible) and Dd2 (multidrug-resistant) strains of *P. falciparum*, using the parasite lactate dehydrogenase method.

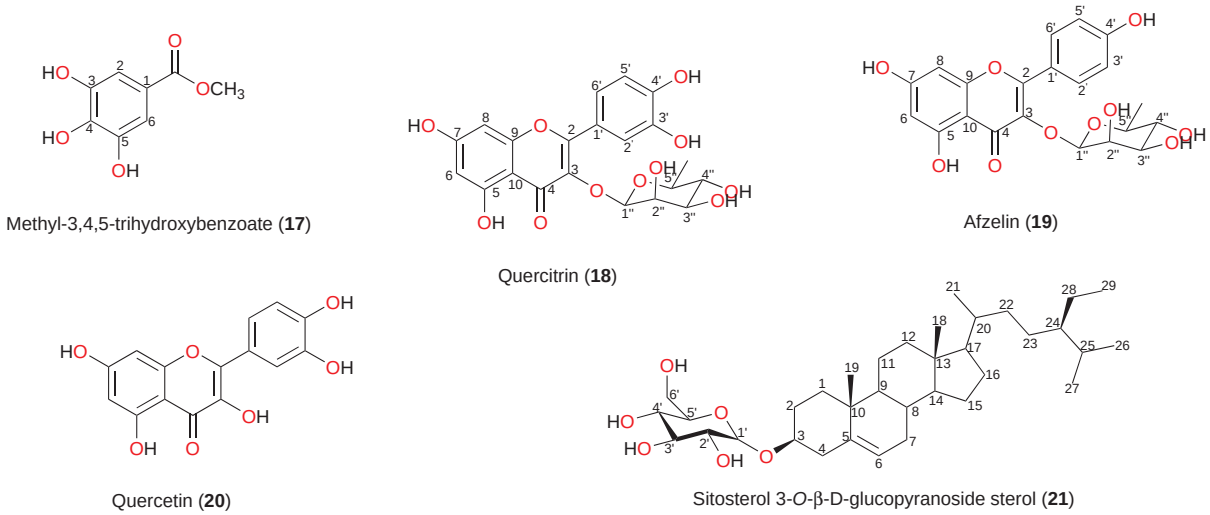


Figure 3.5: Chemical structures of the antimalarial hits from Dacryodes edulis (Burseraceae).

Cytotoxicity studies were carried out on LLC-MK2 monkey kidney epithelial cell line. *In silico* analysis was conducted by calculating molecular descriptors using the MOE software running on a Linux

workstation. The "drug-likeness" of the isolated compounds was assessed using Lipinski criteria, from computed molecular properties of the geometry optimized structures. Computed descriptors often used to predict ADMET were used to assess the pharmacokinetic profiles of the isolated compounds. Antiplasmodial activity was demonstrated for the first time in five major natural products previously identified in *D. edulis*, but not previously tested against malaria parasites. The most active identified compound (**17**, Fig. 3.5) had IC_{50} values of 0.37 and 0.55 μg/mL, against 3D7 and Dd2, respectively. In addition, this compound was shown to act in synergy with quinine, satisfied all criteria of "drug-likeness" and showed the considerable probability of providing an antimalarial lead. The remaining four compounds (**18** to **21**) also showed antiplasmodial activity but were less effective than **17**. None of the tested compounds was cytotoxicity against LLC-MK2 cells, suggesting their selective activities on malaria parasites. Based on the high *in vitro* activity, low toxicity and predicted "drug-likeness" compound **17** merits further investigation as a possible drug lead for the treatment of malaria.

3.4.2 Protease inhibitory and antimicrobial compounds isolated from *Helichrysum* species (Compositae)

Helichrysum species are used extensively for stress-related ailments and as dressings for wounds normally encountered in circumcision rites, bruises, cuts and sores. It has been reported that *Helichrysum* species are used to relieve abdominal pain, heart burn, cough, cold, wounds, female sterility, menstrual pain [134]. From the extracts of *Helichrysum foetidum* (L.) Moench, six known compounds were isolated and identified, which included 7,4'-dihydroxy-5-methoxy-flavanone (**22**), 6'-methoxy-2',4,4'-trihydroxychalcone (**23**), 6'-methoxy-2',4-dihydroxychalcone-4'-*O*-β-D-glucoside (**24**), apigenin (**25**), apigenin-7-*O*-β-D-glucoside (**26**) and kaur-16-en-18-oic acid (**27**) (Fig. 3.6) [134]. Besides, the two known compounds; 3,5,7-trihydroxy-8-methoxyflavone (**28**), 4,5-dicaffeoyl quinic acid (**29**), together with a mixture of phytosterol were also isolated from the methanol extract of *Helichrysum mechowianum* Klatt. Both extracts and all the isolates were screened for protease inhibition, antibacterial and antifungal activities. The results showed that the protease inhibitory activity of *H. foetidum* could be mainly attributed to the constituents of flavonoid glycosides (**24** and **26**), while compound **29** from *H. mechowianum* contributes to the observed stomach protecting effects. In addition, among the antibacterial and antifungal activities of all the isolates, compound **27** was found to possess a potent inhibitory effect against the tested microorganisms. The heterogeneity of the genus is also reflected in its phytochemical diversity. The differential bioactivities and determined constituents support the traditional use of the species. Molecular modelling was carried out by computing selected descriptors related to DMPK properties, showing that for two of the compounds (**25** and **27**), only 1 out of the 46 computed ADMET descriptors fell out of the recommended range for 95% of known drugs, while compound **29** showed up to 5 violations [134].

The results in this section are based on the following article:

Malolo, F. A. E.; Nouga, A. B.; Kakam, A.; Franke, K.; Ngah, L.; Flausino, O. J.; Mpondo, E. M.; **Ntie-Kang, F.;*** Ndom, J. C.; Bolzani, V. S.; Wessjohann, L. Protease-inhibiting, molecular modelling and antimicrobial activities of extracts and constituents of *Helichrysum foetidum* and *Helichrysum mechowianum* (Compositae). *Chemistry Central Journal*, **2015**, *9*, 32.

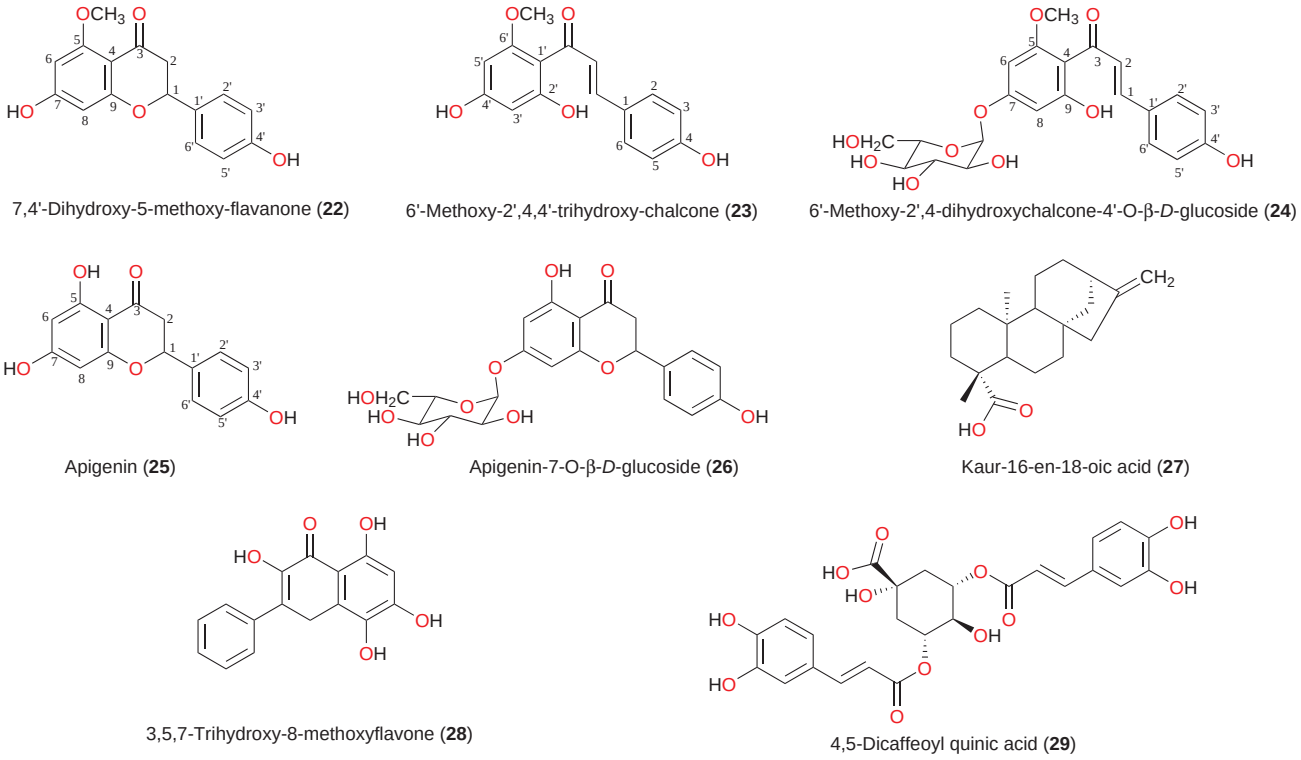


*Figure 3.6: Compounds **22–27** isolated from leaves and flowers of Helichrysum foetidum, together with compounds **28** and **29** from the leaves of Helichrysum mechowianum.*

3.4.3 Anti-*Onchocerca* metabolites from *Cyperus articulatus* (Cyperaecae)

Active ingredients from the roots and rhizomes of *Cyperus articulatus*, used as herbal medicine in Cameroon for the treatment of human onchocerciasis, were investigated in order to assess the efficacy of the metabolites on the *Onchocerca* worm [135]. The antifilarial activity was evaluated *in vitro* on microfilariae (Mfs) and adult worms of the bovine-derived *Onchocerca ochengi*, a close relative of *Onchocerca volvulus*. Cytotoxicity was assessed *in vitro* on monkey kidney epithelial cells. The structures of the active compounds were determined using spectroscopic methods and their drug-likeness evaluated using Lipinski parameters. Two secondary metabolites; mustakone (**30**) and linoleic acid or (9*Z*,12*Z*)-octadeca-9,12-dienoic acid (**31**) were isolated (Fig. 3.7). Both compounds were found to kill both the microfilariae (Mfs) and adult worms of *O. ochengi* in a dose-dependent manner. The IC_{50} values for compound **30** were 15.7 μg/mL for Mfs, 17.4 μg/mL for adult males and 21.9 μg/mL for adult female worms while for linoleic acid the values were, 15.7 μg/mL for Mfs, 31.0 μg/mL for adult males and 44.2 μg/mL for adult females. This report provided the first ever evidence of the anti-

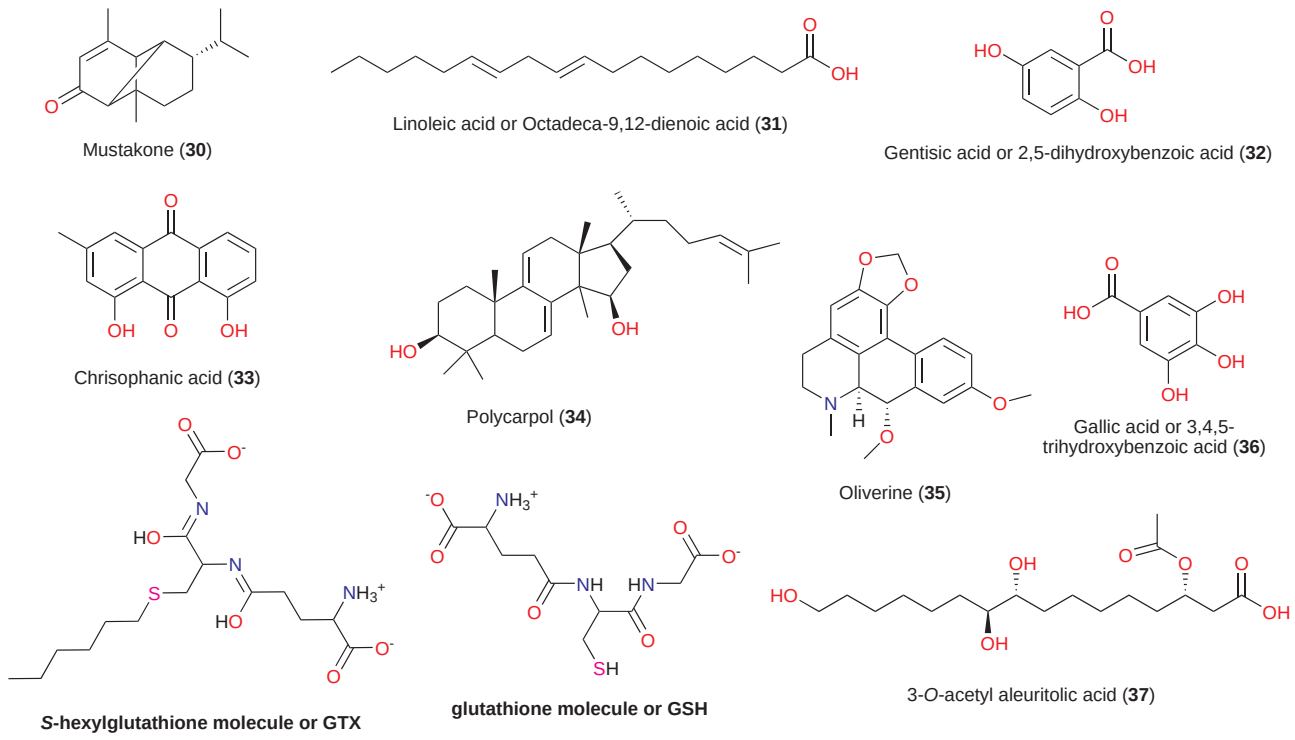


Figure 3.7: Chemical structures of plant-derived anti-Onchocerca compounds and native ligands co-crystallized with the anti-Onchocerca drug target.

Onchocerca efficacy of mustakone and linoleic acid, thus, suggesting these secondary metabolites as lead compounds for the design and development of new antifilarial agents.

In a further investigation, the isolated compounds (**30** and **31**), together with other known plant-based anti-*Onchocerca* compounds (**32** to **37**) were modeled against a validated anti-*Onchocerca* drug target [136]. At the time of the investigation, the only class of drug targets whose X-ray crystal structure had been solved is the glutathione transferases, co-crystallized with a cofactor and a competitive inhibitor (glutathione and *S*-hexylglutathione), Fig. 3.7. This is because structure-based drug discovery efforts against *O. volvulus* have been focused on glutathione *S*-transferases (GSTs). The role of GSTs as promising drug targets is highlighted by the fact that they are considered to play important functions like the regulation of oxidative stress response, drug resistance, and the modulation of host immune defense mechanisms [137]. They also play important roles in detoxification metabolism by catalyzing the nucleophilic addition of reduced glutathione (GSH) to numerous endobiotic and xenobiotic electrophilic substrates, often promoting the inactivation, degradation, and excretion of the former [138]. Within this family of enzymes in *O. volvulus*, the σ-class or *Ov*-GST1 is the prostaglandin D synthase, bound to GSH (PDB code: 2HNL). The π-class glutathione *S*-transferase, *Ov*-GST2, is co-crystallized both with GSH (PDB code: 1TU7) and with *S*-hexylGSH or GTX (PDB code: 1TU8), Fig. 3.8. In comparison with the other π-class counterparts, particularly that of the human host, *Ov*-GST2 shows significant and unusual differences in the sequence and overall structure. In a quest to identify potential hit compounds for drug discovery and to further explore potential inhibitory mechanisms of plant-derived anti-*Onchocerca* compounds, we have carried out an *in silico* study. The goal

has been to devise molecular modeling approaches for virtual screening simulations, which could lead to the identification of potential inhibitors of this drug target from plant chemical libraries. Docking studies have been carried out for 8 known plant-derived compounds showing *in vitro* activities against *Onchocerca* species [136].

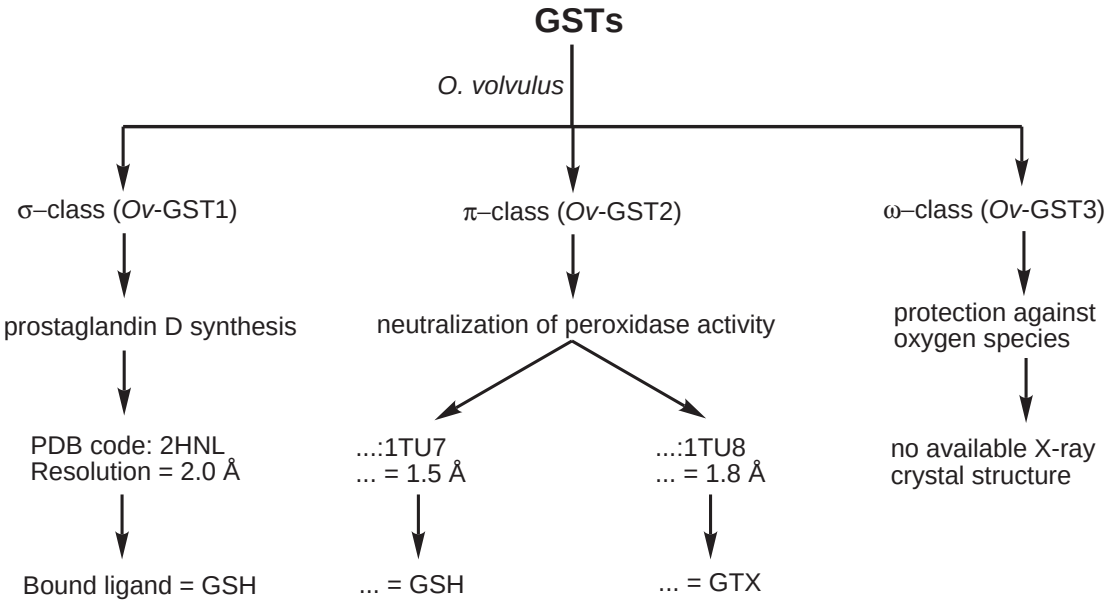


Figure 3.8: Summary of GSTs from Onchocerca volvulus. Figure reproduced by permission.

The predicted binding affinities toward the π-class glutathione *S*-transferase protein were comparable with those of the bound ligand (Fig. 3.9) for 6 out of the 8 identified anti-*Onchocerca* hits. The binding interactions seem to favor the binding of potential inhibitors toward the cofactor binding site of the π-class proteins, but not for the σ-class. This has suggested further investigation of these compounds for potential binding toward the substrate binding sites of the σ-class and the cofactor binding site of the π-class *Ov*-GST in enzyme inhibition assays. Virtual screening studies based on combined structure-based and ligand-based pharmacophore methods for the potential identification of hits from our previously described in-house natural product databases was further suggested. This study has laid a foundation for further investigations of naturally occurring *O. volvulus* drug targets. Explorations of the protein-ligand interactions from the docking poses have provided insight for potential binding interactions of interest, which could be exploited in searching for lead compounds.

The results in this section are based on the following articles:

1. Metuge, J. A.; Babiaka, S. B.; Mbah, J. A.; **Ntie-Kang, F.;** Ayimele G. A.; Cho-Ngwa, F. Anti-*Onchocerca* compounds from *Cyperus articulatus*: isolation, *in vitro* activity and *in silico* 'drug-likeness'. *Natural Products and Bioprospecting*, **2014**, *4*, 243–249.

2. Metuge, J. A.;[†] **Ntie-Kang, F.;**[†*] Ngwa, V. F.; Babiaka, S. B.; Samje, M.; Cho-Ngwa, F. Molecular modelling of plant metabolites with anti-*Onchocerca* activity. *Medicinal Chemistry Research*, **2015**, *24*, 2127–2141.

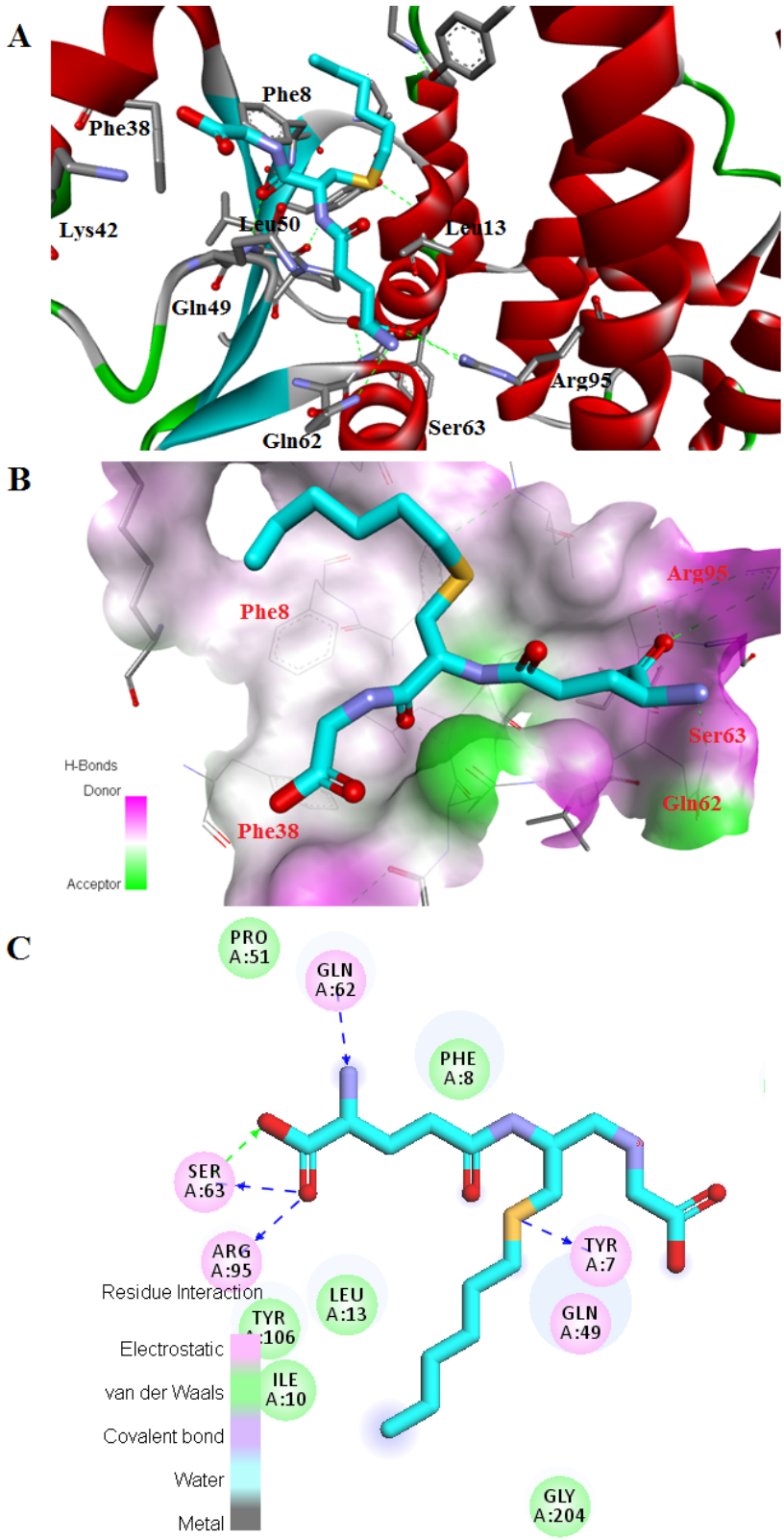


Figure 3.9: Substrate binding site of Ov-GST2 (PDB code: 1TU8) showing features necessary for GTX binding to the drug target: (A) Hydrogen bonds are shown as green broken lines, C-atoms in the protein are in the standard grey colour, C-atoms in the ligand are in cyan, while the other atoms take standard colour codes, e.g. O = red, N = blue, S = yellow. Secondary structural features are also colour-coded; α-helices = red, β-sheets = cyan and turns = green; (B) Showing binding pocket molecular surface, with hydrophobic regions in grey and the polar donor/acceptor regions in pink and green respectively; (C) 2D plot of protein-ligand interactions. Figures reproduced by permission.

3.4.4 Sesquiterpenes from *Scleria striatinux* (Cyperaceae) with antiparasitic properties

The antiparasitic activity and preliminary *in vitro* and *in silico* drug metabolism and pharmacokinetic (DMPK) assessment of six isomeric sesquiterpenes (**38** to **43**, Fig. 3.10), isolated from the Cameroonian spice *Scleria striatinux* De Wild (Cyperaceae), were also described [139]. The study was prompted by the observation that two of the compounds (**38** and **39**) exhibited varying levels of antiparasitic activity on *P. falciparum*, *Trypanosoma brucei rhodesiense*, *T. cruzi* and *Leishmania donovani*. The *in silico* (using QikProp descriptors) and *in vitro* experiments (using human liver microsomes) were employed in the assessment of the metabolic stability of these hits, which were used to correlate theoretical predictions with experimental findings. Overall, the tested compounds have been found to have acceptable physico-chemical properties and fall within the ranges associated with 'drug-like' molecules. Moreover, the compounds exhibited minimal degradation in incubations with human liver microsomes. Although some of these compounds (e.g. **38**, **39**, **41** and **42**) had been reported previously [140, 141, 142], this was the first report on their antiparasitic activities, as well as an assessment of their DMPK profiles. The results have therefore provided a window for further development of this novel class of sesquiterpene molecules as potential antiparasitic drugs.

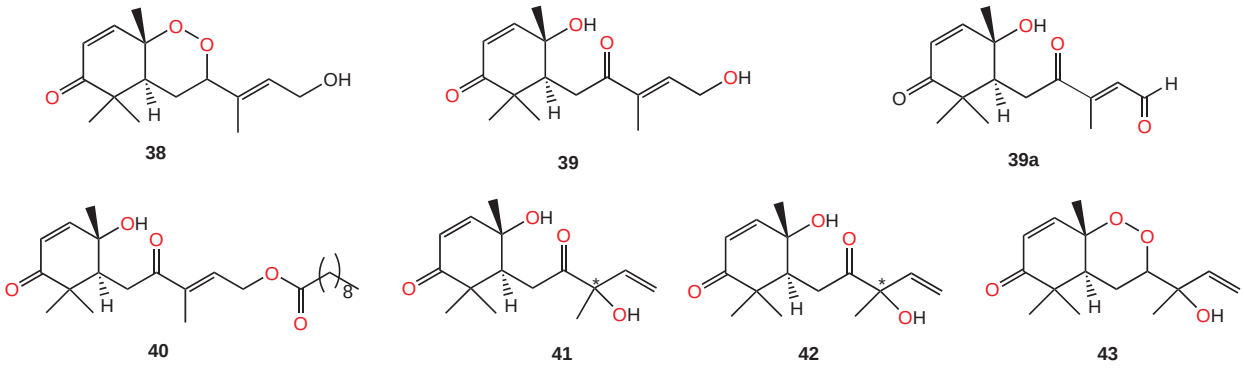


Figure 3.10: Chemical structures of Scleria striatinux lead compounds.

Overall, the tested compounds were found to have acceptable physico-chemical properties, but outstanding amongst them were okundoperoxide (**38**) and sclerienone C (**39**). Compound **38** showed a good solubility profile, moderate *n*-octanol/water partition coefficient and acceptable *in silico* pharmacokinetic properties, while compound **39** had very similar characteristics to compound **38**, although with less optimal parameters for *n*-octanol/water partition coefficient, the polar surface area (PSA) and the NRB. This suggests that compound **38** may have slightly better permeability properties than compound **39**.

The results in this section are based on the following article:

Nyongbela, K. N.; **Ntie-Kang, F.;** Hoye, T. R.; Efange, S. M. N. Antiparasitic sesquiterpenes from the Cameroonian spice *Scleria striatinux* and preliminary *in vitro* and *in silico* DMPK assessment.

Natural Products and Bioprospecting, **2017**, *7*, 235–247.

3.4.5 Natural product-inspired synthetic tetraisoquinolines with antiplasmodial properties

In this project, the 1,2,3,4-tetrahydroisoquinoline scaffold (THIQ, Fig. 3.11), which is abundant in nature (Dioncophyllaceae and Ancistrocladaceae [143, 144, 145, 146]), e.g. in the anti-HIV michellamine B (**44**) and the antiplasmodial dioncophyllines B to E (**45** to **48**), was the source of inspiration for the synthesis of potent antimalarial agents [147]. In total, 21 analogues of 1-aryl-6-hydroxy-1,2,3,4-tetrahydroisoquinoline were synthesized by base-catalyzed Pictet-Spengler reaction and tested *in vitro* against *P. falciparum* using the [^{3}H]hypoxanthine incorporation assay. Two compounds were found to be inactive while seventeen compounds displayed moderate antiplasmodial activity and two compounds were found to be highly active (IC_{50} < 0.2 μg/mL). In order to further optimize the observed activities, a computational study has been conducted on the series of synthesized analogues (results unpublished).

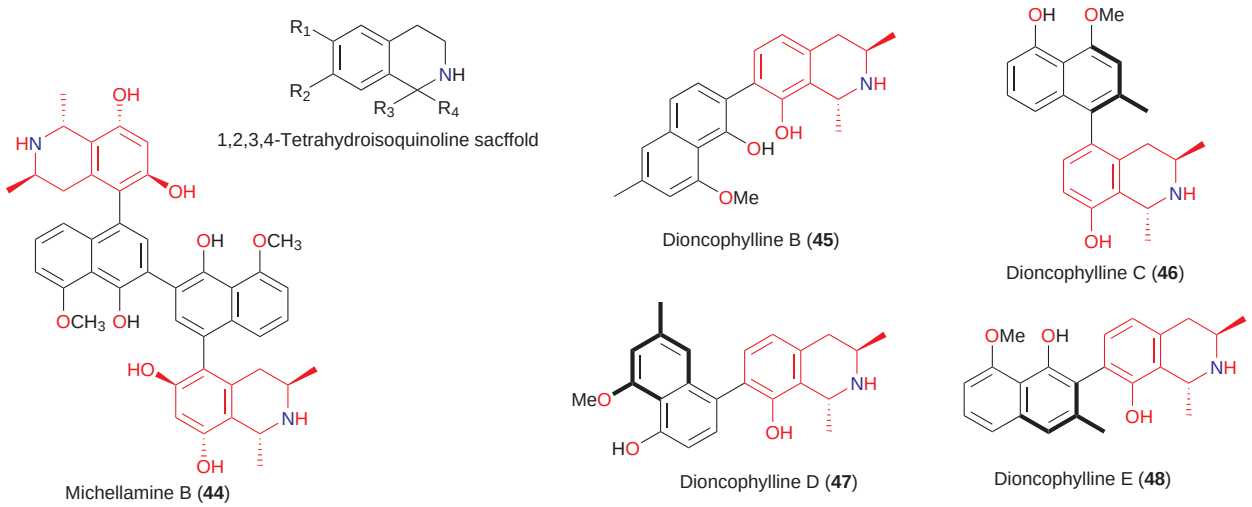


Figure 3.11: Michellamine B and dioncophyllines B to E, with the tetrahydroisoquinoline scaffold shown in red.

Of the 21 compounds tested, only the activities of nineteen were taken into consideration in the computation. In order to computationally design and screen potent antimalarial agents, the synthesized compounds with known biological activities ranging from 0.181 to 10.3 μg/mL, were geometry optimized at the B3LYP/6311+ G(d,p) level of theory using the Gaussian 09W software. To calculate the topological differences, the series of the nineteen compounds was superimposed and a hypermolecule obtained with s = 17 and 20 vertices. Other molecular descriptors were considered in order to build a highly predictive QSAR model. These include, minimal topological difference (MTD), XLogP, $(XLogP)^2$, molar refractivity (MR), two dimensional polarity surface area (2DPSA), dipole moment

(μ), chemical hardness (η), electrophilicity (ω), potential energy (E), electrostatic energy (E_{ele}) and number of rotatable bonds (NRB). From a training set of 15 randomly selected compounds from the series a QSAR equation was derived (R^2 = 0.957677, F = 22.6278, SDEP = 0.0872, Q^2 = 0.5601). The QSAR equation obtained was used to adequately predict the IC_{50} values of 4 compounds in the validation set. Based on the pharmacophore model of the most active compounds in the training set, ten analogues were proposed by searching a fragment library. Amongst the proposed analogues, the most active showed a predicted activity 0.014 μg/mL. Further synthesis of designed analogues is ongoing.

The results in this section are based on the following article:

Ngo Hanna, J.; **Ntie-Kang, F.;** Kaiser, M.; Brun, R.; Efange, S. M. N. 1-Aryl-1,2,3,4-tetrahydroisoquinolines as potential antimalarials: synthesis, *in vitro* antiplasmodial activity and *in silico* pharmacokinetics evaluation. *RSC Advances*, **2014**, *4*, 22856–22865.

3.4.6 Design of piperidines with antiplasmodial activities and sigma binding affinities

Sigma (σ) receptors are membrane-bound proteins characterised by an unusual promiscuous ability to bind a wide variety of drugs and their high affinity for typical neuroleptic drugs, e.g. haloperidol, and their potential as alternative targets for antipsychotic agents [148]. Among the compounds reported to bind σ receptors, a large number of benzylpiperidines and benzylpiperazines (Fig. 3.12) display remarkable affinity.

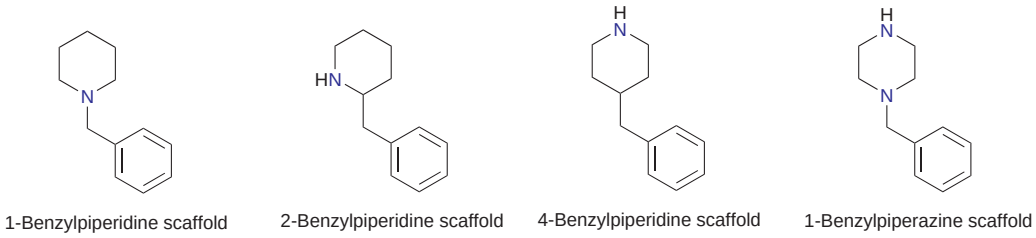


Figure 3.12: Common scaffolds of some sigma receptor binders.

Within this project, 14 compounds were derived by modification of the lead compound spipehthiane, by replacement of the S-atom with a carbonyl group, hydroxyl group and 3-bromobenzylamine with the simultaneous presence of 4-fluorobenzoyl replacing the spirofusion afforded novel potent sigma-1 (σ1) receptor ligands [149]. The derived compounds had sigma binding affinities (K_i) generally below 15 nM for all the compounds except 4 of them, the tightest binder having a K_i value as low as 1.40 nM. It was found that these compounds have higher selectivities for σ1 receptors compared to the starting compound (spipethiane).

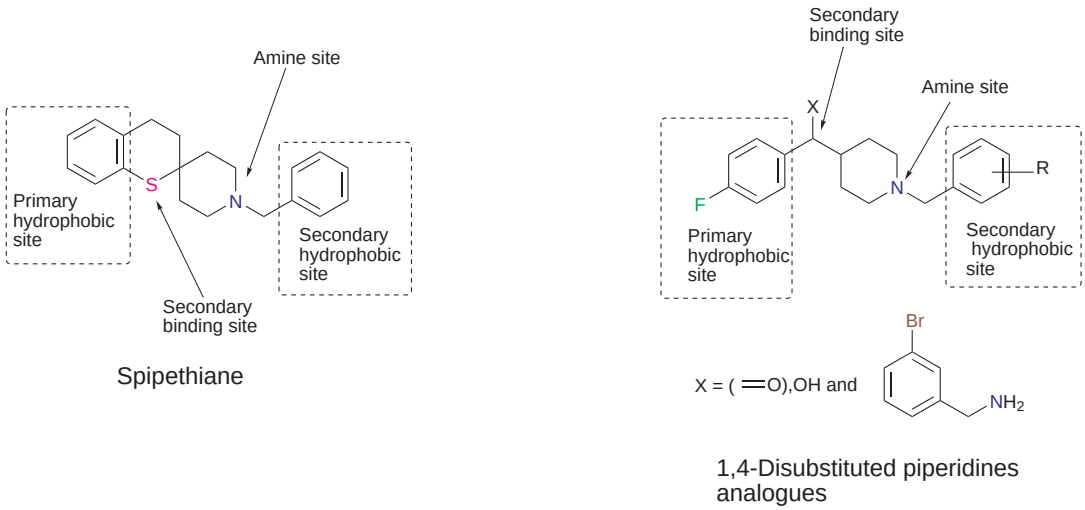


Figure 3.13: Design of 1,4-disubstituted piperidines from proposed pharmacophore model for sigma receptor ligands.

Computational studies were further carried out on the synthesized compounds, based on the previous report by Gund *et al.*, who had modeled of several $\sigma 1$ receptor-specific ligands (including spipethiane, haloperidol and pentazocine) in a bid to develop a common pharmacophore (ph4) for $\sigma 1$ receptor-ligand binding under the assumption that all the compounds interact at the same receptor site [150]. The primary ph4 for the σ binding sites was defined by mapping the topographic arrangements of the phenyl ring, the N-atom, and N lone pair vector; a point was placed 2.8 Å tetrahedrally from N-atoms to represent an interaction between a protonated N-atom and its binding site; dummy atoms were built 3.5 Å above and below a phenyl ring to represent hydrophobic binding to a receptor. The distance from the C-center to the N-atom was 7.14 Å, while that from O and C-center was 3.68 Å and from O- to N-atom was 4.17 Å. The choice of ligands used in the study was based on their potency, selectivity and structural diversity with their affinity ranging from 0.08 to 5.8 nM.

Several predictive QSAR models were derived and validated for 14 molecules ($N = 14$) and 3 molecular descriptors ($k = 3$), among which (Eqn. 3.1).The QSAR studies revealed that $\sigma 1$ binding is driven by hydrophobic interactions.

$$\Delta G^{exp} = -4.19 + 0.13\,S_{vdW} - 0.20\,A_{vdW} + 0.04\,S_{wat}\ (R^2 = 0.77,\ RMSE = 0.51,\ F = 11.2) \quad (3.1)$$

The experimentally derived binding affinities, $\Delta G^{exp} = -RT \ln K_i$, were computed from the ideal gas constant (R) and the absolute temperature (T) and could be accounted for (by ~80%) by multilinear regression involving the 3D van der Waals surface areas (S_{vdW}), the 2D van der Waals surface areas (A_{vdW}) and the 3D water accessible surface areas (S_{wat}) of the molecules in the dataset.

The synthesized compounds were also tested for antiplasmodial activities against cultured chloroquine-sensitive 3D7 and resistant Dd2 strains of *P. falciparum* by *in vitro* parasite growth inhibition, exhibit-

ing 56 to 93% inhibition of parasite growth at 40 μg/mL. Moreover, the tested compounds were more active on the resistant strain (IC_{50} values between 1.03 to 2.52 μg/mL), than the sensitive strain (IC_{50} values between 2.51 to 4.4.3 μg/mL). QSAR studies showed that over 50% correlation of antiplasmodial activity against Dd2 was observed with combined descriptors of molecular structure. Key structural features of the antiplasmodial pharmacophore include two hydrophobic phenyl rings, an amine site and a secondary binding site with a polar C -7' hydroxyl substituent [151].

The results in this section are based on the following articles:

1. Ikome, H. N.; **Ntie-Kang, F.;*** Ngemenya, M. N.; Tu, Z.; Mash, R. H.; Efange, S. M. N. 4-Aroylpiperidines and 4-(α-hydroxyphenyl)piperidines as selective sigma-1 receptor ligands: Synthesis, preliminary pharmacological evaluation and computational studies. *Chemistry Central Journal*, **2016**, *10*, 53.

2. Ngemenya, M. N.; Abwenzoh, N. G.; Ikome, H. N.; Zofou, D.; **Ntie-Kang, F.;** Efange, S. M. N. Structurally simple synthetic 1,4-disubstiuted piperidines with high selectivity for resistant *Plasmodium falciparum*. *BMC Pharmacology and Toxicology*, **2018**, *19*, 42.

3.5 Chapter summary

In this chapter, a total of 33 NPs from African flora and 36 synthesized NP mimics have been described. These compounds have shown a broad range of biological activities, including antiparasitic and enzyme inhibitory potencies. These have been the fruit of several national and international collaborations. Molecular modeling (structure-based docking, ligand-based pharmacophore modeling and QSAR) have both played important roles in the prediction of the biological activities of the identified lead compounds and in the profiling of their DMPK properties. This has been the major contribution to all the results described.

CHAPTER FOUR

TOXICITY PREDICTION AND ANALYSIS OF NATURAL PRODUCT LIBRARIES

4.1 Objectives of the chapter

In this chapter, a knowledge-base tool (Eco-Derek) for toxicity assessment using reasoning rules is presented [152], along with the main results for the toxicity prediction of the generated NP libraries. This has been done using diverse methods.

4.2 Contribution to the development of a knowledge-base for toxicity prediction

There is widespread concern about the toxicological effects of man-made chemicals in the environment, including those of pharmaceutical products and their metabolites. There are databases of, and computer models to predict, aquatic narcosis and, in some cases, excess aquatic toxicity such as ECOSAR [153] but there remains a need for better sharing of human knowledge about the full range of environmental and human toxicological hazards. Computer programs such as Derek [154] are used to share human knowledge about mammalian toxicity and a proof of concept application using the same technology to share knowledge about toxicity to *Tetrahymena pyriformis* and human skin sensitisation has been described [155]. For mammalian toxicity, Derek reports confidence in predictions of activity, or likelihood that activity will be seen, using terms such as "probable", "plausible", etc. Eco-Derek reports the estimated potency of toxicity of a query chemical to *T. pyriformis*, using terms such as "High", "Moderate", "Low" (Fig. 4.1). It takes into account both narcosis and mechanism-based toxicity (often called "excess toxicity" in cases where it is more severe than narcosis).

As part of our work, a new knowledge-based system for predicting environmental toxicity was built using the Nexus platform from Lhasa Limited [156]. The goal was for the system to report both potency and confidence in predictions (e.g. "Predicted toxicity to fish: Moderate. Confidence in the

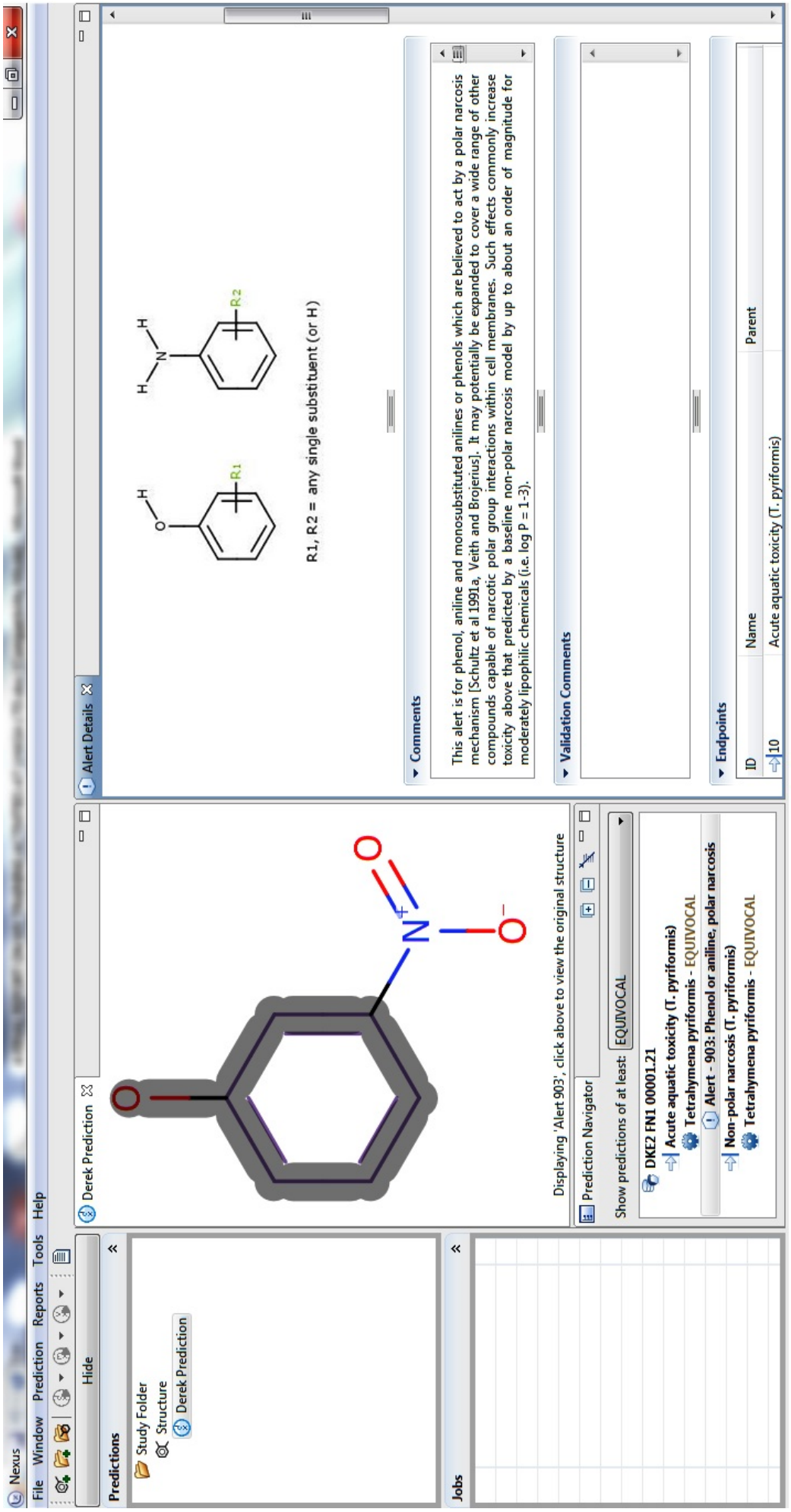


Figure 4.1: Example of a prediction from Eco-Derek.

prediction: High"). However, Nexus currently only supports reporting of confidence (likelihood). So, for the present, knowledge about toxicity to *T. pyriformis* contained in Eco-Derek [155] has been reworked and assessed in terms of confidence about its predictive reliability and incorporated into the new system. A knowledge base covering the environmental toxicity of chemicals was being built, emphasising, but not restricted to, aquatic toxicity. The data was studied to develop new rules for the prediction system. New alerts covering other species not included in the original knowledge base for Eco-Derek were developed. The knowledge base currently contains 52 alerts, 207 patterns, 138 reasoning rules, 79 literature sources, 5 species and 6 toxicity endpoints. Species covered include *Daphnia magna*, *Escherichia coli*, *Pseudokirchneriella subcapitata*, *Danio rerio*, *Pimephales promelas*, etc. The purpose of this project is to facilitate the exchange of knowledge about environmental toxicity between scientists.

The results in this section are based on the following conference paper:

Ntie-Kang, F.;* Philip Judson, P. Knowledge base development for the prediction of acute aquatic toxicity of chemicals. *Journal of Cheminformatics*, **2016**, *8*, P3

4.3 DMPK predictions on the anticancer libraries using QSAR

The ability to predict potential toxicity of either a parent compound or its metabolites is important in novel drug design programs [157, 158]. Computer-based assessment of potential toxicity has become increasingly popular in the past decade [154, 157, 158, 159]. Thus, early and accurate *in silico* toxicity prediction using Derek Nexus is an acceptable way of identifying potentially toxic chemicals, by helping experts to reject unsuitable drug candidates [157]. The Derek system is able to perceive chemical substructures within molecules and relate these to a rule base, linking the substructures with likely types of toxicity [154, 157, 158, 159]. It is intended to aid the selection of compounds based on toxicological considerations or separately to indicate specific toxicological properties to be assayed early in the evaluation of a compound, thus saving time, cutting down costs, and saving the lives of some laboratory animals [160, 161]. This works through the identification of toxicity alerts within the chemical structures of a possible drug candidate. Alerts are collections of structural features observed to result in toxicological activity. Lhasa's Nexus platform helps automate alert identification by mining descriptions of activating structural features or substructures directly from toxicity datasets, which have been included within the program's knowledge base [162]. Each rule contained in the rule base describes the relationship between a structural feature or toxicophore and its associated toxic effect. Derek possesses the particular ability to report the reasoning behind its predictions [154]. The rules are derived by an evaluation of toxicological, mechanistic, and physico-chemical data [160]. This is achieved by an argumentation-based approach using general toxicological and physico-chemical concepts, e.g., log $P_{o/w}$ [154, 160]. In this study, an attempt was made to identify structural patterns within the AfroCancer and NPACT datasets, which may be related to toxicity of some of the compounds. For 390 compounds within the AfroCancer dataset, 1,330 tautomers were generated. A

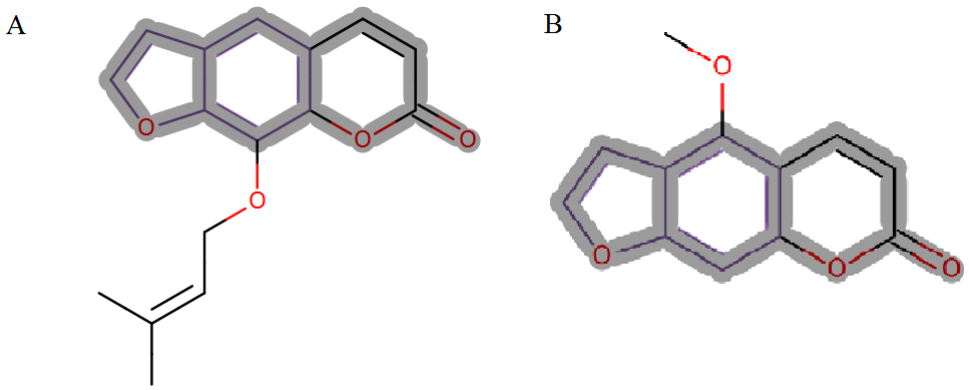


Figure 4.2: Psoralen substructure responsible for chromosome damage predicted as CERTAIN for two compounds from the AfroCancer dataset. Notes: (A) Imperatorin and (B) bergapten, isolated from the stem of Balsamocitrus paniculata harvested in Cameroon and related plant species [162, 164]. The toxicity end point was predicted by Derek to be CERTAIN. Thus, these compounds may rather be toxic, not necessarily exhibiting anticancer activities. Figures reproduced by permission.

corresponding 5,357 tautomers were also generated for the NPACT dataset. Predictions were carried out for all the tautomers. In some cases, the output "NOTHING TO REPORT" was recorded. This means that these compounds do not contain any toxicophores that are described in Derek's current knowledge base. The proportion of tautomers with the NOTHING TO REPORT output was 5.93% for AfroCancer and 4.39% for NPACT. This could also imply that the models in DEREK may not be in the applicability domain of the compounds with the NOTHING TO REPORT output. The remaining compounds showed a number of toxicophores identified with a wide range of toxicity end points. The Derek Nexus prediction includes an overall conclusion about the likelihood of toxicity in a structure and detailed reasoning information for the likelihood (or confidence level). The confidence levels are classified as CERTAIN, PROBABLE, PLAUSIBLE, EQUIVOCAL, and DOUBTED, based on experimental evidence and computed physico-chemical parameters. It is important to mention that an outcome "CERTAIN" indicates that the query compounds themselves (or very closely related analogues) have been tested and found to be active (toxic). As an example, chromosome damage *in vitro* was predicted to be CERTAIN for two compounds from the AfroCancer dataset (Fig. 4.2). The log $P_{o/w}$ value of both compounds, imperatorin and bergapten (isolated from the stem of *Balsamocitrus paniculata* and related Cameroonian Rutaceae species) [163, 164], was computed to be 4.01, while the computed log K_p was -1.52. The coumarin imperatorin is an antimutagene [165], also known to exert antihypertrophic effect both *in vitro* and *in vivo* [166], as well as antimicrobial activities [164]. Both imperatorin and bergapten are also known to be components of the apiaceous Bishop's weed (*Ammi majus*),[1] growing wild in Egypt and the Mediterranean [167]. The two coumarins activated the Derek alert for psoralen, which causes human chromosome damage in the *in vitro* chromosome aberration test [168]. Experimental evidence suggests that activity in the *in vitro* chromosome aberration test may be a result of their DNA intercalating properties. The noncovalent binding of psoralen and several derivatives between two base pairs of DNA has been demonstrated [169]. This mecha-

[1] A plant used for the treatment of leucoderma and skin diseases.

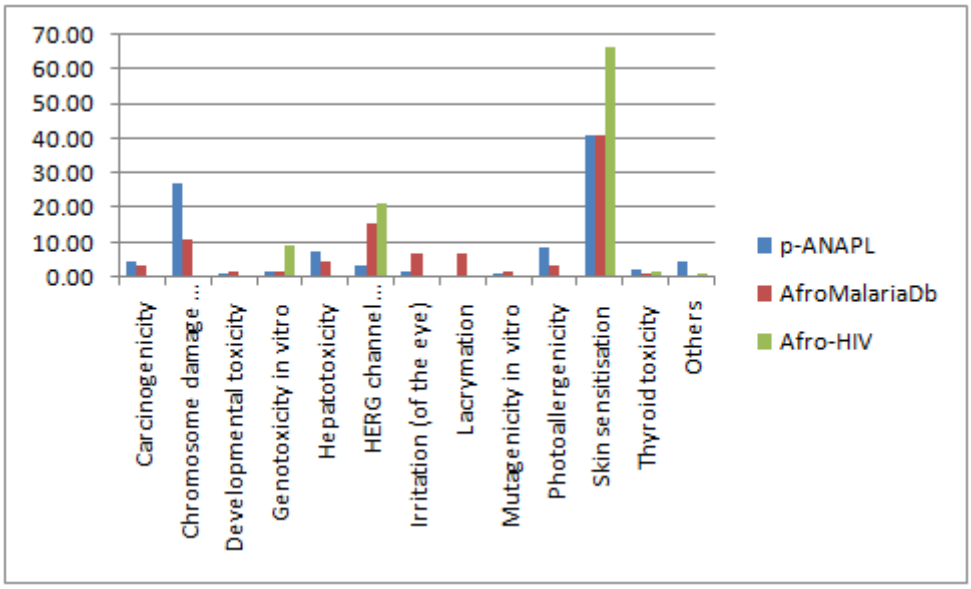


Figure 4.3: Bar chart showing a comparative distribution of alerts predicted as "plausible" for the three datasets (p-ANAPL, AfroMalariaDb and Afro-HIV). Figure reproduced by permission.

nism is also supported by the weak mutagenic activity observed for several psoralen derivatives in the Ames test in *Salmonella typhimurium* strain TA1537 [170], a strain that appears sensitive to other DNA intercalators [171, 172].

The results in this section are based on the following article and conference paper:

1. **Ntie-Kang, F.;**[†*] Simoben, C. V.;[†] Karaman, B.; Ngwa, V. F.; Judson, P. N.; Sippl, W.; Mbaze, L. M.[*] Pharmacophore modeling and *in silico* toxicity assessment of potential anticancer agents from African medicinal plants. *Drug Design, Development and Therapy*, **2016**, *10*, 2137–2154.

2. **Ntie-Kang, F.;**[*] Simoben, C. V.; Lifongo, L. L.; Sippl, W.; Mbaze. L. M. Application of computer modeling in the evaluation of naturally occurring anticancer compounds from African flora. *Journal of Cheminformatics*, **2016**, *8*, P2.

4.4 Chemical alerts of 3 floral compound libraries by use of human reasoning

An analysis of the diversity and chemical toxicity assessment of 3 chemical libraries of compounds from African flora (the p-ANAPL, AfroMalariaDb and Afro-HIV), was conducted (Fig. 4.3 and Table 4.1, [173]). These contain, respectively, compounds exhibiting activities against diverse diseases, malaria and HIV. The diversity of the 3 datasets was done by comparison of the 3 most important principal components computed from standard molecular descriptors. This was also done by a study of the most common substructures (MCSS keys). Meanwhile, the *in silico* toxicity predictions were

Table 4.1: *Distribution of proportions (%) of compounds with alerts showing "plausible" for the three datasets.*

Alert name	***p-ANAPL***	***AfroMalariaDb***	***Afro-HIV***
Carcinogenicity	4.16	3.21	0.30
Chromosome damage *in vitro*	27.10	11.07	0.00
Developmental toxicity	0.71	2.02	0.00
Genotoxicity *in vitro*	1.15	1.55	9.15
Hepatotoxicity	6.82	4.88	0.30
HERG channel inhibition *in vitro*	3.10	15.83	21.34
Irritation (of the eye)	1.42	6.79	0.00
Lacrymation	0.09	6.79	0.00
Mutagenicity *in vitro*	0.89	1.55	0.00
Photoallergenicity	7.97	3.21	0.30
Skin sensitisation	40.66	41.19	66.46
Thyroid toxicity	1.95	1.07	1.52
Others	3.99	0.83	0.61

done through the identification of chemical structural alerts using Lhasa's knowledge-based Derek system. The results show that the libraries occupy different chemical space and that only an insignificant part of the respective libraries could exhibit toxicities beyond acceptable limits. The predicted toxicities end points for compounds which were predicted to be "plausible" were further discussed in the light of available experimental data in the literature. Toxicity predictions are in agreement when using a machine learning approach that employs graph-based structural signatures. The current study sheds further light towards the use of the studied chemical libraries for virtual screening purposes.

It was observed that for the p-ANAPL library, a majority of the skin sensitization predictions showed "plausible", constituting about two-fifths of the predictions, with an almost equivalent prediction for the AfroMalariaDb dataset, meanwhile, about two-thirds of the anti-HIV dataset showed "plausible" predictions for the same end point. Skin sensitisation describes an immunological process whereby heightened responsiveness to a chemical allergen is induced. Skin sensitization is induced when a susceptible individual is exposed topically to the inducing chemical allergen. This chemical allergen provokes a cutaneous immune response which, if of the required magnitude and quality, will result in the development of contact sensitisation. The other significant end point for the p-ANAPL dataset was the predicted *in vitro* chromosome damage, which constitutes about 27% of all predictions, meanwhile for the AfroMalariaDb dataset, this end point was predicted for only about 11% of the compounds and almost 16% of Human ether-a-go-go-related gene (HERG) channel inhibition for the antimalarial dataset. Meanwhile, the prediction of about one-fifth of the anti-HIV dataset was "plausible" *in vitro* for HERG channel inhibition. It should be noted that the HERG K^+ channel is best known for the role it plays in the electrical activity of the heart, by coordinating heart beat [174]. This, therefore, appears to be the molecular target responsible for the cardiac toxicity of a wide range of therapeutic drugs [175]. HERG channel blockage is often associated with potentially toxic compounds, often providing reasonable predictions for cardiac toxicity of drugs in the early stages of drug discovery

[176]. HERG has also been associated with modulating the functions of some cells of the nervous system and with establishing and maintaining cancer-like features in leukemic cells [177].

The results in this section are based on the following article:

Onguéné, P. A;† Simoben, C. V.;† Fotso, G. W.; Andrae-Marobela, K.; Khalid, S. A.; Ngadjui, B. T.; Mbaze, L. M.; **Ntie-Kang, F.*** *In silico* toxicity profiling of natural product compound libraries from African flora with anti-malarial and anti-HIV properties. *Computational Biology and Chemistry*, **2018**, *72*, 136–149.

4.5 Application of machine learning to toxicity prediction for the NANPDB dataset

The toxicity prediction indicated that about three-quarters of NANPDB compounds showed compliance (tested negative) to AMES mutagenic test in bacteria, while none of the compounds was predicted for human ether-a-go-go gene (hERG) I inhibition and only about 8 and 12% were predicted for hepatotoxicity and skin sensitization, respectively (Table 3 of [108]). A positive prediction for AMES test would indicate that a compound is mutagenic and may, therefore, act as a carcinogen. Meanwhile, the inhibition of the potassium ion (K^+) channels, encoded by hERG, is among the main causes for the development of *torsade de pointes* or the long QT syndrome (which leads to fatal ventricular arrhythmia) [46, 177, 178]. Toxicity due to the inhibition of hERG channels has often resulted in the removal of many drugs from the market. The *pk*CSM predictors were built using hERG I and II inhibition information for 368 and 806 compounds, respectively. The *pk*CSM predictor determines whether or not a compound is likely to be an hERG I/II inhibitor. The hepatotoxicity predictor (based on the measured liver associated side effects of 531 compounds observed in humans) helps to classify a compound as hepatotoxic if it is predicted to have at least one pathological or physiological event strongly associated with disruption of normal liver functions. Meanwhile, skin sensitization is the potential of a compound to cause adverse effects (e.g. it can induce allergic contact dermatitis) when applied on the skin.

The human maximum tolerated dose (Table S4, Supporting Information of [108]) or the maximum recommended tolerated dose (MRTD in log mg/kg/day), which provides an estimate of the toxic dose threshold of chemicals in humans, is the maximum recommended starting dose in phase I clinical trials (based on extrapolations from animal data). MRTD is considered low when $\leq$ 0.477 log mg/kg/day and high > 0.477 log mg/kg/day. Based on the mean value of 0.34 log mg/kg/day, the predictions showed that about 60% of NANPDB compounds showed low MRTD, being much lower than the threshold value of 0.477 log mg/kg/day. The oral rat acute toxicity expresses the toxic potency of a compound in terms of the lethal dosage values (LD_{50} in mol/kg), i.e. the amount of a compound administered as a single dose, which causes the death of 50% of a group of test animals. For toxicity against the protozoan *T. pyriformis*, a compound with a predicted $pIGC_{50}$ value (negative logarithm

of the concentration required to inhibit 50% growth in log μg/L) < -0.5 log μg/L is considered to be toxic. This corresponds to only about 1% of NANPDB compounds. For fish (Fathead Minnows), an equivalent lethal concentration value (LC_{50}), representing the concentration of a molecule necessary to cause the death of 50% of experimentally tested Flathead Minnows, LC_{50} < 0.5 mM (i.e. log LC_{50} < -0.3) are regarded to cause high acute toxicity. This corresponds to only about 6% of NANPDB compounds. In both cases, the mean $pIGC_{50}$ and log LC_{50}50 values (0.88 log μg/L and 1.25 log mM respectively, Table 5 of [108]) are both far from the threshold values of -0.5 log μg/L and -0.3 log mM, respectively.

The results in this section are based on the following article:

Ntie-Kang, F.;[†*] Telukunta, K. K.;[†] Döring, K.; Simoben, C. V.; Moumbock, A. F. A.; Malange, Y. I.; Njume, L. E.; Yong, J. N.; Sippl, W.; Günther, S.[*] NANPDB: a resource for natural products from Northern African sources. *Journal of Natural Products*, **2017**, *80*, 2067−2076.

4.6 Chapter summary

It has been shown that, although some of the compounds, hitherto regarded as active or killing certain parasites *in vitro* may just be toxic, a good proportion of the compounds included in the generated databases are relatively predicted to be safe.

CHAPTER FIVE

GENERAL CONCLUSIONS AND PERSPECTIVES

5.1 General conclusions

Although it has been reported that under-exploited plants from African biodiversity offer untold medical and economic promise that should be pursued [179], this project describes the first original work towards the use of computer modeling for the valorisation of the medicinal potential of African medicinal plants. The main highlights include the development of NANPDB (the most comprehensive database of NPs from the Northern Africa region), p-ANAPL (the largest collection of physical collection of NPs from African medicinal plants), etc. The report also includes the identification NP lead molecules with anti-HIV and sirtuin inhibitory activities by virtual screening, followed by *in vitro* assays, along with synthetic NP mimics, whose DMPK profiles were predicted using computer-based methods. The third aspect of the results includes the development of a toxicity prediction tool, as well as toxicity profiling of compounds included in the developed NP databases resources. The results are published in 2 dozen outputs and are a product of several collaborations in which several M.Sc. and Ph.D. students have been trained.

5.2 Perspectives for improving natural product databases and plans towards a unified dataset

The bioactive compounds in the described databases could be further investigated for modes of action and alternative biological activities, while the untested molecules are a valuable resource for future drug discovery efforts. It is intended that data coverage is expanded by continuous data curation so that further releases are more comprehensive datasets that cover all secondary metabolites from source organisms harvested from the entire African continent. It is also intended that the unified African NP database be valorised by including more computed molecular descriptors, experimental data leading to the characterization of the NPs, e.g., NMR and MS data, melting and boiling points,

and possible biosynthesis pathways toward the included metabolites, together with sample availability and/or vendor information for samples dispersed in academic laboratories in the continent.

5.3 Possible lead optimization strategies

5.3.1 Boldine

Fig. 5.1 shows the chemical structures of untested boldine analogues, from the ChemBridge database, available from commercial suppliers. Besides, the heterocylcle containing the N-atom, characteristic of aporphines in boldine (Fig. 5.1), was not part of the pharmacophore used in the virtual screening campaign that led to the identification of boldine as a 'hit'.

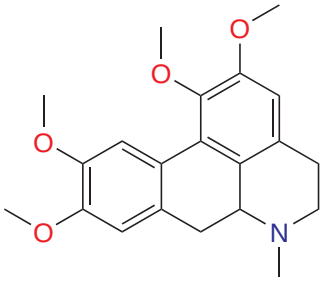
Optimizing the boldine structure could proceed as follows:

- The two aromatic centres (Aro1 and Aro2) were part of the pharmacophore.
- Including the non-aromatic centre (A) would be necessary to ensure a planar and hence rigid structure.
- The inclusion of other hydrophobic groups in the positions of the methoxy substituents would play a role in modifying log $P_{o/w}$, hence remediating possible absorption issues.
- The ideal structure could be symmetric (in the absence of the aporphine heterocycle, shown in dashed lines).
- However, two initial sets of compounds could be synthesized (with same substituents as X, Y, Don and Hyd; one set with the N-atom heterocycle and one without it (the symmetric or quasi-symmetric set). Both could be screened against HIV-vpu and the 'better' set could continue the race towards the lead compound.

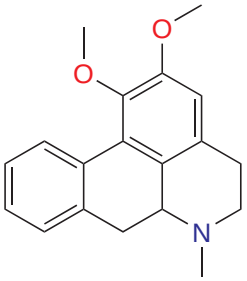
5.3.2 Sirtuin inhibitors

In the present work, target-based virtual screening was combined with experimental testing in order to identify novel modulators of sirt1 and sirt2 within the p-ANAPL database. Molecular docking studies onto available sirt1 and sirt2 crystal structures resulted in two sirt1 and sirt2 inhibitors with moderate inhibitory effect. These compounds have been previously isolated from the twigs [121] and root bark [122] of *Rhus pyroides* Burch (Anacardiaceae), a medicinal plant which is widely distributed in Eastern Botswana.[1] It should be noted that this genus of medicinal plants is also known to be the source

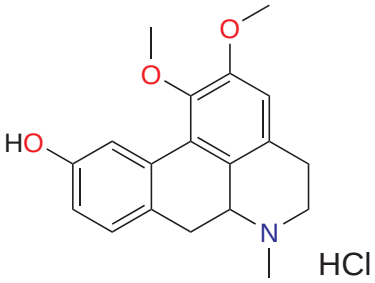
[1] In South Africa, *Rhus pyroides* is traditionally used in the treatment of epilepsy [183]. It has also been observed that this plant is avoided by the corn cricket (*Heterodes popus* L.) [121].



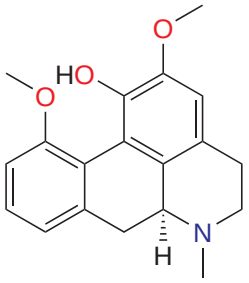
1,2,9,10-tetramethoxy-6-methyl-5,6,6a,7-tetrahydro-4H-dibenzo[de,g]quinoline (**51**)



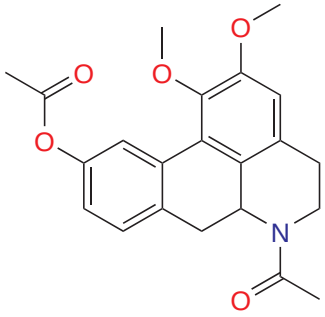
1,2-dimethoxy-6-methyl-5,6,6a,7-tetrahydro-4H-dibenzo[de,g]quinoline (**52**)



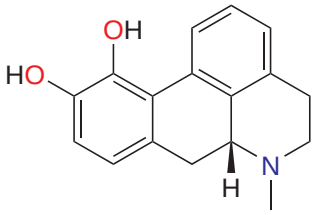
1,2-dimethoxy-5,6,6a,7-tetrahydro-4H-dibenzo[de,g]quinolin-10-ol hydrochloride (**53**)



2,11-dimethoxy-6-methyl-5,6,6a,7-tetrahydro-4H-dibenzo[de,g]quinolin-1-ol (**54**)



6-acetyl-1,2-dimethoxy-5,6,6a,7-tetrahydro-4H-dibenzo[de,g]quinolin-10-yl acetate (**55**)



R-(-)-apomorphine hydrochloride hemihydrate (**56**)

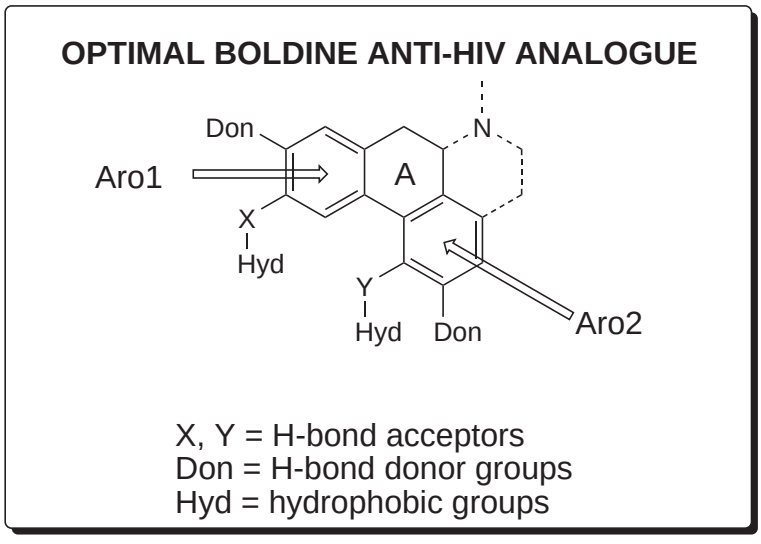


Figure 5.1: Purchasable boldine analogues and ideas about the ideal analogue.

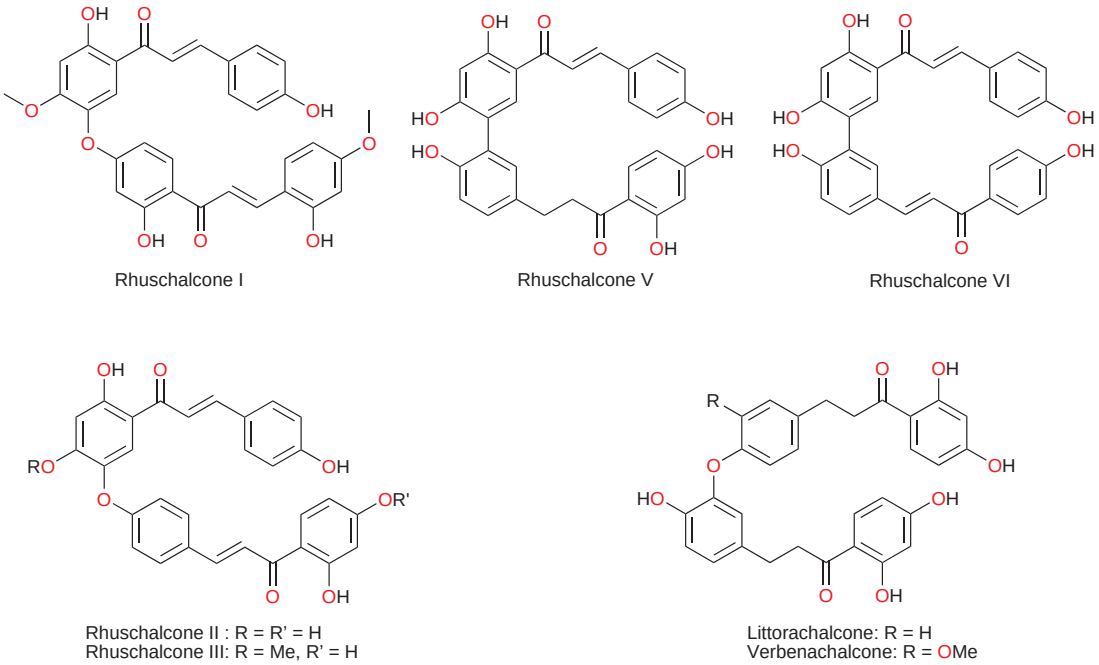


Figure 5.2: Untested bichalcones from Rhus species.

of several O-linked and C-C coupled bichalcones (Fig. 5.2) and biflavonoids, some of which have been obtained by total synthesis [180, 181, 182, 183, 184]. The rhuschalcones and their analogues are known to possess cytotoxic and antiproliferative [122], antiprotozoal, insect antifeedant [180, 181] and carbonic anhydrase inhibitory [182] activities. Meanwhile, biflavones from this plant, e.g. agathisflavone and amentoflavone have shown an affinity for the $GABA_A$/benzodiazepine receptor [183]. It could be further proposed that analogues of the bichalcones (e.g. the O-linked littorachalcone or verbecharcone, verbenachalcone and rhuschalcones I, II and III, together with the C-C linked rhuschalcones V and VI, Fig. 5.2) be tested for possible sirt1, sirt2 and sirt3 inhibition. Also, the binding of these compounds in the extended C pocket could be tested in fluorescence assays. It could be suggested that, unlike the rhuschalcones, both C-C and C-O linked non symmetrical bichalcones be also be synthesized and tested against the sirtuins, with the view of investigating potential selectivities against the isoforms. Although the synthesis of rhuschalcone IV (**13**) and the rhuschalcone I analogue (**14**), along with their analogues have been elaborated and the compounds have been shown to possess other biological activities [122, 180, 181, 182, 183, 184], it is yet unclear if their cytotoxicities are related to their abilities to inhibit sirtuins. However, natural product libraries like the p-ANAPL and the newly developed NANPDB [108] could be good sources to search for novel modulators of sirtuins with novel scaffolds.

5.4 Future Planned Work

From our previous work, extensive databases for molecules isolated from medicinal plants, particularly from the geographical regions of Africa have been built (www.african-compounds.org). Together

with available data from related plant metabolite databases, we propose to investigate pathways for the biosynthesis of anticancer plant metabolites. We shall use computational and experimental methods to unravel previously un-investigated pathways by which these plants make their metabolites, particularly compounds with anticancer properties. This would involve using existing tools originally designed for the prediction of metabolite biosynthesis and/or the development of new tools for predicting plant metabolites from genomic, metabolomic and transcriptomic data. It is also intended to understand which cancer drug target classes bind which naturally occurring compounds (NOCs), metabolite scaffolds and fragments. The scaffold classes to be investigated could range from plant-based, animal-based to synthetic compounds. In addition to investigating potent plant-based metabolites (PBMs), with the potential for drug discovery, it is intended that the effects of environmental factors on metabolite biosynthesis (MB), which may constitute new windows within this area of research, be investigated.

CHAPTER SIX

METHODS

6.1 General methods for database preparation

The chemical databases developed within this work focus on source organisms (plants, corals, endophytes, fungi, etc.) from the geographical region of Africa. They generally include data on source organisms, geographical collection sites, and chemical structures of derived compounds, which have been retrieved from literature sources. Literature sources covered the major international journals on natural products and medicinal chemistry, alongside available Ph.D. theses, spanning the period 1962 to 2016.[1] For journal article data sources, each journal search engine was queried by using the country names as search terms. The resulting articles were checked to verify that the source species were harvested from the African region. The retained articles were downloaded and referred to henceforth as data sources. The data sources were arranged by taxonomic families of the source organisms, in order to avoid duplicate curation. Each data source (abstract and full text) was carefully read, and the related information was tabulated on spreadsheets. The accuracy of the manually curated data was double-checked to minimize errors and redundancy. In double checking, the emphasis was laid on the accuracy of the following:

- chemical information (e.g. SMILES, physico-chemical properties, etc.)
- compound class, subclass, etc.
- biological activity data
- source species information.

The collected information for source organisms includes:

- their scientific and local names, where available
- their known uses (e.g., in traditional medicine)

[1] The updated online version includes data up to 2017.

- the part of species where the compound was identified (e.g., plant roots, leaves, whole animal organism, etc.)
- kingdom and families
- country and region of collection (including GPS coordinates, where available)
- source availability and reference (e.g., herbarium name and voucher reference number)
- date of collection

Furthermore, species information, e.g., alternative taxonomic names and the source species links to taxonomic data in related databases (including the NCBI Taxonomy database, the Prota Africa database, Tropicos database for the Missouri Botanical Garden, the World Register of Marine Species, GenBank, the Mycobank database, etc.) were included [185-192], where additional information and pictures of the source species can be consulted. For the compounds, retrieved data include:

- compound name (trivial and IUPAC name)
- compound class (e.g., terpenoid, flavonoid, steroid, alkaloid)
- compound subclass (e.g., monoterpene, flavanone glycoside, steroidal saponin, pyrrolizidine alkaloid)
- known biological activity (e.g., antioxidant activity, antiacetylcholinesterase activity, antidiabetic activity, anticancer effect)
- mode of action (when available)
- link to PubChem (PubChem IDs are included, where available)
- Additional comments on the reported biological activities of the compounds include, as the case may be, the IC_{50}, K_i and/or EC_{50} values, percentage inhibitory concentrations, and brief descriptions of the biological assays.

Literature sources (or references) information include:

- author names
- literature reference type (e.g., journal article, conference abstract, thesis)
- reference (e.g., journal full name, year, volume, issue, and page numbers)
- reference title
- link to PubMed (PubMed IDs are included, where available)
- reference link to journal citation (doi or directly accessible Web link).

For full details of the workflow, for example, see Fig. 6.1.

6.2 Structure-based virtual screening methods

This was applied for virtual screening, which led to the identification of rhuschalcones as sirtuin inhibitors (Fig. 6.2, [112]). Ligand preparation of the 463 natural compounds in p-ANAPL database was carried out using the LigPrep module in Schrödinger [193]. Ten (10) low energy conformers were generated for each molecule and MMFF94 force field implemented in MOE [194] was used for minimization. Protein preparation of different crystal structures of human sirt1 (PDB code: 4I5I [195], and PDB code: 4ZZJ [196]), was carried out using GOLD program [197, 198, 199]. Hydrogen atoms were added to the ligand molecules, followed by minimization, using MMFFs force field in Maestro [200].

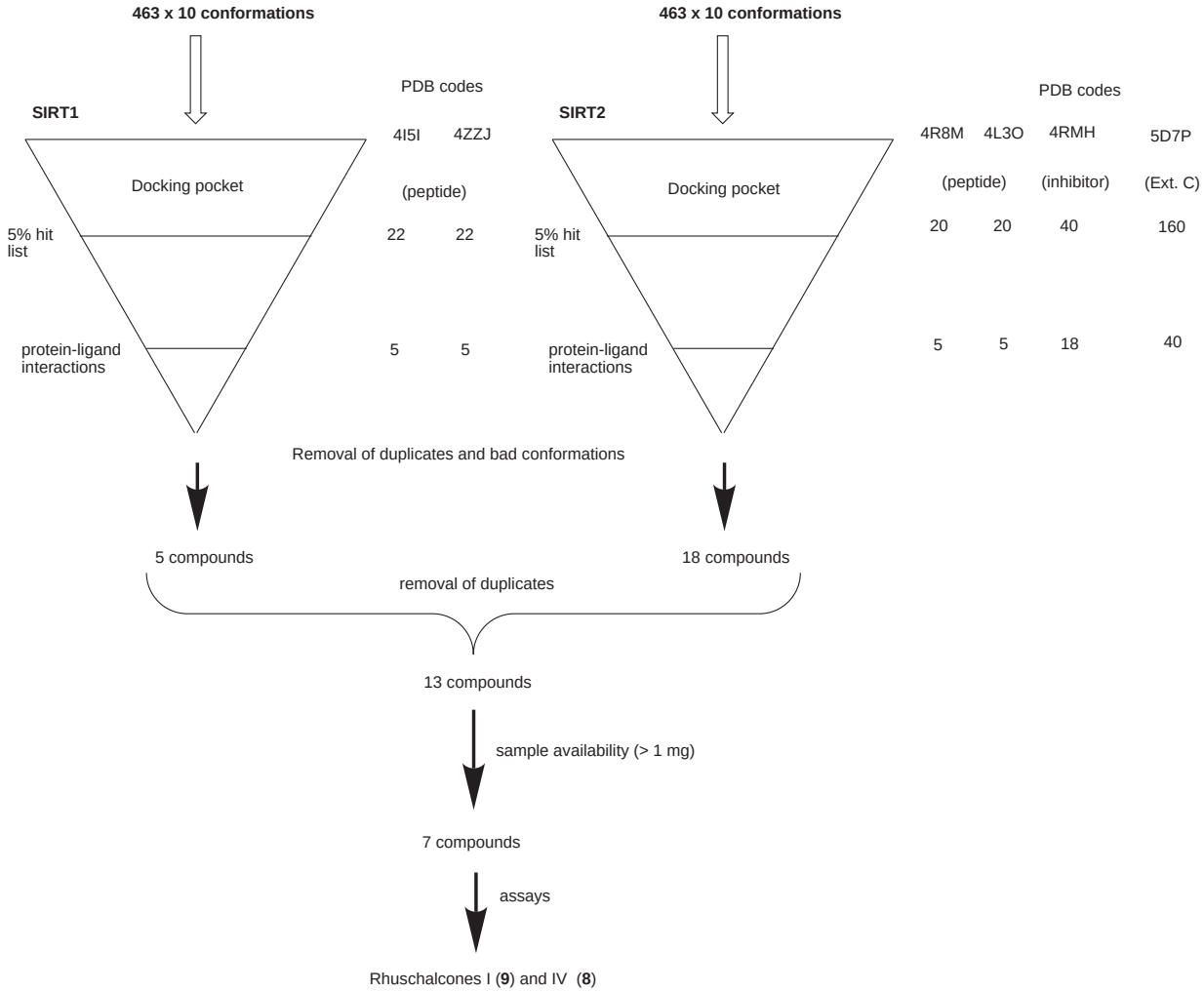


Figure 6.2: Complete workflow of docking and in vitro screening processes for the identification of sirtuin inhibitors. Figure reproduced by permission.

The crystal structure in complex with NAD^+ (PDB code: 4I5I [195]) and the crystal structure co-crystallized with the acetyl lysine peptide (PDB code: 4ZZJ [196]) were both taken from the Protein Data Bank (PDB) [201]. The protein structures were protonated and minimized, using the Amber 99SB force field, implemented in MOE [194]. All water molecules, the cofactor and the peptide

were removed. The location of the native ligand (NAD^+ or peptide) was used to define the docking site, where all protein residues within 6 Å from any heavy atom of this ligand were considered as part of the binding site. GoldScore was used as the fitness function to score all docking poses. All docking poses were analysed by visual inspection and some compounds were chosen to be tested by *in vitro* assays. Meanwhile sirt2 protein structures were prepared as previously described [202]. All molecules, except the zinc ion (Zn^{2+}), were removed from the structures prior to docking. Structural bridging water molecules (where mentioned), were included in the binding site of the protein structures before docking. Docking studies were performed using the Glide program (Schrödinger Suite 2012-5.8) [203]. The dockings were done using Glide high-throughput virtual screening (HTVS) mode, treating ligands flexibly. Ten (10) docking poses were calculated for each conformer. Only the top-ranked poses were retained for each compound for each docking run. Docking poses retrieved for the top-ranked 20 compounds (~5% of the whole database) were visually analysed, the hits being retained based on observed protein-ligand interactions within the target site. In sorting ligand poses by observed protein-ligand interactions, the emphasis was laid on ligand poses with putative interactions within the cofactor (NAD^+) and peptide binding pockets. In the next step, ligands were docked into the substrate-binding pocket of human sirt1 and sirt2. This was carried out using two different docking programs (Gold [197, 198, 199] and Glide [203]). The resulting docking poses were stored. The selection of compounds for testing was carried out by examining protein-ligand interactions in the derived docking poses. In the crystal structures of sirt1, it was shown that substrates make H-bond interactions with the backbone of a conserved valine residue (sirt1 numbering Val412) which is crucial for the correct orientation of the acyl-lysine in the active site [205]. In the case of sirt2, the binding interactions of the native ligands including both the peptide substrates, the cofactor fragments and the co-crystallized inhibitors with the protein were first examined [203]. In the hit selection process, a special importance was given to compounds that were able to interact with residues Phe234, Phe235, Phe190 and Glu237 in the catalytic pocket.

6.3 Ligand-based virtual screening methods

The chemical structures of four known Vpu blockers were retrieved from the literature [204]. The 3D conformations were generated using the (default) MMFF94x forcefield [205], using the MOE software tool [194], following the protocol previously implemented by Daveu *et al.* [206]. The force field parameters were kept at their default values of the Strain Limit of 4 kcal/mol and the Conformations limit of 250 conformations/molecule. The other settings were kept at their default values, with the exception of the Split Output option being turned off, and the Input Filters being turned off. A pharmacophore query was created using the Pharmacophore Query Editor, implemented in MOE. A query consists of a set of constraints on the location and type of pharmacophoric features, which can be used to search a database of molecular conformations. In this work, the query was created and saved, in order to be used later in a pharmacophore search. While a query may be created without a reference molecule (e.g., the most active molecule in our database), in this study,

the common pharmacophore features of all four compounds was used in the virtual screening of the p-ANAPL library (exported in .mdb format in MOE) [194]. The Pharmacophore Search was carried out on the p-ANAPL library [107], using the pharmacophore module of the MOE package [194]. Compounds with four out of the five common query features were selected as 'hits' in this search. The enrichment was measured against a database that has already been enriched by a factor of 10 using MACCS fingerprints. The Pharmacophore Consensus provided suggested features given an aligned set of molecules. In this study, features that may contribute to the pharmacophore alignment of the four Vpu blockers were located. How well the pharmacophore features of the hits fitted into the common pharmacophore of Vpu actives was expressed as a root mean square deviation (RMSD), with the compounds with lowest RMSD selected as hits.

6.4 ADME/Tox prediction methods

Toxicity prediction was carried out using two methods; a knowledge base approach and using a machine learning approach. Lhasa's expert knowledge-based predictive tool, Derek software [207], running on Nexus 1.5.0 platform, was used for the knowledge base approach. The three studied data sets were input in .sdf format. The program first generated tautomers for all compounds in the datasets and proceeded to predict toxicities for each tautomer, based on identified structural alerts. The chosen species was human and eighty-eight (88) toxicity endpoints were selected. The Derek system works by perceiving chemical sub-structures within molecules and relating these to a rule-base, by relating the sub-structures with likely types of toxicity [154, 157, 158, 159]. This is intended for assisting in the process of selecting suitable candidate compounds for biological assays, based on toxicological considerations, thereby avoiding the testing of every single candidate, thus saving time, cutting down costs and saving the lives of some laboratory animals [160, 161], since some of the candidate compounds tested as "active" against certain pathogens may actually just be toxins.

The Derek program works by identifying toxicity alerts within the chemical structures of a possible drug candidate. By definition, a chemical alert is a structural feature observed to result in toxicological activity. The platform allows the user (who may not be an expert toxicologist) to automate alert identification by mining descriptions of activating structural features or substructures directly from toxicity data sets, which have been included within the program's knowledge base [162]. Each rule in Derek describes the relationship between a chemical structural feature or toxicophore and its associated toxic effect. In addition, the program proceeds to report the reasoning behind its predictions [154]. The reasoning rules are derived by an evaluation of toxicological, mechanistic, and physicochemical data [160], achieved by an argumentation-based approach using general toxicological and physico-chemical concepts, like log $P_{o/w}$ [160, 161]. The toxicity prediction run was carried out for the AfroCancer (in comparison with NPACT) [104], and later for the p-ANAPL, AfroMalariaDb and Afro-HIV datasets [173] and the results were analysed.

The compounds in the databases with toxicity alerts predicted from "plausible" were also uploaded

as SMILES files on the freely accessible Cambridge University small-molecule pharmacokinetics prediction (*pk*CSM) web server (University of Cambridge, UK) [208]. These were further assessed for *in silico* ADMET properties, using a machine learning approach that employs graph-based structural signatures, a model developed by Pires and coworkers [209]. The *pk*CSM model is based on 7 predictors for absorption, 4 predictors for distribution, 7 predictors for metabolism, 2 predictors for excretion and 10 predictors for toxicity. For each molecule, the *pk*CSM model generates molecular properties (e.g. general physico-chemical parameters like lipophilicity, *MW*, etc., together with a toxicophore fingerprint and an atomic pharmacophore frequency count). The toxicophore substructures, pharmacophores and molecular properties are computed using the RDkit cheminformatics toolkit. These are then matched with simplified molecular input line entry system arbitrary target specification (SMARTS) queries, which are potential indicators of mutagenicity in AMES test [210]. This allows predictions to be made, based on (graph-based) distance-path patterns or signatures. The results are represented as a cumulative distribution function of the previously generated pharmacophore types.

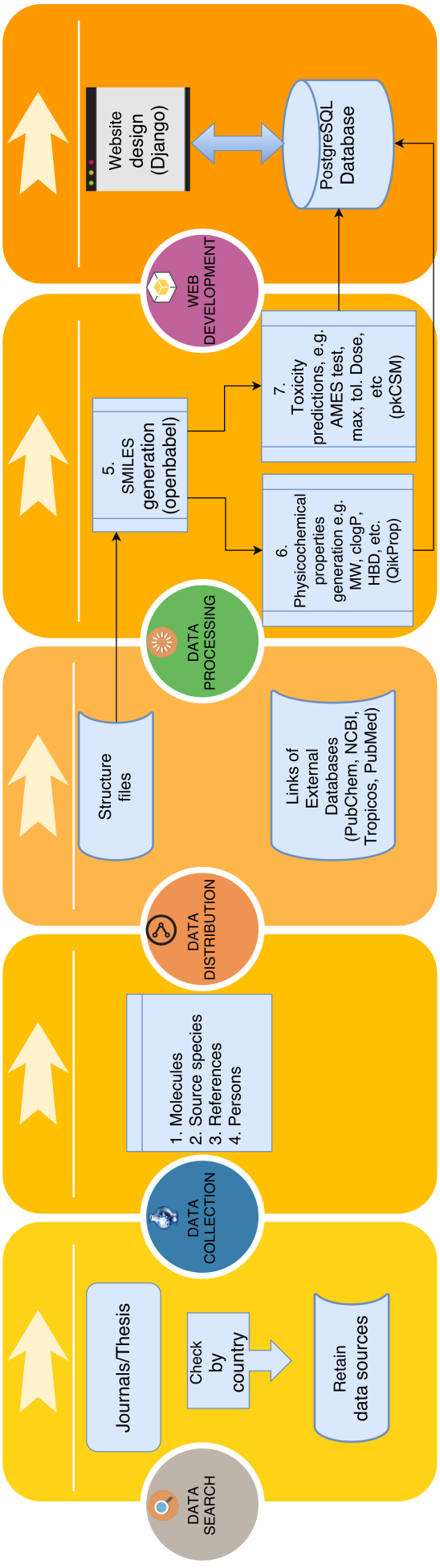


Figure 6.1: Simplified workflow that captures the entire process of construction of the databases, e.g. for NANPDB. Figure reproduced by permission.

CHAPTER SEVEN

APPENDICES

Certification/Eigenständigkeitserklärung

Hiermit erkläre ich an Eides statt, dass ich die vorliegende Arbeit selbstständig und ohne fremde Hilfe angefertigt habe. Ich habe keine anderen als die angegebenen Quellen und Hilfsmittel benutzt und die den verwendeten Werken wörtlich oder inhaltlich entnommenen Stellen als solche kenntlich gemacht.

Ferner erkläre ich, dass ich mich mit der vorliegenden Habilitation erstmals um die Erlangung dieses Titels bewerbe. Die vorliegende Arbeit ist weder im Inland noch im Ausland in gleicher oder ähnlicher Form einer anderen Prüfungsbehörde zum Zweck einer Habilitation oder eines anderen Prüfungsverfahren vorgelegt worden.

English translation

I hereby declare on oath that I have prepared the present work independently and without outside help. I have not used any sources or aids other than the ones indicated and have identified the sites used in the works, either literally or in terms of content, as such.

Furthermore, I declare that I am applying for the first time to obtain this title with the present habilitation. The present work has not been submitted, either in Germany or abroad, in the same or similar form to another examination authority for the purpose of a habilitation or other examination procedure.

Halle (Saale), den 23.04.2019 Dr. Fidele Ntie Kang

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CONTRIBUTIONS IN SELECTED PUBLICATIONS

BOOK CHAPTER

Textbook title, ISBN: Unique Aspects of Anti-cancer Drug Development, ISBN: 978-953-51-5240-8

Editors: J. Latosińska and M. Latosińska.

Publisher name, Country: InTech, Croatia

Full reference: Najjar, A.; **Ntie-Kang, F.;*** Sippl, W. *Application of computer modeling to drug discovery: case study of PRK1 kinase inhibitors as potential drugs in prostate cancer treatment.* ***In*** Unique Aspects of Anti-cancer Drug Development. Latosińska, J.; Latosińska, M. (Editors); Rijeka: InTech: ISBN 978-953-51-5240-8, **2017**, pp. 17–47.

DOI: http://dx.doi.org/10.5772/intechopen.68910

PMID: NA

Citations: 1

Author's contribution: Conceived the entire project, provided the virtual library or screening dataset, participated in interpreting the results, wrote a discussion of results and wrote about 35% of the 1st draft and did the correspondence. Also provided some mentorship to the Ph.D. student.

PAPER 1

Journal title: Molecules

Publisher name, Country: MDPI, Switzerland.

Journal website: http://www.mdpi.com/journal/molecules

Full reference: Karaman, B.;† Alhalabi, Z.;† Swyter, S.; Mihigo, S. O.; Andrae-Marobela, K.; Jung, M.; Sippl, W.; **Ntie-Kang, F.*** Identification of bichalcones as sirtuin inhibitors by virtual screening and *in vitro* testing. *Molecules*, **2018**, *23*, 416.

DOI: https://doi.org/10.3390/molecules23020416

PMID: 29443909

Current impact factor: 3.260

5-year impact factor: 2.988

Citations: 8

Author's contribution: Conceived the project, wrote the proposal and won the grant, participated in literature search, curated data, analysed the data, participated in interpreting the results, discussion of results and writing about 35% of the 1st draft of the paper and did the correspondence.

PAPER 2

Journal title: BMC Pharmacology and Toxicology

Publisher name, Country: Biomed Central, UK.

Journal website: https://link.springer.com/journal/40360

Full reference: Ngemenya, M. N.; Abwenzoh, N. G.; Ikome, H. N.; Zofou, D.; **Ntie-Kang, F.;** Efange, S. M. N. Structurally simple synthetic 1,4-disubstiuted piperidines with high selectivity for resistant *Plasmodium falciparum*. *BMC Pharmacology and Toxicology*, **2018**, *19*, 42.

DOI: NA

PMID: NA

Current impact factor: 2.250

5-year impact factor: 2.437

Citations: 4

Author's contribution: Carried out the computation, analysed the data, interpreting the results, discussion of results and writing about 10% of the 1st draft of the paper. Also hosted the M.Sc. student in my lab.

PAPER 3

Journal title: Computational Biology and Chemistry

Publisher name, Country: Elsevier, The Netherlands.

Journal website: https://www.journals.elsevier.com/computational-biology-and-chemistry

Full reference: Onguéné, P. A;[†] Simoben, C. V.;[†] Fotso, G. W.; Andrae-Marobela, K.; Khalid, S. A.; Ngadjui, B. T.; Mbaze, L. M.; **Ntie-Kang, F.**[*] *In silico* toxicity profiling of natural product compound libraries from African flora with anti-malarial and anti-HIV properties. *Computational Biology and Chemistry*, **2018**, *72*, 136–149.

DOI: https://doi.org/10.1016/j.compbiolchem.2017.12.002

PMID: 29277258

Current impact factor: 1.850

5-year impact factor: 1.437

Citations: 13

Author's contribution: Conceived the project, participated in analysing the data, interpreting the results, discussion of results and writing about 40% of the 1st draft of the paper. Supervised both M.Sc. and Ph.D. students involved in the project and did the correspondence.

PAPER 4

Journal title: Journal of Natural Products

Publisher name, Country: American Chemical Society, USA.

Journal website: http://pubs.acs.org/page/jnprdf/about.html

Full reference: **Ntie-Kang, F.;**[†*] Telukunta, K. K.;[†] Döring, K.; Simoben, C. V.; Moumbock, A. F. A.; Malange, Y. I.; Njume, L. E.; Yong, J. N.; Sippl, W.; Günther, S.[*] NANPDB: a resource for natural products from Northern African sources. *Journal of Natural Products*, **2017**, *80*, 2067−2076.

DOI: http://dx.doi.org/10.1021/acs.jnatprod.7b00283

PMID: 28641017

Current impact factor: 3.281

5-year impact factor: 3.437

Citations: 8

Author's contribution: Conceived the project, wrote the proposal and won the grant, participated in literature search, curated data, analysed the data, designed and implemented the database, participated in interpreting the results, discussion of results and writing about 50% of the 1st draft of the paper and did the correspondence.

PAPER 5

Journal title: Natural Products and Bioprospecting

Publisher name, Country: Springer, USA.

Journal website: https://link.springer.com/journal/13659

Full reference: Nyongbela, K. N.; **Ntie-Kang, F.;** Hoye, T. R.; Efange, S. M. N. Antiparasitic sesquiterpenes from the Cameroonian spice *Scleria striatinux* and preliminary *in vitro* and *in silico* DMPK assessment. *Natural Products and Bioprospecting*, **2017**, *7*, 235–247.

DOI: http://dx.doi.org/10.1007/s13659-017-0125-y

PMID: 28421410

Current impact factor: ND

5-year impact factor: ND

Citations: 3

Author's contribution: Carried out the computation, analysed the data, interpreting the results, discussion of results and writing about 40% of the 1st draft of the paper. I also participated in doing the correspondence when the corresponding author had no internet access.

PAPER 6

Journal title: Medicinal Chemistry Research

Publisher name, Country: Springer, USA.

Journal website: https://link.springer.com/journal/44

Full reference: Ibezim, A.; Debnath, B.; **Ntie-Kang, F.;*** Mbah, C. J.; Nwodo, N. J. Binding of anti-*Trypanosoma* natural products from African flora against selected drug targets: a docking study. *Medicinal Chemistry Research*, **2017**, *26*, 562–579.

DOI: http://dx.doi.org/10.1007/s00044-016-1764-y

PMID: ND

Current impact factor: 1.783

5-year impact factor: 1.280

Citations: 21

Author's contribution: Conceived the project, participated in literature search, curated data, provided the computational tools and resources, participated in the interpretation of results, discussion of results and writing about 20% of the 1st draft of the paper. Also supervised the visiting Ph.D. student at my home lab and did the correspondence.

PAPER 7

Journal title: Chemistry Central Journal

Publisher name, Country: SpringerOpen, Germany.

Journal website: http://www.springer.com/chemistry/journal/13065

Full reference: Ikome, H. N.; **Ntie-Kang, F.;*** Ngemenya, M. N.; Tu, Z.; Mash, R. H.; Efange, S. M. N.* 4-Aroylpiperidines and 4-(α-hydroxyphenyl)piperidines as selective sigma-1 receptor ligands: Synthesis, preliminary pharmacological evaluation and computational studies. *Chemistry Central Journal*, **2016**, *10*, 53.

DOI: http://dx.doi.org/10.1186/s13065-016-0200-1

PMID: 27555879

Current impact factor: 2.442

5-year impact factor: 2.658

Citations: 2

Author's contribution: Carried out the computation, analysed the data, interpreting the results, discussion of results and writing about 40% of the 1st draft of the paper. Also supervised the visiting M.Sc. student at my lab and did the correspondence.

PAPER 8

Journal title: Drug Design, Development and Therapy

Publisher name, Country: Dove Press, UK.

Journal website: https://www.dovepress.com/drug-design-development-and-therapy-journal

Full reference: **Ntie-Kang, F.;**[†*] Simoben, C. V.;[†] Karaman, B.; Ngwa, V. F.; Judson, P. N.; Sippl, W.; Mbaze, L. M.[*] Pharmacophore modeling and *in silico* toxicity assessment of potential anti-cancer agents from African medicinal plants. *Drug Design, Development and Therapy*, **2016**, *10*, 2137–2154.

DOI: http://dx.doi.org/10.2147/DDDT.S108118

PMID: 27445461

Current impact factor: 3.028

5-year impact factor: 2.962

Citations: 21

Author's contribution: Curated the literature data, participated in carrying out the computation, analysed the data, interpreting the results, discussion of results and writing about 50% of the 1st draft of the paper. Also supervised the visiting M.Sc. at my lab and did the correspondence.

PAPER 9

Journal title: Chemistry Central Journal

Publisher name, Country: SpringerOpen, Germany.

Journal website: http://www.springer.com/chemistry/journal/13065

Full reference: Malolo, F. A. E.; Nouga, A. B.; Kakam, A.; Franke, K.; Ngah, L.; Flausino, O. J.; Mpondo, E. M.; **Ntie-Kang, F.;*** Ndom, J. C.; Bolzani, V. S.; Wessjohann, L. Protease-inhibiting, molecular modelling and antimicrobial activities of extracts and constituents of *Helichrysum foetidum* and *Helichrysum mechowianum* (Compositae). *Chemistry Central Journal*, **2015**, *9*, 32.

DOI: http://dx.doi.org/10.1186/s13065-015-0108-1

PMID: 26042155

Current impact factor: 2.498

5-year impact factor: 2.658

Citations: 9

Author's contribution: Carried out the computation, analysed the data, interpreting the results, discussion of results and writing about 10% of the 1st draft of the paper and did the correspondence.

PAPER 10

Journal title: Molecular Informatics

Publisher name, Country: WILEY-VCH Verlag GmbH & Co. KGaA, Germany.

Journal website: http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1868-1751

Full reference: Owono, L. C. O.; **Ntie-Kang, F.;** Keita, M.; Megnassan, E.; Frecer, V.; Miertus, S. Virtually designed triclosan-based inhibitors of enoyl-acyl carrier protein reductase of *Mycobacterium tuberculosis* and of *Plasmodium falciparum*. *Molecular Informatics*, **2015**, *34*, 292–307.

DOI: http://onlinelibrary.wiley.com/doi/10.1002/minf.201400141/full

PMID: 27490275

Current impact factor: 2.741

5-year impact factor: 2.158

Citations: 6

Author's contribution: Carried out the computation, analysed the data, interpreting the results, discussion of results and writing about 50% of the 1st draft of the paper.

PAPER 11

Journal title: PloS ONE

Publisher name, Country: Public Library of Science, USA.

Journal website: http://journals.plos.org/plosone

Full reference: Tietjen, I.; **Ntie-Kang, F.;** Mwimanzi, P.; Onguéné, P. A.; Scull, M. A.; Idowu, T. O.; Ogundaini, A. O.; Mbaze, L. M.; Abegaz, B. M.; Rice, C. M.; Andrae-Marobela, K.; Brockman, M. A.; Brumme, Z. L.; Fedida, D. Screening of the pan-African natural product library identifies ixoratannin A-2 and boldine as novel HIV-1 inhibitors. *PLoS ONE*, **2015**, *10*, e0121099.

DOI: https://doi.org/10.1371/journal.pone.0121099

PMID: 25830320

Current impact factor: 2.740

5-year impact factor: 3.654

Citations: 33

Author's contribution: Conceived the virtual screening work, curated the literature data, participated in carrying out the computation, provided the computational tools and resources, analysed the data, interpreting the results, discussion of results and writing about 20% of the 1st draft of the paper. Also supervised the visiting Ph.D. student at my lab.

PAPER 12

Journal title: Medicinal Chemistry Research

Publisher name, Country: Springer, USA.

Journal website: https://link.springer.com/journal/44

Full reference: Metuge, J. A.;[†] **Ntie-Kang, F.;**[†*] Ngwa, V. F.; Babiaka, S. B.; Samje, M.; Cho-Ngwa, F. Molecular modeling of plant metabolites with anti-*Onchocerca* activity. *Medicinal Chemistry Research*, **2015**, *24*, 2127–2141.

DOI: https://doi.org/10.1007/s00044-014-1280-x

PMID: ND

Current impact factor: 1.277

5-year impact factor: 1.280

Citations: 4

Author's contribution: Conceived the computational work, analysed the data, interpreting the results, discussion of results and writing about 50% of the 1st draft of the paper and did the correspondence. Also supervised the visiting M.Sc. and Ph.D. students at my lab.

PAPER 13

Journal title: Journal of Chemical Information and Modeling

Publisher name, Country: American Chemical Society, USA.

Journal website: http://pubs.acs.org/page/jcisd8/about.html

Full reference: **Ntie-Kang, F.;**[†*] Nwodo, J. N.;[†] Ibezim, A.; Simoben, C. V.; Karaman, B.; Ngwa, V. F.; Sippl, W.; Adikwu, M. U.; Mbaze, L. M. Molecular modeling of potential anticancer agents from African medicinal plants. *Journal of Chemical Information and Modeling*, **2014**, *54*, 2433–2450.

DOI: http://dx.doi.org/10.1021/ci5003697

PMID: 25116740

Current impact factor: 4.549

5-year impact factor: 3.880

Citations: 71

Author's contribution: Conceived the entire project, provided the computational tools and resources, participated in the computation, analysed the data, interpreting the results, wrote a discussion of results and wrote about 60% of the 1st draft of the paper and did the correspondence. Also supervised the visiting M.Sc. and Ph.D. students at my lab.

PAPER 14

Journal title: Organic and Medicinal Chemistry Letters

Publisher name, Country: SpringerOpen, Germany.

Journal website: https://link.springer.com/journal/13588

Full reference: Onguéné, P. A;[†] **Ntie-Kang, F.;**[†*] Mbah, J. A.; Lifongo, L. L.; Ndom, J. C.; Sippl, W.; Mbaze, L. M. The potential of anti-malarial compounds derived from African medicinal plants, part III: An *in silico* evaluation of drug metabolism and pharmacokinetics profiling. *Organic and Medicinal Chemistry Letters*, **2014**, *4*, 6.

DOI: http://dx.doi.org/10.1186/s13588-014-0006-x

PMID: 26548985

Current impact factor: ND

5-year impact factor: ND

Citations: 9

Author's contribution: Conceived the entire project, participated in the data curation and computation, provided the computational tools and resources, analysed the data, interpreting the results, wrote a discussion of results and wrote about 50% of the 1st draft of the paper and did the correspondence. Also supervised the visiting Ph.D. student at my lab.

PAPER 15

Journal title: Natural Products and Bioprospecting

Publisher name, Country: Springer, USA.

Journal website: https://link.springer.com/journal/13659

Full reference: Metuge, J. A.; Babiaka, S. B.; Mbah, J. A.; **Ntie-Kang, F.;** Ayimele G. A.; Cho-Ngwa, F. Anti-*Onchocerca* compounds from *Cyperus articulatus*: isolation, *in vitro* activity and *in silico* 'drug-likeness'. *Natural Products and Bioprospecting*, **2014**, *4*, 243–249.

DOI: http://dx.doi.org/10.1007/s13659-014-0023-5

PMID: 25089243

Current impact factor: ND

5-year impact factor: ND

Citations: 8

Author's contribution: Carried out the computation, analysed the data, interpreting the results, discussion of results and writing about 10% of the 1st draft of the paper and did the initial correspondence.

PAPER 16

Journal title: RSC Advances

Publisher name, Country: Royal Society of Chemistry, UK.

Journal website: http://www.rsc.org/journals-books-databases/about-journals/rsc-advances

Full reference: Ngo Hanna, J.; **Ntie-Kang, F.;** Kaiser, M.; Brun, R.; Efange, S. M. N. 1-Aryl-1,2,3,4-tetrahydroisoquinolines as potential antimalarials: synthesis, *in vitro* antiplasmodial activity and *in silico* pharmacokinetics evaluation. *RSC Advances*, **2014**, *4*, 22856–22865.

DOI: http://dx.doi.org/10.1039/C3RA46791K

PMID: ND

Current impact factor: 3.070

5-year impact factor: 3.254

Citations: 17

Author's contribution: Carried out the computation, analysed the data, interpreting the results, discussion of results and writing about 20% of the 1st draft of the paper and did the initial correspondence.

PAPER 17

Journal title: PloS ONE

Publisher name, Country: Public Library of Science, USA.

Journal website: http://journals.plos.org/plosone

Full reference: **Ntie-Kang, F.;**[†] Onguéné, P. A.;[†] Fotso, G. W.; Andrae-Marobela, K.; Bezabih, M.; Ndom, J. C.; Ngadjui, B. T.; Ogundaini, A. O.; Abegaz, B. M.; Mbaze, L. M. Virtualizing the p-ANAPL compound library: a step towards drug discovery from African medicinal plants. *PLoS ONE*, **2014**, *9*, e90655.

DOI: http://dx.doi.org/10.1371/journal.pone.0090655

PMID: 24599120

Current impact factor: 2.740

5-year impact factor: 3.654

Citations: 46

Author's contribution: Conceived the entire project, participated in the computation, provided the computational tools and resources, analysed the data, wrote a discussion of results, interpreting the results, discussion of results and writing about 50% of the 1st draft of the paper and did the initial correspondence. Also supervised the visiting Ph.D. student at my lab.

PAPER 18

Journal title: Journal of Molecular Modeling

Publisher name, Country: Springer, USA.

Journal website: https://link.springer.com/journal/894

Full reference: **Ntie-Kang, F.;*** Lifongo, L. L.; Judson, P. N.; Sippl, W.; Efange, S. M. N. How "drug-like" are naturally occurring anticancer compounds? *Journal of Molecular Modeling*, **2014**, *20*, 2069.

DOI: http://dx.doi.org/10.1007/s00894-014-2069-z

PMID: 24452907

Current impact factor: 1.346

5-year impact factor: 1.306

Citations: 18

Author's contribution: Conceived the entire project, carried out all the computation, provided the computational tools and resources, analysed the data, wrote a discussion of results, interpreting the results, discussion of results and writing about 95% of the 1st draft of the paper and did the correspondence.

PAPER 19

Journal title: Molecular BioSystems

Publisher name, Country: Royal Society of Chemistry, UK.

Journal website: http://www.rsc.org/journals-books-databases/about-journals/molecular-biosystems

Full reference: **Ntie-Kang, F.;*** Kannan, S.; Wichapong, K.; Owono, L. C. O.; Sippl, W.; Megnassan, E. Binding of pyrazole-based inhibitors to *Mycobacterium tuberculosis* pantothenate synthetase: docking and MM-GB(PB)SA analysis. *Molecular BioSystems*, **2014**, *10*, 223–239.

DOI: http://dx.doi.org/10.1039/C3MB70449A

PMID: 24240974

Current impact factor: 2.830

5-year impact factor: 3.154

Citations: 25

Author's contribution: Conceived the entire project, participated in the data curation and computation, analysed the data, interpreting the results, wrote a discussion of results and wrote about 80% of the 1st draft of the paper and did the correspondence.

PAPER 20

Journal title: RSC Advances

Publisher name, Country: Royal Society of Chemistry, UK.

Journal website: http://www.rsc.org/journals-books-databases/about-journals/rsc-advances

Full reference: **Ntie-Kang, F.;*** Onguéné, P. A.; Scharfe, M.; Mbaze, L. M.; Owono, L. C. O.; Megnassan, E.; Sippl, W.; Efange, S. M. N. ConMedNP: a natural product library from Central African medicinal plants for drug discovery. *RSC Advances*, **2014**, *4*, 409–419.

DOI: http://dx.doi.org/10.1039/C3RA43754J

PMID: ND

Current impact factor: 3.108

5-year impact factor: 3.254

Citations: 29

Author's contribution: Conceived the entire project, participated in the data curation and computation, developed the database, provided the computational tools and resources, analysed the data, interpreting the results, wrote a discussion of results and wrote about 70% of the 1st draft of the paper and did the correspondence. Also supervised the visiting Ph.D. student at my lab.

BRIEF CURRICULUM VITAE

Dr. Fidele Ntie Kang

Curriculum Vitae

Personal data

Name: Ntie Kang, **First name:** Fidele,
Academic title: Dr.,
Birth date: 30.03.1976, in Tiko (Cameroon)
Nationality: Cameroonian
Gender: Male,
Family status: Married, father of one child (born on 23.12.2007)

Academic training

06.18-03.20	ChemJets Research Fellow, Department of Informatics and Chemistry, University of Chemistry and Technology, Prague, Czech Republic, under Assoc. Prof. Daniel Svozil.
03.15-04.18	Alexander von Humboldt Postdoctoral fellow for Pharmaceutical and Medicinal Chemistry, Martin-Luther University of Halle-Wittenberg, Germany, under Prof. Dr. Wolfgang Sippl
03.14-05.14	Commonwealth professional fellow, Lhasa Ltd., Leeds, United Kingdom
09.09-01.14	Ph.D. in Physical Science (Topic: "Computer-aided Design and Virtual Screening of Novel Inhibitors of Pantothenate Synthetase, Enoyl-acyl Carrier Protein Reductase and Multidrug-resistant Strains of *Mycobacterium tuberculosis*"), University of Douala, Cameroon, under Prof. Dr. Luc C. O. Owono and Prof. Dr. Eugene Megnassan.
05.11-10.11	DAAD sandwich fellow (visiting Ph.D. student), for Pharmaceutical and Medicinal Chemistry, Martin-Luther University of Halle-Wittenberg, Germany.
06.10-12.10	Our Common Future fellow, Essen/Hannover, Germany (Molecular Medicine).
05.08-12.08	Research fellow for Combinatorial Chemistry and Molecular Design, (ICS-UNIDO), Trieste, Italy.
09.06-08.07	Masters' 2 Degree in Physics of Matter and Radiation, University of Douala, Cameroon.
09.03-08.04	Masters' 1 Degree in Organic Chemistry, University of Douala, Cameroon.
09.99-08.03	Bachelors' Degree (License) in Chemistry, University of Douala, Cameroon.

Professional career

04.20-03.21	Guest Professor (W2), Institute of Botany, Technical University Dresden, Germany.
09.19-08-22	Adjunct Professor, MEWES, Nelson Mandela African Institution of Science and Technology (NM-AIST), Arusha, Tanzania.
05.15-03.18	Senior Scientist, Institute for Pharmacy, Martin-Luther University, Halle-Wittenberg, Germany.
06.10-present	Part-time Lecturer (later Instructor, Senior Instructor and Assistant Lecturer and Senior Lecturer), Chemistry Department, University of Buea, Cameroon.
11.12-05.15	Research Assistant (later Scientific Manager), Chemical Bioactivity Information Centre, University of Buea, Cameroon.
09.09-05.11	Part-time Lecturer, Institut Supérieur de Technologie et du Design Industriel (ISTDI, a private university), Douala, Cameroon.
06.08-08.09	Graduate Assistant, Chemistry Department, University of Douala, Cameroon.