European Cooperation in the field of Scientific and Technical Research
- COST -

Brussels, 14 November 2014

COST 090/14

MEMORANDUM OF UNDERSTANDING

Subject :	Memorandum of Understanding for the implementation of a European Concerted Research Action designated as COST Action CM1407: Challenging organic syntheses inspired by nature - from natural products chemistry to drug discovery

Delegations will find attached the Memorandum of Understanding for COST Action CM1407 as approved by the COST Committee of Senior Officials (CSO) at its 191th meeting on 12-13 November 2014.

MEMORANDUM OF UNDERSTANDING

For the implementation of a European Concerted Research Action designated as

COST Action CM1407
CHALLENGING ORGANIC SYNTHESES INSPIRED BY NATURE: FROM NATURAL PRODUCTS CHEMISTRY TO DRUG DISCOVERY

The Parties to this Memorandum of Understanding, declaring their common intention to participate in the concerted Action referred to above and described in the technical Annex to the Memorandum, have reached the following understanding:

1. The Action will be carried out in accordance with the provisions of document COST 4114/13 "COST Action Management" and document 4112/13 "Rules for Participation in and Implementation of COST Activities", or in any new document amending or replacing them, the contents of which the Parties are fully aware of.

2. The main objective of the Action is to bring together an interdisciplinary group of motivated scientists from academia and industry to provide natural products of therapeutic relevance, and to promote the translation of research results into possible industrial applications.

3. The economic dimension of the activities carried out under the Action has been estimated, on the basis of information available during the planning of the Action, at EUR 88 million in 2014 prices.

4. The Memorandum of Understanding will take effect on being accepted by at least five Parties.

5. The Memorandum of Understanding will remain in force for a period of 4 years, calculated from the date of the first meeting of the Management Committee, unless the duration of the Action is modified according to the provisions of Section *2. Changes to a COST Action* in the document COST 4114/13.

A. ABSTRACT

Natural products (NP) have had a major impact on chemistry, chemical biology and drug discovery and have been part of medical remedies since ancient times. Nowadays, NP represent a unique source of leads for medicinal chemistry and drugs derived from NP have found widespread use for the treatment of cancer, cardiovascular diseases, bacterial and fungal infections. The general aim of this COST Action is to advance the field and to maintain the high level of expertise in NP chemistry within Europe by combining synthetic chemistry, computational chemistry, chemical biology, and pharmacology to find new lead structures of pharmaceutical relevance. Since chemistry plays a key role in addressing the industrial requirements for preclinical candidates in terms of physicochemical properties of NP and their analogues, this Action further aims to promote the translation between fundamental academic research and industrial drug discovery by means of NP chemistry.
Keywords: Natural Products, Organic Synthesis, Drug Discovery, Molecular Modelling, Chemical Biology

B. BACKGROUND

B.1 General background

Near the end of the 20th century, research aiming at exploiting NP as a resource for drug discovery seriously declined. Many pharmaceutical companies concentrated their efforts on new technologies such as combinatorial chemistry, metagenomics and high-throughput screening to generate new drug candidates. However, these new strategies have not delivered the expected results and recently there has been a renewed interest in the use of NP in drug discovery. Nowadays, NP still represent a unique source of lead structures for the creation of new medicines and in addition they are powerful tools in the hands of pharmacologists to modulate biomolecular systems. Many targets relevant to the treatment of diseases would not have been discovered without NP; notable examples include taxol (microtubule stabilization), rapamycin (mTOR), trichostatin (HDACs) and myriocin (S1P receptors). Additionally, the systematic investigation of the marine environment has led to the discovery of new therapeutic agents which have been approved as drugs. The importance of NP research, including the fields of isolation, structure elucidation, synthesis and biology is undisputed and continued advances in all these areas are essential for progress in biology and medicine.
This Action will foster effective cooperation among multidisciplinary Working Groups (WGs)

focusing on technical issues in the field of NP synthesis/extraction/isolation/purification as well as different therapeutic areas. The COST scheme is also the ideal platform to promote academic-private partnerships and to exchange scientific know-how and regulatory expertise that is generally not readily available to academic researchers. This synergistic approach is significantly under-developed in Europe compared to the USA where very positive outcomes have been obtained from academia-industry partnerships in the area of drug discovery. The involvement of commercial/industrial members since the beginning of the Action is expected to promote this partnership and to lead to future initiatives within the framework Horizon 2020, focusing on the advanced stages of drug development.

B.2 Current state of knowledge

Optimization of NP Synthesis/Isolation/Purification/Characterization. Preclinical and clinical development of NP is often hampered by the low quantities of samples available from natural sources. Access can be improved by the creation of economical synthesis strategies, particularly atom, step and redox economical ones. The bewildering diversity of natural product structures continues to stimulate and challenge chemists to invent new reactions, reagents and strategies to tackle the challenges that nature provides. Radical based or organometallic transformations, use of organocatalysis in synthesis (green chemistry), chemistry in microreactors, solid phase chemistry (reagents, supports) and combinations of synthetic chemistry and biosynthesis (mutasynthesis, precursor directed synthesis) are indispensable for progress in NP chemistry and to provide new and more efficient access to modified NP for biological investigations. The total synthesis of a natural product may lead to the identification of a sub-structural portion of the molecule bearing the essential pharmacophoric features necessary for activity whereas semi-synthetic structural modifications of the NP often provide important structure activity relationships (SAR) that enable subsequent computer-aided ligand optimization and the synthesis of analogues with improved pharmacological properties. Recent prominent examples of this approach are eribulin mesylate, a synthetic analogue of a sub-unit of the complex marine natural product halichondrin B, and the development of an efficient strategy to synthesize (–)-deoxytetracycline, which has enabled the preparation of hundreds of tetracycline congeners, some of which have successfully passed the phase 2 clinical trial.

Cancer. In parallel with advances in cancer biology, anti-cancer drug discovery has focused recently on targets related to cell cycle progression and signal transduction. In particular, targeting

signalling pathways engaged by cancer stem cells (CSC) (e.g. Hedgehog, Wnt/beta-catenin, Notch) or cancer cells represents a promising strategy to develop effective and innovative drug candidates. For instance, the Hedgehog inhibitor Vismodegib has been recently approved by the US Food and Drug Administration (FDA) for the treatment of metastatic basal cell carcinoma. Moreover, the well-known success of Imatinib and related drugs has prompted the scientific community to intensify the efforts in targeting kinases and other regulatory enzymes. However, the major types of solid human tumour are multi-causal in nature and so their treatment with “mechanism-based” agents alone is unlikely to be fully effective. Instead, improved treatment strategies involving combination therapies, such as signal transduction inhibitors with new generation antimitotic compounds, are anticipated in the clinic. Antitumor agents targeting tubulin cause aberrant mitotic spindle formation, cell cycle arrest in mitosis and induction of apoptosis. Besides taxol, other NP such as epothilones, vincristine, vinblastine and the marine macrolide zampanolide have provided new perspectives for the development of a new generation of clinical anticancer agents.

Viral infections. Acquired immune deficiency syndrome (AIDS) is one of the most serious diseases caused by viral infection in the modern era. Although current therapies based on targeting key processes of the human immunodeficiency virus (HIV) replication cycle are potent and selective, several clinical failures have been recorded due to the emergence of drug resistance. Hence, there is an urgent need for novel drugs and alternative therapeutic strategies, which are generally to be found in the design of more potent and selective inhibitors of entry/fusion, reverse transcriptase (RT), integrase (IN) and protease (PR). However, these compounds may lack full activity against drug-resistant virus strains selected by the same drug classes. Consequently, targeting HIV proteins such as the capsid (CA), nucleocapsid (NCp7), negative regulatory factor (Nef), virion infectivity factor (Vif) that are highly conserved among phylogenetically distant viral strains or interact with highly conserved DNA or RNA motifs is currently considered a highly promising anti-HIV strategy. Human diseases such as severe acute respiratory syndrome (SARS), HxNy influenza, avian influenza, hepatitis C and Dengue fever that are caused by emerging or re-emerging viruses as well as infections by adenoviruses and papilloma virus still lack effective treatments. In this respect, NP may serve as unique source of bioactive leads for developing effective therapeutic agents against these viruses.

Tuberculosis. Tuberculosis (TB) kills nearly 2 million people annually and has been declared a global health emergency by the World Health Organization (WHO). Drug resistance and patient noncompliance are two of the key factors that affect the success rate of conventional treatments,

underlining the urgent need for novel anti-TB therapeutic targets and new drugs that could circumvent these problems. During the last decade, exoenzymes secreted into the host cell by *Mycobacterium tuberculosis* (Mtb) to attenuate host immune defenses have emerged as promising therapeutic targets. NP inhibitors of protein tyrosine phosphatase A (PtpA) and B (PtpB) have demonstrated significant therapeutic potential. In addition, the InhA enoyl reductase is a major Mtb drug target highly attractive for inhibition by NP, validated clinically by the prodrugs isoniazid and ethionamide. Finally, recent structural genomics approaches have led to the identification and characterization of putative anti-TB drug targets such as for example PknA and PknB Mtb kinases, for which bioactive NP may function as reliable tools for pharmacological validation as well as lead candidates for anti-TB drug discovery.

This Action addresses the problem of synthesizing and optimizing NP to meet the physicochemical requirements of drug discovery and the challenging problem of finding new lead structures of therapeutic relevance. This COST Action aims at innovatively exploiting NP chemistry to boost the drug discovery-oriented pipeline by combining academic research with industrial needs. The research aim of the Action is to identify NP leads candidates by sharing and disseminating the knowledge present in individual research groups in Europe.

B.3 Reasons for the Action

A European forum promoting NP chemistry in drug discovery is needed. The decreased interest in NP research recorded since the late 1990s led to a fragmentation of research groups involved in the field across Europe. This Action, which is mainly aimed at European scientific/technological advance, will promote the convergence of biology- and chemistry-based research to bring together a highly motivated group of researchers, coming from both academia and industry since the beginning of the Action, dedicated to promoting and disseminating NP chemistry, with a specific focus on drug discovery and related translational activities. In the ended Action CM0804 (Chemical Biology with Natural Products), NP were utilised as tools for probing biology and NP that were available or targets of a synthesis program were investigated. Indeed, Action CM0804 was partly successful in establishing a network of scientists with expertise in bioassays, isolation, purification, structural analysis of NP and target synthesis. In this Action, research groups will work together on the synthesis of a larger collection of NP that would not be possible within a single group.
Immediate benefits. WGs focusing on therapeutic needs will be established. Strong lateral connections between the various WGs will be promoted and supported by the Management

Committee (MC), e.g. through workshops, training schools and Short-Term Scientific Missions (STSM), allowing the exchange of critical information and new technologies. Collaborations between academic and industrial/private research groups, usually confined to a specific research field, will be encouraged to accelerate the drug discovery process.

Future benefits. The Action will provide a variety of leads or lead candidates from NP that will be of general interest to the wider scientific community and is likely to lead to the preparation of a European research proposals (Horizon 2020). Intellectual property (IP) protection and commercial exploitation of any innovation developed by this Action through European small and medium-sized enterprises (SMEs) will be strongly encouraged. Particularly, the establishment of new SMEs by parties involved in this Action will be deemed a top priority.

Main objectives. The main objective of the Action is to advance the field and to maintain and then increase the high level of expertise of NP chemistry within Europe. This objective will be achieved by connecting European scientists who have expertise in synthetic chemistry, computational chemistry, biology, and pharmacology in a collaborative network oriented to exploit NP for drug discovery. The translation of research results and/or technological developments into potential industrial applications for healthcare that are likely to provide Europe with a competitive advantage will be highly encouraged and promoted. The Action's outcomes will be exploited to establish future research networks and/or new SMEs within Europe.

Expected results:

- to re-establish NP and NP chemistry as a key element in drug discovery;
- to deliver new NP of pharmaceutical relevance;
- to promote academic/industry partnership within the Action in order to optimize NP leads;
- to validate relevant pharmacological targets for drug discovery;
- to nurture a new generation of young and skilled scientists within Europe.

B.4 Complementarity with other research programmes

The Action may be considered as an evolution of the ended COST Action CM0804, which focused on Natural products for Chemical Biology, while this Action is specifically focused on the development of NP leads for drug discovery. Partial complementarity and synergy with the Action CM1106 (Chemical Approaches to Targeting Drug Resistance in Cancer Stem Cells) is envisaged, but only with respect to some topics addressed by WG3.

C. OBJECTIVES AND BENEFITS

C.1 Aim

The main objective of the Action is to bring together Natural Products (NP) synthesis, computational chemistry, biology and pharmacology in a drug-discovery oriented strategy to provide NP of therapeutic relevance. This approach will be beneficial to both the fields of NP research and drug discovery. The further aim is to promote the translation of research results into possible industrial applications for healthcare. Moreover, the Action will give rise to a new generation of scientists skilled in bioinformatics, biology and NP chemistry and able to cross boundaries of these disciplines.

C.2 Objectives

The Action expects that most of the major European research groups active in NP chemistry and related drug discovery research, as well as lead commercial/industrial partners devoted to NP drug discovery, will share their efforts to discover NP of therapeutic relevance and to contribute to translating high-quality research results into possible industrial applications. A high degree of knowledge and experience in NP chemistry and drug discovery will be ensured by a comprehensive programme of meetings, workshops, conferences and discussions with international specialists, coming from both academia and industry.

General objectives of this Action are:

- to provide insights into the efficient synthesis of biologically active NP and their analogues for both educational and research purposes;
- to solve important synthetic problems and develop useful reactions with relevance to the chemical industry;
- to train early-stage researchers in the total synthesis of highly complex NP;
- the effective use of molecular modelling to identify potential biomolecular targets for NP and to prioritize highly active NP;
- to address the relevance of NP chemistry with an emphasis on rational optimization of NP as potential therapeutic agents;
- the effective use of biological/biochemical tools to characterize NP leads in the context of specific therapeutic fields.

- to educate young scientists in the basics of adjacent scientific fields through regular workshops or training schools;
- to promote exchanges of early-stage researchers in order to disseminate practical skills and share relevant experience between research groups;
- to promote interactions between European research teams to discover promising new NP leads or lead candidates;
- to work in partnership with and transfer promising results to SMEs or larger companies;
- to identify high quality partners for further research cooperation (i.e. Horizon 2020).

C.3 How networking within the Action will yield the objectives?

The competence, creativity and vision of scientists who are dedicated to NP drug discovery and have a remarkable willingness to work in collaborative environments will drive toward the achievement of the Action objectives. The MC will supervise the collaborative network and will promote and organize Training Schools, Conferences and STSMs. With respect to the technical equipment available within institutions involved in the Action, it would be very difficult, if not impossible, to develop such a network at a local or national level. The labs are excellently equipped with the necessary infrastructure and facilities to carry out advanced research in their respective scientific fields. The technical services of each department involved offer to researchers the latest in high-tech instrumentation. All the research groups involved in the Action have relevant expertise in their fields that guarantees the implementation of the various types of interdisciplinary investigations that are envisaged.

C.4 Potential impact of the Action

Many European researchers operating in NP chemistry and related drug discovery are currently working independently with little interdisciplinary activity. This Action will address the need for more effective exchange of information, experience and skills by bringing together scientists at the forefront of NP chemistry with computational chemists, biologists and pharmacologists from several COST countries to find new NP leads of therapeutic relevance. Connecting high level research teams in NP chemistry and drug discovery from both academia and industry is a major step towards achieving the Action impact. The high quality scientific training will represent a unique opportunity, which would be unavailable otherwise, for early-stage researchers to grow in a collaborative European environment and be deeply involved in research spanning several primary

research fields. The next generation of scientists inspired by this COST Action will be skilled in multiple disciplines and trained to work in a collaborative research environment without boundaries.

C.5 Target groups/end users

The primary topics and expected outcomes of this multidisciplinary Action will be of great interest to the wider scientific community in both academia and industry. Scientists involved in following fields are likely to be stakeholders who will be interested in Action outcomes and results: chemistry, biology, biochemistry, computational chemistry, bioinformatics, structural biology, pharmacology, chemical biology, molecular biology, medicinal chemistry, medicine and also those engaged in research and development (R&D) in related fields from both academia and industry.
Potential end users:

- academic and industrial researchers;
- university professors or lecturers;
- early-stage researchers interested in STSM and training schools;
- European and International research communities;
- pharmaceutical companies and SMEs;
- potential investors;
- press agencies.

D. SCIENTIFIC PROGRAMME

D.1 Scientific focus

This Action aims to provide major discoveries and innovations in NP chemistry, with particular focus on drug discovery and translation of research results into possible industrial applications for healthcare, which is currently an under-developed area of European academic research. The scientific programme is articulated into a WG addressing NP chemistry and related technical issues plus three drug discovery WGs, which will focus on different therapeutic fields (viral infections, cancer and tuberculosis) and share common research tasks integrating target identification and validation, NP hit discovery, NP hit-to-lead optimization and functional characterization of NP leads. The WG dedicated to NP chemistry will engage in tasks that are well integrated in the drug discovery programme, addressing scale-up synthesis of NP, NP hit-to-lead synthesis and the

optimization of synthesis, extraction, isolation and purification procedures.
To facilitate the achievement of the secondary aim of the Action, which is the translation of research results into industrial applications for healthcare, an optional task is planned to progress NP leads up to the preclinical or clinical candidate stages. The MC will have the pivotal role of monitoring NP progression amongst other tasks and, in case of very promising results, to initiate new collaborations with parties devoted to drug development.

Scientific tasks are summarized as follows:
1) *Target identification/validation*. To improve the probability of success of the Action, validated targets will be selected, alongside promising and/or innovative pharmacological targets. In this latter case, efforts will be devoted to target validation. The ideal target should be expressed selectively by the microorganisms or cells to be interfered by NP (i.e. HIV, cancer cells, Mtb) and its three-dimensional structure should be characterized by X-ray crystallography or Nuclear Magnetic Resonance (NMR) to allow the implementation of structure-based ligand design approaches. Alternatively, NP or small molecule modulators of the selected target should be available, to facilitate ligand-based design studies.
2) *NP hit selection*. Although there may be different strategies to prioritize NP for a given biological activity, the Action will promote the use of molecular modelling tools such as pharmacophore modelling, molecular docking and dynamics simulations, structure similarity searches and chemoinformatics approaches that may also be combined in a virtual screening cascade. Indeed, molecular modelling is widely recognized as a fast, efficient and cost effective method by which to identify putative small molecule hits to submit to biological assays. High-throughput screening (HTS) will be also used to screen compound libraries in order to identify NP hits. Alternatively, biologically active NP already identified by partners before joining the Action may be moved directly to further tasks. In this task, individual collections of NP owned by research groups may be also joined to build an Action NP library for screening purposes, which may capture the attention of industrial stakeholders. Currently, the preparation of NP libraries is largely governed by opportunistic principles and therefore is often a random undertaking. The hope is that during this Action some general strategies for the preparation of NP analogues will be formulated. In this regard, synthetic chemists can learn a lot from medicinal chemists. Furthermore, the use of computational chemistry to design NP analogues will be within the focus of this Action. NP will be progressed to further stages if they are endowed with an at least moderate biochemical activity. Results of preliminary biological tests will be used to refine the computational protocol in light of the subsequent hit to lead optimization step (task 3).

3) *NP hit-to-lead optimization*. The aim of this multidisciplinary task is to optimize NP hits delivered in task 2 in terms of potency, selectivity, water solubility and other physicochemical properties up to NP lead candidates. The synergism between NP chemistry and molecular modelling will be crucial if the objectives of the Action are to be achieved. Indeed, the molecular scaffold responsible for the biological activity of the NP hit will be expanded by means of virtual combinatorial libraries that will be designed on the basis of accessible synthetic transformations. After in silico screening, the most promising NP or NP derivatives will be synthesized and submitted for biological evaluation. Biological activity data will help to delineate SAR that may facilitate the further optimization of NP hits and leads by iteratively recalling tasks 2 and 3. Preliminary ADME-Tox profiles of NP lead candidates will be delineated in silico. Notably, NP lead candidates may be tested against targets addressed in different WGs to explore selectivity and possible cross-activity, as well as to enhance interconnections and collaborations among WGs.

4) *Optimization of NP chemistry*. Access NP or their analogues in sufficient quantities to perform biological tests is one of the pivotal assets with regards to this task and it will be necessary to use them efficiently in the context of the Action. Powerful synthetic strategies will be established and executed to provide the desired modification to bioactive NP by total synthesis or semi-synthesis. Tools for precursor-directed synthesis and muta-synthesis will be developed in order to access genetically modified NP within the production platform. Isolation from plants or microorganism will be performed to gain rapid access to a wide variety of NP, while analytical protocols will be used to identify new compounds and to specifically enable large scale isolation of established NP. Large scale production will be accomplished by using flow-synthesis, based on the needs for particular NP and medical purposes.

5) *Functional characterization of NP leads*. The mechanism of action of NP leads delivered by tasks 2 to 4 will be fully elucidated in vitro and, if possible, in vivo using animal models in accordance with specific national and European ethical rules. The structural characterization of the complex between a given biological target and the respective NP lead may be addressed by means of X-ray crystallography or NMR spectroscopy. Novel drug delivery strategies will also be explored to improve the pharmacokinetic profile of NP leads. Outcomes of this task will be of significant interest to the wider scientific community. Providing NP leads is one of the key objectives of the Action (see Part B.3).

SMEs, large industrial partners or academic researchers are likely to be interested in supporting and/or performing the pharmaceutical development of NP leads that exhibit a particularly significant activity. In these cases, a dedicated task (task 6) is planned to facilitate the translation of research results into possible industrial applications for healthcare, which is a further aim of this

Action.

6) *Development of NP leads up to preclinical or clinical candidate stages*. In this optional task, toxicity of the NP leads may be evaluated in vitro and, if possible, in vivo. This task will include genotoxicity assays and profiling off-target activities such as hERG receptor blockade, along with cytochrome P450 enzyme inhibition or induction studies. Pharmaceutical properties of NP leads may be optimized (clearance, oral bioavailability, elimination of metabolic liabilities), while pharmacokinetic studies will be conducted using a combination of in vitro/in vivo correlation and allometric scaling methods. The most appropriate crystalline form to be dosed will also be studied. Information will be transferred in two directions between tasks to optimize the technology in an efficient and timely manner.

D.2 Scientific work plan methods and means

This Action aims to stress the relevance of multidisciplinary WGs in drug discovery by establishing four WGs, one of which focuses on NP chemistry and related technical issues and three others focus on specific therapeutic targets. Information will be transferred within each WG and across different WGs sharing common tasks and methods. Each researcher will collaborate closely with colleagues from the different disciplines, stimulating interdisciplinary networking on all levels. This work plan engages all WGs at the same time and keeps them scientifically active for the duration of the Action.

WG1 – Optimization of NP chemistry/isolation/purification/characterization. NP are highly promising candidate therapeutic agents to fight infection diseases and cancer. Ultimately, access to natural products in sufficient quantities, in order to use them efficiently in the context of this COST Action, will be one of the pivotal assets of WG1. Natural product drug discovery typically starts with crude solvent extracts from various source organisms. This is followed by pre-fractionation and then analysis of the fractions, using either biochemical or cell-based assays. In particular, isolation through fermentation from cultivated microorganisms requires improved concepts and strategies. The isolation of active compounds has been facilitated by enormous progress in analytical techniques, in particular separation methods and mass spectrometry. A general analytical tool that can be used for de-replication when cultivating known or unknown strains will be set up by WG1. The HPLC-MS based de-replication will be used to identify new compounds and specifically to enable large scale isolation of established metabolites. Additionally, cluster analyses will help to identify related but unknown metabolites in fermentation broths. This sets the basis for a general

fermentation unit that has to be available either directly or indirectly for all members in the Action. Once an interesting molecule is discovered, chemists will perform the chemical synthesis to prove its structure, prepare analogues and possibly provide sufficient material for further studies. In this regard, novel synthetic methods and their clever combination will be explored by WG1 to gain access to specific compounds. With regard to the preparation of NP analogues the use of muta-synthesis has delivered promising results in some cases. Complementary to the large scale fermentation, large scale production by chemical syntheses will be established. This will include a large scale production pipeline combined with more efficient access using flow-synthesis.

WG2 – Viral Infections. Viruses are microscopic organisms responsible for several pandemic human diseases, one of the most serious and prevalent being AIDS, which is caused by infection with HIV. The major clinical limitation to treatment of HIV is the onset of drug resistance, i.e. the ability of HIV to mutate and overcome the effects of a given drug. The Action will address this problem by designing more potent and selective NP inhibitors of validated anti-HIV targets (entry/fusion, Reverse Transcriptase, Integrase and Protease) and efforts will be made to discover NP inhibitors of new promising HIV targets, such as the Viral infectivity factor (Vif), the Negative Regulatory Factor (Nef) and the capsid protein (CA). Besides HIV, other viruses that cause widespread disease and offer multiple opportunities for drug discovery will be investigated, such as Hepatitis C Virus (HCV), influenza, papilloma and Dengue viruses and adenoviruses. The relative abundance of experimental data concerning the structures of viral target proteins and their drug resistant mutants facilitates the use of structure-based strategies for NP screening and optimization. Particular attention will be given to the identification of NP and derivatives possessing activities against drug resistant viral strains. To this end, cells infected with viral strains resistant to common drugs will be cultured and used to monitor the efficacy of antiviral NP.

WG3 – Cancer. Cancer still remains one of the most serious human diseases of the modern era. NP have played a key role in targeting the proliferation of cancer cells. For example, Valproic acid has been shown to inhibit Histone Deacetylase enzymes (HDACs) thus serving as a potential effective drug for cancer therapy. Accordingly, epigenetic targets will be addressed by WG3. Recently, targeting CSC has provided impressive outcomes for some cancer types, as underlined by the recent FDA approval of Vismodegib, a Hedgehog (Hh) inhibitor targeting CSC. Notably, several Hh inhibitors are under preclinical and clinical investigation as well as NP or their derivatives that function as allosteric modulators of the Smoothened receptor have been identified, which renders the Action particularly suitable for addressing this topic. The Action will make use of the large

body of knowledge concerning NP chemistry to discover and optimize NP targeting the Hh pathway at different levels. WG3 will address also tubulin, an excellent target for inspiring the search, synthesis and optimization of NP with therapeutic potential. Most of the compounds targeting tubulin, including all those in clinical use, come from natural sources. Indeed, compounds toxic against tubulin are a good universal defence mechanism against predators, so they are used by plants (paclitaxel, vinblastin, colchicines, taccalonolides), bacteria (epothilone), marine sponges (laulimalide, peloruside, discodermolide, sarcodyctins, zampanolide) to confer toxicity to these organisms and deter potential predators. Several different cancer cell lines and biochemical tools as well as animal models, if applicable, will be used by WG3 to monitor the effect of NP leads on cancer. Other anticancer targets will be investigated by WG3 to address therapeutic need and will allow/require incorporation of additional research groups in to the Action at the appropriate time.

WG4 – Tuberculosis. Although tuberculosis is considered to be a global health emergency, fewer pharmacological targets have been validated than in the cases of the topics addressed in WG2 and WG3. Consequently, the Action will attempt to validate innovative and promising targets for pharmacological intervention, with a particular emphasis on those involved in multi- and extensive-drug resistance. WG4 will concentrate on the development of NP inhibitors of the Mtb InhA enoyl reductase, a highly druggable protein validated clinically by the prodrugs isoniazid and ethionamide and inhibited by Pyridomycin and other NP. Moreover, NP have shown significant abilities to inhibit exoenzymes secreted by the Mtb such as PtpA and PtpB, which will be therefore studied by WG4. These enzymes present a unique opportunity to target Mtb without necessarily crossing the MTB cell wall, which is very difficult to penetrate using small molecules. Other targets such as for example the O-acetyl serine sulfhydrylase, L,D-transpeptidase, nitrite reductase, RipA and RipB, PknA and PknB Mtb kinases will be investigated by HTS, structural studies and enzymatic assays. In vitro assays on macrophage cell lines and non-replicating and intracellular Mtb and ex-vivo tests on Mtb infection of activated THP1-derived macrophages will be also used to profile NP as anti-TB leads.

E. ORGANISATION

E.1 Coordination and organisation

The Action will provide the means to promote and perform the activities required for the effective concerted collaboration of the scientists involved. The organization of the Action will follow the

rules and procedures for implementing a COST Action, described in the document COST 4114/13. Research will be performed and financed by the participating countries, while COST will provide support for the networking activities. The MC will monitor the milestones achievements and timeline. Specific examples of organizational milestones that are crucial for the future direction of the Action have been identified as follows (in brackets: months necessary for milestone achievement from the Action beginning):

M1) to establish the MC and starting of the Action (1st MC meeting) (t0)

M2) to establish WGs focusing on specific therapeutic needs (t3)

M3) annual Action meetings (t12, t24, t36, t48)

M4) training schools (t24, t36, t48)

M5) WG meetings (t12, t24, t36, t48)

M6) Teaching materials, documentation on NP leads (t48)

An Action-specific website will be created and kept updated in order to maintain a continuous flow of information to the wider scientific community regarding the activities of the individual research groups and the WGs and to ensure the necessary dissemination and exploitation of Action outcomes. Any scientific achievements that might give to Europe a competitive advantage will be patented before disclosure to the public. An area of the website with access restricted to Action participants will be created, to allow the Action Chair and the MC to monitor the progress of activities with respect to scientific achievements and timeline.

The Action will organise workshops, training schools and STSMs as well as MC and WGs meetings. Meetings and symposia bringing together scientists from all over the world will help to promote the visibility of the Action and to ensure its international standing. World leaders in NP research from outside of Europe will be invited to deliver plenary lectures at workshops and symposia.

E.2 Working Groups

Four interdisciplinary WGs as presented in Part D.2 will be created by connecting researchers with advanced skills in NP chemistry, computational chemistry, biology and pharmacology. Additional participants will be able to join a WG at any time. The composition of WGs will be approved and/or modified by the MC at the first meeting of the Action. Subsequent WG modification will be approved by the MC.

Each WG will be coordinated by a leading scientist with a recognized experience with respect to the WG core activity. The WG Leader will document any scientific progress and achievements and

relay technical, organisational or scientific issues that may arise to the Action Chair and the MC. WG meetings will be organized at least once a year to disseminate WGs outcomes and improve the collaborative network. External experts in the field, coming from both academia and industry, will be invited to WG meetings to contribute to the WGs scientific progress and objectives. Up to two Action meetings, but at least one, will be organized per year. WG and Action meetings will be arranged as open Workshops to stimulate discussion between scientific participants and to ensure active participation of early-stage researchers.

E.3 Liaison and interaction with other research programmes

The Action is partially complementary to the COST Action CM1106 with respect to some of the topics addressed by WG3. Scientists involved in CM1106 may be invited to act as external experts to the WG3 or to full Action meetings.

E.4 Gender balance and involvement of early-stage researchers

This COST Action will respect an appropriate gender balance in all its activities and the Management Committee will place this as a standard item on all its MC agendas. The Action will also be committed to considerably involve early-stage researchers. This item will also be placed as a standard item on all MC agendas.
This Action is convinced that balanced working environments will be of benefit; this not only applies to gender issues but also to the age and ethnicity of the participants and their co-workers. This Action will strive to ensure that the WGs and the pool of participating scientists reflects the diversity of European science with regard to gender, ethnicity and culture so that the Action encompasses the widest possible cross-section of talented scientists. Early-stage researchers will be involved in participating in the organization of training schools, STSM, WG meetings and other activities in the Action. Attention to the gender balance will be given in selecting WG Leaders, MC Chair and Vice-Chair, speakers at meetings as well as external invited experts.

F. TIMETABLE

	1st MC meeting	Workshop/MC meeting	WG meeting	STSM	Training school	Closing Conference
Year 1	X	X	X	X		
Year 2		X	X	X	X	
Year 3		X	X	X	X	
Year 4		X	X	X	X	X

G. ECONOMIC DIMENSION

The following COST countries have actively participated in the preparation of the Action or otherwise indicated their interest: AT, BE, BG, CH, CZ, DE, DK, EL, ES, FI, FR, HU, IE, IT, LU, NL, NO, PL, PT, SE, TR, UK. On the basis of national estimates, the economic dimension of the activities to be carried out under the Action has been estimated at 88 Million € for the total duration of the Action. This estimate is valid under the assumption that all the countries mentioned above but no other countries will participate in the Action. Any departure from this will change the total cost accordingly.

H. DISSEMINATION PLAN

H.1 Who?

This multidisciplinary Action will be of great interest to the general scientific community, which is the target audience for Action outcomes as well as the main recipient of the dissemination plan. Scientific results should also be very relevant for policy makers at the European and National Government levels because these results could drive significant changes in the economic efforts required to combat many diseases that compromise the welfare of the society. Therefore, different levels of target audience for the Action will be considered in the dissemination plan:

- the broad scientific community, including both academia and industry;
- early-stage researchers;
- parties directly involved in the Action;
- policy makers;
- private investors;
- press/media agencies;

- national and European industries active in the areas of NP, synthetic chemistry or drug discovery;
- non-profit organizations dedicated to therapeutic needs addressed by the Action;
- the general public, independent of their level and/or field of education.

H.2 What?

Action outcomes and activities will be disseminated by using of the following instruments:

- an updated Action website with a dedicated newsletter service;
- publication of research results through original research articles, reviews, communications, perspectives and other types of papers in high-quality international peer-reviewed journals;
- publication of books, book chapters or special issues on topics related to the Action;
- organization of training schools;
- organization of meetings, workshops, conferences.

H.3 How?

In addition to the results being made available to all parties of the Action, additional dissemination to the public will be guaranteed through publication of research papers, and an Action-dedicated website. The following actions will be undertaken to ensure the broadest dissemination:
Creating an Action Logo. The Action logo shall be clear and concise and clearly transmit the basic essence of the networking activity established by the Action. The logo will reflect the Action identity and will be used along with the COST logo to mark all official documents released within the Action, as well as presentations at meetings and conferences held by Action members.
Launching the Action website. The Action website will permit the circulation and dissemination of documents to a wider audience. Internal documents such as meeting minutes, scientific results, progress of tasks and WGs will be made available to Action participants through a restricted access area. The website will also serve as source of information and contact point for stakeholders including academic and industrial researchers, possible investors or press agencies and will be updated at least on a monthly basis under the guidance of the Action Chair. Links to all institutions involved in the Action will be available and will be accessible from a dedicated section accessible from the Action webiste.
Dissemination materials. Newsletters will be sent to subscribers of the service (which will be free)

on a periodic basis, to provide updates on the progress of the Action as well as to announce scientific publications, Action press releases or the organization of workshops/meetings, and the participation of Action scientists in conferences dealing with topics related to the Action. The newsletter service will be used to disseminate news and updates to stakeholders in a rapid fashion.

Publications. The Action aims for the publication of scientific results in high-quality international peer-reviewed journals. The contents of conferences and the material presented at training schools will be published in specific books to disseminate the information at different levels and to a variety of audiences. Preparation of articles directed to a more general audience and published in non-specialist journals will enable the Action to expand public knowledge and to engage with policy makers at national and European levels.

Meetings, Conferences and Workshops. Action meetings and WG meetings will be organized to present Action activities and results. These meetings will be organized as workshops for discussion and will be open for participation to external researchers from academia and industry. Concrete solutions to problems encountered in NP chemistry and the related drug discovery process will be addressed. This should encourage and stimulate early-stage researchers to discuss scientific matters with expert researchers. These workshops will represent a unique opportunity to disseminate Action results and methodologies, and to take advantage of potential synergies with other researchers. The dissemination plan will be updated during MC meetings depending on the progress of the Action and the results achieved.