Brussels, 30 October 2015

COST 067/15

**DECISION**

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Subject: **Memorandum of Understanding for the implementation of the COST Action "Multi-target paradigm for innovative ligand identification in the drug discovery process" (MuTaLig) CA15135**

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The COST Member Countries and/or the COST Cooperating State will find attached the Memorandum of Understanding for the COST Action Multi-target paradigm for innovative ligand identification in the drug discovery process approved by the Committee of Senior Officials through written procedure on 30 October 2015.

**MEMORANDUM OF UNDERSTANDING**

For the implementation of a COST Action designated as

**COST Action CA15135**
**MULTI-TARGET PARADIGM FOR INNOVATIVE LIGAND IDENTIFICATION IN THE DRUG DISCOVERY PROCESS (MuTaLig)**

The COST Member Countries and/or the COST Cooperating State, accepting the present Memorandum of Understanding (MoU) wish to undertake joint activities of mutual interest and declare their common intention to participate in the COST Action (the Action), referred to above and described in the Technical Annex of this MoU.

The Action will be carried out in accordance with the set of COST Implementation Rules approved by the Committee of Senior Officials (CSO), or any new document amending or replacing them:

a. "Rules for Participation in and Implementation of COST Activities" (COST 132/14);
b. "COST Action Proposal Submission, Evaluation, Selection and Approval" (COST 133/14);
c. "COST Action Management, Monitoring and Final Assessment" (COST 134/14);
d. "COST International Cooperation and Specific Organisations Participation" (COST 135/14).

The main aim and objective of the Action is to promote European interaction among Medicinal Chemistry research groups. The goal is to speed up the discovery process of novel therapeutic agents against multiple targets, combining competencies from synthetic chemistry, natural products and biophysics, to theoretical chemistry, molecular modelling and biological screening. This will be achieved through the specific objectives detailed in the Technical Annex.

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 20 million in 2015.

The MoU will enter into force once at least five (5) COST Member Countries and/or COST Cooperating State have accepted it, and the corresponding Management Committee Members have been appointed, as described in the CSO Decision COST 134/14.

The COST Action will start from the date of the first Management Committee meeting and shall be implemented for a period of four (4) years, unless an extension is approved by the CSO following the procedure described in the CSO Decision COST 134/14.



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## OVERVIEW

**Summary**
The aim of this COST Action is to join highly-qualified research teams working in disciplines around the field of medicinal chemistry, into a novel network devoted to the multi-target issue in drug discovery. The choice of this theme is related to its marked multidisciplinary character, which can ensure a strong interaction among all COST Action participants. Currently, an important and emerging issue in modern drug discovery is to design novel or identify existing bioactive compounds, endowed with the capability to interact selectively with two or more macromolecular targets, exerting their effects against certain therapeutic goals in a synergic fashion. This leading concept stimulated this COST Action focusing on novel ligands able to recognize selected multiple targets, to promote closer scientific links among European research groups involved in medicinal chemistry field at both academic and industrial level. The research competencies of the network will span around medicinal chemistry, from synthetic chemistry, natural products and biophysics to theoretical chemistry, molecular modelling and biological screening.

| **Areas of Expertise Relevant for the Action** | **Keywords** |
|---|---|
| ● Chemical sciences: Theoretical and computational chemistry<br>● Chemical sciences: Organic chemistry<br>● Chemical sciences: Databases, data mining, data curation, computational modelling<br>● Basic medicine: Pharmacology, pharmacogenomics, drug discovery and design, drug therapy<br>● Chemical engineering: Medicinal chemistry, drug synthesis | ● Medicinal Chemistry<br>● Multi-target paradigm<br>● Lead identification<br>● Chemical databases<br>● Lead optimization |

**Specific Objectives**
To achieve the main objective described in this MoU, the following specific objectives shall be accomplished:

Research Coordination
● Improve the development of a modern Drug Discovery strategy based on the multi-targeting paradigm.
● Increase the scientific connections and collaborations among European research groups using different scientific backgrounds and approaches (medicinal chemistry, synthetic, natural products, biophysical, biological and theoretical) in the field of Drug Discovery.
● Foster lead discovery process using structurally-defined biological macromolecules as driving models for fast identification of new multi-target ligands able to exert synchronized pharmacological activities.

Capacity Building
● Promote the creation of a large European Chemotheca made available by Chemistry research groups assembled by this Action (over 10000 compounds).
● Characterize, by means of pharmacophore models and other computational methods, a large set of biological targets identified as appropriate for multi-target drug discovery.
● Include the participation of Inclusiveness Target Countries and involve Early Career Investigators in the COST Action.


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# DESCRIPTION OF THE COST ACTION

## 1. S&T EXCELLENCE

### 1.1. Challenge

#### 1.1.1. Description of the Challenge (Main Aim)

The multi-target paradigm has recently became a relevant issue in the drug discovery process, that is strongly supported on the multidisciplinary convergence around the Medicinal Chemistry field. The challenge of the COST Action "Multi-target paradigm for innovative ligand identification in the drug discovery process" (MuTaLig) is to promote the interaction among research groups working in Medicinal Chemistry field in European academic and industrial institutions. The goal is to speed up the discovery process of novel therapeutic agents exerting their activity against multiple targets with complementary biological effects. In order to achieve this purpose, the COST Action promotes the creation of a dynamic and unique chemical database based on in house compounds, which will be extended with the inclusion of their metabolic tree. This innovative idea will require the concurrent interest of research competencies spanning around medicinal chemistry, from synthetic chemistry, natural products and biophysics, to theoretical chemistry, molecular modelling and biological screening.

#### 1.1.2. Relevance and timeliness

Relevance

Several examples about the relevance of the multi-target issue in drug discovery can be highlighted. Most burden pathologies in Europe, such as cancer, cardiovascular or neurological diseases, have complex and multifactorial etiologies. The pathophysiological mechanisms involved in these disorders are, by definition, diverse, and a therapeutic innovative solution is required to attain and modulate multiple macromolecular targets (enzymes, receptors and/or nucleic acids). Multikinase inhibitors sunitinib and sorafenib are a successful example of multi-target drugs in cancer therapy. On the other hand, it is well known that side effects are based on the capacity of single drugs, or its metabolites, to exert nonbeneficial multiple target interactions. Many other examples can definitely demonstrate that the paradigm of concurrent involvement of several targets can be followed for a better use of the drugs presently in therapy and to the design of novel compounds with synergistic pharmacological properties. The strategy of repurposing already approved drugs is another natural consequence of its application in the drug discovery programs within academic and industrial research teams.

Timeliness

In order to scientifically address the impact of terms "multitarget" and "polypharmacology", a Scopus search was carried out using as filters "all years < 2015" and document types "Articles and Reviews". This query generated 2087 documents (Figure 1). In the last decade this area has clearly increased its impact, especially after 2008. From 2011 the average number of articles and reviews is about 20 per month. Undoubtedly, this issue is recognized as an "hot-topic" in the international scientific community.

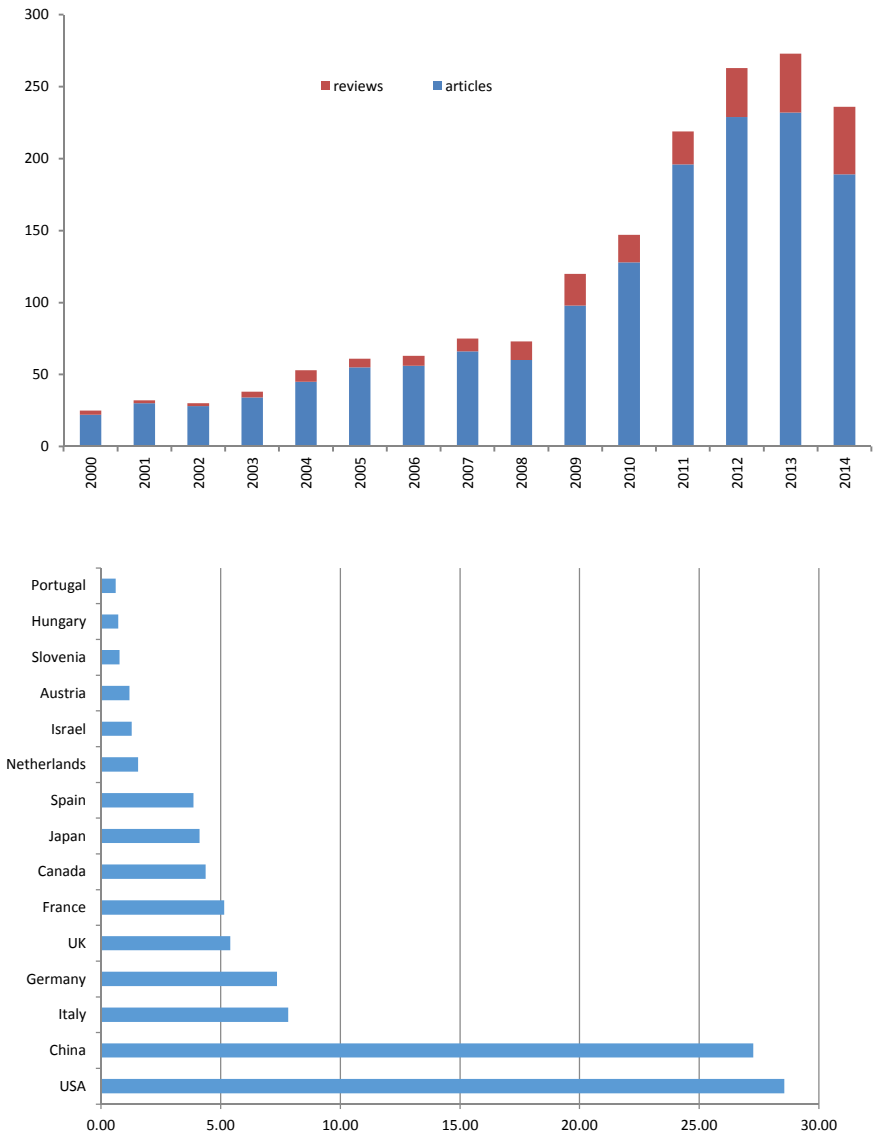


**Figure 1:** Distribution of publications matching the "multitarget" and "polypharmacology" queries in the last 15 years (top histogram) and in top 15 countries (bottom histogram) in %.

Regarding the countries of origin of these selected documents, USA and China are the most active, followed by a list European nations, such as Italy, Germany, UK and France. The idea to create a European network on 'Multi-target paradigm for innovative ligand identification in the drug discovery process'' using the COST Action as a joining driving force has been motivated from this analysis.

## 1.2. Specific Objectives

### 1.2.1. Research Coordination Objectives

Considering the "multi-target issue", and its important role in the Drug Discovery process, the main goals of this COST Action can be listed in the following "SMART objectives":

1. Improve in a new COST European network the development of a modern Drug Discovery strategy based on the multi-targeting paradigm. This first Research Coordination Objective is **specific**, as it is related with a well-defined field of Drug Discovery. It is **measurable**, since vivid



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research activity is observable through bibliometric analysis in this area. It is **achievable**, because there is an increasing interest in this topic. It is **relevant**, due to the noteworthy implications of its success in health and life sciences and a network in this specific field doesn't exist yet. It is **timely**, since some research groups in Europe are already working in multi-target approach in the Drug Discovery field, but often without a clear European synergetic strategy.

2. Increase the scientific connections and collaborations among European research groups using different scientific backgrounds and approaches (medicinal chemistry, synthetic, natural products, biophysical, biological and theoretical) in the field of Drug Discovery. This second Research Coordination Objective is **specific**, since it regards the improvement of particular scientific frontline. It is **measurable**, since the research products in this field can be analytically determined. It is **achievable**, because the participants must be highly-qualified research teams. It is **relevant**, because it ensures a multidisciplinary attitude. It is **timely**, since Europe can improve and consolidate its leadership in this field.
3. Foster lead discovery process using structurally-defined biological macromolecules as driving models for fast identification of new multi-target ligands able to exert synchronized pharmacological activities. This third Research Coordination Objective is **specific**, since it will allow the identification of ligand-target relationships using an innovative approach. It is **measurable**, since the number of new ligands, certified after appropriate biophysical and biological tests, can be analytically determined in all steps of the project. It is **achievable**, because in some cases ligands are already available and not yet screened against multiple targets and in other cases they will be designed and synthesized by the research groups participating in the Action. It is **relevant**, because multi-target effects can explain synergies of action as well as side effects of many biological ligands and/or metabolites. It is **timely**, since this approach can speed up the Drug Discovery process and the development of new drugs for diseases that have no therapeutic solution yet. Biologic assays will be performed by in-house capabilities of the network partners or by including other actors that are experts in the field.

### 1.2.2. Capacity-building Objectives

1. Promote the creation of a large European Chemotheca made available by Chemistry research groups assembled by this Action (over 10000 compounds). The profile of the proposed chemical library will be different from other existing databases, since it will be based on in-house compounds of the participants including the metabolic three predicted by in silico methods. This first Capacity-Building Objective is specific, since it regards the creation of a chemical library within an innovative European network. It is measurable, since the chemical collection can be analytically determined in all steps of the project. It is achievable, because most of participants have, by definition, a set of their own compounds already available to be included into the Chemotheca and a significant number of new compounds or optimized leads will be synthesized during the Action life-time. It is relevant, because it guarantees a rapid exchange of the scientific information within the network and more generally to the scientific community. It is timely, since the chemical database tool is a reality that can contribute to speed up Drug Discovery process.
2. Characterize, by means of pharmacophore models and other computational methods, a large set of biological targets identified as appropriate for multi-target drug discovery. This second Capacity-Building Objective is specific, since it regards the use of particular approaches, such as receptor mapping methods, for classifying the biological targets. It is measurable, since the biological catalog can be analytically determined in all steps of the project. It is achievable, because all models will be selected from scientifically certified sources, such as the Protein Data Bank. It is relevant, because it regards key targets implicated in widely diffused diseases. It is timely, since the pharmacophore tools are a reality in the Drug Discovery process.

Specific objectives, tasks, milestones and deliverables are analytically described for each Working Group in the section 3.1.1. of this document.



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## 1.3. Progress beyond the state-of-the-art and Innovation Potential

### 1.3.1. Description of the state-of-the-art

Drug discovery is a key step in the development of novel therapeutic agents. The overall process is usually a very long trek, which can take 12–15 years and very expensive, sometimes in the order of billions of euro. Only a very limited number of candidates (sometimes only one) can fulfill all steps of the drug discovery and development process. If attrition happens in a late step of the process, when a lot of investments have already been done, the failure is even worse. So there is in the area an increasing pressure to advance with new skills, able to overcome or reduce the failure risk of this complex process.
In a new drug discovery vision has been proposed- “a balanced modulation of several targets can provide a superior therapeutic effect and side effect profile compared to the action of a selective ligand”.
It was proposed a sort of new drug design decalogue, suggesting the need of the re-evaluation of the “one disease-one-drug” paradigm, commonly used in the drug discovery processes of the past few decades. The same authors, in a perspective report, show how the identification and validation of new target combinations constitute a new attractive paradigm from both a disease-relevance and druggability point of view, as posted in several medicinal chemistry case studies.
More recently, they have catalogued bioactive compounds in three groups: designed multiple ligands (DMLs), nonselective or “dirty” drugs and molecules with off-target activities, irrelevant to the disease and frequently associated to deleterious side effects.
Complementary, in 2007, it was proposed the use of fragment-based approach to multi-target drug discovery as leading approach to develop a new generation of compounds with improved physicochemical and pharmacokinetic properties. In 2011, another research group published a review article summarizing ligand- and structure-based methods for the identification of novel compounds endowed with multi-target activities.
They also described a semi-automatic pipeline pilot protocol to speed up the virtual screening approach. The concept of compound repurposing, quite relevant in academic as well as in private research groups, has been reviewed in the context of the multi-target paradigm application to drug discovery.
The creation of global phamacophore platform is considered quite important for target fishing purposes, as stated in another recent book chapter published in 2013.
In conclusion, the multi-target approach is definitively a “hot-topic” in modern drug discovery.

### 1.3.2. Progress beyond the state-of-the-art

Among the most emergent concepts to rationally speed up the drug discovery process, that of developing multiple target ligands is becoming popular in the last years. The reasons can be summarized as follows:

1. Public and private drug discovery institutions have collected a consistent number of novel compounds or intermediate synthons, declared as not useful against a limited set of targets.
2. Chemoinformatics has dramatically improved the ability to treat large amount of data allowing anyone to easily create its own “in-house chemical database”.
3. Metabolomics is a new scientific branch focused on the nature and the effects of chemical metabolites originated by biochemical reactions in the human body.
4. Structural biology improvements increased the knowledge about new and traditional targets, concurrently involved in many diseases.
5. *In silico* prediction of high-affinity ligand-receptor matches by means of different ligand/structure based approaches has improved its performances due a new generation of algorithms and hardware platforms.

### 1.3.3. Innovation in tackling the challenge

The innovation of the MuTaLig COST Action is based on the reasons listed in paragraph 1.3.2. Putting together the strong chemical background collected by academic and industrial participants into a novel and accessible European Chemotheca, expanded by the inclusion of metabolite tree, will enable the screening against most important structurally-known biomolecular targets by means of different biological and *in silico* methods, in view of a new paradigm in the modern rational drug discovery. Additionally, based on knowledge of involvement of different targets in disease networks, multi-target ligands will be designed and synthesized with the aim of achieving a synergic effect by modulation of several targets involved in a particular disease.

## 1.4. Added value of networking

In order to reach the goals of the Action, it is necessary to achieve collaboration of academic and industrial research groups. Training activities will allow participants, especially young Early Career Investigators, to enter into the paradigm of this COST Action using a holistic approach.

The network will consistently stimulate knowledge exchange within the research teams, simplifying the access to experimental and computational facilities among the participants.

The “Advanced Manufacturing and Processing” technology area, proposed within Horizon 2020, will be definitively advanced by the network established in this COST Action. This will set up, accordingly to the COST mission, a selection of different activities, such as Training Schools, Workshops, Short-Term Scientific Missions and Conferences.

### 1.4.1. In relation to the Challenge

The opportunity to involve into this Action qualified public and private research groups will ensure the rapid extension of the number of research teams involved in this COST Action. For example, over 30 research groups involved in the Paul Ehrlich MedChem Euro-PhD network belonging to 15 different European countries might be interested in the collaborative opportunities provided by MuTaLig COST Action. Research groups from other scientific societies and/or with complementary scientific backgrounds will be invited to take part in this COST Action, too. The fruitful interactions will lead to the creation of new chemical tools as well as ligands for translational applications that impact upon human society.

### 1.4.2. In relation to existing efforts at European and/or international level

There are two running COST Actions running that can be related to this Action. The first is CM1402 “From molecules to crystals - how do organic molecules form crystals? (Crystallize)”. The common section is related to some novel macromolecules, such as enzymes or other targets, resolved by experimental methods that can be used in this Action as starting point for the in silico simulations. The latter is CM1407 “Challenging organic syntheses inspired by nature - from natural products chemistry to drug discovery”, which can be related to the topic of natural ligands, but will not be connected with the in-house synthetic compounds and their metabolic derivatives.
So, this Action can complement the above mentioned Actions introducing the challenge of modern multi-target paradigm and also integrating with other international initiatives related with this novel European drug discovery strategy.



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# 2. IMPACT

## 2.1. Expected Impact

### 2.1.1. Short-term and long-term scientific, technological, and/or socioeconomic impacts

The most relevant impacts of this COST Action will be (a) to start new European interdisciplinary collaboration opportunities, (b) to promote the diffusion and the interchange of knowledge and skills among different research groups with expertise in chemical and biological sciences (c) to create a proactive European multi-target drug discovery platform. New synergies, often unfeasible with national resources only, will be established in the context of this innovative drug discovery field that is the main driver of this COST Action. The integration of scientific communities involved in drug discovery will improve the know-how and the definitions of best practices among research groups working on basic protocols of this approach. This COST Action will reserve a special attention to attract in Europe the best young researchers in drug discovery, promoting special training teaching programmes and the preparation of a textbook dedicated to the multi-targeting drug discovery strategy.
COST Action participants will also benefit of innovative carrier prospects in the medicinal and pharmaceutical fields, providing competitive advantage to European public and private Institutions and consequently promoting new Research and Development (R&D) investments in Europe.

## 2.2. Measures to Maximise Impact

In this section the most relevant stakeholders are identified and a plan to involve them as Actions' participants is presented. They are listed as follows:

1. Action's participants;
2. The Scientific Community working in the field of Medicinal Chemistry, with special emphasis to established networks in this area;
3. European PhD programmes related to all steps of drug discovery process;
4. Companies working in the pharmaceutical, fine chemical, and biotech fields;
5. Policy makers;

The general public, including students, secondary school students and their teachers.

### 2.2.1. Plan for involving the most relevant stakeholders

The Action's participants are by definition the main actors exerting initiatives for expanding the network and the scientific impact of the Action. They will be proactive to attract research groups of members of established Scientific Communities networks and societies, such as the Paul Ehrlich MedChem Euro-PhD network or the European Federation for Medicinal Chemistry. Since the multi-target aspect topic in drug discovery learning processes might be inadequately present in training of young researches, special attention should be paid to involving European PhD programmes, with curricula in Medicinal Chemistry and/or Drug Discovery. Likely the most relevant stakeholders to be attracted by this COST Actions are the pharmaceutical, fine chemicals and biotech companies. The strategies to involve them will follow two different arguments: a) the former is toward the recycling and repositioning of proprietary chemical entities for novel applications, i.e. targets not considered in previous drug discovery programs; b) the latter is dedicated to the metabolomics consequences of analysis carried out considering the metabolic tree generated from proprietary in-house chemical databases.

### 2.2.2. Dissemination and/or Exploitation Plan

The dissemination is a key goal of this COST Action. The target audience will be addressed with different approaches. Scientific traditional publications (papers in peer reviewed journals, oral and poster presentations) will be the primary form to take into account for an effective and qualified propagation of the COST Action results. Young researches and participants will definitively prefer

web-based information, so dynamic Action website and social network sites will be implemented from the beginning and for the entire period of the Action. Typically, the activities for disseminating the results of the research groups will include conferences and workshops. Training Schools and Short-Term Scientific Missions (STSMs) will be dedicated to knowledge propagation and exploitation finalities. Electronic documents, such as meeting and annual reports will be posted on the Action's website. Printed documents, such as the final report of the Action, will be sent to the involved stakeholders. Additional information, such as news, announcements, meeting schedules, working opportunities, videos, and non-commercial software downloading options, will be diffused on the Internet for all Action's participants.
Finally, the textbook dedicated to the multi-targeting drug discovery strategy of the COST Action will be promoted among all participating scientific teams, by means of the website and other social media.

## 2.3. Potential for Innovation versus Risk Level

### 2.3.1. Potential for scientific, technological and/or socioeconomic innovation breakthroughs

This COST Action puts together several high-qualified competencies in the hot-topic field of the multi-target drug discovery. Chemists and biologists are joined together to create a strong scientific interaction toward a common objective to increase the knowledge level in this field and also to facilitate the communication using language and arguments understandable for all participants. Often the lack of communication is a critical point for the unsuccess in this field, but the structure of the Action should help to solve this problem. Actually, the unquestionable interest to repurpose the participants' in-house compounds in the new scenario of novel biological targets is a good motivation to improve the contacts of chemistry toward the biology. Conversely, the expertise of biological and biophysical research teams specialized to test the activity of modulators against novel and structurally determined targets will push to favor the interaction of biology with the chemistry participants. These interactions will also contribute to design new multiple ligands, exerting synergistic actions in pathological states, i.e. smart molecules for multifactorial diseases. In other words, the multi-target paradigm represents an innovation opportunity for a up-to-date multidisciplinary collaboration, hopefully able to lead to a successful COST Action.
From the technological point of view this Action has special features. The creation of a European Chemotheca and the massive adoption of in silico methods for the prediction and implementation of metabolites into this database are intrinsically based on high-level technological contents.
From the socio-economical point of view the Action can contribute to speed up the drug discovery process. The consequence of the identification of new bioactive compounds, from the in-house, the metabolic or rationally designed derivatives, is definitively a great opportunity also in the socio-economical field. In this context, the interaction of public and private institutions can play a significant role for the success of this Action.

# 3. IMPLEMENTATION

## 3.1. Description of the Work Plan

### 3.1.1. Description of Working Groups

This COST Action is aimed to be focused on multi-target approach in drug discovery which is an emergent issue in Medicinal Chemistry. This goal requires an integrated team of experts clustered into four complementarity Working Groups (WGs), defined as outlined below. Each WG will collect a complete list of their research activities and expertise to share with the COST Action participants at the beginning of the activities, in order to consolidate the network collaborations and generate

new scientific ideas. This lists will be kept up-to-date by means of the Internet facilities dedicated to this Action.

*WG1: Development of new chemical entities*

WG1 Objectives
This Working Group will provide to Chemoteca new chemical entities, i.e. small organic molecules, preferably based on privileged scaffolds, obtained by means of synthetic traditional and advanced methods or by extraction from natural sources, such as plants, functional foods and microorganisms. This WG will also synthesize the multi-target ligands designed in WG 4.

WG1 Tasks
WG1_T1: up-to-dating synthetic routes applied to drug discovery programs;
WG1_T2: optimizing protocols for easy extractions of essential oils and nutraceuticals;
WG1_T3: synthesis, purification and physico-chemical characterization of bioactive compounds.

WG1 Milestones
WG1_M1: compiling the list of "'in-house" chemical entities;
WG1_M2: updating during the Action the list with new synthetic and/or extracted bioactive compounds;
WG1_M3: scaling up fine-tuning the decoration of the scaffolds, extraction in function of the predicted and/or experimentally determined activities or affinities toward multiple targets.

WG1 Deliverables
WG1_D1: reviewing and optimizing synthetic routes and extraction protocols to obtain compounds of interest;
WG1_D2: starting a chemical catalog program;
WG1_D3: providing with new chemical entities guided by scientific interactions with biologists and computational chemists belonging to other WGs.

*WG2: Selection of biological targets and assessment of biological data*

WG2 Objectives
This Working Group will focus on biophysical and biological tests able to distinctively measure affinities and activities of small molecule ligands against specific macromolecular targets, selected on the basis of their known roles in the pathophysiology of disease. The WG priority will be for bimolecular targets in disease networks, structurally resolved by NMR and/or X-ray experiments in presence of ligands complexed into their binding pockets.

WG2 Tasks
WG2_T1: selecting the therapeutically relevant molecular targets on the basis of structure availability and their role in disease networks;
WG2_T2: up-to-dating best biophysical test for the evaluation of ligands against selected targets;
WG2_T3: optimizing biological protocols for determining the target implication in vitro experiments.

WG2 Milestones
WG2_M1: compiling the list of the targets to be processed in silico by other WGs;
WG2_M2: updating the methods and procedures to biophysically characterize ligand-target interactions;
WG2_M3: optimizing procedures for fast and convenient in vitro biological tests of selected targets.


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WG2 Deliverables
WG2_D1: reviewing and optimizing biophysical and biological tests useful for measuring ligand affinities and/or activities;
WG2_D2: starting a biological catalog program;
WG2_D3: providing with optimized biophysical and biological tests able to simplify the scientific communication with experimental and theoretical chemists of other WGs; list of targets and their combinations relevant for the rational design of multiple ligands.

*WG3: Development of chemical databases*

WG3 Objectives
The standard of widely used chemical databases, such as Zinc and PubChem, will be adopted for the definition of "in-house" 3D catalogs using, as ligand entries, the compounds synthetized and/or extracted by the WG1 participants. Such a database (DB) will be not only limited to the list of proprietary compounds, but will include the large tree of metabolites computationally predicted by specific algorithms. The ultimate objective is the creation of the MuTaLig DB.

WG3 Tasks
WG3_T1: defining best file formats and requirements for an easy and exhaustive implementation of chemical databases based on the WG1 information;
WG3_T2: developing computational protocols for the metabolic prediction of the chemical DB;
WG3_T3: managing the MuTaLig DB for the COST Action and depositing it for further investigations The Chemoteca database will be maintained in order to serve the Medicinal Chemistry community at least for further two years after the Action conclusion.

WG3 Milestones
WG3_M1: compiling the chemical database of the COST Action based on "in-house" compounds;
WG3_M2: performing the metabolite prediction and extend the chemical database of the COST Action into the MuTaLig DB;
WG3_M3: identifying cross-references between the MuTaLig DB and other chemical databases.

WG3 Deliverables
WG3_D1: reviewing and optimizing computational tools for creating chemical databases.
WG3_D2: performing metabolite predictions from the "in-house" chemical catalog and finalize the MuTaLig DB.
WG3_D3: maintaining MuTaLig DB to new entry implementations.

*WG4: Development of Computational methods for multiple ligand design and discovery*

WG4 Objectives
This WG will investigate methods for handling large chemical databases created by WG3 and examine, using high-performing computational tools, the molecular recognition among itemized ligands and targets. Multiple ligands for selected sets of targets will be designed. Consensus analysis with comparative methods will define the priorities on the poly-pharmacodynamics properties.

WG4 Tasks
WG4_T1: selecting and testing the most effective computational tools (software and hardware) for intensive virtual screening simulations;
WG4_T2: performing intensive virtual screening simulations using as the MuTaLig DB against all selected target models;
WG4_T3: performing consensus analysis from multiple-target simulations and rational design of multiple ligands for chosen sets of targets.


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WG4 Milestones
WG4_M1: defining best protocol(s) for intensive virtual screening simulations;
WG4_M2: performing all-against-all simulations, i.e. all MuTaLig entries against all targets;
WG4_M3: generating a consensus report with indications about ligand and/or metabolites potentially active with multi-target properties.

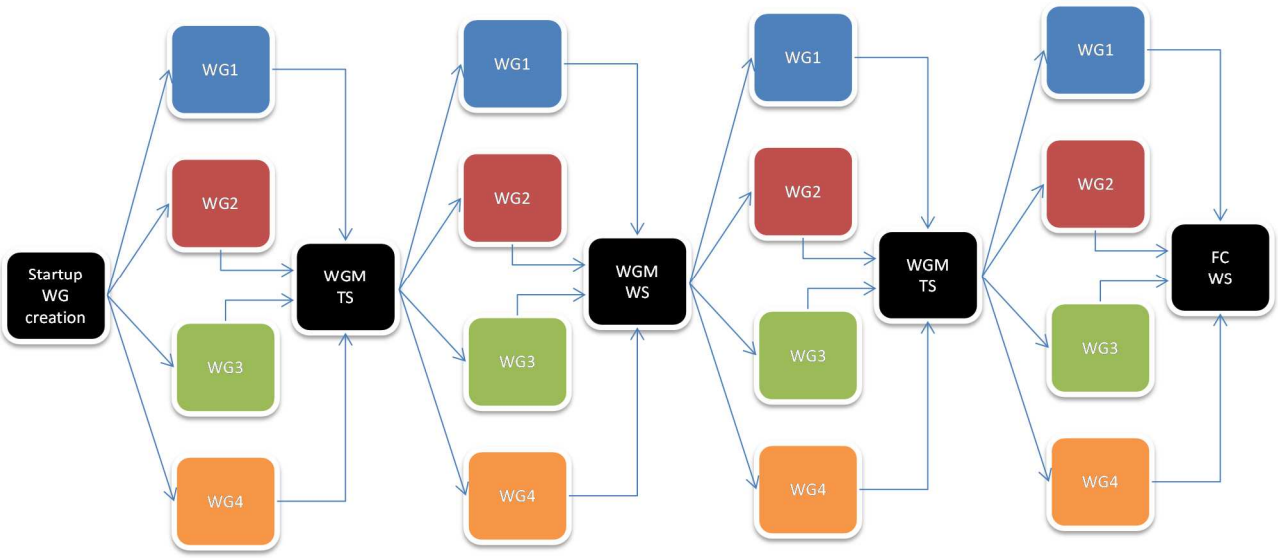
WG4 Deliverables
WG4_D1: Virtual screening protocols for intensive simulations validated and finalised;
WG4_D2: System for managing large virtual screening simulations validated and finalised;
WG4_D3: A defined set of optimal approaches for consensus analysis applied to multi-target based drug discovery paradigms.

### 3.1.2. GANTT Diagram

The activities are indicatively depicted in a period of four years. The Management Committee (MC) will determine the exact number of Short-Term Scientific Missions (STSMs), Training Schools, Meetings, Workshops, and Conferences. When possible, MC and WG meetings will be organized together, in order to contain the expenses. Core Group (CG) and MC meetings will be organized at least once per year and additional organizing contacts among participants will be established on the Internet.

| Activity/meeting | 1st year | | | | 2nd year | | | | 3rd year | | | | 4th year | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ¼ | ½ | ¾ | 1 | ¼ | ½ | ¾ | 1 | ¼ | ½ | ¾ | 1 | ¼ | ½ | ¾ | 1 |
| **WG Creation** | x | | | | | | | | | | | | | | | |
| WG1_T1 | | x | x | x | | | | | | | | | | | | |
| WG1_D1 | | | | x | x | x | | | | | | | | | | |
| WG1_T2 | | | | | | x | x | x | | | | | | | | |
| WG1_D2 | | | | | | | | x | x | x | | | | | | |
| WG1_T3 | | | | | | | | | | x | x | x | | | | |
| WG1_D3 | | | | | | | | | | | | | x | x | x | |
| WG2_T1 | | x | x | x | | | | | | | | | | | | |
| WG2_D1 | | | | x | x | x | | | | | | | | | | |
| WG2_T2 | | | | | | x | x | x | | | | | | | | |
| WG2_D2 | | | | | | | | x | x | x | | | | | | |
| WG2_T3 | | | | | | | | | | x | x | x | | | | |
| WG2_D3 | | | | | | | | | | | | | x | x | x | |
| WG3_T1 | | x | x | x | | | | | | | | | | | | |
| WG3_D1 | | | | x | x | x | | | | | | | | | | |
| WG3_T2 | | | | | | x | x | x | | | | | | | | |
| WG3_D2 | | | | | | | | x | x | x | | | | | | |
| WG3_T3 | | | | | | | | | | x | x | x | | | | |
| WG3_D3 | | | | | | | | | | | | | x | x | x | |
| WG4_T1 | | x | x | x | | | | | | | | | | | | |
| WG4_D1 | | | | x | x | x | | | | | | | | | | |
| WG4_T2 | | | | | | x | x | x | | | | | | | | |
| WG4_D2 | | | | | | | | x | x | x | | | | | | |
| WG4_T3 | | | | | | | | | | x | x | x | | | | |
| WG4_D3 | | | | | | | | | | | | | x | x | x | |
| MC meeting | | x | | x | | x | | x | | x | | x | | x | | x |
| Annual meeting | | x | | | | x | | | | x | | | | x | | |
| WG meeting **WGM** | | | | x | | | | x | | | | x | | | | |
| Training School **TS** | | | | x | | | | | | | | x | | | | |
| Workshops **WS** | | | | | | | | x | | | | | | | | x |
| STSMs | | x | x | x | x | x | x | x | x | x | x | x | x | x | x | |
| Final Conf. **FC** | | | | | | | | | | | | | | | | x |

### 3.1.3. PERT Chart (optional)



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### 3.1.4. Risk and Contingency Plans

The principal aim of this Action is to create a solid basis upon which to develop a joint-force research in the medicinal chemistry field. The goals devised in the corpus of this Action yield the importance of such research to all mankind. The need for contingency planning emerges from a thorough analysis of the risks that the challenge faces.
In devising a contingency plan all research-critical operations have been analyzed and ways to minimize possible losses have been outlined.

The following are the steps taken in performing an in-depth analysis of 'what could go wrong'.

- **Risk identification** - What has the potential to significantly disrupt or harm the Action?

**1. Waning Interest.**

This may be part of the natural progress of the project. Managing interest risk and having consistent motivation are two key aspects to bear in mind while tracing an efficacious risk identification analysis. Staying motivated is a struggle. Drive is constantly assaulted by research downtime and the following shortcomings:

- Lack of confidence

The best way to regain and boost confidence is to genuinely desire to create something valuable for the rest of the world and thus gain recognition and self-esteem.

- Lack of focus

Developing tangible focus: by defining a goal, and devising a set of actions to reach it. The key is moving from an intangible desire to concrete, measurable steps.

- Lack of direction

The final piece in the motivational conundrum is direction. If focus means having an ultimate goal, and a having a day-to-day strategy to achieve it. A lack of direction may bring WGs to succumb to procrastination.

**2. Technical Risk.**

Trouble in the creation and promotion of the "Chemotheca" mentioned in section 1.2 "Objectives", paragraph 3 of thisAction. Research groups may find the creation of a common chemical library far-fetched, impracticable and difficult to carry out. The overall implications could lead to painstaking efforts of implementation and the risk of lengthy procedures.
Once risks are targeted, the second step of the contingency plan can start.

- **Prioritizing risks** – The Action can respond quickly and effectively to a crisis situation when it occurs.

The risk will managed by using existing assets more effectively, or by investing in new resources or services that help manage it.



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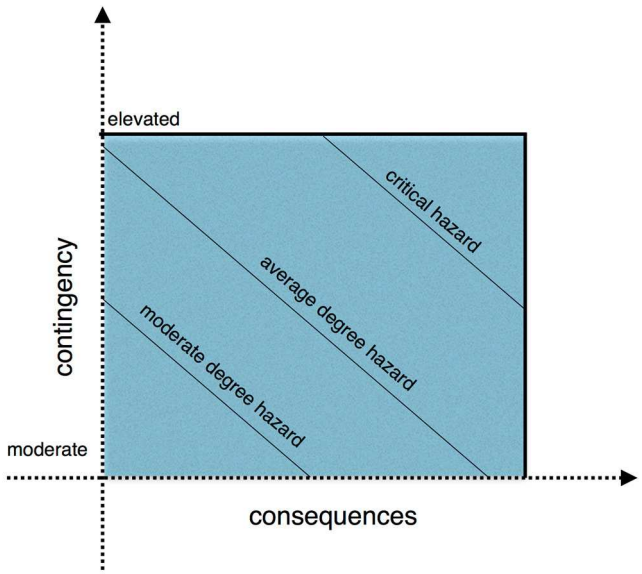


**Figure 2:** Contingency/Consequences graph.

Our Contingency/Consequences plan is based on the criterion that a hazard has two fundamental aspects:

A. Contingency – a risk is an issue that 'can' occur. The possibility that it may happen ranges from slightly above 0% to slightly below 100%.
B. Consequences – a hazard always has a certain unfavorable aftereffect. Nonetheless the breadth of the consequences ranges in terms of the cost and success of this COST Action.

Therefore, setting a priority in the risks of our project, the most plausible is that the participants may undertake the project with a certain amount of enthusiasm that could in time ebb.
The 1st identified risk, "waning interest", falls roughly within the "critical hazard" area of the graph and will be managed as follows. The contingency plan relies on the fact that a prize for those who maintain a certain amount of efficiency and work standard during the development of the project can be envisaged. The most interesting ideas and research activities will thus be published. A special agreement with the editor will envisage a special issue dedicated to the best researchers in the COST Action. This will be an open-access edition.
As for the 2nd contingency plan, that is the "technical risk", (roughly placed within the moderate degree hazard section, Figure 2), the WGs in the critical phases of the Chemotheca draft can be supported by offering them a protocol in order to create their own chemical database in SDF format. This will trigger motivation and help create databases for all the Working Groups with a certain amount of ease.

## 3.2. Management structures and procedures

The management and organisation of this Action will conform to "COST Action Management, Monitoring and Final Assessment" (COST 134/14) and "Rules for Participation in and Implementation of COST Activities" (COST 132/14). The Management Committee (MC) will coordinate, implement and manage the Action, as well as it will supervise the appropriate allocation and use of the budget.
The MC will guarantee and promote, among other things, a proper gender balance amongst participants.
All COST Member countries with their WGs will have a proper and thorough knowledge of the Action MoU to be endorsed by them. This Action will run for 4 years and during the first MC meeting the the MC will appoint the AC (Action Chair) and GH (Grant Holder) and the members of the Core Group.

Action Participation: All Action Participants will strive to achieve the purposes targeted in the MoU and will contribute to the respect of the COST Implementation Rules and the COST Vademecum. At first any conflict of interest, that could jeopardize the entire Action, will be determined. The MC will meet at least once per year to discuss progress, define and re-define operational guidelines and organize future activities. The AC will be the authorized channel between the Action and the COST Association. The Core Group will be made up as follows:

- Action Chair and Vice Chair
- Grant Holder
- Work Group Leaders
- Training Coordinator
- Short Term Scientific Mission Coordinator
- Webmaster and Dissemination Manager

This Core Group (CG) will prepare MC meetings, programs and records. The CG will also supervise the enactment of the Action, facilitate communication with the Scientific Community, , as well as disseminate the outcomes and activities. There will be a strong cooperation between all members of the CG.

To attract the interest of European scientists the Action will be broadly promoted through articles in relevant journals and webpages, at meetings, and through social network resources (e.g. LinkedIn, ResearchGate etc.).

WGs will preliminarily draw up lists of the current research actions and give account of their research members' know-how for all participants to acknowledge and subsequently disseminate all this on the Action website, facilitating group-work opportunities and the spreading of ideas. The list will be frequently updated to allow the monitoring of the Action's success.

The Website and Dissemination Manager will administer the Action website and will be in charge of keeping it up to date with all the new research findings. The website will include details of research skills, Action tasks and procedures including STSMs, Discussion Groups, Training Schools, dissemination, productions and reports. The site will have a dedicated section for Action members only where participants can interact and examine current research activities, designs for future projects and give exposure to results.

Some necessary requirements encompass (a) successful selection of all participants of the CG, (b) allocating participants in proper WGs, (c) creating new research partnerships, (d) disseminating periodical reports and (e) successful accomplishment of Action pursuits.

- Action Objectives: The Action objectives defined in section 1.2 and clearly illustrated in the Action MoU will allow the complete achievement of the goals.

Action Strategy and Structure: The Management Committee will be composed of up to two representatives from each COST Member Country or Cooperating State participating in the Action.

- Coordinate the publishing and use the abilities and expertise that may surface from the Action.
- Performing the reporting duties allowing for the Monitoring and Assessment of the Action as well as Financial Reporting.
- Establish which participants could be eligible for reimbursement.

## 3.3. Network as a whole

During the planning of the Action the network was based on research groups belonging to five different COST Countries. They are all working in the field of Medicinal Chemistry with different expertise. Their affiliations are from academia to private research institutions. This assembly can ensure the presence of an appropriate critical mass, since each of them can expand, within their existing collaboration partners, the size of the network with other qualified participants. The expertise of the participants is already different and individually related to specific issues of the Action. Even if the objectives and the challenges of the Action are not strictly related to the geographical localization, the participants belong to northern and southern European countries, so the diffusion of

the network in other European countries will be easily achievable. The Action includes the involvement of one Inclusiveness Target Country and COST Cooperating State
In conclusion, the Action is a whole entity built to treat scientifically and technically the hot topic of the multi-target paradigm in drug discovery with different competencies and cultural inputs.



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