

Secretariat

DRAFT FULL PROPOSAL

Reference: oc-2008-1-2102

Title: Functional peptidomimetic foldamers: from unnatural amino acids to self-assembling nanomaterials

A. ABSTRACT AND KEYWORDS

Among the non-natural polymers with the propensity to form well-defined secondary structures, the peptidomimetic foldamers are attracting increasing attention. These compounds have found various biomedical applications and their self-assembling systems can form nanostructured materials. The project aims to develop the peptidomimetic foldamers into a technology platform in drug discovery and biomedical applications, which can yield novel drug candidates targeting cellular circuitries being non-druggable thus far with the small molecule or antibody approaches. The challenges addressed in this action are: (i) efficient enantioselective synthesis of building blocks; (ii) stabilizing foldameric secondary structures with chemically diverse side-chain patterns; (iii) efficient synthesis of foldamer libraries; (iv) extensive biological screening of the foldamer libraries on pharmacologically relevant targets; (v) controlled self-assembly of foldamers into functional nanostructured particles.

Keywords: foldamers, peptides, biomimetics, unnatural amino acids, nanomaterials

B. BACKGROUND

B.1 General background

Definition of the research topic. The macromolecules and ligands responsible for the functioning of living organisms are basically built up from a very restricted number of building blocks (e.g. alpha-amino acids and nucleic acids). Proteins with a propensity to fold into well determined hierarchical 3D structures, such as enzymes and receptors, have developed in Nature in an evolutionary time scale. However, scientists now have a clearer picture of the background to these developments: the principles of protein design are not restricted to the realm of the heteropolymers of alpha-amino acids, but can be generalized and extended to any polymer with a tendency to fold into the periodic and/or specific compact structures referred to as foldamers. Such foldamers include synthetic oligomers constructed from unnatural amino acids (AAs) with more than one carbon atom (beta- and gamma-AAs) in the backbone and also from aromatic AAs. In the proposal these building blocks are designated as homologated amino acids (HAAs).

Folded polymers are used in Nature for vital processes, from catalysis to information storage, cellular

signaling, and molecular transport. Non-natural folded polymers, or foldamers, have the potential for similar versatility, and the design of such molecules is of considerable current interest. Peptidomimetic foldamers are the best-characterized systems, as they populate a wide array of side-chain controllable secondary structures (a number of helix types, sheet forming strands and turn motifs), and they can be exploited as rigid and easily tunable molecular scaffolds. These molecules are unique among molecules of synthetic or natural origin, because they behave as a link between the world of small molecules and macromolecules.

Foldameric helices closely similar to the alpha-helix have potential as biomimetic materials in biomedical research. The most attracting applications of this paradigm are in drug discovery, which can yield novel drug candidates targeting cellular circuitries being non-druggable thus far by using small molecule or antibody approach. Peptidic foldamers are useful tools in drug discovery, because they withstand the hydrolase enzymes, and due to their modular structure, they are ideal candidates in a combinatorial approach. The key building blocks are the unnatural amino acids (AAs) with more than one carbon atom (beta- and gamma-AAs) in the backbone (homologated AAs, HAA) including aromatic amino acids, which are important in themselves for the preparation of modified analogues of biologically active peptides. A highly interesting aspect is the foldamer's self-assembly: nanostructures from foldamers with tailored secondary structures can be prepared by propagating the noncovalent forces over a longer scale to create ordered materials. These peptidomimetic self-assembling systems can have biomedical applications (eg. stimuli responsive drug delivery systems).

Need for a COST Action. An emerging field will be covered in a coordinated action. These intriguing molecules with tailored properties and potential biological activities, are anticipated to elegantly solve problems in the fields of biology and chemistry. To achieve success on the application side, an interdisciplinary approach is necessary. An efficient research pipeline requires close cooperation between the following fields: organic synthesis of novel HAAs, foldamer design and synthesis, structural characterizations, computer-aided drug design and biological screening. Cross-fertilization between the participants with different expertise and common goals will result in a well defined and targeted research. Implementation of a COST Action would be effective, since the lack of interdisciplinary communication channels in this field is a more imminent problem than lack of research funds.

To realise the above objectives, a COST Action is the most appropriate instrument. Based on a cross-cutting focus of this Action, synergies can be developed only by a bottom-up network. The planned meetings, workshops and the exchange of young scientists will lead to exchange of knowledge (from the synthetic procedures to highly sophisticated structure analysis) and the development of new strategies and ideas for individual projects within the Action. The state-of-the-art clearly shows that a wide European network is needed in this area. Also, an important feature should be the open access for new participants, clearly a characteristic of the COST programme. This action would facilitate reaching the critical mass to develop the foldamers to a readily available technology platform.

B.2 Current state of knowledge

Current state of the art. An understanding has been developed of the importance of noncovalent interactions in regulating protein folding, assembly and catalysis; these concepts have now been put to the test through the successful computational design of proteins from scratch. However, the rules used in these studies have been largely developed with peptides and proteins composed of alpha-amino acids, which leads to the question of whether our understanding is overly parameterized and specific to conventional peptides, or whether it is truly general in nature. To address this question, systems were extended to the new nonbiological structures, thereby critically testing our understanding of biological structure while simultaneously developing new building blocks and molecular frameworks for the design of pharmaceuticals, diagnostic agents, nanostructures and catalysts. By changing the identity of the backbone, we enter into fundamental questions regarding rules of folding; hence the recent interest in foldamers.

Because of the diversity of sizes, shapes and arrangements available with non-natural monomers, this field offers an astronomical number of combinations for designs of molecular interaction modules supported by foldamer frameworks. The creation of these frameworks has already resulted in many intellectually useful and functionally interesting molecules. So far, a number of promising biological applications have been published where the secondary structure of designed foldamers was essential, such as foldamers capable of mediating cell penetration, inhibitors of fat and cholesterol absorption, selective antibacterial amphiphiles, RNA binding and inhibitors of the interaction between the tumour suppressor p53 and the sequestering factor hDM2. Foldamers have a potential to constitute a novel class of drug scaffolds having designable molecular shape and surface chemistry pattern (besides antibodies and small molecules). As more versatile frameworks are created it will be increasingly possible to design foldamers that bind to almost any surface. Indeed, we are only beginning to scratch the surface of this field.

The chiral homologated amino acid (HAA) building blocks have received an enormous attention, due to their presence in natural products, their relevant pharmacological activities (antitumor, antibacterial, antifungal, etc.) and their use as precursors of beta-lactams (penicillins, cephalosporins). The fact that chiral HAAs are often incorporated in natural products which by evolution often preserve “privileged structures”, means that the class of HAAs generates many potential lead-structures in drug research. Since these HAAs generally contain chiral centers, their synthesis requires modern preparative approaches, most often creative utilization of the natural chiral pool and/or application of sophisticated enantioselective synthetic methods including the enzyme catalyzed conversions.

Current scientific challenges addressed

- 1. Discovery of new foldameric secondary structures and development of de novo design strategies.**
- 2. Effective stabilization of the known secondary structures, especially in the biologically relevant aqueous medium.**
- 3. Design and synthesis of foldamers having biomimetic molecular surface to facilitate interactions with biologically relevant target molecules.**
- 4. Construction of functional self-assembling foldamer systems.**
- 5. Continuous extension of the pool of HAAs is essential to provide access to a broad range of new peptidomimetic foldamers.**
- 6. Synthesis and biological testing of foldamer libraries.**

B.3 Reasons for the Action

Immediate benefits

The application driven research coordinated in this Action will result in (i) novel enantioselective synthesis methods having wider relevance in bioorganic and medicinal chemistry, (ii) new HAAs for foldamer construction that are directly useful also in drug development as highly functionalized building blocks, (iii) foldamer libraries targeted for protein-protein or protein-carbohydrate interactions, (iv) biomimetic foldamers as technology platform for biomedical research. In the time-frame of the project, promising hits or even drug candidates are expected on the basis of the foldamer technology.

Long term benefits

This Action will give rise to a vivid cross-European cooperation, which will lead to a number of patents, thereby creating an intellectual portfolio for the associated and future spin-off companies. Despite the fact that pioneering research on peptidomimetic foldamers was conducted in Europe, only a few research groups embarked on related projects. An analysis of the papers containing the keyword foldamer in the past 5 years reveals that the greatest part of this research was performed in the United States (ca. 50% of the references), while Europe lags behind (25% of the references). Moreover, the publications and patents related to

biomedical applications are overwhelmingly of US origin. Thus, the organization of a network on this complex topic in Europe could reduce this gap between Europe and the United States.

B.4 Complementarity with other research programmes

Larger scale cooperation is apparently absent in Europe. An FP7 IAPP involving a large Pharma company and two academic research groups has just been accepted and an FP7 Initial Training Network (ITN) project is planned. While this Action focuses on the joint planning, the determination of the common goals and the concerted research among the participants, the IAPP ITN project will be responsible for the supply of young and well trained researchers devoted to the field, and will provide entries to the industrial sector.

C. OBJECTIVES AND BENEFITS

C.1 Main/primary objectives

The main objective of the Action is to turn the scattered spectrum of European foldamer research into an application inspired concerted endeavour. Our goal is to relay the ideas, pharmacophore models and requirements among the potential biomedical applications (e.g., inhibition of protein-protein interactions, self-assembling nanostructured drug delivery systems, functional biomimetic materials, etc.), to the laboratories involved in foldamer design and synthesis, and the researchers who are continuously extending the pool of HAAs. This parallel top-down and bottom-up information handling is expected to boost the application oriented foldamer research in Europe.

C.2 Secondary objectives

The main goal will be achieved through the secondary (quantitated) objectives below:

1. Efficient enantioselective synthesis of novel chiral HAA building blocks focused on foldamer construction; 40-50 core skeletons (more than 500 new molecules) are expected during the project.
2. Efforts will be directed toward the creation of a molecular database of the HAA building blocks synthetically available in the laboratories of the partners.
3. Stabilization of the foldameric secondary structures with chemically diverse side-chain patterns. De novo foldamer secondary structure design algorithm will be developed.
4. Efficient synthesis of foldamer arrays based on HAA building blocks. The problem of the oligomer libraries will be addressed by at least two major approaches: (i) in situ array synthesis, (ii) chemical chip printing.
5. Biological screening of the foldamer libraries on pharmacologically relevant targets. The major targets are the immunosuppressant and tumor metastasis related Galectin-1 protein, Alzheimer-disease related amyloid beta-peptide aggregates (oligomers and globulomers) and integrins. The collection of the target molecules will be later extended to other proteins as further participants join the Action.
6. Controlled self-assembly of foldamers into distinct tertiary structures or nanostructured particles with specific function. This part of the research addresses fundamental questions, such as the dependence of the self-assembling propensities on the stereochemical pattern, and on the side-chain chemistry.

C.3 How will the objectives be achieved?

Human resources

At the start, the project will involve approximately 100 researchers including 20 post docs, 50 PhD students, 10 professors/senior researchers, a number of technicians and undergraduate researchers. At least 35% of the staff works in the field of the building block synthesis and characterization, 35% is involved in the foldamer design, synthesis and characterization, 20% in functional foldamer synthesis and in vitro biological screening and 10% performs the necessary high-performance molecular modelling (molecular dynamics, ab initio calculations and docking). Obviously, some overlap is expected between the fields at the personal level of activities. The number of the participating researchers will be doubled by the end of the second year of the project, due to the new research groups entering the project. The molecular biological tests on the targeted protein-ligand interactions, such as binding affinity screening and biomolecular X-ray, NMR and MS measurements will be carried out in the participant's laboratories. The cell level in vitro biological test, and the in vivo screens (if necessary for the highly successful candidate molecules) will be carried out in cooperation with laboratories specialized in the field. Later, their association to the Action is anticipated.

Laboratory surface and equipments

The total laboratory surface currently available for the project is estimated to 700 m² in all the seven currently joined participant laboratories, which will certainly increase with the accessing partners. All the participating laboratories are well equipped meeting the safety requirements for organic synthesis. For the analytical tasks, HPLC, MS, several high-field NMR (triple resonance probes for protein NMR) and X-ray are available at the partners.

C.4 Benefits of the Action

The technical benefit from this COST Action is the technology platform based on the peptidomimetic foldamers, which can be a stepping stone for the future association of companies and further participants. The resulting technologies will provide efficient tools in drug discovery and development and will facilitate addressing pharmacological problems in a chemical biology approach. Implementation and promotion of such technology by this COST Action will thus have economic impact for participating European countries. This will increase competitiveness with respect to other leading countries such as USA.

The major strategic benefit of this Action is the generation of a synergistic approach for the synthesis of the HAA building blocks and their application in bioactive foldamers. Only this combination will lead to breakthroughs and future implementation. An important benefit of the Action is also to bring together experts from different areas and countries with expertise ranging from enantioselective synthetic methods, foldamer research and drug discovery, which is required for the interdisciplinary objectives of this Action. Through short term scientific missions this interchange of knowledge will be promoted, especially among young scientists. The incorporation of small and medium enterprises (SMEs) and leading European companies will benefit the European economy by implementing new technologies and thus increase competitiveness. The field is in an incubation phase, therefore implementation of an integrating COST Action would be highly effective. Subsequently, this project will be eligible for access to the EU framework programmes.

C.5 Target groups/end users

The likely end users will be the biotech and pharma sector. These include all participants in the sector such as government bodies, researchers, consumers, biotechnology/big pharma companies, venture capital

companies, and the academic research establishments with pharmaceutical and life science activities. Small or medium molecular weight self-organizing drugs will be good candidates to address macromolecular interactions undruggable by using small molecules or antibodies, which will also contribute to the health and safety of European citizens.

D. SCIENTIFIC PROGRAMME

D.1 Scientific focus

The scientific focus of this Action is placed on the construction of potentially bioactive and self-assembling foldamers. The peptidomimetic foldamer technology relies heavily on the effective synthesis of carefully designed HAA building blocks. Therefore the scientific work will cover three major tasks: (i) HAA building blocks, (ii) foldameric secondary structures and their controlled self-assembly and (iii) construction of functional foldamers. The separation of the three tasks into WGs is rather formal and has been done to facilitate management purposes. Nonetheless, there will be constant communication between the WG as the goals and outputs are directly linked at several places. These are explicitly indicated in the workplan.

D.2 Scientific work plan – methods and means

WG1: HAA building blocks

The most important challenge addressed in this WG is the advanced enantioselective chemical (photochemical) and biocatalyzed synthesis of cyclic beta-amino acids functionalized in the side chain with diverse groups as those have the greatest potential to serve as building blocks in functional peptidomimetic foldamers. Often, a small ring topology in the backbone governs the self-organization of the foldamer. The most investigated are the structures with a five- or six-membered ring (2-aminocyclopentane- and 2-aminocyclohexanecarboxylic acids), and structures with N and C-3 incorporated in a pyrrolidine or piperidine ring (proline analogs). An important aspect is the application of the most constrained beta-AAs concerning 2-aminocyclopropanecarboxylates, 2-aminocyclobutanecarboxylates, 3-aminoazetidines-2-carboxylates and N-C-3-heterocyclic beta-AAs with an aziridine or azetidine structure. The synthesis of these type of building blocks will be pursued since their structuring effect is to be determined in foldamers and they have biological relevance even in their monomer state (eg.: carboxypeptidase A inhibition, gametocides).

Currently, a challenge in the HAA synthesis in relation to the foldamer design is the functionalization of the side-chains in cyclic HAAs. The functionalized building blocks allow the fine tuning of the hydrophilic properties and pharmacophore anchor points of the designed foldamer without losing the secondary structure. Enantioselective synthesis routes will be developed to introduce various functional groups on the side-chains of the cyclic structures.

The control over the foldamers self-organization properties is possible through several factors, however the effects of the specific side-chain shape and bulkiness are to be studied. To reach this goal, synthesis of cyclic HAAs with special side-chain shapes will be attempted. The utilization of the natural chiral pool will be attempted for HAA synthesis, e.g. natural alpha-AAs, terpene and sugar derivatives can be excellent starting materials.

Although, the syntheses of the open-chain beta2- and beta3-substituted AAs from the natural alpha-AAs are known, novel and increased efficiency methods are still sought. For example, stereoselective methodologies

for the preparation of enantiomerically pure beta,gamma-dehydro-beta-amino acids and cyclic beta-amino acids could be developed by means of the C-N bond formation through asymmetric conjugate addition. Certain open-chain beta,2,3-disubstituted AAs have been synthesized too but the collection of these interesting building blocks should be widened as they have useful structuring effects in foldamers.

In general, improved methods for the synthesis of known and new HAAs including enzymatic conversions and advanced enantioselective syntheses will be developed. The scientific focus will be extended toward the application and development of novel synthetic approaches such as organocatalysis. Moreover, the foldamer design will suggest novel monomer skeletons and functional group patterns, which might give orientation for HAA synthesis.

WG2: Foldameric secondary structures and controlled self-assembly

The conformational pool of peptidic foldamers comprises a number of periodic folded conformations, which can be classified as helices, and nonpolar and polar strands. The latter two are prone to form pleated sheets. The numerous studies that have been performed on the side-chain dependence of the stability of the folded structures allow certain conclusions concerning the principles of design of the peptidic foldamers. The folding process in general is a highly complex phenomenon that is influenced by many factors, such as the residue type, the side-chain topology and chemistry, the hydrophobicity pattern along the backbone, the solvent, the stereochemical pattern along the backbone, etc. It is practically impossible to systematically handle all the variables during the foldamer design, therefore human intuition played important role in the de novo creation of the foldameric secondary structures. A major goal in this WG is to address the above problem and to devise systematic approaches to the de novo foldamer design. Little is known about the combined effects of the backbone homologation and stereochemical patterning. Efforts will be directed toward the development of novel design principles, which facilitate the extension of the pool of foldameric structures via the variation of the side-chain topology and chemistry. An important facet is the application of the highly strained cyclic AAs in the foldamer construction (direct link to the planned developments in WG1). The scientific programme will cover the highly restrained aromatic oligoamide foldamers, and these highly restrained AAs will be tested in combination with various easily available open chain beta-AAAs and natural alpha-AAAs.

A long lasting scientific problem in the foldamer research is to attain reasonably high structural stability in aqueous environment, which would facilitate their application as protein ligands. It was observed that certain helix types exhibit greater stability, while others are stable only in solvents of low polarity. In this respect, a screening of the secondary structure space for inherently stable patterns will be helpful. There are design approaches for stabilization such as salt-bridge formation or hydrophobic stacking between side-chains in juxtapositions, which will be utilized in connection with the helices to be applied as protein ligands. In our approach, the effects of the side-chain shape will also be utilized to stabilize helical folds resembling the natural \pm -helix. For this purpose, HAA building blocks newly prepared in WG1 will be applied.

It has been pointed out that foldameric secondary structures exhibit higher order organization in a secondary structure-dependent way. Helices tend to form bundles, while strands self-assemble into pleated sheets eventually creating nano-sized fibrils. This WG makes an attempt to control these self-assembling properties, which is a fundamental aspect to be resolved for further applications such as affibody mimetics (WG3).

Programmed assembly and self-assembly of soft materials offers significant promise for the generation of new types of materials with useful properties. Through evolutionary processes occurring over billions of years, nature has produced numerous optimised building blocks for the controlled assembly of a wide range of complex architectures. The challenge now is to imitate these naturally occurring processes for technological applications by using foldameric secondary structures to provide a flavour of the utility of soft biological materials for construction purposes. Control over the nanostructured dimensions and behavior of the foldameric aggregates are addressed in this WG.

This WG is extensible toward the studies on chimera systems created from engineered proteins chemically

ligated to foldameric sequences and toward the nucleobase-functionalized foldamer scaffolds, which are promising candidates in terms of molecular architecture. The scientific focus can also be widened to the systematic computer-aided foldamer design approaches.

WG3: Functional foldamers

The major goal in this WG is to design and synthesize bioactive foldamers. In order to inhibit a specific protein-protein or protein-carbohydrate interaction the following options exist as the molecular weight concerned: small-molecule inhibitor (~ 0.5 kD), nanobody and affibody (6-10 kD), antibody (150 kD). The foldamers are in the range 0.5 – 2 kD, and their molecular shape and molecular surface chemistry can be tuned. Peptidomimetic foldamers are well suited for combinatorial approach. Synthesis of foldamer arrays on solid support will be carried out. These arrays will combine the various secondary structures with the diverse side-chain chemistry. Attempts will be made to synthesize these foldamer arrays in situ. High resolution arrays will be created via chemical chip printing. These libraries will be utilized for affinity screening of the target molecules. There is a direct connection between the subtask of de novo helix creation in WG2 and the functional foldamer synthesis, since the screened secondary structure space will be extended to the new helices as soon as they are reliably available.

The target molecules already in the focus of the participants are the cancer-related galectins, integrins and diffusible α -amyloid oligomers. It is an explicit goal to widen the circle of the targeted proteins, which potentially requires new participants in the Action. These subtasks generally start off from a known pharmacophore hypothesis (e.g. glycomimetic peptides for galectins) which will be mimicked by using the foldameric secondary structures. The computer aided drug-design methodologies will be extensively utilized. The design of the foldamer arrays will be directed by molecular modeling, docking studies and already available pharmacophore models. If foldamers with sufficiently high affinity to the target are found the further in vitro inhibition tests will be carried out in the laboratories of the external partners. The work can be extended toward the development of the affibody mimetics, which requires successful experiments with the controlled self-assembling of the helix bundles in WG2.

An important aspect is the structure of the inhibitor-target molecule complex. Where possible, structural biology tools will be deployed (biomolecular NMR, X-ray crystallography) to gain atomic level information about the nature of the interactions, which will greatly help the design and optimization processes.

The work covers the design and synthesis of self-assembling foldameric units and foldamers potentially useful as drug or hapten carrier. These well-defined backbones will be used for the multiple presentation of biological haptens, such as photon harvesting porphyrins or glycoside-type vectors for tumor cell targeting.

E. ORGANISATION

E.1 Coordination and organisation

The COST Action will consist of a Management Committee (MC) and three Working Groups (WG) and a Short-Term Scientific Mission (STSM) programme. All practical work will be carried out within projects planned and financed at the participating institutions/countries, while the coordination of this work will be carried out by this COST Action. This concerted Action will increase the impact of these individual activities.

Besides the responsibilities stipulated in the “Rules and Procedures for implementing COST Actions” (doc. COST 270/07), the Management Committee will be in charge with the following tasks:

- appoint the chairperson, the vice-chair person and the Working Group leaders during the kick-off meeting;
- plan the MC, WG meetings and workshops;

- evaluate and monitor the progress of the Action;
- report the progress annually;
- compare the original objectives with the actual results;
- ensure networking between all participants and Working Groups;
- appoint an STSM manager and assist with evaluation of applications;
- updating of the Website;

Short-term Scientific Missions will be organised to enhance cooperation between different participating countries and institutions. STSMs can also cut across different Working Groups. The research will be strengthened and intensified by the exchange of young scientists between different organisations.

Milestones

1st year: (i) setting up MC and WGs, (ii) identification of the most important lines of joint research, (iii) determination of the detailed WG meeting schedule

2nd year: (i) involvement of new participants in the Action, (ii) actualization of the project portfolio

3rd year: (i) evaluation of the results of the joint research projects, (ii) appearance of the enterprises (SMEs first) in the Action

E.2 Working Groups

The Action will be organized in three Working Groups (see D. Scientific Programme). In joint Workshops each WG will take turn to provide a state-of-the-art report, from where the other WGs are challenged to work out integrative possibilities. Suggestions for the joint projects will be discussed and worked out in the WG meetings. An efficient way for the common research will be realized by material transfers: HAAs to foldamer synthesis, foldamers for screening, etc.

The responsibilities of the Working Group leaders are to:

- organise the Working Group meetings and appoint national organisers;
- coordinate the activities within the WGs in the framework of the objectives;
- promote the set-up of joint research and the writing of common publications;
- report on the WG progress to the chairperson and Management Committee.

E.3 Liaison and interaction with other research programmes

The Action will have an impact on the world-wide forum notably by (i) participation in world conferences (drug discovery; peptide chemistry; combinatorial chemistry; nanostructured materials); (ii) creation associate memberships for active research groups in the field outside Europe and bordering Europe; (iii) representation in global organisations.

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.

In this field, the most important components of the capacity building are the human resource development and the management of relationships between the research programmes. Short term scientific exchange visits of young researchers will be employed as a managerial means especially to create novel, unexpected links between disciplines and equipping individuals with the understanding, skills and access to information, knowledge and training that enables them to perform effectively. This will promote the involvement and carrier building of the early-stage researchers too. Short training courses will be announced during the WG meetings to help the PhD students/early-stage researchers accessing information necessary for their development.

F. TIMETABLE

This Action will last for four years. For several reasons this time frame seems appropriate. First, most projects incorporated in this COST Action will have a duration of between three and five years. Second, the cross-cutting cooperation between specific areas of HAAs synthesis, foldamer design, and functional foldamers also requires a transfer of basic knowledge between experts from these different areas.

The activities to be organised during the course of the Action are shown In Table 1. During the first MC meeting, WG leaders will be selected. WG meetings form the basis of the Action and are usually organised twice a year. Meetings of two different Working Groups (changing the combinations) will usually be held in conjunction. During the annual workshop, special topics will be discussed in various sessions relevant to the Working Groups. Outside experts will be invited to this workshop while special sessions will be organised for the industry and SMEs. Also, young scientists will be given the opportunity to present their results while participants of the STSM programme will present the results of the missions.

Table 1. Overall timetable

Year	1	2	3	4
First MC	X			
Annual workshop		X	X	X
Annual MC meeting	X		X	X
WG meetings*	X	X	X	X

* WG meetings will be organised with the participation of two WGs on a semi-annual event. The combinations of the WGs will be determined on the first MC meeting.

G. ECONOMIC DIMENSION

The following COST countries have actively participated in the preparation of the Action or otherwise indicated their interest: BE, FR, DE, HU, IT, ES, CH, NL, GB. On the basis of national estimates, the economic dimension of the activities to be carried out under the Action has been estimated at 22 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?

These include all participants in the biotechnology/pharma sector such as government bodies, researchers, consumers, biotechnology/big pharma companies, venture capital companies, and the academic research establishments with pharmaceutical and life science activities. Efforts will be exerted to disseminate the results in appropriate form to the general public.

H.2 What?

The results obtained in this Action will be disseminated through the routes described in Table 2.

Table 2. Dissemination methods of the COST Action

Type of dissemination	Main target groups	Quantity
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Website	Public, industry, academics, policy makers and stakeholders	1
Website/limited access	Participants	1
Newsletters	Industry, academia, public	1 per WG
Working Group meetings	Participants	several
Presentations at scientific conferences	Academia	several
Workshops (yearly)	Participants, invited speakers, others	4
Proceedings	Public, industry, academics	1 per workshop and conference
Review article	Scientific community	1 per WG
Teaching	Graduate students	
Book (final proceedings)	Public, industry, academics	1
Interaction with other networks	Network members	various
Manuals	End-users, researchers	various

H.3 How?

An important tool in the dissemination of the results of the COST Action will be a Website platform. Both information for the public, industry, academics and stakeholders will be made available on this Website, while a restricted area will be generated with access for the participants of the Action only. Research results generated within this Action will be published in international peer-reviewed journals and books. Similarly, review articles will be published in cooperation with several Action participants as multi-author papers. Presentations will be given at international scientific conferences. Participants of the STSM-programme will be especially encouraged to present the outcome of the missions at conferences and workshops. On the one hand European technological excellence will be promoted while on the other hand IPR aspects will be considered.

This COST Action will also disseminate new strategies through teaching activities at universities. Participation in the STSM programme will be offered to PhD students to promote transfer of knowledge.

The major communication tool between the participants of the Action will be the annual workshops and Working Group meetings. Keynote speakers will be invited to the annual workshop. Also, special sessions with industrial relevance will be organised. This is especially important to prepare implementation of new processes and attract representatives of industry.

Interaction of the COST Action with other European and national networks and initiatives will be established at the first MC meeting. This dissemination strategy will be continuously updated during the lifetime of the Action.

Part II – Additional Information NOT PART OF THE MoU

Maximum 10 pages

General remark: The main purpose of the second part of the proposal is to facilitate the assessment of the proposal and the nomination of National Representatives to the Management Committee (MC). This part will not be element of the MoU. To some extent, however, the information contained in it may also be useful, when the Action starts and a detailed work programme is being planned. Note that part A (List of Experts) is mandatory as the information given here is important for the later nominations to the MC.

The structure of the Additional Information is not standardised and you are at liberty to structure it in any logical way.

A. LIST OF EXPERTS

Expert 1.

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B. ADDITIONAL INFORMATION

PRELIMINARY WORK PROGRAMME

The Technical Annex covers the complexity of the work programme; specification of further details would probably decrease the flexibility and extensibility of the Scientific Programme at the present stage.

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