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DATE: 19/03/2016

ARTICLE BY PG STUDENT

Review on Histone Deacetylase Inhibitors: Mechanism of action and Therapeutic Uses in Cancer.

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Abstract:

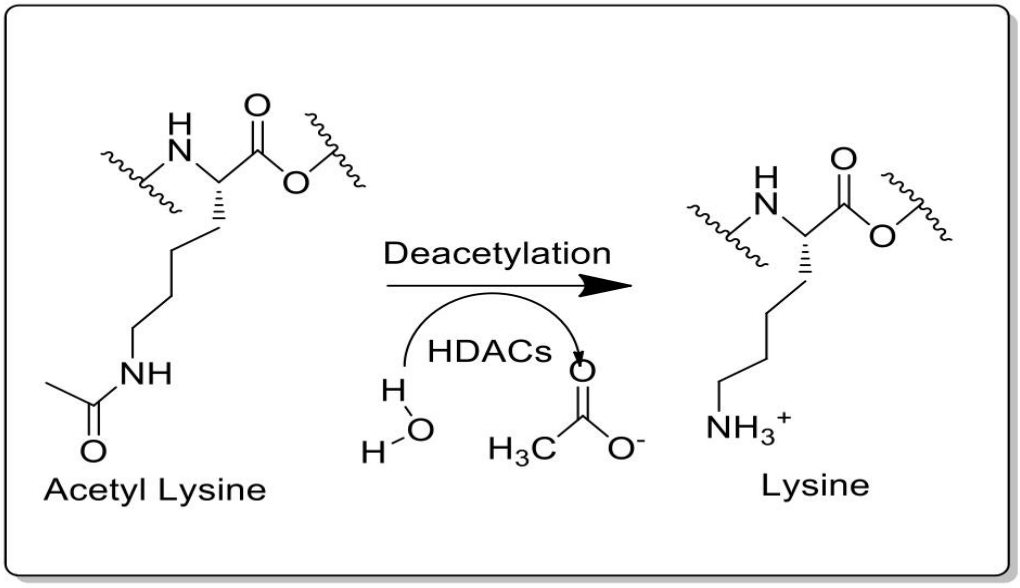
Histone deacetylases (HDACs) are the class of enzymes that remove the acetyl groups of ε-N-lysine amino acid residues of histone tails leading to chromatin compaction and transcriptional repression. HDACs can also influence transcription-independent such as mitosis or deoxyribonucleic acid (DNA) repair and deacetylate non histone proteins involved in cell proliferation and death, altering their function. Histone deacetylase inhibitors (HDACi) interfere the function of the HDACs. HDACi have been shown to induce differentiation, cell-cycle arrest, and apoptosis and to inhibit migration, invasion, and angiogenesis in many cancer cell lines. These compounds inhibit tumor growth in animal models and show antitumor activity in patients. HDACi alone and in combination with a variety of anticancer drugs are being tested in clinical trials, showing significant anticancer activity both in hematological and solid tumors. SAHA (vorinostat, Zolinza) was the first HDACi approved by the US FDA.

Key words: Histone deacetylase inhibitors, Anticancer, Treatment.

Histone Deacetylase (HDAC)

HDACs have emerged as crucial transcriptional co-repressors in highly diverse physiological and pathological systems. Histone Deacetylases are the class of enzymes that remove acetyl group form ε-N-Acetyl lysine aminoacid on histone & it allows the histone to wrap DNA more tightly. DNA expression is regulated by histone acetylation and methylation. It being involved in RNA synthesis and being highly associated with nuclear chromatin.

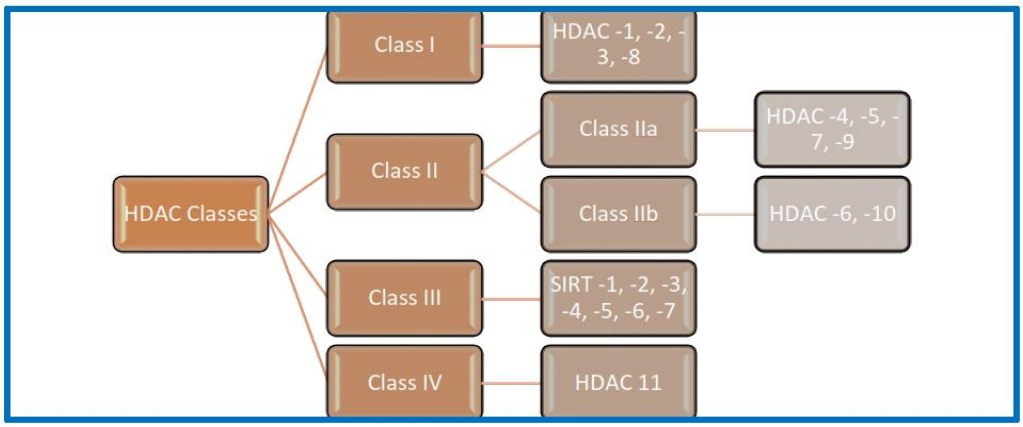
Histone Acetylation determine by the enzymatic activities of both Histone acetyltransferases (HATs) and Histone deacetylases (HDACs).



Lysine deacetylation of HDACs in the presence of water molecule.

There are four main class of histone deactylase based on the cellular localization and function. Class I, II, IV considered as classical whose activity are inhibited by trichostin A and Zinc dependent active site. Where, class III considered as sirtuins and NAD^+ dependent protein.

Class I includes HDACs1, 2, 3 and 8 that are primarily nuclear. Class II are primarily localized to the Cytoplasm, these class divided into class IIa and class IIb. Class IIa includes HDACs 4, 5, 7 and 9 and class IIb includes 6 and 10 which contain two catalytic site. Class III includes SIRTs 1, 2, 3, 4, 5, 6, 7 and Class IV include HDACs 11.



Different types of HDACs.

A typical characteristic of human cancer is the deregulation of DNA methylation and posttranslational histone modifications, in particular histone acetylation, which has the fatal consequence of gene transcription-deregulation.

The role of HDACs in cancer is not restricted to their contribution to histone deacetylation, but also to their role in deacetylation of non-histone proteins. For example, HDAC1 interacts with the tumor suppressor p53 and deacetylates it *in vivo* and *in vitro* p53 is phosphorylated and acetylated under stress conditions. Since lysine residues acetylated in p53 overlap with those that are ubiquitinated, p53 acetylation serves to promote protein stability and activation, inducing checkpoints in the cell-division cycle, permanent cell-division arrest, and cell death.

HDAC Inhibitors

The association of HDAC enzymes and carcinogenesis has increased interest in the use of HDAC inhibitors as antitumor agents. HDAC inhibitors have been shown to induce cellcycle arrest, growth inhibition, chromatin decondensation, differentiation and apoptosis in several cancer cell types.

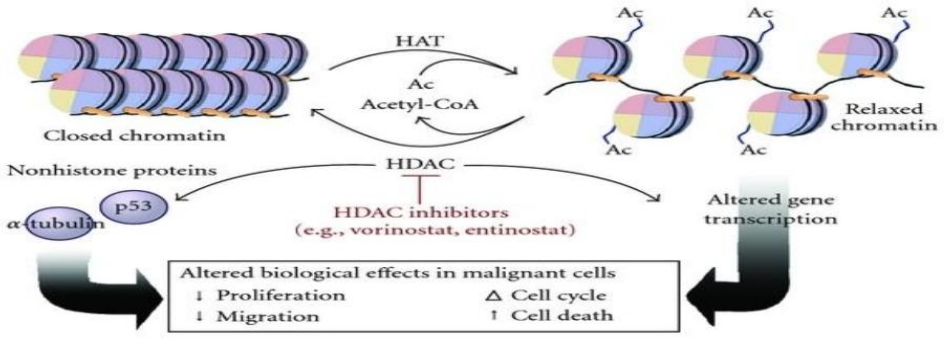
HDAC inhibitors are classified by structure.

1. Short-chain fatty acids – Butyrate and valproic acid (VPA).
2. Hydroxamates – Trichostatin A, SAHA (suberoylanilide hydroxamic acid or Vorinostat) Panobinostat (LBH589), Oxamflatin, Tubacin and Belinostat (PXD101).
3. Benzamides – Entinostat (SNDX275), Mocetinostat (MGCD0103).

4. Cyclic tetrapeptides – Romidepsin (FK228), Trapoxin A, Apicidin.

The compounds are vary in structure as well as they have also the distinct affinity for the different HDACi. The Short chain fatty acids (Butyrate and Valproic acid) and Trapoxin A are the class I and class IIa HDACi. Entinostat (SNDX275) is more specific that inhibit class I HDACs but not HDAC8. Romidepsin (FK228) inhibit HDAC1 and HDAC2. Tubacin inhibit HDAC6. The HDAC inhibitory activity of the naturally occurring compound Butyrate and Valproic acid which are responsible for the ability to cause the cell cycle arrest and differentiation of the transformed cell. Hydroxamates like Vorinostat (SAHA) was the first new HDACi which approved by the FDA October 2006 for the clinical use in the cancer patient for the treatment of cutaneous T-cell lymphoma. Vorinostat (SAHA) was evaluated in phase I clinical trials as an i.v. and orally administered drug. Patients included those with hematologic (Hodgkin's lymphoma, non-Hodgkin's lymphoma, and multiple myeloma) and solid malignancies (prostate, bladder, breast, colon, ovarian, and renal). In the both trials, there was significant anticancer activity at doses that were well tolerated by patients. More than 50 clinical trials with combination therapy with Vorinostat (SAHA) and various agents (carboplatin, paclitaxel, 5-fluorouracil, etc.) in patients with advanced hematologic and solid tumors are in progress. Hydroxamates induce the differentiation or apoptosis of the cancer cell line or both. Mainly use in the treatment of cutaneous T-cell lymphoma. Panobinostat (LBH589) is a hydroxamic acid–based HDACi with a structure similar to Vorinostat.

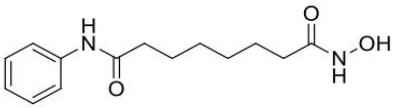
HDAC Mechanism of Action



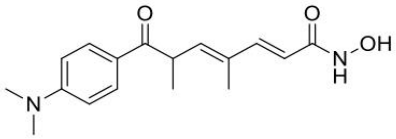
Chemistry of HDACs inhibitors

HDACi can be divided into several structural classes including hydroxamates, cyclic peptides, aliphatic acids, and benzamides TSA was the first natural hydroxamate discovered ti inhibit HDACs. Vorinostat is structurally similar to TSA. A series of aminosuberoyl hydroxamic acids have recently been discovered to inhibit HDACs and transform cell proliferation at nanomolar concentrations. Vorinostat is the first HDACi to be approved for clinical use by the Food and Drug Administration. Vorinostat is a pan-inhibitor of class I and class II HDAC proteins. M-Carboxycinnamic acid bishydroxamate is a potent HDACi and is the structural basis for several derivatives including LAQ-824, LBH-589, and a sulfonamide derivative, belinostat (PXD-101), TopoTarget AS/Cure Gen Coop; ref. These HDACi inhibit class I and class II HDACs. Panobinostat (LBH-589; Novartis AG) is a cinnamic hydroxamic acid analogue of M-carboxycinnamic acid bishydroxamate. IF2357 (Italfarmaco SpA) is an HDACi that contains a hydroxamic acid moiety linked to an aromatic ring. A series of aryloxyalkanoic acid hydroxamides have been synthesized that are HDACi at nanomolar concentrations.

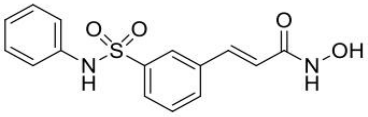
Hydroxamate HDACi



Vorinostat

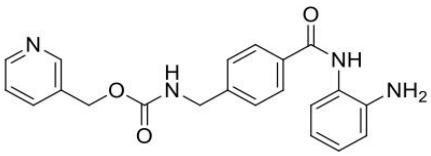


Trichostatin A

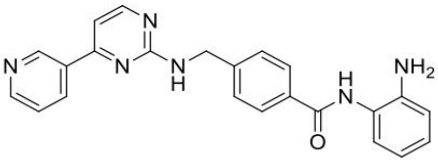


Belinostat

Benzamides HDACi

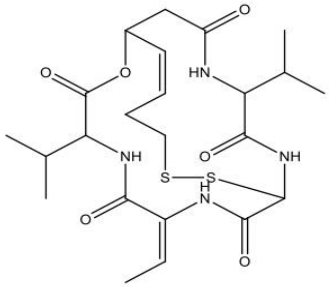


Entinostat

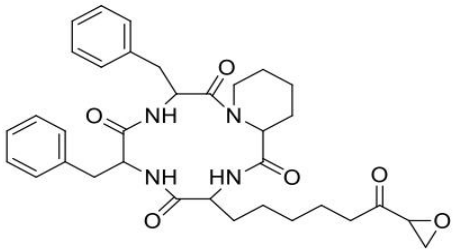


Mocetinostat

Cyclic Tetrapeptides



Romidepsin



Trapoxin A

HDAC Biological activity

Class I HDACs are mostly localized within the nucleus where Class II shuttle between nucleus and cytoplasm. Class I play a role cell survival and proliferation, and class II HDAC have HDACs have tissue specific roles. Class III contains the structurally diverse NAD^+ dependent sirtuin family, which does not act primarily in histones. Class IV which is previously as a part of both Class I and Class II.

Non target HDACs include p53, E2F, GATA-1, YY1, RelA, MaD-Max, c-Myc, NF-kB, HIF-1α, Ku70, α-tubulin, STAT3, Hsp90, TFIIE, TFIIF, and hormone receptors explain some biological activity.

HDACs expression and activity can be altered in many cancers and in both lymphoma and leukemia HDACs is associated with the function of oncogenic-translocation products, such as PML-RARα in acute promyelocytic leukemia.

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ARTICLE BY FACULTY

REVIEW ON NUCLEIC ACID STRUCTURE,DYNAMICS ,COMPUTATIONAL METHODS AND INTERACTIONS

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ABSTRACT

Nucleic acids are an important class of biologicalmacromolecules that carry out a variety of cellular roles. Formany functions, naturally occurring DNA and RNA moleculesneed to fold into precise three-dimensional structures. Due totheir self-assembling characteristics, nucleic acids have alsobeen widely studied in the field of nanotechnology, and adiverse range of intricate three-dimensional nanostructureshave been designed and synthesized. Different physical termssuch as base-pairing and stacking interactions, tertiarycontacts, electrostatic interactions and entropy all affectnucleic acid folding and structure. Here we review generalcomputational approaches developed to model nucleic acidsystems. We focus on four key areas of nucleic acid modelling:molecular representation, potential energy function, degrees offreedom and sampling algorithm. Appropriate choices in eachof these key areas in nucleic acid modelling can effectivelycombine to aid interpretation of experimental data and facilitateprediction of nucleic acid structure.

INTRODUCTION

Unfortunately, experimentally determiningRNA and DNA structures at high resolution is tedious,expensive and not always tractable, particularly for largecomplex systems, which can show significant molecularflexibility.A complementary approach is to study nucleic acid structurein silico. With recent discoveries of RNA's variousgene regulation roles and the potential applications ofnucleic acid nanostructures to biocomputing [1] andnanotechnology [2,3], there has been extensive researchinto developing computational tools for modeling andmanipulating nucleic acid structure .Since computational modeling can be used to address awide range of problems that vary in complexity andresolution (time/size/precision), an appropriate choiceof algorithm or modeling platform is required. Wediscuss four main aspects of nucleic acid modelling here: firstly, molecular representation; secondly, potentialenergy function; thirdly, degrees of freedom; andfourthly, sampling algorithm. We focus on generalmodeling techniques and strategies that are applicableto an array of modeling purposes such as generating anensemble of plausible molecular models, identifying anative-like molecular structure, studying foldingkinetics, probing the effects of base mutations, refiningmolecular models and modeling with limited experimentaldata.

MOLECULAR REPRESENTATION

Modeling nucleic acids with an all-atom representationand consequent precision is computationally expensive, particularly for large systems. Analogous toproteins, coarse-graining nucleic acids is a commonapproach to handle larger molecular systems . Eachnucleic acid base can be represented by a subset of atomsor pseudo-atoms for DNA and for RNA. Alternatively, each base can berepresented as a plane and modeled by rigid bodyparameters . These different coarse-grainedrepresentations have been successfully implemented inRNA structure prediction .For very large nucleic acid systems with many nucleotides,modeling can still be intractable even with suchextensive coarse-graining.

Because base-paired helices ofDNA and RNA are rigid compared to single strands ofbases, another coarse-graining strategy is to depart fromatomic-level detail and instead represent each nucleicacid helix as a cylinder. Clearly this coarsegrainingis only applicable for exploring global conformationsrather than for extracting fine molecular information.What molecular representation is most suitable? Forpractical considerations, it makes most sense to use theminimum possible representation that is still able tocapture the phenomenon of interest with reasonablecomputational cost . While all-atom molecularmodelling is usually favoured due to the high level ofstructural detail, the cost could become astronomical for large systems, making coarse-graining an absolutenecessity. Perhaps an appropriate compromise wouldbe to coarse-grain selected regions, and model importantinteracting sites at all-atom representation, however sucha choice would require development of an interactionpotential to traverse different molecular representations.Alternatively, one could also retain a high level of detail inthe molecular representation, but decrease the number ofdegrees of freedom (DOFs) that are used in the samplingprocess . A lessstraightforward process is to first model with a coarsegrainedrepresentation, then restore all-atom resolutionbased on known or idealized nucleotide geometry.It is also important to note that here we have onlydiscussed different representations of the nucleic acidstructure, not those of its surrounding solvent or counterions,which can be expressed implicitly and/or explicitly.Nucleic acids carry high negative charges and hencesolvent and ions must be correctly treated in order toaccurately model RNA and DNA.[2]

POTENTIAL ENERGY FUNCTION

In molecular modeling, a potential energy function isrequired to distinguish physical and biologicallyrelevant conformations. These potentials come in varyingdegrees of precision and complexity,ranging from a primitive function considering onlysteric restraints to one that depends on quantum mechanicalcalculations. The choice of potential is critical tothe efficacy of molecular modelling: the accuracy ofmodeling depends on the correctness of the potentialwhereas sampling efficiency varies with the nature ofthe potential guiding the simulation.Traditional physics-based potentials such as AMBER and CHARMM approximate atomic-level interactionsas bonded (bond, bend-angle stretching, torsionalrotations) and pairwise non-bonded terms, each describedby analyticalmathematical formulas. Parameters for thesemathematical expressions were optimized using experimentalobservations on small molecules or else by fittingto quantum chemical calculations. A significant advantageof such physics-based potentials is their applicability tomolecular dynamics simulationsCoarse-grained systems are usually modelled with knowledge-based potentials that are typically derived from structuralinformation gathered from high-resolutionexperimental structures , from molecularmodels produced by all-atom simulations with physicsbased potentials , or both . A major advantage ofknowledge-based potentials is the ability to tune potentialsto the particular molecular representation just by adjustingthe information that is extracted from known structures. Forinstance, one could use different nucleotide representationsto generate potentials based on known physical interactionssuch as nucleic acid base-pairing and stacking , or from interatomic distances or torsional angles, or a combination of the above.Recently, a coarse-grained potential was developed forRNA using parameterized bonded and non-bonded termslike those in traditional physics-based potentials .Another advantage of knowledge-based potentials is thattheir mathematical forms can be easily adjusted. In somecases, these potentials are discontinuous;

it was shown thatRNA molecules can be efficiently modeled using a discretizedknowledge-based potential [3]. Additionally,because knowledge-based potentials implicitly capture solventeffects, they are less computationally intensive to use,in that water molecules and ions need not be explicitlyincluded.

While physics-based potentials have been applied widely,knowledge-based potentials have mostly been used toselect native-like structures; in some cases their accuraciessupersede those using physics-based potentials. Despite successes in distinguishing native-likeconformations, because knowledge-based parametersare usually derived from static experimental structures,it is unclear how accurate they would be for studyingnucleic acid dynamics and folding pathways, particularlyin different ionic solution conditions than those used tosolve the experimental structures Another class of potentials can be derived from constraintsthat come in the form of secondary structureinformation or low-resolution experimental data. Suchlimited experimental data appears to provide sufficientconstraints so that RNA structure determination can bemore tractable, particularly for larger systems .

DEGREES OF FREEDOM(DOFs)

Another approach to coarse-graining large systems is touse alternate sets of DOFs while retaining an all-atomrepresentation. By modeling using dihedral or torsionalDOFs instead of all-atom Cartesian DOFs, dimensionality(number of DOFs) is substantially reduced. Thistechnique is motivated by the limited flexibility of bondlengths and bond angles: any conformational rearrangementin Cartesian space can be accurately expressed intorsional space because bond lengths and bond angles are Unfortunately, the benefits of modeling with torsionalDOFs are less obvious when modeling large and complexmolecular assemblies. The root of the problem is the leverarm effect caused by rotating a dihedral angle about asingle bond: a small torsional rotation about a bond canlead to substantial conformational change distant from it,rather like how a small rotation about one's elbow resultsin a large movement of the hand. The solution to thislever arm problem is to use torsional DOFs that onlyaffect local conformation. However, doing this will breakthe continuity of the molecular chain, which needs to berepaired with a chain-closure algorithm . The computationalcomplexity of standard chain-closure algorithmsmakes them very expensive, encouraging thedevelopment of closure algorithms that are of reasonablecomputational cost. This need has been met with a linearcomplexity stochastic chain-closure algorithm thatopens up new avenues of application: arbitrary sets ofDOFs can be used, since the chain-closure algorithm caneffectively restore multiple chain breakages.[4]

DNA DYNAMICS

Although it is not surprising that base sequence affectsthe flexibility of DNA, probing this experimentally isoften difficult. Crystal packing effects can perturb the typically occur on the microsecond to millisecond timescale.Despite this, a few events have been observed, including recent studies showing surprising andunexpectedly fast base pair opening in RNA [5]. Toprobe base pair opening and the free energies of openingtowards the minor or major grooves, two different groupsused extensive MD simulation and umbrella samplingmethods (with different force fields) to force opening.The results are consistent and modestly favor openingtowards the major groove, particularly for larger purinebases . Flipping by the major groove pathwayis clearly favored when the DNA is bound bycytosine 5-methyltransferase, which lowers the barrierto flipping by 17 kcal/mol. Differences in the dynamics of specific

nucleic acidsequences provide another mechanism — beyond directsequence readout — for specific recognition by proteins.Byun and Beveridgesuggest that the enhancedbendability, and facility for deformation, of specificDNA steps outside the sequence bound by the papilloma.virus E3 protein provides an indirect readout mechanismthat is important for recognition. The enhanced flexibilityof AUA/TAT compared to GUG/CAC sequences, asexemplified by lower bending constants for the AUAsequence, can explain the enhanced efficiency of theuracil DNA glycosylase DNA repair enzyme . Inaddition, the facility for sugar repuckering in certainsequences may also be an important recognition element.This is shown in a study of experimental structures ofprotein–DNA complexes; hydrophobic residues werefound to poke into the minor groove and induce A-likesugar conformations and kinks at pyrimidine-purine (YR)steps [38]. MD simulation and estimates of the potentialof mean force for kinking a base pair step by insertion of aprotein sidechain partially agree with these interpretations,but suggest that the energetic costs come largelyfrom the reorganization of the bases rather than thebackbone [39]. TheThe enhanced dynamics at mismatchedsequences probably provide a mechanism for recognitionby DNA repair enzymes. Osman and co-workerslooked at a wobble base pair that displayedenhanced bending and the ability to open up into themajor groove. This enhanced variability in helicoidalparameters was also observed in MD simulations of amismatch.The coupling of MD simulation and density functionalcalculations has allowed a deeper and more detailed studyof the influence of thermal motions on the electronicproperties of DNA; this is something that is not possiblewith classical MD simulations alone. Unlike the smooth,diffuse and extended electronic states of perfectly periodiccanonical DNA, when thermal motion is present theelectronic states display varied spatial distributions withsignificant charge and electronic state localization. Theselocalized states appear to be rather dynamic and move from nucleotide to nucleotide on a rapid (picosecond)times.The influence of ions and solvent on nucleicacid structure and dynamics.Beyond the intrinsic structure and sequence effects, thestructure and dynamics of nucleic acids are profoundlyinfluenced by their environment, including the surroundingions and solvent. This includes not only the integralMg2þ ions found in some RNA structures, but monovalent

cations and even anions. Probing this in simulationscan be tricky due to the long lifetimes of bound ions,conformational sampling limitations and force field balanceissues . For example, we suggest (based onsimulations of phased A-tract DNA sequences undermultiple conditions) that it may take on the order of500 ns for the monovalent ion distribution in the minorgroove to converge.However, NMR and X-ray experiments are not alwaysdefinitive, as is clearly exemplified by the controversiesabout monovalent ion binding and its influence on DNAstructure . That ion association and charge mightaffect DNA structure is not a surprising observation asDNA is a polyanion. Simulations ofDNA in the gas That ion association and charge mightaffect DNA structure is not a surprising observation asDNA is a polyanion. Simulations ofDNA in the gas phaseclearly show that duplex stability in the gas phaserequires neutralization of some of the phosphates and newer experiments are clearly demonstratingthe binding of monovalent ions to DNA in solution.The simulation data are less conclusive, withstudies strongly supporting the tight binding of Naþ ionsin the minor groove of A-tract sequences and otherssuggesting that Naþ ion binding is rare in such sequences. Of particular concern for simulations probing ionoccupancy is the subtle dependence of the results on theinitial ion placement (which may bias placement atfavorable electrostatic pockets in the groove that maynot otherwise be readily sampled in nanosecond-

scalesimulation if the ion is not placed there initially) and onthe ion parameters themselves. Despite controversy

about the role of ions, MD simulation can readily reproduceA-tract bending [56]. Although nucleic acids are largely anionic, they do presentelectropositive features that can support binding ofanions. This is shown rather nicely in recent work byAuffinger, Westhof and co-workers, who modeled andinvestigated various RNA structures, and presented acompelling case that some assigned Mg2þ ions in crystalstructures may in fact be anions such as SO42. Thisgroup also suggested, via MD simulation, that the binuclearmetal cluster of Mg2þ ions in the 5S rRNA loop Emotif is better described by partial occupancy at each siteand subsequent MD simulations clearly displayseveral deep groove Kþ-binding sites . Other simulationstudies focused on interaction with ions include thoseof Korolev and co-workers , who used MD simulationto probe the effect of variously charged sperminelike ions on DNA fibers in a hexagonal lattice. The ionsinteract most commonly with the phosphates, preferentiallyto the minor groove (O1P) side. Spermine, whenbound preferentially in the major groove, has also beendemonstrated to slow down the A-DNA to B-DNA transitionin MD simulation . The importance of ions inthe major groove for stabilizing A-DNA is also shown inreversible MD simulations of the A-DNA to B-DNAequilibrium at various salt concentrations in a dropletmodel.Solvent is also important for nucleic acid stability. Simulationsby Orozco and co-workers of DNA duplexesin vacuo show clear distortion of the DNA double helix(albeit not complete disruption of the helical and basepairedstructure when the duplex is appropriately neutralized).The stabilization effects of water are due to bothmobile water and specifically bound water. The importance importanceof specific water binding is seen in simulations ofdrug–DNA interaction (as previously described) and alsoin simulation of O20-methylated DNA; the enhancedstability of methylated DNA is explained by specificwater–nucleic acid interactions in simulations ofr(CpG)12 . It is also an integral part of the protein–DNA interface . Water is also shown to be importantin RNA duplex melting. As the temperature increases, itis hypothesized that the entropy of the solvent increasessuch that it overcomes the enthalpic stabilization, leadingto a premelting of the solvent that facilitates duplexdisruption .

EMPIRICAL FORCE FIELD FOR NUCLEIC ACIDS

how well do they do?Empirical force fields for nucleic acids perform surprisinglywell, despite the absence of dynamic polarizabilityand the simplicity of the models. MD simulation on the14 ns timescale is shown to correspond well to the NMRNOESY data , although more recent studies questionthe ability of unrestrained MD simulations to reproreproducemethane C–H order parameters measured by NMR. We have also done an extensive force field comparisonand show that several of the current and widelyapplied nucleic acid force fields do an excellent job ofreproducing a variety of nucleic acid structures. The excellentperformance of the methods and force fields has enabledsome groups to push the methods to probe novel DNAstructures, such as an antiparallel Hoogsteen DNAduplex , base tautomers, carcinogen-damagedDNA [5-7], DNA on surfaces and antiparalleltriplex stabilization by modified bases . Continuedstudies on DNA quadruplex structures investigate theformation process via extensiveMDsampling of plausibleintermediates on the formation pathway, highlighting theimportance of the bound cations. Two 5S rRNA loopE motifs, with seven consecutive non-Watson–Crick basepairs, are well characterized inMDsimulation and display interesting structural features, including longlivedbound waters (10–20 times longer

than has beenseen in other MD simulations with similar methods) andtight monovalent or divalent ion binding sites that stabilizethe deep . MD simulations also haveprovided molecular insight into subtle differences inRNA loop–loop interactions with different base pairsclosing the hairpin and different sequences .One significant concern in the simulation of nucleic acidsto date relates not to the nucleic acid model itself, butto its surrounding salt and water environment. Whereasnucleic acid force fields have improved, correspondingchanges in the ion parameters have not emerged. RecentMD studies display a wide range of observed radialdistribution functions, coordination numbers and lifetimesacross a large set of commonly used ion parameters.The observed differences are a sobering reminder oflimitations as subtle misbalances that can lead to artifacts.For example, salt crystal formation was observedin simulations of phased A-tracts (TE Cheatham, unpublished).Balance of the parameters is a significantconcern and this led to the optimization of atomic radiiused in continuum electrostatics calculations with theCHARMM all27 force field.

SAMPLING ALGORYTHM

Finally, one needs to choose an appropriate dynamical/ sampling/optimization algorithm to guide exploration of conformational space. The choice is primarily dependent on the question at hand. If one is interested in kinetics or folding dynamics, molecular dynamics should be used; ithas been successfully employed to study folding processes of nucleic acids. Alternatively, Monte Carlo is a general sampling algorithm that can be used to generate conformational ensembles with continuous or discontinuous potentials alike. Such ensemblescan then be used to extract distributions of physical observables or to provide diverse models in structure prediction . If instead the objective is to locate local or globalminima of the scoring energy surface , optimization algorithms such as conjugategradient minimization or simulated annealing can be used.A major issue in molecular modeling is that sampledconformations often remain close to the initial startingmodel. This is because almost all potential energy functionsgive rise to energy barriers between low energyconformational basins; these barriers hinder transitionsbetween different low energy states. Sometimes suchbarriers are unnaturally high due to the potentials andDOFs used. Hence conformational transitions occur withlow probability in simulations, impeding effectivesampling of conformational space .In order to overcome these limitations, several technologicalinnovations have been proposed to speed upconformational exploration using the aforementionedsampling algorithms. Perhaps the most popular approachis to implement multi-canonical sampling algorithms thatmanipulate either the temperature or the potential. Other solutions to overcome barriers in extradimensions include data augmentation and couplingto extended systems . More complex solutionsreformulate the basic partition function (that describesthe system in thermodynamic equilibrium) in terms ofnew variables or change the underlying potential surface.

CONCLUSIONS

We have reviewed some key aspects and recent developmentsin the field of nucleic acid modeling. Despiteimproved computational resources and increased importanceof modeling in nucleic acid nanotechnology andbiomedicine, it remains crucial to interpret modelling results with utmost care: the accuracy of any particularmolecular modeling technique is only as good as thepotential energy function used. To avoid overinterpretationof modeling data, one needs

to be aware of thelimitations of the selected modeling protocol. Nonetheless,in many instances, carefully selected combinations ofthe appropriate molecular representation, potential energyfunction, DOFs and sampling algorithm yield sufficientlyaccuratemodeling results that can facilitate interpretationof experimental data and/or to guide future experiments.

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RSC Advances

PAPER

Anti-convulsant potential of quinazolinones†

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A series of novel quinazoline derivatives were synthesized, virtually screened through different filters and evaluated for their anticonvulsant activity against electrically and chemically induced seizures, compared with that of the standard drugs methaqualone and sodium valproate. Compound **48**, 3-(2-aminophenyl)-7-chloro-2-phenylquinazolin-4(3*H*)-one, was found to be the most potent compound of the series accompanied by relatively low neurotoxicity and low toxicity in the median lethal dose test as compared with the reference drugs. The obtained results showed that compounds **12**, **48**, **49** and **50** could be useful templates for future design, optimization, and investigation to construct more active analogs.

1. Introduction

Epilepsy is one of the most common neurological disorders, affecting about 1% of the world's population.[1] Being one of the world's oldest recognized disorders, it is surrounded by fear, discrimination, and social and frightening manifestations.[2] A global campaign against epilepsy conducted by the World Health Organization (WHO) in partnership with the International Bureau for Epilepsy (IBE) and the International League Against Epilepsy (ILAE) suggests that around 1% of the world's population at any time (about 50 million people worldwide) is afflicted with this neurological disorder.[3–6]

Methaqualone (a quinazoline analog) is an important landmark in the field of synthetic anticonvulsants; its chloro analog (mecloqualone) has been found to possess marked anticonvulsant potency, being 1.5 times more potent than phenytoin sodium against electroshock-induced convulsions and 10 times more active than troxidone against pentylenetetrazol (PTZ)-induced seizures.[7–12] A persistent problem with these compounds arises from the fact that nearly every derivative exhibits neurotoxicity values (TD_{50}'s) that are less than or only slightly higher than the effective doses (ED_{50}'s). Consequently, the protective index (PI) corresponding to TD_{50}/ED_{50} is too low.[13,14]

In view of the previous rationale and in continuation of an ongoing program aimed at finding new structure leads with potential anticonvulsant activities,[15] a new series of the 4(3*H*)-quinazoline pharmacophore was designed with substituted moieties possessing different electronic environments in the hope of developing potent and safe new effective compounds.

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2. Rationale

Various reported facts were analyzed before the chemical synthesis of our target compounds. The first fact was that modifications at the second and third positions of methaqualone have led to the generation of many CNS active agents such as afloqualone, etaqualone, mebroqualone and mecloqualone (Fig. 1). The second was that the presence of a phenyl group at the second position of quinazolin-4(3*H*)-one was more significant than a methyl and yielded more potent CNS active agents.[16,17] The third fact explained that substitution of the quinazolinone ring with halogens or an electron rich group at the sixth, seventh or eighth positions greatly enhanced the anticonvulsant activity and these compounds were reported to possess better activity, a longer duration and lower toxicity than phenytoin.[18,19] Fig. 1 represents the structural similarities and pharmacophoric features of some reported anticonvulsant quinazolinones and our designed compounds. Fig. 1 shows that the structure of the title final compounds fulfilled all of the pharmacophoric structural requirements. These requirements include: a quinazolin-4(3*H*)-one moiety as the hydrophobic portion, the *N* of the quinazoline ring as an electron donor system, the carbonyl group as a hydrogen bonding site and the phenyl ring at the 2-position as a hydrophobic domain responsible for controlling the pharmacokinetic properties of the anti-epileptic activity. Based on the previously mentioned facts,[16–18] the current study was carried out in the hope of developing potent, safe, new and effective anticonvulsant agents with low dose related toxicity and without idiosyncratic side effects.

3. Chemistry

Anthranilic acid **1** and 4-chloro 2-amino benzoic acid **39**, reacting with benzoyl chloride **2**, yielded 2-phenyl-4*H*-3,1-

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Review Article

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A review on endophytic fungi from *Musa paradisiaca* as anti-diabetic agent

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Abstract

Anciently fungi and photosynthetic organisms are used for the interactions like mutation and antagonism with providing the diversity for the chemical constituents who will lead to increase the synthesis of secondary metabolites. The approach is identical and providing the knowledge of potential secondary metabolite that fungi offer. Endophytic fungi are one of the sources of the phytoconstituents which are actively present in the plants. Endophytic fungi grow within host plant without causing disease symptoms. Few secondary metabolites have been produced isolated from the endophytic fungi relatively higher as compared to from soil sample. So, screening of endophytic fungi from herbaceous plants should be performed for the isolation of their biological activities and chemical properties. There are some factors which associated with the endophytic fungi growth like enzymes, good affinity between fungal endophyte and plant host, inhibition of photosynthesis of the host plant by fungal metabolites. Endophytic fungi are a group of multi cellular organisms in colonies like fungi grown in internal tissues of plants without causing any damagorial effects. It is estimated that approximately 1 million spieces of endophytic fungi available residing in plants. Endophytes may produce a substance that potentially useful to modern medicine, agriculture and industry such as antibiotics, antimycotics, immunosuppresants and anticancer and anti diabetic compounds will helpful us to identify new drugs from the endophytes for treatment of new disease in human and animals. *Musa paradisiaca* is a monoherbacious plant, belonging to Musaceae family, known as coarse banana in India. This plants belonging to 2 genera and 42 species among which 35 species are belongs to Musa species. The whole plant and its parts like Flowers, unripe fruits, leaves and stems of plant extract and its active chemical constituents utilized for the treatment of large number of human disease treatment. The chemical constituent in the different parts are available in the form of tannins, saponins, reducing and non-reducing sugars, sterols and triterpenes. Fruit consists of carbohydrates, amino acids, sugar, starch, protein was rich in arginine, aspartic acid, glutamic acid, methionine and tryptophan. The traditionally claimed the methanolic extracts of riped fruit of *Musa paradisiaca* significantly reduces the blood glucose concentration useful as a source of antidiabetic agent.

Key Words: *Musa paradisiaca;* antidiabetic agent; Endophytic fungi.

Introduction

Medicinal plants are frequently used in traditional medicine to treat different disease condition all over world (T. Ngarivhume *et al.*, 2015). The knowledge about this traditional medicine system has been significantly helping to develop more and more effective treatment options to cure disease without or least side effects. The ongoing process of finding new bioactive molecules for pharmaceutical and medicinal need, requires continues optimization. As per current novel drug molecule discovery practice one new molecule is found from the screening of 10000 natural products (B. Schulz *et al.*, 2002). The biologically active natural substances have played an important role in discovery of new beneficial chemical entities (M. Balunas *et al.*, 2005). A traditional plant which is used since decades, having multiple therapeutic use known as "*Musa paradisiaca* L" belonging to family Musaceae. It provides a important source of carbohydrate (food) all over the world (M. Zafar *et al.*, 2011). Commonly it is used to treat some disorders such as diarrhoea, diabetes, uraemia, hypertension, nephritis, gout, cardiac disease (D. Swathi *et al.*, 2011). Around the world there are more than 100 common name used for *Musa paradisiaca* but in most of the regions known as "Banana". More than 70 species have been identified of it. According to the study almost all parts it is having some kind of therapeutic activity (S. Kumar *et al.*, 2012). Here we are focusing on anti-diabetic activity of endophytic fungi which grows on flower of *Musa Paradisiaca*. Concentration of bio active molecules involved anti diabetic activity can be gradually increased by growing endophytic fungi on the flower. Such a natural product is adapted to specific function in nature; the search for novel secondary metabolites should concentrate on organism that inhibits novel biotopes. Endophytic fungi inhibit such as biotopes. Correlation is found between biological activity & biotopes. The relationship between flower and its endophyte is symbiotic whereby endophytes colonies the internal tissue of the plants without any adverse effect on the host. The potential role of endophyte and its biologically active compound relation with the host has been identified. The fungal endophytes possess some 'Exo-enzymes help to enhance colonise their hosts and they grow well in apoplastic washing fluid of their host. Therefore, endophyte utilize those biotopes of his and increase the concentration of secondary bioactive metabolites directly or indirectly (B. Schulz *et al.*, 2002). Worldwide the increasing cases of disease such as cancer, diabetes and other infectious disease resulted to an urgent need for new remedy drugs for novel mode of action. Clearly there is need for new and beneficial bio active compounds that provide relief against disease. Globally as an investigation report, it is estimated that the in world 285 million people are suffering from type-2 diabetes. In 2013 an estimated 381 people had diabetes. This number is increasing rapidly and by 2030, this number is estimated double (S. Wild *et al.*, 2004). Diabetes mellitus occur throughout the world but more commonly spreading in the

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BIOGRAPHY OF CARL NEUBERG

Carl Neuberg

Carl Alexander Neuberg (1877–1956) was an early pioneer in biochemistry, and he is often referred to as the "father of modern biochemistry". His notable contribution to science includes the discovery of the carboxylase and the elucidation of alcoholic fermentation which he showed to be a process of successive enzymatic steps, an understanding that became crucial as to how metabolic pathways would be investigated by later researchers.

Carl Sandel Neuberg was born on 29 July 1877 to a Jewish family in Hanover as the first child of Julius and Alma Neuberg. He was educated in the classical language gymnasium Lyceum I of the Ratsgymnasium until he was 15. In 1892 he moved with his parents to Berlin where he attended Friedrich-Werdersches Gymnasium. After graduating school in 1896, he studied astronomy, but soon switched to chemistry to comply with his father's wishes for him to become a master of brewery. He studied at the University of Würzburg and University of Berlin as well as Technischen Hochschule Charlottenburg.

On 21 May 1907, Neuberg married Franziska Helene (Hela) Lewinski, with whom he had two daughters, Irene Stephanie in 1908 and Marianne in 1911. His wife died from leukemia on 24 March 1929 at the age of 45. Neuberg was forced out of his job in 1934 under pressure from the Nazis. Just before the outbreak of the Second World War, he left Germany to work for a while at the University of Amsterdam, then travelled to Palestine via France during the war, eventually leaving in 1940 to move to the United States to join his daughters who had already settled there. He died on 30 May 1956 in New York after a prolonged illness.

Neuberg began his professional career working as an assistant in the physiological chemistry department of Charité in 1898 while he was still working on his doctoral thesis. He gained his PhD in 1900 working on the chemistry of glyceraldehyde under the supervision of Alfred Wohl at the University of Berlin. In 1903, Neuberg became a *privatdozent*, and in 1906 a professor at the University of Berlin.

Neuberg was the first editor of the journal *Biochemische Zeitschrift* he founded in 1906 which is now known as the *FEBS Journal*. In his early work in Germany, he worked on solubility and transport in cells, the chemistry of carbohydrates,photochemistry, as well as investigating and classifying different types of fermentation. He was also a pioneer in the study of the chemistry of amino acids and enzymes.

In 1913, Neuberg was invited to head the biochemistry section of the Kaiser Wilhelm Institute for Experimental Therapy, the director of which was August von Wasserman. Neuberg discovered in 1911 an enzyme "carboxylase" which catalyzed the decarboxylation of pyruvic acid. He also introduced methods for trapping of intermediate metabolites which allowed him to correctly interpret the steps and mechanisms of reactions, and formulate a theory for the alcoholic fermentation of glucose. Support for his theory was bolstered when he helped develop an industrial process that contributed materially to the German war effort in World War I, manufacturing glycerol—for the production of explosives—by the fermentation of sugar.

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