Anil Kumar Saxena ·
Sisir Nandi *Editors*

Global Trends in Health, Technology and Management

Proceedings of the 1st International Symposium GTHTM-2024

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Editors
Anil Kumar Saxena
Global Institute of Pharmaceutical Education and Research
Kashipur, Uttarakhand, India

Sisir Nandi
Global Institute of Pharmaceutical Education and Research
Kashipur, Uttarakhand, India

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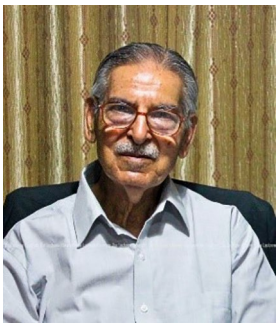
Tribute to Dr Nityanand and Dr V. P. Kamboj

As chairman of GIPER, GHTMF, and parent body Krishna Memorial Trust, it gives me immense pleasure to welcome you all to this international symposium. The Krishna Memorial Trust was founded in 1988 by the settler late Smt. Parwati Devi, my aunt/buaji, my father late Sri A L Saxena, and my mother late Mrs RD Saxena.

My father's principles that one should serve the place where he is born and my buaji wish to impart education to society inspired me to establish a primary school the Krishna Public Collegiate in the year 1987 which we started in huts. Now, after almost 37 years the small primary school has grown into a 10+2 school and a pharmaceutical research institute. Next to my father, Dr Nityanand, my mentor (guru) has been a key person who has supported me in my career and also beyond it.



Dr Nityanand was born on 1st January 1925 at Lyalpur, now in Pakistan. He got his B.Sc. from Lahore in 1943 and moved to St. Stephen's College, Delhi, for his M.Sc. in chemistry which he completed in 1945. He did his first Ph.D. from UDCT Mumbai with Prof K. Venkatraman and his second Ph.D. from Cambridge under Nobel laureate Lord Todd in 1949. He joined CSIR-CDRI in 1951 as a junior scientific officer and continued to work there till he retired on 31st Dec 1984 as Director CDRI. He made an immense contribution to Medicinal Chemistry in terms of more than 400 research publications, 130 patents, and 30 book chapters. During his tenure, he guided 90 Ph.D. students and above all invented drugs like Centbutindole, which was the first drug to be released from CDRI in the year 1986 and the other important one which is marketed under the name of Chaya, an oral contraceptive. Dr Nityanand has been awarded numerous awards including Padma Shri in 2012.

Dr. Nityanand has been associated with us and it was his love and affection that he dedicated the fully developed KPC from primary to 10+2 in the year 2002 and later the building of GIPER in the year 2020 to the society. He has been a guide in the development of GIPER through his message at many international conferences organised by the institute.

During my stay at CDRI, one other eminent scientist and a gem of a person who had been my close senior colleague and friend was Dr. Ved Prakash Kamboj. Dr Kamboj was born in Jalandhar on 1st April 1937 and did his B.Sc., M.Sc., and Ph.D. from the Punjab University, Chandigarh. He joined CDRI in the year 1961 as a research scientist and later also worked as director of the institute from 1995–1998. He obtained advanced training in reproductive biology from West Germany in the year 1975 and has been a pioneer in the country when it comes to the use of reproductive medicine. During his scientific tenure, he published over 300 research papers and had been very closely associated with the development of Chaya as a biologist.

He has also been closely associated with KPC and GIPER on various occasions including international conferences and annual functions.

Unfortunately, Dr Kamboj at age of 86 and Dr Nityanand at age of 99 left us on 21 November 2023 and 27 January 2024, respectively, towards immortality. We are missing both of them physically from this world, but I am sure their blessings are with us. I am sure their journey and dedication to science will be a source of inspiration to researchers and young students in years to come and their legacy will continue.

—Anil Kumar Saxena, Kashipur, India

Preface

The international symposium on Global Trends in Health, Technology and Management (GTHTM-2024) was organized by Global Health Techno Management Forum (GHTMF), Global Institute of Pharmaceutical Education and Research (GIPER), Kashipur, and Veer Madho Singh Bhandari Uttarakhand Technical University at Dehradun during March 15–17, in continuation of the previous international symposiums: Drug Design and Development Research (DDDR-2021), Current Trends in Pharmaceutical and Medical Sciences (CTPMS-2020), Computational Methods in Toxicology and Pharmacology Integrating Internet Resources (CMTPI-2017), and International Seminar on Pharmaceutical Education and Research (ISPER-2010). The symposium GTHTM-2024 (online and offline mode) started with the welcome of chief guest and participants from 14 countries by Hon'ble Vice-chancellor Prof. (Dr.) Onkar Singh followed by a tribute to eminent scientists Dr. Nityanand and Dr. V. P. Kamboj who had been deeply associated with the symposiums by me. In the inaugural session, lectures were delivered by His Excellency, the Hon'ble Governor of Uttarakhand, Lt. General Gurmit Singh, the Vice-Chancellor of KGMU, Prof. (Dr.) Soniya Nityanand, Dr. Omer Saka, a Health Economist and Business Development expert from Switzerland, and an online lecture by Prof. (Dr.) Gunda Georg, Regents Professor, University of Minnesota, USA.

There were 23 invited/plenary lectures and several oral and poster presentations covering a wide range of topics in the field of drug discovery and development including diseases like cancer, tropical and lifestyle diseases, agroecology, artificial intelligence, machine learning, environmental protection, green agriculture, global warming, digitalization in health care. Out of these 15 abstracts of invited lectures, one of the best oral and two abstracts of the best poster presentations along with the details of organizing committee and advisory board members have been included in the proceedings as the back and front materials respectively in addition to 22 chapters as the major contents in the proceeding of GTHTM-2024.

It has been a great pleasure in editing and compiling this proceeding along with my co-editor Dr. Sisir Nandi. I am very thankful to him and to all authors of 22 chapters for their contributions and valuable time in preparing the chapters. I also thank all the reviewers for their timely feedback and constructive comments. I gratefully acknowledge all the series editors of Topics in Medicinal Chemistry, particularly Prof. (Dr.) Gunda Georg, for the cooperation and support. Last but not least, thanks are also due to Dr. Sofia Costa and Ms. Neelofar Yasmeen and their team from Springer for their valuable assistance. I wish that this volume of proceeding will be useful to the researchers working in the field of health and its techno-management.

Kashipur, India — Anil Kumar Saxena

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12 March, 2024

Message

It is interesting to note that the Veer Madho Singh Bhandari Uttarakhand Technical University is organizing an International Symposium on "Global Trends in Health, Technology and Management" (GTHTM-2024) in association with Global Techno Management Forum and Global Institute of Pharmaceutical Education and Research (GIPER), Kashipur between March 15-17, 2024.

Global trends in health, technology, and management are rapidly evolving, reshaping industries and societies worldwide. In health, there's a shift towards personalized medicine, leveraging genomics and data analytics to tailor treatments. Telemedicine is also on the rise, improving access to healthcare, especially in remote areas. Technology trends like artificial intelligence (AI) and machine learning are revolutionizing management practices, enabling data-driven decision-making and automation of routine tasks. Virtual and augmented reality are transforming training and simulation in various industries, including healthcare and education. These trends highlight the need for continuous adaptation and innovation to stay competitive in the global landscape.

My best wishes to the organizers for the success of the international symposium, which will help accelerate sustainable growth in the field of health and its techno-management.

Gurmit

Lt Gen Gurmit Singh
PVSM, UYSM, AVSM, VSM(Retd)

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Prof. (Dr.) Onkar Singh
Vice Chancellor
प्रो० (डॉ०) ओंकार सिंह
कुलपति

Office Address :
Chakrata Road, P.O. Chandanwari, Premnagar, Suddhowala
Dehradun - 248007, Uttarakhand (India)
Phone No. : 0135-2774068,
Email : vc@uktech.ac.in, Website : www.uktech.ac.in

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It is my great pleasure to note that **Global Institute of Pharmaceutical Education and Research (GIPER), Kashipur** has formed an international forum by the name of Global Health Techno Management Forum (GHTMF) and is organizing an international symposium entitled **"International Symposium on Global Trends in Health, Technology and Management" (GTHTM-2024)** under the aegis of Veer Madho Singh Bhandari Uttarakhand Technical University from March 15-17, 2024. It makes a very good sense for excellent in the begining of 2024 because this both offline and online symposia will be a brain storming for the leading scientists, young researchers, academicians and students globally to create an open platform for discussing and resolving pertinent issues in the field of health, medicine, technology and management. I complement you all for the great efforts which may create enough well-trained human resources in the field so that these benefits are available to society all the time.

With warm wishes for the success of this symposia.

6/03/2024

Vice-Chancellor
Veer Madho Singh Bhandari Uttarakhand Technical University,
Dehradun, India

GLOBAL INSTITUTE OF PHARMACEUTICAL EDUCATION & RESEARCH (GIPER)

CONDUCTING BACHELOR IN PHARMACY (B. PHARM) & MASTER IN PHARMACY (M. PHARM)
Approved by AICTE & PCI, New Delhi. Affiliated to Uttarakhand Technical University, Dehradun

It is of immense pleasure that the Global Institute of Pharmaceutical Education and Research (GIPER), Kashipur, has formed an international forum by the name of Global Health Techno Management Forum (GHTMF) and is organizing an international symposium entitled **"International Symposium on Global Trends in Health, Technology and Management" (GTHTM-2024)** under the aegis of Veer Madho Singh Bhandari Uttarakhand Technical University from March 15-17, 2024. The conference covers several topics under the broad research heads pharmaceuticals, medical and biomedical sciences, health and technology management, environmental protection, natural resources, green agriculture, cyber security, sustainable development goals, digitalization in health care and public health. The recent COVID-19 pandemic has shown the need for multi-sectoral coordination and collaboration when it comes to solving unpredicted challenges such as natural calamities or disease outbreaks. It will be useful to provide a common platform for the innovative minds of a large number of eminent thinkers, scientists, educationists, business leaders, researchers and students to develop collaborative relationships among different specialities, industrial sectors and public-private organizations. One must think from a border perspective and there is a need for collaboration at a global level. This International Symposium provides a platform to bring stakeholders from different fields of expertise to come together, exchange their ideas and work together for the betterment of society. I wish that due emphasis on these aspects shall be helpful to translate the real benefits of the current developments to the common man for improving health and the environment in which GIPER may play an important role.

It is very graceful to combine the inauguration of this conference with the blessings of my mentor Dr. Nitya Anand who passed away at 99 years.

I welcome you all and look forward to your active participation in making this event a success. I take this opportunity to thank an elite gathering of scientists, educationists, business leaders and other professionals for taking pains to grace this occasion with their benign presence. I appreciate the sincere efforts of the members of the organizing committee and staff and students of the Global Institute of Pharmaceutical Education and Research, Kashipur and Veer Madho Singh Bhandari Uttarakhand Technical University for their active participation. I hope this event is a success.

Dr Anil Kumar Saxena
Chairman

Jaspur Road, Kashipur-244713, Udham Singh Nagar (Uttarakhand)
Ph. : 9219476108, 9839012951, 9997722274, www.giper.edu.in, E-mail : kmt.giper@gmail.com

Contents

Quantitative Structure Interaction Activity Relationship (QSIAR) as a Novel Approach to Drug Design: A Case Study of Anti-tubercular Agents

Anil K. Saxena[1] (✉)

[1] Department of Pharmaceutical Chemistry, Global Institute of Pharmaceutical Education and Research, Kashipur, Uttarakhand, India

Abstract Computer-aided drug design (CADD)—an effective tool in the process of drug design and discovery—consists of ligand-based drug design (LBDD) and structure-based drug design (SBDD). The SBDD has gained importance in recent years due to the developments in molecular biology including genomics, proteomics, and structural information of new targets. Docking scores play a key role in analysing the results in terms of interactions between the structural components of the interacting molecule with the target protein. The docking scores generally do not correlate with the observed biological activity. This may be attributed to the limitations in scoring functions used in docking algorithms that often fail to account for crucial factors like entropy change, solvation effects, and interactions, contributing to binding affinity limiting the accurate prediction of binding energy changes, which may result in the poor correlations between observed biological activity and docking scoring functions. In this context, a maiden novel approach (quantitative structure interaction activity relationship (QSIAR)) has been applied to address this issue by taking into account the specific interactions between a ligand and the amino acid residues present at the active site as independent and biological activity as dependent parameter(s) in quantitative terms to explain the observed anti-tubercular activity as mycobacterium ATP synthase inhibitory activity in diverse molecules such as 4-substituted amino sulphonyl-2-methyl-7-chloroquinolines, bisquinoline, imidazo[1,2-a]pyridine ethers, and squaramides. The developed and validated quantitative model(s) have led to the identification of novel leads through virtual screening of the focussed libraries for the development of new anti-tubercular agents.

Keywords Tuberculosis · ATP synthase · QSIAR · Virtual screening · SBDD

A. K. Saxena, S. Nandi (eds.), *Global Trends in Health, Technology and Management*, https://doi.org/10.1007/978-3-031-75457-9_1

1 Introduction

The quest for identifying novel chemical entities (NCEs) as therapeutic agents requires exhaustive research. It is intensive both in terms of time and expenses and requires the integration of chemistry and biology. As per the current updates, the time required for a new chemical to reach clinical trials is approximately 8.3 years with a median cost of $985 million dollars [1]. The estimated cost, of introducing a new drug from the starting of the process of drug discovery and development till the approval of drug for marketing, in terms of time and money is approximately 12 years and 2.6 billion dollars, respectively [2, 3]. The principles of early drug discovery during the preclinical development phase involve target identification, target validation, hit discovery, or NCE identification for optimization leading to candidate drug for development [4]. In the past, the above process depended on chance findings or conventional trial-and-error techniques, frequently requiring decades and significant resources with little assurance of success [5]. It is understandable that both time and money need saving and unsurprisingly the research and development units of pharmaceutical companies sought ways to overcome these limitations through the advancements in computational technology and molecular biology in the late twentieth century. In recent years, there has been an increase in computing capacity of the machines, development in machine learning, and accumulation of omics data [6]. More recently, the emergence of artificial intelligence (AI) has been a game changer [7–9] in the identification of hits/lead compounds and faster validation of drug targets for improved optimization in the process of drug design and discovery [10, 11]. The drug design and development through computers also known as computer-aided drug design (CADD) has been a cornerstone in the process of drug discovery. CADD combines the complex biological systems with predictive computational algorithms and helps in the development of selected databases containing chemical and biological data [12]. The CADD has resulted in the discovery and optimization of various drugs such as saquinavir, boceprevir, oseltamivir, rupintrivir, zanamivir, aliskiren, captopril, dorzolamide, nolatrexed, etc. [13]. The identification and optimization of ligands for therapeutic application has been a major goal of computer-aided drug design, which incorporates both structure-based and ligand-based techniques. When a group of bioactive chemicals share a similar target but lack protein structure information, ligand-based (indirect) drug design makes it easier to identify important chemical structural features in the group. The main aim of ligand-based drug design (LBDD) is to create predictive models capable of quantitatively grading the molecules between actives and inactives. The LBDD was the main technique used in CADD until the middle of the 1980s, and from 1990s onwards, structure-based drug design (SBDD) began to appear in the horizon, which with the advent of identification of molecular targets through molecular biology and genomics began to flourish [14]. This then further led to the integration of both LBDD and SBDD in developing more robust models than the ones developed through either of the approaches [15]. This integrated approach has been widely used for virtual screening, which is an efficient tool for drug discovery process [16]. The SBDD involves the prior knowledge of a validated protein target (associated with a particular human disease) and also gives information about the important amino acid residues involved in ligand-target interactions resulting

through the binding of the ligand to the target. Molecular docking is routinely used to understand the interaction pattern of the ligand binding at the target site and to enumerate important contacts, such as van der Waals interactions, polar contacts, etc. The typical algorithm for molecular docking involves using sampling methods to generate potential ligand binding conformations, after which a scoring function is employed to rank the ligands based on their binding affinity, determined by energy terms (binding energy) [17, 18]. The ligand-receptor docking is performed through computer programs that rely on some scoring functions, which essentially describe the interactions between the ligand and the protein target (receptor). The SBDD offers several advantages over the LBDD, the main being the consideration of protein structure making it more biologically relevant, in addition to ligand structures, along with the determination of active conformation of the ligand. It also suffers from certain disadvantages such as non-consideration of protein flexibility in most of the software, accuracy in the pose prediction, and non-proportionality between the docking scores (binding energy) [16]. Pose prediction is linked with the scoring function since the most probable orientation of the ligand in the active site is ranked as per the scoring functions obtained through docking [19]. The scoring functions used in molecular docking are classically categorized as force field and knowledge-based, in addition to empirical scoring functions. These scoring functions evaluate the binding affinity of the compounds with the target protein [20–22]. The limitations of these scoring functions have been reported and may be attributed to (i) neglecting the overall entropic changes and solvation effects, (ii) oversimplification of binding affinity between the ligand and the protein only as a linear relationship between binding affinity and ligand-protein interactions with an additive approach, and (iii) inability to predict uncommon protein-ligand interactions [23–25]. Despite advancements in the classical scoring functions, unsatisfactory correlations with experimental binding affinity still exist with some of the classical scoring functions overestimating the accuracies of protein-ligand interactions in certain cases [26]. In recent years, these limitations in the classical scoring functions have been addressed by the introduction of machine learning scoring functions based on neural network approximations of the binding affinity as a function of the positions and identities of atoms of protein and ligand [27]. However, increasing concerns have emerged about the generalizability of machine learning models in terms of dataset biases instead of actual physical interactions leading to scoring errors and incorrect predictions of the biological activity [28–30]. It is also known that due to some of these problems, the binding energy often does not correlate with the observed biological activity. Moreover, the binding preference of a ligand at the receptor site is influenced not only by a favourable complementary interaction pattern but also by its competing interactions with the solvent and the flexibility at the receptor site [31]. Hence, it has become a necessity to formulate a novel methodology to address this chronic issue. In this paper, we discuss a novel methodology, known as quantitative structure interaction activity relationship (QSIAR), where the docking interactions between the ligand and the amino acid residues (AARs) present at the active site of the protein target are given weightage, which circumvents the reliance on the scoring functions. The weighed interactions are treated as independent and the observed biological activity as dependent variable for the development of predictive models through multiple regression analysis. This methodology also addresses a very peculiar issue of dealing with enantiomers where the activity of

racemic compounds is only given, which makes the prediction of individual enantiomer a grave issue. We also present the case studies wherein this methodology has been used for the identification of novel chemical entities as ATPase inhibitors for the prevention of tuberculosis (TB) [32, 33].

2 Quantitative Structure Interaction Activity Relationship (QSIAR)

The novel maiden methodology to address the issues highlighted above, known as quantitative structure interaction activity relationship (QSIAR), takes into account the specific interactions between a ligand and the amino acid residues present in the active site. This methodology is based on the utilization of the results of the docking studies in terms of interactions between the ligand and amino acid residues (AARs). Thus, the interactions of the ligand molecule with the amino acid residues of the target protein are given weightage and are considered as independent parameters, while the binding energy/affinity, docking scores/biological activity, is considered as a dependent parameter. However, a particular amino acid residue may sometimes show more than one interaction with different atoms/groups constituting the ligand molecule, while in some cases, it may show just one interaction. A protocol to give weightage to such type of interactions was devised in such a way that in case of multiple interactions of one AAR with the ligands, the interactions were considered by adding all the interactions to yield the parameter describing the combined interactions, whereas, in case of single interaction protocol, just the presence or absence of interaction (instead of counting all the interactions) is considered and assigned the value of '1' and '0', respectively. Hence, an interaction matrix is designed where the number of interactions present with each AAR is meticulously noted and the resultant data is organized in two ways, namely, the single weightage (S) and combined weightage (C). So, for 'S', any number of interactions with a particular residue was considered as a single interaction parameter describing the presence of interaction(s) with a particular AAR and is assigned a value of '1' for this parameter, while in the absence of any interaction, the same was given a value of '0'. In case of the combined weightage (C), all interactions with a particular AAR were added, considering each additional interaction to contribute to its score to get the value of (C). The above solution is easily applicable for normal molecules without any asymmetric atom or achiral molecules; however, in case of chiral molecules, all enantiomers need to be considered for docking studies in spite of the available biological data for racemic compounds. Hence, for the racemic compounds, the interactions are considered for constituting enantiomers, and the combined interaction parameter for each AAR present in one or all enantiomers is calculated by adding the number of interactions present in each enantiomer for that AAR. Thus, these weighted parameters describing the number of interactions of the ligand molecule with the amino acid residues of the target protein are considered as independent parameters, while the binding energy/affinity, docking scores/biological activity, is considered as a dependent parameter. The QSIAR

model(s) are then developed on the curated data using MLR or other statistical analyses used in QSAR. The QSIAR model can be presented in the following form:

$$\mathbf{BA} = \mathbf{Const.} + \mathbf{a}_1\mathbf{AAR}_1 + \mathbf{a}_2\mathbf{AAR}_2 + \ldots\ldots\ldots\mathbf{a}_n\mathbf{AAR}_n \quad (1)$$

where:BA = binding energy/affinity, docking scores/biological activityAAR = interacting amino acid residue

The protocol described above is explained in Fig. 1 where the interactions of Glu65b AAR are described. In the case of compound 1, the AARs are Glu65b (AAR_1), Leu63a (AAR_2), Phe69b (AAR_3), Leu72b (AAR_4), and HOHb (AAR_5), which display interactions with the ligand molecule. The Glu65b residue shows one interaction each with the hydroxyl group, methylene group, nitrogen of the amino group, N-ethyl group, and phenylene group of the ligand molecule, thus accounting for a total of five interactions. As per the protocol discussed above, the combined weightage (C) of Glu65b will be 5; hence, the value of the independent combined interaction parameter for AAR_1 will also be 5. In the case of single weightage (S), we just see the presence and absence of interaction; hence, the value of independent single interaction parameter AAR_1 will be 1. Similarly, the independent combined and independent single interaction parameter values for each of AAR_2 (Leu63a), AAR_4 (Leu72b), and AAR_5 (HOHb) will be 1 and 1, respectively, while for AAR_3 (Phe69b), which has two interactions, these values will be 2 for (C) and 1 for (S). In the case of enantiomers, the interactions for each enantiomer were noted, and after obtaining the parameter values for both enantiomers by (C) and (S) protocols, the interactions of both enantiomers were combined separately for both (C) and (S) protocols to yield the final composite weightage of interaction parameters for the racemic molecule. This is described taking the example of compound 2 for which the docking results of both the enantiomers (R and S) were analysed. The (R) enantiomer of compound 2 showed interactions with Glu65b (AAR_1), Leu63a (AAR_2), Leu72b (AAR_3), HOHb (AAR_4), Tyr68b (AAR_5), and Ile70a (AAR_6). So, the (C) values for AAR_1, AAR_2, and AAR_6 were 7, 3, and 2, respectively, while the (C) values for the rest of AARs were 1 due to the presence of just one interaction. The (S) values for all the AARs will be 1 based on the presence of the interaction. The (S) enantiomer also

Comp. No.	R/S	Activity	Glu65b	HOHb	Tyr68b	Ala66b	Phe69b	Asp32b	Leu72b	Ile70b	Val61b	Gly62b	Phe57b	Phe58b	Phe74b	Leu63a	Ile70a	Ala66a	Phe74a	Ile59a	Gly62a	Glu65c	Phe69c	Leu72c	Docking score
01	-	0.443	5	1	0	0	2	0	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	-4.767
02	R	1.301	7	1	1	0	0	0	1	0	0	0	0	0	0	3	2	0	0	0	0	0	0	0	-6.778
	S	1.301	7	1	1	0	0	0	1	0	0	0	0	0	0	3	1	0	1	0	0	0	0	0	-7.332

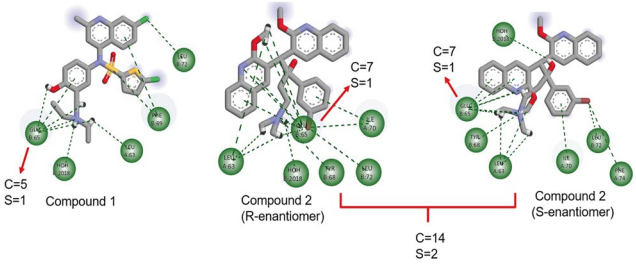


Fig. 1 Detailed discussion of providing weightage through the combined 'C' and single 'S' protocols

shows the above AARs in addition to Phe74a (AAR_7). The (C) values for AAR_1 and AAR_2 were 7 and 3, while for the rest of AARs, the (C) values were 1. The (S) value will be 1 for all the AARs. These individual values of AARs obtained for both the enantiomers are added to give the combined weightage of the racemic compound in which the (C) values for AAR_1, AAR_2, AAR_3, AAR_4, AAR_5, AAR_6, and AAR_7 will be 14, 6, 2, 2, 2, 3, and 1, respectively, while the (S) values will be 2 each for AAR_1 to AAR_6 and 1 for AAR_7.

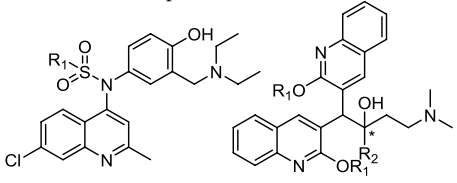
3 Case Study on the Docking Analysis of M.Tb. ATP Synthase Inhibitors

Tuberculosis (TB) is a serious infectious disease that affected around 10.6 million and claimed 1.3 million lives in 2022 [34]. The severity of TB increased with the resistance to normally used TB drugs leading to multi-drug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB). There have been numerous studies on the chemotherapeutics to contain this dreadful disease [35–38]. There has also been development towards the identification of novel drug targets against which NCEs can be developed [39, 40]. Among the different drug targets, the ATP synthase of mycobacterium is particularly significant because it has recently been identified as a target for newly introduced potential anti-TB compounds, notably bedaquiline (BDQ). ATP synthase is an important enzyme in the process of oxidative phosphorylation involved in the production of adenosine triphosphate (ATP) [41, 42]. BDQ became a drug of choice for the MDR-TB but has recently been reported for resistance through various mechanisms [43–45]. The emergence of resistance has prompted researchers to search for new molecules against ATP synthase.

In quest for finding NCEs active against TB, the QSIAR methodology was applied for the first time on the docking studies on the dataset of analogues of 4-substituted amino sulphonyl-2-methyl-7-chloroquinolines (1–16) and bisquinoline (17–25) cores [46, 47] (Table 1) as M.Tb. ATP synthase inhibitors. The docking studies were performed using the crystal structure of a mycobacterial ATP synthase rotor ring in complex with bedaquiline (pdb id: 4V1F) [48] imported from the protein data bank (www.rcsb.org).

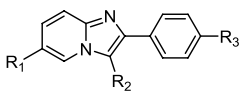
As discussed above, the interactions were noted using both as discussed above and described in Fig. 1. Since the dataset comprised of inhibitory activity of the racemic molecules also, the average docking scores were obtained from the respective enantiomers (both R and S) of the racemic molecules. Since the docking scores and the observed biological activities do not usually correlate, the same was observed for this dataset, which also showed a poor correlation of 0.0351 and 0.0617 for compounds 1–16 and 17–25, respectively. Both the datasets (compounds 1–16 and 17–25) were later combined so that a larger number of independent parameters as compared to individual datasets may be used in the QSIAR analysis. The correlation studies between the independent interaction parameters developed as per the (S) and (C) protocols and the observed biological activity as dependent parameter were done through the Minitab

Table 1 Compounds from the dataset with ATP synthase inhibitory activity reported in the literature [44, 45, 48]

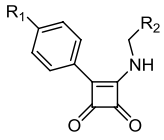


1-16

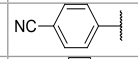
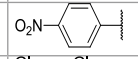
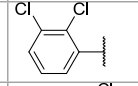
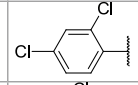
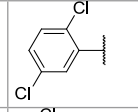
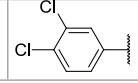
17-24



25-46

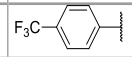
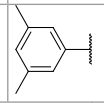
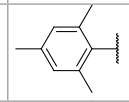
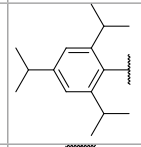
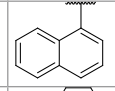
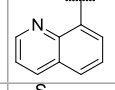
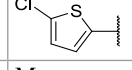


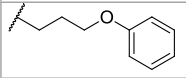
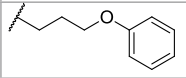
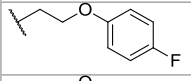
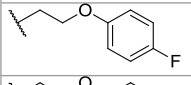
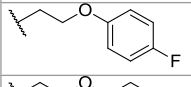
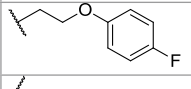
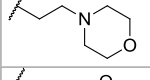
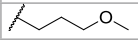
47-52

Comp no.	R_1	R_2	R_3	Activity in pIC_{50} (μM)		Combined interaction parameter (C) values				
				Observed	Estimated/predicted[a]	Glu65b	HOHB	Ala66b	Phe69b	I
1		–	–	0.275	−0.263	3	1	0	0	1
2[b]		–	–	0.13	−0.268	2	0	1	2	1
3[b]		–	–	0.408	0.405	4	1	1	0	1
4[b]		–	–	0.292	0.91	4	0	0	0	1
5[b]		–	–	0.2	−0.648	5	2	0	1	1
6[b]		–	–	−0.127	−0.681	3	1	1	2	1
7		–	–	−0.1	−0.964	0	0	0	1	1

(continued)

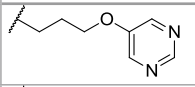
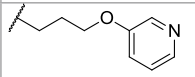
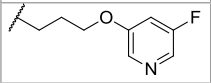
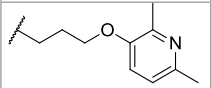
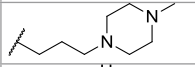
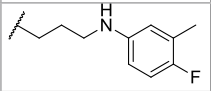
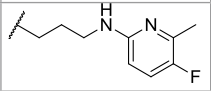
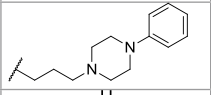
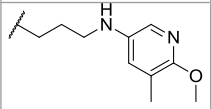
Table 1 (continued)

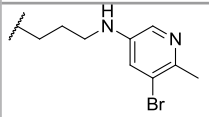
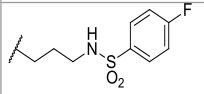
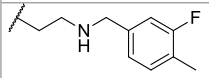
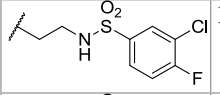
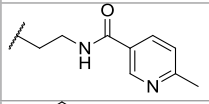
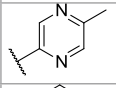
Comp no.	R_1	R_2	R_3	Activity in pIC_{50} (μM)		Combined interaction parameter (C) values				
				Observed	Estimated/predicted[a]	Glu65b	HOHB	Ala66b	Phe69b	I
8		–	–	−0.133	−0.203	2	0	0	1	1
9		–	–	−0.262	0.177	3	0	0	1	1
10[b]		–	–	−0.017	0.139	4	0	1	3	1
11		–	–	−0.517	−0.324	0	0	1	0	1
12		–	–	0	−0.0152	4	1	2	2	1
13[b]		–	–	0.036	0.084	2	0	1	1	1
14[b]		–	–	−0.267	−0.356	2	1	1	0	1
15[b]		–	–	−0.195	−0.241	3	0	1	3	1
16		–	–	0.443	−0.209	5	1	0	2	1
17	Me	Phenyl	–	1.154	2.179	10	2	2	0	1
18	Me	3-Bromophenyl	–	1.301	3.1258	14	2	0	0	1

Comp no.	R_1	R_2	R_3	Activity in pIC_{50} (μM)		Combined interaction parameter (C) values				
				Observed	Estimated/predicted[a]	Glu65b	HOHB	Ala66b	Phe69b	I
19[b]	CH_2 - CH = CH_2	Phenyl	–	1.397	1.634	11	2	0	1	1
20	CH_2 - CH = CH_2	3-Bromophenyl	–	1.522	1.5662	11	2	1	2	1
21[b]	CH_2 - CH = CH_2	4-Bromophenyl	–	0.522	1.448	9	2	2	1	1
22[b]	CH_2 - CH_2 - CH = CH_2	4-Bromophenyl	–	1.096	1.182	9	1	2	4	1
23[b]	Me	2-Naphthyl	–	1.522	1.388	10	3	2	1	1
24	Me	4-Bromophenyl	–	2	1.252	10	2	0	1	1
25[b]	H		H	0.886	0.926	1	0	1	0	0
26[b]	CH_3		H	1.522	1.307	2	0	1	0	0
27	H		H	1.097	0.926	1	0	1	0	0
28	Cl		H	1.398	1.019	2	0	0	0	0
29[b]	CH_3		H	1.301	0.227	2	1	0	0	0
30[b]	CH_3		F	1.699	0.514	2	1	1	0	0
31[b]	Cl		H	−1.557	−1.04	0	2	1	0	0
32	H		H	−1.276	−1.04	0	2	1	0	0

(continued)

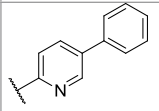
Table 1 (continued)

Comp no.	R_1	R_2	R_3	Activity in pIC_{50} (μM)		Combined interaction parameter (C) values				
				Observed	Estimated/predicted[a]	Glu65b	HOHB	Ala66b	Phe69b	I
33[b]	H		H	−0.748	−0.599	0	1	1	1	0
34	CH_3		F	0.796	0.926	1	0	1	0	0
35	CH_3		F	1.222	1.306	2	0	1	0	0
36	CH_3		F	1.046	1.213	1	0	2	0	0
37	CH_3		H	−0.806	−0.507	1	1	0	1	0
38[b]	CH_3		F	2.301	1.687	3	0	1	0	0
39[b]	CH_3		F	1.222	1.019	2	0	0	0	0
40	CH_3		F	1.301	1.306	2	0	1	0	0
41[b]	CH_3		F	1.097	0.536	2	0	2	3	0

Comp no.	R_1	R_2	R_3	Activity in pIC_{50} (μM)		Combined interaction parameter (C) values				
				Observed	Estimated/predicted[a]	Glu65b	HOHB	Ala66b	Phe69b	I
42[b]	CH_3		F	0.678	1.148	1	0	3	1	0
43	CH_3		F	0.155	−0.313	0	1	2	1	0
44[b]	CH_3		F	1.155	1.307	2	0	1	0	0
45	CH_3		F	0.398	0.926	1	0	1	0	0
46[b]	CH_3		F	−0.857	0.259	0	0	0	0	0
47	CF_3		–	0.523	−0.286	1	1	2	2	0
48	CF_3		–	−0.924	−0.094	0	0	0	1	0
49[b]	CN		–	−1.823	−0.859	1	1	0	2	0
50			–	1.523	0.226	2	1	0	0	0

(continued)

Table 1 (continued)

Comp no.	R_1	R_2	R_3	Activity in pIC_{50} (μM)		Combined interaction parameter (C) values				
				Observed	Estimated/predicted[a]	Glu65b	HOHB	Ala66b	Phe69b	I
51			–	0.113	−0.573	1	1	1	2	0
52[b]			–	−0.978	−0.534	0	1	0	0	0

[a]Estimated and predicted activity of the training and test compounds, respectively, using Eq. (5)

[b]Training set compounds (remaining compounds comprised the test set)

software and are discussed in detail in the paper [32]. Firstly, the (S) protocol was used for the model development. However, the initially developed model containing all the parameters was not considered in view of very poor degrees of freedom as per the concept of five observations per parameter that is to say three degrees of freedom per parameter. Hence, the independent parameters describing the correlation were subsequently reduced in a backward stepwise regression manner, which gave a statistically significant (>99.9%) equation (Eq. (2)) having R^2 value of 82.4% and good correlation coefficient (R = 0.907).

$$\mathbf{pIC_{50}} = -0.881 + 0.659(\pm 0.1999)\text{Glu65b} + 0.595(\pm 0.1738)\ \ \text{HOHb} \\ -0.468(\pm 0.2444)\text{Ala66a} + 0.569(\pm 0.2083)\text{Gly62a} \tag{2}$$

$$n = 25, R^2 = 82.4\%, R - Sq(adj) = 78.9\%, F = 23.37, S = 0.3945, R - Sq(pred) = 68.09\%$$

Secondly, to check the importance of number of interactions between the AARs and the ligand molecule and to compare the results between the (S) and (C) protocols, a model based on the independent combined interaction (C) parameter was developed containing all the parameters, which was also reduced on similar grounds as described for (S) protocol to derive Eq. (2). During the reduction process, one compound acting as outlier because of its exceptional behaviour was removed [32]. It resulted in the development of single parameter equation (Eq. (3)), which was statistically significant (>99.9%) and explained 82.5% variation in activity with a good correlation coefficient value of R = 0.908.

$$\mathbf{pIC_{50}} = -0.428 + 0.161(\pm 0.01582)\text{Glu65b} \tag{3}$$

$$n = 24, R^2 = 82.5\% R^2(adj) = 81.7\%, S = 0.301, F = 103.89, R - Sq(pred) = 77.71\%$$

Although both Eq. (2) and Eq. (3) explained the variance in activity, there is a slight advantage of Eq. (3) over Eq. (2). The activity variance was explained by just one parameter (Glu65b) in Eq. (3), which was being explained by four parameters in Eq. (2), and moreover, the regression coefficient for the combined interaction parameter (C) for Glu65b is 100% significant in Eq. (3), unlike the regression coefficients for the (S) parameter of the four AARs in Eq. (2). The importance of Glu65b has also been explained in previous reported literature [48]. Nonetheless, both the developed models (Eq. (2) and Eq. (3)) were used to predict an external dataset [49] where the biological activity was reported in IC_{90}. An unbiased selection of 12 compounds from external 71 compounds comprising of the most, the least, and some evenly spaced compounds was used for the purpose of prediction. The results were overwhelmingly in favour of the protocol (C) (Eq. (3)), which showed correlation coefficient (R_{ext}) of 0.851 as compared to 0.14 obtained through (S) protocol (Eq. (2)) (Fig. 2).

Further to explore the QSIAR methodology described above in the development of predictive models, a diverse set of 28 compounds belonging to imidazo[1,2-a]pyridine

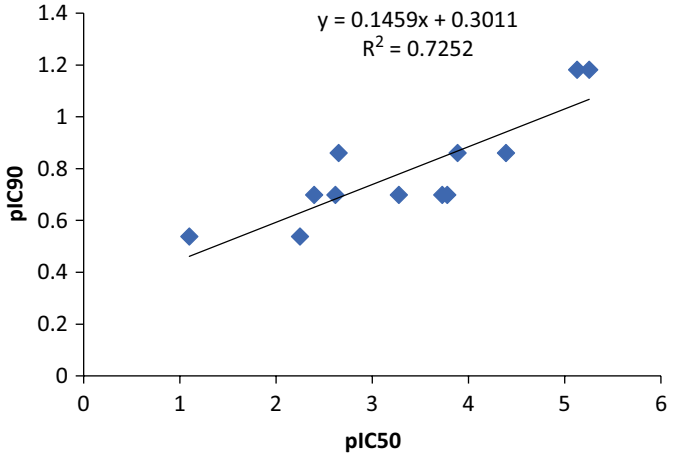


Fig. 2 Correlation between the predicted pIC_{50} vs observed pIC_{90} values of the external dataset (12 compounds)

ethers and squaramides [50] (Table 1; compound no. 25–52) was considered. In view of the better results of the protocol (C) than (S), the same procedure using the (C) protocol was applied, which resulted in the initial equation with all the parameters, which on reduction (as discussed for Eq. (2) and Eq. (3)), till no further improvement was possible, resulted in equation (Eq. (4)) with a correlation coefficient (R) value of 0.84 explaining 71% variation in activity.

$$\mathbf{pIC_{50}} = -0.845 + 1.094\left(\pm 0.137\right)\mathrm{Glu65b} \tag{4}$$

$$n = 28, R^2 = 71.00\%, R - Sq\left(adj\right) = 69.88\%, S = 0.615, F = 63.65, R - Sq\left(pred\right) = 67.75\%$$

The results obtained in Eq. (4) were similar to Eq. (3) since both the equations explained the variance in activity by just one similar parameter, i.e. Glu65b. Encouraged by these results, the datasets used in developing Eq. (3) and Eq. (4) were combined to yield a larger dataset of 52 compounds, which was divided into training and test set for further analysis. All the 52 molecules were first arranged in decreasing order of activity and divided into 2 sets [training set (27 molecules) included the most and the least active molecules along with every alternate molecule, while the test set (25 molecules) included the rest of the molecules]. To account for the difference in the structures and to also give weightage to the important quinoline substructure, an indicator variable (I) was added where the value of (I) was assigned as 1 and 0 for the presence and absence of quinoline substructure, respectively. The modelling on the training set of 27 molecules yielded Eq. (5) with five parameters, which was >99.9% statistically significant having correlation coefficient (R) value of 0.82 with explained variance of 67.7%.