ONOMY Science

American Journal of Petrochemistry

Research Article Open Access

A unique Mycobacterium ESX-1 protein Inhibitors Identified by Virtual Screening and 4D Fingerprints

Donescu D T and Rivera Kukhar

Centro de Nanociencias y Nanotecnología, Universidad Nacional Autónoma de México, Ensenada, Baja California, C.P. 22860, Mexico

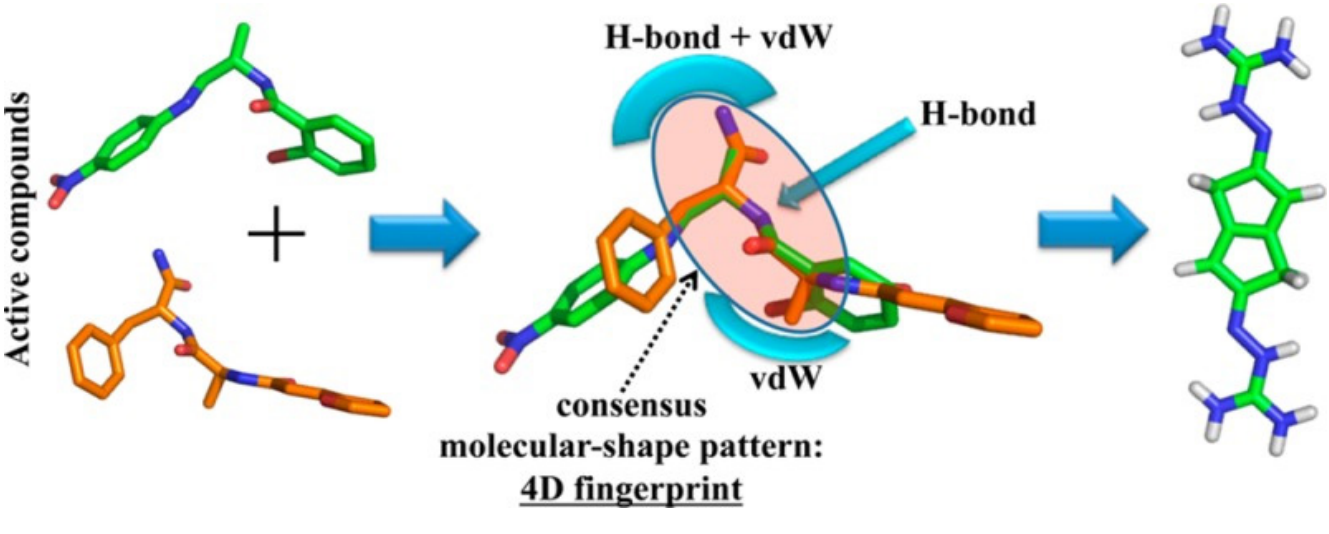
***Corresponding Author:** Rivera Kukhar, Centro de Nanociencias y Nanotecnología, Universidad Nacional Autónoma de México, Ensenada, Baja California, C.P. 22860, Mexico

Citation: A unique Mycobacterium ESX-1 protein Inhibitors Identified by Virtual Screening and 4D Fingerprints. Am J Petroche. 2019; 1(1): 001-007.

Submitted: 16 May 2019; **Approved:** 28 May 2019; **Published:** 29 May 2019

Abstract

The rise of drug-resistant Mycobacterium tuberculosis lends urgency to the need for new drugs for the treatment of tuberculosis (TB). The identification of a serine protease, mycosin protease-1 (MycP1), as the crucial agent in hydrolyzing the virulence factor, ESX-secretion-associated protein B (EspB), potentially opens the door to new tuberculosis treatment options. Using the crystal structure of mycobacterial MycP1 in the apo form, we performed an iterative ligand- and structure-based virtual screening (VS) strategy to identify novel, nonpeptide, small-molecule inhibitors against MycP1 protease. Screening of ~485 000 ligands from databases at the Genomics Research Institute (GRI) at the University of Cincinnati and the National Cancer Institute (NCI) using our VS approach, which integrated a pharmacophore model and consensus molecular shape patterns of active ligands (4D fingerprints), identified 81 putative inhibitors, and in vitro testing subsequently confirmed two of them as active inhibitors. Thereafter, the lead structures of each VS round were used to generate a new 4D fingerprint that enabled virtual rescreening of the chemical libraries. Finally, the iterative process identified a number of diverse scaffolds as lead compounds that were tested and found to have micromolar IC50 values against the MycP1 target. This study validated the efficiency of the SABRE 4D fingerprints as a means of identifying novel lead compounds in each screening round of the databases. Together, these results underscored the value of using a combination of in silico iterative ligand- and structure-based virtual screening of chemical libraries with experimental validation for the identification of promising structural scaffolds, such as the MycP1 inhibitors.



Cite this article: A unique Mycobacterium ESX-1 protein Inhibitors Identified by Virtual Screening and 4D Fingerprints. Am J Petroche. 2019; 1(1): 001-007.

Introduction

Mycobacterium tuberculosis, the agent causing tuberculosis (TB), is responsible for significant worldwide morbidity and mortality, estimated at more than 1.3 million deaths in 2012 according to the World Health Organization.1 This ancient but persistent disease still lacks effective antimicrobial treatment regimens, particularly in cases of multidrug-resistant tuberculosis.2,3 An attractive target for development of new antimicrobials is the recently identified mycobacterial protein-export machinery.4−6M. tuberculosis relies on specialized ESX secretion systems, also called Type VII Secretion (T7S) Systems, to evade the human immune system and promote bacterial survival within host cells,7,8 and it possesses five gene clusters that encode sets of conserved proteins comprising the ESX systems.9 Each of these gene clusters, called ESX-1 through ESX-5, includes essential mycosin proteases, which are named MycP1 through MycP5, respectively.

The mycosins are membrane-bound serine proteases belonging to the subtilisin family of proteases.10,11 The crystal structures of MycP1 and MycP3 revealed that these mycosins are characterized by a relatively deep, broad, substrate-binding groove and by the absence of an autoinhibitory propeptide, making them the first subtilisins that do not undergo post-translational processing.12−14 MycP1 is known to hydrolyze the important virulence factor ESX secretion-associated protein B (EspB).15−17 MycP1 cleaves the unstructured C-terminal part of EspB, possibly activating EspB for phospholipid binding.18 Most importantly, inactivation of MycP1 leads to decreased virulence of M. tuberculosis and increased survival in the mouse model of TB.17 These data, combined with the availability of MycP1 crystallographic structures, make MycP1 an attractive target for development of antimicrobial compounds for the treatment of TB.19,20 The structural characteristics of the MycP1 substrate-binding pocket differ substantially from known subtilisins whose structures were solved with bound inhibitors,21 and the commercially available subtilisin inhibitors and protease inhibitor cocktails displayed little or no inhibition of MycP1 (Supporting Information Table 1).

In vitro High Throughput Screening (HTS) in conjunction with in silico virtual screening represent complementary methods for the identification of MycP1 inhibitors. Although HTS alone has been used successfully to identify new leads in drug discovery, it remains a costly and time-consuming process. Various computational approaches are available at present to complement HTS technologies, including the popular, virtual screening (VS) techniques.22−25 VS consists of approaches that either take the structure of the target protein into account (structure-based screening) or rely solely on structures of known bioactive molecules (ligand-based screening). The ligand- and structure-based VS strategies are not mutually exclusive and are often used in parallel. We and others have reported the successful application of these VS methods for lead structure identification,26−29 and many VS software packages are available,30−32 as summarized by Reddy.33 Although the algorithms for these VS methods exploit different types of structural "fingerprints" and scoring functions, their performance varies significantly depending on the specific targets.34−36

As part of an integrated, reiterative program of virtual in silico lead identification, in vitro screening, and laboratory synthesis, we developed two approaches that enhance the effectiveness of the combined ligand- and structure-based VS and hold promise for the development of new classes of MycP1 inhibitors. Previously, we reported an efficient 3D shape-based similarity algorithm including an effective 3D shape-fitting procedure and a robust scoring function (HWZ score).37 We also improved the VS algorithm using an enhanced molecular shape-density model called Shape Approach Based Routines Enhanced (SABRE),37 and we applied this algorithm to a number of medically relevant proteins.38−42 SABRE is unique in that it takes advantage of the structural features of known ligands to generate a consensus molecular-shape pattern (i.e., a "4D fingerprint") that filters out unacceptable candidates and identifies desired candidates that fit in the binding pocket. The successful performance of SABRE37,43,44 in ranking screened compounds for the 40 databases of the Directory of Useful Decoys (DUD) prompted us to apply this method to the challenging MycP1 target for which no inhibitors have been thus far reported.

We now report the successful application of this ligand- and structure-based virtual screening approach in the discovery of inhibitors that target the active site of the MycP1 protease. Four compounds were identified by SABRE that showed inhibitory activity against MycP1 with IC50 values in the micromolar range and that provide diverse scaffolds as starting points for the development of small-molecule antagonists of MycP1. This study further validated the SABRE 4D fingerprint algorithm as a means of identifying potential inhibitors and providing departure points for laboratory synthesis.

Methods

To identify potential inhibitors of MycP1 protease, we employed VS, according to the flowchart in Figure Figure1,1, using a merged compound library from GRI and the NCI downloaded from the ZINC

Cite this article: A unique Mycobacterium ESX-1 protein Inhibitors Identified by Virtual Screening and 4D Fingerprints. Am J Petroche. 2019; 1(1): 001-007.

database.45 The structure-based VS (docking) study utilized the recently reported X-ray structure of M. thermoresistibile MycP1 protease (PDB ID: 4HVL).12 We generated multiple conformations of each ligand in the database using OMEGA (OpenEye Scientific Software).46–48 Atom typing, energy calculations, and geometry optimization in OMEGA were performed using the Merck Molecular Force Field (MMFF). The maximum allowed number of conformations per compound was 200, and the energy window, which was the value used to discard high-energy conformations, was set at 10 kcal/mol.

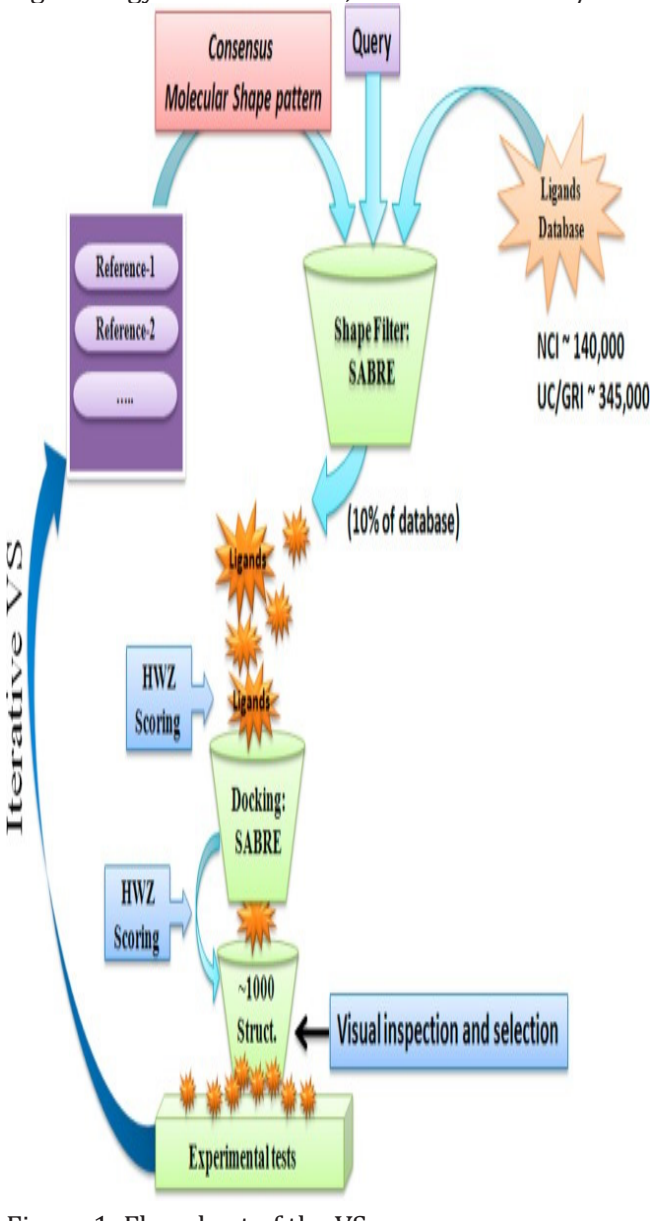


Figure 1: Flowchart of the VS process.

Ligand Shape-Based Virtual Screening

The ligand 3D-shape-based similarity method of SABRE was used as the first filter in the VS strategy.37,43,44 Briefly, the shape-based VS method takes into account both the structural diversity of each ligand and the HWZ scoring function. Thus, the superimposition of molecules A and B is scored according to the shape-density overlap VAB between the query (molecule A) with shape-density VA and testing structure (B) with shape-density VB. Subsequently, the ligands are ranked according to a uniform scoring function, denoted by Hamza–Wei–Zhan (HWZ) score for convenience.37

The coefficients ak, bk, and ck have been recalibrated from the previous version.

The VS approach includes two stages: the calculation of the optimal coefficients of the shape-density function using a set of known lead compounds and the utilization of these optimal coefficients during the automated ligand/structure shape-based screening of candidate structures. The active structures are ranked according to how well they complement the shape of the binding site and by the degree of differences in molecular shape between the active ligand and inactive (decoy) molecules. SABRE builds a consensus molecular-shape pattern (i.e., a 4D fingerprint) defined by the coefficients [c1, c2, ...,cn] using a set of active ligands, in which the maximum diversity of pharmacophores is taken into account during the screening of the compound library.43,44

Unlike other ligand based shape-overlapping methods,36,49,50 our approach efficiently detects the key pharmacophore groups of the active ligands responsible for binding to the target. The main improvement in our method lies with consideration of "virtual" similar inactive structures (decoys) during the consensus molecular shape pattern detection process. After similarity scoring, the selected structures are further ranked according to the shape complementarity of the receptor-binding site.

In the SABRE algorithm, the shape-density model is enhanced and defined as a linear combination of weighted atomic Gaussian functions.37 Thus, the molecular shape-density is the sum of all individual weighted pharmacophore densities, and the molecular volume can be rewritten as where Vkpharm is the volume of the pharmacophore k.

The optimal coefficients Ck are determined by iteratively adjusting the coefficients using the set of known active ligands {Ai} and "virtual" decoy structures {Bi} (virtual decoys are chemically possible compounds that are not necessarily synthetically feasible) until they satisfy these two criteria: for A ∈ {Ai} The algorithm builds an efficient consensus molecular-shape pattern in which the optimal coefficients {Ck} define the 4D fingerprint of the entire set of active ligands and take into account the structural similarity and chemical features of inactive structures (decoys).37,44 Therefore, the "4D fingerprint" encodes the (3D) shapes of the known active ligand structures in their multi conformational states (1D).

Cite this article: A unique Mycobacterium ESX-1 protein Inhibitors Identified by Virtual Screening and 4D Fingerprints. Am J Petroche. 2019; 1(1): 001-007.

REFERENCES

1. Early Alzheimer's Disease: Patterns of Functional MRI Activation-The Neural Substrates of Semantic Memory Deficits. Am J Bra Dis and Tum. 2018; 1(1): 001-010.
2. H Chahal, S W D Souza, A J Barson and P Slater. How to develop human brain using magnesium of N-methyl-D-aspartate receptors, Am J Bra Dis and Tum. 2018; 1(1): 001-005.
3. F S LaBella, et al.Concepts and correlations related to general anaesthesia and cytochrome P450 oxygenases. Am J Anest and Pai med. 2018; 1(1): 01-05.
4. Hazim J Safi, et al. The long term method with the elephant trunk for the repair of aortic aneurysms. Am J Anest and Pai med. 2018; 1(1): 001-008.
5. Yoshitaka Fujii, et al. Diaphragmatic Fatigue is treated with Inhaled Aminophylline Therapy in an Experimental Canine procedure. Am J Anest and Pai med. 2018; 1(1): 001-003.
6. O Demirkiran, et al. Complications in patients with Crush syndrome after the Marmara earthquake. Am J Anest and Pai med. 2018; 1(1): 001-005.
7. Qi Wei, et al. Laparoscopic choledochotomy after Biliary drainage: Study. Am J Anest and Pai med. 2018; 1(1): 001-007.
8. Mark Palazzo, et al. Unilateral Babinski/Plantar Reflex - Acute Inflammatory Demyelinating Polyneuropathy. Am J Anest and Pai med. 2018; 2(1): 01-02.
9. Hakan Alfredson, et al. Achilles and patellar tendon operations performed in local anestesia, Am J Anest and Pai med. 2018; 1(1): 001-002.
10. Naemeh Nikvarz, et al. Evaluation The Analgesic Effect of Duloxtine Drug in Burn Pationts. Am J Anest and Pai med. 2019; 2(1): 01-07.
11. Chuandong Zheng, et al. Intravascular Plaque: Cause for Radial Arterial Catheterization Failure. Am J Anest and Pai med. 2019; 2(1): 01-05.
12. Laura Tyler Perryman, et al. Wireless Dorsal Root Ganglion Stimulation: An Introduction and Early Experience with the New Approach for Chronic Pain Management. Am J Anest and Pai med. 2019; 2(1): 01-04.
13. Lazraq Mohamed, et al. Pediatric Pre-Anesthesia Consultation: What are Parents Expectations?. Am J Anest and Pai med. 2019; 2(1): 01-02.
14. Alaa Ali M. Elzohry, et al. Safety and Efficacy of Intraperitoneal Irrigation of Levo-Bupivacaine plus Morphine in Patients Undergoing Major Abdominal Cancer Surgeries. Am J Anest and Pai med. 2019; 2(1): 01- 07.
15. Yıldız K, et al.Comparison between Anesthesia Methods In Orthopaedics Initiatives of Upper Extremity. Am J Anest and Pai med. 2019; 2(2): 01-03.
16. Jianming Liu, et al. The Analgesic Effects Nalbuphine Hydrochloride Combined With Sufentanil for Patients after Thoracoscopic Lobectomy. Am J Anest and Pai med. 2019; 2(2): 01-03.
17. Fudong Shi, et al. The Patient Controlled Intravenous Analgesia of Dezocine on the Elderly Patients After Orthopedic Surgery. Am J Anest and Pai med. 2019; 2(1): 01-04.
18. GE Meglia, et al. Investigation in blood Leukocytes and Neutrophils in Periparturient Dairy Cow. Sci J of Ani and Vet Sci. 2018; 1(1): 001-009.
19. G E Duhamel, et al.DNA Sequence Analysis of an Immunogenic Glucose-Galactose Mglb. Sci J of Ani and Vet Sci. 2018; 1(1): 001-009.
20. David G. White, et al. Chloramphenicol and Florfenicol Resistance in Escherichia Coli of Characterization . Sci J of Ani and Vet Sci. 2018; 1(1): 001-006.
21. N B Alhaji, et al. Anophthalmia and Choanal Atresia In Two Months Old Kid. Sci J of Ani and Vet Sci. 2018; 1(1): 001-004.
22. Christopher W Olsen, et al.Isolation and Characterization of H4N6 Avian and Influenza Viruses. Sci J of Ani and Vet Sci. 2018; 1(1): 001-0025.
23. Teresa Lopez-Arteaga, et al. Apathy as a Psychiatric Manifestation of Meningioma. Am J Bra Dis and Tum. 2018; 1(1): 001-004.
24. David R Murdoch, et al. The Use of Brain Natriuretic Peptide- Whole Blood can be Measured, Am J Bra Dis and Tum. 2018; 1(1): 001-003.
25. Stefan Brocke, et al. Antibodies to Integrin α4 and CD44, but not CD62L, Prevent CNS Inflammation and Experimental Encephalomyelitis by Blocking Secondary Leukocyte Recruitment. Am J Bra Dis and Tum. 2018; 1(1): 001-006.
26. Andrew J Saykin, et al. Early Alzheimer's Disease: Patterns of Functional MRI Activation-The Neural Substrates of Semantic Memory Deficits. Am J Bra Dis and Tum. 2018; 1(1): 001-010.
27. P Slater, et al.How to develop human brain using magnesium of N-methyl-D-aspartate receptors, Am J Bra Dis and Tum. 2018; 1(1): 001-005.
28. Clyde W Hodge, et al. The Paraventricular Nucleus Interactively Modulate Ethanol Consumption -Norepinephrine and Serotonin Receptors, Am J Bra Dis and Tum. 2018; 1(1): 001-005.
29. Paulo C Carvalho, et al. Bioinformatics grid application in simple - Squid. Sci J Biome and Biost. 2018; 1(1): 001-004.
30. Mahmoud A E Abdelrahman, et al. On The New Exact Solutions for the Nonlinear Models Arising In Plasma Physics. Sci J Biome and Biost. 2018; 1(1): 001-004.
31. Weicheng Shen, et al. Based on Personal Identification- Automated Biometrics. Sci J Biome and Biost. 2018; 1(1): 001-002.
32. V Prasathkumar, et al.Fingerprint Biometric System - Using of Personal Authentication. Sci J Biome and Biost. 2018; 1(1): 001-003.
33. SavitaChoudhary, et al. Software Development Environment : Design of Biometric Based Transaction System. Sci J Biome and Biost . 2018; 1(1): 001-003.
34. D J Lawrence, et al. Measuring the effectiveness in reliability and validity of a visual function outcomes instrument in cataract surgery. Sci J Biome and Biost. 2018; 1(1): 001-004.
35. Z Suvakovic, et al. Evaluation of early detection of gastric cancer requries more than gastroscopy. Anna of Can Ther and Phar. 2018; 1(1): 05.
36. Ho GY, et al. Informing and involving personalised computer based data for cancer patients. Anna of Can Ther and Phar. 2018; 1(1): 001-005.
37. Ray Jones, et al. Prostate Cancer Risk is associated with Polymorphism of Insulin gene. Anna of Can Ther and Phar. 2018; 1(1): 001-005.
38. : Jean-Pierre J. Issa, et al. Role of DNA Methylation in Tumor Suppressor Gene Silencing in Colorectal Cancer. Anna of Can Ther and Phar. 2018; 1(1): 001-008.
39. Jules J Berman, et al. Histological classification of tumour and molecular analysis meets Aristotle. Anna of Can Ther and Phar. 2018; 1(1): 001-005.
40. Kafil Akhtar, et al. Tuberculosis of the Tongue with Coexistent Squamous Cell Carcinoma: An Interesting Case Presentation, Anna of Can Ther and Phar. 2018; 1(1): 001-002.
41. Serafin Morales Murillo, et al. Vitamin D as A Prognostic Factor in Triple Negative Breast Cancer. Anna of Can Ther and Phar. 2019; 2(1): 01-08.
42. Ahmet Fuat, et al. A Qualitative Study of Accurate Diagnosis and Effective Management of Heart Failure in Primary Care. Am J of Card and Cardiovas Disc. 2018; 1(1): 01-05.
43. Jesús Millán Núñez-Cortés, et al. Prescription Habits for Statins in Patients with Impaired Glucose Metabolism. Results of a program with Focus Groups to Assess the Selection Criteria. Am J of Card and Cardiovas Disc. 2019; 1(1): 01-04.
44. G D Kolovou, et al. Evaluation of Postprandial hyper

Cite this article: A unique Mycobacterium ESX-1 protein Inhibitors Identified by Virtual Screening and 4D Fingerprints. Am J Petroche. 2019; 1(1): 001-007.

triglyceridaemia in patients withTangier disease. Am J of Card and Cardiovas Disc. 2018; 1(1): 01-04.
45. Brian O rourke, et al. Determination of The Mitochondrial Redox Waves and Subcellular Metabolic Transients in Heart Cells. Am J of Card and Cardiovas Disc. 2018; 1(1): 01-04.
46. Shuixiang Yang, et al. Radiofrequency Ablation Treating Atrial Fibrillation Can Reverse the Changes of Mirnas Regulating Ion Channel Proteins. Am J of Card and Cardiovas Disc. 2018; 1(1): 01-08.
47. Hadi abdulsalam Abo Aljadayel, et al. Penetrating War Cardiac and Great Vessels Injury, Surgical Outcome Analysis in 24 Patients. Am J of Card and Cardiovas Disc. 2018; 1(2): 01-05.
48. Hatice Yorulmaz, et al. Assessment of the Death Anxiety and Death Depression Levels of Cardiac Patients. Am J of Card and Cardiovas Disc. 2019; 2(1): 01-06.
49. Camara Abdoulaye, et al. Cardiomyopathie Du Peripartum Compliquee D'accident Vasculaire Cerebral Cas D'une Guinéenne De 19ans : Cas Clinique. Am J of Card and Cardiovas Disc. 2019; (1): 01-03.
50. Sergio F. Estrada-Orihuela, et al. Lasalocid, Interrupts and Reverses, Within One Minute, The Myocardial Damage Caused By Coronary Anoxia Reperfusion in Rat Heart. Am J of Card and Cardiovas Disc. 2019; (1): 01-05.
51. Jesus Millan Nunez-Cortes, et al. Prescription Habits for Statins in Patients with Impaired Glucose Metabolism. Results of a program with Focus Groups to Assess the Selection Criteria. Am J of Card and Cardiovas Disc. 2019; 1(1): 01-06.
52. Federico Cacciapuoti, et al. The Dilemma of Diastolic Heart Failure. Am J of Card and Cardiovas Disc. 2019; 1(1): 01-03.
53. Elad Boaz, Bowel Ischemia and Vascular Air-Fluid Levels. Anna Cas Rep and Ima Surg. 2018; 1(1): 001-00.
54. Sinisa Franjic, et al. A Patient With A Maxillofacial Problem. Anna Cas Rep and Ima Surg. 2018; 1(1): 001-004.
55. Davidson W, et al. Case Presentation: Hantavirus pulmonary syndrome [HPS]. Anna Cas Rep and Ima Surg. 2018; 1(1): 001-005.
56. Farid ZM, et al. Uropathy Secondary Chronic obstructive to Ureter Inguinal Herniation. Anna Cas Rep and Ima Surg. 2018; 1(1): 001-002.
57. De Letter DJ, et al. Cornual Molar Ectopic Pregnancy Diagnosis and Treatment. Anna Cas Rep and Ima Surg. 2018; 1(1): 001-003.
58. Ameni Touati, et al. Silver Russell Syndrome: Case Reports from North Africa and Review on The Literature. Anna Cas Rep and Ima Surg. 2019; 1(1): 001- 004.
59. Kunst WM, et al. Case Reports and Review of Spontaneous Rupture of Hyperreactive Malarial Splenomegaly [HMS]. Anna Cas Rep and Ima Surg. 2018; 1(1): 001-005.
60. F Hanefeld, et al. A Review of The Literature an Emerging Community Pathogen methicillin-Resistant Staphylococcus. Anna Cas Rep and Ima Surg. 2018; 1(1): 001-0011.
61. Page W Caufield, et al. Evidence for a Discrete Window of Infectivity. Am J Den and Ora Car. 2018; 1(1): 001-006.
62. Robert T Dirksen, et al. Dihydropyridine Receptors and Ryanodine Receptors: Bi-Directional Coupling . Am J Den and Ora Car. 2018; 1(1): 001-009.
63. IJ Jacobs, et al. Cancer and Intraepithelial Neoplasia-Tissue-specific apoptotic effects of the p53 codon 72 polymorphism . Am J Den and Ora Car. 2018; 1(1): 001-003.
64. Iain L C Chapple, et al. Human Immunodeficiency Virus disease in oral health significances. Am J Den and Ora Car. 2018; 1(1): 001-007.
65. H Larjava, et al. Activity of αvβ6 Integrin in Oral Leukoplakia. Am J Den and Ora Car. 2018; 1(1): 001-005.
66. Siddharth Kothari, et al. Effectiveness of Counselling and Home Care Self-Management Strategies in Reducing Masticatory Muscle Pain: A Review. Am J Den and Ora Car. 2019; 2(1): 001-007.
67. Betania Maria Soares, et al. Use of Blue LED and Curcumin for Photosensitization of Candida Albicans. Am J Den and Ora Car. 2019; 2(1): 001-005.
68. Jing Guo, et al. Advances in Methods of Maxillary Transverse Expansion. Am J Den and Ora Car. 2019; 2(1): 01-05.
69. Dario C. Altieri, et al. Cell division by p34cdc2 phosphorylation of survivin- Regulation . Sci J of Der and Ven. 2018; 1(1): 001-005.
70. Axel Trautmann, et al. Eczematous dermatitis: T cell and keratinocyte apoptosis plays a key pathogenetic . Sci J of Der and Ven. 2018; 1(1): 001-007.
71. JD Fine, et al. Epidermolysis bullosa Cardiomyopathy in inherited . Sci J of Der and Ven. 2018; 1(1): 001-004.
72. NE Fusenig, et al. Human Skin Angiogenic Switch Occurs Squamous Cell Carcinomas . Sci J of Der and Ven. 2018; 1(1): 001-007.
73. Tapani Tuomi, et al. Water- Damaged Building and Mycotoxins in Crude Building Materials. Sci J of Der and Ven. 2018; 1(1): 001-005.
74. John S Davies, et al. The Use of Social Media among Doctors Under taking a Post-Graduate Endocrinology Diploma. Sci J Endo and Meta. 2018; 1(1): 001-004.
75. Juan J Gagliardino, et al. By Short-Term Dietary Manipulation: The Endocrine Pancreas Activity of Tyrosine Hydroxylase. Sci J Endo and Meta. 2018; 1(1): 001-005.
76. Colin A. Leech, et al. The Glucose Dependent in Pancreatic β-Cells : Voltage-Independent Calcium Channels Mediate Slow Oscillations of Cytosolic CalciumPancreatic β-Cells. Sci J Endo and Meta. 2018; 1(1): 001-009.
77. Colin A. Leech, et al. The Voltage-Independent Activation of Inward Membrane Currents and Elevation of Intracellular Calcium in HIT-T15 Insulinoma CellsPituitary Adenylate Cyclase-Activating Polypeptide Induces. Sci J Endo and Meta. 2018; 1(1): 001-008.
78. Suhail AR Doi, et al. Making Use Of Combined Criteria - Diagnostic Criteria For Diabetes. Sci J Endo and Meta. 2018; 1(1): 001-006.
79. Maria I Borelli, et al. Effect Of Endogenous Islet Catecholamines Possible Modulatory On Insulin Secretion. Sci J Endo and Meta. 2018; 1(1): 001-005.
80. Louis Irwin, et al. Effect of exercise in combination with dietary nopal and zucchini on chronic and acute glucohomeostasis in genetically obese mice. Inte J Expe Bio. 2018; 1(1): 001-005.
81. Vijaya Saradhi Settaluri, et al. Validation of Non Essential Amino Acids and Total Protein Content in Different Categories of Tea. Inte J Expe Bio. 2018; 1(1): 01-04.
82. Patrick D Craig, et al. T Antigen: Polyomavirus Middle of Natural Biology. Inte J Expe Bio. 2018; 1(1): 001-007.
83. Yoshinori Ohsumi, et al. The HIV Coreceptor CCR5 - Recycling and Endocytosis. Inte J Expe Bio. 2018; 1(1): 001-008.
84. Marino Zerial, et al. Elicitation of the Angiogenic Phenotype1: Transforming Myc Protein for In Vivo. Inte J Expe Bio. 2018; 1(1): 001-008.
85. Zhang Y, et al. Odorant Receptor In Mammali : The Caenorhabditis Elegans Seven-Transmembrane Protein ODR-10 Functions on Cells. Inte J Expe Bio. 2019; 1(1): 001-008.
86. Kazuo Maeda, et al. Improved Outcome with Novel Studies in Fetal Monitoring. Sci J of Gyne and Obste. 2019; 2(1): 001-004.
87. Sunil J. Wimalawansa, et al. Vitamin D Deficiency-Related Reproductive Consequences. Sci J of Gyne and Obste. 2019; 2(1): 001-006.
88. Munch A, et al.Investigation in blood Leukocytes and Neutrophils in Periparturient Dairy Cow. Sci J of Gas and Hepa. 2018; 1(1): 001-006.
89. Jie Song Hua, et al. Primary Helicobacter Pylori Resist

Cite this article: A unique Mycobacterium ESX-1 protein Inhibitors Identified by Virtual Screening and 4D Fingerprints. Am J Petroche. 2019; 1(1): 001-007.

ance to Clarithromycin and Metronidazole in Singapore. Sci J of Gas and Hepa. 2018; 1(1): 001-003.
90. Paul Moayyedi, et al. A Systematic Review and Economic Analysis: Proton Pump Inhibitors in Nonulcer Dyspepsia Efficacy. Sci J of Gas and Hepa. 2018; 1(1): 001-003.
91. Zhen-Ning Wang, et al.Gastric Cancer: Collagen IV Expression and Biological Behavior. Sci J of Gas and Hepa. 2018; 1(1): 001-002.
92. Zhen-Ning Wang, et al. A Possible Pathophysiologic Contribution to Necrotizing Enterocolitis: Human Intestine Inflammation. Sci J of Gas and Hepa. 2018; 1(1): 001-006.
93. Paul M Wassarman, et al. Egg Interaction during Mammalian Fertilization in the Molecular Basis of Sperm . Sci J of Gyne and Obste 2018; 1(1): 001-006.
94. Mary Lou Moore, et al. Breastfeeding Benefits Support -Research. Sci J of Gyne and Obste 2018; 1(1): 001-002.
95. Pepita Gimenez-Bonafe, et al. Preservation of Fertility in Patients with Cancer. Sci J of Gyne and Obste 2018; 1(2): 001-006.
96. Yueyang F Fei, et al. Non-Hemorrhagic Unilateral Adrenal Infarct In Pregnancy: A Case Report. Sci J of Gyne and Obste. 2019; 1(1): 001-002.
97. Karen Pierre, et al. Protein-Energy Adequacy of Dialysis Patients in Trinidad and Tobago. Am J of Nep and Ther. 2018; 1(1): 01-05.
98. Balakrishna N, Tenckhoff Catheter Surgical under Local Anesthesia. Am J of Nep and Ther. 2018; 1(1): 001-003.
99. J T Ohlsson, et al. Man in angiotensin and noradrenaline inhibits the Endothelin. Am J of Nep and Ther. 2018; 1(1): 001-005.
100. David J, et al. Apoptosis and Ischemic Renal Injury Reduce the Guanosine Supplementation. Am J of Nep and Ther. 2018; 1(1): 001-005.
101. R W Baldeweg, et al. Tumor-induced osteomalacia : Cloning and characterization of Fibroblast Growth Factor 23. Am J of Nep and Ther. 2018; 1(1): 001-006.
102. Amitabh Arya, et al. Post Pyeloplasty Follow Up In Children And Adolescents: Diuretic Renography Or Renal Ultrasonography? Am J of Nep and Ther. 2019; 2(1): 001-005.
103. Amitabh Arya, et al. Post Pyeloplasty Follow Up In Children And Adolescents: Diuretic Renography Or Renal Ultrasonography? Am J of Nep and Ther. 2019; 2(1): 001-005.
104. Richard Lechtenberg, et al. Tau Interferon in Multiple Sclerosis. Amer J Neur & Neurophysi. 2018; 1(1): 001-002.
105. Eva Guy Rodriguez, et al. Discussion of the differential diagnosis of bilateral thalamic lesions-Bilateral thalamic infarcts due to occlusion of the Artery of Percheron. Amer J Neur & Neurophysi. 2018; 1(1): 001-004.
106. Yhashi Chang, et al. IVIg for Miller Fisher syndrome: Cerebral infarction. Amer J Neur & Neurophysi. 2018; 1(1): 001-002.
107. Fredrick J. Seil, et al. T cell responses to Myelin Antigens and Antimyelin Antibodies. Amer J Neur & Neurophysi. 2018; 1(1): 001-005.
108. Y Niimi, et al. Embolization of Spinal Cord AVMs: Neurophysiologic Provocative Testing. Amer J Neur & Neurophysi. 2018; 1(1): 001-002.
109. Ameni Touati, et al. Some Reducibility Results for Differentiable Sets. Amer J Neur & Neurophysi. 2019; 1(1): 001-005.
110. Chrisostomos Sofoudis, et al. Sofoudis C. Septic Abortion Accompanied with Dessiminated Intravascular Coagulation and Acute Cardiomyopathy Presentation of a Rare Case and Mini Review. Am J Nur & Pract. 2018;1(1): 001-00.
111. Nick Jones, et al. Nurse Practitioners and Family Physicians Ethics Health Care Services. Am J Nur & Pract. 2018; 1(1): 001-005.
112. Thomas R A, et al. Human Infants Learning by Prenatal and Postnatal Flavor . Am J Nur & Pract. 2018; 1(1): 001- 006.
113. D. J Wise, et al. A Randomized, Double-Blind, Placebo-Controlled - Milk Production in Mothers of PremaTure Newborns Domperidone Drug effect. Am J Nur & Pract. 2018; 1(1): 001-005.
114. Bronagh Bufton, et al. Effects of Nursing Homes Ownership Compromise the Quality of Care. Am J Nur & Pract. 2018; 1(1): 001-005.
115. Kerstin Ekberg, et al. How Physicians Deal With the Task of Sickness Certification in Cause-Based and Comprehensive Disability Systems – A Scoping Review. Am J Nur & Pract. 2019; 2(1): 01-10.
116. Michael J. Vives, et al. Factors in Choosing the Surgical Approach: Cervical Spondylotic Myelopathy. Am J Orth and Rhe. 2018; 1(1): 001-004.
117. M. Runge, et al. Geriatric Patients in Balance Training and Exercise. Am J Orth and Rhe. 2018; 1(1): 001-003.
118. Ukoha Ukoha Ukoha, et al. Nutrient Foramina in Long Bones : Study. Am J Orth and Rhe. 2018; 1(1): 001-003.
119. Zhiquan An, et al. Human Humeral Diaphysis of the Nutrient Foramina : Anatomical Study : Study. Am J Orth and Rhe. 2018; 1(1): 001-007.
120. K-P Günther, et al. Hip Replacement in Rates: International Variation: Study. Am J Orth and Rhe. 2018; 1(1): 001-005.
121. Saeed Taj din, et al. Level of Physical Activity among Diabetic Patients of Rural and Urban Areas. Am J Orth and Rhe. 2019; 2(1): 001-004.
122. Carolina Caleza Jiménez, et al. Breastfeeding, Bed-Sharing and Early Childhood Caries. Is There An Association? A Review of the Literature. Am J Pedi and Heal care. 2018; 1(1): 001-004.
123. Katarzyna Niewiadomska-Jarosik, et al. Lipid Profile in Children Born As Small for Gestational Age . Am J Pedi and Heal care 2018; 2(1): 01-03.
124. Mustafa Aydin, et al. Antibiotic Susceptibility Pattern and Clinical Features of Klebsiella Sepsis in Newborn Infants. Am J Pedi and Heal care 2019; 1(1): 01-04.
125. H Dele Davies, et al. Necrotizing Fasciitis- Flesh-Eating Bacteria Disease. Am J Pedi and Heal care 2019; 1(1): 01-06.
126. Marie Westwood, et al. The diagnosis of urinary tract infection (UTI) in children under five years: Rapid tests and urine sampling techniques. Am J Pedi and Heal care 2019; 1(1): 01-09.
127. Folkert Fehr, et al. What Entrustable Professional Activities Add To a Primary Care Residency Curriculum. Am J Pedi and Heal care 2019; 2(1): 01-06.
128. Sonya Martin, et al. Spatially Modulated Illumination Microscopy□D measures the size of Biological Nanostructures . Ann of Phar Nano Tech and Nanomedi. 2018; 1(1): 01-05.
129. Sonya Martin, et al. Genetic analysis of Fis interactions with their binding sites. Ann of Phar Nano Tech and Nanomedi. 2018; 1(1): 01-07.
130. John H Reif, et al. Nucleation assembly of DNA tile complexes is directed by barcode-patterned lattices. Ann of Phar Nano Tech and Nanomedi. 2018; 1(1): 01-07.
131. Thomas H LaBean, et al. Self assembly of DNA nanotubes from triple-crossover tiles as templates for conductive nanowires. Ann of Phar Nano Tech and Nanomedi. 2018; 1(1): 01-05.
132. Ulrich Kettling, et al. Dual-Photon Fluorescence Coincidence Analysis: Rapid quantification of Enzyme activity. Ann of Phar Nano Tech and Nanomedi. 2018; 1(1): 01-05.
133. Ahmed R. Gardouh, et al. Design, Optimization and In-Vitro Evaluation of Antifungal Activity of Nanostructured Lipid Carriers of Tolnaftate Ann of Phar Nano Tech and Nanomedi. 2019; 2(1): 01-05.
134. Mohammed Khalid, et al. Khalid M. Predictors of Prognosis in Pulmonary Hypertension. Anna Pul and Crit Car Med.

Cite this article: A unique Mycobacterium ESX-1 protein Inhibitors Identified by Virtual Screening and 4D Fingerprints. Am J Petroche. 2019; 1(1): 001-007.

2018; 1(1): 001-004.
135. Abdullah Alsaeedi, et al. The Prevalence of Smoking among sample of Kuwait Asthmatics and its impact on the response of the treatment, Anna Pul and Crit Car Med. 2018; 1(2): 001-002.
136. Nicolau Beckmann, et al. Resolving the Oedematous Signals Induced by OVA Challenge in the Lungs of Actively Sensitised Rats. Anna Pul and Crit Car Med.. 2018; 1(1): 01-06.
137. Thomas J walsh, et al. Investigate the performance of non-invasive diagnostic tests such as galactomannan enzyme immunoassay and quantitative Caspofungin in the early diagnosis of invasive aspergillosis (IA). Anna Pul and Crit Car Med.. 2018; 1(1): 01-06.
138. Charles B. Huddleston, et al. Lung Transplantation in pediatrics. Anna Pul and Crit Car Med.. 2018; 1(1): 01-05.
139. Jeffrey P. Lamont, et al. Comparision of valved vs non-valved implantable ports for vascular access:A randomized trial. Anna Pul and Crit Car Med.. 2018; 1(1): 01-03.
140. D Inwald, et al. Risk and relevance of open lung biopsy in Nonneonatal extracorporeal membrane oxygenation (ECMO) patients. Anna Pul and Crit Car Med.. 2018; 1(1): 01-04.
141. Guillaume Mortamet, et al. Does Esophageal Pressure Monitoring Reliably Permit To Estimate Trans pulmonary Pressure In Children?. Anna Pul and Crit Car Med.. 2018; 2(2): 01-05.
142. Yang Jin, et al. Extracellular Vesicle-Shuttling MicroRNAs Regulate the Development of Inflammatory Lung Responses. Anna Pul and Crit Car Med.. 2018; 1(2): 01-04.
143. Nicola Clemente, et al. Pneumonectomy As A Salvage Therapy: A Rare Indication For A Gastric Malt Lymphoma Disseminated To The Lung. Anna Pul and Crit Car Med.. 2018; 1(2): 01-04.
144. Nicola Clemente, et al. Pneumonectomy As A Salvage Therapy: A Rare Indication For A Gastric Malt Lymphoma Disseminated To The Lung. Anna Pul and Crit Car Med.. 2018; 1(2): 01-04.
145. Victor Chew, et al. Pulmonary Cement Embolism. Anna Pul and Crit Car Med. 2019; 2(1): 01-02.
146. Victor Chew, et al. An Unusual Cause of a Tension Pneumothorax. Anna Pul and Crit Car Med. 2019; 2(1): 01-03.
147. Mark C. Lavigne, et al. A Performance Summary of Agents Used in Oral Care for Non-Ventilated and Mechanically-Ventilated Patients. Anna Pul and Crit Car Med. 2019; 2(2): 01-34.
148. Elisangela Hermes, et al. Psychomotricity in Vestibular Dysfunction Therapy (VDT): A Collective Health Question. Am J Rhin and Otolo. 2018; 1(1): 001- 005.
149. Ramtej J Verma, et al. Diethanolamine-Induced Hepatic Injury and Its Amelioration by Curcumin. Am J Toxi and Res. 2018; 1(1): 001-004.
150. Chee Kong Yap, et al. A Preliminary Screening of Cd and Pb Concentrations in the Some Traditional Chinese Herbal Medicines Bought From Selected Shops in Peninsular Malaysia. Am J Toxi & Res. 2018; 1(1): 001-004.
151. Geza Bozoky, et al. Acute Silent Non-Massive (submassive) Pulmonary Embolism. Am J Ang and Surg . 2018; 1(1): 001-003.
152. Muhammad Imran Qadir, et al. Is Hunting Lovering Associates with Pulse Rate. Am J of Viro and Dis. 2019; 1(1): 01.
153. Mujahid Rasheed, et al. Relation of Blood Group with Motion Sickness. Am J of Viro and Dis. 2019; 1(1): 02.
154. Mujahid Rasheed, et al. Views of University Paramedical Students about Causes of Pharyngitis, Its Transmission and Medicinal Control. Am J of Viro and Dis. 2019; 1(1): 02.
155. Kainat Rafaqat, et al. Views of University Paramedical Students about Causes of Pharyngitis, Its Transmission and Medicinal Control. Am J of Viro and Dis. 2019; 1(1): 02.
156. Sajid Ullah, et al. HCV Prevalence in the Volunteer Blood Donors in District Bajaur Khyber Pakhtunkhwa Pakistan. Am J of Viro and Dis. 2019; 1(1): 02.
157. Rabbia Aslam, Analogue of Breathing With Lizard Fright Am J of Viro and Dis. 2019; 1(1): 01.
158. Hurain Shaukat, et al. Linkage of Body Temperature with Exercise Am J of Viro and Dis. 2019; 1(1): 01.
159. Mariyam Javed, et al. How Breathe Rate Relates With Cricket Likeness? Am J of Viro and Dis. 2019; 1(1): 02.
160. Hakan Alfredson, et al. Achilles and patellar tendon operations performed in local anestesia, Am J Anest and Pai med. 2018; 1(1): 001-002.
161. Richard Lechtenberg, et al. Tau Interferon in Multiple Sclerosis. Amer J Neur & Neurophysi. 2018; 1(1): 001-002.

Cite this article: A unique Mycobacterium ESX-1 protein Inhibitors Identified by Virtual Screening and 4D Fingerprints. Am J Petroche. 2019; 1(1): 001-007.