SYNTHESIS AND DOCKING OF DERIVATIVES OF PARABENZOQUINONE MOLECULE TARGETED 2Z9I AND 3ZXV ENZYME FOR ANTI-TB AND ANTI-TB MDR

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Abstract:
Tuberculosis disease is chronic disorder and caused in worldwide which 10th is leading death in the world surpassing HIV/AIDS.[1] Approx 1.3 to 1.5million people died on every year. Many researchers have done so many molecules and working continuously. The most potent molecule was found from scorpion *Diplocentrus melici* ,there two types of molecules found first one 1,4 benzoquinone also known as blue benzoquinone and 1,2 bezoquinone also known as red benzoquinone, according to research the blue one have strong anti TB as well as anti MDR and red one showed only anti TB properties. We have taken idea from this molecules blue benzoquinone for working on both site of action. Gated the most superficies enzymes involve for caused mycolic acid synthesis and MDR also. We got some enzyme that is good for binding in docking software. PDB id for both enzymes is 3ZXV and 2Z9i.The first line drug found drug resistance isoniazide, rifampin, also in some time of fluoroquinolone drugs, in second line drugs like amikacin, kanamycine. 3ZXV is the Mycobacterium tuberculosis Glutamine synthetase and 2Z9i is proteolytically active. These two enzymes where found in tuberculosis bacterial function after getting infection and this two enzyme can elaborated the solving problem for bactericidal activity and multi drug resistance. [23] 3ZXV pdb id which is targeted on MtGS (Mycobacterium tuberculosis glutamine synthetase), responsible for cell wall synthesis of *M. tuberculosis*, the parabenzoquinone molecule binds with 3ZXV receptor and getting that good respond on the bases of molecular docking result. Some drugs are already given in tuberculosis that is not treatment effects at the time and some potential drugs having resistance.

Keywords: Synthesis; Docking of Derivatives; HtrA2; MtGS; Molecule Targeted 2Z9i; 3ZXV; Tuberculosis

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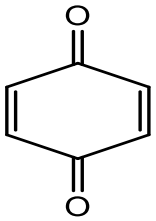
INTRODUCTION

Today in current treatment minimum days required for treatment is 6 month of the first line drug like-Isoniazide, rifampicin, pyrazinamide and ethambutol for TB. In this duration of timing and high counting pills caused side effects resulting in poor patient they can't complete the eradication of TB than led to drug resistance. After first line choosing second line drug anti-TB used in drug resistance TB strain (MDR-multi drug resistance) due to their limited efficacy, drug toxicity and high price compare to first line drug that will be inconvenient to the patient. [1,2] Due to this problem in first line and second line drug in current situation need more efficacy , MDR drug, chief drugs and minimum side effects to the patient are urgently. The membrane protein large 3 (MmpL3) which is targeted point responsible for mycolic acid translocation (MAs) of mycobacterium tuberculosis plasma membrane. [3, 4] This are completed in total five steps, first four steps are responsible for biosynthesis of MAs precursor, name is trehalose monomycolate (TMM) in cytoplasm. The last 5th steps are responsible for release TMM from inner cell membrane by the help of membrane transporter MmpL3 into periplasm. After that MAs is accumulate in the M.*tb* cell wall which is highly hydrophobic in nature and impermeable Bilayer. [5] This formidable protective layer is present on the mycobacterium *tb* which is work as a insulate against some exogenous compounds like antibiotics, host's immune system, resulting in that mycobacterium is surviving in the host's cell. [6, 7] Hence the lipophilicity of anti tubercular drugs derivatives (ClogP) have found positive effects against anti-TB activity. [8] Therefore the anti *tb* derivatives can easily diffuse inside the cell wall of M.*tb* and enhance efficacy. The major role of mmpL3 is stopping the TMM across the cytoplasmic membrane in *M. smegmatis* when the reducing level of MmpL3 leads to accumulation of TMM in intracellular space resulting in the losses of cell wall mycolation. [9] In depletion of MmpL3 resulting led to stopping the cell division and after that having rapid cell death. There was two 1, 4 benzoquinone derivatives found from scorpion venom *Diplocentrus melici.* Extracted from white venom had two compounds found which was characterized in anti *tb* activity, they have two different colors one red and other blue obtained after chromatography, after getting NMR and mass spectroscopy red colour compound was determine to be 3,5 dimethoxy,2(methylthio) cyclohexa-2,5 diene-1,4-dione,and blue compound was determine by 5-methoxy,2-3 bis (methylthio) cyclohexa-2,5-diene-1,4-dione.The extract from venom have been collected in extremely small amount therefore need to synthesis in laboratory allow to produce biological activities. [10-11] For red benzoquinone is effective against *Staphylococcus aureus* (MIC=4 µg/mL) where the blue benzoquine effective against *Mycobacterium tuberculosis* (MIC=4 µg/mL) and even against multidrug-résistance (MDR).The importantly for blue benzoquinone have found good result in four mice for 2month treatment against MDR in vivo, eventually decrease pulmonary loads and decrease the tissue cell damage and getting negative tolerate as well as without any adverse and side effects. [12]



1, 4 Parabenzoquinone

MATERIALS AND METHODS

Ligand preparation:

The 1,4 parabenzoquinone were first isolated from scorpion species name Diplocentrus melici obtained two parabenzoquinone first one red and second one blue that blue benzoquinone is responsible for both effects on ant TB for resistance and cell wall synthesis inhibitor. That parabenzoquinone derivative was prepared on the bases of this blue extract parabnezoquinone. This is for hypothetically design as per some functional groups. Sketched in Chem draw ultra 12.0 and chem. [13] 3D pro 12.0, having formed total 8th derivative for Argus lab molecular docking by the help of removing hydrogen atom than reconfiguration and adding hydrogen again after that to select for preparing ligand. The derivative of parabenzoquinone are follows ATB-1, 2,3,4,5,6,7,8. [14]

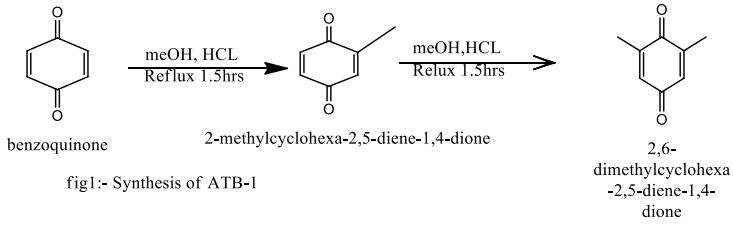


fig1:- Synthesis of ATB-1

Fig: 1. The ATB-1(2, 6-dimethylcyclohexa-2, 5-diene-1, 4-Dione) synthesised by precursor parabenzoquinone reacted with meOH, HCL, reflux 1.5hrs for twice in a time.

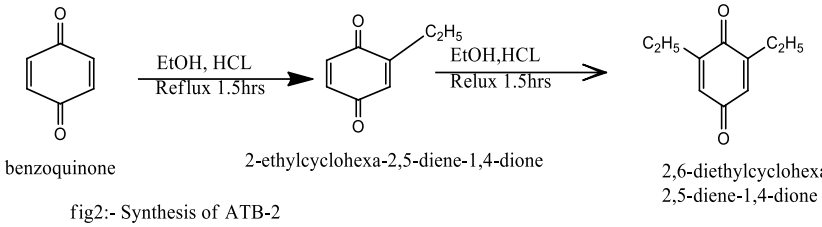


fig2:- Synthesis of ATB-2

Fig: 2. The ATB-2(2, 6-diethylcyclohexa-2, 5-diene-1, 4-Dione) synthesised by precursor parabenzoquinone reacted with EtOH, HCL, reflux 1.5hrs for twice in a time.

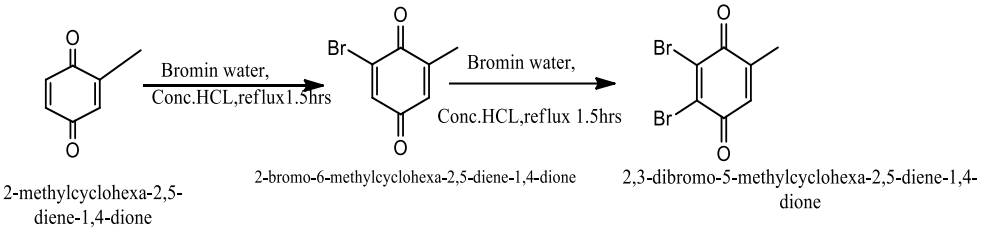


Fig 3:- synthesis of ATB-3

Fig: 3. The ATB-3 (2, 3-dibromo-5-methylcyclohexa-2,5-diene-1,4-dione) synthesised by precursor 2-methylcyclohexa-2,5-diene-1,4-dione with bromine water and concentrated HCL reflux 1.5hrs for twice in a time.

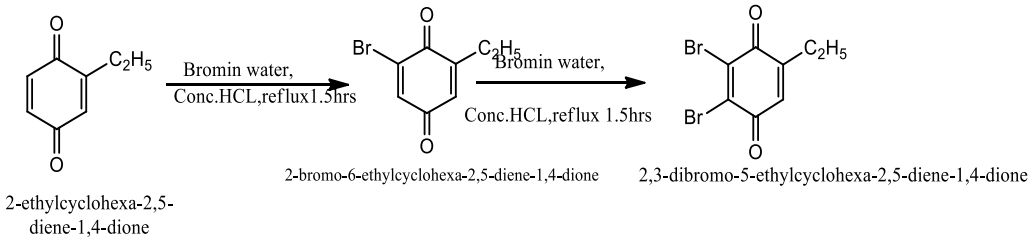


Fig 4:- synthesis of ATB-4

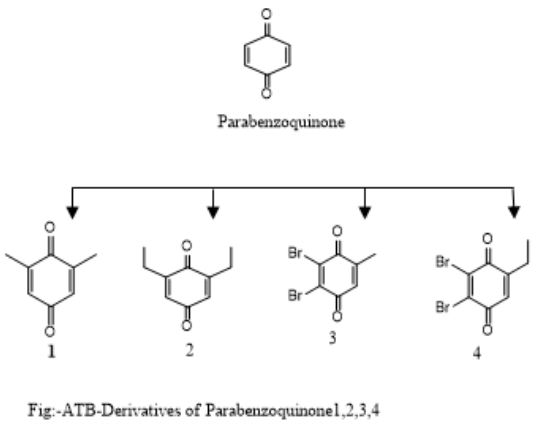


Fig:-ATB-Derivatives of Parabenzoquinone1,2,3,4

Fig: 4. The ATB-4 (2, 3-dibromo-5-ethylcyclohexa-2, 5-diene-1, 4-Dione) synthesised by precursor 2-ethylcyclohexa-2, 5-diene-1, 4-dione with bromine water and concentrated HCL reflux 1.5hrs for twice in a time.

Protein preparation:

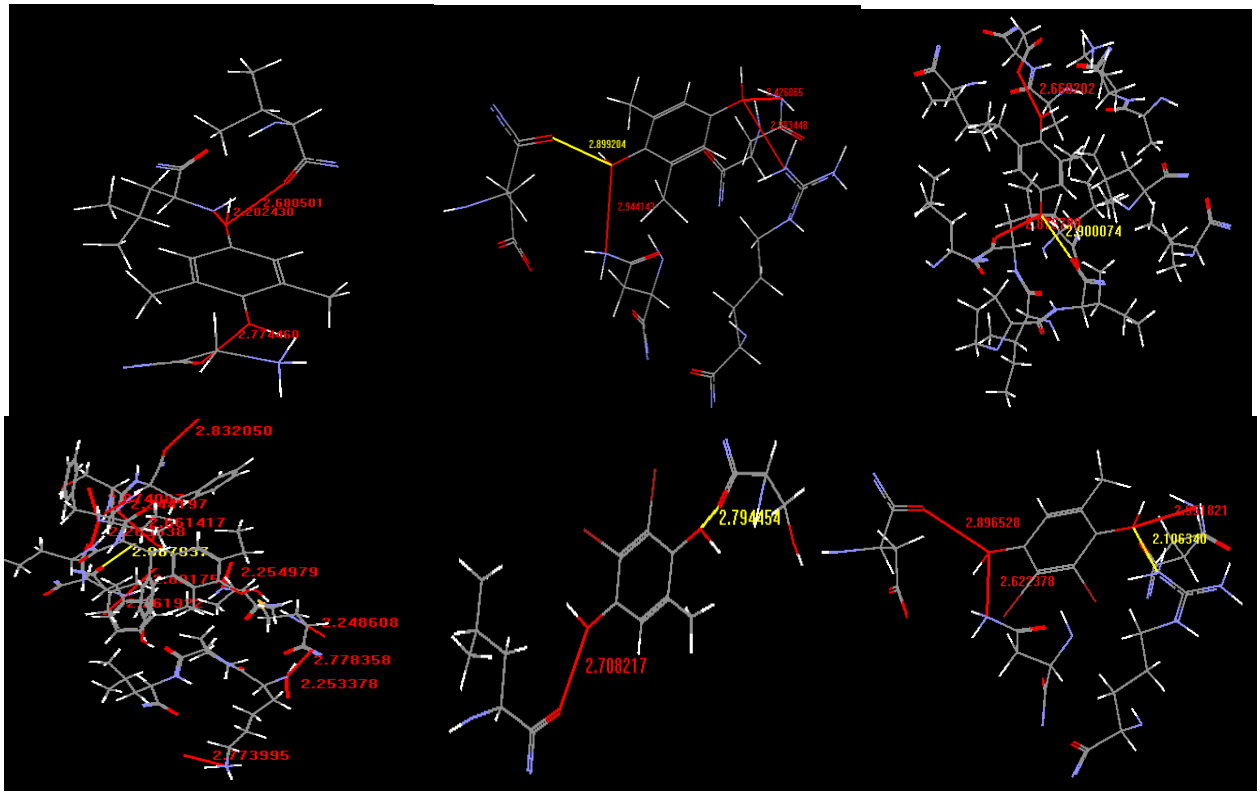
The Structure of HtrA2 protein (PDB ID: 2Z9I) and MtGS protein (PDB ID: 3ZXV) was downloaded from Protein data bank site and imported and prepared by ArgusLab.exe (4.0.1).It was especially used in minimize energy configuration of protein by the removed residue, miscellaneous, after that go to amino acids lists selected all after that the restore their final structure by the help of adding hydrogen, after that go to residue and made a group for binding site. After set binding site calculate the size of protein structure for binding ligand. [15]

Molecular docking studies:

Docking studies have done by Argus lab software which was predicted from 2Z9I and 3ZXV receptors grid by the calculated by 80x60x80 $Å^3$ grids with default inner grids 60x30x60 $Å^3$ calculated and this calculated points have minimum 30,00000.00 to 80,00000.00grids covered and start the docking process and gated binding energy and distance in Å between two amino acids by hydrogen bonds. [16]

RESULT AND DISCUSSION

After prepare protein and legend preparation to select the dimension of targeted HtrA2 protein (PDB ID: 2Z9I according to selectivity of molecular docking capacity by X, Y, Z axis. After select the criteria stared the docking process by Argus lab. After done the docking we gated a different bond length with amino acid with different bond energy. For The ATB-1(2, 6-dimethylcyclohexa-2, 5-diene-1, 4-Dione) we gated some best results for maximum hydrogen bond length 2.774460Å between 7529Oxygen to 581Glycine, other results are hydrogen bond length 2.680501Å between 9690Oxygen to 731 Valine, hydrogen bond length 2.202430Å between 682 Leucine to 11338 Oxygen, obtained minimum grid energy was obtained total 150, best Ligand pose energy -7.78044 kcal/mole at 82 seconds, from Total number of grid points: 5372127. [17]



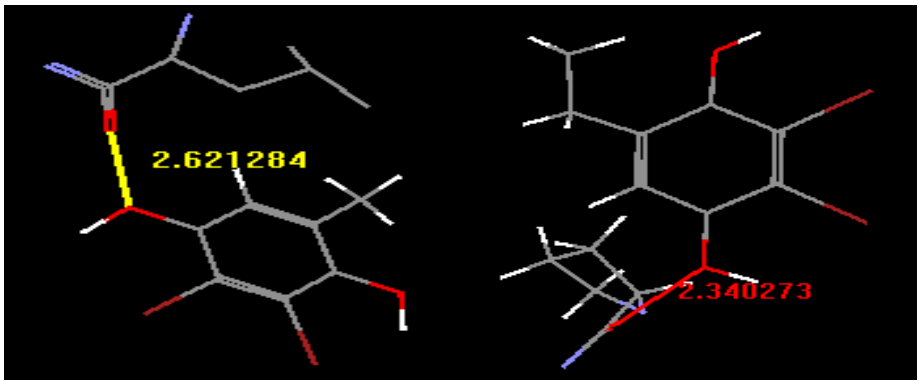


Fig: 5. Predicted active site residues and docked residues with atb-1 with 2z9i, 3zxv, atb-2 with 2z9i a, 3zxv, atb-3 with 2z9i, 3zxv, atb-4 with 2z9i, 3zxv.

MtGS protein (PDB ID: 3ZXV according to selectivity of molecular docking capacity by X, Y, Z axis. After select the criteria stared the docking process by Argus lab. After done the docking we gated a different bond length with amino acid with different bond energy. For The ATB-1(2, 6-dimethylcyclohexa-2, 5-diene-1, 4-Dione) we gated some best results for maximum hydrogen bond length was obtained 2.993446 Å between 499 Arginine and 44144 numbers of Oxygen, obtained minimum grid energy was obtained total 155,best ligand pose energy -8.21607447 kcal/mole at 80 seconds, from Total number of grid points : 6372127 [18]

HtrA2 protein (PDB ID: 2Z9I according to selectivity of molecular docking capacity by X, Y, Z axis. After select the criteria stared the docking process by Argus lab. After done the docking we gated a different bond length with amino acid with different bond energy. For The ATB-2(2, 6-diethylcyclohexa-2, 5-diene-1, 4-Dione) we gated some best results for maximum hydrogen bond length was obtained 2.900074Å between 399Isoleucin and 5117 Number of Oxygen. Total number of grid points: 3032533 Best Ligand Pose: energy = -8.38245 kcal/mol Final poses: 101 final, time = 60 seconds. [19]

MtGS protein (PDB ID: 3ZXV according to selectivity of molecular docking capacity by X, Y, Z axis. After select the criteria stared the docking process by Argus lab. After done the docking we gated a different bond length with amino acid with different bond energy. For The ATB-2(2, 6-diethylcyclohexa-2, 5-diene-1, 4-Dione) we gated some best results for maximum hydrogen bond length was obtained 2.867937Å between 1564 Phenylanaline nucleic acid and24188 number of Oxygen and other residue between 1684 Threonine and 26015number of nitrogen atom. Total number of grid points: 3442951 Best Ligand Pose: energy = -8.96969 kcal/mol.Docking run: elapsed time = 102 seconds final poses: 101 final. [20]

HtrA2 protein (PDB ID: 2Z9I according to selectivity of molecular docking capacity by X, Y, Z axis. After select the criteria stared the docking process by Argus lab. After done the docking we gated a different bond length with amino acid with different bond energy. For The ATB-3 (2, 3-dibromo-5-methylcyclohexa-2,5-diene-1,4-dione) we gated some best results for maximum hydrogen bond length was obtained 2.794454Å distance between 707 serine nucleic acid and 9367 number of Oxygen atom, other residues are also obtained 113370 number of Oxygen atoms. Total number of grid points : 6048090 Best Ligand Pose : energy = -8.51205 kcal/mol, Docking run: elapsed time = 66 seconds Number of candidate poses found = 150. [21]

MtGS protein (PDB ID: 3ZXV according to selectivity of molecular docking capacity by X, Y, Z axis. After select the criteria stared the docking process by Argus lab. After done the docking we gated a different bond length with amino acid with different bond energy. For The ATB-3 (2, 3-dibromo-5-methylcyclohexa-2,5-diene-1,4-dione) we gated some best results for maximum hydrogen bond length was obtained distance 2.951821Å between 565 Asparagine and 44143 numbers of oxygen. Total number of grid points: 7048090 Best Ligand Pose: energy = -8.61205 kcal/mol, Docking run: elapsed time = 82 seconds Number of candidate poses found = 170. [22]

HtrA2 protein (PDB ID: 2Z9I according to selectivity of molecular docking capacity by X, Y, Z axis. After select the criteria stared the docking process by Argus lab. After done the docking we gated a different bond length with amino acid with different bond energy. For The ATB-4 (2, 3-

dibromo-5-ethylcyclohexa-2, 5-diene-1, 4-Dione) we gated some best results for maximum hydrogen bond length was obtained distance 2.621284Å between 420 leucine and 2654 number of oxygen atom. Total number of grid points: 4625010Best Ligand Pose: energy = -8.13087 kcal/mol, Docking run: elapsed time = 48 seconds the final poses: 127 final unique configurations. [23]

MtGS protein (PDB ID: 3ZXV according to selectivity of molecular docking capacity by X, Y, Z axis. After select the criteria stared the docking process by Argus lab. After done the docking we gated a different bond length with amino acid with different bond energy. For The ATB-4 (2, 3-dibromo-5-ethylcyclohexa-2, 5-diene-1, 4-Dione) we gated some best results for maximum hydrogen bond length was obtained distance 2.340273Å between 1691 proline and 26135 number of Oxygen. Total number of grid points: 6625010Best Ligand Pose: energy = -8.63087 kcal/mol, Docking run: elapsed time = 68 seconds the final poses: 190 final unique configurations. [24]

COCLUSION

In this docking method have done from various molecules obtained from protein molecule MtGS & HtrA2 is very great result obtained as compared with different molecule. About different ATB molecule gated best pose energy was obtained ATB-2,-8.96969kcal/mol, with bond distance 2.867937Å & -8.38245kcal/mol with bond distance 2.90007Å second one ATB-3,-8.63087 with bond distance 2.340273Å, -8.13087kcal/mol with bond distance 2.621284kcal/mol third one obtained ATB-3,-8.61205kcal/mol, with bond distance 2.95182Å, -8.51205kcal/mol with bond distance 2.794454Å. The overall getting best pose energy was found ATB-2molecules. From MtGS& HtrA2 proteins are responsible for anti TB and anti-TB MDR.

REFERENCES

1. World Health Organization Global Tuberculosis Report, Geneva, 2019, Search PubMed .
2. S. Tiberi , A. Scardigli , R. Centis , L. D' Ambrosio , M. Munoz-Torrico , M. A. Salazar-Lezama , A. Spanevello , D. Visca , A. Zumla , G. B. Migliori and J. A. Caminero Luna , Int. J. Infect. Dis., 2017, 56, 181-184.
3. H. W. Al-Humadi , R. J. Al-Saigh and A. W. Al-Humadi , Front. Pharmacol. 2017, 8, 689.
4. G. Sotgiu , R. Centis , L. D'Ambrosio and G. B. Migliori , Cold Spring Harbor Perspect. Med., 2015, 5, a017822.
5. W. Li , A. Upadhyay , F. L. Fontes , E. J. North , Y. Wang , D. C. Crans , A. E. Grzegorzewicz , V. Jones , S. G. Franzblau , R. E. Lee , D. C. Crick and M. Jackson, Antimicrob. Agents Chemother. 2014, 58, 6413-6423.
6. Z. Xu , V. A. Meshcheryakov , G. Poce and S. S. Chng , Proc. Natl. Acad. Sci. U. S. A., 2017, 114 , 7993-7998.
7. S. S. R. Alsayed , C. C. Beh , N. R. Foster , A. D. Payne , Y. Yu and H. Gunosewoyo , Curr. Mol. Pharmacol., 2019, 12 , 27-49
8. P. J. Brennan and H. Nikaido, Annu. Rev. Biochem., 1995, 64 , 29 63 Cross Ref CAS PubMed .
9. V. Nataraj , C. Varela , A. Javid , A. Singh , G. S. Besra and A. Bhatt , Mol. Microbiol., 2015, 98 , 7-16.
10. K. Takayama , C. Wang and G. S. Besra , Clin. Microbiol. Rev., 2005, 18, 81-101
11. M. V. de Almeida, M. F. Saraiva , M. V. de Souza , C. F. da Costa , F. R. Vicente and M. C. Lourenco , Bioorg. Med. Chem. Lett., 2007, 17 , 5661-5664.
12. Y. Q. Hu , S. Zhang , F. Zhao , C. Gao , L. S. Feng , Z. S. Lv , Z. Xu and X. Wu , Eur. J. Med. Chem., 2017, 133 , 255-267
13. B. D. Palmer , A. M. Thompson , H. S. Sutherland , A. Blaser , I. Kmentova , S. G. Franzblau , B. Wan , Y. Wang , Z. Ma and W. A. Denny , J. Med. Chem., 2010, 53 , 282 — 294.
14. J. Stec , O. K. Onajole , S. Lun , H. Guo , B. Merenbloom , G. Vistoli , W. R. Bishai and A. P. Kozikowski , J. Med. Chem., 2016, 59 , 6232-6247.
15. A. S. T. Tong , P. J. Choi , A. Blaser , H. S. Sutherland , S. K. Y. Tsang , J. Guillemont , M. Motte , C. B. Cooper , K. Andries , W. Van den Broeck , S. G. Franzblau , A. M. Upton , W. A. Denny , B. D. Palmer and D. Conole , ACS Med. Chem. Lett., 2017, 8 , 1019-1024.
16. E. Uh , E. R. Jackson , G. San Jose , M. Maddox , R. E. Lee , R. E. Lee , H. I. Boshoff and C. S. Dowd , Bioorg. Med. Chem. Lett., 2011, 21, 6973-6976.
17. A. E. Grzegorzewicz , H. Pham , V. A. Gundi , M. S. Scherman , E. J. North , T. Hess , V. Jones , V. Gruppo , S. E. Born , J. Kordulakova , S. S. Chavadi , C. Morisseau , A. J. Lenaerts , R. E. Lee , M. R. McNeil and M. Jackson , Nat. Chem. Biol., 2012, 8 , 334-341.

18. K. Tahlan , R. Wilson , D. B. Kastrinsky , K. Arora , V. Nair , E. Fischer , S. W. Barnes , J. R. Walker , D. Alland , C. E. Barry 3rd and H. I. Boshoff , Antimicrob. Agents Chemother. 2012, 56, 1797-1809.
19. C.Varela , D.Rittmann , A.Singh , K. Krumbach , K. Bhatt , L. Eggeling , G. S. Besra and A. Bhatt , Chem. Biol., 2012, 19 , 498-506.
20. G. Degiacomi , A. Benjak , J. Madacki , F. Boldrin , R. Provvedi , G. Palu , J. Kordula-kova , S. T. Cole and R. Manganelli , Sci. Rep., 2017, 7 , 43495.
21. W. Li , A. Obregon-Henao , J. B. Wallach, E. J. North , R. E. Lee , M. Gonzalez-Juarrero , D. Schnappinger and M. Jackson , Antimicrob. Agents Chemother. 2016, 60, 5198-5207.
22. Edson Norberto Carcamo-Noriega, Shvam sathyamoorthi, Shibdas Banerjee, Elumalai Gnanamani, Monserrat Mendoza-Trujillo, Dulce mata-Espinosa, Rogelio Hernandez-Pando,Jose lgnacio Veytia-Bucheli, Lourival D.Possani and Richard N. Zare, worked on 1,4 benzoquinone against anti tb derivatives. june 2019: 116(26): 12642-12647.
23. Lig Prep, version 2.3. Schrödinger, LLC: New York; 2009.
24. Glide, version 5.0. Schrödinger, LLC: New York; 2008.