PUBLICATIONS

A. Publications in peer-reviewed international journals from thesis work

1. **Das, B.**, Patra, A., and Mukherjee, A. K. (2020). Correlation of venom toxinome composition of Indian red scorpion (*Mesobuthus tamulus*) with clinical manifestations of scorpion stings: failure of commercial antivenom to immune-recognize the abundance of low molecular mass toxins of this venom. *Journal of Proteome Research*, *19*(4), 1847-1856. ***IF- 5.370***
2. **Das, B.**, Saviola, A. J., and Mukherjee, A. K. (2021). Biochemical and proteomic characterization, and pharmacological insights of Indian red scorpion venom toxins. *Frontiers in Pharmacology*, *12*, 710680. ***IF- 5.988***
3. **Das, B.,** Patra, A., Puzari, U., Deb, P., and Mukherjee, A. K. (2022). *In vitro* laboratory analyses of commercial anti-scorpion (*Mesobuthus tamulus*) antivenoms reveal their quality and safety but the prevalence of a low proportion of venom-specific antibodies. *Toxicon*, *215*, 37-48. ***IF- 3.035***
4. Das, B., Madhubala, D., Mahanta, S., Patra, A., Puzari, U., Khan, M. R., & Mukherjee, A. K. (2023). A Novel Therapeutic Formulation for the Improved Treatment of Indian Red Scorpion (*Mesobuthus tamulus*) Venom-Induced Toxicity-Tested in *Caenorhabditis elegans* and Rodent Models. *Toxins*, *15*(8), 504. ***IF- 4.2.***

B. Mass spectrometry data submitted to ProteomeXchange Consortium via the PRIDE tool

1. **Project Name:** Proteomic analysis of Indian red scorpion (*Mesobuthus tamulus*) venom. **Dataset Identifier:** PXD017433.

C. Publications in National and International conferences

1. **Das, B.,** Patra, A., and Mukherjee, A. K. (2022) "Correlation of venom toxinome composition of Indian red scorpion (*Mesobuthus tamulus*) with clinical manifestations of scorpion stings: failure of commercial antivenom to immune-recognize the abundance of low molecular mass toxins of this venom."

at the **National seminar on Biology Is Fascinating,** Tezpur University, Napaam, 1st March, 2022.

2. **Das, B.,** Roy, A., and Mukherjee, A. K. (2022) "Proteomic characterization of Indian red scorpion and *in vitro* laboratory analyses of commercial anti-scorpion antivenoms" at the **National symposium on Snake and Scorpion Envenomation and Therapy: National and Internation Perspectives,** IASST, Guwahati, 16th July, 2022.
3. **Das, B.,** Patra, A., and Mukherjee, A. K. (2022) "A comparative study of proteome composition of Indian red scorpion venom with other scorpion venom proteome: Failure of commercial antivenom to immunerecognize the abundance of low molecular mass toxins of venom" at the **14th Annual Meeting of the Proteomics Society , India and International Conference on Proteins & Proteomics (PSI-ICPP 2022),** CSIR-Indian Institute of Chemical Biology, Kolkata, 03-05, November, 2022.

Journal of proteome research

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Correlation of Venom Toxinome Composition of Indian Red Scorpion (*Mesobuthus tamulus*) with Clinical Manifestations of Scorpion Stings: Failure of Commercial Antivenom to Immune-Recognize the Abundance of Low Molecular Mass Toxins of This Venom

Bhabana Das, Aparup Patra, and Ashis Kumar Mukherjee*

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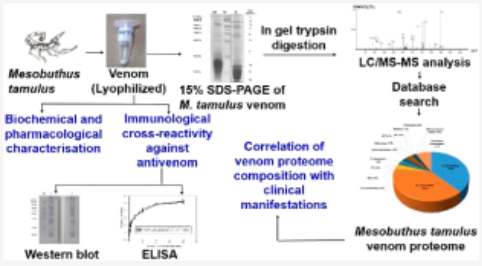
ABSTRACT: The Indian red scorpion (*Mesobuthus tamulus*), with its life-threatening sting, is the world's most dangerous species of scorpion. The toxinome composition of *M. tamulus* venom was determined by tandem mass spectrometry (MS) analysis of venom protein bands separated by SDS-PAGE. A total of 110 venom toxins were identified from searching the MS data against the Buthidae family (taxid: 6855) of toxin entries in nonredundant protein databases. The Na^+ and K^+ ion channel toxins taken together are the most abundant toxins (76.7%) giving rise to the neurotoxic nature of this venom. The other minor toxin classes in the *M. tamulus* venom proteome are serine protease-like protein (2.9%), serine protease inhibitor (2.2%), antimicrobial peptide (2.3%), hyaluronidase (2.2%), makatoxin (2.1%), lipolysis potentiating peptides (1.2%), neurotoxin affecting Cl^- channel (1%), parabutoporin (0.6%), Ca^{2+} channel toxins (0.8%), bradykinin potentiating peptides (0.2%), HMG CoA reductase inhibitor (0.1%), and other toxins with unknown pharmacological activity (7.7%). Several of these toxins have been shown to be promising drug candidates. *M. tamulus* venom does not show enzymatic activity (phospholipase A_2, L-amino acid oxidase, adenosine tri-, di-, and monophosphatase, hyaluronidase, metalloproteinase, and fibrinogenolytic), *in vitro* hemolytic activity, interference with blood coagulation, or platelet modulation properties. The clinical manifestations post *M. tamulus* sting have been described in the literature and are well correlated with its venom proteome composition. An abundance of low molecular mass toxins (3−15 kDa) are responsible for exerting the major pharmacological effects of *M. tamulus* venom, though they are poorly immune-recognized by commercial scorpion antivenom. This is a major concern for the development of effective antivenom therapy against scorpion stings.



KEYWORDS: *red scorpion venom, ESI-LC-MS/MS, Buthidae, ion-channel toxins, neurotoxins, autonomic storm, toxinomics*

1. INTRODUCTION

Scorpion stings can present a life-threatening acute medical emergency and are a neglected public health problem in tropical and subtropical nations, particularly in North Africa, the Middle East, Latin America, and India.[1] Annually, scorpions cause 1.2 million stings resulting in 3250 deaths.[2] The statistical data on scorpion stings in India is limited, though it seems to be similar to the snakebite problem, and scorpion stings should also be included with the group of neglected tropical diseases. Children under the age of seven years whose immune systems are developing and elderly individuals who may be immuno-compromised are categories of vulnerable people who are most affected post scorpion sting.[3] After a scorpion sting, clinical manifestations will depend on some crucial factors like the size of the scorpion, qualitative and quantitative distribution of toxins in the venom, status of the telson, venom duct, number of stings, and the victim's age and health status.[3,4]

Scorpion venom is a complex mixture of enzymatic and predominantly nonenzymatic toxins. On the basis of their chain length, scorpion toxins are classified into two broad categories: (i) short toxins comprised of 30−40 amino acids, and (ii) long toxins comprised of 60−70 amino acids.[5] Despite

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REVIEW
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Biochemical and Proteomic Characterization, and Pharmacological Insights of Indian Red Scorpion Venom Toxins

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The Indian red scorpion (Mesobuthus tamulus) is one of the world's deadliest scorpions, with stings representing a life-threatening medical emergency. This species is distributed throughout the Indian sub-continent, including eastern Pakistan, eastern Nepal, and Sri Lanka. In India, Indian red scorpions are broadly distributed in western Maharashtra, Saurashtra, Kerala, Andhra Pradesh, Tamil Nadu, and Karnataka; however, fatal envenomations have been recorded primarily in the Konkan region of Maharashtra. The Indian red scorpion venom proteome comprises 110 proteins belonging to 13 venom protein families. The significant pharmacological activity is predominantly caused by the low molecular mass non-enzymatic Na^+ and K^+ ion channel toxins. Other minor toxins comprise 15.6% of the total venom proteome. Indian red scorpion stings induce the release of catecholamine, which leads to pathophysiological abnormalities in the victim. A strong correlation has been observed between venom proteome composition and local (swelling, redness, heat, and regional lymph node involvement) and systemic (tachycardia, mydriasis, hyperglycemia, hypertension, toxic myocarditis, cardiac failure, and pulmonary edema) manifestations. Immediate administration of antivenom is the preferred treatment for Indian red scorpion stings. However, scorpion-specific antivenoms have exhibited poor immunorecognition and neutralization of the low molecular mass toxins. The proteomic analysis also suggests that Indian red scorpion venom is a rich source of pharmacologically active molecules that may be envisaged as drug prototypes. The following review summarizes the progress made towards understanding the venom proteome of the Indian red scorpion and addresses the current understanding of the pathophysiology associated with its sting.

Keywords: Indian red scorpion, venom composition, pathophysiology of scorpion sting, catecholamines, therapy against Mesobuthus tamulus scorpion sting

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In vitro laboratory analyses of commercial anti-scorpion (*Mesobuthus tamulus)* antivenoms reveal their quality and safety but the prevalence of a low proportion of venom-specific antibodies

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ABSTRACT

Mesobuthus tamulus (Indian Red Scorpion) sting is a severe but neglected health issue in India. The accomplishment of in-patient scorpion sting management is highly dependent on the safety, efficacy, and homogeneity of scorpion antivenom preparation. Therefore, in this study, the above qualities of commercial anti-scorpion antivenoms manufactured in India were assessed by *in vitro* laboratory analyses. Biophysical characterization of venom by sodium dodecyl sulfate-polyacrylamide gel electrophoresis, size exclusion chromatography, and proteomics analysis demonstrated that anti-scorpion antivenoms (ASAs) mostly contain $F(ab')_2$ molecules with a trace amount of undigested immunoglobulin (Ig) G. The physicochemical characterization, electron microscopy, and dynamic light scattering studies revealed that ASAs were prepared according to the guidelines of World Health Organization (WHO), and were devoid of aggregate content and virus particles. ASAs did not show IgE contamination and bacterial endotoxin but demonstrated moderate complement activation properties, which may have adverse effects in treated patients. Spectrofluorometric and atomic force microscopy analyses showed poor binding of venom with commercial ASAs. The percent of antibodies raised against the venom toxins in commercial ASAs was determined at the range of 5.3–6.3%, which is a reason for their poor efficacy. This study advocates the importance of *in vitro* laboratory analyses for assessing commercial antivenom's quality and safety parameters before their pre-clinical research and clinical use to treat Indian red scorpion sting.

1. Introduction

Scorpion sting is a severe but neglected public health issue in tropical and sub-tropical countries, causing 1.23 million stings globally, which results in 3250 deaths annually (Bawaskar, 1984; Chippaux and Goyffon, 2008). Notably, scorpions are the second most noxious animal after the snake, causing significant problems to children and adolescents. The *Mesobuthus tamulus* (Indian red scorpion) is reported as one of the lethal scorpions of the ecosphere, and epidemiological data show that this species is distributed in India, Sri Lanka, eastern Nepal, and eastern Pakistan (Badhe et al., 2007; Bhadani et al., 2006; Kovarík, 2007; Kularatne et al., 2015). In India, maximum mortalities due to scorpion sting is reported in Kerala, Tamil Nadu, Andhra Pradesh, western Maharashtra, Saurashtra, and Karnataka states (Agrawal et al., 2015; Bawaskar and Bawaskar, 1996, 1998; Yuvaraja et al., 2019).

M. tamulus venom is predominated (76.7%) by low molecular mass toxins bind to ion-channels, for example, Na^+ and K^+ channels affecting toxins (Das et al., 2020), which are mainly responsible for inducing pharmacological activity and clinical manifestations. Further, stimulation of α-adrenergic receptor resulted in myocardial dysfunction, pulmonary edema, tachycardia, hypertension, and cool extremities, and these pathophysiological conditions play a significant role in the pharmacology of Indian red scorpion sting (Bawaskar and Bawaskar, 1992; Dutta and Deshpande, 2011; Kumar et al., 2012; Rowan et al., 1992; SinghDeshpande, 2005; Strong et al., 2015). Treatment of *M.tamulus* sting is a medical emergency, and administration of specific anti-scorpion antivenom (ASA) is an inevitable choice for treatment in case of severe envenomation (Chippaux, 2012; Das et al., 2021). To date nineteen ASAs are manufactured worldwide including India for their intended use in humans and animals against scorpion sting (Laustsen

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toxins

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Article

A Novel Therapeutic Formulation for the Improved Treatment of Indian Red Scorpion (*Mesobuthus tamulus*) Venom-Induced Toxicity-Tested in *Caenorhabditis elegans* and Rodent Models

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Abstract: Indian Red Scorpion (*Mesobuthus tamulus*) stings are a neglected public health problem in tropical and sub-tropical countries, including India. The drawbacks of conventional therapies using commercial anti-scorpion antivenom (ASA) and α1-adrenoreceptor antagonists (AAA) have prompted us to search for an adequate formulation to improve treatment against *M. tamulus* stings. Novel therapeutic drug formulations (TDF) of low doses of commercial ASA, AAA, and ascorbic acid have remarkably improved in neutralising the in vivo toxic effects of *M. tamulus* venom (MTV) tested in *Caenorhabditis elegans* and Wistar strain albino rats in vivo models. The neutralisation of MTV-induced production of free radicals, alteration of the mitochondrial transmembrane potential, and upregulated expression of genes involved in apoptosis, detoxification, and stress response in *C. elegans* by TDF surpassed the same effect shown by individual components of the TDF. Further, TDF efficiently neutralized the MTV-induced increase in blood glucose level within 30 to 60 min post-treatment, organ tissue damage, necrosis, and pulmonary oedema in Wistar rats, indicating its clinical application for effecting treating *M. tamulus* envenomation. This study demonstrates for the first time that *C. elegans* can be a model organism for screening the neutralization potency of the drug molecules against a neurotoxic scorpion venom.

Keywords: *M. tamulus* venom; neutralisation potency; formulated drug

Key Contribution: A novel drug formulation showed higher efficiency in neutralizing MTV-induced toxicity; free radical generation; alteration of mitochondrial transmembrane potential; gene expression in the *Caenorhabiditis elegans* model. Further, MTV-induced hyperglycaemia; biochemical changes of serum; toxicity in Wistar albino rats were better neutralized by the novel formulation than the individual components.

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1. Introduction

Scorpion sting, an under-researched prevalence, is responsible for many mortalities in most countries. The Indian red scorpion (*Mesobuthus tamulus*), with its life-threatening sting, is one of the world's most dangerous scorpions [1]. The qualitative and quantitative occurrence of different venom toxins influences the pharmacological properties and toxicity of venom. Proteomic analysis has demonstrated the relative proportion of various toxins in the *M. tamulus* venom (MTV) [2]. Notably, the potent toxicity of MTV is attributed to the

APPENDIX

Appendix fig. A1. Alignment of tryptic and semi-tryptic peptide sequences derived from LC-MS/MS analysis. The protein alignment was done using Clustal Omega programme (https://www.ebi.ac.uk/Tools/msa/clustalo/). The distinct peptides obtained for each of the following proteins has been highlighted in green or blue or purple (three colours have been used in case of adjacent distinct/unique peptides). The amino acid substitutions within the unique/distinct peptides obtained from MS/MS are highlighted in red colour.

1. Venom peptide having unknown target:

>sp|D2CFI7.1|
Signal peptide[1-21] mature chain[22-123]
MSIKISAIALFMLSFTVFVNGIPFFLTKGRIDTCKTLTGETIKIGESWHDPNSCSVYYCEVNSLGAMLIGKTCATVFYPSNCR
EEPGTGLYPDCCNKVVCGEEEMVVYPYEERSLRRYYFSKF

2. Parabutoporin:

>sp|P83312.1|
Mature chain [1-45]
FKLGSFLKKAWKSKLAKKLRAKGKEMLKDYAKGLLEGGSEEVPGQ

3. Toxin plt:

>sp|P0C5J8.1|
Mature chain[1-17]
LCEKFKVQRLVELNCVD

4. OPRD1 receptor:

>sp|Q9Y0X6.2|
Signal+ propeptide[1-34]
MIFHQFYSILILCLIFPNQVVQSDKERQDWIPSDYGGYMNPAGRSDEERQDWIPSDYGGHMNPAGRSDEERQDWIPSDYGGHM
NPAGRSNEERQDWIPSDYGGYMNPAGRSDEERQDWIPSDYGGHMNPAGRSNEERQDWIPSDYGGYMNPAGRSDEERQDWIPSD
YGGHMNPAGRSDEERQDWIPSDYGGYMNPAGRSD

5. Seine protease like protein:

>sp|P0C8M2.1|
Mature chain[1-40]
IFGGTFAKNGEYPWMVVIDLPEFACGGVLISKKFVLTAAH

6. Serine protease inhibitor:

```
sp|P0DJ47.1|

-------------------
KHGSINCRLPPERGPCRGNITKYYYHNESRTCRTFSYGGCEGNSNNFRNRHYCMKYCARKRHGWLGTGWI-------------
----------------------     70
sp|P0DJ49.1|

----------------------QKDCSLPVDTGRGKGWFLRYYYNKNSKTCESFIYGGVGGNKNNFLNIENCCKICKAKNC--
----------------------------------------      59

               .  *.*           * . *   .
```

7. Makatoxin:

```
sp|Q86BW9.1|
MNYLIVISFALLLMTSVESGRDAYIADSENCTYFCGSNPYCNDLCTENGAKSGYCQWAGRYGNACWCIDLPDKVPIRIPGPCR
GR     85
sp|P59853.1|

MNYLIVISFALLLMTGVESGRDAYIAKKENCTYFCALNPYCNDLCTKNGAKSGYCQWAGRYGNACWCIDLPDKVPIRIPGPCI
GR     85
                                       *******..*****                              *.
*********:****************************** * *
```

8. Lipolysis activating peptide 1-beta chain:

```
sp|P84809.1|
MISVQVIFIAFISIIAFSMVCGGNVFPNRELGILYGCKGYGNAFCDKVCKMHLARGGGRCGEPNPVMWACECIDIDEDNGYFL
NALEKQCPLLKG---     95
sp|B8XGZ8.1|
MANVQVIFVAYIAVIAFSMVYGDDYKPFGEHNSYYGCKKQTDEFCNKICKLHLAKKGGFCHQPAPFVELCKCLDIDYDNTYFL
KAMEKQCPKLKGNVN     98

           * .*****:*:*::****** *.:   *   * .   ****    : **:*:**:***: ** * :* *.:
*:*:*** ** ***:*:***** **
```

9. Lipolysis activating peptide 1-alpha chain:

```
sp|Q6WJF5.3|

MMKFVLFGMIVILFSLMGSIRGDDDPGNYPTNAYGNKYYCTILGENEYCRKICKLHGVTYGYCYNSRCWCEKLEDKDVTIWNA
VKNHCTNTILYPNGK     98

             ***:****:******::***:*.*     *****     *:*****     *******::*:****:***
****:******* **:***.**:***.**.******:**
```

10. Bradykinin potentiating peptide:

```
sp|Q9TWD3.1|                          ----------------------------------------------
LRDYANRVINGGPVEAAGPPA---   21
sp|Q9Y0X4.1|
MNKKTLLVIFFVTMLIVDEVNSFRFGSFLKKVWKSKLAKKLRSKGKQLLKDYANKVLNGPEEEAAAPAERRR  72
*:****:*:**    ***.*
```

11. Insecticidal toxin with unknown toxin target:

```
sp|P60268.1|      MCMPCFTTDHQTARRCRDCCGGRGRKCFGQCLCGYD      36
sp|P15220.1|      MCMPCFTTRPDMAQQCRACCKGRGKCFGPQCLCGYD      36
sp|P15222.2|      MCMPCFTTDPNMAKKCRDCCGGNGKCFGPQCLCNR-      35
sp|P60270.1|      MCMPCFTTDPNMANKCRDCCGGGKKCFGPQCLCNR-      35
                  ********  : *.:** ** *  :    ****.
```

12. Antimicrobial peptide:

```
sp|B8XH50                                                MKSQAFFLLFLVVLLLATTQSEAFI---
MDLLGKIFGRRSMRNMDTMKYLYDPSLSAADLKTLQKLMENY
sp|E4VP07MKSQTFFLLFLVVFLLAITQSEAIFGAIAGLLKNIFGKRSLRDMDTMKYLYDPSLSAADLKTLQKLMENY


sp|Q9GQW4MKSQTFFLLFLVVLLLAISQSEAFIGAVAGLLSKIFGKRSMRDMDTMKYLYDPSLSAADLKTLQKLMENY
sp|Q6JQN2
MKSQTFFLLFLVVLLLAISQSEAFIGAIANLLSKIFGKRSMRDMDTMKYLYDPSLSAADLKTLQKLMENY


               ****:********:***        :****::                                .**
:***:**:*:**************************
```

13. Hyaluronidase:

>sp|P86100.2|
Signal[1-25] Mature chain[26-409]
MTQNIQMTEMYQIILFASILAAISATSADFKVVWEVPSIMCSKKFKINVTDLLTSHKILVNQEETFNGDKIVIFYESQLGKYP
HIESHGDINGGMLQVSDLANHLKIARDNISKFIPDPNFNGVIIDWEAWRPLWKYNWGRMSEYRDRSKDLVKAKHPDWSPAQIE
KVAIEEWENSAKEWMLKTLKLVEDMRPNAAWCYYLFPDCYNYGGKDQPSEYFCKNDIQEANDKLSWLWKQSTALCPSIYMQES
HITKYNTSQRAWWIYARLRETIRLSHPNTLIYPYINYILPGTKKTVPSMDFKRVLGQIGSLGLDGAIIWGSSYHVNTEEMCKE
MKTYVKDVIAPVASTVIQNVNRCSQQICKGRGNCVWPEEPYTSWKYLIDPKNPTFKHTNISCKCKGGYTGRYCQIAP

14. Neurotoxin with cl channel blocker:

```
sp|Q9BJW4.1|      MKFLYGIVFIALFLTVMFATQTDGCGPCFTTDANMARKCRECCGGNGKCFGPQCLCNRE   59
sp|Q9UAD0.1|      MKFLYGIVFIALFLTVMFATQTDGCGPCFTTDANMARKCRECCGGIGKCFGPQCLCNRI   59
******************************************** ************
```

15. Neurotoxin having unknown target:

```
sp|Q7M463.1|      ----------------------LPYPVNCKTECECVMCGLGIICKQCYYQQ---29
sp|Q7Z0H4.1|      MKIFFAVLVILVLFSMLIWTAYGTPYPVNCKTDRDCVMCGLGISCKNGYCQGCTR 55
                                        ********: :******** **: * *
```

16. Ca channel blocker:

>sp|Q8I6X9.2|
Signal[1-18] Mature chain[28-64]
MNTFVVVFLLLTAILCHAEHALDETARGCNRLNKKCNSDGDCCRYGERCISTGVNYYCRPDFGP

17. Na channel blocker:

```
sp|M4GX67.1|      ---MKAALLLVI-STLMLIGVLTKKSGY-PIQ--HDGCKNWCVF-N-HFCENICETYGG--------
SGYCYF---WKLACWCDNIHNWVPTWSR-ETN-KCRAK-83

sp|Q9NBW2.1|      ---MKAALLLVI-FSLMLIGVLTKKSGY-PTD--HEGCKNWCVL-N-HSCGILCEGYGG--------
SGYCYF---WKLACWCDLIHNWVPTWSR-ATN-KCRAK-83


sp|Q9UAC8.1|      ---MKIIIFLIVCSFVLIGVKA-DNGYLLNK-YTGCKIWCVI-NNESCNSECKLRRGN---------
YGYCYF---WKLACYCEGAPK-SELWAY-ETN-KCNGKM    85
sp|P86406.2|      --MMKIIIFLIVSSLVLIGVK-TDNGYLLDK—YTGCKVWCVI-NNESCNSECKIRRGN---------
YGYCYF---WKLACYCEGAPK-SELWHY-ETN-KCNGRM 86
```

```
sp|Q8I0K7.1|     ---MKLFLLLVFFASMLIDGLVN-ADGY-IRG--SNGCKISCLW-GNEGCNKECKGFGAY-------
YGYCWT---WGLACWCEGLPD-DKTWKS-ESN-TCGGKK-85

sp|Q17231.2|     -------------------------DGY-IRG--SNGCKVSCLW-GNEGCNKECRAYGAS-------
YGYCWT---WGLACWCEGLPD-DKTWKS-ESN-TCGRKK-64



sp|P0C5F0.1|   ----------------------KIDGY-PVD--NWNCKRICWY-NNKYCYDLCKGLKAD---------
SGYCWG---WTLSCYCEGLPD-NARIKR-G-G-RCN--62
sp|P58910.1|   ----------------------KIDGY-PVD--YWNCKRICWY-NNKYCNDLCKGLKAD---------
SGYCWG---WTLSCYCQGLPD-NARIKR-S-G-RCRA-63


sp|P01485.2|   ---------------LVMAGVESVKDGYIVDD---RNCTYFCG--RNAYCNEECTKLKGE---------
SGYCQWASPYGNACYCYKVPD-HVRTK--GPGR-CN--72

sp|P01486.1|   ----------------------LKDGYIVDD---RNCTYFCG--TNAYCNEECVKLKGE---------
SGYCQWVGRYGNACWCYKLPD-HVRTV--QAGR-CRS-65sp|P01490.1|         ----------------------
VRDGYIADD---KDCAYFCG--RNAYCDEECKK-GAE---------SGKCWYAQQYGNACWCYKLPD-WVPIKQKVSGK-CN-
-65sp|Q9NJC7.1|  ---MNYMV-IISLALLVMTGVESVKDGYIADD---RNCPYFCG--RNAYCDGECKKNRAE-------
--SGYCQWASKYGNACWCYKLPD-DARIM--KPGR-CNGG85sp|P82815.1|       ----------------------
VRDGYIADD---KNCAYFCG--RNAYCDEECIINGAE---------SGYCQQAGVYGNACWCYKLPD-KVPIR--VSGE-
CQQ-65sp|P86408.2|  ---MNSLV-MISLALLVMTGVESVRDGYIADD---KNCAYFCG--RNAYCDEECKKKGAE----
-----SGYCQWAGQYGNACWCYKLPD-KVPIK--VSGK-CNGR85
sp|G4V3T9.1|   ----------------------VKDGYIVDD---KNCAYFCG--RNAYCDDECEKNGAE---------
SGYCQWAGVYGNACWCYKLPD-KVPIR--VPGR-CNG-65

sp|Q9GYX2.1|   ---MNYLV-FFSLALLLMTGVGSVRDGYIADD---KNCPYFCG--RNAYCDDECKKNGAE---------
SGYCQWAGVYGNACWCYKLPD-KVPIR--VPGK-CNGG85

sp|Q9GNG8.1|   ---MNYLV-FFSLALLVMTGVESVRDGYIADD---KNCAYFCG--RNAYCDDECKKNGAE---------
SGYCQWAGVYGNACWCYKLPD-KVPIR--VPGK-CNGG85

sp|Q4TUA4.1|   ---MNYLV-FFSLALLLMTGVESVRDGYIADD---KNCAYFCG--RNAYCDDECKKKGAE---------
SGYCQWAGVYGNACWCYKLPD-KVPIR--VPGR-CNGG85

sp|Q9GUA7.1|   ---MNYLV-FFSLALLLMTGVESVRDGYIADD---KNCAYFCG--RNAYCDDECKKKGAE---------
SGYCQWAGVYGNACWCYKLPD-KVPIR--VPGK-CNGG85

sp|P86403.2|   ---MNYLV-MISLALLLMTGVESARDAYIAND---RNCVYTCA--LNPYCDSECKKNGAD---------
SGYCQWFGRFGNACWCKNLPD-KVPIRI--PG-ECRGR85

sp|P09982.1|   ----------------------ARDAYIADD---RNCVYTCA--LNPYCDSECKKNGAD---------
GSYCQWLGRFGNACWCKNLPD-DVPIRKI-PGEECR--66
```

```
sp|P13488.1|   ----------------------GRDGYIAQP---ENCVYHCFP-GSSGCDTLCKEKGAT---------
SGHCGFLPGSGVACWCDNLPN-KVPIVV--GGEKCH--66
sp|Q9GQW3.1|   ---MNYLV-MISFAFLLMTGVESVRDAYIAQN---YNCVYHCA--RDAYCNELCTKNGAK---------
SGSCPYLGEHKFACYCKDLPD-NVPIRV--PGK-CHRR85

sp|P60256.1|   ----------------------VRDAYIAQN---YNCVYDCA--RDAYCNELCTKNGAK---------
SGHCEWFGPHGDACWCIDLPN-NVPIKV--EGK-CHRK66

sp|E7CAU3.1|   ----------------------GRDAYIAQN---YNCVYHCF--RDDYCNGLCTENGAD---------
SGYCYLAGKYGHACWCINLPD-DKPIRI--PGK-CHRR66

sp|Q9NJC4.1|   ---------------LLMTGVESGRDAYIAKN---YNCVYHCF--RDDYCNGLCTENGAD---------
SGYCYLAGKYGNACWCINLPD-DKPIRI--PGK-CHRR74

sp|P54135.1|   ----------------------GRDAYIADS---ENCTYFCG--SNPYCNDVCTENGAK---------
SGYCQWAGRYGNACYCIDLPA-SERIKE--PGK-CG--64

sp|P0CF76.1|  ----------------------GRDAYIADS---ENCTYT-----------------------------
-------------------------------------15

sp|P0DMH9.1|   ---MNYLI-VISFALLLMTGVQSGRDAYIADS---ENCTYTCA--LNPYCNDLCTKNGAK---------
SGYCQWAGRYGNACWCIDLPD-KVPIRI--SGS-CRGR85

sp|P59854.1|   ----------------------VRDGYIALP---HNCAYGCL--NNEYCNNLCTKDGAK---------
IGYCNIVGKYGNACWCIQLPD-NVPIRV--PGR-CHPA66
sp|P86404.2|   ---MNYLI-LISFALLVITGVESARDAYIAKP---HNCVYECFDAFSSYCNGVCTKNGAK---------
SGYCQILGTYGNGCWCIVLPD-NVPIRI--PGK-CHR--86

sp|O61705.1|   ---MNYLV-MISFALLLMKGVESVRDAYIAKP---ENCVYECG--ITQDCNKLCTENGAE---------
SGYCQWGGKYGNACWCIKLPD-SVPIRV--PGK-CQR-84


sp|Q9NJC5.1|   ---MNYLV-MVSFALLLMTGVESVRDGYIALP---HNCAYGCL--LNEFCNDLCTKNGAK---------
IGYCNIQGKYGNACWCIELPD-NVPIRV--PGR-CHPS85


sp|Q9N682.1|   ---MNYLV-MISFALLLMTGVESVRDAYIAKP---ENCVYHCA--TNEGCNKLCTDNGAE---------
SGYCQWGGKYGNACWCIKLPD-DVPIRV--PGK-CHR-84

sp|P45698.1|   ---------MISFALLLMTGVESVRDAYIAKP---ENCVYHCA--TNEGCNKLCTDNGAE---------
SGYCQWGGRYGNACWCIKLPD-RVPIRV--PGK-CHR-79

sp|P58328.1|   ----------------------VRDAYIAKP---ENCVYHCA--GNEGCNKLCTDNGAE---------
SGYCQWGGRYGNACWCIKLPD-DVPIRV--PGK-CH--64
```

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sp|Q9GQV6.1|   ---MNYLV-MISFALLLMTGVESVRDAYIAKP---HNCVYECA--RNEYCNDLCTKNGAK---------
SGYCQWVGKYGNGCWCKELPD-NVPIRV--PGK-CHR-84
sp|P58488.1|   ----------------------VRDAYIAKP---HNCVYECA--RNEYCNNLCTKNGAK---------
SGYCQWSGKYGNGCWCIELPD-NVPIRV--PGK-CH--64
sp|P01483.1|   ----------------------GRDAYIAQP---ENCVYECA--KNSYCNDLCTKNGAK---------
SGYCQWLGRWGNACYCIDLPD-KVPIRI--EGK-CHF-65

sp|P01488.2|   ----------------------GRDAYIAQP---ENCVYECA--QNSYCNDLCTKNGAI---------
SGYCQWLGKYGNACWCKDLPD-NVPIRI--PGK-CHF--65

sp|P59354.1|   ----------------------GRDAYIAQP---ENCVYECA--KNSYCNDLCTKNGAK---------
SGYCQWLGKYGNACWCEDLPD-NVPIRI--PGK-CHF--65
```

18. K channel blocker:

```
sp|P86402.1|-----------------------------------------------------MCMPCFT---------
--TRPDMAQQCRD-CC--GGNGKCFG--------Y-QCLCNR-------  35

sp|Q9NJC6.1|-MMKQQFFLFLAVIVMISSVIEAGRGKEIMKNIKEKLTEVK-DKMKHSWNKLTSMSEYACPV---------
--IEKWCEDHCAA--K--KAIGKCED--------T-ECKCLKLRK----  90

sp|P0CH57.1|-MMKQQFFLFLAVIVMISSVIEAGRGREFMSNLKEKLSGVK-EKMKNSWNRLTSMSEYACPV---------
--IEKWCEDHCQA--K--NAIGRCEN--------T-ECKCLSK------  88


sp|E4VP04.1|--MKNYCGIITLFLA---------------------------------I---ISATGVFCVDF---
PNKGGKCDRKECRKTCKKL----NYRGKCFP--------N-YCRCFPG------60

sp|Q95P89.1|--MNRL-TTIILMLIVIN------------------------VIMDDISESKVAAGIVCKV---------
--CKIICG----M-QG--KKVNICKA--------PIKCKCKKG------60

sp|Q9NJP7.1|--MSRL-FTLVLIVLAM----------------------------NVMMAIISDPVVEAVGCEE---------
--CPMHCKGKNAK--------PTCDD--------G-VCNCNV-------56

sp|C0HJQ5.1|--MSRL-YAIILIALVF--------------------------NVIMTIMPDMKVEAVSCED---------
--CPPHCATKDQR--------AKCEN--------D-KCVCEPK------57


sp|P86400.2|--MSRL-YAIILIALVF--------------------------NVIMTIMPDMKVEAVSCED---------
--CPEHCATKDQR--------AKCDN--------D-KCVCEPK------57

sp|A9XE59.1|--MQRN-LVVLLFLGMVALSSCGFREKHFQRFVKYAVPESTLRTVLQTVVHKVGKTQFGCSA---------
--YQGYCDDHCQD-IE--KKEGFCHG--------F-KCKCGIPMGF---91
```

```
sp|B8XH40.1|--MQRN-LVVLLLLLGMVALSSCGLREKHFQKLVKYAVPESTLRTILQTAVHKLGKTQFGCPA----------
-YQGYCDDHCQD-IK--KEEGFCHG--------M-KCKCGIPMGF---91

sp|A0A059UI30.1|--MQRN-LVVLLFLGMVALSSCGLREKHFQKLVKYAVPEGTLRTIIQTAVHKLGKTQFGCPA------
-----YQGYCDDHCQD-IK--KQEGFCHG--------F-KCKCGIPMGF---91


sp|C0HJQ2.1|-------------------------------------------------------AAC-----------
--YSSDCRVKCRA-MG--FSSGKCID--------S-KCKCYK-------31

sp|P83407.1|-------------------------------------------------------AAC-----------
--YSSDCRVKCVA-MG--FSSGKCIN--------S-KCKCYK-------31

sp|E4VP41.1|--MSRL-LIFILTAVVL--S----------------------VIIDILNNSKVEGQYCCYT---------
--CIPDCSKSCQD-SG--LRFKACIP--------YRSCLCQY-------63

sp|A7KJJ7.1|--MSRL-FVFILIALFL--S----------------------AIIDVMSNFKVEGA--------------
--CSKPCRKYCID-KG--ARNGKCIN--------G-RCHCYY-------57

sp|P0DL65.1|-MMSRL-SVFILIALVL--S----------------------VIIDVLNNSKVEGA--------------
--CVENCRKYCQD-KG--ARNGKCIN--------S-NCHCYY-------58

sp|Q8MUB1.2|--MQKLFIVFVLFCI-LRLDAEV----------------------D-----GRTATFC-----------
--TQSICEESCKRQNK----NGRCVIEAEGSLIYH-LCKCY--------62

sp|B8XH30.1|--MQKLFIVLLLFCI-LRLDAEV----------------------D-----GRTMSHC-----------
--NQSECQEKCKKKNK----NGRCITEFEMNYVYN-RCRCN--------62

sp|B8XH45.1|--MQKLFIVLLLFCI-LRLDAEV----------------------D-----GRRATFC-----------
--KQPGCQEACKKENK----NGRCVDKFDNNFSYN-ICRCY--------62
sp|P0DL62.1|-----------------------------------------------------AGSMDSCS----------
--ETGVCMKACSERIRQVENDNKCPA--------G-ECICTT-------39

sp|B5KF99.1|--MNKVYLV--AVLV-LFLALTI----------------------NESNEAVPTGG-C-----------
PFSDFFCAKRCKDMKF--GNTGRCTGPN-----KT-VCKCSI-------64

sp|Q5F1N4.1|MKLKISFLILVLFSV-FFAIEGI----------------------I---
KWFPASVNGKGHSSCTNGLEMTEEDFCKMLCGIDGK--LRESKCVD--------H-WCYCSQILFP---78


sp|P0DMR9.1|-------------------------------------------------------QRQCERL--------
----RDCYKYCMS-------PKRCTY--------G-TCYCEPSP-----31
sp|P0DMR8.1|-------------------------------------------------------QRQCQNV--------
----QNCYKYCMS-------PKKCEY--------G-TCYCEPSP-----31
```

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sp|Q967F9.1|--MKIFFAILLILAV-CSMAIWT----------------------V---NGTPFAIKCATD--------
----ADCSRKCPG-------NPSCRN--------G-FCACT--------54

sp|Q9BKB4.1|--MKIFFAILLILAV-CSMAIWT----------------------V---NGTPFAIKCATN--------
----ADCSRKCPG-------NPPCRN--------G-FCACT--------54

sp|Q9BJX2.1|--MKIFFAILLILAV-CSMAIWT----------------------V---NGTPFEVRCATD--------
----ADCSRKCPG-------NPPCRN--------G-FCACT--------54
sp|A0ASK0.1|--MKIFFAILLILAV-CSMAIWT----------------------V---NGTPFEVRCATD--------
----ADCARKCPG-------NPPCRN--------G-FCACT--------54

sp|B8XH38.1|--MKISALVMITLLI-CSMMILC----------------------Q---GQKILSNRCNNS--------
----SECIPHCIRIFG--TRAAKCIN--------R-KCYCYP-------60

sp|P0CH12.1|--MNKLPILIFMLLV-CSMFISS----------------------D---CQKHTDIKCSSS--------
----SSCYEPCRGVTG--RAHGKCMN--------G-RCTCYY-------60


sp|P59936.2|--------------------WC------------------------------STCLDLACGAS--------
----RECYDPCFKAFG--RAHGKCMN--------N-KCRCYT-------40

sp|B8XH42.1|--MKILSVLLIALII-CSINICS----------------------E---A-GLIDVRCYAS--------
----RECWEPCRRVTG--SAQAKCQN--------N-QCRCY--------58

sp|P0DL46.1|-----------------------------------------------------GLIDVRCYAS--------
----RECWEPCRKVTG--SGQAKCQN--------N-QCRCY--------36

sp|P0DL45.1|-----------------------------------------------------GLIDVKCYAS--------
----RECWEPCRKVTG--SGQAKCQN--------N-QCRCY--------36

sp|Q8MQL0.1|--MKIFSILLVALII-CSISICT----------------------E---AFGLIDVKCFAS--------
----SECWIACKKVTG--SVQGKCQN--------N-QCRCY--------59

sp|B3EWY1.2|--MKILSILLIALVI-CSISICT----------------------E---AFGLIDVKCSAS--------
----RECWVACKKVTG--SGQGKCQN--------N-QCRCY--------59

sp|Q9BKB7.1|--MKISFVLLLTLFI-CS--IGW----------------------S---EARPTDIKCSES--------
----YQCFPVCKSRFG--KTNGRCVN--------G-FCDCF--------57


sp|C0HJQ8.1|--MKISFLLLLALVI-CS--IGW----------------------S---EAQFTDVKCTGT--------
----KQCWPVCKKMFG--RPNGKCMN--------G-KCRCYP-------58
sp|C0HJQ7.1|-----------------------------------------------------QFTDVKCTVT--------
----KQCWPVCKKMFG--RPNGKCMN--------G-KCRCYS-------37
```

```
sp|Q9NII5.1|--MKISFLLLLAIVI-CS--IGW----------------------T---EAQFTNVSCSAS--------
----SQCWPVCKKLFG--TYRGKCMN--------S-KCRCYS-------58


sp|H2ETQ6.1|-MKKISFLLLLAIVI-CS--IGW----------------------T---DGQFTDVRCSAS--------
----SKCWPVCKKLFG--TYKGKCKN--------S-KCRCYS-------59

sp|Q8I0L5.1|--MKFSSIILLTLLI-CSMSKFG----------------------N---CQVETNVKCQG---------
----GSCASVCRKAIG--VAAGKCIN--------G-RCVCYP-------59

sp|Q86BX0.1|--MKFSSIILLTLLI-CSMSIFG----------------------N---CQVQTNVKCQG---------
----GSCASVCRREIG--VAAGKCIN--------G-KCVCYRN------60

sp|K7XFK5.1|  -MKVFSAVLIILFV-CSMIIGI----------------------S---EGKEIPVKCKHS--------
----GQCLQPCKDA-G--MRFGKCMN--------G-KCNCTPK------  60


sp|C0HJQ4.1|--MKMFFTVLVTLFV-CSMIIGI----------------------C---EGREIPVKCKGS---------
----KQCLQSCKEA-G--MTYGKCMN--------G-KCNCTPKG-----61

sp|P83112.1|-----------------------------------------------------EVDMRCKSS---------
----KECLVKCKQATG--RPNGKCMN--------R-KCKCYPR------37

sp|P46114.1|-----------------------------------------------VFINAKCRGS---------
----PECLPKCKEAIG--KAAGKCMN--------G-KCKCYP-------37
*             * *




sp|P86402.1|          -----       35
sp|Q9NJC6.1|          -----       90
sp|P0CH57.1|          -----       88
sp|E4VP04.1|          -----       60
sp|Q95P89.1|          -----       60
sp|Q9NJP7.1|          -----       56
sp|C0HJQ5.1|          -----       57
sp|P86400.2|          -----       57
sp|A9XE59.1|          -----       91
sp|B8XH40.1|          -----       91
sp|A0A059UI30.1|      -----       91
sp|A0A059UEE4.1|      KNN--       73

sp|C0HJQ2.1|          -----       31
sp|P83407.1|          -----       31
sp|E4VP41.1|          -----       63
```

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sp|A7KJJ7.1|          -----       57
sp|P0DL65.1|          -----       58
sp|Q8MUB1.2|          -----       62
sp|B8XH30.1|          -----       62
sp|B8XH45.1|          -----       62
sp|P0DL62.1|          -----       39
sp|B5KF99.1|          -----       64
sp|Q5F1N4.1|          -----       78
sp|P0DMR9.1|          -----       31
sp|P0DMR8.1|          -----       31
sp|Q967F9.1|          -----       54
sp|Q9BKB4.1|          -----       54
sp|Q9BJX2.1|          -----       54
sp|A0ASK0.1|          -----       54
sp|B8XH38.1|          -----       60
sp|P0CH12.1|          -----       60
sp|P59936.2|          -----       40
sp|B8XH42.1|          -----       58
sp|P0DL46.1|          -----       36
sp|P0DL45.1|          -----       36
sp|Q8MQL0.1|          -----       59
sp|B3EWY1.2|          -----       59
sp|Q9BKB7.1|          -----       57
sp|C0HJQ8.1|          -----       58
sp|C0HJQ7.1|          -----       37
sp|Q9NII5.1|          -----       58
sp|H2ETQ6.1|          -----       59
sp|Q8I0L5.1|          -----       59
sp|Q86BX0.1|          -----       60
sp|K7XFK5.1|          -----       60
sp|C0HJQ4.1|          -----       61
sp|P83112.1|          -----       37
sp|P46114.1|          -----       37
```

19. HMG COA REDUCTASE:

```
>sp|Q95P90.2|
Signal [1-22]              mature chain[23-94]
MVKMQVIFIAFIAVIACSMVYGDSLSPWNEGDTYYGCQRQTDEFCNKICKLHLASGGSCQQPAPFVKLCTCQGIDYDNSFFFG
ALEKQCPKLRG
```

20. Mucin-25:

>sp|P0CH58.1|

Signal[1-31]

MFRIEYSLVQLLLRNVTIPLLLIIQMHIMSSVKLIQIRIWIQYVTVLQMFSMKTKQ

21. Meucin-49

>sp|P86407.2|

MNKKILLVIFIVTMLIVDEVNSFKFGSFIKRMWRSKLAKKLRAKGKELLRDYANRVLSPEEEAAAPAPVP

AKRRR

sp|E4VP07|

MKSQTFFLLFLVVFLLAITQSEAIFGALAGLLKNIFGKRSLRDMDTMKYLYDPSLSAADLKTLQKLMENY 70

Protein-ligand interactions:

Generation of the 3D structure of Prazosin Hydrochloride [PMCID: 68546]:

Canonical SMILES:
COC1=C(C=C2C(=C1)C(=NC(=N2)N3CCN(CC3)C(=O)C4=CC=CO4)N)OC.Cl

Molecular Formula:

C19H22ClN5O4

3D structure was generated using Corina Classic software.

Generation of the 3D structure of Terazosin hydrochloride [PMCID: 44383]:

Canonical SMILES:
COC1=C(C=C2C(=C1)C(=NC(=N2)N3CCN(CC3)C(=O)C4CCCO4)N)OC.Cl

Molecular Formula:

C19H26ClN5O4

3D structure was generated using Corina Classic software.

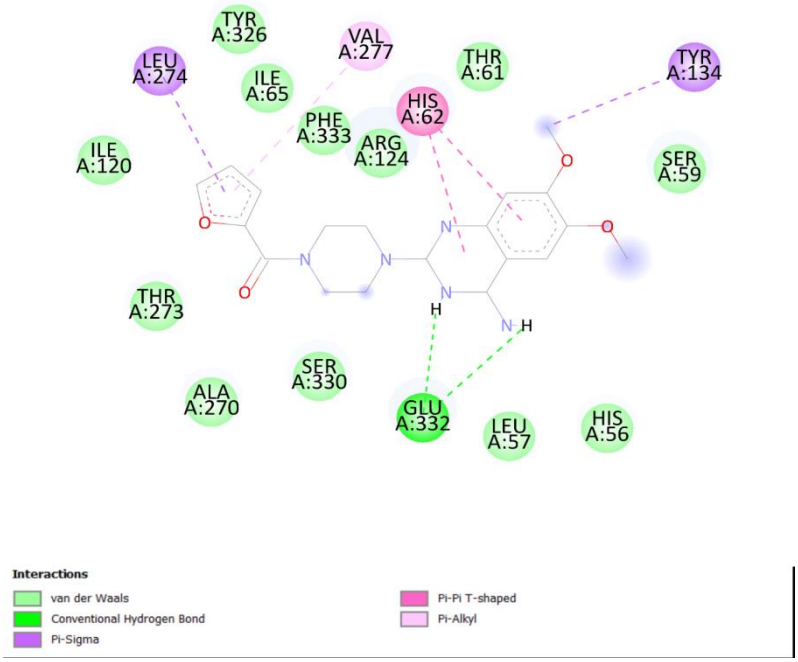
Generation of the 3D structure of Silodosin [PMCID: 5312125]:

Canonical SMILES:
CC(CC1=CC2=C(C(=C1)C(=O)N)N(CC2)CCCO)NCCOC3=CC=CC=C3OCC(F)(F)F

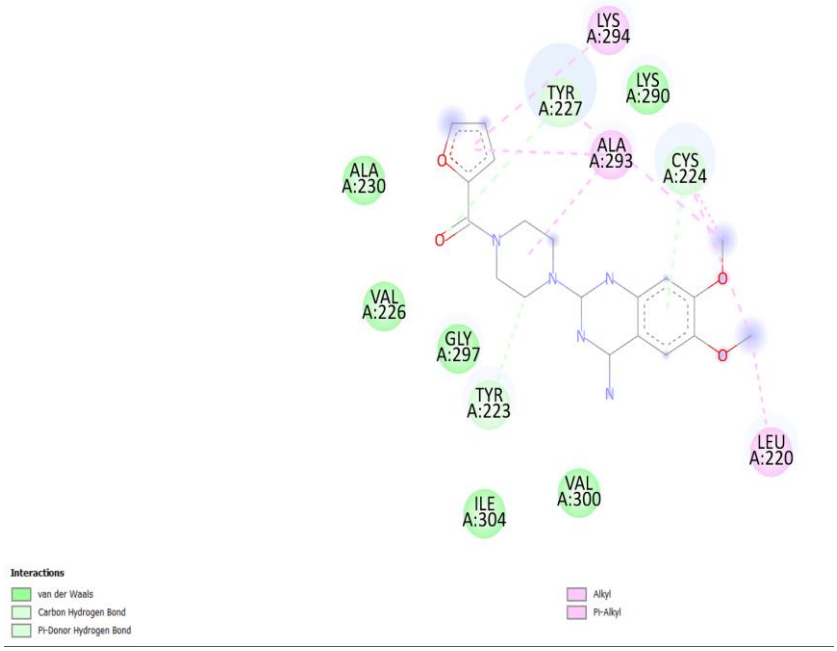
Molecular Formula:

C25H32F3N3O4

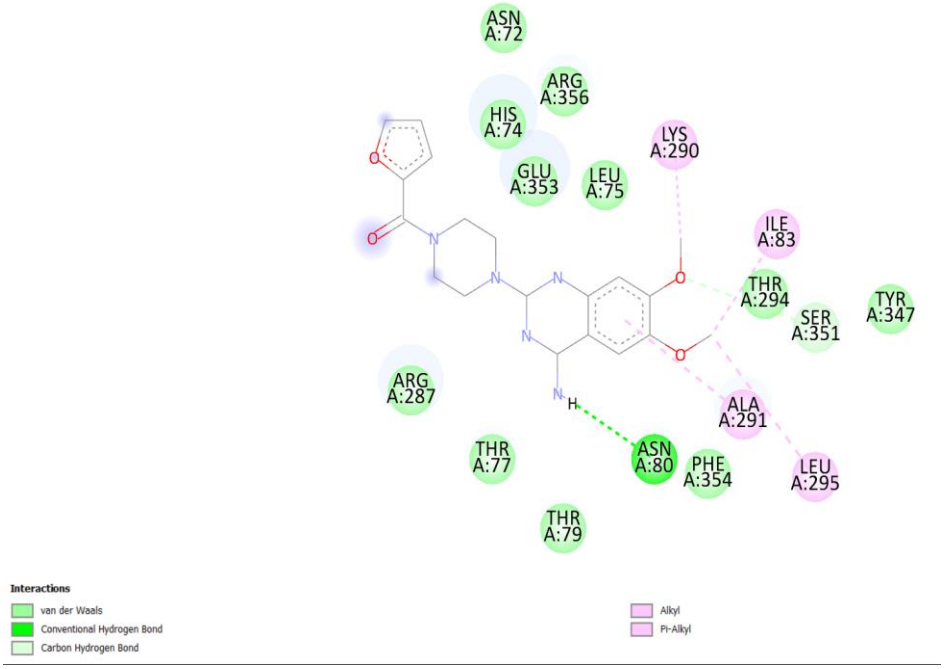
3D structure was generated using Corina Classic software.



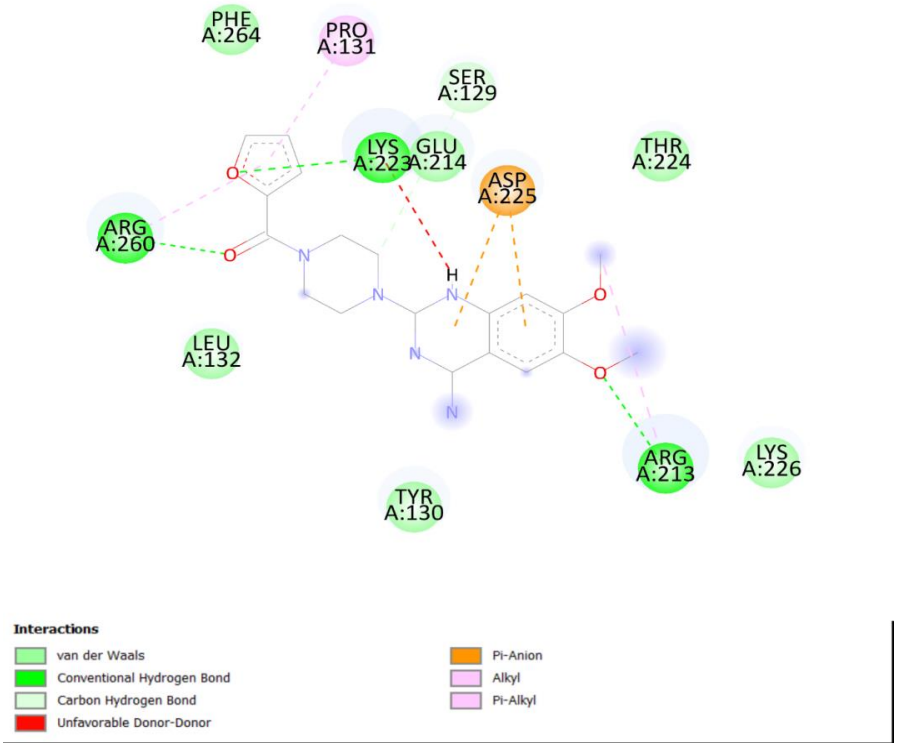
1.a AAAR (human) + Prazosin-HCL [AlphaFold identifier of AAAR: AF-P35348-F1, SwissProt Accession No.: P35348]



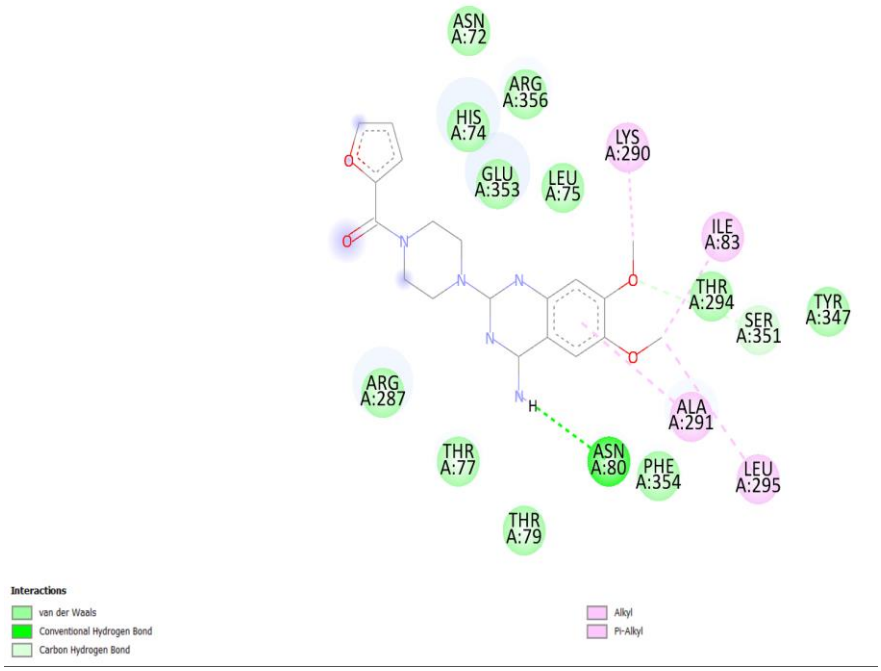
1.b ABAR (human)+ Prazosin-HCL [AlphaFold identifier of ABAR: AF-P35368-F1, SwissProt Accession No.: P35368]



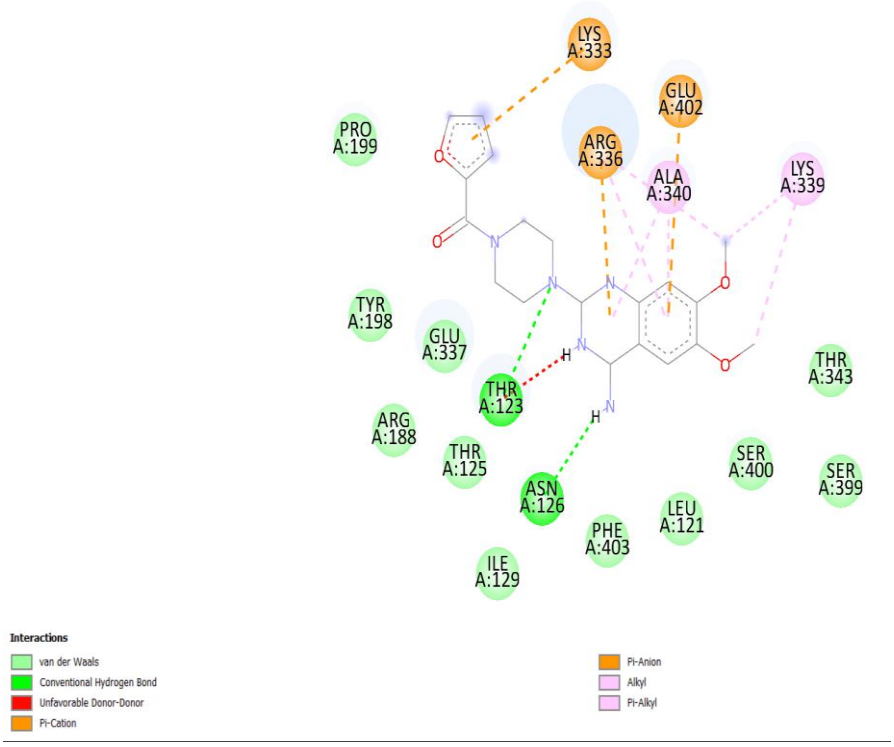
1.c ADAR (human)+ Prazosin-HCL [AlphaFold identifier of ADAR: AF-P25100-F1, SwissProt Accession No.: P25100]



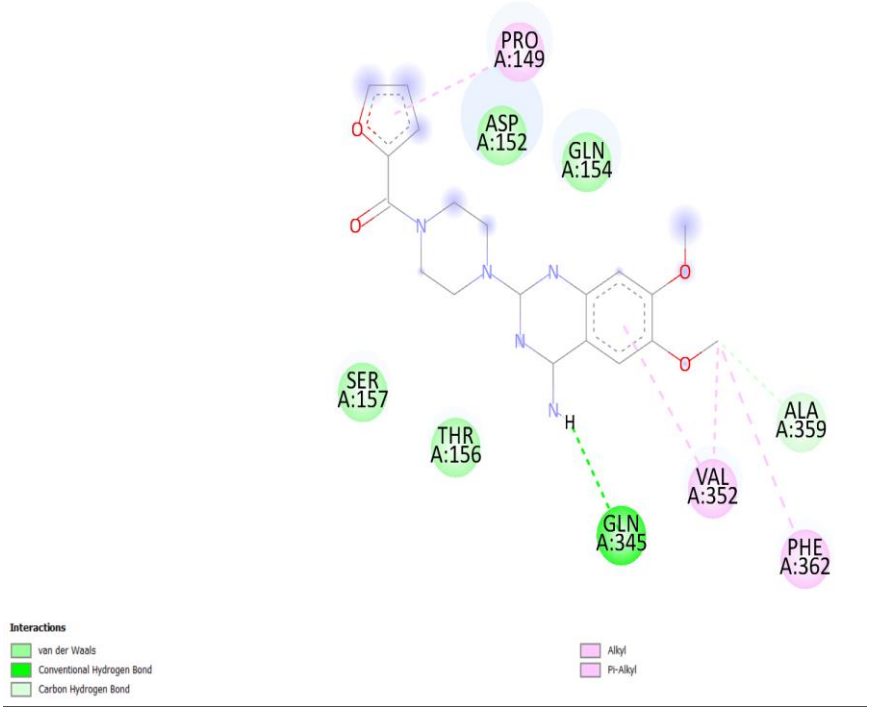
1.d AAAR (Mouse)+ Prazosin-HCL [AlphaFold identifier of AAAR: AF-P97718-F1, SwissProt Accession No.: P97718]



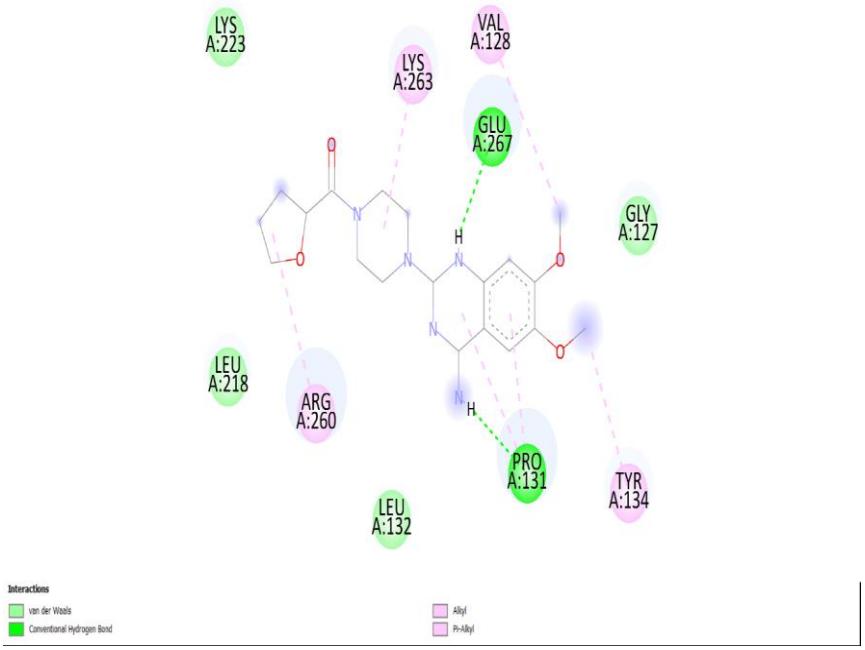
1.e ABAR (Mouse)+ Prazosin-HCL [AlphaFold identifier of ABAR: AF-P97717-F1, SwissProt Accession No.: P97717]



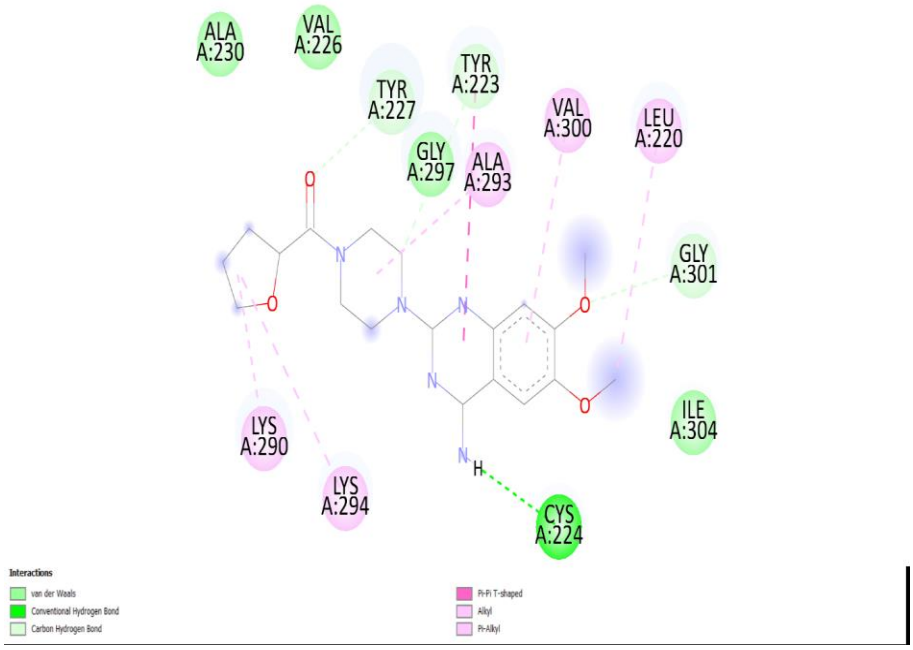
1.f ADAR (Mouse)+ Prazosin-HCL [AlphaFold identifier of ADAR: AF-P97714-F1, SwissProt Accession No.: P97714]



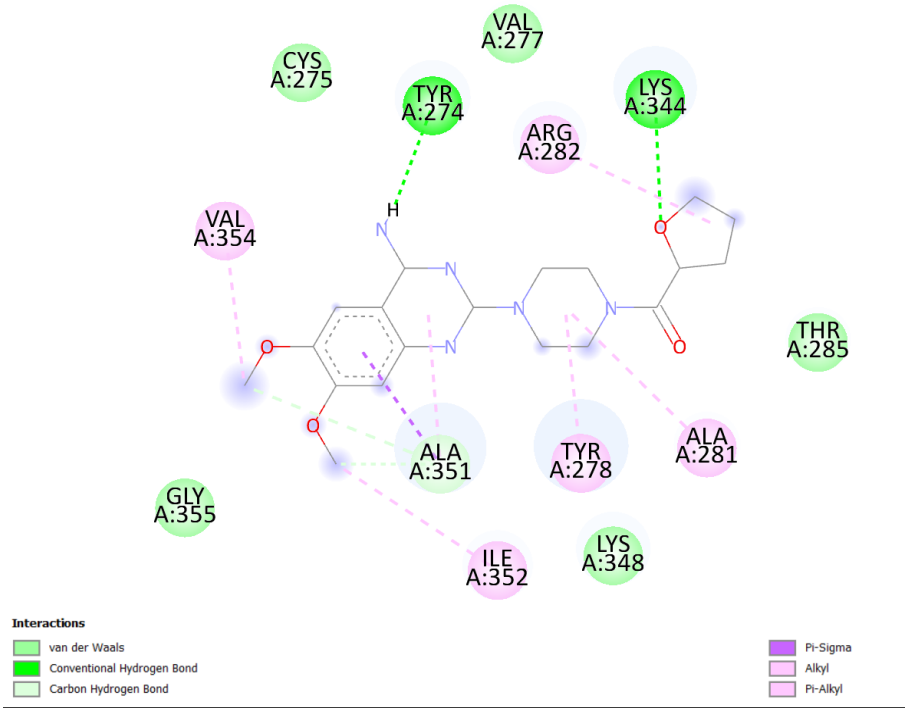
1.g SER6 receptor (*C. elegans*)+ Prazosin-HCL [AlphaFold identifier: AF-Q8MXS7-F1, SwissProt Accession No.: Q8MXS7]



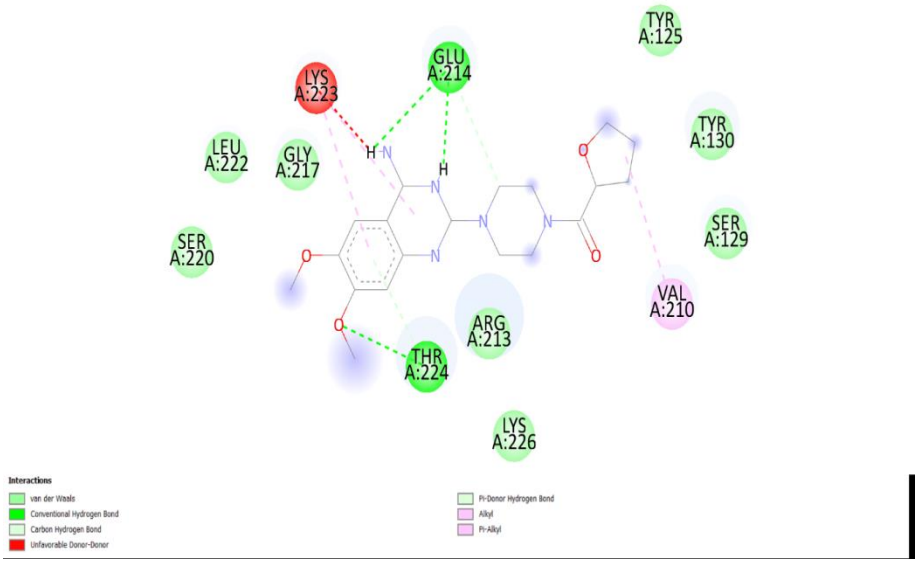
1.h AAAR (human) + Terazosin-HCL [AlphaFold identifier of AAAR: AF-P35348-F1, SwissProt Accession No.: P35348]



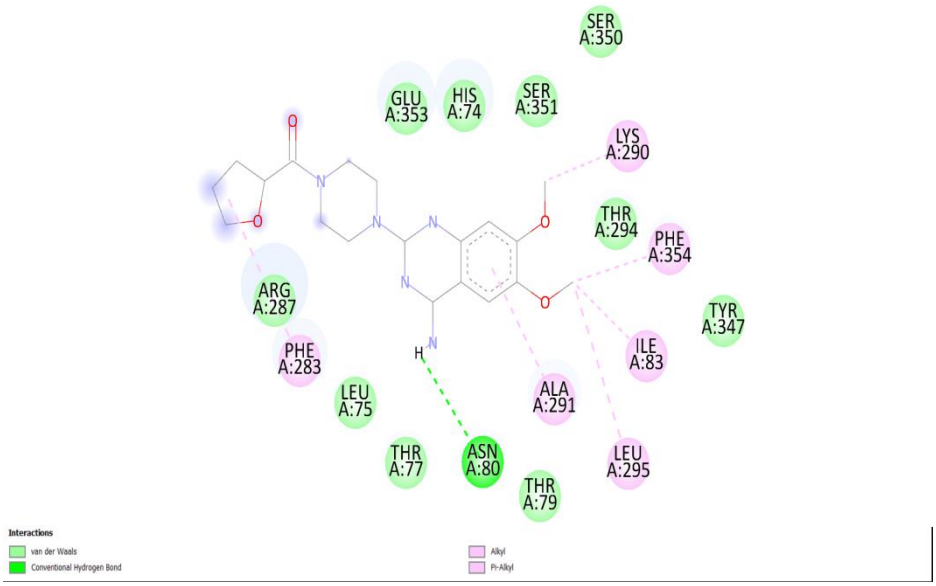
1.i ABAR (human)+ Terazosin-HCL [AlphaFold identifier of ABAR: AF-P35368-F1, SwissProt Accession No.: P35368]



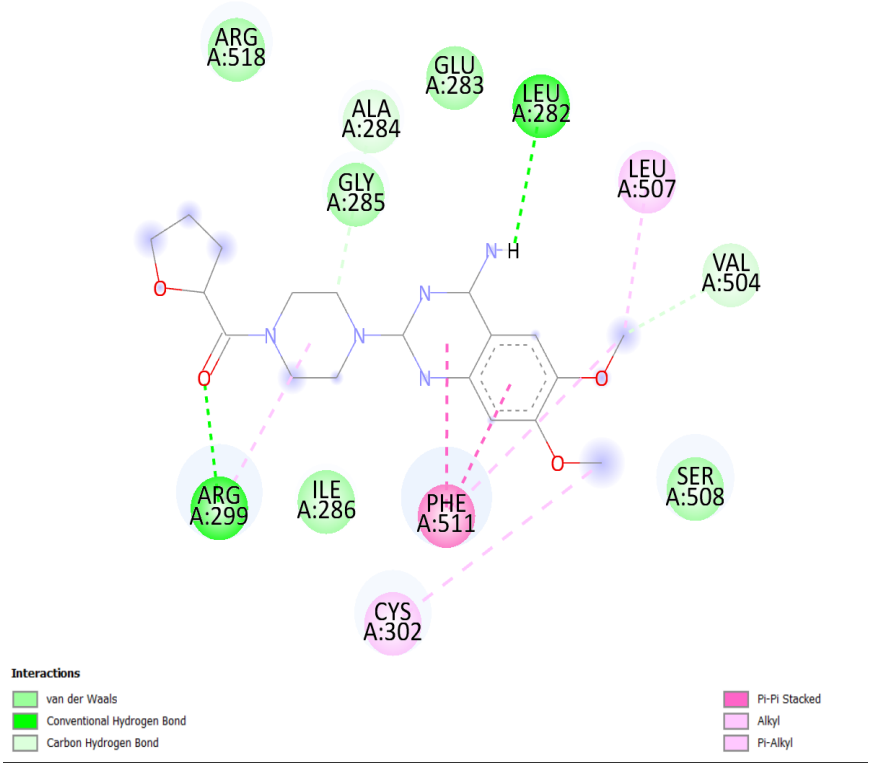
1.j ADAR (human)+ Terazosin-HCL [AlphaFold identifier of ADAR: AF-P25100-F1, SwissProt Accession No.: P25100]



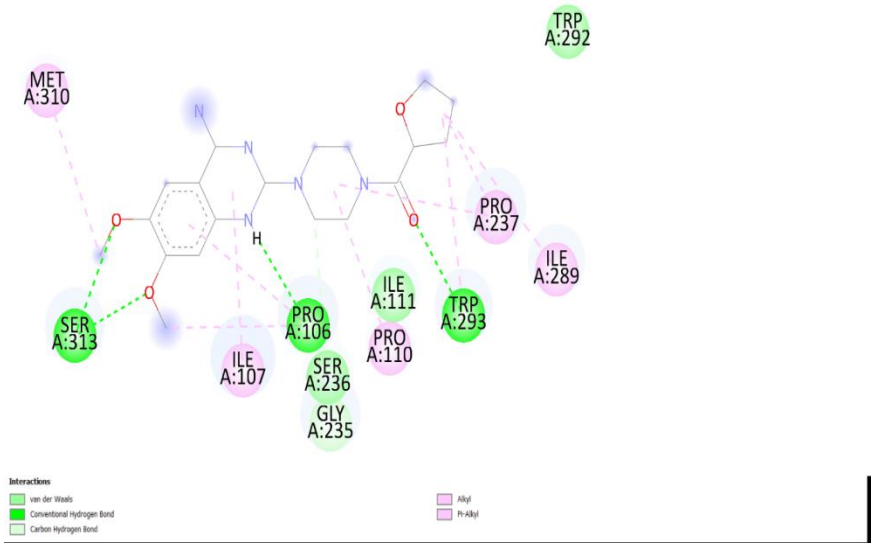
1.k AAAR (Mouse)+ Terazosin-HCL [AlphaFold identifier of AAAR: AF-P97718-F1, SwissProt Accession No.: P97718]



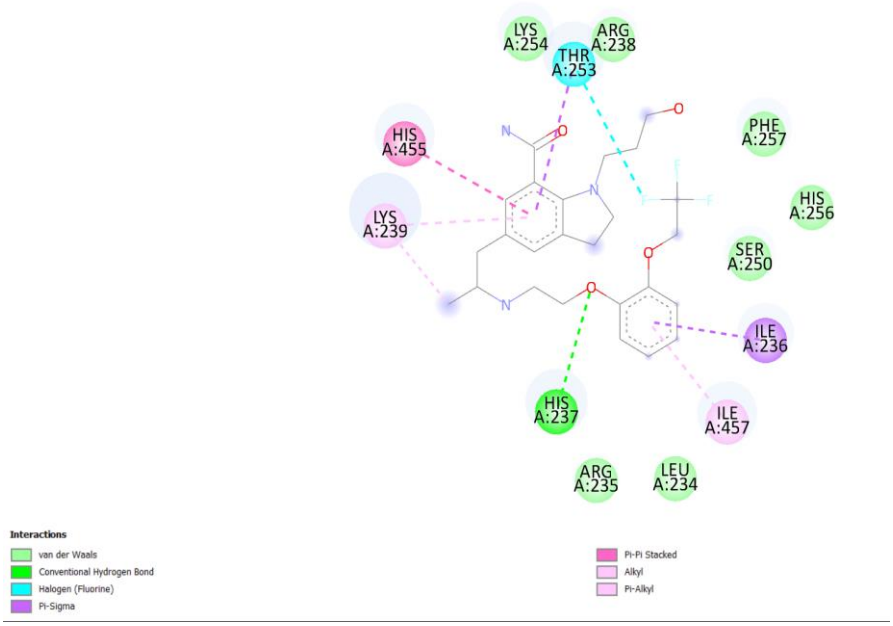
1.l ABAR (Mouse)+ Terazosin-HCL [AlphaFold identifier of ABAR: AF-P97717-F1, SwissProt Accession No.: P97717]



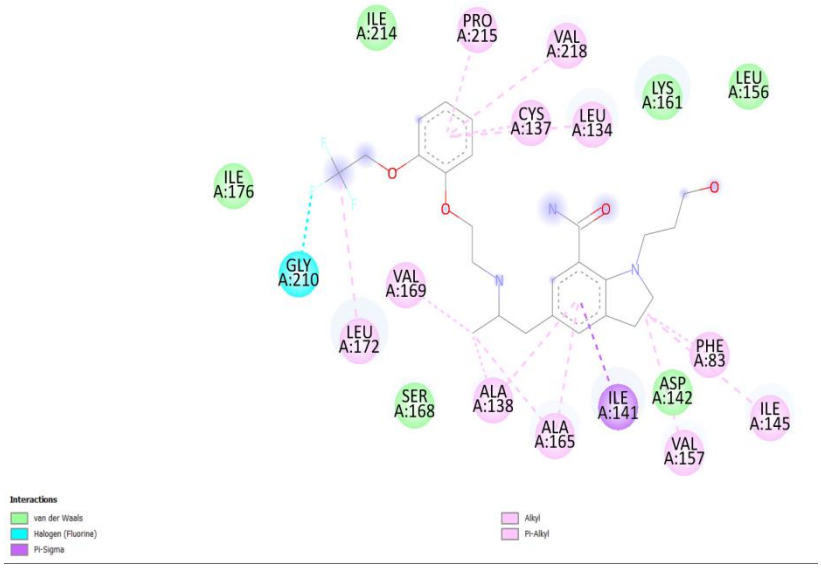
1.m ADAR (Mouse)+ Terazosin-HCL [AlphaFold identifier of ADAR: AF-P97714-F1, SwissProt Accession No.: P97714]



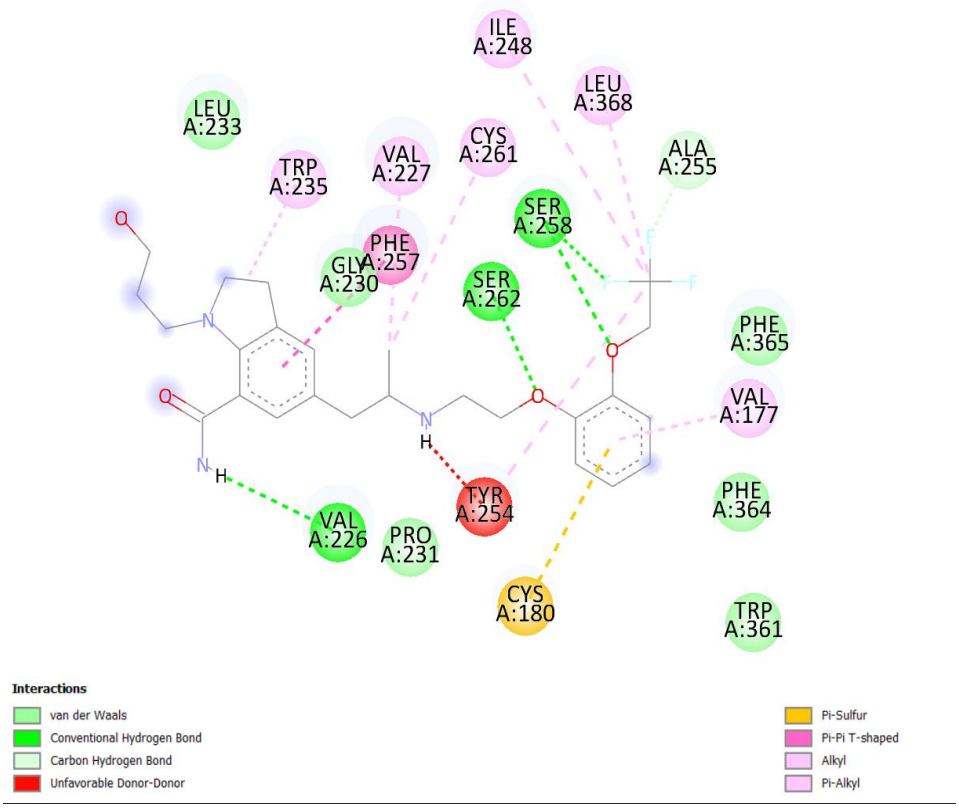
1.n SER6 receptor (*C. elegans*)+ Terazosin-HCL [AlphaFold identifier: AF-Q8MXS7-F1, SwissProt Accession No.: Q8MXS7]



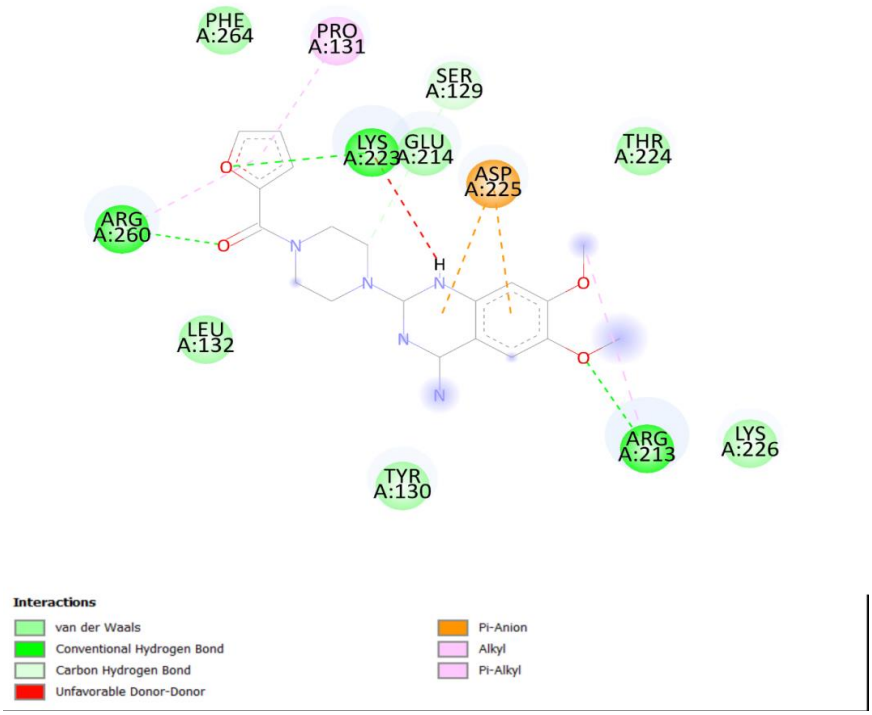
1.o AAAR (human) + Silodosin [AlphaFold identifier of AAAR: AF-P35348-F1, SwissProt Accession No.: P35348]



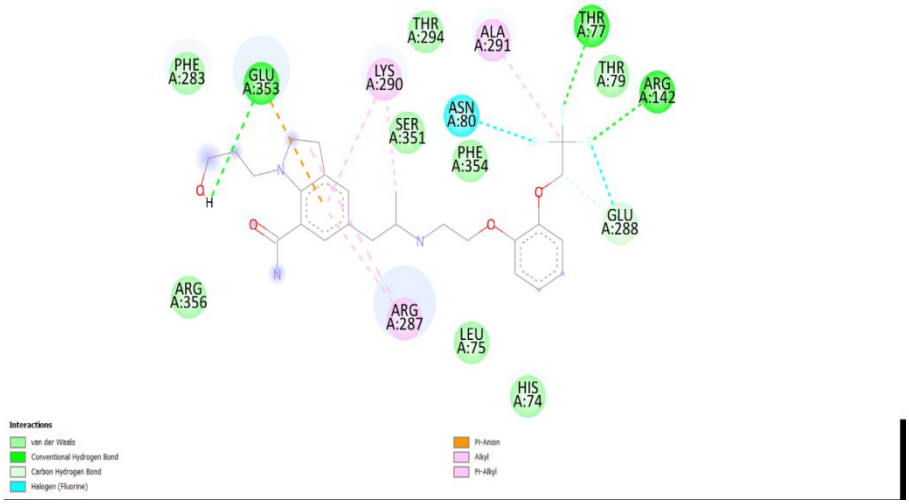
1.p ABAR (human)+ Silodosin [AlphaFold identifier of ABAR: AF-P35368-F1, SwissProt Accession No.: P35368]



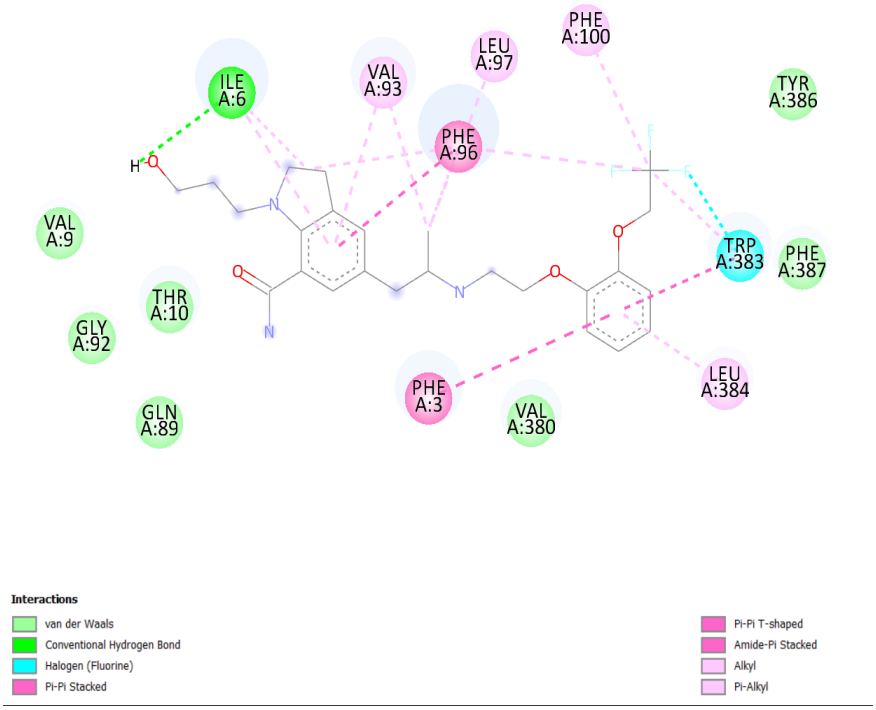
1.q ADAR (human)+ Silodosin [AlphaFold identifier of ADAR: AF-P25100-F1, SwissProt Accession No.: P25100]



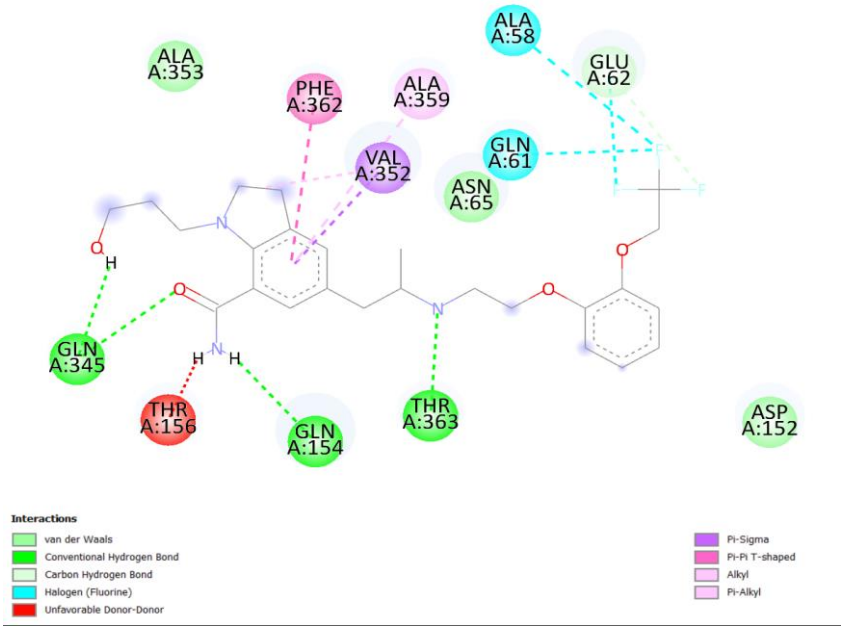
1.r AAAR (Mouse)+ Silodosin[AlphaFold identifier of AAAR: AF-P97718-F1, SwissProt Accession No.: P97718]



1.s ABAR (Mouse)+ Silodosin [AlphaFold identifier of ABAR: AF-P97717-F1, SwissProt Accession No.: P97717]

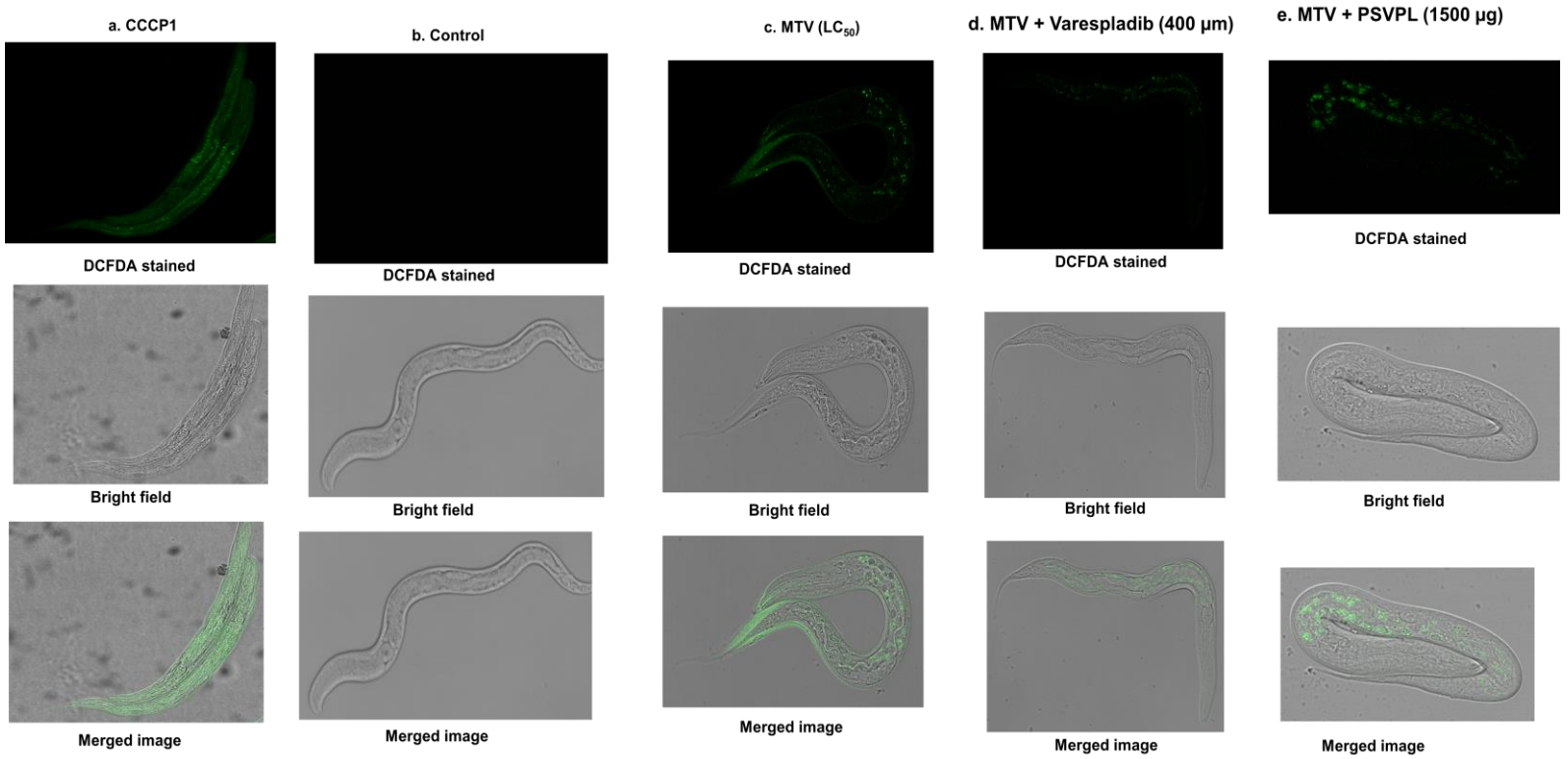


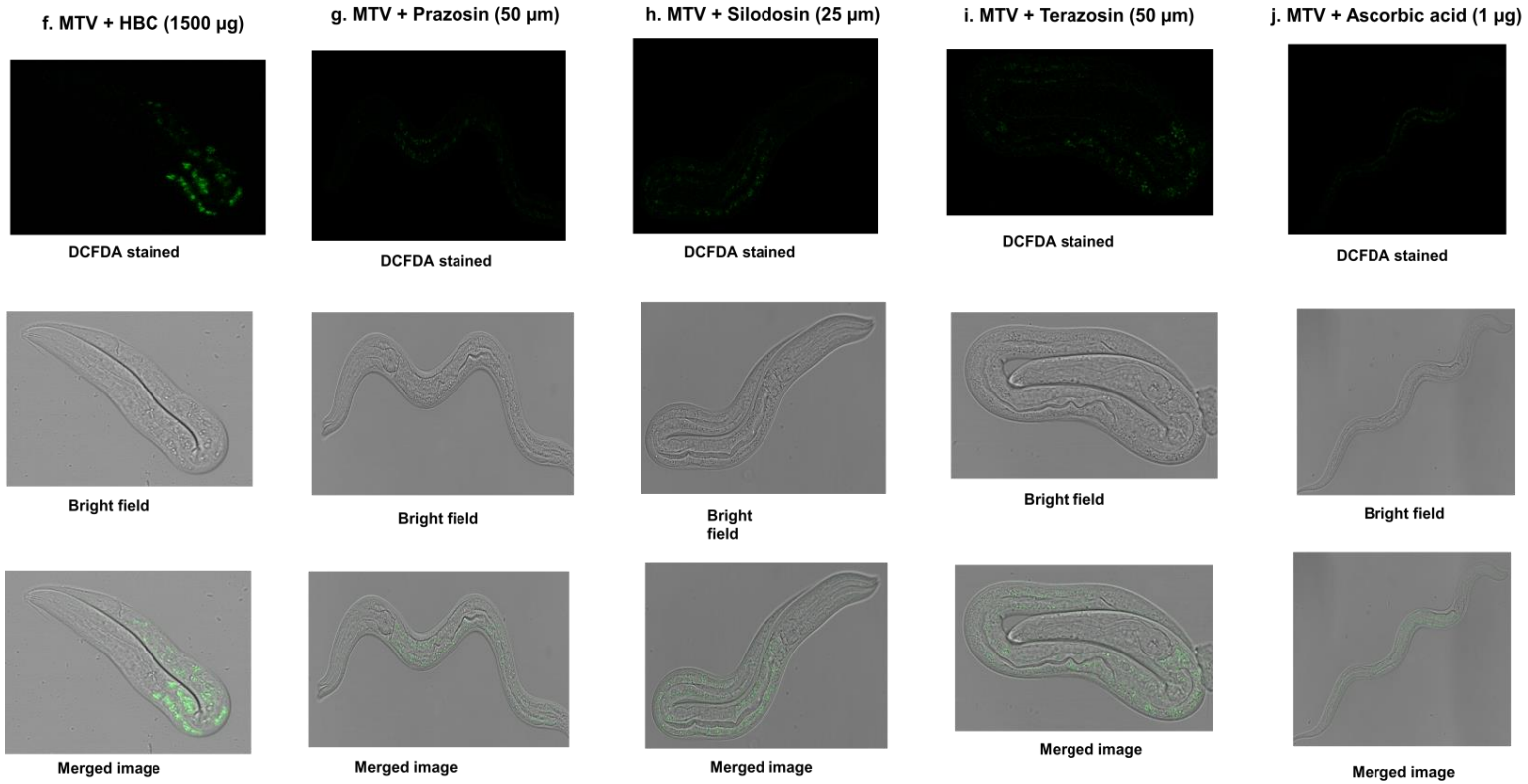
1.t ADAR (Mouse)+ Silodosin [AlphaFold identifier of ADAR: AF-P97714-F1, SwissProt Accession No.: P97714]



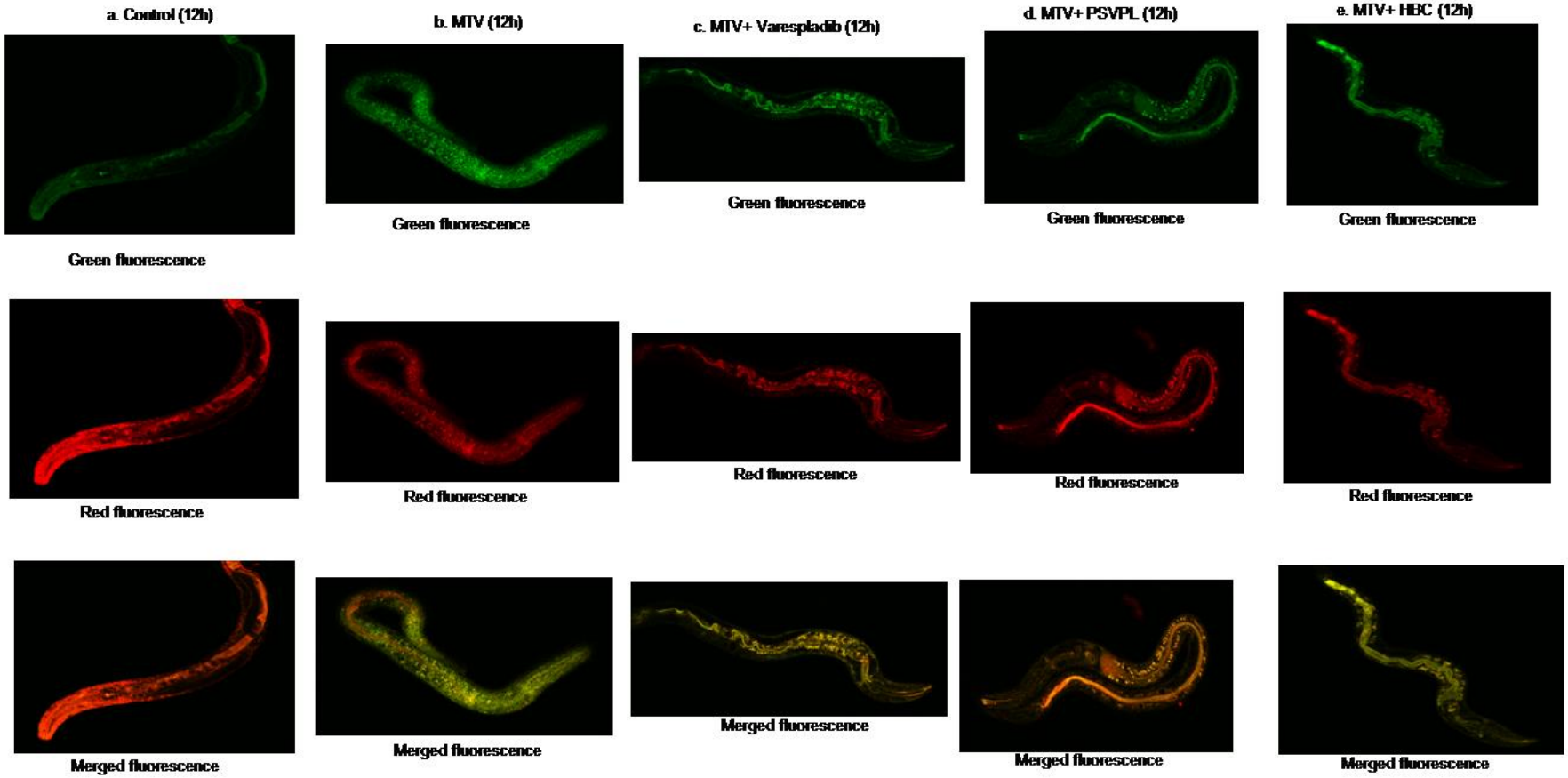
1.u SER6 receptor (*C. elegans*)+ Silodosin [AlphaFold identifier: AF-Q8MXS7-F1, SwissProt Accession No.: Q8MXS7]

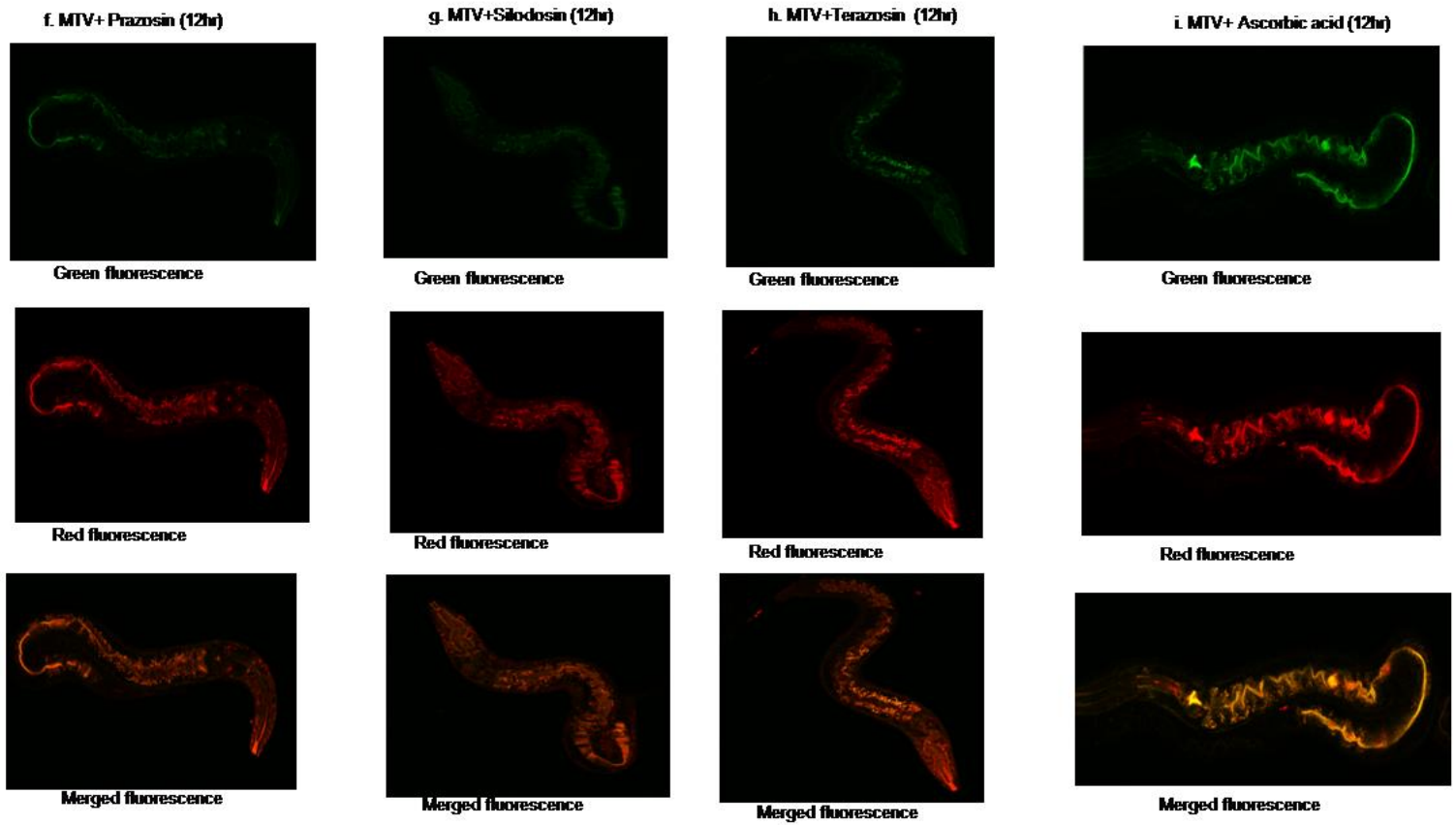
Appendix Fig. A2 a-u. Homology modelled structures of the following proteins taken from SwissProt [Structure through AlphaFold]. Protein-ligand interactions of α1-adrenoreceptor antagonist (AAA) with α1-adrenergic receptor.


a. CCCP1
b. Control
c. MTV (LC_{50})
d. MTV + Varespladib (400 µm)
e. MTV + PSVPL (1500 µg)
DCFDA stained
DCFDA stained
DCFDA stained
DCFDA stained
DCFDA stained
Bright field
Bright field
Bright field
Bright field
Bright field
Merged image
Merged image
Merged image
Merged image
Merged image

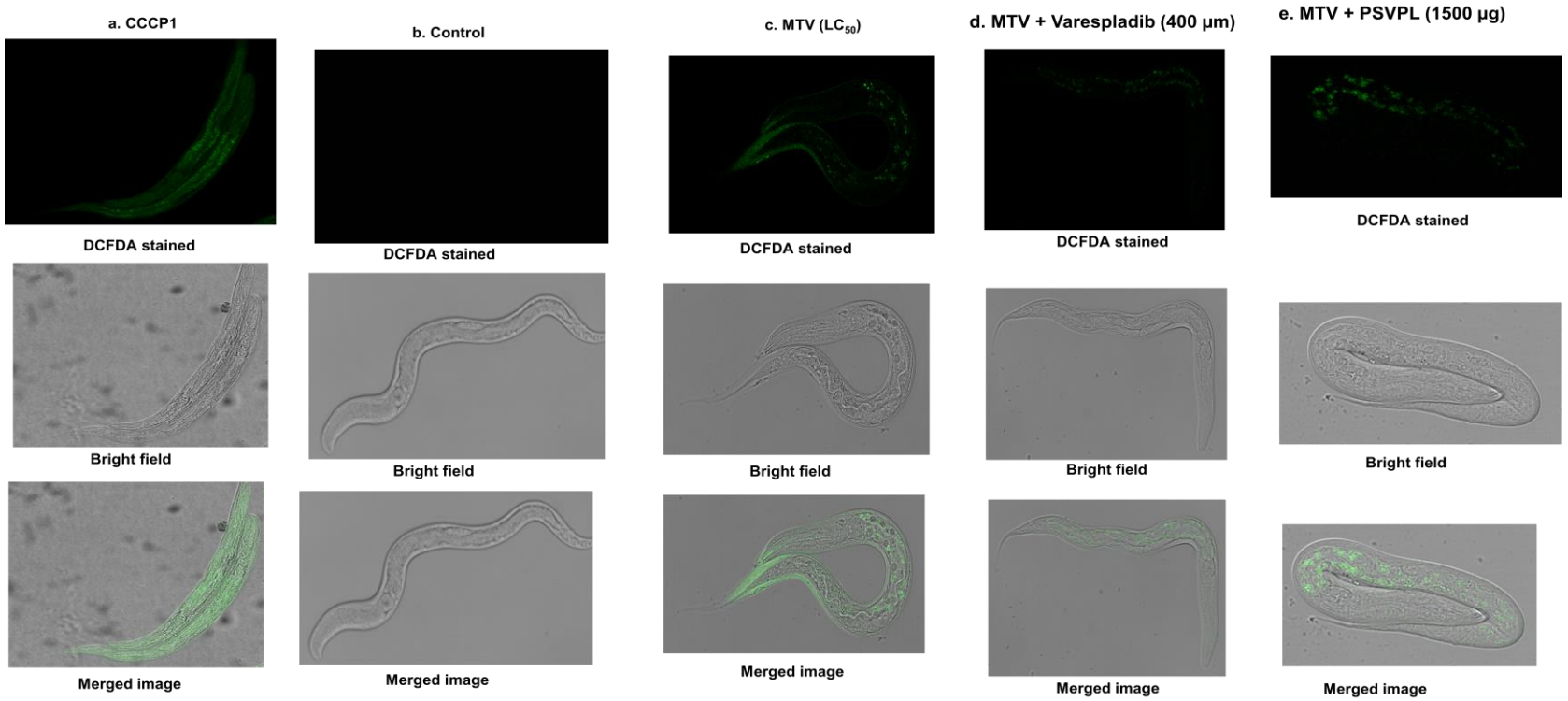


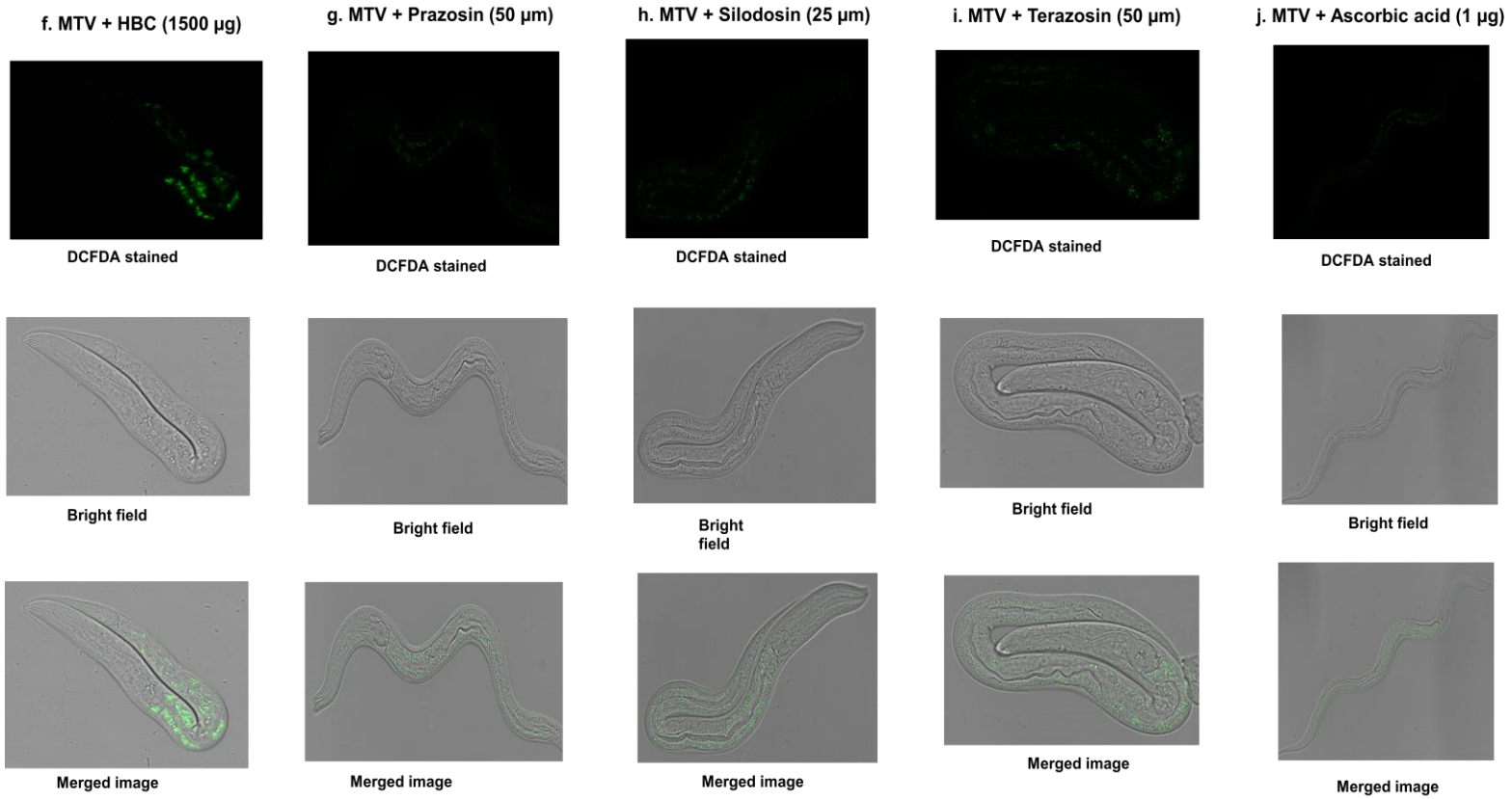
Appendix fig. A3. Fluorescence image of confocal microscopy of *M. tamulus* venom induced ROS generation in *C. elegans* after 6h of *M. tamulus* venom (LC_{50} concentration) treatment and its neutralization by Prazosin, Silodosin and Terazosin. ROS level in positive control (CCCP1) *C. elegans* was considered as baseline (100%) and other values were compared with that.

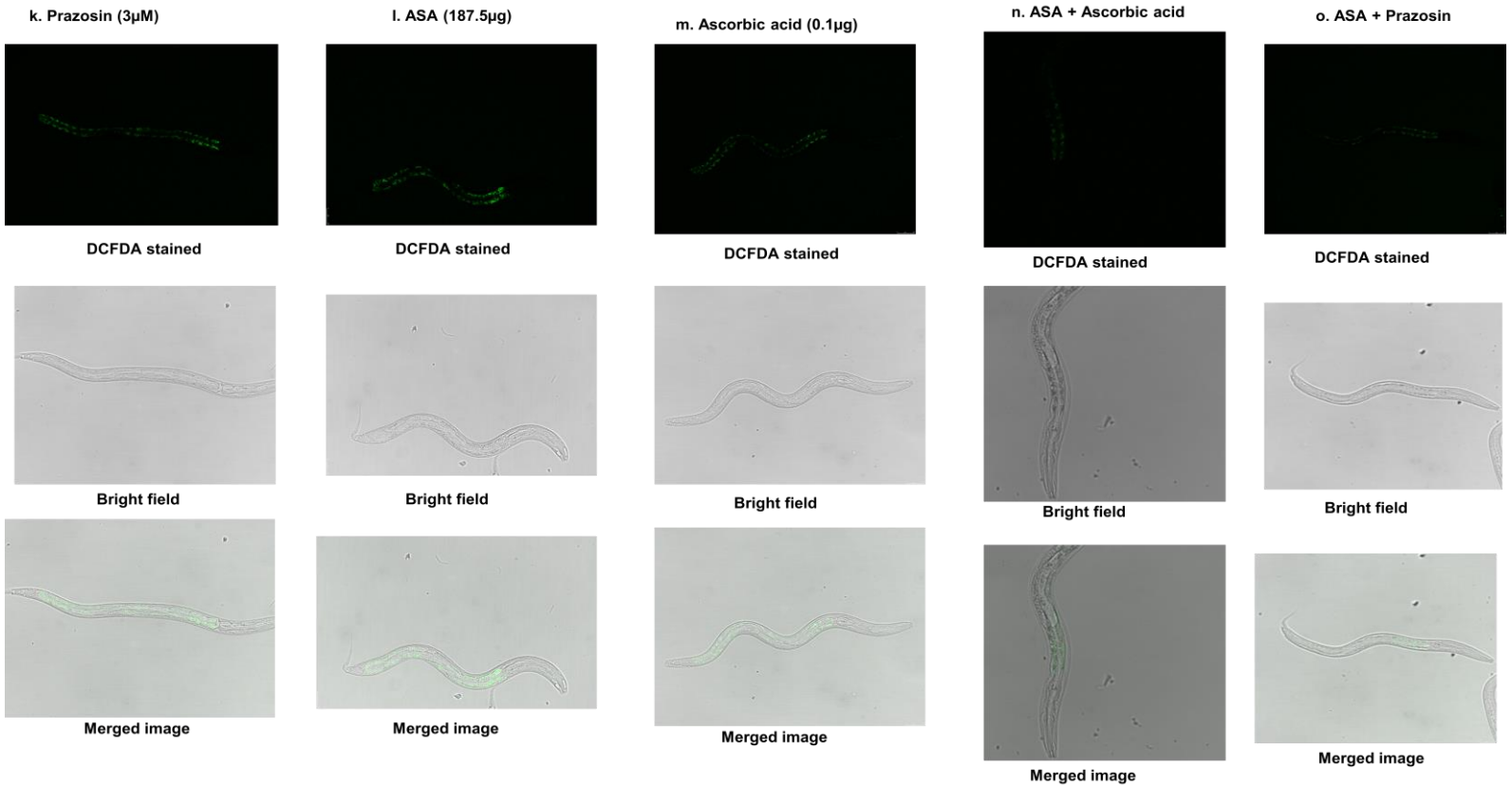

a. Control (12h)
b. MTV (12h)
c. MTV+ Varespladib (12h)
d. MTV+ PSVPL (12h)
e. MTV+ HBC (12h)
Green fluorescence
Green fluorescence
Green fluorescence
Green fluorescence
Green fluorescence
Red fluorescence
Red fluorescence
Red fluorescence
Red fluorescence
Red fluorescence
Merged fluorescence
Merged fluorescence
Merged fluorescence
Merged fluorescence
Merged fluorescence

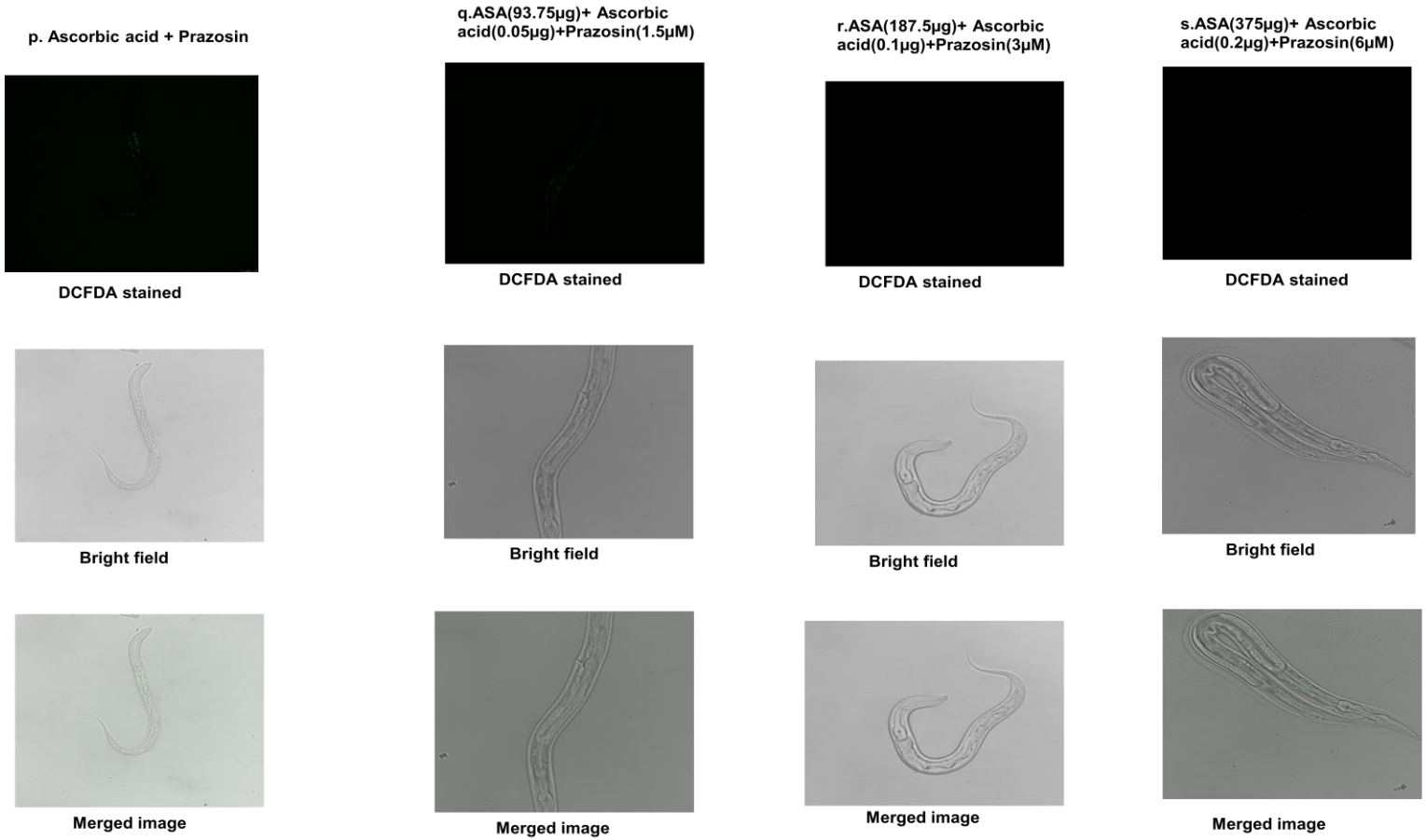


Appendix fig. A4. Fluorescence image of confocal microscopy of MTV-induced alteration of mitochondrial membrane potential and its neutralization by commercial ASAs (PSVPL and HBC), AAAs (Prazosin, Silodosin and Terazosin) and Ascorbic acid. ROS level in positive control (CCCP1) *C. elegans* was considered as baseline (100%) and other values were compared with that.

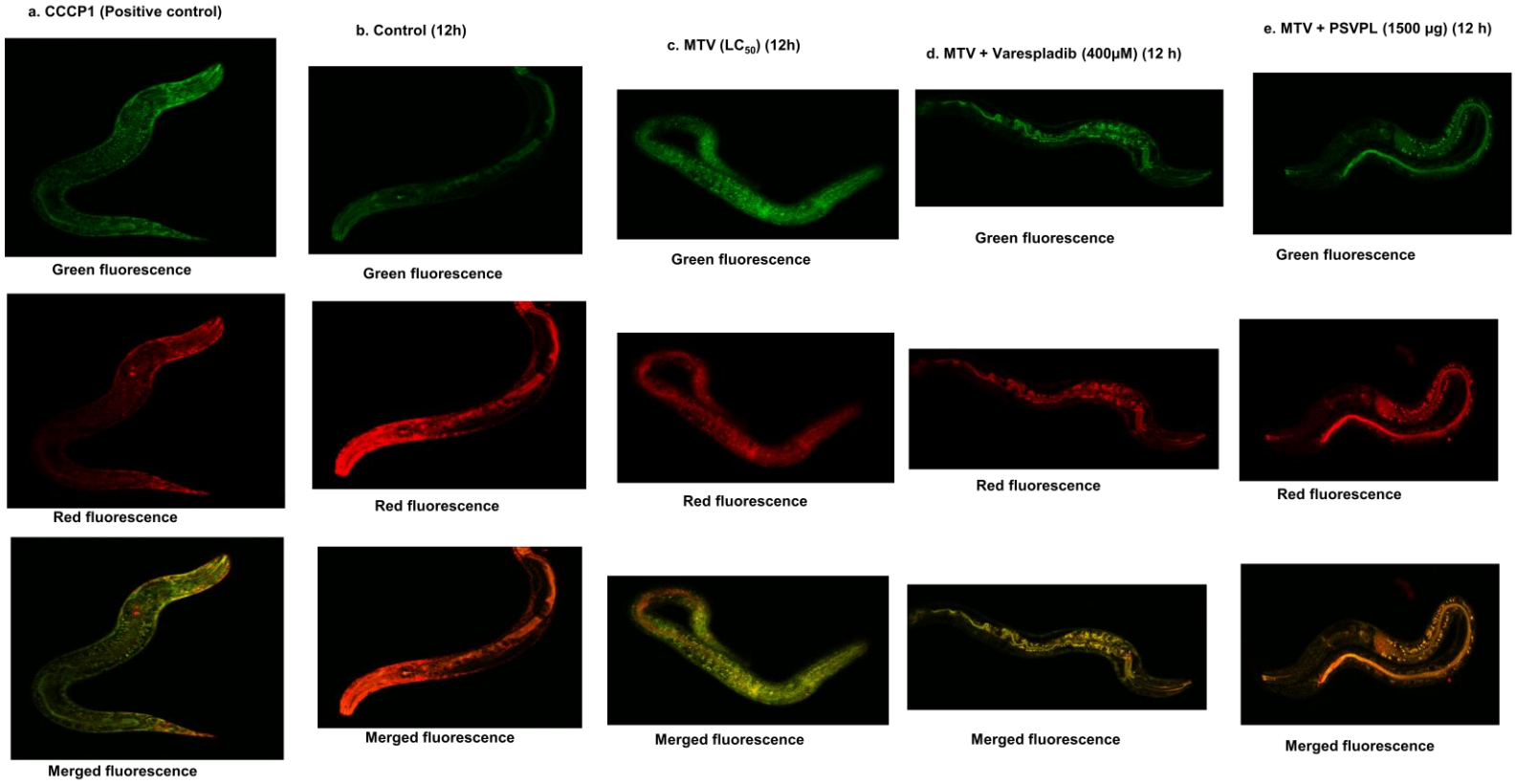

a. CCCP1
b. Control
c. MTV (LC_{50})
d. MTV + Varespladib (400 µm)
e. MTV + PSVPL (1500 µg)
DCFDA stained
DCFDA stained
DCFDA stained
DCFDA stained
DCFDA stained
Bright field
Bright field
Bright field
Bright field
Bright field
Merged image
Merged image
Merged image
Merged image
Merged image

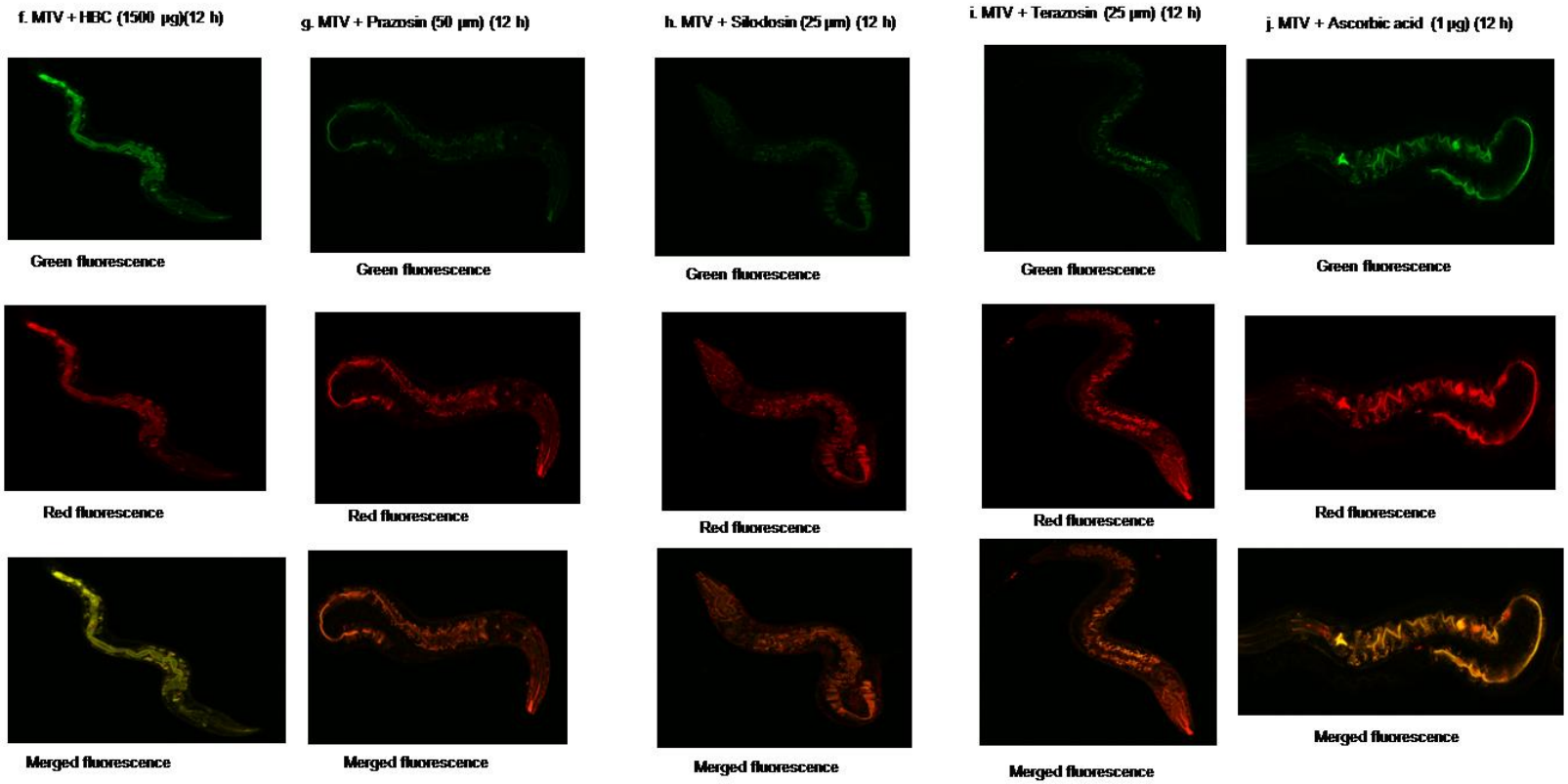

f. MTV + HBC (1500 µg)
g. MTV + Prazosin (50 µm)
h. MTV + Silodosin (25 µm)
i. MTV + Terazosin (50 µm)
j. MTV + Ascorbic acid (1 µg)
DCFDA stained
DCFDA stained
DCFDA stained
DCFDA stained
DCFDA stained
Bright field
Bright field
Bright field
Bright field
Bright field
Merged image
Merged image
Merged image
Merged image
Merged image

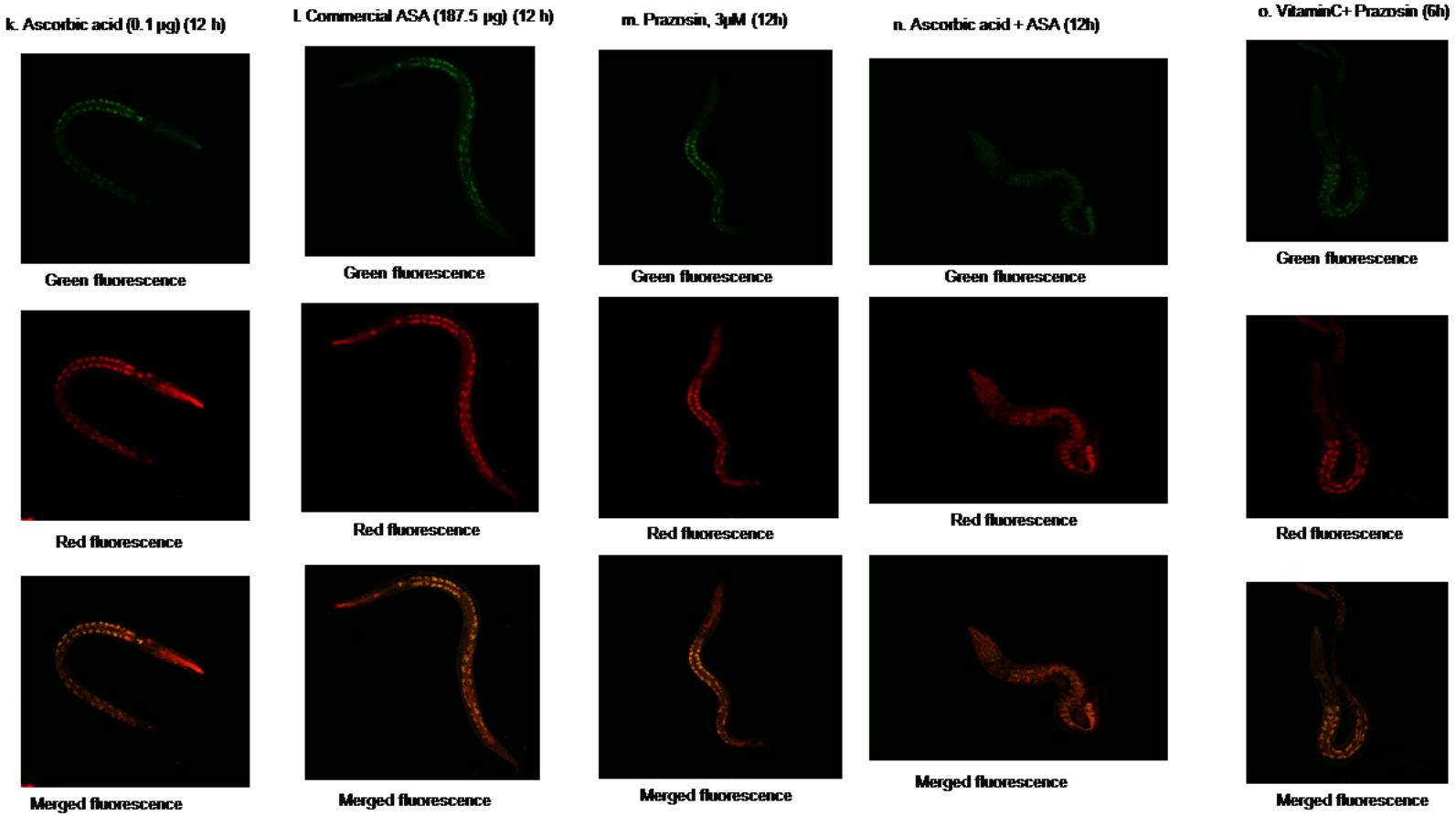

k. Prazosin (3μM)
l. ASA (187.5μg)
m. Ascorbic acid (0.1μg)
n. ASA + Ascorbic acid
o. ASA + Prazosin
DCFDA stained
DCFDA stained
DCFDA stained
DCFDA stained
DCFDA stained
Bright field
Bright field
Bright field
Bright field
Bright field
Merged image
Merged image
Merged image
Merged image
Merged image

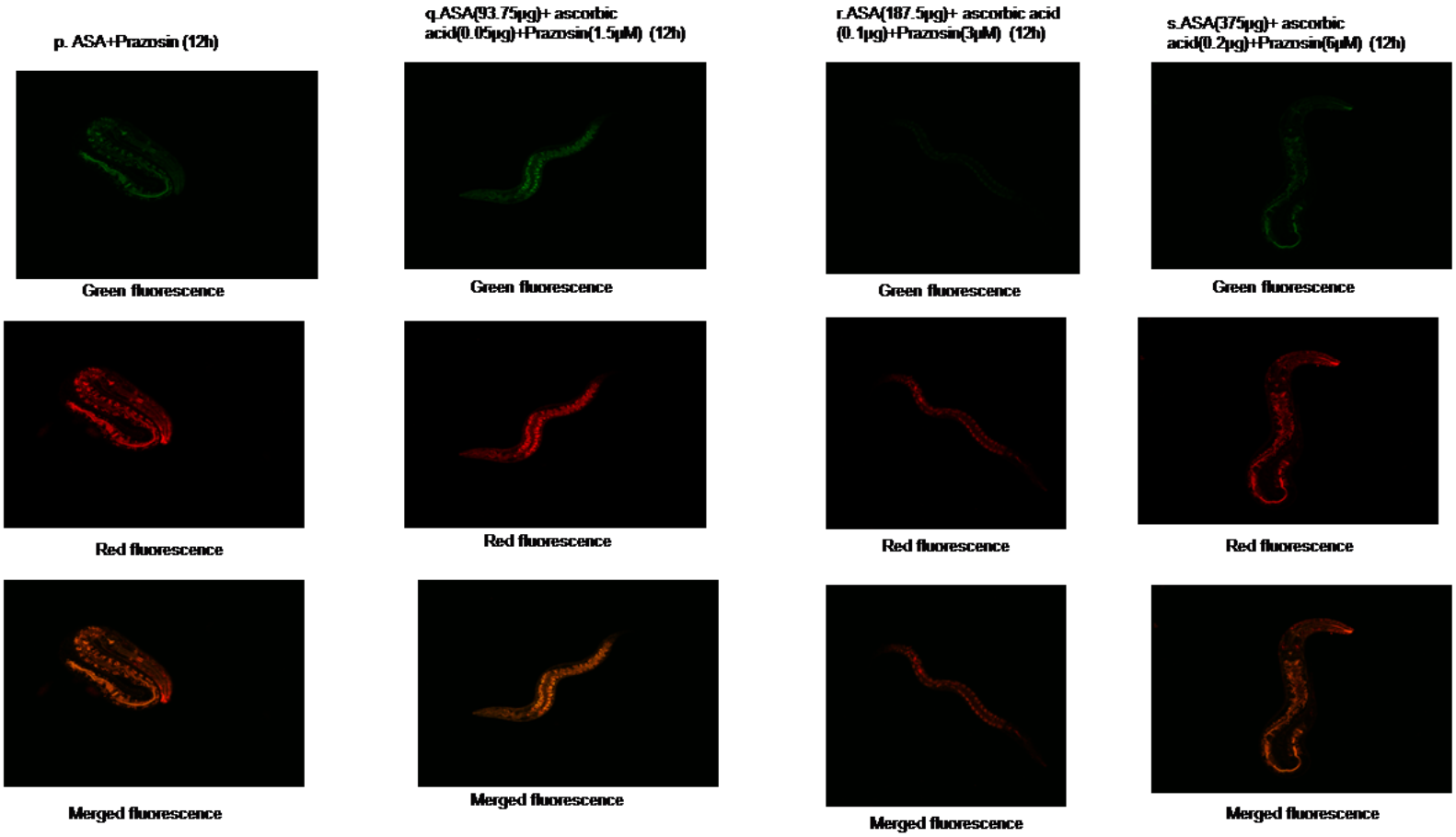


Appendic fig. A5 Fluorescence image of confocal microscopy of *M. tamulus* venom induced ROS generation in *C. elegans* after 6 h of *M. tamulus* venom (LC_{50} concentration) treatment and its neutralization by formulation 2, individual components of formulation and their combinations. ROS level in positive control (CCCP1) *C. elegans* was considered as baseline (100%) and other values were compared with that.


a. CCCP1 (Positive control)
b. Control (12h)
c. MTV (LC_{50}) (12h)
d. MTV + Varespladib (400μM) (12 h)
e. MTV + PSVPL (1500 μg) (12 h)
Green fluorescence
Green fluorescence
Green fluorescence
Green fluorescence
Green fluorescence
Red fluorescence
Red fluorescence
Red fluorescence
Red fluorescence
Red fluorescence
Merged fluorescence
Merged fluorescence
Merged fluorescence
Merged fluorescence
Merged fluorescence


f. MTV + HBC (1500 µg)(12 h)
g. MTV + Prazosin (50 µm) (12 h)
h. MTV + Silodosin (25 µm) (12 h)
i. MTV + Terazosin (25 µm) (12 h)
j. MTV + Ascorbic acid (1 µg) (12 h)
Green fluorescence
Green fluorescence
Green fluorescence
Green fluorescence
Green fluorescence
Red fluorescence
Red fluorescence
Red fluorescence
Red fluorescence
Red fluorescence
Merged fluorescence
Merged fluorescence
Merged fluorescence
Merged fluorescence
Merged fluorescence


k. Ascorbic acid (0.1 µg) (12 h)
l. Commercial ASA (187.5 µg) (12 h)
m. Prazosin, 3µM (12h)
n. Ascorbic acid + ASA (12h)
o. VitaminC+ Prazosin (6h)
Green fluorescence
Green fluorescence
Green fluorescence
Green fluorescence
Green fluorescence
Red fluorescence
Red fluorescence
Red fluorescence
Red fluorescence
Red fluorescence
Merged fluorescence
Merged fluorescence
Merged fluorescence
Merged fluorescence
Merged fluorescence



Appendix fig. A6. Fluorescence image of confocal microscopy of MTV-induced alteration of mitochondrial membrane potential and its neutralization by formulation 2, individual components of formulation and their combinations. ROS level in positive control (CCCP1) *C. elegans* was considered as baseline (100%) and other values were compared with that.

Appendix table A1. List of proteins identified in *M. tamulus* venom by LC-MS/MS analysis followed by database search against Buthidae family (taxid: 6855) protein entries of the non-redundant NCBI databases. The gel sections are indicated in Fig. 1.

K channel inhibitor							
Accession No.	**Protein Description**	**Source organism**	**Sequence coverage (%)**	**Identified peptide sequences**	**Morpheus score**	**Theoretical mass (Da)**	**SDS-PAGE gel section**
K7XFK5	Potassium channel toxin alpha-KTx 3.16	*Mesobuthus gibbosus*	48.30%	EIPVKCK	12	872.48	1
				VFSAVLIILFVCSMIIGISEGK	12	2395.33	9
Q95P89	Putative potassium channel blocker TXKS1	*Mesobuthus martensii*	41.6	VCKIICGMQGKK	22	1420.74	1
				KVNICKAPIK	8	1169.70	5
				VAAGIVCKVCKIICGMQGK	13	2107.08	9
				MNRLTTIILMLIVINVIMDDISESK	11	2922.55	9
				IICGMQGKKVNICK	9	1647.86	10
A7KJJ7	Potassium channel toxin alpha-KTx 26.1	*Mesobuthus martensii*	31.50%	VEGACSKPCRK	11	1290.62	9
				GARNGKCINGR	9	1201.61	10
A9XE59	Potassium channel toxin MeuTXK-beta-2	*Mesobuthus eupeus*	32.90%	FVKYAVPESTLR	10	1408.77	3
				TVLQTVVHKVGK	10	1307.79	3
				EKHFQR	7	843.44	10
B5KF99	Potassium channel toxin alpha-KTx J123	*Mesobuthus martensii*	34.30%	TVCKCSI	7	866.40	2
				DMKFGNTGRCTGPNK	15	1697.76	9
				FGNTGRCTGPNKTVCK	12	1795.85	9

C0HJQ8	Potassium channel toxin alpha-KTx 1.16	*Mesobuthus eupeus*	36.20%	CTGTKQCWPVCK	8	1523.67	7
				MFGRPNGKCMNGK	9	1527.67	9
				KMFGRPNGK	9	1049.54	10
E4VP04	Potassium channel toxin MeuTXKalpha3	*Mesobuthus eupeus*	90.60%	KECRK	8	719.37	2
				KLNYR	6	692.40	2
				GGKCDR	6	691.31	3
				CFPNYCRCFPG	10	1476.57	5
				GKCFPNYCR	8	1200.52	7
				MKNYCGIITLFLAIISATGVFCVDFPNKGGK	13	3449.75	9
Q8I0L5	Potassium channel toxin alpha-KTx 15.2	*Mesobuthus martensii*	50.80%	KAIGVAAGKCINGR	10	1413.79	7
				FSSIILLTLLICSMSK	11	1825.01	8
Q967F9	Potassium channel toxin alpha-KTx 14.1	*Mesobuthus martensii*	96.20%	CPGNPSCRNGFCACT	8	1756.65	2
				IFFAILLILAVCSMAIWTVNGTPFAIKCATDADCSRK	10	4189.12	8
Q9NJC6	Potassium channel toxin BmTXK-beta	*Mesobuthus martensii*	50%	GKEIMKNIK	8	1075.61	4
				AIGKCEDTECK	8	1309.56	4
				EKLTEVK	8	845.49	5
				EIMKNIKEK	9	1131.63	6
				CEDTECKCLK	8	1341.54	8
				vi)MMKQQFFLFLAVIVMISSVIEAGRGK	12	2942.59	9
				vii)LTEVKDKMK	7	1106.60	9
Q86BX0	Potassium channel	*Mesobuthus*	96.60%	REIGVAAGKCINGK	9	1471.79	3

	toxin alpha-KTx 15.8	*martensii*		FSSIILLTLLICSMSIFGNCQVQTNVKCQGGSCASVCRR	8	4464.17	7
				CVCYRN	6	870.35	8
C0HJQ2	Potassium channel toxin alpha-KTx 19.2	*Buthus occitanus tunetanus*	54.80%	AMGFSSGKCIDSK	11	1386.63	10
				VKCRAMGFSSGK	9	1326.65	10
P0DL46	Potassium channel toxin alpha-KTx 16.9	*Buthus paris*	30.50%	GLIDVRCYASR	7	1308.66	2
C0HJQ7	Potassium channel toxin alpha-KTx 1.17	*Mesobuthus eupeus*	16.20%	QFTDVK	6	736.38	3
Q8MQL0	Potassium channel toxin alpha-KTx 16.3	*Mesobuthus martensi*	20.30%	CFASSECWIACK	8	1517.61	8
Q8MUB1	Potassium channel toxin alpha-KTx 22.1	*Mesobuthus martensii*	43.50%	RQNKNGR	8	871.47	8
				LFIVFVLFCILRLDAEVDGR	12	2394.31	9
E4VP41	Potassium channel toxin MeuTXKalpha4	*Mesobuthus eupeus*	12.60%	FKACIPYR	7	1053.54	3
P0CH57	Potassium channel toxin	*Mesobuthus eupeus*	26.10%	EFMSNLKEKLSGVK	12	1608.85	3
				MKNSWNR	6	934.44	8

	MeuTXKbeta3-meucin-24			LSGVKEKMK	9	1034.58	10
Q9BJX2	Potassium channel toxin alpha-KTx 14.3	*Mesobuthus martensii*	46.20%	CPGNPPCRNGFCACT	10	1766.67	9
				CATDADCSRK	9	1182.48	9
B8XH40	Potassium channel toxin BuTXK-beta	*Buthus occitanus israeli*	62.60%	LVKYAVPESTLR	11	1374.79	3
				NLVVLLLLGMVALSSCGLREK	10	2300.30	3
				KEEGFCHGMKCK	9	1525.65	7
				TILQTAVHKLGK	8	1307.79	8
P83112	Potassium channel toxin alpha-KTx 1.10	*Parabuthus transvaalicus*	62%	QATGRPNGKCMNR	10	1504.70	8
				EVDMRCKSSK	9	1238.57	8
Q9NII5	Potassium channel toxin alpha-KTx 1.6	*Mesobuthus martensii*	91.30%	KLFGTYRGK	8	1068.61	4
				ISFLLLLAIVICSIGWTEAQFTNVSCSASSQCWPVCKKLFGTYR	11	5110.56	7
				GKCMNSKCR	8	1139.50	7
A0A059UI30	Potassium channel toxin Meg-beta-KTx1	*Mesobuthus gibbosus*	13.10%	KQEGFCHGFKCK	10	1524.70	5
				YAVPEGTLR	10	1004.53	9

B8XH44	Potassium channel toxin alpha-KTx 27.1	*Buthus occitanus israelis*		YGSDCAEPCK	9	1185.44	5
				CTCYPSIKIK	8	1268.63	8
C0HJQ4	Potassium channel toxin alpha-KTx 3.18	*Mesobuthus eupeus*	47.50%	EAGMTYGKCMNGKCNCTPK	13	2221.90	9
				EIPVKCKGSK	8	1144.63	9
H2ETQ6	Potassium channel toxin alpha-KTx 1.14	*Mesobuthus martensii*	11.80%	KLFGTYK	7	855.49	5
P0DL45	Potassium channel toxin alpha-KTx 16.8	*Buthus paris*	25%	KVTGSGQAK	9	874.49	5
P0DL62	Potassium channel toxin alpha-KTx 31.1	*Buthus occitanus tunetanus*	100%	CPAGECICTT	7	1167.44	5
				ACSERIRQVENDNK	10	1717.82	6
				AGSMDSCSETGVCMK	10	1618.61	7

Q9BKB7	Potassium channel toxin gamma-KTx 2.1	*Mesobuthus eupeus*	15.20%	SRFGKTNGR	8	1021.54	9
P0DMR9	Toxin BmKK16 OS=Mesobuthus martensii	*Mesobuthus martensii*	34.50%	LRDCYKYCMSPK	9	1635.72	5
B3EWY1	Potassium channel toxin alpha-KTx 16.7	*Mesobuthus gibbosus*	25.40%	KVTGSGQGKCQNNQCR	10	1820.84	6
P46114	Potassium channel toxin alpha-KTx 4.1	*Tityus serrulatus*	24.30%	EAIGKAAGK	9	843.48	6
Q5F1N4	Toxin BmTxKS4	*Mesobuthus martensii*	28.20%	MLCGIDGKLRESK	10	1521.76	6
Q5F1N4	Toxin BmTxKS4	*Mesobuthus martensii*		WFPASVNGK	8	1004.51	10
B8XH30	Potassium channel toxin alpha-KTx Tx308	*Buthus occitanus israelis*	53.20%	LFIVLLLFCILRLDAEVDGRTMSHCNQSECQEK	11	4009.95	7

B8XH38	Potassium channel toxin-like Tx677	*Buthus occitanus israelis*	13.30%	AAKCINRK	7	959.53	7
B8XH45	Potassium channel toxin alpha-KTx Tx773	*Buthus occitanus israelis*	59.60%	LDAEVDGRR	8	1029.52	7
				KENKNGR	10	844.45	8
				QPGCQEACKKENK	12	1575.71	10
				LFIVLLLFCILR	9	1518.94	10
Q9NJP7	Potassium channel toxin alpha-KTx 9.1	*Mesobuthus martensii*	53.50%	LFTLVLIVLAMNVMMAIISDPVVEAVGCEECPMHCKGK	10	4322.10	7
P0DL65	Mesomartoxin	*Mesobuthus martensii*	32.20%	YCQDKGARNGK	11	1295.60	9
				VEGACVENCR	11	1192.50	9
				GARNGKCINSNCHCYY	11	1972.81	9
				KYCQDKGAR	9	1124.54	10
B8XH42	Potassium channel toxin alpha-KTx 16.6	*Buthus occitanus israelis*	15.50%	RVTGSAQAK	9	916.51	8
P0DMR8	Toxin BmKK12	*Mesobuthus martensii*		QCQNVQNCYKYCMSPK	9	2122.87	7
A0ASK0	Potassium channel	*Mesobuthus*	70.30%	MKIFFAILLILAVCSMAIWTVNGTPFEVRCATDADCAR	10	4360.17	8

	toxin alpha-KTx 14.x	*martensii*					
C0HJQ5	Potassium channel toxin alpha-KTx 8.7	*Mesobuthus eupeus*	17.50%	DQRAKCENDK	8	1262.57	8
P86400	Potassium channel toxin alpha-KTx 8.6	*Mesobuthus eupeus*	43.80%	MSRLYAIILIALVFNVIMTIMPDMK	11	2943.57	9
|Q9BKB4	Potassium channel toxin alpha-KTx 14.4	*Mesobuthus martensii*	16.60%	CATNADCSR	8	1053.40	9
P83407	Potassium channel toxin alpha-KTx 19.1	*Mesobuthus martensii*	48.30%	CVAMGFSSGKCINSK	14	1644.74	9
P86402	Neurotoxin MeuClTx-1	*Mesobuthus eupeus*	71.40%	MCMPCFTTRPDMAQQCRDCCGGNGK	11	3053.16	9

Na^+ channel inhibitor							
Accession No.	**Protein Description**	**Source organism**	**Sequence coverage (%)**	**Base Peptide Sequence**	**Morpheus Score**	**Theoretical mass(Da)**	**SDS-PAGE gel section**
P01485	Alpha-mammal toxin Bot3	*Buthus occitanus tunetanus*	52.70%	LVMAGVESVKDGYIVDDRNCTYFCGR	40	3023.39	1
				VPDHVRTKGPGR	11	1317.73	3
M4GX67	BmKBT-like peptide	*Mesobuthus martensii*	63.80%	KSGYPIQHDGCK	12	1388.65	8
				MKAALLLVISTLMLIGVLTKK	14	2255.41	9
				LACWCDNIHNWVPTWSRETNK	13	2686.22	9
P0CF76	Toxin BmKNJX11	*Mesobuthus martensii*	86.60%	DAYIADSENCTYT	8	1521.59	2
Q4TUA4	Alpha-toxin 4	*Mesobuthus martensii*	43.50%	VPIRVPGRCNGG	8	1280.68	2
				LPDKVPIRVPGR	11	1345.82	7
Q9GNG8	Toxin BmKaTX15	*Mesobuthus martensii*	72.90%	NGAESGYCQWAGVYGNACWCYKLPDK	11	3053.29	7
				VPIRVPGKCNGG	9	1252.67	8
				MNYLVFFSLALLVMTGVESVRDGYIADDK	11	3297.63	9
Q9GQV6	Toxin BmKaTx16	*Mesobuthus martensii*	15.40%	ELPDNVPIRVPGK	11	1432.80	3
Q9NBW2	Toxin BmKBT	*Mesobuthus martensii*	54.20%	MKAALLLVIFSLMLIGVLTK	10	2173.33	2
				LACWCDDIHNWVPTWSRATNKCR	12	2945.33	9

				ATNKCRAK	8	947.50	9
Q9NJC4	Toxin BmKaTx17	*Mesobuthus martensi*	54%	LLMTGVESGRDAYIAK	9	1722.90	3
				NYNCVYHCFR	8	1431.58	**7**
				YGNACWCINLPDDK	9	1724.73	9
							9
Q9NJC5	BmKaTx10	*Mesobuthus martensii*	35.20%	IGYCNIQGK	9	1051.51	5
Q9NJC7	BmK AGP-SYPU2	*Mesobuthus martensii*	89.40%	NRAESGYCQWASK	9	1555.68	2
				PGRCNGG	6	716.30	5
				NAYCDGECKK	10	1243.50	6
				MNYMVIISLALLVMTGVESVKDGYIA DDR	10	3247.62	7
				IMKPGRCNGG	8	1104.52	7
				DGYIADDRNCPYFCGR	12	1977.81	9
				KNRAESGYCQWASK	11	1683.78	9
				LPDDARIMKPGR	9	1383.73	9
Q9UAC8	Beta-toxin BmKAs1	*Mesobuthus martensii*	40%	LACYCEGAPKSELWAYETNK	11	2389.07	3
				ADNGYLLNK	9	1006.51	6
				CNGKM	6	624.24	7
				SELWAYETNKCNGK	11	1698.77	9
P0C5F0	Alpha-toxin PgKL1	*Parabuthus granulatu*	22.50%	IDGYPVDNWNCKR	9	1635.75	2
				KIDGYPVDNWNCK	9	1607.74	6
P01486	Alpha-toxin Bot11	*Buthus occitanus tunetanus*	49.20%	LKDGYIVDDR	9	1192.61	3
				YGNACWCYK	9	1220.47	7

				LKGESGYCQWVGR	9	1538.73	7
				LPDHVRTVQAGRCR	8	1663.87	8
Q9GYX2	Toxin BmKa1	*Mesobuthus martensii*	43.50%	NYLVFFSLALLLMTGVGSVRDGYIADD KNCPYFCGR	9	4147.00	3
P01488	Alpha-toxin Bot1	*Buthus occitanus tunetanus*	40%	NGATSGYCQWLGK	10	1440.65	6
				DLPDNVPIRIPGK	9	1432.80	6
P58328	Alpha-like toxin BmK-M4	*Mesobuthus martensii*	28.10%	LPDDVPIRVPGKCH	10	1601.83	6
P59354	Alpha-like toxin Bom4	*Buthus occitanus mardochei*	20%	NGAKSGYCQWLGK	9	1467.69	5
P60256	Toxin Boma6b	*Buthus occitanus mardochei*	12.10%	VEGKCHRK	9	1012.52	5
P82815	Bukatoxin	*Mesobuthus martensii*	50.70%	LPDKVPIRVSGECQQ	9	1724.89	5
				VRDGYIADDK	9	1150.56	8
				NCAYFCGR	8	1046.41	8
Q9GQW3	Toxin BmKaIT1	*Mesobuthus martensii*	42.30%	NYLVMISFAFLLMTGVESVRDAYIAQN YNCVYHCAR	8	4320.03	8
				NGAKSGSCPYLGEHK	11	1603.74	9
P01490	Alpha-toxin BeM10	*Mesobuthus eupeus*	69.20%	NAYCDEECKKGAESGK	9	1844.77	6
				LPDWVPIKQKVSGK	8	1593.92	8
				GAESGKCWYAGQYGNACWCYK	13	2515.01	9

P09982	Toxin BeM14	*Mesobuthus eupeus*	28.70%	NLPDDVPIR	9	1037.55	9
				ARDAYIADDR	9	1164.55	10
P54135	Alpha-mammal toxin BmK M8	*Mesobuthus martensii*	23.40%	IKEPGKCG	8	887.45	6
P58488	Alpha-like toxin BmK-M2	*Mesobuthus martensii*	14%	SGYCQWSGK	9	1071.44	6
Q17231	Toxin BmKIT3	*Mesobuthus martensii*	31.20%	SESNTCGRKK	7	1165.55	6
				DGYIRGSNGCK	12	1225.55	9
P58910	Kurtoxin	*Parabuthus transvaalicus*	22.50%	KIDGYPVDYWNCKR	12	1812.86	7
Q9GUA7	Toxin BmKa3	*Mesobuthus martensii*	34.10%	GAESGYCQWAGVYGNACWCYKLPDK VPIR	9	3404.55	7
P13488	Alpha-like toxin Bom3	*Buthus occitanus mardochei*	16.60%	VPIVVGGEKCH	8	1193.62	8
P59854	Alpha-like toxin BmK-M1	*Mesobuthus martensii*	12.10%	VPGRCHPA	9	892.43	9
Q8I0K7	Depressant scorpion toxin BmKIM	*Mesobuthus martensii*	29.40%	ISCLWGNEGCNKECK	14	1853.79	9
				SESNTCGGKK	12	1066.47	9
P0DMH9	Alpha-toxin BmalphaTx47	*Mesobuthus martensii*	9.40%	ISGSCRGR	7	891.43	10

E7CAU3	Neurotoxin BmK AGP-SYPU1	*Mesobuthus martensii*	21.20%	YGHACWCINLPDDK	9	1747.74	5
P01483	Neurotoxin Bot2	*Buthus occitanus tunetanus*	24.60%	SGYCQWLGR	8	1125.50	5
				IEGKCHF	7	889.41	5
G4V3T9	Neurotoxin BmK AGAP-SYPU2	*Mesobuthus martensii*	26.10%	VKDGYIVDDK	8	1150.59	9
				VPGRCNG	8	758.35	10
P86408	Neurotoxin MeuNaTx-1	*Mesobuthus eupeus*	49.40%	NCAYFCGRNAYCDEECK	13	2215.82	9
				GAESGYCQWAGQYGNACWCYKLPDK	12	2968.24	9
P86404	Neurotoxin MeuNaTx-4	*Mesobuthus eupeus*	6.90%	NGAKSGYCQILGIYGNGCWCIALPDNV PIR	43	3365.61	1
				IPGKCH	6	710.35	6
Q9N682	A Neurotoxin BmK-M11	*Mesobuthus martensii*	46.40%	DAYIAKPENCVYHCATNEGCNKLCTD NGAESGYCQWGGK	42	4496.86	1
O61705	Neurotoxin BmK-M10	*Mesobuthus martensii*	35.70%	VPGKCQR	7	843.44	3
				LPDSVPIRVPGK	13	1276.75	8
				NYLVMISFALLLMK	8	1686.91	10
P45698	Neurotoxin BmK-M9	*Mesobuthus martensii*	36.70%	MISFALLLMTGVESVR	12	1781.94	9
P86403	Neurotoxin MeuNaTx-2	*Mesobuthus*	68.20%	FGNACWCKNLPDK	10	1608.72	2

		eupeus		NLPDKVPIR	14	1050.62	9
				KNGADSGYCQWFGRFGNACWCK	12	2668.12	9
				ARDAYIANDRNCVYTCALNPYCDSEC K	12	3298.39	9
P86406	Neurotoxin MeuNaTx-6	*Mesobuthus eupeus*	29%	LACYCEGAPKSELWHYETNKCNGR	12	2942.29	9

Serine protease- like protein							
Accession No.	**Protein Description**	**Source organism**	**Sequence coverage (%)**	**Base Peptide Sequence**	**Morpheus Score**	**Theoretical Mass (Da)**	**SDS-PAGE gel section**
P0C8M2	Serine proteinase-like BMK-CBP	*Mesobuthus martensii*	40%	IFGGTFAK	14.01938846	839.45	1
				KFVLTAAH	10.00816679	885.50	9

Serine protease inhibitor							
Accession No.	**Protein Description**	**Source organism**	**Sequence coverage(%)**	**Base Peptide Sequence**	**Morpheus Score**	**Theoretical Mass (Da)**	**SDS-PAGE gel section**
P0DJ47	Kunitz-type serine protease inhibitor	*Mesobuthus martensii*	60%	KRHGWLGTGWI	9	1309.70	2
				HGSINCRLPPER	9	1434.72	3

	BmKTT-3			NRHYCMKYCAR	8	1557.68	5
				KHGSINCRLPPER	8	1562.81	8
				YYYHNESR	7	1130.48	9
P0DJ49	Kunitz-type serine protease inhibitor BmKTT-1	*Mesobuthus martensii*	64.40%	TCESFIYGGVGGNK	10	1487.67	5
				QKDCSLPVDTGR	9	1374.66	6
				GKGWFLRYYYNK	8	1593.81	10

Parabutoporin							
Accession No.	**Protein Description**	**Source organism**	**Sequence coverage(%)**	**Base Peptide Sequence**	**Morpheus Score**	**Theoretical Mass (Da)**	**SDS-PAGE gel section**
P83312	Parabutoporin	*Parabuthus schlechteri*	91.1%	SKLAKK	7	673.45	5
				FKLGSFLKK	8	1066.65	7
				LGSFLKKAWK	8	1176.70	8
				GKEMLKDYAK	9	1181.61	10
				GLLEGGSEEVPGQ	8	1270.60	10

Lipolysis-potentiating peptides							
Accession No.	**Protein Description**	**Source organism**	**Sequence coverage(%)**	**Base Peptide Sequence**	**Morpheus Score**	**Theoretical Mass (Da)**	**SDS-PAGE gel section**
P84809	Lipolysis-activating peptide 1-beta chain	*Buthus occitanus tunetanus*	69.4%	VCKMHLARGGGR	22	1356.69	1
				QCPLLKG	7	814.44	3
				MISVQVIFIAFISIIAFSMVCGGNVFPNRELGILYGCK	12	4279.21	6
				GYGNAFCDK	7	1030.42	8
B8XGZ8	Lipolysis-activating peptide 1-beta chain	*Buthus occitanus israelis*	52%	ICKLHLAKK	16	1109.67	1
				GGFCHQPAPFVELCKCLDIDYDNTYFLKAMEK	10	3865.76	8
				AMEKQCPK	8	990.46	8
				QCPKLKGNVN	9	1156.60	10
Q6WJF5	Lipolysis-activating peptide 1-alpha chain	*Mesobuthus martensii*	45.9%	CWCEKLEDK	8	1266.54	6
				MKFVLFGMIVILFSLMGSIRGDDDPGNYPTNAYGNK	12	3995.96	8

Bradykinin-potentiating peptide							
Accession No.	**Protein Description**	**Source organism**	**Sequence coverage(%)**	**Base Peptide Sequence**	**Morpheus Score**	**Theoretical Mass (Da)**	**SDS-PAGE gel section**
Q9TWD3	Bradykinin-potentiating peptide K12	*Buthus occitanus*	100%	LRDYANRVINGGPVEAAGPPA	10	2136.11	8

Q9Y0X4	Bradykinin-potentiating peptide BmKbpp	*Mesobuthus martensii*	15.2%	GKQLLKDYANK	8	1276.71	5
Antimicrobial peptide							
Accession No.	**Protein Description**	**Source organism**	**Sequence coverage(%)**	**Base Peptide Sequence**	**Morpheus Score**	**Theoretical Mass (Da)**	**SDS-PAGE gel section**
Q6JQN2	Peptide BmKn2	*Mesobuthus martensii*	8.5%	YLYDPSLSAADLK	23	1454.73	1
				DMDTMK	7	755.28	9
B8XH50	Amphipathic peptide Tx348	*Buthus occitanus israelis*	14.9%	RSMRNMDTMK	9	1300.57	3
Q9GQW4	Peptide BmKn1	*Mesobuthus martensii*	62.8%	MKSQTFFLLFLVVLLLAISQSEAFIGAVAGLLSKIFGK	9	4099.36	5
E4VP07	Venom antimicrobial peptide-6	*Mesobuthus eupeus*	68.5%	SLRDMDTMK	10	1111.50	9
				MKSQTFFLLFLVVFLLAITQSEAIFGAIAGLLKNIFGK	9	4188.38	9
				NIFGKRSLR	7	1089.64	10

Hyaluronidase							
Accession No.	**Protein Description**	**Source organism**	**Sequence coverage(%)**	**Base Peptide Sequence**	**Morpheus Score**	**Theoretical Mass (Da)**	**SDS-PAGE gel section**
P86100	Hyaluronidase-1	*Mesobuthus martensii*	54%	HTNISCKCK	8	1146.53	2
				NPTFKHTNISCK	8	1445.71	2

				KTVPSMDFKR	9	1223.63	3
				GNCVWPEEPYTSWK	9	1751.76	3
				GGYTGR	6	609.29	3
				VAIEEWENSAKEWMLK	11	1977.95	5
				EMKTYVK	7	897.46	5
				YNTSQR	6	767.36	5
				VVWEVPSIMCSKK	11	1561.80	6
				ILVNQEETFNGDK	9	1505.74	6
				SKDLVKAK	9	887.54	6
				IARDNISK	8	915.51	6
				INVTDLLTSHK	11	1239.68	8
				YLIDPKNPTFK	9	1334.72	8
				AKHPDWSPAQIEK	9	1505.76	8
				DQPSEYFCKNDIQEANDK	13	2199.94	9
				ETIRLSHPNTLIYPYINYILPGTKK	12	2943.62	9
				IVIFYESQLGKYPHIESHGDINGGMLQVSDLANHLK	12	4038.03	9

Ca^{2+} channel inhibitor							
Accession No.	**Protein Description**	**Source organism**	**Sequence coverage (%)**	**Base Peptide Sequence**	**Morpheus Score**	**Theoretical Mass (Da)**	**SDS-PAGE gel section**
Q8I6X9	Toxin BmCa-1	*Mesobuthus martensii*	31.25%	GCNRLNK	8	860.43	5
				CNSDGDCCRYGER	8	1647.58	9

Cl^- channel inhibitor							
Accession No.	**Protein Description**	**Source organism**	**Sequence coverage (%)**	**Base Peptide Sequence**	**Morpheus Score**	**Theoretical Mass (Da)**	**SDS-PAGE gel section**
Q9BJW4	Neurotoxin Bm12-b	*Mesobuthus martensii*	77.9%	ECCGGNGK	9	880.32	5
Q9UAD0	Neurotoxin BmK CT	*Mesobuthus martensii*	81.35%	KCRECCGGIGK	8	1323.58	7
				MKFLYGIVFIALFLTVMFATQTDGCGPCFTTDANMARK	9	4351.10	9

HMG-CoA reductase inhibitor							
Accession No.	**Protein Description**	**Source organism**	**Sequence coverage(%)**	**Base Peptide Sequence**	**Morpheus Score**	**Theoretical Mass (Da)**	**SDS-PAGE gel section**
Q95P90	HMG-CoA reductase inhibitor bumarsin	*Mesobuthus martensii*	18%	LHLASGGSCQQPAPFVK	12	1795.90	6

Proteins with unknown target

Accession No.	Protein Description	Source organism	Sequence coverage(%)	Base Peptide Sequence	Morpheus Score	Theoretical Mass (Da)	SDS-PAGE gel section
P0CH58	Meucin-25	*Mesobuthus eupeus*	62.50%	IEYSLVQLLLRNVTIPLLLIIQMHIMSSVKLIQIR	8	4100.43	10
Q9Y0X6	BmK-YA precursor	*Mesobuthus martensii*	13.5%	SDEERQDWIPSDYGGHMNPAGRSNEER	13	3147.33	9
P0C5J8	Toxin Plt	*Parabuthus liosoma*	52.9%	FKVQR	7	676.40	2
				LCEKFK	6	823.43	8
Q7M463	Neurotoxin BmK A3-6	*Mesobuthus martensii*	72.4%	TECECVMCGLGIICKQCYYQQ	9	2699.10	8
Q7Z0H4	Neurotoxin BmP08	*Mesobuthus martensii*	16.3%	NGYCQGCTR	7	1114.43	10
P15220	Insectotoxin-I1	*Mesobuthus eupeus*	58.3%	MCMPCFTTRPDMAQQCRACCK	9	2724.06	3
P15222	Insectotoxin-I5A	*Mesobuthus eupeus*	22%	DCCGGNGK	7	866.30	3
				CMPCFTTDPNMAKK	9	1699.72	6
P60270	Insectotoxin-I5	*Mesobuthus eupeus*	51.4%	DCCGGGKKCFGPQCLCNR	12	2172.87	9
P60268	Insectotoxin-I3	*Mesobuthus eupeus*	25%	RCRDCCGGR	8	1195.48	8
D2CFI7	Venom peptide MmKTx1	*Mesobuthus martensii*	40.6%	SLRRYYFSK	8	1218.65	6
				TCATVFYPSNCR	12	1474.63	9
				IDTCKTLTGETIK	10	1478.76	9
				EEPGTGLYPDCCNK	8	1638.66	10
				GRIDTCK	7	848.41	10

Makatoxin							

Accession No.	Protein Description	Source organism	Sequence coverage(%)	Base Peptide Sequence	Morpheus Score	Theoretical Mass (Da)	SDS-PAGE gel section
Q86BW9	Makatoxin-2	*Mesobuthus martensii*	27%	YGNACWCIDLPDK	9	1610.69	10
				VPIRIPGPCR	7	1163.66	10
P59853	Makatoxin-3	*Mesobuthus martensii*	52.9%	YGNACWCIDLPDK	9	1610.69	6
				NYLIVISFALLLMTGVESGR	12	2211.20	9
				VPIRIPGPCIGR	9	1333.77	9

Appendix table A2: List of proteins identified from LC-MS/MS analysis of PSVPL and HBC ASAs using Mascot software. Data were searched against *Equus caballus* protein entries in uniprot database.

ASA (PSVPL)				
Accession No.	**Description**	**Avg. mass**	**emPAI**	**Protein score**
Immunoglobulin				
A0A0A1E470	Immmunoglobulin lambda light chain variable region	23807	2.25	555
A0A0A1E417	Immmunoglobulin lambda light chain variable region	23705	1.67	553
A0A0A1E6Q9	Immmunoglobulin lambda light chain variable region	23322	1.23	534
A0A0A1E6K2	Immmunoglobulin lambda light chain variable region	23669	1.68	533

A0A0A1E406	Immmunoglobulin lambda light chain variable region	23496	1.7	532
A0A0A1E538	Immmunoglobulin lambda light chain variable region	23232	1.73	531
A0A0A1E9D0	Immmunoglobulin lambda light chain variable region	23557	1.21	531
A0A0A1E6F7	Immmunoglobulin lambda light chain variable region	23567	1.7	209
A0A0A1E993	Immmunoglobulin lambda light chain variable region	23195	1.73	208
A0A0A1E458	Immmunoglobulin lambda light chain variable region	23486	1.7	200
A0A0A1E4I0	Immmunoglobulin lambda light chain variable region	23032	1.25	182
A0A0A1E476	Immmunoglobulin lambda light chain variable region	23234	1.24	178
A0A0A1E487	Immmunoglobulin lambda light chain variable region	23382	0.82	106
A0A3Q2H3F6	Inter-alpha-trypsin inhibitor heavy chain family member	100051	0.05	34
A0A0B4J1C4	Joining chain of multimeric IgA and IgM	18297	0.66	66
Plasminogen				
A0A3Q2L7R0	Plasminogen	94612	0.1	64
Alpha2-macroglobulin				
F6R942	Alpha2-macroglobulin	161167	0.09	171
A0A3Q2H333	Serum albumin	71310	0.14	96
Fibronectin				
A0A3Q2H4P9	Fibronectin	237286	0.4	383
Fibrinogen				

A0A3Q2HTG2	Fibrinogen alpha chain	77864	0.83	212
P14452	Fibrinogen alpha chain	1516	12.72	53
F6W2Y1	Fibrinogen gamma chain	50391	0.45	145
F6PH38	Fibrinogen beta chain	56898	0.28	75
Globin				
A0A3Q2HBR4	Haptoglobin	41296	0.76	104
A0A1K0FUE2	Globin A1	16186	0.33	91
ASA (HBC)				
Accession No.	**Description**	**Avg. mass**	**emPAI**	**Protein score**
Immunoglobulin				
A0A0A1E470	Immmunoglobulin lambda light chain variable region	23805	2.96	556
A0A0A1E417	Immmunoglobulin lambda light chain variable region	23705	2.25	550
A0A0A1E6E8	Immmunoglobulin lambda light chain variable region	23386	2.31	540
A0A0A1E6Q9	Immmunoglobulin lambda light chain variable region	23322	1.72	521
A0A0A1E9A3	Immmunoglobulin lambda light chain variable region	23276	1.72	509
A0A0A1E483	Immmunoglobulin lambda light chain variable region	23753	1.67	504
A0A0A1E422	Immmunoglobulin lambda light chain variable region	23586	0.81	186
A0A0A1E691	Immmunoglobulin lambda light chain variable region	23308	1.23	155

A0A0A1E6L5	Immmunoglobulin lambda light chain variable region	23551	1.21	154
A0A0A1E1C4	Joining chain of multimeric IgA and IgM	18297	0.29	46
Q95M34	Immunoglobulin gamma 1 heavy chain constant region	37985	0.28	45
Fibrinogen				
A0A3Q2HTG2	Fibrinogen alpha chain	77864	0.53	225
F6W2Y1	Fibrinogen gamma chain	50391	0.2	194
F6PH38	Fibrinogen beta chain	56898	0.39	122
Fibronectin				
A0A3Q2H4P9	Fibronectin	237286	0.46	468
Alpha-2-macroglobulin				
F6RI47	Alpha-2-macroglobulin	165246	0.72	300
Plasminogen				
A0A3Q2H333	Plasminogen	94612	0.42	150
Globin				
A0A3Q2HBR4	Haptoglobin	41296	0.98	137
Serum albumin				
A0A3Q2H333	Serum albumin	71310	5.78	1407