XXX Symposium on Bioinformatics and Computer-Aided Drug Discovery

# VIRTUAL SCREENING OF NEW POTENTIAL INSECT EPOXIDASE CYP15A1 INHIBITORS

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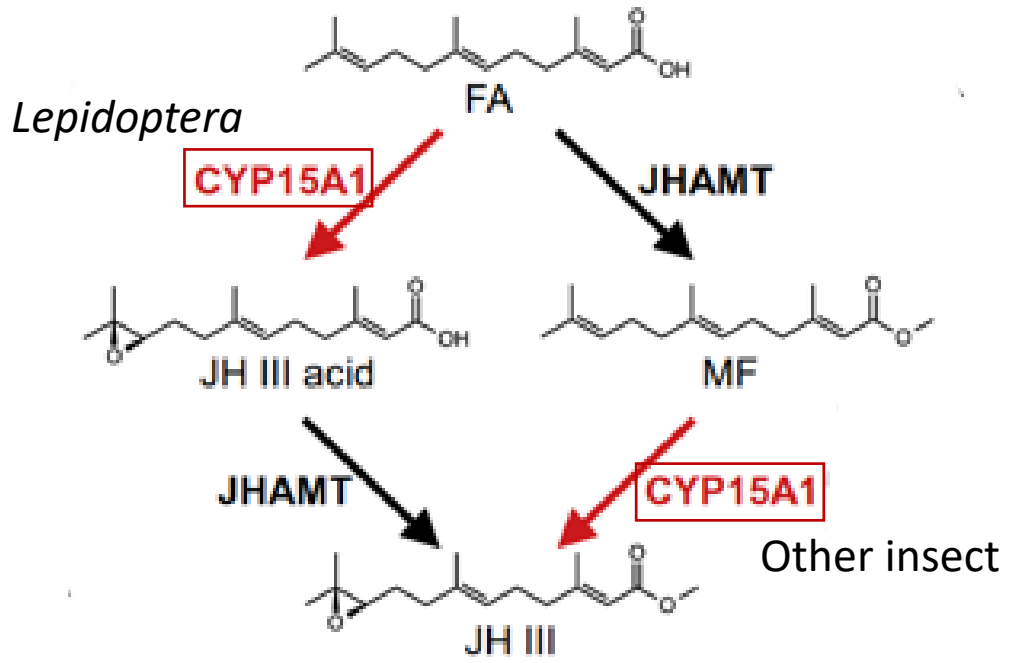
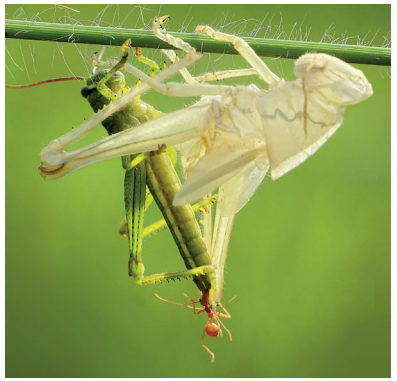
# CYP15A1 epoxidase as insecticide target

- Long-term use of synthetic or natural insect growth regulators often leads to the development of resistance to them in insects.
- In insects, **JH** refers to a **group of hormones**, which ensure growth of the larva, while **preventing metamorphosis**.
- The last stage of juvenile hormone biosynthesis, **epoxidation** by the **CYP15a1**, is **specific to insects → insecticide target**. Efficient and selective **inhibitors of CYP15a1** may represent **"biorational" regulators of insect populations** with **low toxicity to non-target organisms.**

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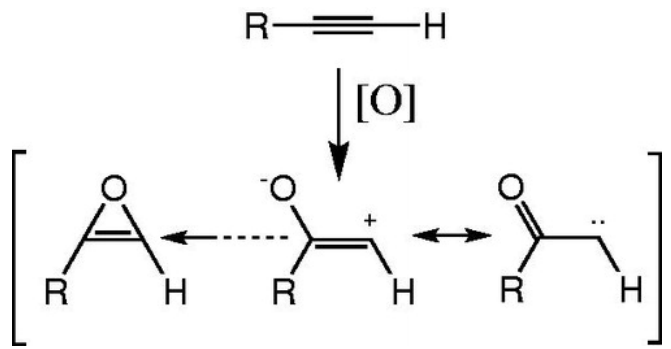
# Cytochrome inhibitor or substrates screening strategy

Oxidation of alkyne fragments in compounds by cytochromes P450 generates **highly reactive electrophilic intermediates** capable of **covalently binding to nucleophilic groups**, such as **heme nitrogen atoms**, which can lead to inhibition of enzyme activity.




**Ligands**: **40 structures** of **compounds from plants** for screening, including **medicinal and edible** ones **containing an alkyne or alkene fragment**.

**Target protein**: model 3D structures of insect **cytochrome CYP15a1**, created using the **Alphafold 3** (https://alphafoldserver.com/about) from **23 available sequences** of this protein from the **UniProt database**.

The distance from the alkyne or alkene fragment of the ligand structure to the iron atom of the gem in the protein-ligand complexes obtained *in silico* did not exceed each **0.49 nm**.

# The tools we used:

- **Autodock Vina** together with the **auxiliary tool FYTdock (Faletrov Y.V.)** for virtual screening
- **Alphafold 3** artificial intelligence web-service for creating model 3D structures of protein

## FYTdock

- программа-помощник для полуавтоматической **организации, запуска и обработки результатов** докинга программой AutodockVina в режиме высокопроизводительного обратного скрининга


FIND
YOUR molecule's
TARGET protein
docking
it with (all)
desirable
3D proteome

Faletrov, Y.V., Staravoitava, V.A, Dudko, A.R. PREPRINT. Doi: 10.21203/rs.3.rs-1456627/v1

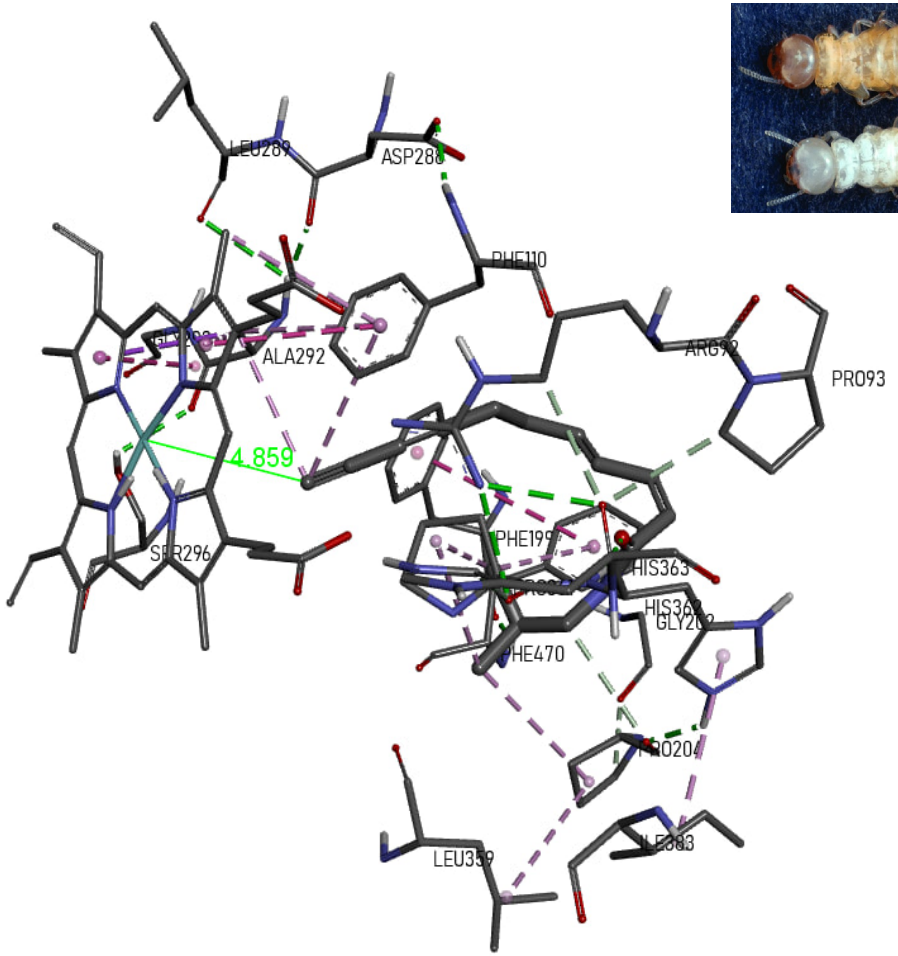
# ALL RESULTS IN THE TABLE

| Ligand | | Protein | | Binding energy, kcal/mol |
|---|---|---|---|---|
| **Name and PubChem code** | **Organism** | **UniProt CYP15a1 code** | **Organism** | |
| **3'-Geranylchalconaringenin (CID10070028)** | *Humulus lupulus* | A0A2J7PVT0 | *Cryptotermes secundus* | -11,4 |
| | | A0A836ELH5 | *Pseudoatta argentina* | -8.3 |
| **Xanthoangelol (CID643007)** | *Artocarpus altilis, Angelica keiskei* | A0A2J7PVT0 | *Cryptotermes secundus* | -10.9 |
| | | A0A836ELH5 | *Pseudoatta argentina* | -8.4 |
| **Ostruthin (Pubchem: CID5281420)** | *Halosciastrum melanotilingia* | A0A2J7PVT0 | *Cryptotermes secundus* | -10.6 |
| **Xanthoangelol B (CID10409180)** | *Angelica keiskei* | A0A2J7PVT0 | *Cryptotermes secundus* | -10.5 |
| **9-Angeloyloxy-7-methoxy-10,11-epoxy-6,7,10,11-tetrahydro-5,6-dehydro-alpha-farnesene (Pubchem: CID129829779)** | *Anisotome pilifera* | A0A2J7PVT0 | *Cryptotermes secundus* | -8.9 |
| **2,4,14-eicosatrienoic acid isobutylamide (Pubchem database number CID10338645)** | *Piper longum* | A0A2J7PVT0 | *Cryptotermes secundus* | -8.7 |
| **N-Isobutyl-2,4,8,10,12-tetradecapentaenamide (Pubchem: CID5318518)** | *Zanthoxylum piperitum* | A0A2J7PVT0 | *Cryptotermes secundus* | -8.4 |
| **(2Z,4E)-N-(2-methylpropyl)undeca-2,4-dien-8,10-diynamide (Pubchem: CID15609885)** | *Echinacea angustifolia, Spilanthes* | A0A2J7PVT0 | *Cryptotermes secundus* | -8.0 |
| **Neopellitorine A (Pubchem: CID636555)** | *Artemisia dracunculus* | A0A2J7PVT0 | *Cryptotermes secundus* | -7.9 |

# RESULTS

**(2Z,4E)-N-(2-methylpropyl)undeca-2,4-dien-8,10-diynamide (1)** (Pubchem: CID15609885) from *Echinacea angustifolia, Spilanthes* and other plants binds to the structure of CYP15a1 (UniProt: A0A2J7PVT0) from *Cryptotermes secundus* with and the orientation of **the terminal alkyne near the heme (Ebind -8.0 kcal/mol).**

**(1)**

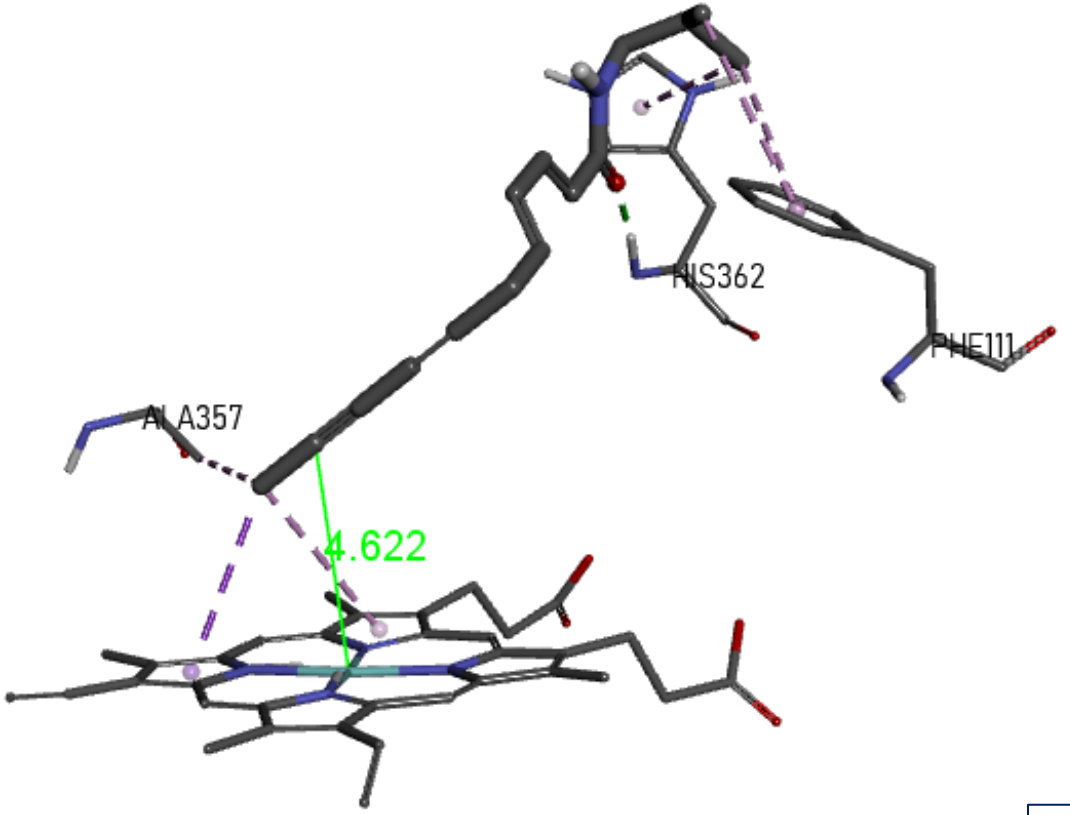






**Neopellitorine A (2)** (Pubchem: CID636555) from *Artemisia dracunculus* binds to this structure with the orientation of **the triple bond at position 9 near the heme (Ebind -7.9 kcal/mol)**.

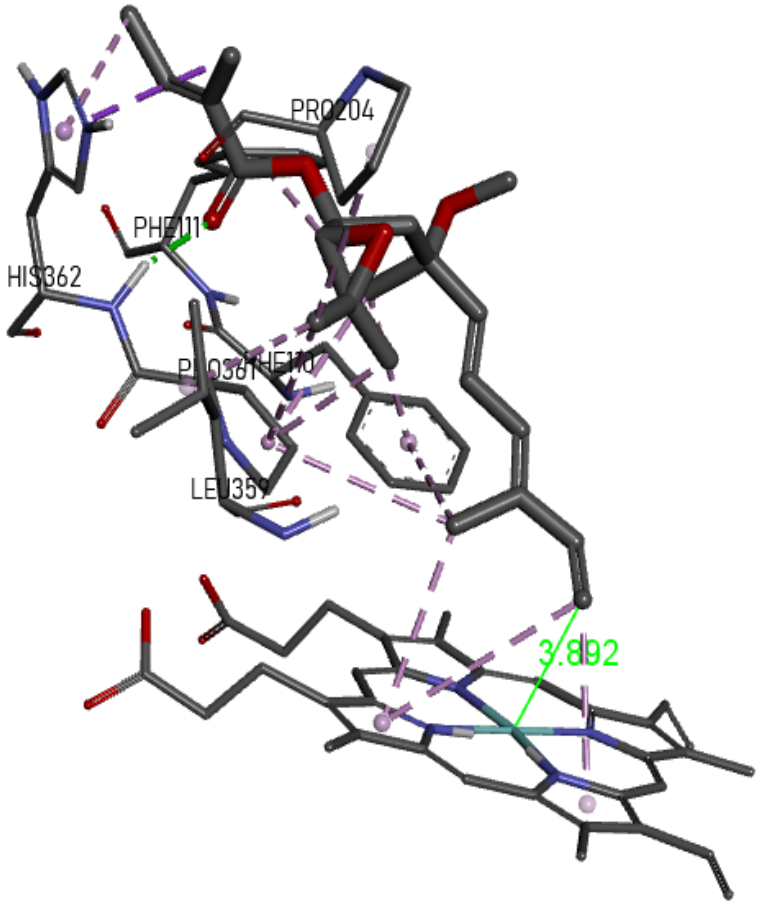
**(2)**



# RESULTS

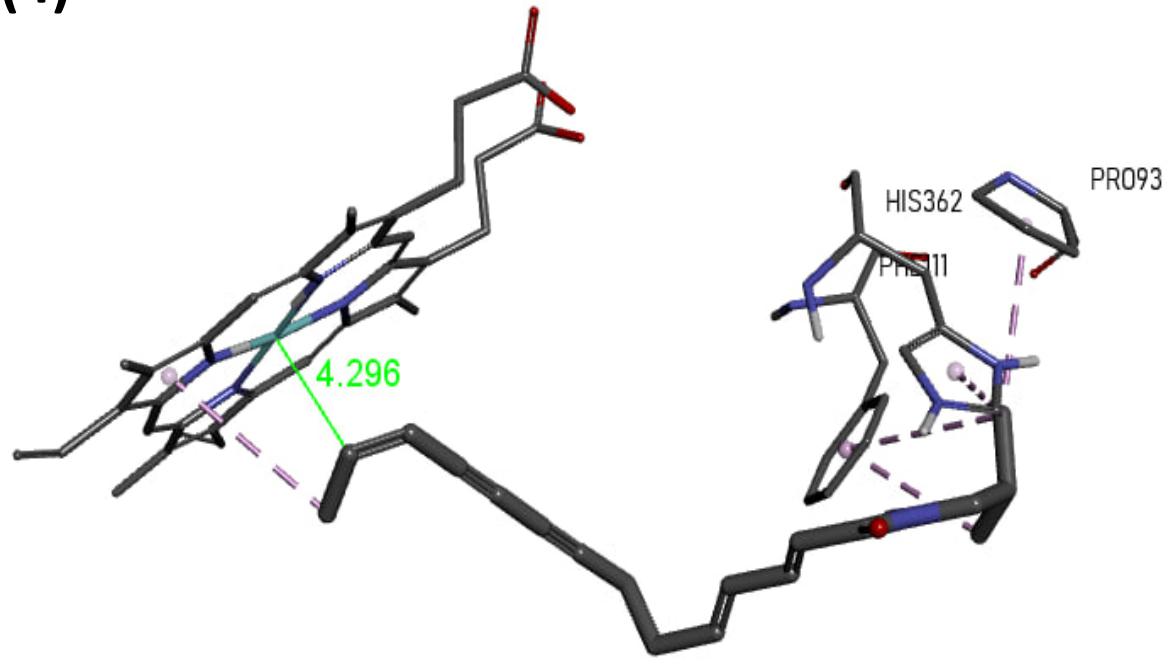
**9-Angeloyloxy-7-methoxy-10,11-epoxy-6,7,10,11-tetrahydro-5,6-dehydro-alpha-farnesene (3)** (Pubchem: CID129829779) from *Anisotome pilifera* binds to the structure of cytochrome CYP15a1 (UniProt: A0A2J7PVT0) *from Cryptotermes secundus* with **the orientation of the terminal alkene near the heme** (**Ebind -8.9 kcal/mol**)

**(3)**




**N-Isobutyl-2,4,8,10,12-tetradecapentaenamide (4)** (Pubchem database number: CID5318518) from *Zanthoxylum piperitum* binds to this structure **with the orientation of the double bond at position 12 near the heme** (**Ebind -8.4 kcal/mol**).

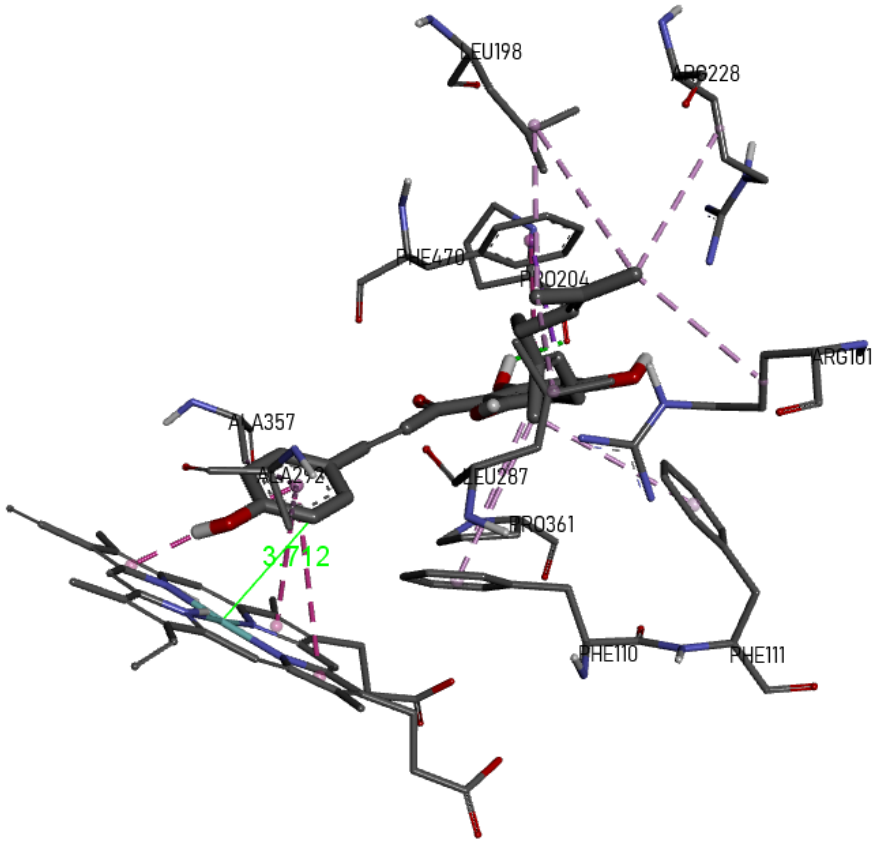
**(4)**



# RESULTS

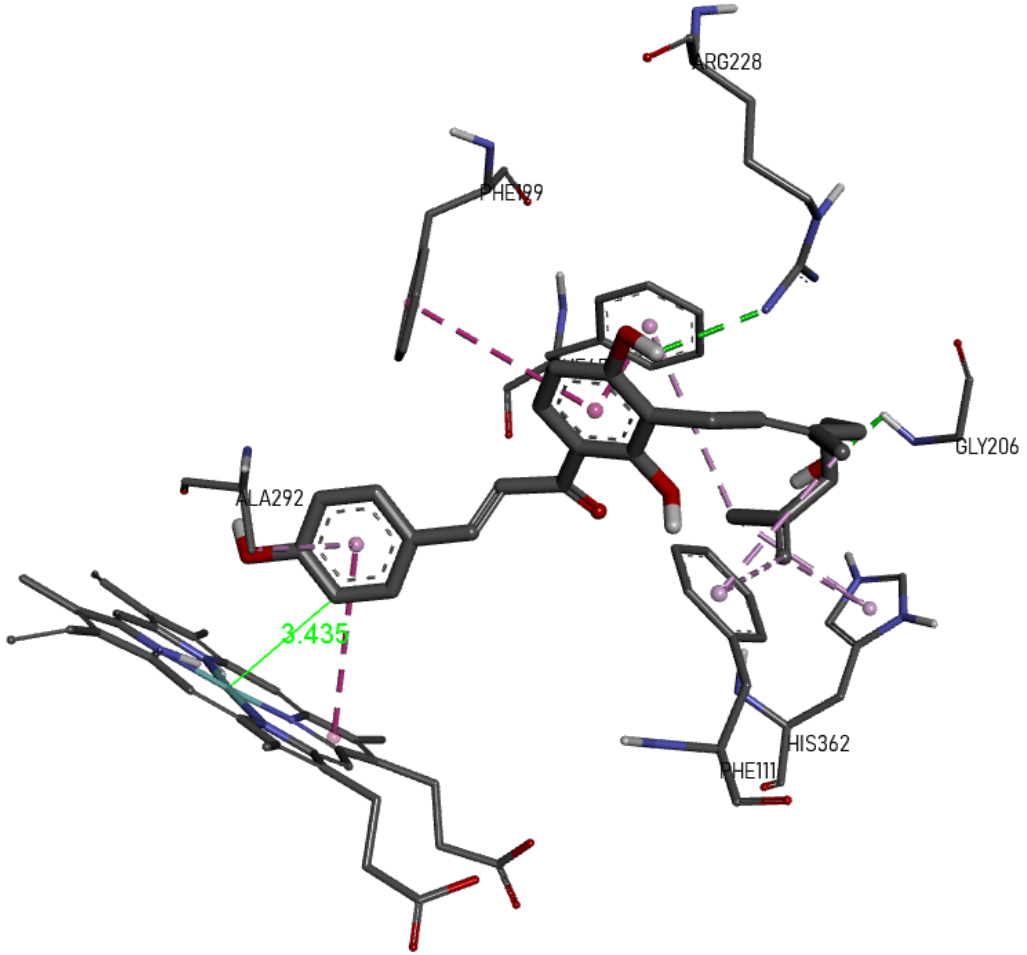
**3'-Geranylchalconaringenin (5)** (Pubchem: CID10070028) from *Humulus lupulus* binds to the structures of CYP15a1 (UniProt: A0A2J7PVT0, A0A836ELH5) from the termites *Cryptotermes secundus* with **localization of the phenolic fragment near the heme (Ebind = -11.4 kcal/mol).**

**(5)**



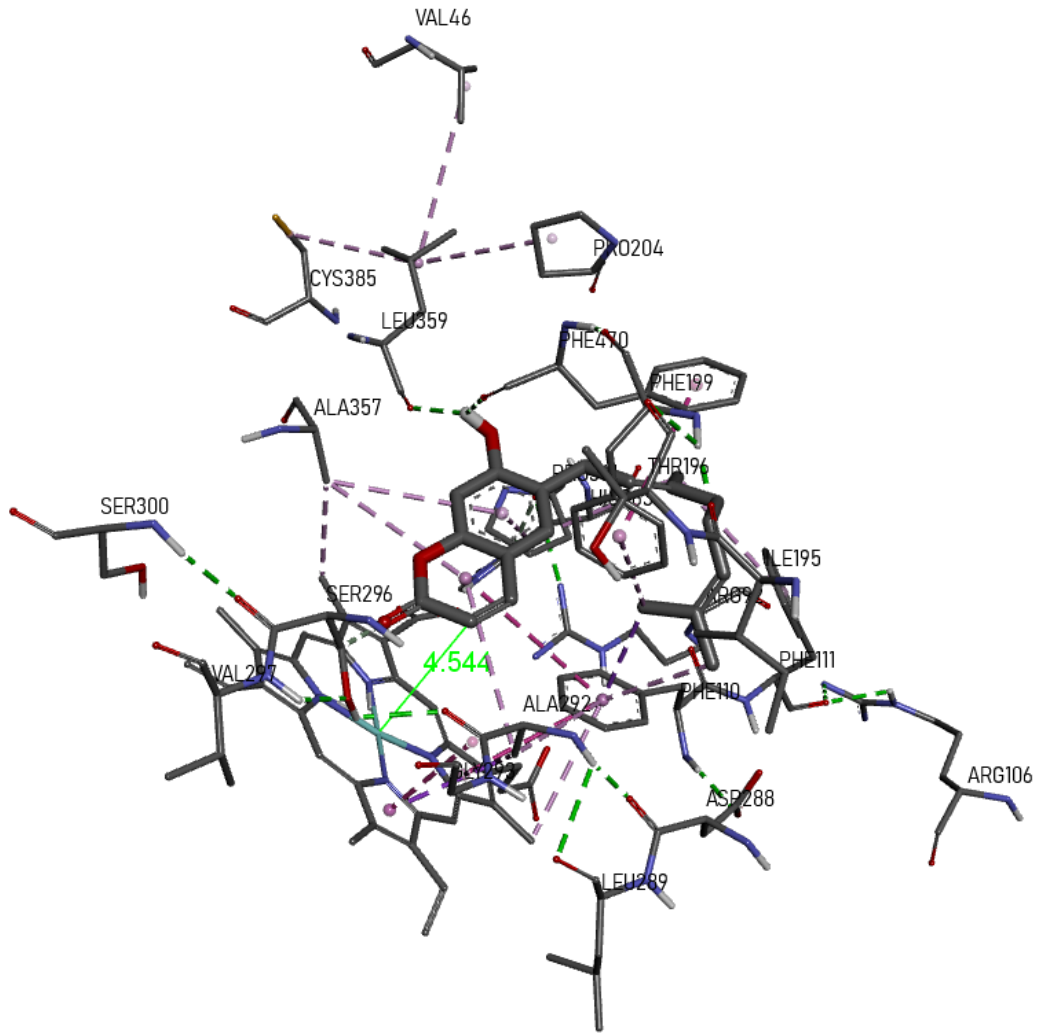

**Xanthoangelol B (6)** (Pubchem: CID10409180) from *Angelica keiskei* with the structure of CYP15a1 (UniProt:A0A2J7PVT0) from *Cryptotermes secundus* with **the location of the phenolic fragment near the heme (Ebind -10.5 kcal/mol).**

**(6)**



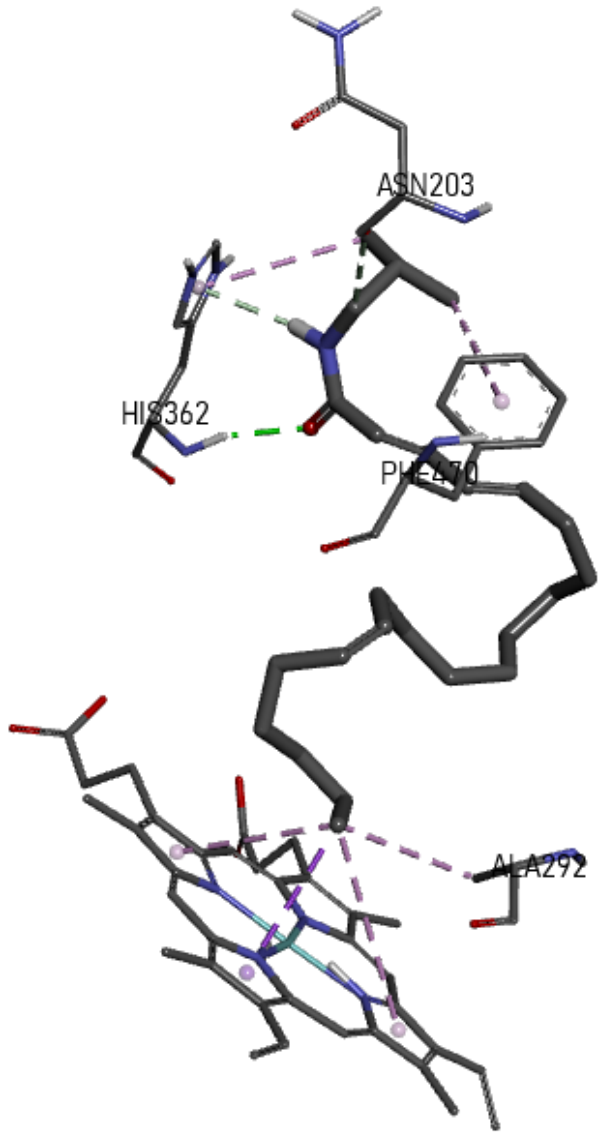
# RESULTS

**Ostruthin (7)** (Pubchem: CID5281420) from *Pamburus missionis, Halosciastrum melanotilingia* and other plants binds to the structure of CYP15a1 (UniProt: A0A2J7PVT0) from *Cryptotermes secundus* with **the orientation of the coumarin moiety near the heme (Ebind -10.6 kcal/mol).**



# RESULTS

For **2,4,14-eicosatrienoic acid isobutylamide (8)** (Pubchem: CID10338645) from *Piper longum*, the location of the methyl fragment in the ω-position of the fatty acid residue was found at a distance of 0.30 nm from the heme iron atom of the CYP15a1 epoxidase (UniProt:A0A2J7PVT0, Ebind = -8.7), which may indicate the potential for catalysis of **ω-hydroxylation** by cytochrome CYP15a1, which has not been previously identified for this enzyme.



# CONCLUSION

- Based on *in silico* evaluation, a **number of natural compounds**, including those from medicinal or edible plants, were identified as potential **inhibitors or substrate of CYP15a1** epoxidase from the termite *Cryptotermes Secundus*, which are pests for buildings, trees, agricultural lands, and the ant *Pseudoatta argentina*.
- Thus, the data obtained allow us to substantiate the importance of ***in vitro* experimental studies of these compounds as potential regulators of insect populations.**

# Many thanks:

- **To the organizers** for the opportunity to share our results at the symposium in the format of a flash presentation.
- **To the financial support** by the grant of the State Scientific Research Institute (Belarus) No 20210560.
- **To my supervisor Faletrov Y.F.** for support and mentoring.
- **To you all** for your attention!