

Identification of less harmful pesticides against honey bees: shape-based similarity analysis

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OVERVIEW

- ❖ The high concentration of the pesticide residues existing in vegetation, crops, and various edible products and the prolonged exposure to them, can harm human life and contribute to the disappearance of honey bees, several avian and animal species.
- ❖ The honey bees (*Apis mellifera*), efficient pollinators in addition to honey producers, are also considered important non-target test species for terrestrial toxicity assessment of chemicals.
- ❖ In this context, using thiacloprid and acetamiprid as queries, we performed a 3D similarity search to select new potential products with less harmful effects against bees. For similarity search, a small dataset of 302 compounds with pesticide activity, compiled from literature, was used. The first 10 compounds were selected and structurally analyzed according to the TanimotoCombo metrics, and compared with each of these two queries known to be effective, easily metabolized, and less toxic for bees.
- ❖ This approach came as a forward step in the research of pesticide ecotoxicological risk assessment, for the evaluation of their potential impact on the pollinator insects and the environment.



METHODS

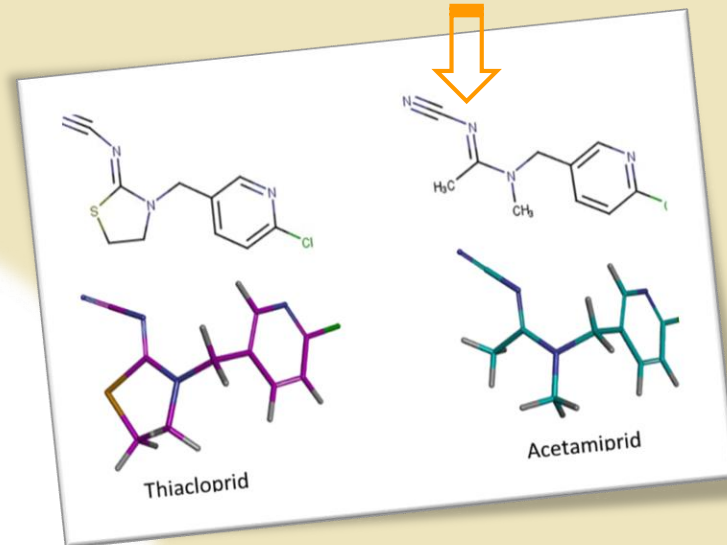
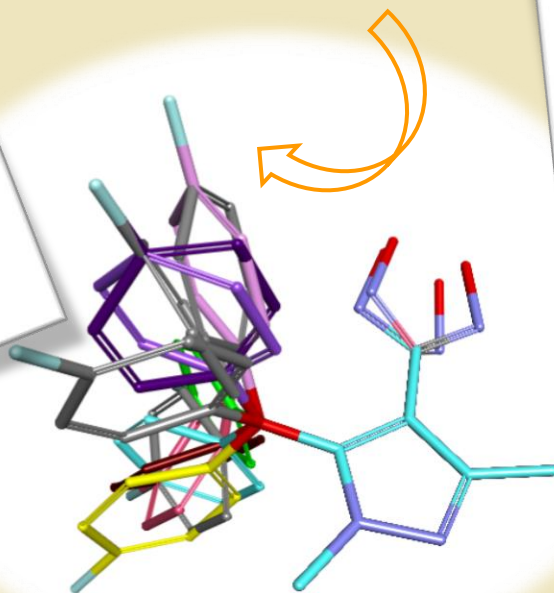
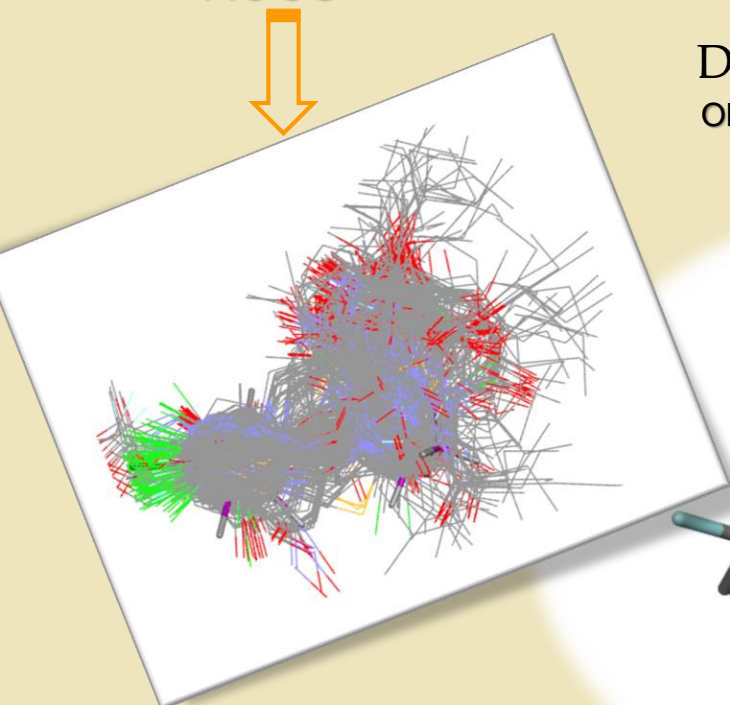
Dataset collection
Literature

Workflow scheme

Dataset Preparation
OMEGA conformer generation

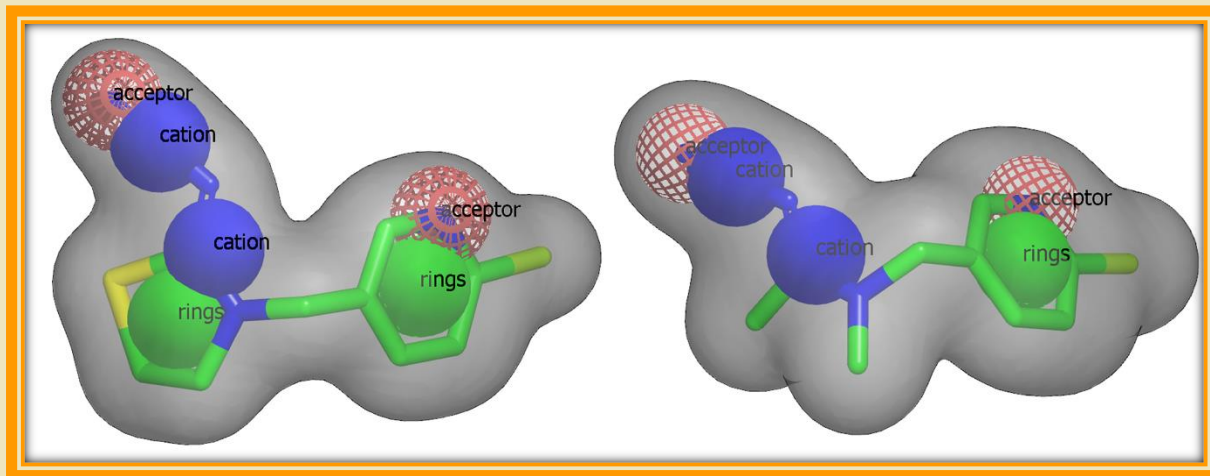
3D Similarity search
ROCS

Queries compounds
non-harmful to bees

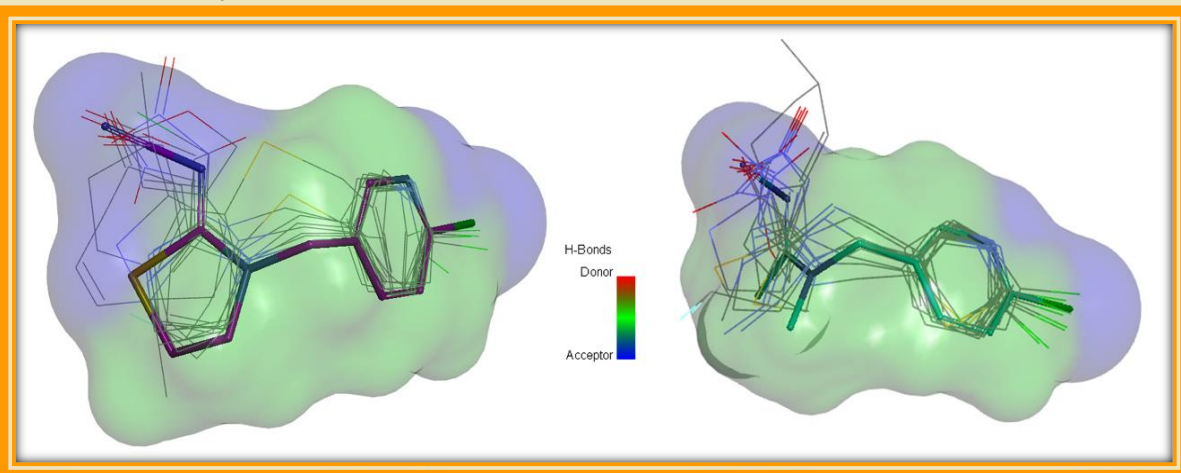


RESULTS AND DISCUSSIONS

Queries Molecular shapes



3D overlay with ROCS for the top ten compounds ranked by TanimotoCombo



RESULTS AND DISCUSSIONS

- The structures of the top ten compounds ranked by TanimotoCombo;
 - thiacloprid (left)
 - acetamiprid (right)

- All ten prioritized compounds for each query show values for:

- ☐ TC (TanimotoCombo) > 1.2
- ☐ ShT (ShapeTanimoto) > 0.8
- ☐ CS (ComboScore) > 1.2

2-chloro-5-(4,5-dihydroimidazol-1-ylmethyl)pyridine, **I**, (green circles) is the second compound prioritized by thiacloprid and the 7th by acetamiprid.

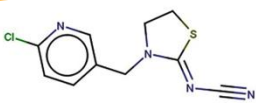
(2S)-1-[(6-chloropyridin-3-yl)methyl]imidazolidine-2-carbaldehyde, **II**, (blue circles) is the 3rd compound prioritized by thiacloprid and the 4th by acetamiprid.

4-[[[(6-chloropyridin-3-yl)methyl](2,2-difluoroethyl)amino]-5H-furan-2-one, **III**, (purple circles) is the 4th compound prioritized by thiacloprid and the 3rd by acetamiprid.

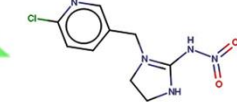
2-chloro-5-[[[(7R)-7-methyl-2H,3H,5H,6H,7H-imidazo[1,2-a]pyridin-1-yl]methyl]pyridine, **IV**, (cyan circles) is the 3rd compound prioritized by thiacloprid and the 8th by acetamiprid.



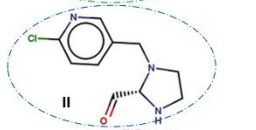
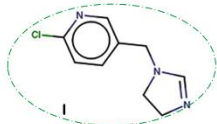
TC = 1.430
ST = 0.934
CS = 1.707



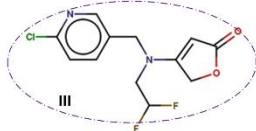
TC = 1.341
ST = 0.849
CS = 1.454



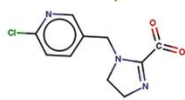
TC = 1.308
ST = 0.866
CS = 1.530



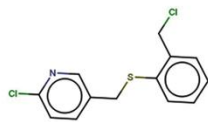
TC = 1.294
ST = 0.866
CS = 1.415



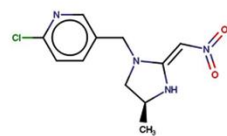
TC = 1.291
ST = 0.902
CS = 1.555



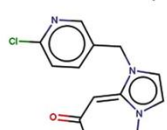
TC = 1.274
ST = 0.788
CS = 1.278



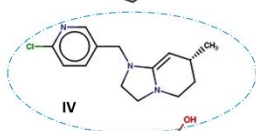
TC = 1.268
ST = 0.882
CS = 1.578



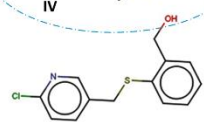
TC = 1.266
ST = 0.809
CS = 1.489



TC = 1.264
ST = 0.888
CS = 1.435

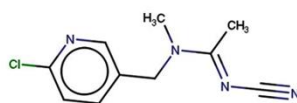


TC = 1.244
ST = 0.806
CS = 1.364

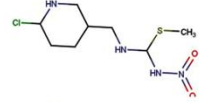


Tanimoto (Tc)

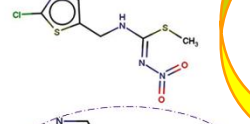
TC = 1.300
ST = 0.869
CS = 1.618



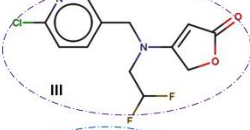
TC = 1.300
ST = 0.830
CS = 1.597



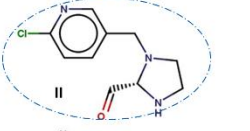
TC = 1.288
ST = 0.792
CS = 1.455



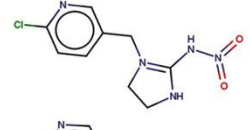
TC = 1.264
ST = 0.813
CS = 1.559



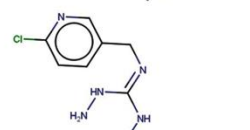
TC = 1.261
ST = 0.858
CS = 1.604



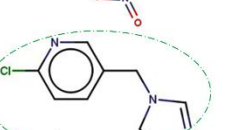
TC = 1.237
ST = 0.865
CS = 1.625



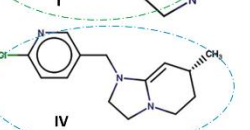
TC = 1.232
ST = 0.821
CS = 1.403



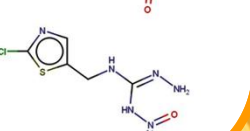
TC = 1.230
ST = 0.718
CS = 1.462



TC = 1.221
ST = 0.820
CS = 1.564



TC = 1.211
ST = 0.814
CS = 1.552



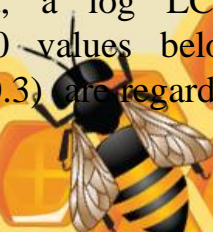
Tanimoto (Tc)

	Thiacloprid	Acetamidrid	I	II	III	IV	
Molecule properties	MW	252.73	222.679	195.653	225.679	288.681	263.772
	LogP	2.12088	2.06628	1.5789	0.6652	2.2428	2.7338
	#RBN	2	2	2	3	5	2
	#Acceptors	4	3	3	4	4	3
	#Donors	0	0	0	1	0	0
	Surface Area	102.944	93.827	82.063	93.244	113.179	113.057
	Max. tolerated dose (human)						
	MRTD (log mg/kg/day)	0.488	0.766	0.555	0.1	0.304	0.192
	hERG I inhibitor	No	No	No	No	No	No
	hERG II inhibitor	No	No	No	No	No	No
Toxicity	Oral Rat Acute Toxicity (LD50)	3.085	2.906	2.675	2.793	2.969	2.864
	Oral Rat Chronic Toxicity (LOAEL) (log mg/kg_bw/day)	0.699	0.795	0.904	1.186	1.567	0.877
	Hepatotoxicity	Yes	Yes	Yes	Yes	No	Yes
	Skin Sensitisation	No	No	Yes	No	No	No
	T.Pyiformis toxicity						
	pIGC50 (log ug/L)	1.132	0.986	0.869	0.026	0.807	1.025
	Minnow toxicity						
	LC50 (log mM)	1.441	1.566	2.072	2.601	1.892	1.568
	VDss (human) (LogL/kg)	-0.134	-0.217	0.161	0.749	-0.074	0.475
	Fraction unbound (human)	0.486	0.507	0.576	0.897	0.507	0.444
Distribution	BBB permeability (log BB)	0.114	0.132	0.192	-0.264	0.289	0.593
	CNS permeability (logPS)	-2.922	-2.867	-3.199	-3.442	-3.688	-3.475
	Total Clearance (log ml/min/kg)	0.201	0.193	0.489	0.9	0.484	0.203
Excretion	Renal OCT2 substrate	No	No	No	No	No	No

RESULTS AND DISCUSSIONS

*MW- Molecular Weight; RBN - Rotatable Bonds; VDss - volume of distribution at steady state; BBB- blood-brain barrier;

- VDss is considered low if below 0.71 L/kg (log VDss < -0.15) and high if above 2.81 L/kg (log VDss > 0.45).
- For a given compound, a logBB >0.3 considered to readily cross the blood-brain barrier while molecules with logBB < -1 are poorly distributed to the brain.
- Compounds with a logPS > -2 are considered to penetrate the Central Nervous System (CNS), while those with logPS < -3 are considered as unable to penetrate the CNS.
- For a given compound, a MRTD of less than or equal to 0.477 log(mg/kg/day) is considered low, and high if greater than 0.477 log(mg/kg/day).
- For a given compound, the pIGC50 (negative logarithm of the concentration required to inhibit 50% growth in log ug/L) is predicted, with a value > -0.5 log ug/L is considered toxic.
- For a given compound, a log LC50 will be predicted. LC50 values below 0.5 mM (log LC50 < -0.3) are regarded as high acute toxicity.



CONCLUSIONS

In this study, thiacloprid and acetamiprid were used as queries to find new potential compounds with less harmful effects against bees.

Four compounds :

- (2-chloro-5-(4,5-dihydroimidazol-1-ylmethyl)pyridine
- (2S)-1-[(6-chloropyridin-3-yl)methyl]imidazolidine-2-carbaldehyde
- 4-{[(6-chloropyridin-3-yl)methyl](2,2-difluoroethyl)amino}-5H-furan-2-one
- 2-chloro-5-{[(7R)-7-methyl-2H,3H,5H,6H,7H-imidazo[1,2-a]pyridin-1-yl)methyl}pyridine)

were selected as similar in shape and volume with both queries.

This approach is a first attempt to find novel compounds with enhanced safety profile against the pollinator insects and the environment.





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