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SUPPORTING INFORMATION TO

Insecticide discovery by drug repurposing: new synergistic inhibitors against Periplaneta americana

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Workflow overview

In our contribution, we propose a Virtual Screening (VS) pipeline to find new chemical compounds that inhibit the American cockroach Na_vPaS, and may eventually act as synergistic of current insecticides to improve their response and/or mortality, by screening the Drug Bank (DB) database that contains ca 10000 compounds.

Our VS methodology uses two ligand-based VS procedures; the commercial Glide solution, one of the industry standard in VS investigations, and the recently developed METADOCK 2.0, which provides a blind docking search by scanning the whole target surface. These energy interactions, obtained by Glide and METADOCK 2.0, are further refined by using MMGBSA rescoring to provide homogeneous energy interaction figures. Best ranked compounds are proposed for *in vivo* testing. This last step is determined by the availability of the identified products and/or their economic viability. The main contributions of the paper includes the following:

1. An in-depth VS procedure is proposed, combining two different ligand-based docking approaches and curating their results by MMGBSA rescoring. METADOCK 2.0 has higher throughput in terms of the number of conformations simulated; 0.74 miliseconds/pose (METADOCK 2.0) *vs.* 27.72 seconds/pose (Glide). Moreover, METADOCK 2.0 increases the interaction with the target by stabilizing the pose, offering wider picture of the binding mode to target Na_vPaS.

2. The DB database is fully screened virtually for Na_vPaS inhibitors of the American cockroach. Best-ranked compounds are listed with high energy interaction figures.

3. A positive control is established with the predominant compound in household insecticides to eliminate cockroaches (i.e. pyrethroids) to determine the energetic interaction threshold of the docking methods and also to validate our target (i.e. Na_vPaS).

4. Five compounds are tested with *in vivo* models, which lead to two novel synergistic compounds that improve the activity of currently used insecticides.

5. Our *in vivo* experimental results show that miglitol reduces the knockdown time by a factor of up to 12 times, from 60 minutes to 5 minutes, showing 100% of mortality rate.

METADOCK 2.0 is freely available on

`https://Baldoimbernon@bitbucket.org/Baldoimbernon/metadock_2.git.`

Computational Details

Table 1: The nineteen metaheuristic parameters used for $METADOCK2.0$.

Metaheuristic Parameters		Description
6*$ParamIni$	$INEIni$	Number of initial ligand conformations.
	$IIEFlex$	The intensification of the flexibility in the improvement functions.
	$PEIIni$	Percentage of the best conformations that are improved in the function Initialize.
	$IIEIni$	The intensification of the improvement in the function Initialize.
	$PBEIni$	Percentage of best conformations to be included in the initial set for the next iterations.\end{tabular
	$PWEIni$	Percentage of worst conformations to be included in the initial set for the next iterations.
2*$ParamSel$	$PBESel$	Percentage of the best conformations to be selected for combination.
	$PWESel$	Percentage of the worst conformations to be selected for combination.
3*$ParamCom$	$PBBCom$	Percentage of best-best conformations to be combined.
	$PWWCom$	Percentage of worst-worst conformations to be combined.
	$PBWCom$	Percentage of best-worst conformations to be combined.
2*$ParamMut$	$PMUCom$	Percentage of best conformations of the combination to be muted.
	$IMUCom$	The intensification of the mutation of elements generated by combination.
2*$ParamImp$	$PEIImp$	Percentage of best conformations of the combination to be improved.
	$IIEImp$	The intensification of the improvement of elements generated by combination.
$ParamInc$	$PBEInc$	Percentage of best conformations to be included in the reference set.
2*$ParamEnd$	$NIREnd$	Maximum number of steps without improvement.
	$MNIEnd$	Maximum number of iterations with or without improvement.

Table 2: Parameter setting selected by HYPERDOCK with which the METADOCK experiments have been developed.

INEIni	300	Number of initial ligand conformations.
IIEFlex	20	The intensification of the flexibility in the improvement functions.
PEIIni	100	Percentage of the best conformations that are improved in the function Initialize.
IIEIni	200	The intensification of the improvement in the function Initialize.
PBEIni	100	Percentage of best conformations to be included in the initial set for the next iterations.
PWEIni	0	Percentage of worst conformations to be included in the initial set for the next iterations.
PBESel	50	Percentage of the best conformations to be selected for combination.
PWESel	50	Percentage of the worst conformations to be selected for combination.
PBBCom	50	Percentage of best-best conformations to be combined.
PWWCom	20	Percentage of worst-worst conformations to be combined.
PBWCom	10	Percentage of best-worst conformations to be combined.
PMUCom	20	Percentage of best conformations of the combination to be muted.
IMUCom	10	The intensification of the mutation of elements generated by combination.
PEIImp	50	Percentage of best conformations of the combination to be improved.
IIEImp	100	The intensification of the improvement of elements generated by combination.
PBEInc	50	Percentage of best conformations to be included in the reference set.
NIREnd	3	Maximum number of steps without improvement.
MNIEnd	3	Maximum number of iterations with or without improvement.

Table 3: Main active ingredients, solvents and emulsifiers used for *in vivo* testing

CAS number	Materials	Supplier
72432-03-2	Miglitol	Target Molecule Corp.
56180-94-0	Acarbose	Glentham Life Sciences Ltd
56391-57-2	Netilmicin sulfate	Glentham Life Sciences Ltd
1143532-39-1	Capivasertib	Target Molecule Corp.
128-46-1	Dihydrostreptomycin	Carbosynth Ltd
23031-36-9	Prallethrin	Endura S.p.A.
7732-18-5	Water	–
68-12-2	Dimethylformamide (DMF)	Fluorochem
67-68-5	Dimethyl sulfoxide (DMSO)	TCI EUROPE N.V
–	Tween 20	Croda Iberica SA
70559-25-0	Emulsogen TS100	Clariant Produkte (Deutschland) GmbH
–	Calsogen 4814	Clariant Produkte (Deutschland) GmbH
61788-85-0	Sabowax EL-H 40	SABO SpA