Identification of sulfonamide compounds active on the insect nervous system: Molecular modeling, synthesis and biological evaluation

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Identification of sulfonamide compounds as modulators of insect Nicotinic Acetylcholine receptors: molecular modeling, synthesis and biological evaluation

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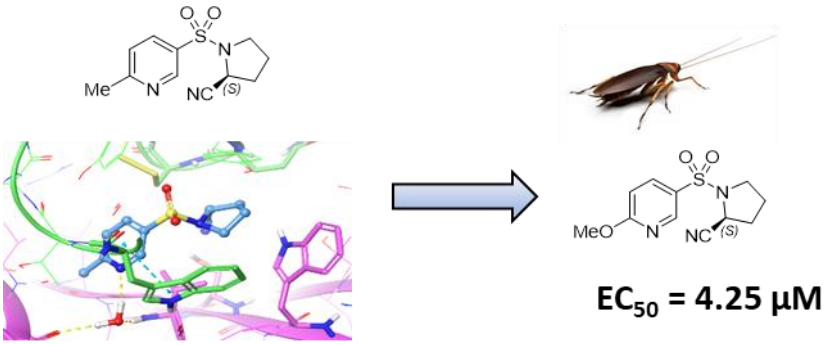
KEYWORDS. Insect nicotinic acetylcholine receptor, molecular docking, sulfonamide compounds, electrophysiological studies, cockroach, honeybee.

ABSTRACT. Insect nicotinic acetylcholine receptors (nAChRs) are a recognized target for insecticide design. In this work, we have identified, from a structure-based approach using molecular modeling tools, ligands with potential selective activity for pests versus pollinators. A high-throughput virtual screening with the Openeye software was performed using a library from the ZINC database, thiacloprid being used as the target structure. The top sixteen molecules were then docked in α6 cockroach and honeybee homomeric nAChRs to check from a theoretical point of view relevant descriptors in favor of pest selectivity. Among the selected molecules, one original sulfonamide compound has afterward been synthesized, together with various analogs. Two compounds of this family have been shown to behave as activators of the cockroach cholinergic synaptic transmission.

Graphical Abstract



Insecticides agrochemistry is faced with the development of resistance of insect pests to chemical control agents[1] but also with environmental concerns[2] such as their impacts on ecologically and economically important arthropods and pollinators. Specific ligands of the nicotinic acetylcholine receptors (nAChRs), one of the major neuroactive insecticide targets, particularly neonicotinoids, have been identified to have harmful effects towards pollinators associated with consequences on biodiversity.[3] If neonicotinoids have led the global insecticide sales during several years, some of them such as the bestseller imidacloprid (Figure 1) have been submitted to restrictions in Europe.[4] For sulfoxaflor, one recent pesticide from the sulfoximine class (Insecticide Resistance Action Committee - Group 4C) (Figure 1), despite distinct chemical features with respect to neonicotinoids, the question of harmlessness in terms of environmental concerns remains a controversial subject.[5] In this framework, alternative tools for pest management need to be found. In the case of nAChR competitive modulators, several studies have been carried out in the last years to design new, efficient and harmless neonicotinoids compounds[6-9] as well as original molecules exhibiting specific synergistic activity with conventional insecticides.[10,11]

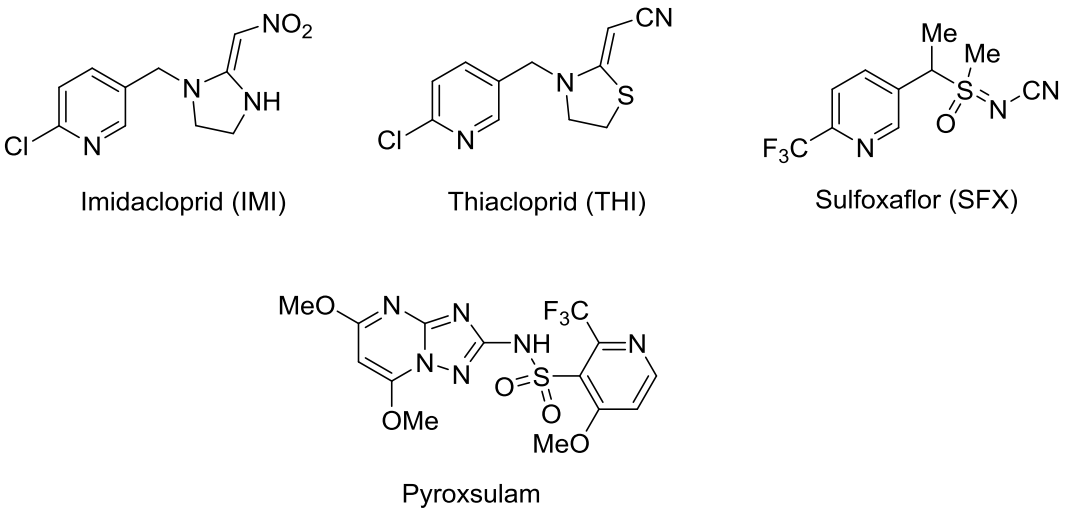


Figure 1. Structure of some pesticides on the market

The work described herein relates to a series of original sulfonamide compounds discovered from a structure-based design approach and evaluated as potential pesticides. Sulfur compounds with a sulfonamide (SO_2–NH-) function have been extensively developed as pharmaceutical[12] or agricultural agents.[13] As therapeutic agents, sulfonamide compounds were shown to possess antiinflammatory, antibacterial activities[14] antiviral or anti-cancer properties [15] and were also identified as potential enzyme inhibitors such as proteases[16] or metalloenzymes inhibitors.[17] Some of them have also been shown to act at the central nervous system targeting neuronal enzymes[18] or receptors such as nAChRs.[19] In agrochemistry, sulfonamide herbicides have emerged in the 90th and research progress has led to the identification of active compounds such as aryl sulfonamides[20] or heteroaromatic sulfonamides among which the triazolopyrimidine pyroxsulam (Quasar^{TM}, Figure 1), one representative commercial example.[21-23] If sulfur compounds bearing a sulfonimide function such as sulfoxaflor (Figure 1, SFX) have also recently been developed as novel and efficient pesticides, sulfonamide compounds with insecticidal activity still remain quite rare.[24, 25] Thus, to the best of our knowledge, the novel compounds designed and synthesized here,

61 exhibiting a promising insecticide activity, have never been claimed in the literature for this
62 application.

63 We started the study with a high-throughput virtual screening carried out with the Openeye
64 software using thiacloprid, a representative of the neonicotinoid family (Figure 1, THI), as the
65 template in the shape screening mode. The compounds emerged from this analysis were then
66 docked in the 3D models of the ligand binding domain (LBD) of cockroach (*Periplaneta*
67 *Americana)* and honeybee (*Apis mellifera)* of the α6 homomeric nAChRs, set up in our
68 previous study.[26] Indeed, Hawkins and collaborators have recently reported a functional
69 expression of α6 homomeric insect nAChR with an EC_{50} value of 0.88 μM for
70 acetylcholine.[27] Moreover, Lu and collaborators newly studied the susceptibility of
71 *Drosophila melanogaster* nAChR subunit mutants to eleven known insecticides, concluding
72 that the α6 mutant was sensitive to neonicotinoids such as thiacloprid or sulfoxaflor and that
73 the spynosins family could only target the α6 homomeric channel.[28]

74 The virtual screening procedure using the lead-like subset of the ZINC database, led to 16
75 compounds with a Tanimoto index superior to 0.6 compared to THI. Each of these
76 compounds were carefully examined before the docking stage. The chemical structure of most
77 of these compounds (except two molecules) have been modified to fulfill several criteria.
78 First, if the compounds exist under several protonation states, only the neutral form was
79 retained for further analysis. Furthermore, when the ZINC compounds bear aromatic rings,
80 heteroatoms have been introduced in relevant positions to increase the potential of specific
81 molecular interactions (for example an aromatic benzene ring was changed into a pyridine
82 ring). Lastly, aliphatic substituents (Me, *i*-Pr) carried by heterocyclic rings have generally
83 been removed.

For the molecular docking, the ligands were prioritized according to (i) their protonation state (ii) the docking scores (iii) the Glide interactions energies. In any case, the compounds were docked in their neutral state, on the basis on the recognized pharmacophore of insect nAChR competitive modulators.

Table 1 presents the docking scores (DS) and Glide energies (GE) obtained following the docking of the 16 compounds (**M1**-**M16**) considered in the binding sites of α6 cockroach and honeybee homomeric nAChRs. As recalled above, on the basis of the pharmacophore of insect nAChR competitive modulators, only compounds coming out from the virtual screening and that cannot be easily protonated at physiological *p*H were considered.

Table 1. Docking scores (DS) and Glide energies (GE) (see experimental section), in kJ/mol, computed following the flexible docking of the top 16 compounds coming out from the virtual screening study on α6 homomeric cockroach and honeybee nAChRs.

Compound	α6 cockroach nAChR		α6 honeybee nAChR	
	DS	**GE**	**DS**	**GE**
M1	-40.6	-243.9	-31.8	-176.1
M2	-33.9	-216.3	-34.3	-264.4
M3	**-25.5**	**-190.8**	**-21.3**	**-117.6**
M4	-38.1	-243.5	-28.0	-136.8
M5	-40.6	-243.9	-34.3	-167.4
M6	-34.3	-217.1	-38.5	-215.9
M7	-29.7	-170.7	-32.2	-204.6
M8	-35.1	-179.5	-34.7	-141.8
M9	-25.1	-97.9	-25.5	-155.6
M10	-29.7	-170.3	-15.5	-143.5
M11	-26.8	-83.3	-15.9	-74.1

M12	-42.7	-236.4	-45.2	-200.0
M13	-37.2	-237.2	-41.4	-213.8
M14	-25.9	-166.9	-25.5	-182.8
M15	-38.9	-180.7	-39.7	-184.5
M16	-41.4	-247.3	[a]	[a]

[a] The docking of this compound was not possible in honeybee α6 homomeric nAChR.

Among these sixteen compounds, seven appeared promising competitive candidates **(M1, M3, M4, M5, M10, M11, M16**) since their docking parameters (DS and GE) were significantly more favorable for α6 cockroach nAChR compared to α6 honeybee nAChR. Indeed, for **M2**, **M6**, **M8-9** and **M14-15**, one or both of the discriminating parameters have very similar values for both insect models, no selectivity emerging from these results. For two compounds (**M12**, **M13**), no clear conclusions could be given from their results since the trends suggested with the docking scores and the Glide energies are opposite. Finally for compound **M7**, both values were in favor of the α6 honeybee nAChR, suggesting a possible selectivity for this specie.

To go further with this structure-based design study, among the seven relevant molecules **(M1**, **M3**, **M4**, **M5**, **M10**, **M11**, **M16**), we have focused on the sulfonamide **M3** because of its relative simple synthesis. As shown in Figure 2a, it is worth noticing that **M3** has an asymmetric center and can therefore interact with nAChRs through two stereoisomers (*R* or *S*). We have only investigated in this work the binding of the (*S*) enantiomer since a molecular fitting of the chemical structures of the most promising compounds have shown that only this enantiomer gave the optimal orientations of the relevant chemical fragments in the binding site of the α6 homomeric nAChRs (see SI; Figure S1).

The interactions of the (*S*)-**M3** enantiomer in the binding site of α6 cockroach and honeybee nAChRs are shown in Figure 2b. It can first be seen that a hydrogen-bond interaction involves the pyridine nitrogen of the ligand and main chain CO and NH groups of α6 nAChR residues through a water molecule in both insect species. This feature agrees with the role played by a water molecule that appears conserved in several cocrystallized ligand-nAChR complexe models[29, 30] and has been suggested to be incorporated in the binding pocket for the construction of a pharmacophore and the design of new ligands. In both cases, Trp residues (Trp 175 and 200 for α6 cockroach and honeybee nAChRs, respectively) have a pivotal contribution in the binding of the ligand, as well as with the five membered saturated ring and the pyridine ring. These trends are in line with the prominence of this residue pointed out in the literature by experimental studies[31, 32] and rationalized by computational investigations.[33-35]

Lastly, it is worth noticing that the key cysteine residues (Cys219-Cys220 or Cys244-Cys245) are in both binding sites (α6 cockroach and honeybee nAChRs, respectively) in close vicinity with the ligand, a sulfur atom being in close contact with the oxygen atom of the sulfonamide group. This feature highlights the potential of interaction of the sulfone moiety, found in recent nAChRs modulators acting as insecticides, in particular the sulfonimide compound sulfoxaflor, designed by Dow Agrosciences.[36]

a)

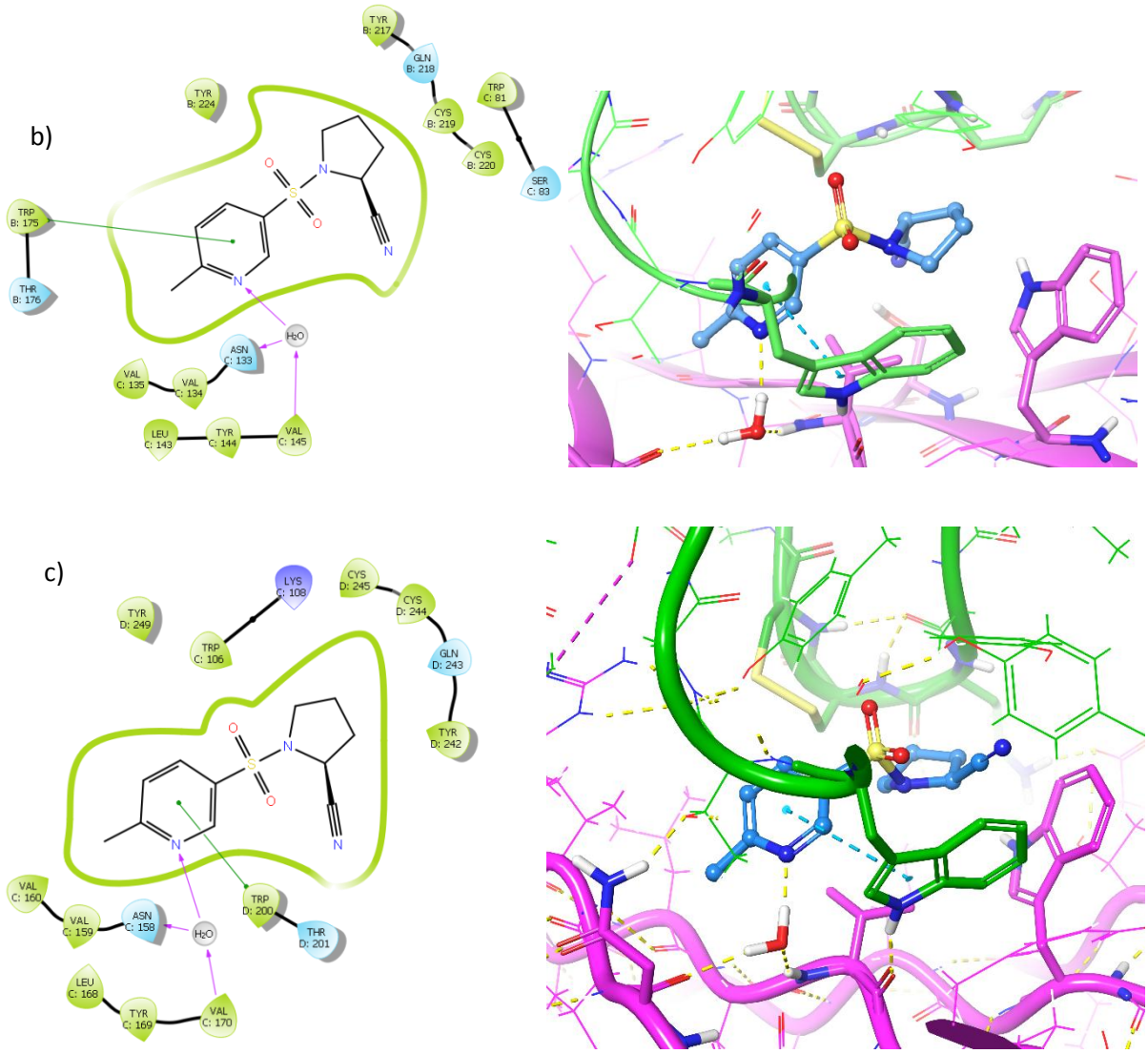


Figure 2. (a) **M3** (*R*) and (*S*)-enantiomers chemical structures. 2D ligand interaction plots and 3D views of the interactions between the (*S*) enantiomer of **M3** (compound **3d**) and (b) cockroach α6 nAChR or (c) honeybee α6 nAChR.

From this analysis, no clear difference of interactions appeared therefore for the (*S*) enantiomer of **M3** for cockroach and honeybee α6 nAChRs binding sites. In fact, a further examination of the interaction energies rationalizes its better affinity for α6 cockroach nAChR. Indeed, table 2 shows that for the main amino acid residues involved in the binding and discussed above, the stabilization is significantly greater for cockroach α6 nAChRs. The present molecular modeling results, validated by their good agreement with known

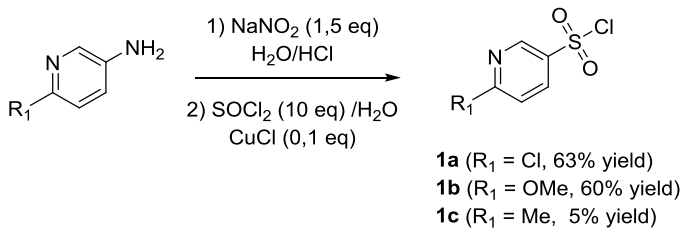
(experimental) structural features[37] for the interaction of nAChRs modulators and their target, are therefore promising for the insecticide activity of **M3** and its potential selectivity for pests.

Table 2. Interaction energies (kJ/mol) computed by the Glide program for the main components of the α6 cockroach and honeybee nAChRs binding sites with the *S* enantiomer of **M3**. Docking scores (DS) and Glide energies (GE) (kJ/mol) are reminded for clarity.

M3 (*S*)	**α6 cockroach nAChR model**						
	Trp81	**Val145**	**Trp175**	**Tyr217**	**Cys219**	**DS**	**GE**
	-10.9	-21.3	-23.0	-20.1	-10.5	-25.5	-190.8
	α6 honeybee nAChR model						
	Trp106	**Val170**	**Trp200**	**Tyr242**	**Cys245**	**DS**	**GE**
	>0	-9.6	-18.8	-12.1	-8.4	-21.3	-117.6

The heteroaromatic compound **M3** (or **3d**) and analogs **3a-c** displaying a sulfonamide function, could be simply prepared from nucleophilic substitution of a sulfonyl chloride precursor **1** with the corresponding pyrrolidine **2** as depicted in scheme 2. We started with the synthesis of the selected sulfonyl chlorides **1a-c** bearing a chloride, a methoxy or a methyl group on the C6 position of the pyridine ring. Access to such heteroaromatic sulfonyl chloride compounds could be achieved starting from halogeno heterocycles, by nucleophilic substitution with methylthiolate followed by oxidative chlorination of thiol intermediate with chlorine[38] or with 2,4-dichloro-5,5-dimethylhydantoin.[39] Woolven and collaborators also proposed to prepare those sulfonyl chloride reagents, starting from Grignard derivatives and the DABSO (DABCO-*bis*(sulfur dioxide complex) a stable sulfur dioxide equivalent, followed by addition of sulfuryl chloride.[40] For our study we chose to apply the one-pot two

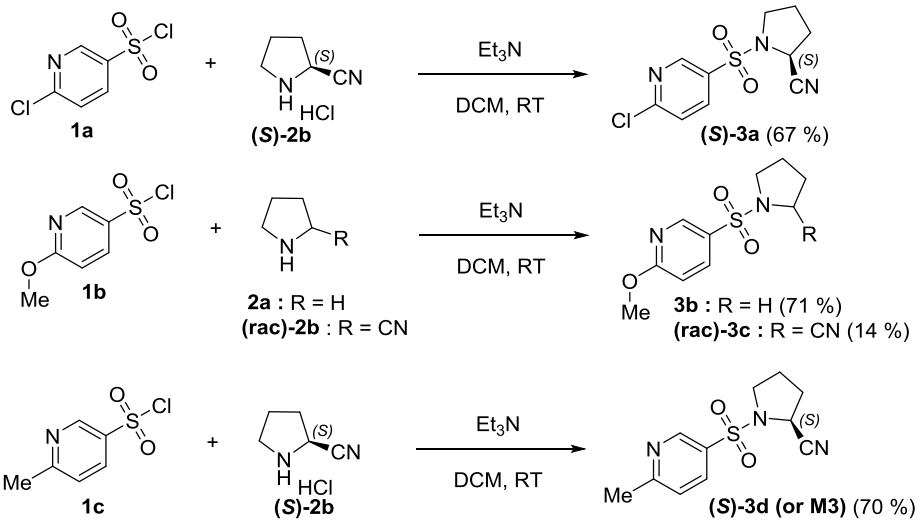
steps Sandmeyer-sulfonylation approach starting with 3-amino pyridines. This process was proved to work well with thionyl chloride in aqueous conditions and at low temperature.[41] Starting with commercial 3-amino-6-substituted pyridines, the targeted chlorosulfonyl reagents **1a-c** were obtained with good yields excepted for compound **1c** which failed to precipitate in this aqueous medium (Scheme 1).



Scheme 1. Synthesis of the selected pyridine-3-sulfonyl chloride reagents **1a-c**

To access to the racemic 2-cyano pyrrolidine (Scheme 2, **(rac)-2b,** R = CN), some synthetic ways were proposed in the literature, such as the oxidation of pyrrolidine with aqueous sodium peroxodisulfate to furnish the corresponding trimer being hydrocyanated with HCN [42] or TMSCN.[43] Applying this last method we prepared racemic pyrrolidine **(rac)-2b** in 34% overall yield in two steps after purification by distillation.

The expected sulfonamides **3a** to **3d** were finally prepared by nucleophilic substitution of the heteroaromatic sulfonyl chlorides **1a-c** with the commercially available pyrrolidines **2a** and **(*S*)-2b** or synthesized racemic pyrrolidine **(rac)-2b**, in classical reaction conditions (Scheme 2).[44] They were obtained with good yield excepted for compound **3c** which yield was not optimized.



Scheme 2. Synthesis of compounds **3a-3d**

These sulphonamide compounds **3** were then evaluated on the cholinergic synaptic transmission in cockroach *Periplaneta americana*. Experiments were performed on the cercal nerve giant interneuron synapses located within the cockroach sixth abdominal ganglion (A6 (abbreviated SAG); see SI, Figure S2) using the mannitol-gap method pioneered by Callec.[45]

The electrophysiological properties of the sulfonamide compounds **3** emerged from the modeling studies (**M3**=**3d**) are presented in Figure 3. We first compared the pharmacological properties of the four compounds **3a-3d** on insect cholinergic synaptic transmission with imidacloprid (IMI, Figure 1), the forerunner of neonicotinoid insecticides. We aimed to demonstrate if our compounds were able to depolarize the sixth abdominal ganglion as found with IMI. Indeed, previous studies demonstrated that bath applications of neonicotinoid insecticides such as IMI[46] and clothianidin[47] on the sixth abdominal ganglion induced its depolarization through activation of postsynaptic nAChRs. Here, we found that bath application of the four compounds blocked the amplitude of the excitatory postsynaptic potentials (EPSPs) evoked by electrical stimulation of the ipsilateral cercal nerve XI (see SI, Figure S3) when the depolarization reached a peak (Figure 3), suggesting that as found with IMI, these compounds activated postsynaptic nAChRs.[46]

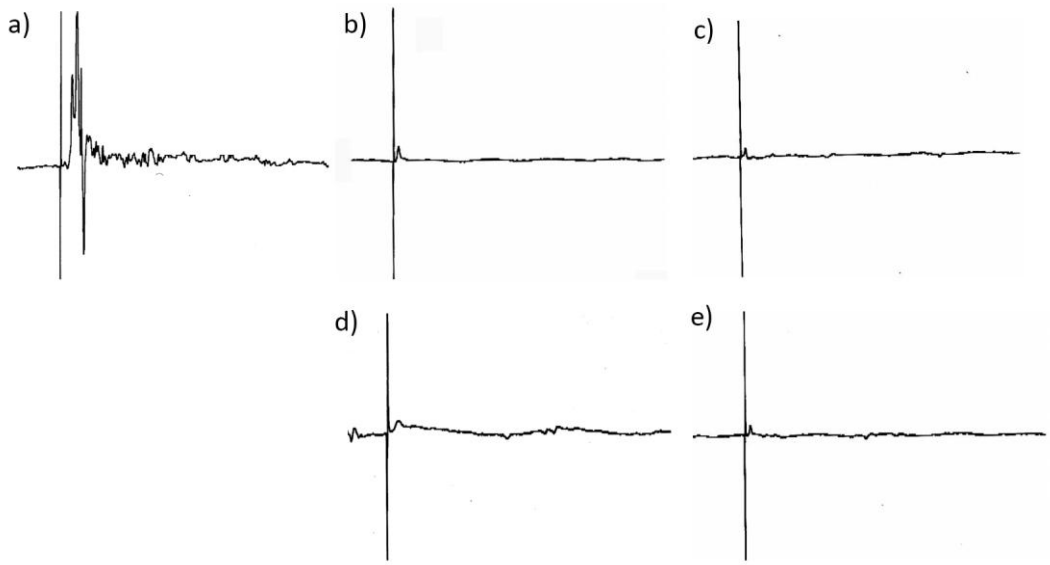


Figure 3. Effect of 100 µM of compounds **3a**, **3b**, **3c** and **3d** on electrical stimulations of the ipsilateral nerve XI. Stimulation of the nerve XI induces a EPSP (a: control condition) which is blocked under bath application of the four compounds (b: **3a**, c: **3b**, d: **3c** and e: **3d**)

The dose-response curves plotted according to the known equation (see SI) demonstrated that the four compounds (**3a**, **3b**, **3c** and **3d**) induced a depolarization of the

sixth abdominal ganglion (Figure 4). Note that, for the four compounds, their effect on synaptic depolarization was not reversed after wash-out.

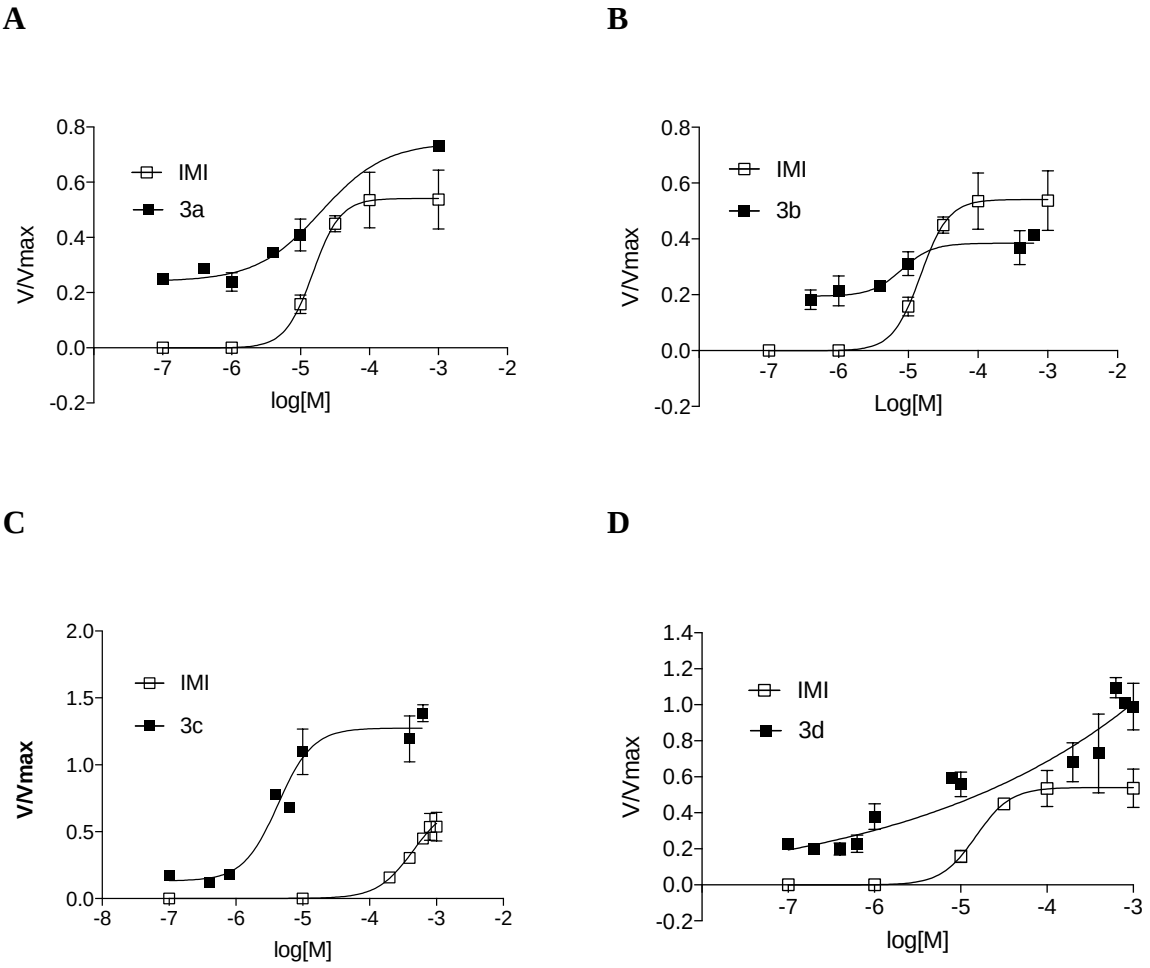


Figure 4. Dose-response curves of the synaptic depolarization induced by the four compounds **3a** (A) **3b** (B) **3c** (C) and **3d** (D), compared with IMI-induced depolarization. Concentration ranges from 0.1 µM to 1 mM. Data are mean values of the amplitude of the peak depolarization. Each point represents n = 8 recordings.

The EC_{50} values for compounds **3a**, **3b** and **3c** were evaluated as 19 µM, 8.02 µM and 4.25 µM respectively. For compound **3d**, we were unable to determine the EC_{50} value. The 6-methoxy-pyridinyl sulfonamide compounds **3b** and **3c** as well as the 6-chloro analog **3a** gave EC_{50} values in the same range. Thus, among this series, the most effective compounds appeared to be **3b** (EC_{50} = 8.02 µM) and **3c** (EC_{50} = 4.25 µM), bearing the methoxy substituent on the pyridine ring. We could also observe that the addition of a cyano group at

220 the 2-position of the pyrrolidine ring (compound **3c**) very slightly improved the EC_{50} value
221 compared to **3b**. Than, in comparison with our hit candidate **M3** (**3d**) bearing a methyl group
222 on the pyridine ring, electrophysiological assays on the cockroach nervous system showed
223 that the three analogs **3a-3c,** bearing a methoxy or chloro substituent on the pyridine ring,
224 appeared as better activators of the cholinergic synaptic transmission.

225 In summary, a new family of potential competitive modulators of insect nAChRs has been
226 designed in the present work. From a cross-disciplinary approach, a sulfonamide compound
227 **M3**, identified by molecular modeling, has been synthesized (**M3** or **3d**) together with three
228 relevant analogs (**3a**, **3b** and **3c**). The cholinergic synaptic effect of these four compounds on
229 nAChRs has been evidenced through electrophysiological measurements in cockroach, and
230 was found to be similar to imidacloprid one, the neonicotinoid forerunner. Thus, the
231 compounds designed and evaluated in the present work can be regarded as a promising
232 chemical tool to help to characterize and study insect nAChRs. Further investigations are also
233 in progress in our laboratories with the best sulfonamide compounds, particularly lethality
234 experiments with pests compared to bees, to complement the promising data presented herein.

235

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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A. Supplementary data.

Complementary figures, tables, for molecular modeling and experimental parts: synthesis and NMR data of the compounds (**1a-c** and **3a-d**) and biological tests experimental data. These data are free of charge via the Internet.

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