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

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

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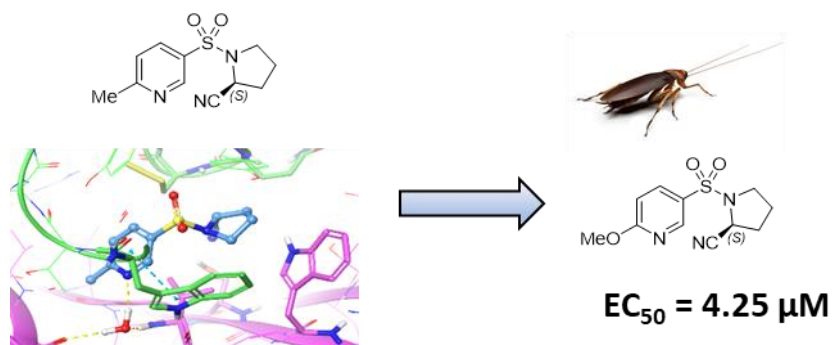
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13 *KEYWORDS.* Insect nicotinic acetylcholine receptor, molecular docking, sulfonamide  
14 compounds, electrophysiological studies, cockroach, honeybee.

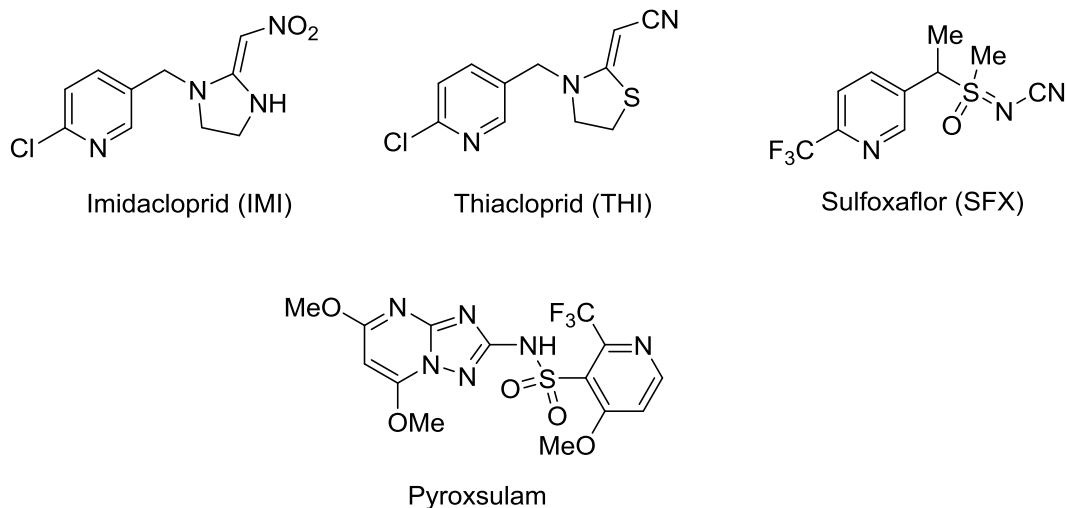
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16 *ABSTRACT.* Insect nicotinic acetylcholine receptors (nAChRs) are a recognized target for  
17 insecticide design. In this work, we have identified, from a structure-based approach using  
18 molecular modeling tools, ligands with potential selective activity for pests versus pollinators.  
19 A high-throughput virtual screening with the Openeye software was performed using a library  
20 from the ZINC database, thiacloprid being used as the target structure. The top sixteen  
21 molecules were then docked in  $\alpha 6$  cockroach and honeybee homomeric nAChRs to check  
22 from a theoretical point of view relevant descriptors in favor of pest selectivity. Among the  
23 selected molecules, one original sulfonamide compound has afterward been synthesized,  
24 together with various analogs. Two compounds of this family have been shown to behave as  
25 activators of the cockroach cholinergic synaptic transmission.

26 **Graphical Abstract**



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



44

45

**Figure 1.** Structure of some pesticides on the market

46 The work described herein relates to a series of original sulfonamide compounds  
 47 discovered from a structure-based design approach and evaluated as potential pesticides.  
 48 Sulfur compounds with a sulfonamide (SO<sub>2</sub>-NH-) function have been extensively developed  
 49 as pharmaceutical<sup>12</sup> or agricultural agents.<sup>13</sup> As therapeutic agents, sulfonamide compounds  
 50 were shown to possess antiinflammatory, antibacterial activities<sup>14</sup> antiviral or anti-cancer  
 51 properties<sup>15</sup> and were also identified as potential enzyme inhibitors such as proteases<sup>16</sup> or  
 52 metalloenzymes inhibitors.<sup>17</sup> Some of them have also been shown to act at the central nervous  
 53 system targeting neuronal enzymes<sup>18</sup> or receptors such as nAChRs.<sup>19</sup> In agrochemistry,  
 54 sulfonamide herbicides have emerged in the 90<sup>th</sup> and research progress has led to the  
 55 identification of active compounds such as aryl sulfonamides<sup>20</sup> or heteroaromatic  
 56 sulfonamides among which the triazolopyrimidine pyroxsulam (Quasar<sup>TM</sup>, Figure 1), one  
 57 representative commercial example.<sup>21-23</sup> If sulfur compounds bearing a sulfonimide function  
 58 such as sulfoxaflor (Figure 1, SFX) have also recently been developed as novel and efficient  
 59 pesticides, sulfonamide compounds with insecticidal activity still remain quite rare.<sup>24, 25</sup>  
 60 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  $\alpha 6$  homomeric nAChRs, set up in our  
68 previous study.<sup>26</sup> Indeed, Hawkins and collaborators have recently reported a functional  
69 expression of  $\alpha 6$  homomeric insect nAChR with an EC<sub>50</sub> value of 0.88  $\mu$ M for  
70 acetylcholine.<sup>27</sup> Moreover, Lu and collaborators newly studied the susceptibility of  
71 *Drosophila melanogaster* nAChR subunit mutants to eleven known insecticides, concluding  
72 that the  $\alpha 6$  mutant was sensitive to neonicotinoids such as thiacloprid or sulfoxaflor and that  
73 the spynosins family could only target the  $\alpha 6$  homomeric channel.<sup>28</sup>

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.

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

88 Table 1 presents the docking scores (DS) and Glide energies (GE) obtained following the  
89 docking of the 16 compounds (**M1-M16**) considered in the binding sites of  $\alpha 6$  cockroach and  
90 honeybee homomeric nAChRs. As recalled above, on the basis of the pharmacophore of  
91 insect nAChR competitive modulators, only compounds coming out from the virtual  
92 screening and that cannot be easily protonated at physiological *pH* were considered.

93 **Table 1.** Docking scores (DS) and Glide energies (GE) (see experimental section), in kJ/mol,  
94 computed following the flexible docking of the top 16 compounds coming out from the  
95 virtual screening study on  $\alpha 6$  homomeric cockroach and honeybee nAChRs.

Compound	$\alpha 6$ cockroach nAChR		$\alpha 6$ honeybee nAChR	
	DS	GE	DS	GE
<b>M1</b>	-40.6	-243.9	-31.8	-176.1
<b>M2</b>	-33.9	-216.3	-34.3	-264.4
<b>M3</b>	<b>-25.5</b>	<b>-190.8</b>	<b>-21.3</b>	<b>-117.6</b>
<b>M4</b>	-38.1	-243.5	-28.0	-136.8
<b>M5</b>	-40.6	-243.9	-34.3	-167.4
<b>M6</b>	-34.3	-217.1	-38.5	-215.9
<b>M7</b>	-29.7	-170.7	-32.2	-204.6
<b>M8</b>	-35.1	-179.5	-34.7	-141.8
<b>M9</b>	-25.1	-97.9	-25.5	-155.6
<b>M10</b>	-29.7	-170.3	-15.5	-143.5
<b>M11</b>	-26.8	-83.3	-15.9	-74.1

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

96 <sup>a</sup> The docking of this compound was not possible in honeybee  $\alpha 6$  homomeric nAChR.

97

98 Among these sixteen compounds, seven appeared promising competitive candidates (**M1**,  
99 **M3**, **M4**, **M5**, **M10**, **M11**, **M16**) since their docking parameters (DS and GE) were  
100 significantly more favorable for  $\alpha 6$  cockroach nAChR compared to  $\alpha 6$  honeybee nAChR.  
101 Indeed, for **M2**, **M6**, **M8-9** and **M14-15**, one or both of the discriminating parameters have  
102 very similar values for both insect models, no selectivity emerging from these results. For two  
103 compounds (**M12**, **M13**), no clear conclusions could be given from their results since the  
104 trends suggested with the docking scores and the Glide energies are opposite. Finally for  
105 compound **M7**, both values were in favor of the  $\alpha 6$  honeybee nAChR, suggesting a possible  
106 selectivity for this specie.

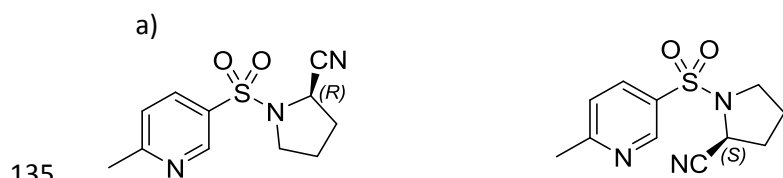
107 To go further with this structure-based design study, among the seven relevant molecules  
108 (**M1**, **M3**, **M4**, **M5**, **M10**, **M11**, **M16**), we have focused on the sulfonamide **M3** because of its  
109 relative simple synthesis. As shown in Figure 2a, it is worth noticing that **M3** has an  
110 asymmetric center and can therefore interact with nAChRs through two stereoisomers (*R* or  
111 *S*). We have only investigated in this work the binding of the (*S*) enantiomer since a molecular  
112 fitting of the chemical structures of the most promising compounds have shown that only this  
113 enantiomer gave the optimal orientations of the relevant chemical fragments in the binding  
114 site of the  $\alpha 6$  homomeric nAChRs (see SI; Figure S1).

115 The interactions of the (*S*)-**M3** enantiomer in the binding site of  $\alpha 6$  cockroach and  
116 honeybee nAChRs are shown in Figure 2b. It can first be seen that a hydrogen-bond  
117 interaction involves the pyridine nitrogen of the ligand and main chain CO and NH groups of  
118  $\alpha 6$  nAChR residues through a water molecule in both insect species. This feature agrees with  
119 the role played by a water molecule that appears conserved in several cocrystallized ligand-  
120 nAChR complex models<sup>29, 30</sup> and has been suggested to be incorporated in the binding  
121 pocket for the construction of a pharmacophore and the design of new ligands. In both cases,  
122 Trp residues (Trp 175 and 200 for  $\alpha 6$  cockroach and honeybee nAChRs, respectively) have a  
123 pivotal contribution in the binding of the ligand, as well as with the five membered saturated  
124 ring and the pyridine ring. These trends are in line with the prominence of this residue pointed  
125 out in the literature by experimental studies<sup>31, 32</sup> and rationalized by computational  
126 investigations.<sup>33-35</sup>

127 Lastly, it is worth noticing that the key cysteine residues (Cys219-Cys220 or Cys244-  
128 Cys245) are in both binding sites ( $\alpha 6$  cockroach and honeybee nAChRs, respectively) in close  
129 vicinity with the ligand, a sulfur atom being in close contact with the oxygen atom of the  
130 sulfonamide group. This feature highlights the potential of interaction of the sulfone moiety,  
131 found in recent nAChRs modulators acting as insecticides, in particular the sulfonimide  
132 compound sulfoxaflor, designed by Dow Agrosiences.<sup>36</sup>

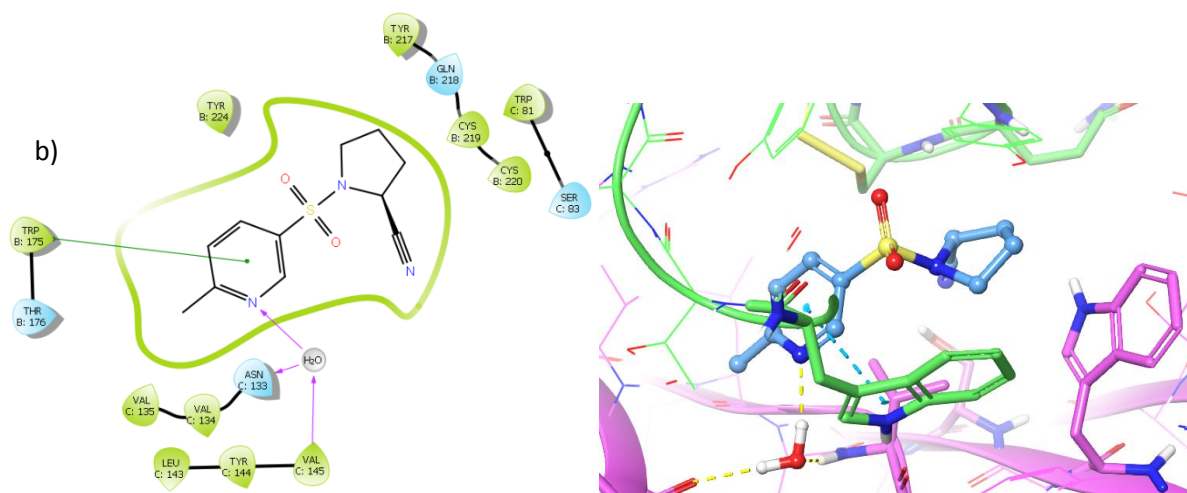
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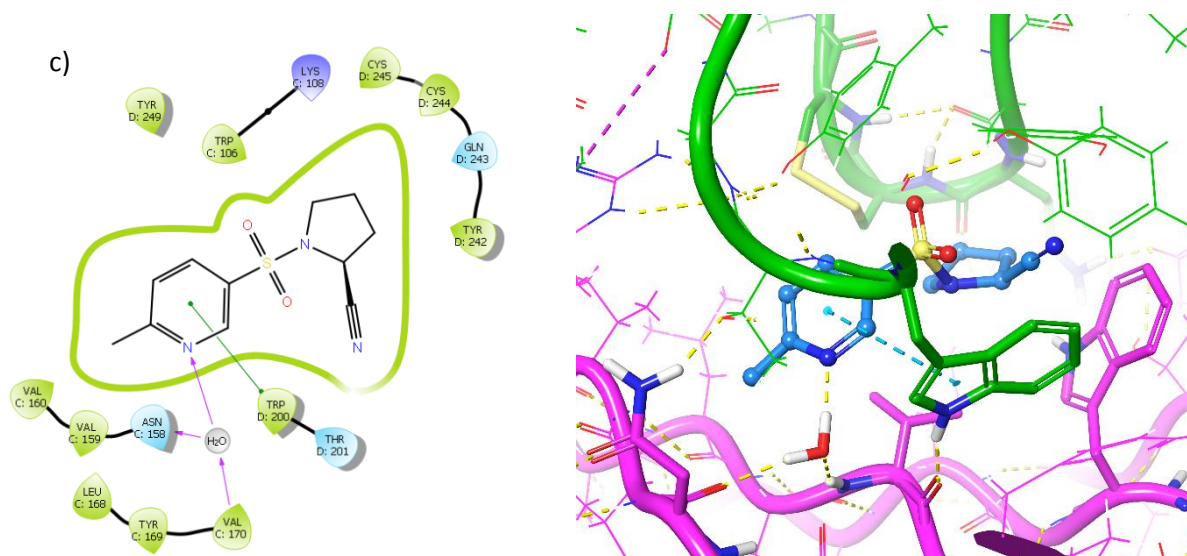




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138

139 **Figure 2.** (a) **M3** (*R*) and (*S*)-enantiomers chemical structures. 2D ligand interaction plots  
140 and 3D views of the interactions between the (*S*) enantiomer of **M3** (compound **3d**) and (b)  
141 cockroach  $\alpha 6$  nAChR or (c) honeybee  $\alpha 6$  nAChR.

142 From this analysis, no clear difference of interactions appeared therefore for the (*S*)  
143 enantiomer of **M3** for cockroach and honeybee  $\alpha 6$  nAChRs binding sites. In fact, a further  
144 examination of the interaction energies rationalizes its better affinity for  $\alpha 6$  cockroach  
145 nAChR. Indeed, table 2 shows that for the main amino acid residues involved in the binding  
146 and discussed above, the stabilization is significantly greater for cockroach  $\alpha 6$  nAChRs. The  
147 present molecular modeling results, validated by their good agreement with known

148 (experimental) structural features<sup>37</sup> for the interaction of nAChRs modulators and their target,  
149 are therefore promising for the insecticide activity of **M3** and its potential selectivity for pests.

150 **Table 2.** Interaction energies (kJ/mol) computed by the Glide program for the main  
151 components of the  $\alpha 6$  cockroach and honeybee nAChRs binding sites with the *S* enantiomer  
152 of **M3**. Docking scores (DS) and Glide energies (GE) (kJ/mol) are reminded for clarity.

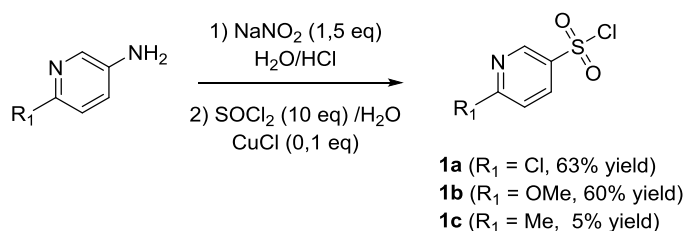
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		$\alpha 6$ cockroach nAChR model						
		Trp81	Val145	Trp175	Tyr217	Cys219	DS	GE
<b>M3</b>		-10.9	-21.3	-23.0	-20.1	-10.5	-25.5	-190.8
		$\alpha 6$ honeybee nAChR model						
<b>(S)</b>	Trp106	Val170	Trp200	Tyr242	Cys245	DS	GE	
	>0	-9.6	-18.8	-12.1	-8.4	-21.3	-117.6	

154

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

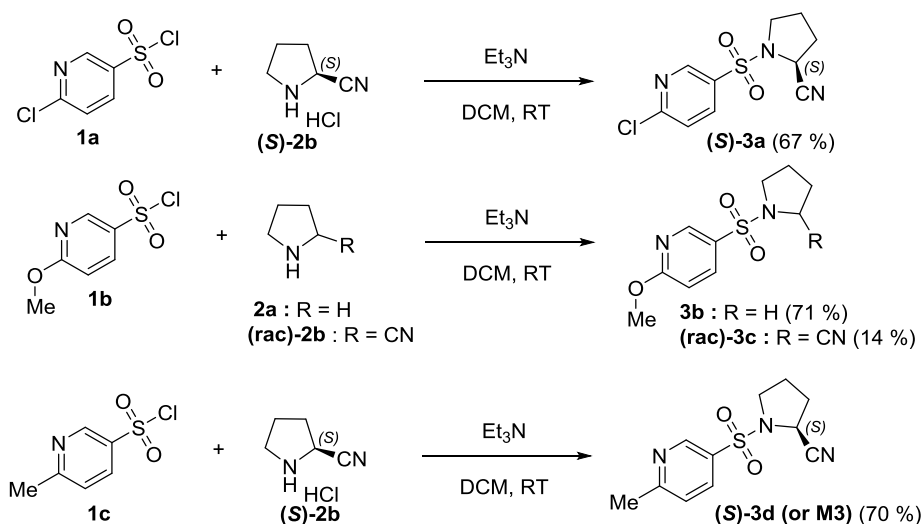
166 steps Sandmeyer-sulfonylation approach starting with 3-amino pyridines. This process was  
167 proved to work well with thionyl chloride in aqueous conditions and at low temperature.<sup>41</sup>  
168 Starting with commercial 3-amino-6-substituted pyridines, the targeted chlorosulfonyl  
169 reagents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



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

179 To access to the racemic 2-cyano pyrrolidine (Scheme 2, (**rac**)-**2b**, R = CN), some  
180 synthetic ways were proposed in the literature, such as the oxidation of pyrrolidine with  
181 aqueous sodium peroxodisulfate to furnish the corresponding trimer being hydrocyanated  
182 with HCN<sup>42</sup> or TMSCN.<sup>43</sup> Applying this last method we prepared racemic pyrrolidine (**rac**)-  
183 **2b** in 34% overall yield in two steps after purification by distillation.

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



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185

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

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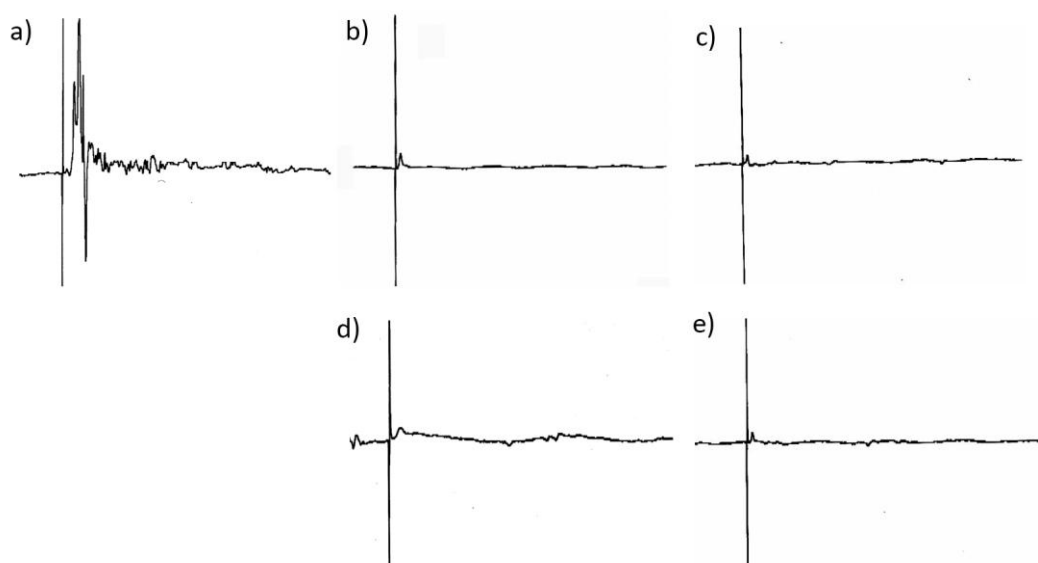
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These sulphonamide compounds **3** were then evaluated on the cholinergic synaptic transmission in cockroach *Periplaneta americana*. Experiments were performed on the cercal nerve giant interneuron synapses located within the cockroach sixth abdominal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

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

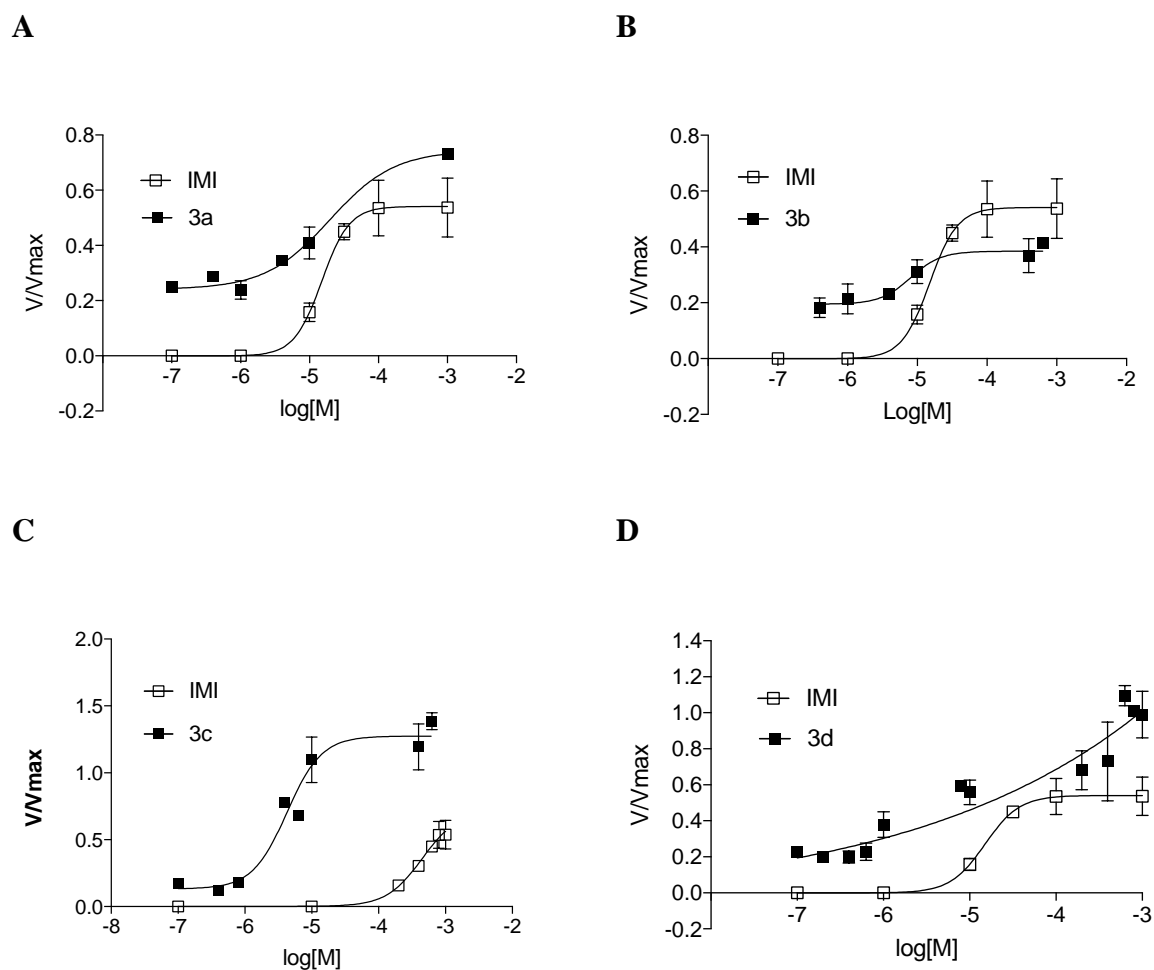


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203 **Figure 3.** Effect of 100  $\mu\text{M}$  of compounds **3a**, **3b**, **3c** and **3d** on electrical stimulations  
204 of the ipsilateral nerve XI. Stimulation of the nerve XI induces a EPSP (a: control condition)  
205 which is blocked under bath application of the four compounds (b: **3a**, c: **3b**, d: **3c** and e: **3d**)

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

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



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

214 The  $\text{EC}_{50}$  values for compounds **3a**, **3b** and **3c** were evaluated as 19  $\mu\text{M}$ , 8.02  $\mu\text{M}$  and  
215 4.25  $\mu\text{M}$  respectively. For compound **3d**, we were unable to determine the  $\text{EC}_{50}$  value. The 6-  
216 methoxy-pyridinyl sulfonamide compounds **3b** and **3c** as well as the 6-chloro analog **3a** gave  
217  $\text{EC}_{50}$  values in the same range. Thus, among this series, the most effective compounds  
218 appeared to be **3b** ( $\text{EC}_{50} = 8.02 \mu\text{M}$ ) and **3c** ( $\text{EC}_{50} = 4.25 \mu\text{M}$ ), bearing the methoxy  
219 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<sub>50</sub> value  
221 compared to **3b**. Then, 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

236 **Declaration of Competing Interest**

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

239

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245

246 **A. Supplementary data.**

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

250

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265 Supervision: Chemistry: M.M-A, J.L.; Electrophysiology: S.H.T.; Molecular Modeling: J.-

266 Y.L.Q.; A.L. J.G. Writing: J.-Y.L.Q., M.M.-A., B.S., S.H.T.J. G., A.L.; Experiments: B.S.,

267 E.L., A.C.

268

269 **References**

- 270 [1] Sparks, T. C.; Nauen, R., IRAC: Mode of action classification and insecticide resistance  
271 management. *Pestic. Biochem. Physiol.* **2015**, *121*, 122-128.
- 272 [2] Casida, J. E.; Neonicotinoids and Other Insect Nicotinic Receptor Competitive  
273 Modulators: Progress and Prospects. *Annu. Rev. Entomol.* **2018**, *63*, 125-144.  
274
- 275 [3] Moffat, C.; Buckland, S. T.; Samson, A. J.; McArthur, R.; Pino, V. C.; Bollan, K. A.; Huang, J.  
276 T. J.; Connolly, C. N., Neonicotinoids target distinct nicotinic acetylcholine receptors and  
277 neurons, leading to differential risks to bumblebees. *Sci. Rep.* **2016**, *6*.  
278
- 279 [4] a) Demortain, D., The science behind the ban: the outstanding impact of ecotoxicological  
280 research on the regulation of neonicotinoids. *Curr. Opin. Insect. Sci.* **2021**, *46*, 78–82.  
281
- 282 [5] a) Gross M., Bee worries beyond neonicotinoids. *Current Biology* *2018*, *28*, R1121–  
283 R1142. b) Watson, G. B. ; Siebert, M. W. ; Wang , N. X. ; Loso, M. R. ; Sparks, T. C.  
284 Sulfoxaflor – A sulfoximine insecticide: Review and analysis of mode of action, resistance and  
285 cross-resistance. *Pestic. Biochem. Physiol.* **2021**, *178*, 104924.  
286
- 287 [6] Zhang, X.; Yu, W.; Xu, X.; Shao, X. S.; Li, Z., Synthesis, crystal structure, and biological  
288 evaluation of a novel eight-membered dinitration neonicotinoid analogues. *Bioorg. Med.*  
289 *Chem. Lett.* **2021**, *43*, 127960.  
290
- 291 [7] El-Dean, A. M. K.; Abd-Ella, A. A.; Hassanien, R.; El-Sayed, M. E. A.; Abdel-Raheem, S. A.  
292 A., Design, Synthesis, Characterization, and Insecticidal Bioefficacy Screening of Some New  
293 Pyridine Derivatives. *ACS Omega* **2019**, *4*, 8406-8412.  
294
- 295 [8] Bora, A.; Suzuki, T.; Funar-Timofei, S., Neonicotinoid insecticide design: molecular  
296 docking, multiple chemometric approaches, and toxicity relationship with Cowpea aphids.  
297 *Environ. Sci. Pollut. Res.* **2019**, *26*, 14547-14561.  
298
- 299 [9] Chen, Y.; Cao, X.; Chen, X.; Li, Z.; Xu, X., The structure modification of seven-membered  
300 aza-brigded neonicotinoids in order to investigate their impact on honey bees. *J Chem Res.*  
301 **2021**, *45*, 835-844.  
302
- 303 [10] Zhang, X.; Wang, Y.; Xu, Z.; Shao, X.; Liu, Z.; Xu, X.; Maienfisch, P.; Li, Z., Design,  
304 Synthesis, and Synergistic Activity of Eight-Membered Oxabridge Neonicotinoid Analogues. *J.*  
305 *Agric. Food Chem.* **2021**, *69*, 3005-3014.  
306
- 307 [11] Taillebois, E.; Cartereau, A.; Graton, J.; Le Questel, J.-Y.; Lebreton, J.; Mathé-Allainmat,  
308 M.; Thany, S., Synergic effect of a quinuclidine benzamide complexed with borane, the  
309 LMA10233, in combination with seven pesticides *Pestic. Biochem. Physiol.* **2020**, *168*,  
310 104633.  
311
- 312 [12] Ondal, S. ; Malakar, S., Synthesis of sulfonamide and their synthetic and therapeutic  
313 applications: Recent advances. *Tetrahedron.* **2020**, *76*, 131662. b) Apaydin, S ; Török, M.

314 Sulfonamide derivatives as multi-target agents for complex diseases. *Bioorg. Med. Chem.*  
315 *Lett.* **2019**, *29*, 2042–2050. <https://doi.org/10.1016/j.bmcl.2019.06.041>.

316

317 [13] Devendar, P., Yang, GF. Sulfur-Containing Agrochemicals. *Top Curr. Chem. (Z)* **2017**, *375*,  
318 *82*. <https://doi.org/10.1007/s41061-017-0169-9>.

319

320 [14] a) Verma, S. K. ; Verma, R. ; Xue, F. ; Kumar Thakur, P. ; Girish , Y. R. ; d, Rakesh, K. P.  
321 Antibacterial activities of sulfonyl or sulfonamide containing heterocyclic derivatives and its  
322 structure-activity relationships (SAR) studies: A critical review. *Bioorg. Chem.* **2020**, *105*,  
323 104400. b) Shah, S. S. A.; Rivera, G.; Ashfaq, M., Recent Advances in Medicinal Chemistry of  
324 Sulfonamides. Rational Design as Anti-Tumoral, Anti-Bacterial and Anti-Inflammatory Agents.  
325 *Mini Rev. Med. Chem.* **2013**, *13*, 70-86.

326

327 [15] Scozzafava, A.; Owa, T.; Mastrolorenzo, A.; Supuran, C. T., Anticancer and antiviral  
328 sulfonamides. *Curr. Med. Chem.* **2003**, *10*, 925-953.

329

330 [16] Winum, J. Y.; Scozzafava, A.; Montero, J. L.; Supuran, C. T., Therapeutic potential of  
331 sulfamides as enzyme inhibitors. *Med. Res. Rev.* **2006**, *26*, 767-792. . b) Supuran, C. T.; Casini,  
332 A.; Scozzafava, A., Protease inhibitors of the sulfonamide type: Anticancer, antiinflammatory,  
333 and antiviral agents. *Med. Res. Rev.* **2003**, *23*, 535-558.

334

335 [17] Jain, P.; Saravanan, C.; Singh, S. K., Sulphonamides: Deserving class as MMP inhibitors?  
336 *Eur. J. Med. Chem.* **2013**, *60*, 89-100.

337

338 [18] Kosak, U.; Knez, D.; Coquelle, N.; Brus, B.; Pisljar, A.; Nachon, F.; Brazzolotto, X.; Kos, J.;  
339 Colletier, J. P.; Gobec, S., N-Propargylpiperidines with naphthalene-2-carboxamide or  
340 naphthalene-2-sulfonamide moieties: Potential multifunctional anti-Alzheimer's agents.  
341 *Bioorg. Med. Chem.* **2017**, *25*, 633-645.

342

343 [19] Sinha, N.; Karche, N. P.; Kalyan Verma, M.; Walunj, S. S.; Nigade, P. B.; Jana, G.;  
344 Kurhade, S. P.; Hajare, A. K.; Tilekar, A. R.; Jadhav, G. R.; Thube, B. R.; Shaikh, J. S.; Balgude,  
345 S.; Bikramjit Singh, L.; Mahimane, V.; Adurkar, S. K.; Hatnapure, G.; Raje, F.; Bhosale, Y.;  
346 Bhanage, D.; Sachchidanand, S.; Dixit, R.; Gupta, R.; Bokare, A. M.; Dandekar, M.; Bharne, A.;  
347 Chatterjee, M.; Desai, S.; Koul, S.; Modi, D.; Mehta, M.; Patil, V.; Singh, M.; Gundu, J.; Goel, R.  
348 N.; Shah, C.; Sharma, S.; Bakhle, D.; Kamboj, R. J.; Palle, V. P. Discovery of novel, potent,  
349 brain-permeable, and orally efficacious positive allosteric modulator of  $\alpha 7$  Nicotinic  
350 Acetylcholine receptor [4-(5-(4-Chlorophenyl)-4-methyl-2-propionylthiophen-3-  
351 yl)benzenesulfonamide]: Structure–Activity Relationship and preclinical characterization. *J.*  
352 *Med. Chem.* **2020**, *63*, 944–960.

353

354 [20] Hosokawa, A.; Katsurada, M.; Ikeda, O.; Minami, N.; Jikihara, T., Synthesis of optically  
355 active N-(2-pyridyloxiran-2-ylmethyl) benzenesulfonamide derivatives and their herbicidal  
356 activity. *Biosci. Biotechnol. Biochem.* **2001**, *65*, 1482-1488.

357

358 [21] Yang, G. F.; Liu, H. Y.; Yang, H. Z., QSAR and 3D-QSAR analysis of structurally diverse ALS  
359 inhibitors: sulfonylureas and triazolopyrimidine-2-sulfonamides. *Pestic. Sci.* **1999**, *55*, 1143-  
360 1150.

361  
362 [22] Gonzalez, M. A.; Gorman, D. B.; Hamilton, C. T.; Roth, G. A., Process development for  
363 the sulfonamide herbicide pyroxsulam. *Org. Process Res. Dev.* **2008**, *12*, 301-303.  
364  
365 [23] Satchivi, N. M.; deBoer, G. J.; Bell, J. L., Understanding the Differential Response of  
366 *Setaria viridis* L. (green foxtail) and *Setaria pumila* Poir. (yellow foxtail) to Pyroxsulam. . *J.*  
367 *Agric. Food Chem.* **2017**, *65*, 7328-7336.  
368  
369 [24] Soliman, N. N.; Abd El Salam, M.; Fadda, A. A.; Abdel-Motaal, M., Synthesis,  
370 Characterization, and Biochemical Impacts of Some New Bioactive Sulfonamide Thiazole  
371 Derivatives as Potential Insecticidal Agents against the Cotton Leafworm, *Spodoptera*  
372 *littoralis*. . *J. Agric. Food Chem.* **2020**, *68*, 5790-5805.  
373  
374 [25] Gang, F.; Li, X.; Yang, C.; Han, L.; Qian, H.; Wei, S.; Wu, W.; Zhang, J., Synthesis and  
375 Insecticidal Activity Evaluation of Virtually Screened Phenylsulfonamides. . *J. Agric. Food*  
376 *Chem.* **2020**, *68*, 11665-11671.  
377  
378 [26] Selvam, B.; Graton, J.; Laurent, A. D.; Alamiddine, Z.; Mathe-Allainmat, M.; Lebreton, J.;  
379 Coqueret, O.; Olivier, C.; Thany, S. H.; Le Questel, J.-Y., Imidacloprid and thiacloprid  
380 neonicotinoids bind more favourably to cockroach than to honeybee alpha 6 nicotinic  
381 acetylcholine receptor: Insights from computational studies. *J. Mol. Graph. Model.* **2015**, *55*,  
382 1-12.  
383  
384 [27] Hawkins, J. ; Mitchell, E. L ; Jones ; K. A. NACHO permits functional heterologous  
385 expression of an insect homomeric  $\alpha 6$  nicotinic acetylcholine receptor. *Pestic. Biochem.*  
386 *Physiol.* **2022**, *181* , 105030.  
387  
388 [28] Lu W.; Liu Z.; Fan X.; Zhang X.; Qiao X.; Huang J. Nicotinic acetylcholine receptor  
389 modulator insecticides act on diverse receptor subtypes with distinct subunit compositions.  
390 *PLoS Genet* **2022**, 18(1): e1009920. <https://doi.org/10.1371/journal.pgen.1009920>  
391  
392 [29] Blum, A. P.; Lester, H. A.; Dougherty, D. A., Nicotinic pharmacophore: The pyridine N of  
393 nicotine and carbonyl of acetylcholine hydrogen bond across a subunit interface to a  
394 backbone NH. *Proceedings of the National Academy of Sciences of the United States of*  
395 *America* **2010**, *107*, 13206-13211.  
396  
397 [30] Amiri, S.; Sansom, M. S. P.; Biggin, P. C., Molecular dynamics studies of AChBP with  
398 nicotine and carbamylcholine: the role of water in the binding pocket. *Protein Engineering*  
399 *Design & Selection* **2007**, *20*, 353-359.  
400  
401 [31] Sine, S. M. End-plate acetylcholine receptor : structure, mechanism, pharmacology, and  
402 disease. *Physiol. Rev.* **2012**, *92*, 1189-1234.  
403  
404 [32] Celie, P. H. N.; Van Rossum-Fikkert, S. E.; Van Dijk, W. J.; Brejc, K.; Smit, A. B.; Sixma, T.  
405 K., Nicotine and carbamylcholine binding to nicotinic acetylcholine receptors as studied in  
406 AChBP crystal structures. *Neuron* **2004**, *41*, 907-914.  
407

- 408 [33] Ceron-Carrasco, J. P.; Jacquemin, D.; Graton, J.; Thany, S.; Le Questel, J.-Y., New Insights  
409 on the Molecular Recognition of Imidacloprid with *Aplysia californica* AChBP: A  
410 Computational Study. *J. Phys. Chem. B* **2013**, *117*, 3944-3953.
- 411  
412 [34] Alamiddine, Z.; Thany, S.; Graton, J.; Le Questel, J. Y., Conformations and Binding  
413 Properties of Thiametoxam and Clothianidin Neonicotinoid Insecticides to Nicotinic  
414 Acetylcholine Receptors: The Contribution of sigma-Hole Interactions. *ChemPhysChem* **2018**,  
415 *19*, 3069-3083.
- 416  
417 [35] Alamiddine, Z.; Selvam, B.; Graton, J.; Laurent, A. D.; Landagaray, E.; Lebreton, J.;  
418 Mathé-Allainmat, M.; Thany, S. H.; Le Questel, J.-Y., Binding of Sulfoxaflor to *Aplysia*  
419 *californica*-AChBP: Computational Insights from Multiscale Approaches. *J. Chem. Inf. Model.*  
420 **2019**, *59*(9), 3755-3769.
- 421  
422 [36] Sparks, T. C.; Watson, G. B.; Loso, M. R.; Geng, C.; Babcock, J. M.; Thomas, J. D.  
423 Sulfoxaflor and the sulfoximine insecticides: Chemistry, mode of action and basis for efficacy  
424 on resistant insects. *Pestic. Biochem. Physiol.* **2013**, *107*, 1-7.
- 425  
426 [37] Talley, T. T.; Harel, M.; Hibbs, R. E.; Radic, Z.; Tomizawa, M.; Casida, J. E.; Taylor, P.  
427 Atomic Interactions of Neonicotinoid Agonists with AChBP: Molecular Recognition of the  
428 Distinctive Electronegative Pharmacophore. *Proc. Natl. Acad. Sci. U.S.A.* **2008**, *105*,  
429 7606-7611.
- 430  
431 [38] Maslankiewicz, A.; Marciniak, K.; Pawlowski, M.; Zajdel, P., From haloquinolines and  
432 halopyridines to quinoline- and pyridinesulfonyl chlorides and sulfonamides. *Heterocycles*  
433 **2007**, *71*, 1975-1990.
- 434  
435 [39] Pu, Y. M.; Christesen, A.; Ku, Y. Y., A simple and highly effective oxidative chlorination  
436 protocol for the preparation of arenesulfonyl chlorides. *Tetrahedron Lett.* **2010**, *51*, 418-421.
- 437  
438 [40] Woolven, H.; González-Rodríguez, C.; Marco, I.; Thompson, A. L.; Willis, M. C. DABCO-  
439 Bis(sulfur dioxide), DABSO, as a Convenient Source of Sulfur Dioxide for Organic Synthesis:  
440 Utility in Sulfonamide and Sulfamide Preparation. *Org. Lett.*, **2011**, *13*( 18 ), 4876-4878.
- 441  
442 [41] Hogan, P. J.; Cox, B. G., Aqueous Process Chemistry: The Preparation of Aryl Sulfonyl  
443 Chlorides. *Org. Process Res. Dev.* **2009**, *13*, 875-879.
- 444  
445 [42] De Kimpe, N. G.; Stevens, C. V.; Keppens, M. A., Synthesis of 2-acetyl-1-pyrroline, the  
446 principal rice flavor component. *J. Agric. Food Chem.* **1993**, *41*, 1458-1461.
- 447  
448 [43] Köhler, V.; Bailey, K. R.; Znabet, A.; Raftery, J.; Helliwell, M.; Turner, N. J.,  
449 Enantioselective Biocatalytic Oxidative Desymmetrization of Substituted Pyrrolidines.  
450 *Angew. Chem. Int. Ed.* **2010**, *49*, 2182-2184.
- 451  
452 [44] Seong-Mook Kang a, Ky-Youb Namb, Seung-Youn Jung a, Kyung-Hee Song a, Seongho  
453 Kho a, Kyoung Tai No c, Hyun Kyung Choi d,†,y, Jie-Young Song . Inhibition of cancer cell

454 invasion by new ((3,4-dihydroxy benzylidene)hydrazinyl)pyridine-3-sulfonamide analogs.  
455 *Bioorg. Med. Chem. Lett.* **2016**, *26*, 1322–1328.

456

457 [45] Callec, J. J.; Sattelle, D. B., A simple technique for monitoring the synaptic actions of  
458 pharmacological agents. *J. Exp. Biol.* **1973**, *59*, 725-38.

459

460 [46] Buckingham, S. D.; Lapied, B.; LeCorronc, H.; Grolleau, F.; Sattelle, D. B., Imidacloprid  
461 actions on insect neuronal acetylcholine receptors. *J. Exp. Biol.* **1997**, *200*, 2685-2692.

462

463 [47] Thany, S. H., Agonist actions of clothianidin on synaptic and extrasynaptic nicotinic  
464 acetylcholine receptors expressed on cockroach sixth abdominal ganglion. *Neurotoxicology*  
465 **2009**, *30*, 1045-1052.

466

467

468

469

470

471

472

473

474

475