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## LuxR-dependent quorum sensing: Computer aided discovery of new inhibitors structurally unrelated to *N*-acylhomoserine lactones

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## ABSTRACT

A virtual screening, involving flexible docking sequences within the LuxR, TraR and LasR binding sites, was used as a structural binding sites similarity filter to specifically target conserved residues in the proteins of the LuxR family (namely Tyr62, Trp66, Tyr70, Asp79, Trp94 for LuxR). This docking-based screening, employing a genetic algorithm, was performed on a 2344 chemical compounds library, together with empirical binding free energy ( $\Delta G_{\text{bind}}$ ) calculations. Docking results were analysed, and the compounds detected with reproducible low  $\Delta G_{\text{bind}}$  values or identified as being in the top 120 for most of the docking sequences, were selected as hits candidates which interact with conserved residues. Biological evaluation with LuxR-dependent quorum sensing led to the discovery of some new inhibitors, namely tamoxifen, sertraline, pimethixene, terfenadine, fendiline and calmidazolium. Notably, calmidazolium was identified as one of the most potent AHL-structurally unrelated inhibitors of LuxR-dependent quorum sensing, with an  $IC_{50}$  value of  $7.0 \pm 0.2 \mu\text{M}$ .

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Bacteria are able to communicate with each other using a specific system called 'Quorum Sensing' (QS). This cell to cell communication system is based on the correlation between population size and the concentration of small diffusible chemical messengers called autoinducers. When a critical concentration is reached, target genes encoding for phenotypes such as bioluminescence, biofilm formation or virulence are expressed allowing bacteria to adapt their behaviour to their environment.<sup>1–6</sup> Consequently, QS is now targeted for the design of potential antibacterial drugs.<sup>7–10</sup> In Gram negative bacteria, quorum sensing involves *N*-acyl homoserine lactones (AHLs) as autoinducers, associated with transcriptional regulators belonging to proteins of the LuxR family. Most studies describing the discovery of LuxR-protein antagonists are based on the rational design of AHL analogues or on biological screenings of compound libraries.<sup>11</sup> To date, in silico screening of ligand databases, which has become a key methodology in drug discovery,<sup>12–15</sup> has been only moderately employed to discover new QS inhibitors,<sup>16–18</sup> especially using LuxR-type proteins. In 2008, Zeng et al. reported the virtual screening of active compounds from Traditional Chinese Medicines with antibacterial activity using docking simulations and the TraR protein.<sup>19</sup> More recently, Yang et al. described an interesting study involving docking-based virtual screening, within the binding site of LasR, using structural alignment

with the natural ligand, 3-oxo- $C_{12}$ -HSL which led to the discovery of new antagonists, namely salicylic acid, nifuroxazide, and chlorzoxazone.<sup>20</sup>

As a part of our research programme, aimed at discovering potential modulators of the AHLs-dependent transcriptional regulators,<sup>21–23</sup> we describe here a virtual screening using a genetic algorithm and involving flexible docking sequences within the LuxR, TraR and LasR binding sites. This protocol was used as a structural binding sites similarity filter to specifically target conserved residues in the LuxR-proteins. Indeed, as shown in other studies,<sup>24,25</sup> agonistic or antagonistic activities are related to the interactions of ligands with the conserved residues (namely Tyr62, Trp66, Tyr70, Asp79, Trp94 for LuxR). Thus, four docking sequences for each protein were performed then analysed in order to select compounds that target specifically these residues due to structural homology.

The docking-based virtual screening, employing a genetic algorithm (GADock)<sup>26–28</sup> which randomly generates conformations within a binding site, was performed with 2344 biologically relevant compounds from the ChEMBL subset chemical library of Ligand.Info Meta-Database.<sup>14,29,30</sup> ChEMBL was, in fact, created for the discovery of small molecules that modulate specific biological pathways using a chemical genetics approach.<sup>31,32</sup> Among the 2344 structures, 2289 compounds<sup>33</sup> were docked within a binding site and ranked, according to the binding free energy calculations ( $\Delta G_{\text{bind}}$ ),<sup>28</sup> resulting in one docking sequence. Subsequently, with reference to four docking sequences within each binding site of LuxR, TraR and LasR (12 sequences, 27468 docking experiments),

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all the docking results were analysed as follows: (i) compounds detected with reproducible low  $\Delta G_{\text{bind}}$  values and high ranks were selected; (ii) like manolide, known to be a QS inhibitor<sup>34</sup> and identified six times in the top 120, compounds detected at least seven times in the top 120 (according to the docking sequences) were selected and identified as potential hit candidates targeting conserved residues (Fig. 1).

Some of the hit candidates can be classified according to their biological activity, with lipids arising from the arachidonic acid cascade (leukotriene or prostaglandin derived compounds), vitamin A derived compounds, vitamin A derived compounds, steroid hormones ( $\beta$ -estradiol or progesterone derived compounds), and several compounds known as calcium channel modulators (vitamin D3 derived compounds, flu-

narizine, cinnarizine, fendiline, calmidazolium and torasemide). Finally, clofocetol, tamoxifen, mitotane, sertraline, pimethixene, fenvalerate, terfenadine and manolide were also identified. It was interesting to note that some potential QS modulators are related to hormones or to calcium channel modulators, suggesting a possible bacteria-host cross-talk as already proposed in the literature.<sup>35,36</sup> Interestingly, manolide has also been reported as being a calcium channel inhibitor.<sup>37</sup> In addition, AHLs have been shown to modulate host cell responses through calcium signalling.<sup>38</sup> Natural AHL ligands (3-oxo-C<sub>6</sub>-, 3-oxo-C<sub>8</sub>-, 3-oxo-C<sub>12</sub>-HSL) were not selected by this screening protocol, although a consistent influence of the size of the hydrophobic acyl chain on the  $\Delta G_{\text{bind}}$  values was observed, with better affinity when increasing the chain length,

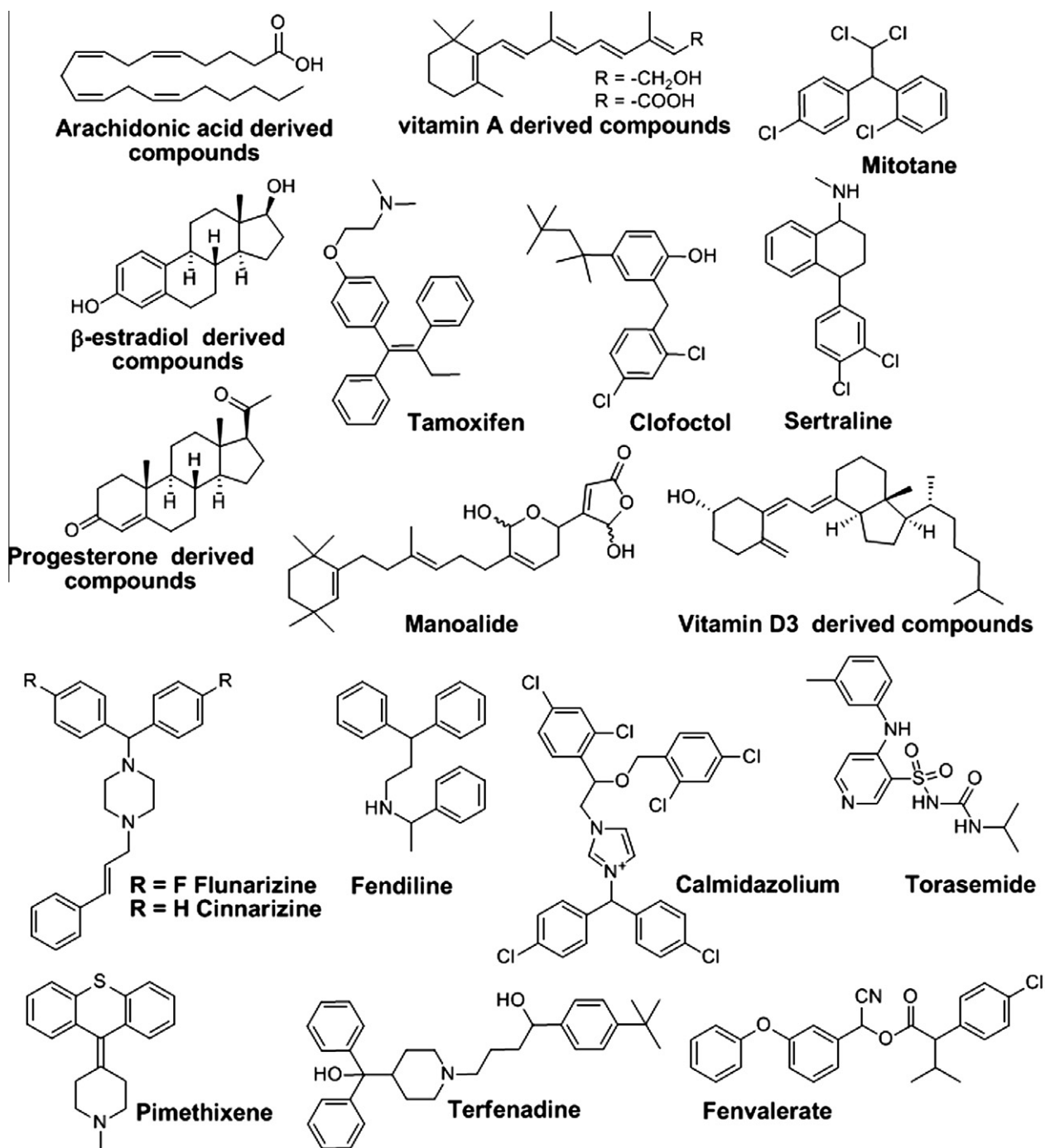


Figure 1. Structures of compounds identified as hit candidates.

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