Virtual Screening of Fargesin Analogs as Candidates as Inhibitors of Aedes aegypti Sterol Carrier Protein

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ABSTRACT

Background: Fargesin is a natural product that was identified by our group in previous work as a potent ligand of the sterol-binding protein-2 (SCP-2) of Aedes aegypti, the mosquito that causes the propagation of diseases such as zika, dengue, Chikungunya, and yellow fever. Objectives: propose structural analogs synthetically accessible to be evaluated by molecular docking, preserving the fargesin privileged group’s benzdioxol and methoxybenzene, with different spacer groups. Materials and Methods: Structures were obtained in PubChem® and SciFinder® databases, in .sdf format. Chemical structures were converted to pdbqt format by the OpenBabel GUI® program. Macromolecular target SCP-2 (PDB ID: 1PZ4) was extracted from the RSCB-PDB® platform, and molecular docking was performed using the Autodock vina program. The target binding site was defined based on the crystallographic ligand (palmitic acid), with grid box dimensions 16x12x18 Å. Results: The database built had 1231 molecules, with molecules that had binding energy lower than -6.9 Kcal/mol considered valid results. Thus, of the 447 molecules that were most favorable, the best results were for the compounds: 188 (-12.6 Kcal/mol), 350 (-12.6 Kcal/mol), 351 (-12.3 Kcal/mol), 773 (-12.3 Kcal/mol) and 831 (-12.1 Kcal/mol). Conclusion: The results of this paper showed that isoflavonoids synthetically accessible are promising candidates for larvicial agents, which corroborates with other published data from our research group and encourages experimental investigations.

Key words: Aedes aegypti, Fargesin, Isoflavonoids, Molecular docking, Synthetic Analogs.

INTRODUCTION

Every year more than one million people die from vector-borne diseases, of which mosquito-borne diseases represent a significant proportion. One of the most important vectors that transmit diseases is the Aedes aegypti mosquito, which causes the propagation of diseases such as zika, dengue, Chikungunya, and yellow fever. Given that a single mosquito is the primary vector of multiple human diseases, the development of new strategies for mosquito control is crucial. The most common way to combat the mosquito is with insecticides. However, they are toxic to humans and the environment. Another concern about chemical agents is the increasing resistance of the mosquito vector. In this context, natural products, especially secondary metabolites, have emerged as agents that are generally safer for humans and that generate fewer residues in the environment.

In a previous work of our laboratory, we investigated the affinity of 248 secondary metabolites of plants from the Caatinga Biome as potential ligands of Steroid Carrier Protein-2 (SCP-2) from Aedes aegypti. Among the highlighted compounds, we identified Fargesin, a compound with multiple pharmacological activities, including attenuation of oxidative stress and anti-inflammatory activity in monocyte cells, increase in basal glucose uptake by translocating Insulin-Sensitive Glucose Transporter (GLUT4), antihypertensive activity, inhibition of melanin synthesis, and antitrypanosomal activity. Fargesin belongs to the class of lignans (also known as neolignans). Lignans are found in plants of Aristolochia genus popularly known as “mil-homens” or “jarrinha”; and in plants of Magnolia genus commonly known as “pinha – do – brejo” or “baguacu”.

This metabolite is derived from the oxidative coupling of two phenylpropanoid units and propenylphenols (isoegenol and coniferyl alcohol), with regiospecific and diasterospecific control. Different monomeric precursors generate new subgroups of lignans by cyclization or modifications in the carbon skeleton, resulting in a wide variety of substances. Within these subclasses, Fargesin is classified as furanic lignan, characterized by a benzdioxol ring, bonded to a linker structure of furanoid rings bonded to dimethoxybenzene (Figure 1).
Molecular docking

Before MD, redocking (RDK) was conducted with the co-crystallographic ligand to determine the accuracy of the docking procedure. All calculations were performed with the Autodock® Vina module. The grid box dimensions chosen were 16x12x18Å, centered on the ligand and with the standard spacing of 1Å between the internal grid points. The same parameters previously described were applied to the docking of the 1231 synthetic analogs of Fargesin. The 3D images and diagrams were generated with the free module of the Schrödinger Maestro software (Maestro, Schrödinger, LLC, New York, NY, 2021).

RESULTS AND DISCUSSION

After searches in PubChem® and SciFinder®, 1231 Fargesin analogs were extracted and tested on the Aedes aegypti sterol-binding protein. Table 1 shows the compounds that had energy lower than -6.9 Kcal/mol, totaling 447 favorable compounds. Table 1 also shows the redocking (RDK) result. It was found that molecules 188, 350, 351, 773, and 831 had an excellent interaction with the protein, achieving binding energy almost twice as stable as RDK and with very slight energy variation between each other. In other words, binding energies had close values. This study aims to discuss the best five molecules.

Of the compounds that stabilized the protein, with energies from -12 kcal/mol, three are synthetic isoflavonoids, like molecules 188, named (2-methyl-4-oxo-3-phenylchromen-7-yl)-1,3-benzodioxol-5-carboxylate; 350, named [3-(4-methoxyphenoxyl)-2-methyl-4-oxochromen-7-yl]-1,3-benzodioxol-5-carboxylate; and 351, named [3-(4-methoxyphenyl)-4-oxochromen-7-yl]-1,3-benzodioxol-5-carboxylate. All molecules are analogous to each other. The structures of these compounds are formed by a benzodioxol ring linked by the ester function to the chromone ring, linked to the methoxybenzene ring. For molecule 188, only the benzene ring has no substituent (Figure 2).

The isoflavonoids contain a methoxyl group at the “para” position of the ring B. Compounds 188, 350, and 351 are derived from 7-hydroxy-4-methoxyflavone, a naturally occurring isoflavonoid known as Formononetin, found in legumes. The molecules are obtained through the alcoholysis reaction, where Formononetin participates as a reagent and thereby forms analogous and biosynthetic molecules. Formononetin derivatives are widely studied because they can reverse multidrug resistance by inhibiting the efflux pump. Furthermore, also have antihypertensive, anti-parasitic, breast and prostate cancer, and antioxidant activity.

Figure 3 shows molecules 188, 350, 351 and their interactions. Note that in all three molecules, the carboxylate group, which binds the benzodioxol group to the chromone ring, interacts with the same amino acids as the native ligand in the main chain, which are Valine 26 (Val 26), Glycine 25 (Gln 25), and Arginine 24 (Arg 24). These interactions occur through hydrogen bonds, represented by the pink arrow in the 2D diagram. Besides the hydrogen bond with these amino acid residues, there is another hydrogen bond between Arg 15 and the oxygen of benzodioxol.

Molecule 773, namely 3-[(E)-3-(1,3-benzodioxol-5-yl)prop-2-enoyl]-7-[(3-methoxyphenyl)methoxy]chromen-2-one belongs to the class of polyoxygenated cinnamoylcoumarins. This class is derived from curcumin, which is obtained through the synthetic route with hydroxysalicylaldehyde as a reagent. Like other molecules discussed, cinnamoylcoumarins have biological importance. Resembling curcumin, they possess antioxidant properties, as well as cytotoxic and anticancer effects.

Structurally, molecule 773 has a methoxyl at the “ortho” position of ring A. It can also be observed that between the benzodioxol ring and the...
**Table 1: Binding energy of compounds for larvicidal activity in ascending order.**

| Compounds | Binding Energy | Compounds | Binding Energy | Compounds | Binding Energy | Compounds | Binding Energy | Compounds | Binding Energy |
|-----------|----------------|-----------|----------------|-----------|----------------|-----------|----------------|-----------|----------------|
| 188       | −12.6          | 1209      | −10            | 1113      | −9.5           | 25        | −9.1           |
| 350       | −12.6          | 108       | −10            | 5         | −9.4           | 379       | −9.1           |
| 351       | −12.3          | 862       | −10            | 100       | −9.4           | 21        | −9             |
| 773       | −12.3          | 932       | −10            | 576       | −9.4           | 66        | −9             |
| 831       | −12.1          | 74        | −10            | 836       | −9.4           | 858       | −9             |
| 1074      | −11.9          | 579       | −10            | 1095      | −9.4           | 1089      | −9             |
| 346       | −11.9          | 586       | −10            | 1103      | −9.4           | 1102      | −9             |
| 349       | −11.6          | 1225      | −10            | 102       | −9.4           | 464       | −9             |
| 347       | −11.6          | 200       | −10            | 105       | −9.4           | 1138      | −9             |
| 494       | −11.5          | 631       | −10            | 225       | −9.4           | 1159      | −9             |
| 343       | −11.5          | 308       | −9.9           | 1116      | −9.4           | 71        | −9             |
| 495       | −11.5          | 1112      | −9.9           | 1171      | −9.4           | 465       | −9             |
| 348       | −11.4          | 209       | −9.9           | 337       | −9.4           | 502       | −9             |
| 492       | −11.4          | 973       | −9.9           | 972       | −9.4           | 868       | −9             |
| 493       | −11.4          | 967       | −9.9           | 135       | −9.4           | 848       | −9             |
| 826       | −11.4          | 298       | −9.8           | 210       | −9.4           | 1087      | −8.9           |
| 827       | −11.2          | 1134      | −9.8           | 333       | −9.4           | 259       | −8.9           |
| 876       | −11.2          | 104       | −9.8           | 977       | −9.4           | 267       | −8.9           |
| 341       | −11.1          | 1158      | −9.8           | 1155      | −9.3           | 854       | −8.9           |
| 884       | −11.1          | 578       | −9.8           | 1184      | −9.3           | 1090      | −8.9           |
| 345       | −11            | 761       | −9.8           | 487       | −9.3           | 340       | −8.9           |
| 218       | −10.9          | 901       | −9.8           | 1083      | −9.3           | 256       | −8.9           |
| 1114      | −10.8          | 1172      | −9.8           | 1108      | −9.3           | 352       | −8.9           |
| 1210      | −10.7          | 70        | −9.8           | 1161      | −9.3           | 463       | −8.9           |
| 344       | −10.7          | 299       | −9.8           | 136       | −9.3           | 54        | −8.9           |
| 49        | −10.7          | 602       | −9.7           | 270       | −9.3           | 941       | −8.9           |
| 69        | −10.6          | 1198      | −9.7           | 863       | −9.3           | 58        | −8.8           |
| 226       | −10.6          | 4         | −9.7           | 364       | −9.3           | 197       | −8.8           |
| 886       | −10.6          | 331       | −9.7           | 875       | −9.3           | 593       | −8.8           |
| 60        | −10.6          | 353       | −9.7           | 1104      | −9.3           | 22        | −8.8           |
| 292       | −10.5          | 101       | −9.7           | 1186      | −9.3           | 186       | −8.8           |
| 885       | −10.5          | 1107      | −9.7           | 568       | −9.3           | 1091      | −8.8           |
| 839       | −10.5          | 1132      | −9.7           | 570       | −9.3           | 1196      | −8.8           |
| 913       | −10.5          | 466       | −9.7           | 823       | −9.3           | 470       | −8.8           |
| 971       | −10.5          | 542       | −9.7           | 1109      | −9.2           | 1094      | −8.8           |
| 758       | −10.5          | 604       | −9.7           | 1174      | −9.2           | 1111      | −8.8           |
| 802       | −10.5          | 207       | −9.6           | 296       | −9.2           | 1131      | −8.8           |
| 1224      | −10.5          | 1115      | −9.6           | 594       | −9.2           | 205       | −8.8           |
| 1092      | −10.4          | 65        | −9.6           | 824       | −9.2           | 61        | −8.8           |
| 1147      | −10.4          | 222       | −9.6           | 187       | −9.2           | 380       | −8.8           |
| 805       | −10.4          | 307       | −9.6           | 467       | −9.2           | 1099      | −8.8           |
| 227       | −10.4          | 1117      | −9.6           | 1148      | −9.2           | 835       | −8.8           |
| 220       | −10.3          | 1178      | −9.6           | 1223      | −9.2           | 1170      | −8.7           |
| 910       | −10.3          | 1017      | −9.6           | 960       | −9.2           | 193       | −8.7           |
| 837       | −10.3          | 680       | −9.6           | 80        | −9.1           | 272       | −8.7           |
| 216       | −10.2          | 297       | −9.6           | 120       | −9.1           | 497       | −8.7           |

continued...
**Table 1: Binding energy of compounds for larvicidal activity in ascending order.**

| Compounds | Binding Energy | Compounds | Binding Energy | Compounds | Binding Energy | Compounds | Binding Energy |
|-----------|----------------|-----------|----------------|-----------|----------------|-----------|----------------|
| 342       | −10.2          | 249       | −9.6           | 756       | −9.1           | 591       | −8.7           |
| 630       | −10.2          | 489       | −9.6           | 909       | −9.1           | 1088      | −8.7           |
| 911       | −10.2          | 23        | −9.5           | 1097      | −9.1           | 1133      | −8.7           |
| 905       | −10.2          | 223       | −9.5           | 1110      | −9.1           | 1140      | −8.7           |
| 801       | −10.1          | 262       | −9.5           | 1143      | −9.1           | 1151      | −8.7           |
| 48        | −10.1          | 853       | −9.5           | 861       | −9.1           | 119       | −8.7           |
| 613       | −10.1          | 933       | −9.5           | 969       | −9.1           | 334       | −8.7           |
| 1197      | −10.1          | 1192      | −9.5           | 945       | −9.1           | 469       | −8.7           |
| 587       | −10.1          | 263       | −9.5           | 45        | −9.1           | 1093      | −8.7           |
| 621       | −10.1          | 850       | −9.5           | 596       | −9.1           | 1229      | −8.7           |
| 759       | −10.1          | 68        | −9.5           | 757       | −9.1           | 675       | −8.7           |
| 198       | −10            | 566       | −9.5           | 951       | −9.1           | 772       | −8.7           |
| 946       | −10            | 683       | −9.5           | 24        | −9.1           | 255       | −8.7           |
| 301       | −8.7           | 503       | −8.2           | 1105      | −7.8           | 1010      | −7.4           |
| 940       | −8.7           | 1176      | −8.2           | 673       | −7.8           | 797       | −7.4           |
| 770       | −8.7           | 931       | −8.2           | 845       | −7.8           | 1185      | −7.4           |
| 460       | −8.6           | 950       | −8.2           | 1080      | −7.8           | 27        | −7.3           |
| 605       | −8.6           | 1213      | −8.2           | 1218      | −7.8           | 63        | −7.3           |
| 1018      | −8.6           | 851       | −8.2           | 72        | −7.8           | 1165      | −7.3           |
| 1100      | −8.6           | 295       | −8.2           | 461       | −7.8           | 874       | −7.3           |
| 1157      | −8.6           | 871       | −8.2           | 974       | −7.8           | 483       | −7.3           |
| 1211      | −8.6           | 1205      | −8.2           | 33        | −7.8           | 26        | −7.3           |
| 219       | −8.6           | 62        | −8.2           | 484       | −7.8           | 90        | −7.3           |
| 475       | −8.6           | 224       | −8.2           | 903       | −7.8           | 804       | −7.3           |
| 926       | −8.6           | 112       | −8.1           | 269       | −7.7           | 206       | −7.2           |
| 253       | −8.6           | 251       | −8.1           | 1230      | −7.7           | 355       | −7.2           |
| 288       | −8.6           | 284       | −8.1           | 592       | −7.7           | 1141      | −7.2           |
| 332       | −8.6           | 760       | −8.1           | 796       | −7.7           | 1189      | −7.2           |
| 366       | −8.6           | 829       | −8.1           | 1154      | −7.7           | 73        | −7.2           |
| 462       | −8.6           | 968       | −8.1           | 28        | −7.7           | 324       | −7.2           |
| 509       | −8.6           | 975       | −8.1           | 211       | −7.7           | 603       | −7.2           |
| 679       | −8.6           | 1187      | −8.1           | 300       | −7.7           | 91        | −7.2           |
| 995       | −8.6           | 1188      | −8.1           | 869       | −7.7           | 252       | −7.2           |
| 1177      | −8.6           | 1220      | −8.1           | 359       | −7.7           | 258       | −7.1           |
| 89        | −8.6           | 319       | −8.1           | 970       | −7.7           | 552       | −7.1           |
| 476       | −8.5           | 922       | −8.1           | 928       | −7.6           | 734       | −7.1           |
| 477       | −8.5           | 1217      | −8.1           | 31        | −7.6           | 1208      | −7.1           |
| 486       | −8.5           | 38        | −8.1           | 283       | −7.6           | 32        | −7.1           |
| 852       | −8.5           | 1164      | −8.1           | 287       | −7.6           | 1144      | −7            |
| 1145      | −8.5           | 870       | −8.1           | 488       | −7.6           | 325       | −7            |
| 1181      | −8.5           | 185       | −8             | 677       | −7.6           | 1160      | −7            |
| 257       | −8.5           | 678       | −8             | 887       | −7.6           | 474       | −7            |
| 481       | −8.5           | 116       | −8             | 260       | −7.6           | 1135      | −7            |
| 367       | −8.5           | 681       | −8             | 261       | −7.6           | 271       | −7            |
| 457       | −8.5           | 763       | −8             | 930       | −7.6           | 762       | −7            |
| 828       | −8.5           | 766       | −8             | 1012      | −7.6           | 285       | −7            |

continued...
Table 1: Binding energy of compounds for larvicidal activity in ascending order.

| Compounds | Binding Energy | Compounds | Binding Energy | Compounds | Binding Energy | Compounds | Binding Energy |
|-----------|----------------|-----------|----------------|-----------|----------------|-----------|----------------|
| 840       | -8.5           | 956       | -8             | 378       | -7.6           | 739       | -7            |
| 976       | -8.5           | 291       | -8             | 1146      | -7.6           | RDK       | -6.9          |
| 111       | -8.4           | 774       | -8             | 40        | -7.6           |           |               |
| 328       | -8.4           | 1204      | -8             | 67        | -7.6           |           |               |
| 29        | -8.4           | 290       | -8             | 268       | -7.6           |           |               |
| 468       | -8.4           | 597       | -8             | 771       | -7.6           |           |               |
| 819       | -8.4           | 855       | -8             | 866       | -7.6           |           |               |
| 920       | -8.4           | 316       | -7.9           | 1190      | -7.6           |           |               |
| 264       | -8.4           | 814       | -7.9           | 1126      | -7.5           |           |               |
| 265       | -8.4           | 856       | -7.9           | 228       | -7.5           |           |               |
| 480       | -8.4           | 999       | -7.9           | 479       | -7.5           |           |               |
| 201       | -8.4           | 1096      | -7.9           | 872       | -7.5           |           |               |
| 310       | -8.4           | 929       | -7.9           | 959       | -7.5           |           |               |
| 441       | -8.4           | 1153      | -7.9           | 1162      | -7.5           |           |               |
| 849       | -8.3           | 86        | -7.9           | 952       | -7.5           |           |               |
| 1098      | -8.3           | 590       | -7.9           | 1231      | -7.5           |           |               |
| 322       | -8.3           | 64        | -7.9           | 36        | -7.5           |           |               |
| 1180      | -8.3           | 302       | -7.9           | 966       | -7.5           |           |               |
| 674       | -8.3           | 599       | -7.9           | 670       | -7.5           |           |               |
| 82        | -8.3           | 859       | -7.9           | 245       | -7.4           |           |               |
| 458       | -8.3           | 1169      | -7.9           | 182       | -7.4           |           |               |
| 944       | -8.3           | 1221      | -7.9           | 273       | -7.4           |           |               |
| 459       | -8.3           | 908       | -7.9           | 309       | -7.4           |           |               |
| 1101      | -8.2           | 834       | -7.8           | 701       | -7.4           |           |               |
| 846       | -8.2           | 294       | -7.8           | 765       | -7.4           |           |               |
| 1106      | -8.2           | 755       | -7.8           | 842       | -7.4           |           |               |

Binding energies are represented in kcal/mol. RDK: roeking.

Figure 2: Compounds 188 (A), 350 (B) and 351 (C) in 2D and complexed with 1PZ4.

Figure 3: Molecules 188 (A), 350 (B) e 351 (C) interacting with amino acid residues in the protein. In green pi-cation-type bond, in yellow hydrogen bond, in cyan aromatic.
CONCLUSION

In this paper, we evidenciated natural product analogs with potential against *Aedes aegypti* mosquitoes. Among the most stable compounds evaluated by dockings, the results emphasizes the isoflavonoid class as the best potential to interruption of the mosquito’s life cycle. The synthetic obtention of these analogs has a simpler methodology and the reagents used are economically accessible, making them promising candidates for Sterol Carrier Protein-2 inhibition. Therefore, this work encourages the experimental evaluation of formononetin and analogs.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

SCP-2: Steroid Carrier Protein-2; GLUT4: Insulin-Sensitive Glucose Transporter; MD: molecular docking; RDK: redocking.

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