Supplementary materials

Network Toxicology and Molecular Docking to Investigate the non-AChE Mechanisms of Organophosphate-Induced   
Neurodevelopmental Toxicity

Juliana Alves da Costa Ribeiro Souza1,2, Terezinha Souza2, Isadora Louise Alves da Costa Ribeiro Quintans3 and Davi Farias1,2 \*

**Table S1.** - Topological measurements of nodes in the PPI network of diazinon oxon-induced developmental neurotoxicity.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Protein** | **Node** | **k** | **Clustering Coefficient** | **BC** | **ASPL** | **CC** |
|  |  |  |  |  |  |  |
| Epidermal growth factor receptor | EGFR | 14 | 0.1648 | 0.2748 | 2.1429 | 0.4667 |
| Proto-oncogene tyrosine kinase SRC | SRC | 13 | 0.2179 | 0.1544 | 2.2857 | 0.4375 |
| Heat shock protein HSP 90-alpha | HSP90AA1 | 11 | 0.1091 | 0.1543 | 2.4286 | 0.4118 |
| Histone acetyltransferase p300 | EP300 | 9 | 0.0278 | 0.3026 | 2.4898 | 0.4016 |
| Phosphatidylinositol 3-kinase regulatory subunit alpha | PIK3R1 | 9 | 0.2500 | 0.2378 | 2.4082 | 0.4153 |
| **Signal transducer and activator of transcription 3** | STAT3 | 8 | 0.1786 | 0.1418 | 2.3265 | 0.4298 |
| Estrogen receptor | ESR1 | 7 | 0.1905 | 0.2018 | 2.2449 | 0.4455 |
| Calmodulin-1 | CALM1 | 7 | 0.0000 | 0.1683 | 2.6531 | 0.3769 |
| Tyrosine-protein phosphatase non-receptor type 11 | PTPN11 | 7 | 0.4286 | 0.0164 | 2.7143 | 0.3684 |
| Insulin-like growth factor 1 receptor | IGF1R | 6 | 0.1333 | 0.0556 | 2.5918 | 0.3858 |
| Mitogen-activated protein kinase1 | MAPK1 | 6 | 0.2000 | 0.0520 | 3.0612 | 0.3267 |
| Signal transducer and activator of transcription 1-alpha/beta | STAT1 | 5 | 0.5000 | 0.0375 | 2.4694 | 0.4050 |
| Presenilin | PSEN1 | 4 | 0.5000 | 0.5333 | 1.3333 | 0.7500 |
| Nicastrin | NCSTN | 4 | 0.8333 | 0.0667 | 1.5000 | 0.6667 |
| Gamma-secretase subunit APH-1A | APH1A | 4 | 0.8333 | 0.0667 | 1.5000 | 0.6667 |
| Gamma-secretase subunit PEN-2 | PSENEN | 4 | 0.8333 | 0.0667 | 1.5000 | 0.6667 |
| Tyrosine-protein phosphatase non-receptor type 1 | PTPN1 | 4 | 0.5000 | 0.0036 | 2.8980 | 0.3451 |
| Platelet-derived growth factor receptor beta | PDGFRB | 4 | 0.6667 | 0.0030 | 2.8163 | 0.3551 |
| Hepatocyte growth factor receptor | MET | 4 | 0.8333 | 0.0002 | 2.9184 | 0.3427 |
| Cell division control protein 42 homolog | CDC42 | 3 | 0.0000 | 0.1556 | 3.2245 | 0.3101 |
| **Poly [ADP-ribose] polymerase 1** | PARP1 | 3 | 0.0000 | 0.1178 | 3.3469 | 0.2988 |
| Mitogen-activated protein kinase14 | MAPK14 | 3 | 0.3333 | 0.0312 | 2.9592 | 0.3379 |
| Androgen receptor | AR | 3 | 0.3333 | 0.0230 | 2.6939 | 0.3712 |
| Serine/threonine-protein kinase B-raf | BRAF | 3 | 0.3333 | 0.0185 | 3.2449 | 0.3082 |
| Tyrosine-protein kinase ABL1 | ABL1 | 3 | 0.6667 | 0.0079 | 2.7347 | 0.3657 |
| Tyrosine-protein kinase Lck | LCK | 3 | 0.3333 | 0.0037 | 3.0000 | 0.3333 |
| Heat Shock cognate 71 kDa protein | HSPA8 | 3 | 0.6667 | 0.0007 | 2.6939 | 0.3712 |
| Presenilin-2 | PSEN2 | 3 | 1.0000 | 0.0000 | 2.0000 | 0.5000 |
| **C-C motif chemokine 5** | CCL5 | 2 | 0.0000 | 1.0000 | 1.0000 | 1.0000 |
| **Gamma-aminobutyric acid receptor subunit alpha-1** | GABRA1 | 2 | 0.0000 | 1.0000 | 1.0000 | 1.0000 |
| **Glycogen synthase kinase-3 beta** | GSK3B | 2 | 0.0000 | 0.3333 | 1.8333 | 0.5455 |
| Mitogen-activated protein kinase8 | MAPK8 | 2 | 0.0000 | 0.0799 | 4.1224 | 0.2426 |
| **Glutathione S-transferase P** | GSTP1 | 2 | 0.0000 | 0.0408 | 5.0612 | 0.1976 |
| Cyclin-dependent kinase 1 | CDK1 | 2 | 0.0000 | 0.0300 | 3.0408 | 0.3289 |
| **Caspase-7** | CASP7 | 2 | 0.0000 | 0.0200 | 4.2857 | 0.2333 |
| **Caspase-3** | CASP3 | 2 | 0.0000 | 0.0200 | 4.2857 | 0.2333 |
| Cyclin-dependent kinase 2 | CDK2 | 2 | 0.0000 | 0.0134 | 3.3878 | 0.2952 |
| **Nitric oxide synthase, endotelial** | NOS3 | 2 | 0.0000 | 0.0079 | 3.2041 | 0.3121 |
| **Cyclin-A2** | CCNA2 | 2 | 0.0000 | 0.0043 | 3.6122 | 0.2768 |
| Glucocorticoid receptor | NR3C1 | 2 | 0.0000 | 0.0005 | 3.0816 | 0.3245 |
| **E3 ubiquitin-protein ligase XIAP** | XIAP | 2 | 0.0000 | 0.0004 | 5.2245 | 0.1914 |
| **Dual specificity mitogen-activated protein kinase kinase 1** | MAP2K1 | 2 | 1.0000 | 0.0000 | 3.8776 | 0.2579 |
| Receptor tyrosine-protein kinase erbB-4 | ERBB4 | 2 | 1.0000 | 0.0000 | 3.0408 | 0.3289 |
| MAP kinase-activated protein kinase 2 | MAPKAPK2 | 2 | 1.0000 | 0.0000 | 3.5918 | 0.2784 |
| **Annexin A5** | ANXA5 | 1 | 0.0000 | 0.0000 | 1.0000 | 1.0000 |
| **Arachidonate 5-lipoxygenase-activating protein** | ALOX5AP | 1 | 0.0000 | 0.0000 | 1.0000 | 1.0000 |
| **Bcl-2-like protein 1** | BCL2L1 | 1 | 0.0000 | 0.0000 | 1.0000 | 1.0000 |
| **Retinol-binding protein 4** | RBP4 | 1 | 0.0000 | 0.0000 | 1.0000 | 1.0000 |
| **Polyunsaturated fatty acid 5-lipoxygenase** | ALOX5 | 1 | 0.0000 | 0.0000 | 1.0000 | 1.0000 |
| Adenosine kinase | ADK | 1 | 0.0000 | 0.0000 | 6.0408 | 0.1655 |
| **Aurora kinase A** | AURKA | 1 | 0.0000 | 0.0000 | 1.0000 | 1.0000 |
| **TGF-beta receptor type-1** | TGFBR1 | 1 | 0.0000 | 0.0000 | 3.4082 | 0.2934 |
| **Serine/threonine-protein kinase PLK1** | PLK1 | 1 | 0.0000 | 0.0000 | 1.0000 | 1.0000 |
| **Bifunctional purine biosynthesis protein ATIC** | ATIC | 1 | 0.0000 | 0.0000 | 1.0000 | 1.0000 |
| **Beta-2-microglobulin** | B2M | 1 | 0.0000 | 0.0000 | 1.0000 | 1.0000 |
| **Histone acetyltransferase KAT2B** | KAT2B | 1 | 0.0000 | 0.0000 | 3.4694 | 0.2882 |
| Peroxisome proliferator-activated receptor gamma | PPARG | 1 | 0.0000 | 0.0000 | 3.4694 | 0.2882 |
| Cyclin-dependent kinase 5 activator 1 | CDK5R1 | 1 | 0.0000 | 0.0000 | 1.0000 | 1.0000 |
| **Triosephosphate isomerase** | TPI1 | 1 | 0.0000 | 0.0000 | 1.0000 | 1.0000 |
| **Apoptotic protease-activating factor 1** | APAF1 | 1 | 0.0000 | 0.0000 | 1.0000 | 1.0000 |
| **Transthyretin** | TTR | 1 | 0.0000 | 0.0000 | 1.0000 | 1.0000 |
| **Fibroblast growth factor receptor 1** | FGFR1 | 1 | 0.0000 | 0.0000 | 3.3878 | 0.2952 |
| **Gamma-aminobutyric acid receptor subunit gamma-2** | GABRG2 | 1 | 0.0000 | 0.0000 | 1.5000 | 0.6667 |
| **Gamma-aminobutyric acid receptor subunit beta-3** | GABRB3 | 1 | 0.0000 | 0.0000 | 1.5000 | 0.6667 |
| **Adenine phosphoribosyltransferase** | APRT | 1 | 0.0000 | 0.0000 | 1.0000 | 1.0000 |
| **Alanine--glyoxylate aminotransferase** | AGXT | 1 | 0.0000 | 0.0000 | 1.0000 | 1.0000 |
| Cyclin-dependent kinase 5 | CDK5 | 1 | 0.0000 | 0.0000 | 1.0000 | 1.0000 |
| **Death-associated protein kinase 1** | DAPK1 | 1 | 0.0000 | 0.0000 | 3.6327 | 0.2753 |
| **Insulin-like growth factor I** | IGF1 | 1 | 0.0000 | 0.0000 | 3.5714 | 0.2800 |
| **Peroxisome proliferator-activated receptor alpha** | PPARA | 1 | 0.0000 | 0.0000 | 3.4694 | 0.2882 |
| **Serine/threonine-protein kinase PAK 6** | PAK6 | 1 | 0.0000 | 0.0000 | 4.2041 | 0.2379 |
| **Protein S100-A9** | S100A9 | 1 | 0.0000 | 0.0000 | 1.0000 | 1.0000 |
| **Vascular endothelial growth factor receptor 2** | KDR | 1 | 0.0000 | 0.0000 | 3.2653 | 0.3062 |
| **C-C chemokine receptor type 1** | CCR1 | 1 | 0.0000 | 0.0000 | 1.5000 | 0.6667 |
| Nitric oxide synthase, inducible | NOS2 | 1 | 0.0000 | 0.0000 | 3.6327 | 0.2753 |
| **RAC-beta serine/threonine-protein kinase** | AKT2 | 1 | 0.0000 | 0.0000 | 2.6667 | 0.3750 |
| Albumin | ALB | 1 | 0.0000 | 0.0000 | 1.0000 | 1.0000 |
| **Voltage-dependent L-type calcium channel subunit alpha-1C** | CACNA1C | 1 | 0.0000 | 0.0000 | 3.6327 | 0.2753 |
| **C-C chemokine receptor type 5** | CCR5 | 1 | 0.0000 | 0.0000 | 1.5000 | 0.6667 |
| **Vitamin D3 receptor** | VDR | 1 | 0.0000 | 0.0000 | 3.2653 | 0.3062 |
| Nitric oxide synthase, brain | NOS1 | 1 | 0.0000 | 0.0000 | 3.6327 | 0.2753 |

**Table S2.** - Topological measurements of nodes in the PPI network of chlorpyrifos oxon-induced developmental neurotoxicity.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Protein** | **Node** | **k** | **Clustering coefficient** | **BC** | **ASPL** | **CC** |
| Heat shock protein HSP 90-alpha | HSP90AA1 | 11 | 0.109 | 0.382 | 2.034 | 0.492 |
| Epidermal growth factor receptor | EGFR | 8 | 0.179 | 0.276 | 2.172 | 0.460 |
| Estrogen receptor | ESR1 | 7 | 0.143 | 0.269 | 2.103 | 0.475 |
| Proto-oncogene tyrosine kinase SRC | SRC | 6 | 0.400 | 0.071 | 2.276 | 0.439 |
| Histone acetyltransferase p300 | EP300 | 5 | 0.000 | 0.308 | 2.552 | 0.392 |
| Calmodulin-1 | CALM1 | 5 | 0.000 | 0.158 | 2.414 | 0.414 |
| Mitogen-activated protein kinase1 | MAPK1 | 5 | 0.100 | 0.095 | 3.172 | 0.315 |
| Tyrosine-protein phosphatase non-receptor type 1 | PTPN1 | 4 | 0.500 | 0.017 | 2.759 | 0.363 |
| **Poly [ADP-ribose] polymerase 1** | PARP1 | 3 | 0.000 | 0.135 | 3.379 | 0.296 |
| Mitogen-activated protein kinase14 | MAPK14 | 3 | 0.333 | 0.090 | 2.862 | 0.349 |
| Androgen receptor | AR | 3 | 0.333 | 0.088 | 2.448 | 0.408 |
| Heat Shock cognate 71 kDa protein | HSPA8 | 3 | 0.667 | 0.008 | 2.379 | 0.420 |
| Hepatocyte growth factor receptor | MET | 3 | 1.000 | 0.000 | 2.793 | 0.358 |
| Adenosine receptor A2a | ADORA2A | 2 | 0.000 | 1.000 | 1.000 | 1.000 |
| Cyclin-dependent kinase 1 | CDK1 | 2 | 0.000 | 0.057 | 2.828 | 0.354 |
| Tyrosine-protein kinase Lck | LCK | 2 | 0.000 | 0.044 | 2.759 | 0.363 |
| Serine/threonine-protein kinase B-raf | BRAF | 2 | 0.000 | 0.044 | 2.759 | 0.363 |
| Cyclin-dependent kinase 2 | CDK2 | 2 | 0.000 | 0.032 | 3.276 | 0.305 |
| **Cyclin-A2** | CCNA2 | 2 | 0.000 | 0.025 | 3.310 | 0.302 |
| **Nitric oxide synthase, endotelial** | NOS3 | 2 | 0.000 | 0.014 | 2.793 | 0.358 |
| Insulin-like growth factor 1 receptor | IGF1R | 2 | 0.000 | 0.007 | 2.828 | 0.354 |
| MAP kinase-activated protein kinase 2 | MAPKAPK2 | 2 | 1.000 | 0.000 | 3.690 | 0.271 |
| Aryl hydrocarbon receptor | AHR | 2 | 1.000 | 0.000 | 2.621 | 0.382 |
| Cyclin-dependent kinase 5 | CDK5 | 1 | 0.000 | 0.000 | 1.000 | 1.000 |
| D(2) dopamine receptor | DRD2 | 1 | 0.000 | 0.000 | 1.500 | 0.667 |
| **TGF-beta receptor type-1** | TGFBR1 | 1 | 0.000 | 0.000 | 3.000 | 0.333 |
| **Glutathione S-transferase P** | GSTP1 | 1 | 0.000 | 0.000 | 1.000 | 1.000 |
| Dual specific protein phosphatase 6 | DUSP6 | 1 | 0.000 | 0.000 | 4.138 | 0.242 |
| Cannabinoid receptor 1 | CNR1 | 1 | 0.000 | 0.000 | 1.500 | 0.667 |
| Nitric oxide synthase, inducible | NOS2 | 1 | 0.000 | 0.000 | 3.379 | 0.296 |
| Glucocorticoid receptor | NR3C1 | 1 | 0.000 | 0.000 | 3.000 | 0.333 |
| Peroxisome proliferator-activated receptor gamma | PPARG | 1 | 0.000 | 0.000 | 3.517 | 0.284 |
| Cyclin-dependent kinase 5 activator 1 | CDK5R1 | 1 | 0.000 | 0.000 | 1.000 | 1.000 |
| Nitric oxide synthase, brain | NOS1 | 1 | 0.000 | 0.000 | 3.379 | 0.296 |
| Mitogen-activated protein kinase8 | MAPK8 | 1 | 0.000 | 0.000 | 1.000 | 1.000 |
| **Caspase-7** | CASP7 | 1 | 0.000 | 0.000 | 4.345 | 0.230 |
| **Caspase-3** | CASP3 | 1 | 0.000 | 0.000 | 4.345 | 0.230 |

**Table S3.** - Topological measurements of nodes in the PPI network of paraoxon-induced developmental neurotoxicity.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Protein** | **Node** | **k** | **Clustering coefficient** | **BC** | **ASPL** | **CC** |
| Heat shock protein HSP 90-alpha | HSP90AA1 | 15 | 0.095 | 0.378 | 1.925 | 0.519 |
| Epidermal growth factor receptor | EGFR | 14 | 0.198 | 0.312 | 1.800 | 0.556 |
| Proto-oncogene tyrosine kinase SRC | SRC | 14 | 0.220 | 0.264 | 1.875 | 0.533 |
| Phosphatidylinositol 3-kinase regulatory subunit alpha | PIK3R1 | 10 | 0.289 | 0.180 | 2.150 | 0.465 |
| Tyrosine-protein phosphatase non-receptor type 11 | PTPN11 | 9 | 0.361 | 0.059 | 2.225 | 0.449 |
| Estrogen receptor | ESR1 | 6 | 0.267 | 0.091 | 2.150 | 0.465 |
| Receptor tyrosine-protein kinase erbB-2 | ERBB2 | 6 | 0.667 | 0.026 | 2.100 | 0.476 |
| Calmodulin-1 | CALM1 | 5 | 0.000 | 0.108 | 2.525 | 0.396 |
| Insulin-like growth factor 1 receptor | IGF1R | 5 | 0.200 | 0.054 | 2.550 | 0.392 |
| Mitogen-activated protein kinase1 | MAPK1 | 5 | 0.200 | 0.021 | 3.150 | 0.317 |
| Heat Shock cognate 71 kDa protein | HSPA8 | 5 | 0.400 | 0.021 | 2.350 | 0.426 |
| Presenilin | PSEN1 | 4 | 0.500 | 0.400 | 1.200 | 0.833 |
| Gamma-secretase subunit APH-1A | APH1A | 4 | 0.833 | 0.067 | 1.200 | 0.833 |
| Nicastrin | NCSTN | 4 | 0.833 | 0.067 | 1.200 | 0.833 |
| Gamma-secretase subunit PEN-2 | PSENEN | 4 | 0.833 | 0.067 | 1.200 | 0.833 |
| Signal transducer and activator of transcription 1-alpha/beta | STAT1 | 4 | 0.333 | 0.019 | 2.500 | 0.400 |
| Tyrosine-protein phosphatase non-receptor type 1 | PTPN1 | 4 | 0.500 | 0.009 | 2.450 | 0.408 |
| Platelet-derived growth factor receptor beta | PDGFRB | 4 | 0.667 | 0.003 | 2.575 | 0.388 |
| Hepatocyte growth factor receptor | MET | 4 | 0.833 | 0.001 | 2.450 | 0.408 |
| Mitogen-activated protein kinase14 | MAPK14 | 3 | 0.333 | 0.069 | 2.575 | 0.388 |
| Serine/threonine-protein kinase B-raf | BRAF | 3 | 0.333 | 0.052 | 2.725 | 0.367 |
| Tyrosine-protein kinase ABL1 | ABL1 | 3 | 0.667 | 0.009 | 2.275 | 0.440 |
| Presenilin-2 | PSEN2 | 3 | 1.000 | 0.000 | 1.600 | 0.625 |
| Receptor tyrosine-protein kinase erbB-4 | ERBB4 | 3 | 1.000 | 0.000 | 2.625 | 0.381 |
| **Glutathione S-transferase P** | GSTP1 | 2 | 0.000 | 1.000 | 1.000 | 1.000 |
| **Gamma-aminobutyric acid receptor subunit alpha-1** | GABRA1 | 2 | 0.000 | 1.000 | 1.000 | 1.000 |
| **Caspase-3** | CASP3 | 2 | 0.000 | 0.167 | 1.333 | 0.750 |
| **Poly [ADP-ribose] polymerase 1** | PARP1 | 2 | 0.000 | 0.167 | 1.333 | 0.750 |
| **E3 ubiquitin-protein ligase XIAP** | XIAP | 2 | 0.000 | 0.167 | 1.333 | 0.750 |
| **Caspase-7** | CASP7 | 2 | 0.000 | 0.167 | 1.333 | 0.750 |
| **Fibroblast growth factor receptor 1** | FGFR1 | 2 | 0.000 | 0.097 | 3.025 | 0.331 |
| **Fibroblast growth factor 1** | FGF1 | 2 | 0.000 | 0.050 | 3.950 | 0.253 |
| **Vascular endothelial growth factor receptor 2** | KDR | 2 | 0.000 | 0.050 | 2.800 | 0.357 |
| Tyrosine-protein kinase Lck | LCK | 2 | 0.000 | 0.013 | 2.750 | 0.364 |
| **Nitric oxide synthase, endotelial** | NOS3 | 2 | 0.000 | 0.011 | 2.750 | 0.364 |
| **Tyrosine-protein kinase JAK1** | JAK1 | 2 | 0.000 | 0.001 | 3.150 | 0.317 |
| Androgen receptor | AR | 2 | 1.000 | 0.000 | 2.525 | 0.396 |
| **Dual specificity mitogen-activated protein kinase kinase 1** | MAP2K1 | 2 | 1.000 | 0.000 | 3.600 | 0.278 |
| **Macrophage colony-stimulating factor 1 receptor** | CSF1R | 2 | 1.000 | 0.000 | 2.675 | 0.374 |
| **Leucine-rich repeat serine/threonine-protein kinase 2** | LRRK2 | 2 | 1.000 | 0.000 | 2.875 | 0.348 |
| **Heat shock 70 kDa protein 1A** | HSPA1A | 2 | 1.000 | 0.000 | 2.875 | 0.348 |
| MAP kinase-activated protein kinase 2 | MAPKAPK2 | 2 | 1.000 | 0.000 | 3.450 | 0.290 |
| Adenosine kinase | ADK | 1 | 0.000 | 0.000 | 1.500 | 0.667 |
| **Alanine--glyoxylate aminotransferase** | AGXT | 1 | 0.000 | 0.000 | 1.000 | 1.000 |
| **Triosephosphate isomerase** | TPI1 | 1 | 0.000 | 0.000 | 1.000 | 1.000 |
| Albumin | ALB | 1 | 0.000 | 0.000 | 1.000 | 1.000 |
| **Beta-2-microglobulin** | B2M | 1 | 0.000 | 0.000 | 1.000 | 1.000 |
| **Adenine phosphoribosyltransferase** | APRT | 1 | 0.000 | 0.000 | 1.000 | 1.000 |
| **Bifunctional purine biosynthesis protein ATIC** | ATIC | 1 | 0.000 | 0.000 | 1.000 | 1.000 |
| **Aurora kinase A** | AURKA | 1 | 0.000 | 0.000 | 1.000 | 1.000 |
| **Serine/threonine-protein kinase PLK1** | PLK1 | 1 | 0.000 | 0.000 | 1.000 | 1.000 |
| Nitric oxide synthase, inducible | NOS2 | 1 | 0.000 | 0.000 | 3.500 | 0.286 |
| **Death-associated protein kinase 1** | DAPK1 | 1 | 0.000 | 0.000 | 3.500 | 0.286 |
| **Cyclin-A2** | CCNA2 | 1 | 0.000 | 0.000 | 1.000 | 1.000 |
| Cyclin-dependent kinase 2 | CDK2 | 1 | 0.000 | 0.000 | 1.000 | 1.000 |
| **Protein kinase C alpha type** | PRKCA | 1 | 0.000 | 0.000 | 2.775 | 0.360 |
| **Prothrombin** | F2 | 1 | 0.000 | 0.000 | 1.000 | 1.000 |
| **Fibrinogen gamma chain** | FGG | 1 | 0.000 | 0.000 | 1.000 | 1.000 |
| **Fibroblast growth factor receptor 2** | FGFR2 | 1 | 0.000 | 0.000 | 4.925 | 0.203 |
| **Gamma-aminobutyric acid receptor subunit beta-3** | GABRB3 | 1 | 0.000 | 0.000 | 1.500 | 0.667 |
| **Gamma-aminobutyric acid receptor subunit gamma-2** | GABRG2 | 1 | 0.000 | 0.000 | 1.500 | 0.667 |
| **Glycogen synthase kinase-3 beta** | GSK3B | 1 | 0.000 | 0.000 | 2.000 | 0.500 |
| Mitogen-activated protein kinase8 | MAPK8 | 1 | 0.000 | 0.000 | 1.500 | 0.667 |
| Glucocorticoid receptor | NR3C1 | 1 | 0.000 | 0.000 | 2.900 | 0.345 |
| **Telomerase reverse transcriptase** | TERT | 1 | 0.000 | 0.000 | 2.900 | 0.345 |
| TGF-beta receptor type-1 | TGFBR1 | 1 | 0.000 | 0.000 | 2.900 | 0.345 |
| **Insulin-like growth factor I** | IGF1 | 1 | 0.000 | 0.000 | 3.525 | 0.284 |
| **Vascular endothelial growth factor A** | VEGFA | 1 | 0.000 | 0.000 | 3.775 | 0.265 |
| **Retinol-binding protein 4** | RBP4 | 1 | 0.000 | 0.000 | 1.000 | 1.000 |
| **Transthyretin** | TTR | 1 | 0.000 | 0.000 | 1.000 | 1.000 |
| **Vitamin D3 receptor** | VDR | 1 | 0.000 | 0.000 | 2.850 | 0.351 |

**Table S4.** - Binding energies of molecular docking between organophosphates and their respective hub nodes.

|  |  |  |  |
| --- | --- | --- | --- |
| **Target** | **PDB entry** | **Ligand** | **Docking energy (kJ/mol)** |
| HSP90AA1 | 1UY9 | PU6\* | -9.0 |
| Diazinon oxon | -7.2 |
| Chlorpyrifos oxon | -6.9 |
| Paraoxon | -7.0 |
| HSPA8 | 3FZK | 3BK\* | -8.5 |
| Chlorpyrifos oxon | -6.9 |
| ESR1 | 1A52 | EST\* | -10.4 |
| Chlorpyrifos oxon | -6.8 |
| EP300 | 6V8N | QS1\* | -12.2 |
| Chlorpyrifos oxon | -6.6 |
| PIK3R1 | 3ZIM | KKR\* | -9.6 |
| Diazinon oxon | -6.6 |
| Paraoxon | -6.2 |
| MET | 2RFN | AM7\* | -11.1 |
| Diazinon oxon | -6.2 |
| Chlorpyrifos oxon | -5.7 |
| Paraoxon | -6.1 |
| MAPK1 | 1PME | SB2\* | -8.4 |
| Chlorpyrifos oxon | -6.1 |
| EGFR | 1M17 | AQ4\* | -7.2 |
| Diazinon oxon | -6.0 |
| Chlorpyrifos oxon | -5.9 |
| Paraoxon | -6.2 |
| APH1A | 5A63 | PC1\* | -4.8 |
| Diazinon oxon | -5.7 |
| Paraoxon | -5.4 |
| PTPN11 | 3MOW | B2B\* | -6.0 |
| Diazinon oxon | -5.3 |
| Paraoxon | -5.7 |
| CALM1 | 1CTR | TFP\* | -7.5 |
| Chlorpyrifos oxon | -4.9 |
| STAT3 | 6NUQ | KQV\* | -6.7 |
| Diazinon oxon | -4.8 |
| ERBB2 | 1N8Z | NAG\* | -4.9 |
| Paraoxon | -4.7 |
| SRC | 1O46 | 903\* | -7.7 |
| Diazinon oxon | -4.6 |
| Chlorpyrifos oxon | -4.2 |
| Paraoxon | -4.7 |
| NCSTN | 5A63 | NAG\* | -4.7 |
| Diazinon oxon | -4.7 |
| Paraoxon | -4.5 |
| PSENEN | 6IDF | NAG\* | -4.4 |
| Diazinon oxon | -4.2 |
| Paraoxon | -4.3 |
| PTPN1 | 1C84 | 761\* | -8.1 |
| Chlorpyrifos oxon | -5.0 |

\*Original ligand

**Table S5.** - Intermolecular interactions of complexes between HSP90AA1, EGFR, MET, and SRC and the organophosphates.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Complex** | **Hydrogen bond (HB) interaction** | **Distance (Å) for HB interaction** | **Carbon-hydrogen interaction** | **Pi-sigma interaction** | **Pi-Alkyl interaction** | **Pi-Pi interaction** |
| HSP90AA1 – DZO |  |  |  | Trp162, Leu107 | Tyr139 | Phe138 |
| HSP90AA1 – CPO |  |  | Leu103 | Leu107 | Phe22, Phe170, Ala111 | Phe138 |
| HSP90AA1 – PO | Trp162 | 2.66, 5.09,5.78 |  | Leu107 |  | Phe138 |
| EGFR-DZO | Thr830  Thr766 | 1.99  2.26 |  | Leu820 | Met742, Lys721, Leu764, Leu 694, Val702, Ala719 |  |
| EGFR-CPO | Thr766  Met769 | 2.04  4.63 |  | Val702 | Ala719, Leu768, Leu820, Leu694 |  |
| EGFR-PO | Lys721  Met769  Thr830 | 1.93  1.96  2.4 | Gly772 | Leu820 | Phe699, Val, 702, Ala719 |  |
| MET-DZO |  |  |  | Val1092, Met1211, Phe1089 | Tyr1159, Met1160, Ala1108, Leu1140, Ile1084, Leu1157 |  |
| MET-CPO |  |  |  |  | Ile1145, Leu1142, Phe1124, Met1131, Ala1221, Val1155, Phe1089, Leu1157 |  |
| MET-PO |  |  |  | Leu1157 | Val1092, Val1155, Leu1112 | Phe1089 |
| SRC-DZO | Lys62  Arg14 | 2.73, 4.52  2.10, 2.82 |  |  |  |  |
| SRC-CPO | Lys62 | 3.5 |  |  | His60, Cys44 |  |
| SRC- PO | Leu96  Gly95  Tyr89 | 2.26  2.21  2.87 |  | Ile73 | Tyr61 |  |

**Figure S1.** - Protein-ligand interactions between organophosphates and hub nodes generated using BIOVIA Discovery Studio Visualizer.

|  |  |
| --- | --- |
| **HSP90AA1** | |
| PU6\* | Diazinon oxon |
| Diagrama  Descrição gerada automaticamente | Diagrama  Descrição gerada automaticamente |
| Chlorpyrifos oxon | Paraoxon |
| Diagrama  Descrição gerada automaticamente com confiança média | Diagrama  Descrição gerada automaticamente |
| **HSPA8** | |
| 2BK\* | Chlorpyrifos oxon |
| Uma imagem contendo Diagrama  Descrição gerada automaticamente | Diagrama  Descrição gerada automaticamente |
| **ESR1** | |
| EST\* | Chlorpyrifos oxon |
| Diagrama, Esquemático  Descrição gerada automaticamente | Diagrama  Descrição gerada automaticamente |
| **EP300** | |
| QS1\* | Chlorpyrifos oxon |
| Diagrama  Descrição gerada automaticamente | Diagrama  Descrição gerada automaticamente |
| **PIK3R1** | |
| KKR\* | Diazinon oxon |
| Diagrama  Descrição gerada automaticamente | Gráfico, Gráfico de dispersão  Descrição gerada automaticamente |
| Paraoxon |  |
| Uma imagem contendo Linha do tempo  Descrição gerada automaticamente |  |
| **MET** | |
| AM7\* | Diazinon oxon |
| Diagrama  Descrição gerada automaticamente | Diagrama  Descrição gerada automaticamente |
| Chlorpyrifos oxon | Paraoxon |
| Uma imagem contendo Diagrama  Descrição gerada automaticamente | Diagrama  Descrição gerada automaticamente |
| **MAPK1** | |
| SB2\* | Chlorpyrifos oxon |
| Diagrama  Descrição gerada automaticamente | Diagrama  Descrição gerada automaticamente |
| **EGFR** | |
| AQ4\* | Diazinon oxon |
| Diagrama  Descrição gerada automaticamente | Diagrama  Descrição gerada automaticamente |
| Chlorpyrifos oxon | Paraoxon |
| Uma imagem contendo Diagrama  Descrição gerada automaticamente | Diagrama  Descrição gerada automaticamente |
| **APH1A** | |
| PC1\* | Diazinon oxon |
| Mapa  Descrição gerada automaticamente | Diagrama  Descrição gerada automaticamente |
| Paraoxon |  |
| Uma imagem contendo Diagrama  Descrição gerada automaticamente |  |
| **PTPN11** | |
| B2B\* | Diazinon oxon |
| Gráfico, Gráfico de dispersão  Descrição gerada automaticamente | Diagrama  Descrição gerada automaticamente |
| Paraoxon |  |
| Diagrama  Descrição gerada automaticamente com confiança média |  |
| **CALM1** | |
| TFP\* | Chlorpyrifos oxom |
| Diagrama  Descrição gerada automaticamente | Diagrama  Descrição gerada automaticamente |
| **STAT3** | |
| KQV\* | Diazinon oxon |
| Diagrama  Descrição gerada automaticamente com confiança média | Diagrama  Descrição gerada automaticamente |
| **ERBB2** | |
| NAG\* | Paraoxon |
| Diagrama  Descrição gerada automaticamente | Mapa  Descrição gerada automaticamente com confiança média |
| **SRC** | |
| 903\* | Diazinon oxon |
| Gráfico de dispersão  Descrição gerada automaticamente | Mapa  Descrição gerada automaticamente |
| Chlorpyrifos oxon | Paraoxon |
| Uma imagem contendo Mapa  Descrição gerada automaticamente | Diagrama  Descrição gerada automaticamente |
| **NCSTN** | |
| NAG\* | Diazinon oxon |
| Diagrama  Descrição gerada automaticamente | Diagrama  Descrição gerada automaticamente |
| Paraoxon |  |
| Diagrama  Descrição gerada automaticamente |  |
| **PSENEN** | |
| NAG\* | Diazinon oxon |
| Diagrama  Descrição gerada automaticamente | Uma imagem contendo Mapa  Descrição gerada automaticamente |
| Paraoxon |  |
| Mapa  Descrição gerada automaticamente |  |
| **PTPN1** | |
| 761\* | Chlorpyrifos oxon |
| Diagrama  Descrição gerada automaticamente | Diagrama  Descrição gerada automaticamente |

\* original ligand