**Table S3**. Interactions of dual active alkaloids with Spike Glycoprotein

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Alkaloid Name** | **Interacting residues** | **Bond type** | **Distance** | **Energy****kcal/mol** | **Residues involved in hydrophobic interaction** |
| Adouetine Y | Gln98 | H-donor | 3.10 | -2.66 | Lys94, Leu95, Tyr196, Trp203, Gly205, AAsp206, Glu208, Asn210, Glu398, Lys562, and Pro565. |
| Gln98 | H-acceptor | 2.66 | -1.2 |
| Ergosine | Leu95 | H-bond | 2.40 | --- | Leu95, Tyr196, Try202, Trp203, Asp206, Glu208, Asn210, and Glu398 |
| Gln98 | H-acceptor | 3.24 | -0.8 |
| Gly102 | H-acceptor | 3.04 | -0.8 |
| Gly205 | H-donor | 3.02 | -3.3 |
| Asn210 | H-bond | 2.20 | --- |
| Lys562 | H-acceptor | 3.26 | -1.1 |
| Evodiamide C | Gln98 | H-bond | 1.80 | --- | Leu91, Lys94, Leu95, Ala99, Tyr202, Trp203, Gly205, Asp206, Glu208, Val209, Asn210, Gly211 Val212, Leu391, Glu398, and Lys562. |
| Gln102 | H-bond | 2.50 | --- |
| Thr196 | H-bond | 2.40 | --- |
| Gly205 | H-bond | 1.90 | --- |
| Lys562 | H-bond | 2.90 | --- |
| Lys562 | Pi-cation | 3.94 | -1.3 |
| Reserpine | Gln208 | H-bond | 2.80 | --- | Leu91, Lys94, Leu95, Ala99, Trp203, Gly205, Asp206 Glu208, Val209, Leu391, Ala396, Glu398, Lys562, and Trp566. |
| Asn210 | H-bond | 2.95 | -3.1 |
| Lys562 | H-bond | 3.00 | --- |
| Pelosine | Tyr202 | H-donor | 2.95 | -1.0 | Leu95, Gln98, Ala99, Gln102, Tyr196, Tyr202, Trp203, Gly205, Asp206, Val209, Asn210, Arg219, Leu391, Asn394, Glu398, and Lys562. |
| Hayatinine | Gln98 | H-donor | 2.10 | --- | Leu95, Gln98, Ala99, Gln102, Tyr196, Tyr202, Trp203, Gly205, Asp206, Val209, Arg219, Leu391, Asn394, Glu398, and Lys563. |
| Lys562 | Pi-cation | 3.24 | -1.3 |
| Homoarmoline | Gln98 | H-bond | 2.00 | --- | Leu95, Ala99, Gln102, Tyr196, Tyr202, Trp203, Gly205, Asp206, Leu391, and Glu398. |
| His195 | H-bond | 2.40 | --- |
| Asn210 | H-bond | 2.50 | --- |
| Arg219 | H-bond | 2.30 | --- |
| Arg219 | H-bond | 2.70 | --- |
| Lys562 | H-acceptor | 3.05 | -1.4 |
| Isatithioetherine C  | Gln98 | H-acceptor | 3.06 | -1.5 | Leu91, Leu95, Ala99, Gln102, Tyr202, Trp203, Gly205, Asp206, Glu208, Asn210, Leu391, Asn394, and Glu398. |
| Tyr202 | H-bond | 1.90 | --- |
| Glu208 | H-bond | 2.40 | --- |
| Glu208 | H-bond | 3.40 | --- |
| Asn210 | H-bond | 3.60 | --- |
| Lys562 | H-acceptor | 4.03 | -6.9 |
| N,alpha-L-rhamnopyranosyl vincosamide | Gln98 | H-donor | 2.66 | -1.3 | Leu91, Lys94, Leu95, Ala99, Tyr196, Tyr202, Trp203, Gly205, Val209, Leu392, Asn394, Glu398, Ser563, Glu564, Pro565, and Trp566. |
| Gln102 | H-acceptor | 3.19 | -1.4 |
| Asn210 | H-bond | 2.20 | --- |
| Lys562 | H-acceptor | 3.12 | -3.5 |
| Toddalidimerine | Gln98 | H-bond | 2.60 | --- | Leu95, Ala99, Gln102, Tyr196, Tyr202, Trp203, Gly205, Asp206, Glu208, Asn210, Leu391, Leu392, Ala396, Glu398, Lys562, Glu564, Pro565, and Trp566. |
|  | Val209 | Pi-H | 4.49 | -0.6 |
| Lys562 | Pi-cation | 3.34 | -0.9 |
| Toddayanis | Gln98 | H-acceptor | 2.62 | -0.9 | Leu95, Ala99, Gln102, Tyr196, Tyr202, Trp203, Gly205, Asp206, Glu208, Val209, Asn210, Leu391, Leu392, Asn394, Glu398, and Lys562. |
|  | Lys562 | Pi-cation | 3.57 | -1.7 |
| Zanthocadinanine | Gln102 | H-bond | 1.70 | --- | Leu91, Lys94, Leu95, Gln98, Ala99, Gln102, His195,Tyr196, Val209, Asn210, Tyr202, Trp203, Gly205, Asp206, Glu208, Val212, Arg219,Leu392, Asn394, Glu398, Lys562, Lys562, Ser563, Glu564, Pro565, and Trp566. |
| Tyr196 | H-bond | 2.60 | --- |
| Asn210 | Pi-H | 4.34 | -0.6 |