CHLOROQUINE ANALOGS, SYNTHESIZED BY THERMAL AND ULTRASONIC MEANS, ARE ENDOWED WITH ANTI-ZIKA VIRUS ACTIVITY

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Zika virus (ZIKV), an emerging Flavivirus, was recently associated with severe neurological complications and congenital diseases. Therefore, development of antiviral agents capable of inhibiting ZIKV replication is urgent. Chloroquine is a molecule with confirmed safety history for use by pregnant women and exhibited anti-ZIKV activity at concentrations around 10 µM. This suggests that modifications to the chloroquine structure could be promising for obtaining more effective anti-ZIKV agents. Here, we report the synthesis of a series of twenty N-(2-(arylmethylimino) ethyl)-7-chloroquinolin-4-amine derivatives obtained by thermal and ultrasonic means. The ultrasonic procedures are simple, safe and with short reaction times – 30-180 seconds compared to 30-180 minutes reactions times for the thermal method. Furthermore, we demonstrated the ability of these derivatives to inhibit ZIKV replication in vitro. We found that the quinoline derivative, N-(2-(5-nitrofuran-2-yl)methylimino)ethyl)-7-chloroquinolin-4-amine (40), was the most potent compound within this series, reducing ZIKV replication by 72 % at 10 µM. Compound 40 exhibited an EC50 value of 0.8 ± 0.07 µM, compared to 12 ± 3.2 µM for chloroquine. Good activities were also obtained for other compounds, including those with aryl groups = phenyl, 4-fluorophenyl, 4-nitrophenyl, 2,6-dimethoxyphenyl, 3-pyridinyl and 5-nitrothien-2-yl. Importantly, the number, the positions and the types of substituents attached to the aromatic ring are critical factors for the biological activity. These results indicate that this group of compounds is a good follow-up point for the potential discovery of new drugs against Zika disease.