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AMINOQUINOLINE/ANTIMALARIAL BINDING TO FLUID LIPID ASSEMBLIES DEPENDS ON ELECTRON DENSITY ON QUINOLINE

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BACKGROUND, MOTIVATION AND OBJECTIVE

Aminoquinolines (AQ) are the base compounds for antimalarials (AM) such as sitamaquine and primaquine phosphate. The mechanism of their biological activity is of prime interest [1-3]. As a result, in order to understand the molecular initiating events (MIEs) in the biological activity of AQ and AM compounds, it is essential as a first step to elucidate their interactions with biological membrane models [4]. Fig. 1(i) summarises two of the structures of the compounds investigated. The aim was to investigate the molecular descriptors which facilitated binding and subsequent damage to the lipid assemblies.

STATEMENT OF CONTRIBUTION / METHODS

1. Compounds were screened using the HISENTS-SABYDOMA dioleoyl phosphatidylcholine (DOPC) membrane sensor element on microfabricated Pt/Hg electrodes in an online high throughput flow system in PBS at pH 7.4 [5,6]. This technology screens compounds for their ability to bind to, modify and damage a fluid DOPC structure. The sensor metric of limit of detection (LoD) was estimated for each interaction and expressed as –log (LoD) where its magnitude is related to the extent of interaction [7].

2. Results were combined with literature values of log *P* (and log D^{pH74})) and the pK_a of the compounds to assess descriptors of the molecules which facilitated AQ/AM-DOPC binding and subsequent DOPC assembly structural modification.

RESULTS AND DISCUSSION

-log (LoD) relates to the AQ/AM-DOPC binding and the subsequent assembly modification. Thus –log (LoD) includes (a) the thermodynamic affinity of the AQ/AM for the DOPC which is related to log *P* or more correctly log $D^{pH7.4}$ for ionizable compounds and, (b) a molecular binding to the DOPC. –log (LoD) values have therefore been normalized by log $D^{pH7.4}$ to give direct information on AQ-DOPC binding. Fig. 1(ii) displays plots of [–log (LoD) –log $D^{pH7.4}$] for all 7 AQ compounds' interaction versus the NH_2 position on the quinoline rings. The plot peaks at the NH_2-positions on the quinoline of 4 and 7. A model is proposed whereby the ability of the AQ to bind with the DOPC is related to the electron donating tendency of the NH_2- group to the quinoline rings which is related to the pK_a value of the AQ. Accordingly a plot of [–log (LoD)–log $D^{pH7.4}$] versus the AQ pK_a value is linear (Fig. 1(iii)) with R^2 value of 0.8. Interestingly plots of [–log (LoD)–log $D^{pH7.4}$] versus pK_a for all AM/DOPC interactions shows that sitamaquine and promaquine with highest pK_a show strongest interaction with DOPC (Fig. 1(iv)). A higher pK_a is correlated with increased electron donating capability of substituents and greater stability of the base cation. Increased electron density on the quinoline rings leads to increased interaction with DOPC apolar tails [8]. The 2-AQ interaction outlier in Fig. 1(iii) is due to the geometrical restriction on the polarizable heterocyclic N to enter the DOPC apolar region. This study demonstrates the power of the HISENTS-SABYDOMA biomembrane sensor in elucidating QSARs of molecule/nanoparticle binding to lipid assemblies as MIEs in their biological activities.

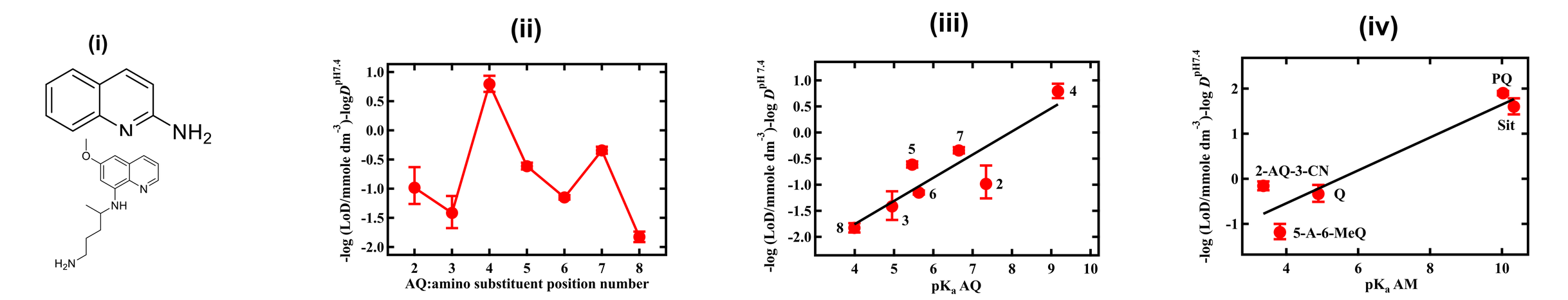

Figure 1: (i) structures of, top, 2-aminoquinoline and, bottom, primaquine, (ii) [–log (LoD)–log $D^{pH7.4}$] vs NH_2- position for AQs, (iii) [–log (LoD)–log $D^{pH7.4}$] vs pK_a for AQs, (iv) [–log (LoD)–log $D^{pH7.4}$] vs pK_a for Ams: **PQ**:primaquine, **Sit**:sitamaquine, **Q**:quinoline, **2-AQ-3-CN**: 2-AQ-3-carbonitrile, **5-A-6-MeQ**: 5 amino-6-methylQ

CONCLUSION

The ability of AQ and AM compounds to bind to and damage fluid lipid assemblies as model membranes is related to the electron donating capability of the aromatic substituents. The increased electron density on the quinoline ring increases the interaction between the quinoline ring and the apolar region of the fluid phospholipid sensor element.

REFERENCES

[1] Kaschula, C.H., Egan, T.J., Hunter, R., Basilico, N., Parapini, S., Taramelli, D., Pasini, E. and Monti, D., 2002. Journal of Medicinal Chemistry, 45(16), 3531. [2] Bourne, S.A., De Villiers, K. and Egan, T.J., 2006. Acta Crystallographica Section C: Crystal Structure Communications, 62(2), o53. [3] Loiseau, P.M., Cojean, S. and Schrével, J., 2011. Journal de la Société Fra [4] Barroso, R.P., Basso, L.G. and Costa-Filho, A.J., 2015. Chemistry and Physics of Lipids, 186, 68. [5] Mohamadi, S., Tate, D.J., Vakurov, A. and Nelson, A., 2014. Analytica Chimica Acta, 813, 83. [6] Owen, J., Kuznecovs, M., Bhamji, R., William, N., Domenech-Garcia, N., Hesler, M., Knoll, T., Kohl, Y., Nelson, A. and Kapur, N., 2020. Review of Scientific Instruments, 91(2), 025002. [7] William, N., Nelson, A., Gutsell, S., Hodges, G., Rabone, J. and Teixeira, A., 2019. Analytica Chimica Acta, 1069, 98. [8] Nelson, A., Auffret, N. and Borlakoglu, J., 1990. Biochimica et Biophysica Acta (BBA)-Biomembranes, 1021(2), pp.205.

The research for this work has received funding from the project SABYDOMA (Grant Agreement No 862296) under the European Union's Horizon 2020 research and innovation programme.

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