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# IN-SILICO EXPLORATION OF 4 AMINOQUINOLINES AS LYSINE METHYLTRANSFERASE G9A AND DNA METHYLTRANSFERASE INHIBITORS

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**ABSTRACT** Aminoquinolines areheterocyclic molecules with broad range of biological activities. Recently, they were evaluated for Lysine Methyltransferase G9a and DNAMethyltransferase inhibitors inhibitory activity. In the present work, an effort has been made using In-Silico (Bio-informatics approach) to evolve a useful pharmacophoric model using highly active 4 Aminoquinolines for Lysine Methyltransferase G9a and DNAMethyltransferase inhibitors inhibitory activity. The analysis points out that the anti-cancer profile of 4 Aminoquinolines has robust relationship with H-bond acceptor/donor and lipophilic features of the molecules. The analysis could be advantageous for evolving one or more 4 Aminoquinoline derivative with improved anti-cancer activity profile.

**KEYWORDS :** Pharmacophore modeling, Cancer, 4 Aminoquinolines, Lysine Methyltransferase G9a, NAMethyltransferase

## INTRODUCTION:

Cancer is a leading cause of deaths in many countries. This deadly disease with unembellishedfinancialburden on patients is actually a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body. Patients have a choice of treatment methodologies like chemotherpay,radiation, surgery, etc. Generally, patients prefer chemotherapy. But chemotherapy is a long, expensive and a patient faces a lot of side effects [Rabal et. al. 2018 and San José-Enériz et. al. 2017]. Recently, Rabal*et al* [2018] explored chemical space for 4 Aminoquinolinesas effective agents against cancer. Even though, they describeddetailed and extensive SAR (Structure-Activity Relationships) in good details, but no attempt was made by them to develop a consensus pharmacophore model. Hence, the present work is intended to achieve development of such a pharmacophore model.

### Experimental Methodology [Masand et. al. 2017]:

**1. Selection of Dataset:** In the present work, a dataset of 58 molecules was used for developing the consensus model [Rabal et. al. 2018 and San José-Enériz et. al. 2017]. The dataset comprises a variety of isomers of 4 Aminoquin olineslike stereo, positional and functional. The 4 Aminoquin oline derivatives used in this work possess a variety of substituents, which resulted in a broad chemical space for analysis. The reported activity value for Lysine Methyltra nsferase G9a and DNAMethyltransferaseinhibitory activity were used to identify most active molecules. The Table 1 contains top active molecules used for model building.

**Table 1. SMILES notations and activity values $IC_{50}$ (nM) for top five molecules used for alignment**

| S.N. | SMILES | G9a IC50 |
|---|---|---|
| 1 | CCc1oc(cc1)c2cc(NCC3C4CCC3CN(C)C4)c5cc(OC)c(OCCCN6CCCC6)cc5n2 | 5 |
| 2 | COc1cc2c(NC3CC4(CCN(CC4)C(C)C)C3)cc(nc2cc1OCCCN5CCCC5)c6oc(C)cc6 | 7 |
| 3 | COc1cc2c(NC3CC4(CCN(C)C4)C3)cc(nc2cc1OCCCN5CCCC5)c6oc(C)cc6 | 11 |
| 4 | COc1cc2c(NCC3CCN(CC3)C(C)C)cc(nc2cc1OCCCN4CCCC4)c5oc(C)cc5 | 13 |
| 5 | COc1cc2c(NC3CC4CCC(C3)N4C)cc(nc2cc1OCCCN5CCCC5)c6oc(C)cc6 | 13 |

**2. Development of model:** For developing a consensus pharma cophore model, the structures of molecules were sketched using ChemSketch 12 freeware. For 3D-optimization, Avogadro 1.1 was used with default settings for the 3D- structure of all the molecules, followed by alignment using Open3Dalign (using default settings). For modeling purpose, top five active aligned molecules were imported in PyMOL 2.2. Then, PyMOL plugin 'LIQUID' was used to derive final model using default settings.

## RESULT AND DISCUSSIONS:

The present *in-silico* analysis discloses that the anti-cancer activity of 4 Aminoquinoline derivatives has correlation with lipophilic and H-Bond acceptor/donor parts of the present set 4 Aminoquinoline derivatives. The final and consensus pharmacophore model has been depicted in figure 1.

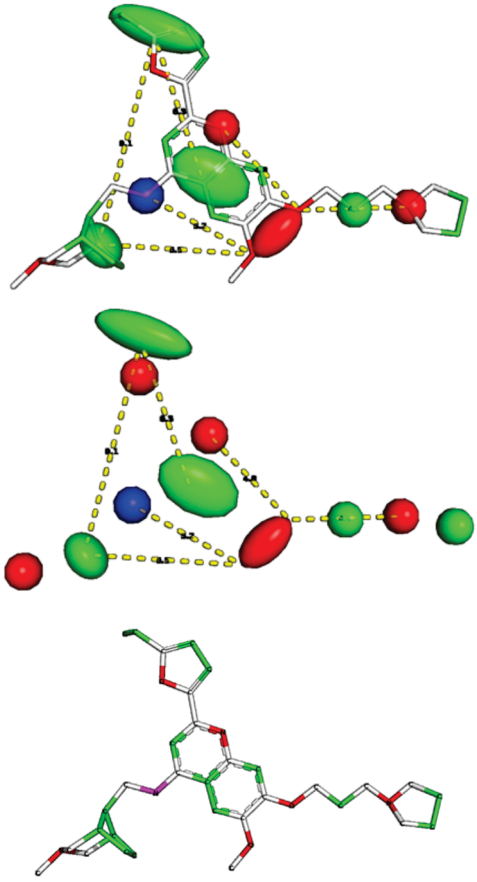

Figure 1. Common pharmacophore model with and without molecule and contours for different regions (Green: Lipophilic, Blue: H-bond donor and Red: H-bond acceptor)

From Figure 1, it is evident that anti-cancer activity changes with five H-bond acceptor, one H-bond donor and five lipophilic regions. These different regions are important for the activity preservation and expansion; hence such groups shall be retained in future also. The regions highlight the importance of quinoline and furan ring as well as groups like -O- (as a linker).

## CONCLUSIONS:

The anti-cancer activity of 4 Aminoquinoline derivatives has robust association with lipophilic and H-bond acceptor/donor features, which must be retained in future optimization to have good activity. The present analysis was successful in highlighting useful features for future optimizations.

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