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Pharmacophore Modeling for AG-270, a First-in-Class Oral MAT2A Inhibitor for the Treatment of Tumours with Homozygous MTAP Deletion

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Abstract: ***Computer Aided Drug Design (CADD) has gained a high popularity among drug designers and medicinal chemists due to several advances associated with it. There are many examples when CADD has revealed new ideas to develop a drug. Pharmacophore modeling, molecular modeling & QSAR and other branches of CADD has contributed successfully in developing many new block buster drugs. The dataset of forty-seven compounds for enzymatic inhibition of MAT2A was selected to identify the consensus pharmacophoric features that govern their inhibition activity against MAT2A. Out of these the dataset of three compounds were taken for investigation. The standard procedure was adapted to develop the pharmacophoric models for AG-270, AGI-25696 as a most active compound. The consensus pharmacophore model highlighted the importance of structural features and their correlation with the biological activity. The outcome of the present work could be used effectively in future optimizations.***

Keywords: ***Pharmacophore modeling, AG-270, AGI-25696, MAT2A inhibitor, Drug design.***

I. INTRODUCTION

The methylthioadenosine phosphorylase (MTAP) gene is located adjacent to the CDKN2A tumour suppressor and is codeleted with CDKN2A in approximately 15% of all cancers, leading to aggressive tumours with poor prognoses for which no effective molecularly targeted therapies exist [1-3] The metabolic enzyme methionine adenosyltransferase 2A (MAT2A) has an important role in metabolism and epigenetics because it is the primary producer of the universal methyl donor S-adenosyl methionine (SAM). The activity of the SAM-utilizing type II protein arginine N-methyltransferase 5 (PRMT5) is inhibited by the MTAP substrate, 5′-methylthioadenosine (MTA), which accumulates when MTAP is deleted. Within this tumour environment, the catalytic activity of the PRMT5 enzyme is reduced, and it becomes vulnerable to further inhibition by reduction of SAM levels, whereas its activity in normal tissues and MTAP-proficient tumours remains largely unaffected [2]

Previous work investigating MTAP loss in cancer cells revealed that MTA accumulation sensitizes cells to short hairpin RNA-mediated depletion of MAT2A and the SAM-utilizing enzyme PRMT5. However, existing clinical-stage inhibitors of PRMT5 fail to recapitulate this MTAP-dependent effect, likely because the existing inhibitors have a SAM-uncompetitive mechanism that is not synergistic with MTA [4,5] and thus fail to selectively inhibit the proliferation of MTAP-null versus MTAP-WT cancer cells. In contrast, reduction of SAM levels via MAT2A inhibition can act synergistically with MTA elevation to selectively inhibit PRMT5 in MTAP-deleted cells, thereby inhibiting cell growth. Thus, the inhibition of MAT2A allows for the selective inhibition of PRMT5 activity in MTAP-null cancer cells and tumours by limiting the availability of SAM and is predicted to afford a greater therapeutic window than known PRMT5 inhibitors by limiting the potential toxicity of PRMT5 inhibition in normal, MTAP-WT tissues [6-8].

Although these results suggest that targeting MAT2A may prove beneficial in MTAP-deleted cancers, past efforts to devise effective MAT2A inhibitors have been challenging. Methionine analogues such as cycloleucine [9,10] as well as stilbene derivatives [11] have been reported in the literature to be inhibitors of MAT2A; however, their weak biochemical potency (>10 μM) and very weak cellular activity did not enable their development into useful therapeutics. The recent discovery of a moderately potent allosteric MAT2A inhibitor, PF-9366 [12], demonstrates the potential to drug MAT2A via an allosteric mechanism. Unfortunately, PF-9366 treatment in cells induced cellular adaptation, particularly upregulation of MAT2A itself, which blunted cellular potency and led to inadequate antiproliferative effects.

Recently, Computer Aided Drug Design (CADD) has gained a high popularity among drug designers and medicinal chemists due to several advances associated with it. There are many examples when CADD has revealed new ideas to develop a drug. Pharmacophore modeling molecular modeling & QSAR and other branches of CADD has contributed successfully in developing many new block buster drugs.

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Pharmacophore modeling is an efficient and useful approach to identify important patterns in a series of molecules for lead-optimizations [13]. Hence, in this analysis, developed consensus model for AG-270, a first-in-class oral MAT2A inhibitor for the treatment of tumours with homozygous MTAP deletion.

The discovery of potent and selective inhibitors of MAT2A via structure-guided design, starting from a fragment with very low potency. The potent pharmacologic inhibition of MAT2A inhibits the growth of MTAP-deleted cancers in vivo with good tolerability, thus validating MAT2A as a therapeutic target for a biomarker-selected patient population of significant size. On the basis of these discoveries, AG-270, an oral, first-in class MAT2A inhibitor, has entered clinical development and is under investigation in a phase 1 trial that is currently enrolling patients with MTAP-deleted solid tumours and lymphomas [14]. However, no attempt was instigated to produce a consensus pharmacophore model for AG-270, a first-in-class oral MAT2A inhibitor for the treatment of tumours with homozygous MTAP deletion. Thus, this is first ever effort to develop a consensus pharmacophore model for AG-270 using alignment approach. The outcomes could be advantageous to chemists while developing a new drug.

II. EXPERIMENTAL METHODOLOGY

A. Dataset

The dataset comprises forty-seven compounds for enzymatic inhibition of MAT2A displaying the inhibition activity (IC_{50}) against MAT2A in the range 0.014 to 620.525 µM [14]. Out of these the dataset of three compounds has been tabulated in table1.

TABLE 1: SMILES notation of different compounds for enzymatic inhibition of MAT2A along with reported IC_{50} values.

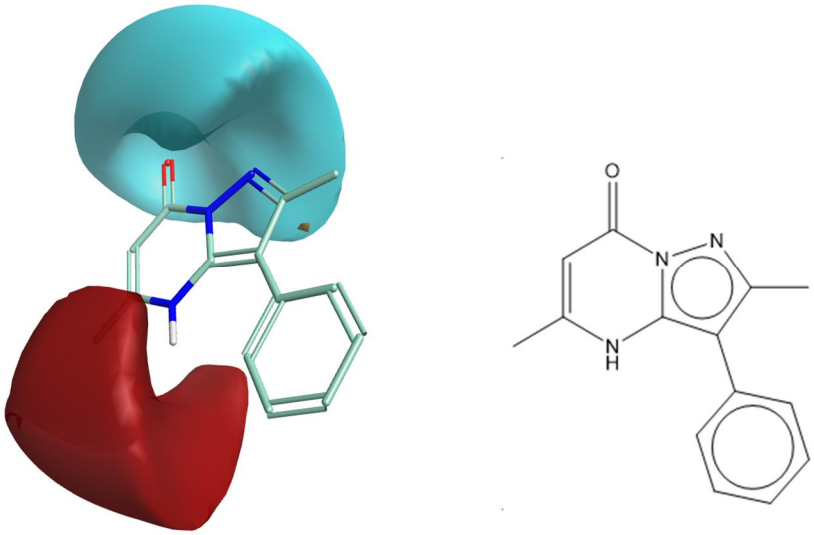
Compound ID	SMILES Notation	IC_{50} (µM)
Compound 1	O=C1C=C(C)Nc2n1nc(C)c2c3ccccc3	620.525
AGI-25696	O=C1C(c2ccc3ncccc3c2)=C(C)Nc4n1nc(c5ccccc5)c4c6ccccc6	0.097
AG-270	O=C1C(c2ccc(OC)cc2)=C(Nc3ccccn3)Nc4n1nc(c5ccccc5)c4C6=CCCCC6	0.014

B. Pharmacophore Model Generation

The procedure used in the present work for developing consensus pharmacophore modeling involves recommended steps in the literature [13]. The core stages are:

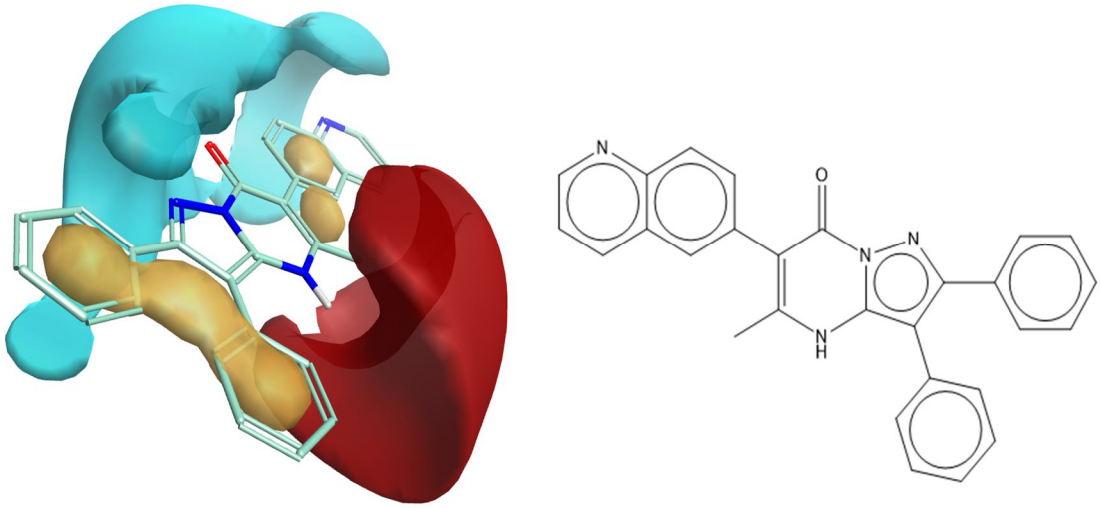
1) *Stage 1:* Drawing the structures using a software (ChemSketch 2010 freeware)
2) *Stage 2:* Optimization using a suitable method (MOPAC 2012 using AM1 method)
3) *Stage 3:* Aligning all the molecules in the dataset using suitable approach (Open 3D Align software with default setting)
4) *Stage 4:* Generation of a consensus pharmacophore model (PyMOl 2.0)

III. RESULT AND DISCUSSION

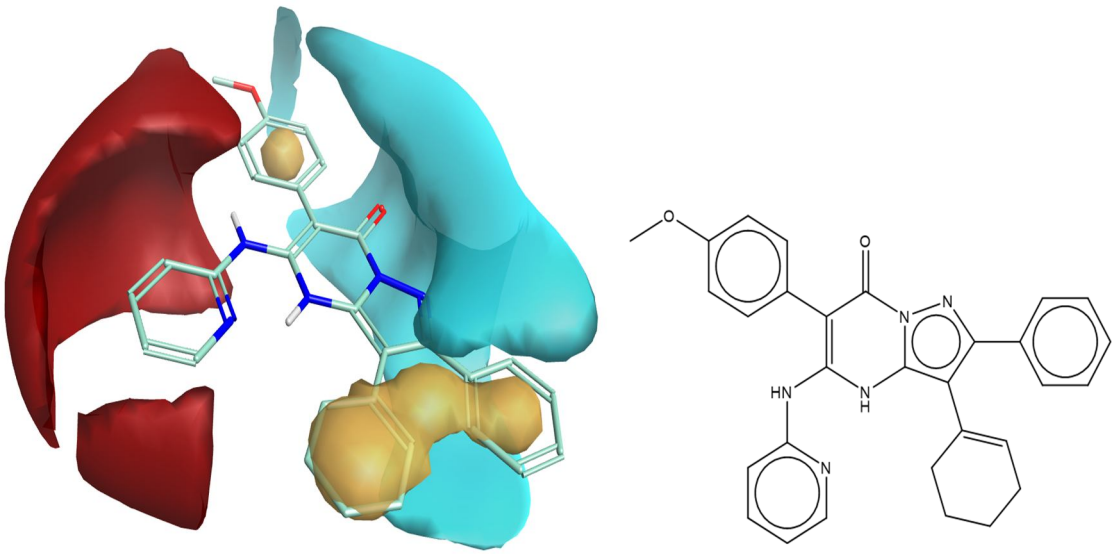


(A) Compound 1

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(B) AGI-25696



(C) AG-270

Fig. 1 – 3D- representation of consensus pharmacophoric pattern for (A) Compound 1 (B) AGI-25696 (C) AG-270

From fig. 1, it is observed that, the consensus pharmacophoric pattern of three molecules represent three contour regions (Yellow: Hydrophobic, Blue: Negative and Red: Positive). The consensus pharmacophore modeling identified three significant contour regions in the molecules which have relationship with a first-in-class oral MAT2A inhibitor for the treatment of tumours with homozygous MTAP deletion. The utmost key contour regions are: (1) One hydrophobic/lipophilic region due to benzene attached to five-member heterocyclic ring (shown by yellow contours), (2) A negatively charged region (shown by blue contour) present over the five-member heterocyclic rings and extending up to carbonyl group (3) A positively charged contour (shown by red colour) which is present due to the six-member heterocyclic rings and extending towards cyclic alkene group. It is also observed that, in AG-270, two positively charged contour (shown by red colour) are present as compared to Compound 1 and AGI-25696.

IV. CONCLUSION

The present work revealed important pharmacophoric patterns for AG-270, a first-in-class oral MAT2A inhibitor for the treatment of tumours with homozygous MTAP deletion. This highlights the importance of heterocyclic rings and aromatic moiety and their correlation with the biological activity; hence these features must be used effectively in future optimizations. The outcomes could be advantageous to chemists while developing a new drug.

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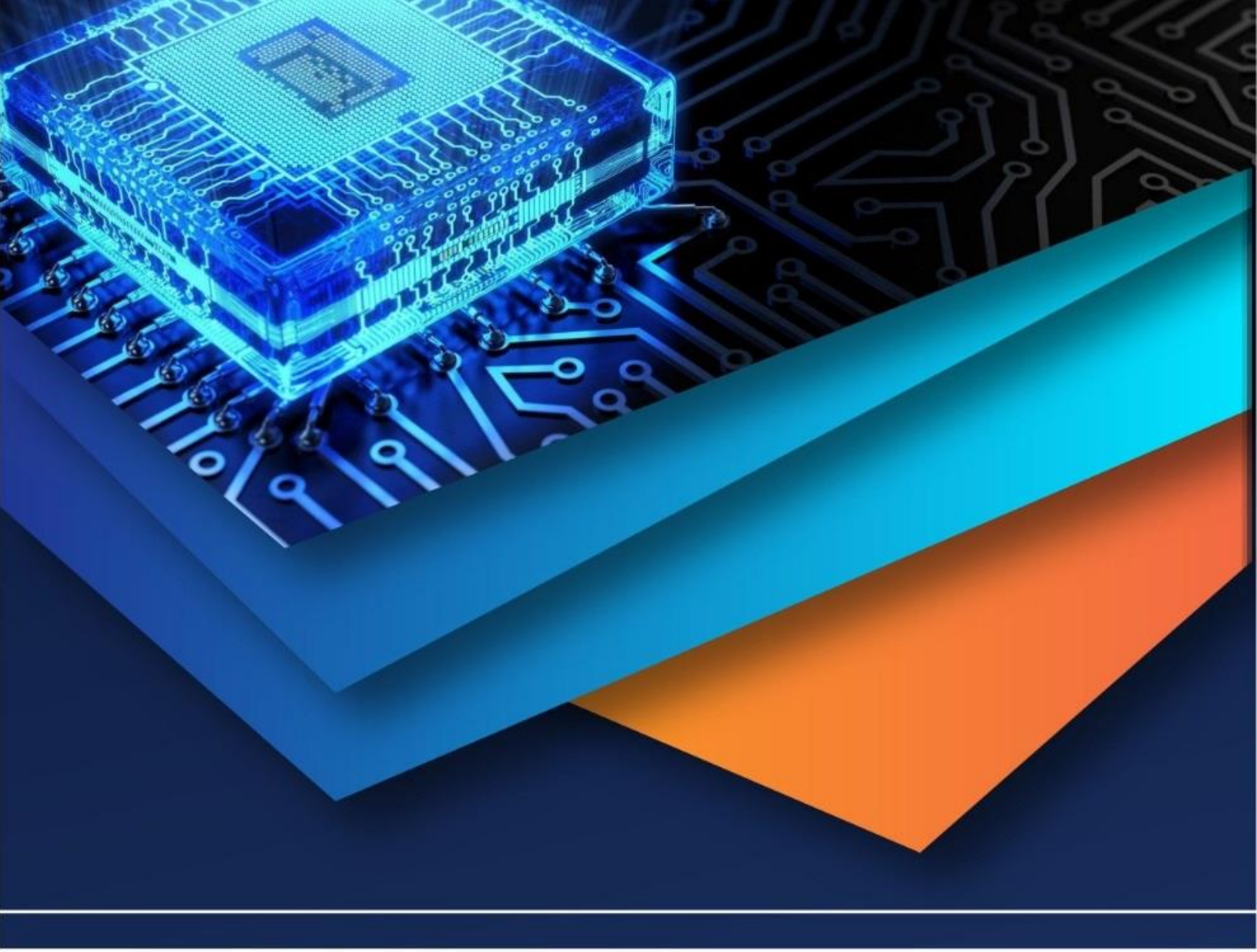
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