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DIPOLE MOMENT STUDIES ON ANTICANCER POLYAROMATIC COMPOUNDS

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Abstract: Synthesis of polyaromatic hydrocarbons by various methods is studied. The metabolic activation of these types of hydrocarbons is investigated. However, methods to prepare new anticancer compounds from polyaromatic hydrocarbons are not investigated. We report here synthesis and biological evaluation of a few derivatives derived from polyaromatic molecules. Several interesting results are obtained and therefore, the use of these agents for further anticancer research is identified.

Introduction: Synthetic and biochemical research on polyaromatic hydrocarbons has received excellent recognitions from scientific community [1]. But there has been poor attention on the use of the derivatives of these molecules as anticancer agents. Bair *et al.* had identified a correlation between the effectiveness of a few of these derivatives against cancer cell lines [2]. As a result of these efforts, benzylic aminopropanediols were investigated. Some of these compounds were believed to be active against numerous cancer cell lines. These compounds were also found to interact with DNA by intercalation and showed topoisomerase inhibitory activities. The intercalative properties were confirmed for the potent napthalimides, amonafide and mitonafide [3-6].
Studies by Denny *et al.* raised doubts regarding the validity of the target by poly aromatic-based antitumor compounds. These crucial studies prompted our group to offer excellent possibilities to expand research on poly aromatic compounds to demonstrate their effective synthesis and selective anticancer activities *in vitro* and *in vivo* [7-12].
In vitro assays were conducted using 72h of continuous exposure to the molecules. Relative cell growth was determined following MTT method. The final concentration of solvent was kept below <0.625%, which is found non-toxic to the cells. Dilutions were made in RPMI 1640 with 10% FBS. Cancer Cell growth inhibition data was expressed in $IC_{50.}$
To demonstrate activity or non-activity and for a comparison, the following terms were used. Compounds that demonstrated IC_{50} values above 10.0 μM was described as inactive; 5.0 μM <10 μM as limited activity; 2.5 μM < 5.0 μM as modest activity, and below 2.5 μM as active. The controls for the MTT assay were maintained including in every run two known anticancer compounds including a well-known drug cisplatin or adriamycin. To obtain

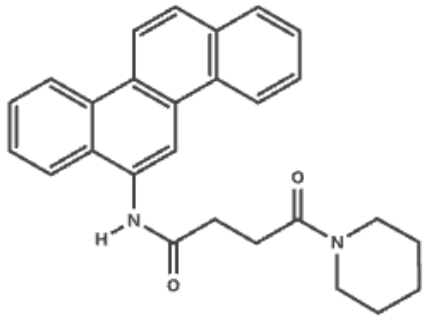
consistent and reliable results, in the majority of the experiments, an inactive polyaromatic molecule was used as a negative control, but the experiment was not counted valid unless at least one new synthesized molecule expressed positive and another negative inhibition data. This consistency experiment of the *in vitro* test was performed repeatedly comparing all molecules (particularly the promising groups) over 20 months. There was minor changes of the inhibition data in the result of a given compound and cisplatin against a single tumor line. But it was remarkable to note that in the vast majority of the examples, the active or inactive compound's status remained within its original activity classification as described above.

Interestingly **1a**, the amide with a terminal piperidine moiety of chrysene was inactive against all cancer cell lines, a similar molecule **1b** with a terminal piperazine group demonstrated limited activity against 4/7 cancer cell lines. The molecule **2a**, the amino derivative of chrysene with a terminal piperidine group demonstrated modest activity against three/seven and was active against four/seven cancer cell lines.

The *in vitro* cytotoxicity data of 6, 12-disubstituted amide derivatives demonstrated interesting variations between symmetrical and asymmetrical molecules. Surprisingly, the symmetrical *bis* molecules with terminal piperidine group **3a** and with terminal piperazine ring **3b** were all inactive against the tested cancer cell lines. Compound **4a** and 4b was active against all seven tumor cells.

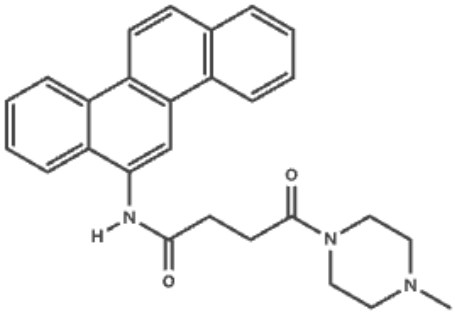
An excellent activity of the amino compounds was observed against almost every cancer cell lines tested, regardless of its structural alterations. To support this claim, the data showed that each of the amino compounds **including the 4a and 4b** behaved similarly and they were active.

In general, electronegative atoms tend to increase the polarity of the molecules. However, this electronegative character can decrease the dipole moment of molecules. In compound 1b, the presence of the N-methyl group can act as an electron donor and thereby can decrease the overall charge density in molecule 1b compared to 1a.



1a

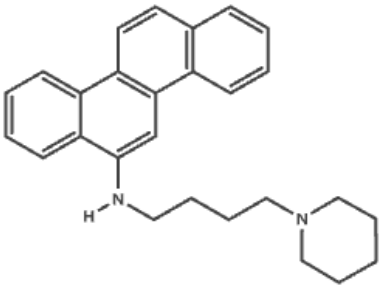
1a (DM:3D)



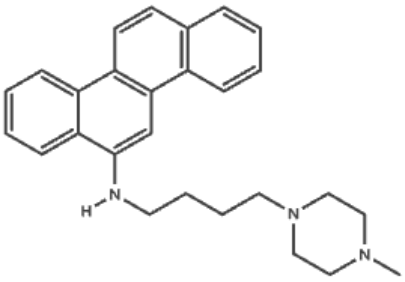
1b

1b (DM:2.77)

In the amine series 2a and 2b, the dipole moments are lower compared to amides 1a and 1b. Two electronegative oxygens of the amide structures in 1a and 1b are reduced to obtain 8a and 8b. Because of the presence of the N-methyl group in 2b, the dipole moment of this compound becomes lower than that of 2a.



2a (DM:2.68)

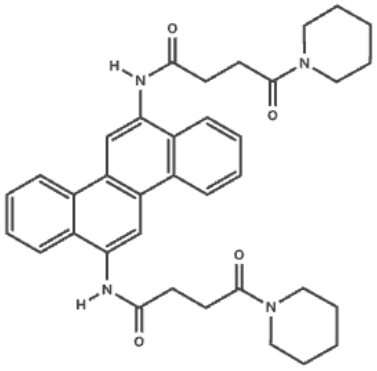


2b (DM:1.06)

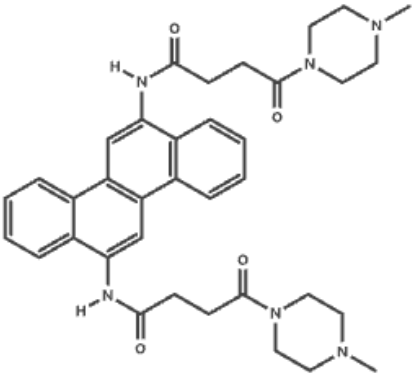
The differences of dipole moments in 8 and 7 are an interesting observation. The electron withdrawing carbonyl groups in 7 are responsible for the higher dipole moments for the amides compared to the amines. The compounds that have lower dipole moments in an identical series have superior anticancer activity.

The two chains in tetramides make 3a and 3b highly polar compared to 1a and 1b. However, the dipole moment of 32a and 32b is close to each other, whereas the differences of the dipole moment in 1a and 1b are high. Because of the symmetrical nature of the molecules 3a and 3b, electron releasing property of the N-methyl group does not affect the electron denisity within these two molecules 3a and 3b. Therefore, the dipole moment data of both 3a and 3b remains very similar.

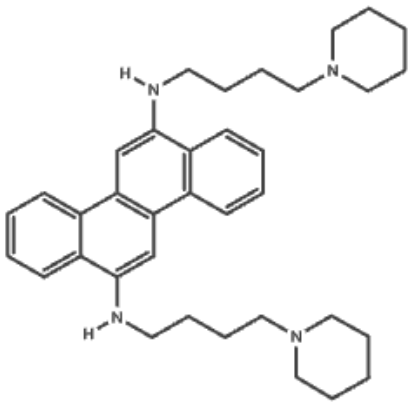
The dipole moment of the tetra amines 4a and 4b is lower than that of 3a and 3b because the carbonyl groups are not present in 4a and 4b.



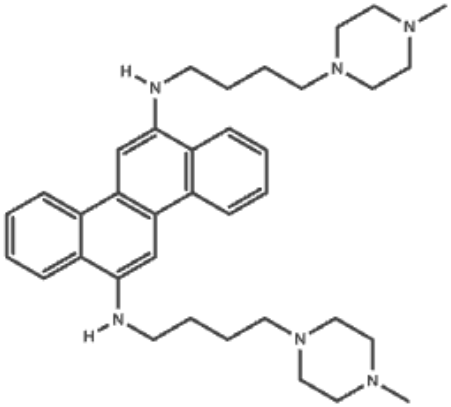
3a (DM:3.2)



3b (DM:3.07)



4a (DM:1.15)



4b (DM:1.75)

	1a	**1b**	**2a**	**2b**	**3a**	**3b**	**4a**	**4b**
DFT	**3**	**2.77**	**2.68**	**1.06**	**3**	**3.07**	**1.15**	**1.75**

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