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Correlation of Aqueous Solubility and Anti-Cancer Activity of Novel Triazolium and Imidazolium Salts

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CORRELATION OF AQUEOUS SOLUBILITY AND ANTI-CANCER ACTIVITY OF NOVEL TRIAZOLIUM AND IMIDAZOLIUM SALTS

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JARED J. BIES

ABSTRACT

Novel triazolium, imidazolium, and benzimidazolium salts are known to possess anti-cancer properties and have potential as cancer therapeutics. This thesis describes the aqueous solubility and the differential activity of *N,N'*-bis-substituted-1,2,4-triazolium bromide salts and *N,N'*-bis(naphthylmethyl)imidazolium bromide salts against MDA-MB-468 breast cancer cells and PC-3 prostate carcinomas. Using a microscale technique, the partition coefficient (log P) of each salt was determined. The log P value was explored to determine the bioavailability of each derivative.

DEDICATION

I would like to dedicate this thesis to my mother, father, grandmother, brother and members of the Bies Family. I would be nothing without each and every one of you. Thank you for your love and support!

ACKNOWLEDGMENTS

I would like to acknowledge my thesis director, Dr. Jonathan Meyers, for all his support and mentorship during this journey. Thank you for investing your time and energy to help me complete this Honors Thesis. Your guidance and knowledge has been greatly appreciated throughout this process.

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Special thanks to the number of organizations that provided funding for this project: Columbus State University (CSU) Student Research and Creative Endeavors Committee, American Chemical Society (ACS) National Chapter, ACS Auburn Local Section Chapter, CSU ACS Chapter, and CSU Honors College. A portion of the financial assistance was utilized to present this research at the 2018 ACS National Meeting in New Orleans, Louisiana. Thank you to the Department of Chemistry for providing me with the laboratory space and funding to conduct my undergraduate research.

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Introduction

I. Cancer

Cancer is a devastating disease that effects over 1.5 million people each year and the annual death toll exceeds 550,000 deaths making it the second leading cause of death in the United States.[1,2] Cancer is also one of the leading causes of death worldwide. It contributed to 8.2 million deaths in 2012.[3] Due to its prevalence, an enormous amount of funding is dedicated to establishing treatments and cures.

Cancer is characterized by deregulated cell proliferation. The rapidly dividing cells require several biomolecules, including fatty acids and membrane lipids, to fulfill their needs.[4] Cancer has various forms and can begin in any part of the body. Left untreated, malignant cancers can metastasize. When cancer metastasis occurs, cancerous cells have the potential to compromise the integrity of other organ systems within the body and lead to death.

II. Triazolium and Imidazolium Salt Derivatives

Cell-specific cancer treatments exist only for a few cancers.[5] Traditional chemotherapies tend to lack cell-specificity, which leads to the damage of healthy cells. Imidazole and triazole based compounds have long garnered attention for their cancer killing potential, and their salt derivatives have been shown to possess selective anticancer properties.[6,7] A recent study presented a novel 1,2,3-triazolium salt that

arrested the growth of the drug resistant 7T subline of laryngeal carcinoma HEp-2 cells.[8] Another study has shown that a series of imidazolium salts were found to be selectively toxic to two highly tumorigenic breast cancer cell lines and not to normal breast cells.[9]

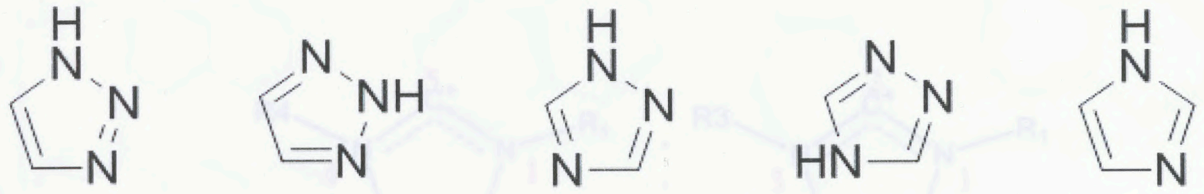

Figure 1: Triazole and Imidazole Compounds. Triazoles are heterocyclic compounds containing three nitrogen atoms. The five membered rings can have four structures (Left to right: 1H-1,2,3-Triazole; 2H-1,2,3-Triazole; 1H-1,2,4-Triazole; 4H-1,2,4-Triazole). Imidazole (far right) is a heterocyclic compound with two nitrogen atoms.

Triazoles are heterocyclic compounds containing three nitrogen atoms. The five membered rings can have four structures (Figure 1). Imidazole is also a heterocyclic five-membered ring, but with two nitrogen atoms (Figure 1). Heterocyclic compounds are key components of many biologically active compounds. The imidazole ring is a constituent of purine, histamine, histidine, and nucleic acid bases.[10] In addition, the heterocyclic composition of triazole derivatives garners biological significance as they can have many biological properties such as serving as selective adenosine receptor agonists and antagonists.[11]

Due to the poor solubility of triazole and imidazole compounds, most studies have utilized the ionic form of these heterocyclic rings. Both imidazole and triazole have weakly acidic protons and can undergo deprotonation upon treatment with a strong base. Alternatively, di-substitution produces the cationic forms (Figure 2).

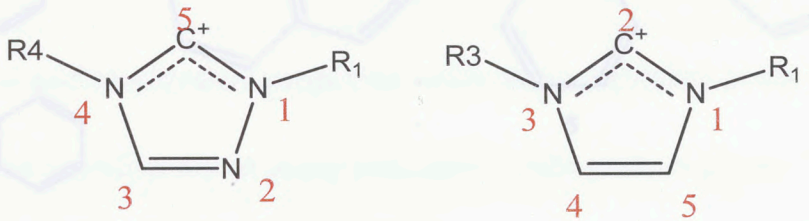

Figure 2. *N,N'*-bis-substituted 1,2,4-triazolium and imidazolium cations. 1,2,4-triazolium (left) and imidazolium (right) cations formed by di-substitution.

Numerous studies have highlighted the importance of the substituent structure in determining the physical and chemical properties of the resulting triazolium and imidazolium salts.[8] Using this information, a set of *N,N'*-bis-substituted-1,2,4-triazolium bromide salts (**1 - 3,** Figure 3) were synthesized and tested for anti-proliferative activity against MDA-MB-468 breast cancer cells and PC-3 prostate cancer cells. These novel 1,2,4-triazolium salts (**1 – 3**) were also tested against previously reported imidazolium salts (**4** and **5**) to determine the role of the parent compound (i.e. imidazole, triazole, benzimidazole) on aqueous solubility and activity.

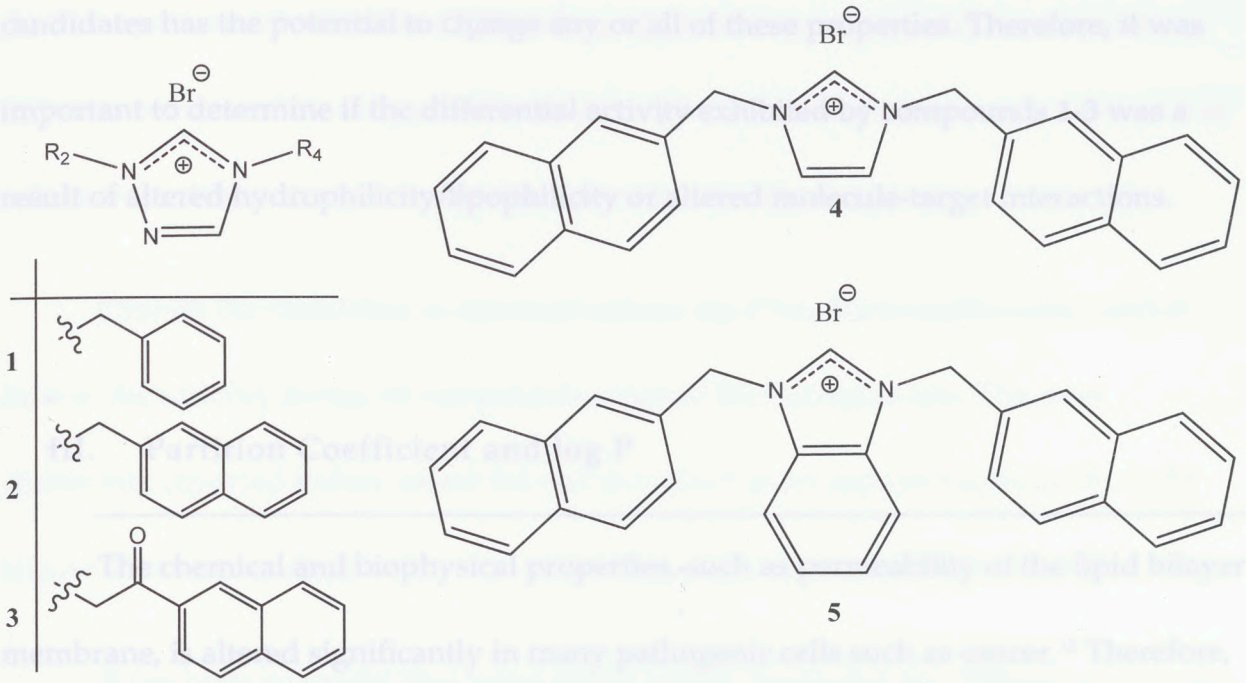

Figure 3. Schematic representation of *N,N'*-bis-substituted-1,2,4-triazolium bromide salts (1-3), *N,N'*-bis(naphthylmethyl)imidazolium bromide (4) and *N,N'*-bis(naphthylmethyl)benzimidazolium bromide (5) compounds.

The novel compounds (**1-3**) exhibited a range of anti-proliferative activities. However, it was unclear if differential activity was due to modified receptor-ligand interactions or a result of altered solubility and bioavailability. Rational drug design is complicated by the need to balance many stringent and often competing requirements. In order for a molecule to have biological activity, it must have a chemical structure that is complimentary to its target. However, even the most potent drug is useless if it cannot reach its target. Often this means the compound must have an aqueous solubility high enough to allow transport via the bloodstream, yet still retain sufficient lipophilic character to cross the cellular membrane. Modification of potential drug

candidates has the potential to change any or all of these properties. Therefore, it was important to determine if the differential activity exhibited by compounds **1-3** was a result of altered hydrophilicity/lipophilicity or altered molecule-target interactions.

III. Partition Coefficient and log P

The chemical and biophysical properties, such as permeability of the lipid bilayer membrane, is altered significantly in many pathogenic cells such as cancer.[12] Therefore, the balance between hydrophilic and lipophilic character must be optimized to allow for both distribution and uptake. The partition coefficient, which describes the partitioning of a solute between an organic and an aqueous phase, is used extensively in medicinal chemistry and drug design.[13] In this study, the octanol/water partition coefficient (K_{ow}) was utilized. The octanol/water partition coefficient is K_{ow}, see Equation 1.

$$K_{ow} = \frac{final\ concentration\ in\ octanol\ layer}{final\ concentration\ in\ aqueous\ layer} = \frac{C_{of}}{C_{wf}} \qquad (1)$$

Taking the mathematical logarithm of K_{ow} yields the log P value. The log P values are weakly dependent on solute concentration and highly dependent on temperature. It is also important to note that reported K_{ow} and log P values often vary

due to experimental differences. Therefore, rigorous comparison of these values for different compounds is only possible within a given data set. It is strongly advised that values from different experiments should not be directly compared.

Despite the variability in reported values, log P has been traditionally used to inform the rational design of compounds targeted for biological use. The most commonly reported values reflect the use of octanol as an approximation of the lipid bilayer that surrounds all cells.

It has been proposed that novel drugs which can exploit the differences between cancer and healthy cells may be a route to selective anti-cancer treatments. The log P value of new drugs offers an insight in the development of target-oriented cancer therapies.

IV. Methods and Materials

A. Materials

Triazolium and imidazolium compounds. All reagents and solvents used in the synthesis of compounds **1 – 5** were purchased from commercial sources and used without purification. Compounds **1 – 5** were provided by the Taylor Lab.

Partition Coefficients. Octanol and dimethyl sulfoxide were purchased from Sigma Aldrich. The following instruments were used: a Thermo Fisher Genesys 10s UV-Vis spectrophotometer, a Sorvall Lynxx 4000 Superspeed Centrifuge, a Thermo Micro 17 Microcentrifuge, and a 700-µL quartz cuvette (Thor Labs).

Cell Culture. MDA-MB-468 breast cancer cells and PC-3 prostate cancer cells (ATCC) were grown in L-15 and DMEM/F12K media supplemented with 10% FBS and 1% antibiotic/antimycotic. PC-3 cells were grown in 5% CO_2 incubator at 37°C. MDA-MB-468 cells were grown in the absence of CO_2 at 37°C. Media was replaced every 3 days and split once 80% confluency was reached.

MTT assays. Cells were plated in triplicate at $1x10^6$ cells/mL with 0.1 mL per well in 96-well plates and allowed to adhere overnight. After 24 h incubation, media was removed, and cells were treated with 0, 1, 5, 15 and 30 µM of compounds **1 – 5** solubilized in fresh complete growth media for 72 h at 37°C. After incubation, MTT reagent (ATCC) was added to each well and returned to the incubator for 4 h at 37°C to produce formazan crystals in the dark. Next, MTT detergent was added to solubilize

crystals and incubated for another 2 h in the dark. Absorbance was read at 570 nm with a reference wavelength of 655 nm.

B. Determination of Lambda Max (λ_{max})

The lambda max represents the wavelength at which a compound absorbs the maximum light. To scan for the lambda max of each compound, very dilute samples of **1 – 5** were prepared in dH_2O and the absorbance spectrum from $200 - 300\ nm$ was measured. After scanning each compound, the lambda max for each compound was measured to be close to or at 223 nm. Therefore, all absorbance measurements were conducted at 223 nm.

C. Determination of Linear Range

Molar absorption coefficients (**ε**) for the novel *N,N'*-bis-substituted-1,2,4-triazolium bromide salts (**1-3**) and *N,N'*-bis(naphthylmethyl)imidazolium bromide salts (**4** and **5**) compounds were not directly measured. However, the linear range for absorbance vs. concentration was determined. Each compound was dissolved in a 50 mL centrifuge tube with dH_2O. If the compound did not dissolve completely, a 1 mL aliquot was placed in a 1.5 mL microcentrifuge tube and centrifuged for 5 minutes at max speed in the Sorvall Lynxx 4000 Superspeed Centrifuge. The supernatant was pipetted to a new 1.5 mL microcentrifuge tube. The absorbance of the supernatant was

measured at 223 nm. The solutions were diluted, and the absorbance measured until there was a direct correlation between dilution factor and absorbance. It was determined that concentrations that produced an absorbance around 0.500 were in the linear range for all compounds.

D. Preparation and Measurement of Partition Coefficients

To determine the log P value of each compound, a microscale approach using 1.5 mL microcentrifuge tubes was utilized. Each log P measurement was performed in triplicate. Briefly, 700 μL of octanol and 700 μL of the water dissolved compound were vigorously mixed using a lab mixer. Each sample was then allowed to fully equilibrate overnight. The next day, each sample was briefly centrifuged using a Thermo Micro 17 Microcentrifuge to further aid separation of the solvent layers. Then 300 μL of the top octanol layer was removed and placed into a separate 1.5 mL microcentrifuge tube to avoid any overspill caused by volume displacement upon pipette tip insertion. Immediately, 300 μL from the very bottom of the aqueous layer were removed, avoiding any octanol contamination, and placed into a separate 1.5 mL microcentrifuge tube. Then this sample was diluted with 200 μL of water and mixed briefly before the absorbance at 223 nm was measured. The absorbance of the compound in the aqueous layer before and after incubation with octanol was used to determine the K_{ow} and log P values for each compound.

E. Calculations

Due to time constraints, it was impractical to fully explore the changes in the UV absorbance spectrum for each compound in both water and octanol. Therefore, all characterization was carried out on the aqueous layer. The law of conservation of mass, along with Beer's Law, makes it possible to calculate the concentration of samples in the octanol layer by measuring the change in concentration in the aqueous layer. The partition coefficient is the ratio of the final concentration of the compound in octanol ($[C]_{of}$) and the final concentration of compound in the aqueous layers ($[C]_{wf}$) as seen in Equation 1.

$$K_{ow} = \frac{[C]_{of}}{[C]_{wf}} \quad (1)$$

Mass conservation means that the amount of compound that enters the octanol layer (ΔM_o) can be determined by measuring the amount of compound lost from the aqueous layer ($-\Delta M_w$, Equation 2).

$$\Delta M_o = -\Delta M_w \quad (2)$$

The mass (m) of a compound present is directly related to the volume (V), molar concentration $[C]$ and molecular weight (MW).

$$m = [C] * MW * V \quad (3)$$

We can determine the change in mass by combining Equations 2 and 3 to give Equation 4.

$$\Delta([C]_o * MW * V_o) = -\Delta([C]_w * MW * V_w) \quad (4)$$

Under conditions in which the molecular weight does not change and the volume of the two solvents are equal, the equation can be simplified, as shown in Equation 5.

$$\Delta[C]_o = -\Delta[C]_w \quad (5)$$

Given the situation where initial concentration of compound in the octanol is zero, the change in compound concentration is simply equal to the final concentration (Equation 6).

$$\Delta[C]_o = ([C]_{of} - [C]_{oi}) = ([C]_{of} - 0) = [C]_{of} \quad (6)$$

Combining Equations 5 and 6 gives us the final compound concentration in the octanol layer in terms of the compound concentration in the water layer (Equation 7).

$$[\boldsymbol{C}]_{\boldsymbol{of}} = -\Delta[\boldsymbol{C}]_{\boldsymbol{w}} \quad (7)$$

The partition coefficient equation can now be written in terms of the compounds concentration in the water level (Equation 8).

$$K_{ow} = \frac{[C]_{of}}{[C]_{wf}} = \frac{-\Delta[C]_w}{[C]_{wf}} \quad (8)$$

Beer's Law relates the light absorbance (A) of an analyte to the molar absorption coefficient (ε), the length of the light traveled through the sample (l), and the molar concentration of the analyte (Equation 9).

$$A = \varepsilon C l \quad (9)$$

Rearrangement allows the concentration to be determined when the absorbance is known, assuming that the molar absorption coefficient is not zero (Equation 10).

$$C = \frac{A}{\varepsilon l} \quad (10)$$

The variable of concentration can be substituted into the partition coefficient Equation 8, to give Equation 11.

$$K_{ow} = \frac{-\Delta(\frac{A}{\varepsilon l})_w}{(\frac{A}{\varepsilon l})_{wf}} \quad (11)$$

Since all measurements are of the water layer, the molar absorption coefficient is constant. Likewise, the path length is a constant. Therefore, the partition coefficient can be determined directly from the absorbance values (Equation 12).

$$\mathrm{K_{ow}} = \frac{-\Delta \mathrm{A_w}}{\mathrm{A_{wf}}} \quad (12)$$

VI. Results and Discussion

A. Partition Coefficient (log P) Analysis

The partition coefficient of each novel triazolium salt **1-3**, imidazolium salt **4**, and benzimidazolium salt **5** derivative is shown in Figure 4. Compound **1** exhibited the highest aqueous solubility among all salt derivatives and would have the greatest bioavailability. Compound **5** exhibited the greatest octanol solubility among the salt derivatives and would have the lowest bioavailability. Compounds **2-4** exhibited variability in solubility and bioavailability.

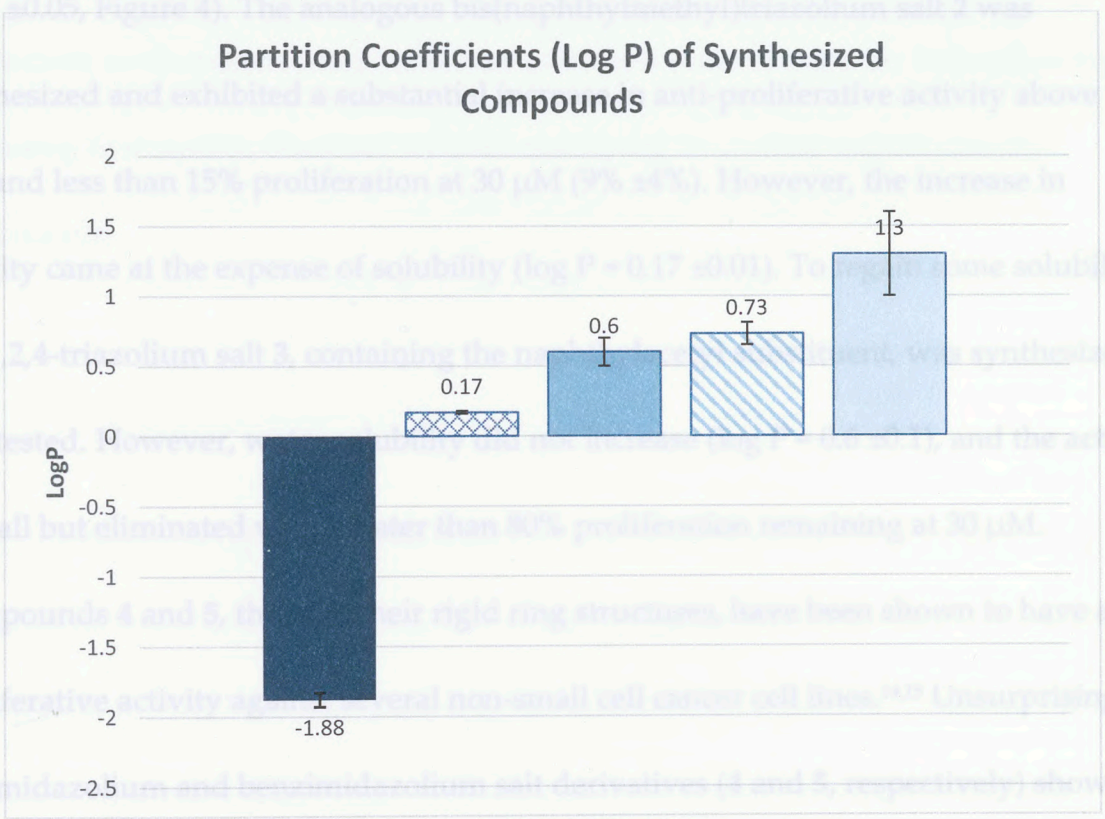

Figure 4. Partition Coefficient of Synthesized Compounds. Compound identification: Compound **1** (Dark blue), Compound **2** (Crosshatched), Compound **3** (Medium blue) Compound **4** (Diagonal lines), and Compound **5** (Light blue with dark outline). The octanol/water coefficient of compounds **1-5** was determined in a microscale assay. Positive Log P values represent an increased affinity for the octanol layer.

B. MDA-MB-468 Breast Cancer Cell Proliferation Assay

Once the partition coefficient of each novel compound was determined, a proliferation assay was conducted on MDA-MB-468 breast cancer cells to distinguish the correlation between the determined partition coefficients and effectiveness in reducing cancer cell proliferation rates. Compound **1** exhibited very poor anti-proliferative activity against MDA-MB-468 breast cancer cells with more than 70% proliferation at 30 μM (73% ±19%, Figure 5) despite favorable water solubility (log P = -1.88 ±0.05, Figure 4). The analogous bis(naphthylmethyl)triazolium salt **2** was synthesized and exhibited a substantial increase in anti-proliferative activity above 15 μM and less than 15% proliferation at 30 μM (9% ±4%). However, the increase in activity came at the expense of solubility (log P = 0.17 ±0.01). To regain some solubility, the 1,2,4-triazolium salt **3**, containing the naphthylacetyl substituent, was synthesized and tested. However, water solubility did not increase (log P = 0.6 ±0.1), and the activity was all but eliminated with greater than 80% proliferation remaining at 30 μM. Compounds **4** and **5**, through their rigid ring structures, have been shown to have anti-proliferative activity against several non-small cell cancer cell lines.[14,15] Unsurprisingly, the imidazolium and benzimidazolium salt derivatives (**4** and **5,** respectively) showed similar anti-proliferation effects in the breast cancer cell assays. This anti-proliferative activity was present despite the unfavorable water solubility in **4** (log P = 0.73 ±0.08) and **5** (log P = 1.3 ±0.3).

After conducting the MDA-MB-468 breast cancer cell proliferation assay, it was seen that **2** exhibited similar effects on cell proliferation much like that of **4** and **5** at 30 μM, but not at lower concentrations. The similar anti-proliferative effect of **2** was at a 4-fold increase in water solubility (log P = 0.17 ±0.01) compared to **4** (log P = 0.73 ±0.08) and **5** (log P = 1.3 ±0.3). This increased solubility was due to the introduction of the additional unsubstituted nitrogen. The marked differences in activity of **2** at lower concentrations suggests that modification of the parent core may impact solubility more drastically than anti-cancer activity. It also suggests that using the triazolium heterocycle as the parent compound may provide a route to superior bioavailability by increasing hydrophilic character without modifying the crucial naphthylmethyl substituents.

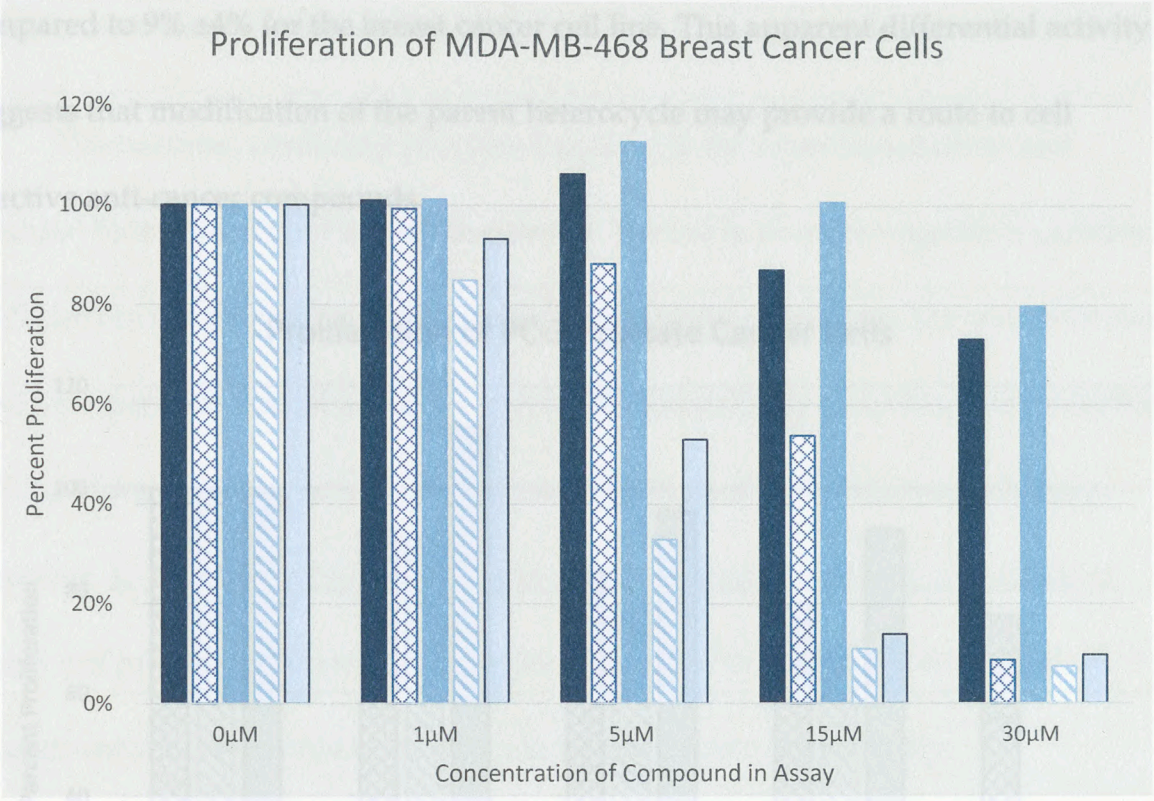

Figure 5. Proliferation of MDA-MB-468 Breast Cancer Cells Treated with 1-5. Coloring is the same as Figure 4. Compounds **1** and **3** had very little anti-proliferative effects even at 30 μM. Compounds **2**, **4**, and **5** showed similar anti-proliferative effects at 30 μM.

C. PC-3 Prostate Cancer Cell Proliferation Assay

To determine the effectiveness of **2** on additional cancers, its activity against PC-3 prostate cancer cells was compared to **4** and **5.** Compounds **4** and **5** have previously been shown to exhibit similar activity against several non-small cell cancer cell lines.[14,15] Unsurprisingly, the imidazolium and benzimidazolium salt derivatives (**4** and **5,** respectively) showed similar anti-proliferation effects in both the breast and prostate cancer assays. Interestingly, the triazolium salt **2** had a marked decrease in effectiveness against the prostate cells with more than 70% proliferation at 30 μM (75% ±4%, Figure 6)

compared to 9% ±4% for the breast cancer cell line. This apparent differential activity suggests that modification of the parent heterocycle may provide a route to cell selective anti-cancer compounds.

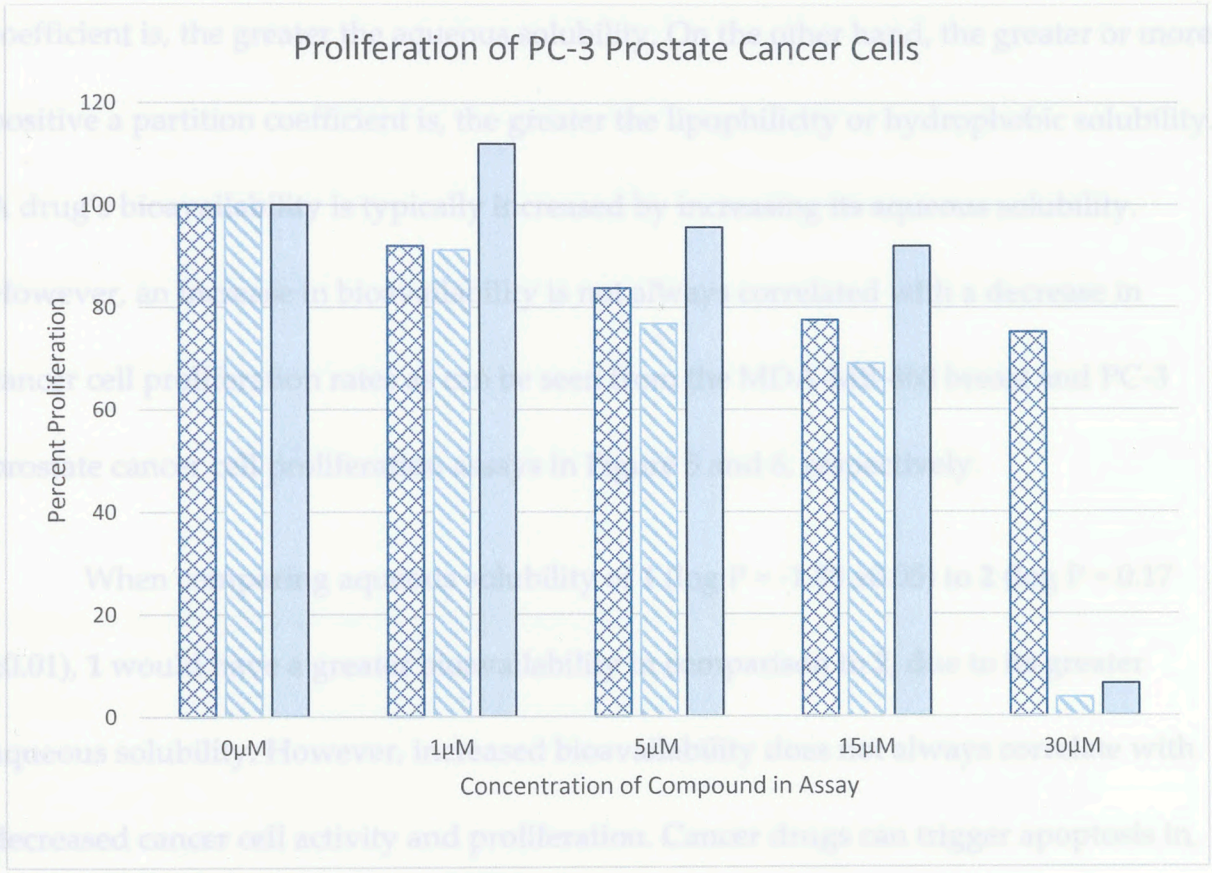

Figure 6. Proliferation of PC-3 Prostate Cancer Cells Treated with 2, 4, and 5. Coloring is the same as Figure 5. In contrast to activity against the breast cancer cell line, compound **2** exhibited very low activity against the prostate cancer cell line. In contrast, **4** and **5** showed similar anti-proliferative effects against both cancer types.

D. Correlation of Aqueous Solubility and Anti-Cancer Activity

The partition coefficient provides insight into the aqueous solubility and potential bioavailability of novel compounds. The lower or more negative a partition coefficient is, the greater the aqueous solubility. On the other hand, the greater or more positive a partition coefficient is, the greater the lipophilicity or hydrophobic solubility. A drug's bioavailability is typically increased by increasing its aqueous solubility. However, an increase in bioavailability is not always correlated with a decrease in cancer cell proliferation rates as can be seen from the MDA-MB-468 breast and PC-3 prostate cancer cell proliferation assays in Figure 5 and 6, respectively.

When comparing aqueous solubility of **1** (log P = -1.88 ±0.05) to **2** (log P = 0.17 ±0.01), **1** would have a greater bioavailability in comparison to **2,** due to its greater aqueous solubility. However, increased bioavailability does not always correlate with decreased cancer cell activity and proliferation. Cancer drugs can trigger apoptosis in cancer cells via binding to surface receptors or diffusing into the cells. These two factors are significantly affected by both a compound's structure and solubility. That is, if a compound does not exhibit the proper structural domains/functional groups necessary to trigger programmed cell death, even if soluble, apoptosis will not occur. Therefore, this explains the observation between the triazolium salt compounds **1** and **2**. Although, **1** had greater bioavailability due to its increased aqueous solubility, it did not have the

same anti-proliferative effects as **2** against the MDA-MB-468 breast cancer cell line due to its structure.

VII. Conclusion and future work

This study was conducted to determine the correlation of aqueous solubility and anti-cancer activity of novel triazolium, imidazolium, and benzimidazolium salt derivatives through determination of their partition coefficient. It was determined that the triazolium salts **1** and **3**, did not exhibit any significant anti-proliferative cancer activity. However, the triazolium salt **2**, in comparison to the imidazolium salts **4** and **5**, demonstrated similar anti-proliferative activity against the MDA-MB-468 breast cancer cell line at an increased aqueous solubility. The same anti-proliferative activity against the PC-3 prostate cancer cell line was not observed in **2**. The marked selectivity of **2**, indicates that related triazolium salt derivatives may provide a route to increased aqueous solubility and selective anti-cancer activity.

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Appendix

I. Abbreviations

A	absorbance	log P	Partition Coefficient
λ_{max}	Lambda Max	MDA-MB-468	breast cancer cell line
[C]	concentration of compound	M	molarity of compound
$[C]_o$	concentration in octanol	M_o	molarity of compound in octanol
$[C]_{oi}$	initial concentration in octanol	M_w	molarity of compound in water
$[C]_{of}$	final concentration in octanol	mL	milliliters
$[C]_w$	concentration in water	nm	nanometers
$[C]_{wi}$	initial concentration in water	PC-3	prostate cancer cell line
$[C]_{wf}$	final concentration in water	µL	microliters
dH_2O	distilled water	UV	Ultraviolet
ε	molar absorption coefficient	V	volume
K_{ow}	octanol/water constant	V_o	volume of octanol
l	path length	V_w	volume of water

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A Thesis Submitted to the

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for Honors in the Degree of

BACHELOR OF ARTS
CHEMISTRY
COLLEGE OF LETTERS & SCIENCES

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