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EXAMINATION OF THE ISOSTERE AND BIOISOSTERE SUBSTITUTIONS IN STRUCTURES OF GEMCITABINE, CAPECITABINE, AND PACLITAXEL: THREE AGENTS UTILIZED FOR TREATMENT OF PANCREATIC CANCER

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ABSTRACT

This study presents analysis of isosteres and bioisosteres of gemcitabine, capecitabine, and paclitaxel, which are utilized in the clinical treatment of pancreatic cancer. Pancreatic cancer most commonly occurs (90%) in the form of adenocarcinoma (ductal carcinoma). This is an aggressive and difficult form of cancer to treat, with fewer than 50% of patients surviving past five years. Gemcitabine, capecitabine, and paclitaxel have been shown to be effective in clinical treatment, their molecular properties are determined and presented here for comparison. To increase the number of pharmaceutical agents having potential for treatment of this lethal cancer, the isosteres and bioisosteres of these three agents are shown, along with their molecular properties. Isosteric and bioisosteric substitutions within their molecular structures will bring about changes in molecular properties that are also closely associated with favorable drug-likeness. The molecular properties of the isosteric and bioisosteric substituted compounds are presented and statistically analysed to reveal alterations, however subtle, and statistically analysed for comparison. Summary statistics are shown, with one-way ANOVA (analysis of variance) and one-way ANOSIM (analysis of similarities). In addition, the pattern recognition methodology neighbor joining cluster analysis was applied to reveal with high resolution, the underlying numerical relationships of the molecular properties, as well as revealing similarities or dissimilarities of their molecular properties.

KEYWORDS: Pancreatic Cancer, Gemcitabine, Capecitabine, Paclitaxel, Isosteres.

INTRODUCTION

It is estimated that approximately 90% of all pancreatic carcinomas are in fact pancreatic adenocarcinoma, inclusive of all its variants.[1] The 5-year survival rate is rather bleak, for the current global 5-year survival rate is estimated to be merely 6%.[1] The development of pancreatic adenocarcinoma progresses through specific precursor lesions before reaching an invasive malignancy.[1] The risk of pancreatic cancer is influenced by various immutable factors such as age, gender, family history, blood group (apparently blood group A has higher risk), diabetes, ethnicity, and even the microbiota within the gut.[1] Other factors which can be controlled include smoking, consumption of alcohol, obesity, infection (increased risks with *Helicobacter pylori* or hepatitis C infections), diet, and progressive inflammatory conditions of the pancreas.[1] A higher 5-year survival rate is achieved for patients that present early enough to allow successful surgical resection, however, currently only about 20% of patients that do present will fall into this category.[1] Treatment options encompass surgical resection (Pancreatico-duodenectomy or Whipple's procedure, distal or total pancreatectomy), pharmaceutical treatment that can include capecitabine and gemcitabine (utilized for both advanced and the metastatic disease state), mFOLFIRONOX (which is actually a combination of oxaliplatin, irinotecan, and leucovorin),[1] and paclitaxel.[2]

Classical Bioisosteres are a substitution of atoms with those having the same valence electrons in the structure, have similar structural properties, and maintains similar biological properties.[3] Non-classical Bioisosteres are

those directed primarily by the binding requirements of the ligand to be substituted. Bioisosteres also include classical isosteres.[3] Classical isosteres can function as Bioisosteres. [4] Examples of classical isosteres include: -F, -Cl. -OH, -NH2, and -CH3.[5,6,7] Nonclassical isosteres do not adhere to the steric and electronic definition of classical isosteres and do not have the same number of atoms as that of the moiety they are to replace.[5,6,7] In addition, isosteres (which can be ions) have similar number of atoms and valence electrons.[5,6] The utilization of isosteres and Bioisosteres has been well established and are very powerful tools for the beneficial design and modification of anticancer agents.[8,9] These modifications allow the rational design of drug molecules that enhances their pharmacological properties including selectivity, binding affinity, metabolic stability, pharmacokinetics, and minimizing toxicity.[9] This study presents the examination of isosteres and Bioisosteres of three pharmaceutical agents that are effective in treating pancreatic cancer. These three agents are gemcitabine, capecitabine, and paclitaxel. Their various molecular properties such as molecular weight, polar surface area, Log P, number of hydrogen bond donors, etc, have been determined and analysed for similarities (by summary statistics and one-way ANOVA), ANOSIM, and by the pattern recognition method neighbor joining cluster analysis. Useful observations concerning these three anticancer agents are obtained that enhance the consideration as to their efficacy for pancreatic cancer treatment.

MATERIALS AND METHODS

Molecular Modeling and Platforms for Determination of Molecular Properties

Heuristic platforms are readily available for the calculation of numerical values for molecular properties such as Log P, polar surface area, molecular weight, number of atoms, refractivity, hydrogen bond donors and hydrogen bond acceptors, and violations of the Rule of 5 (RO5). In this study, the molecular property values for all compounds was determined by Mcule (mcule.com, Palo Alto California USA). An added convenience when utilizing Mcule, is the input of the SMILES (Simplified Molecular Input Line Entry System) identification of the compound, to procure drug-likeness properties of the compounds and determination of various molecular properties. For structure elucidation, this study utilized ACD ChemSketch. Modeling v. 12.01 (Advanced Chemistry Development, 110 Yonge Street, Toronto Ontario, M5C 1T4 Canada). The environmental based software EPI Suite can also be utilized for molecular properties determination (US EPA Estimation Programs Interface v. 1.40, 2012, epa.com).[10]

Pattern Recognition Method and Statistical Analysis

The determination of one-way ANOVA (one way analysis of variance), one-way ANOSIM, as well as summary statistics including median, mean, range, and standard deviation, was accomplished utilizing PAST version 2.15 (copyright Hammer and Harper, 1999-2012).[11] Pattern recognition analysis utilizing neighbor joining cluster analysis was accomplished utilizing PAST version 2.15 (copyright Hammer and Harper, 1999-2012).[11] Shepard Plots were determined using PAST version 2.15, and following non-metric multidimensional scaling.

RESULTS AND DISCUSSION

The application of isosteres and Bioisosteres in drug design and development has been higly successful, efficient, and useful.[8] Such approaches have solved a variety of developmental problems in a beneficial manner. The formal definition of isosteres are those atoms (molecules) that have the same number of valence electrons.[3,4,5] That for Bioisosteres is broader in context and refers to charge, shape, and size to pursue similar pharmacological activity, and not merely identical structure.[5,6,7] With these efforts, ratioinal drug development can achieve reduction in toxicity, improved selectivity, enhance pharmacokinetics, and maximuze potency.[4,5,6]

In the broad genre of anticancer drugs and cancer treatment, it is possible to circumvent developed drug resistance and developed tolerance by the pathology toward chemotherapeutics and/or the targeting medicaments.[9] In these instances, the modification of molecular structure by isosteres and/or Bioisosteres can be substantially beneficial and solve the tolerance and resistance issue in favor of patient survivability.[9]

Considerable amount of study has been achieved to enhance drug design and development. The determination of the polar atoms (primarily nitrogen and oxygen) across the exposed surface of a molecule determines the polar surface area, which can be calculated by available heuristic platforms (see MATERAL AND METHODS). Previous studies have shown that the polar surface area (PSA) of a medicament can greatly influence the activity of the drug. Studies have shown that a PSA greater than 140 Angstroms^2 will indicate the drug will have low cell membrane permeability and poor oral bioavailibility.[12] In addition, effective penetration across the blood-brain barrier, requires a PSA less than 90 Angstroms^2 (more specifically 60 to 70 Angstroms^2).[12] Furthermore, the Rule of 5 (RO5) has been developed to aid the identification of drugs having favorable oral activity if there is no more than one violation of the following parameters: 1) Molecular weight is less than 500 Daltons; 2) Less than or equal to 5 hydrogen bond donors; 3) Less than or equal to 10 hydrogen bond acceptors; 4) The octanol-water partition coefficient (Log P) is less than or equal to 5.[13] Statisrtical analysis and pattern recognition methods are an extremely useful and are considered an important component of pharmaceutical development. Mathematical techniques in summary statistics, numercial analysis, and pattern recognition are amenable and beneficial to understand crucial relationships within drug classes and their

development.[14]

Gemcitabine Isosteres and Bioisosteres

Gemcitabine is utilized for the clinical treatment of pancreatic cancer, but also for bladder cancer, testicular cancer, breast cancer, ovarian cancer, and non-small cell lung cancer.[15] Working as a nucleoside analog agent (pyrimidine antimetabolite), gemcitabine is used as a first-line treatment for pancreatic cancer.[15] Gemcitabine is a very important tool for the treatment of pancreatic cancer, that cancer being one of the foremost causes of cancer deaths.[15] Clearly, the study of isosteres and Bioisosteres of gemcitabine has the potential for increasing the number of effective agents in the treatment of pancreatic cancer. Presented in Fig. 1, are the structures of gemcitabine and six structures of isosteres/bioisosters. The atoms or molecule groups constitiuting the isosteric/bioisosteric substitution are circled (see Fig. 1). Substitutions involved include: -CH_3, -NH_2, -OH, and -F atoms.

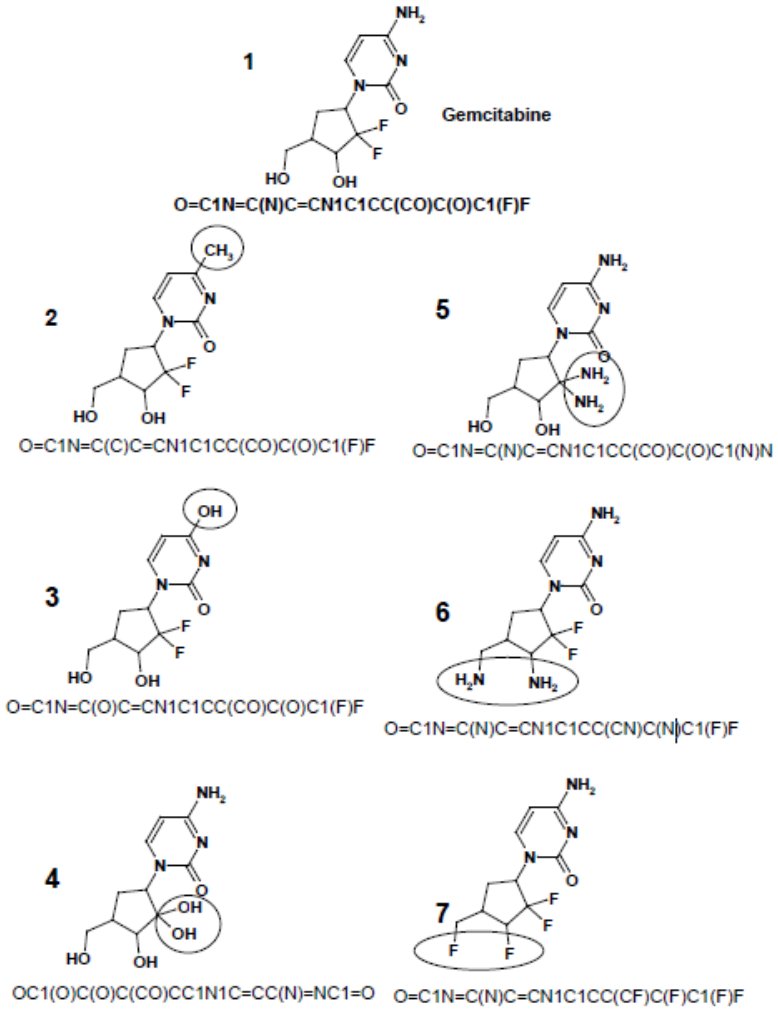

Figure 1: Isosteres and Bioisosteres of gemcitabine. SMILES notation is adjacent to structures. The isosteric/bioisosteric substitutions are circled.

Table 1: Molecular Properties of Gemcitabine Isosteres and Bioisosteres.

Compound	Molecular Weight	Log P	Polar Surface Area (A^2)	Hydrogen Bond Acceptors	Hydrogen Bond Donors	Number of Atoms	Refractivity	Rule of Five Fault
1 Gemcitabine	261.2	-0.044	101.4	8	3	31	58.5	0
2	260.2	0.101	75.4	7	2	32	59.1	0
3	261.2	-0.044	101.4	8	3	31	58.5	0
4	257.2	-2.00	141.8	8	5	33	60.8	0
5	255.3	-0.66	153.4	8	5	35	63.9	0
6	259.3	1.29	113.0	8	3	33	61.6	0
7	265.2	1.91	60.9	8	1	29	56.3	0

Table 2: Summary Statistics of Molecular Properties.

Statistic	Molecular Weight	Log P	Polar Surface Area (A^2)	Hydrogen Bond Acceptors	Hydrogen Bond Donors	Number of Atoms	Refractivity	Rule of Five Fault
Mean	259.9	0.079	106.8	8	3	32	59.8	0
Median	260.2	-0.044	101.4	8	3	32	59.1	0
Standard Deviation	3.1	1.3	33	0	1.5	2.0	3	0
Range	255.3-265.2	-2.0 -1.9	60.9-153.4	7-8	1-5	29-35	56.3-63.9	0

The molecular properties for compounds 1 to 7 have been determined and are shown in Table 1, with summary statistics compiled in Table 2. Immerdiately recognized is that compounds 1, 2, 3, 6 and 7, having PSA less than 140 Anstroms^2, and will have favorable cell permeation and oral bioavailability.[12] This observation is further substantiated by the zero violations of RO5 for all compounds.[13] In addition, compounds 2 and 7 could effectively cross the blood-brain barrier based on their PSA less than 90 Angstroms^2.[12]

The objective of one-way ANOVA statistical test, is to determine if there is any significant differences among the means of multiple independent groups (the eight molecular properties for each isostere/bioisostere in this study).[14] For one-way ANOVA, the value of (***P*=1.0**), which indicates that the molecular properties mean of the parent compound (gemcitabine here) are not statistically different from that of the same properties for each of the isosteres/Bioisosteres, and to each other, shown in Table 1.[14]

The objective for ANOSIM (Analysis of Similarities) is to determine if the composition of multiple groups of data are different and that the difference has statistical significance.[14] For ANOSIM analysis, the value of (***P*=.85**) and (**R=-.34**), for Table 1. This indicates that the group of molecular properties for each isostere/bioisostere are not different in composition, but are statistically alike. The value of (**R= -.34**) indicates these groups of molecular properties are statistically indistinguishable.

Summary statistics for these molecular properties are shown in Table 2, showing concise ranges for molecular weight, Log P, etc, which helps define boundaries for potential analogs to gemtacibine, in addition for allowing estimation of potential effectiveness of similar agents. The favorable values of RO5 at zero does substantiates that these compounds will have favorable oral bioavailability. Interestingly, there is considerable range in Log P (-2.0 to 1.9), hydrogen bond donors (1 to 5), and polar surface area (60.9 to 153.4 Angstroms^2). Hydrogen bond donors and Log P are an essential part of RO5.[13]

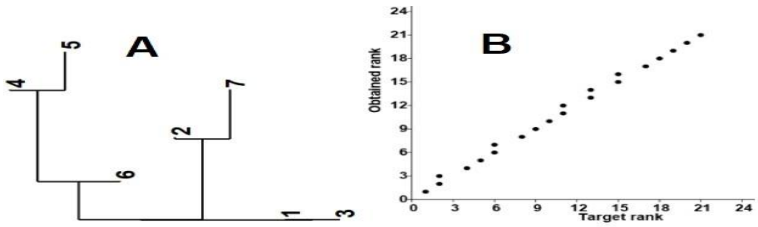

Figure 2: Plot (A) is neighbor joining cluster analysis of Table 1. This result with high resolution of analysis indicated compounds 1 and 3 to be most similar. Compounds 2 and 7 are most similar. Compounds 4, 5, and 6 are clustered and more similar, but with compounds 4 and 6 to have a long leaf from 6, and therefore somewhat distinct. Plot (B) is a highly linear Shepard plot onto a steep and linear line, indicating the lower dimensional neighbor joining cluster plot is highly accurate and representative of the data in Table 1.

Underlying relationships of molecular properties presented in Table 1 and Table 2, can be elucidated with high resolution utilizing neighbor joining cluster analysis.[14] By definition the substitution via isosteres and Bioisosteres maintains vital characteristics of the parent compound in order to preserve effective clinical activity. This goal encompasses the beneficial modifications of the molecular properties (see Table 1 and Table 2) as well. Still, it is possible to identify subtle underlying relationships of molecular properties by use of high resolution pattern recognition methods, such as neighbor joining cluster analysis.[14]

What is shown in Fig. 2, Plot A, is the results of neighbor joining cluster analysis of Table 1 molecular properties, where these seven compounds are placed in groups having the greatest similarity based on their molecular properties. Here, clearly seen are that compound 1 (parent compound gemcitabine) and compound 3 are most similar. Following this, compounds 2 and 7 have highest similarity. Furthermore, compounds 4 and 5, although somewhat distinct from compound 6 based on the length of the longer segment, are most similar to each other. Plot B, Fig. 2, is a steep highly linear Shepard plot showing that the lower dimensional neighbor joining cluster plot is highly accurate data reduction scenario, that distances in the lower dimensional space are an exact match to the original data, and representative of the

data in Table 1.[14] The Shepard Plot is a means to evaluate the "goodness of fit" of the lower dimensional analysis technique to the actual distance between data from the original higher dimensional data set.[14,16]

Capecitabine Isosteres and Bioisosteres

Capecitabine is an anticancer agent that is administered orally and is applied for clinical treatment of pancreatic cancer, colon cancer, rectal cancer, stomach cancer, and breast cancer.[17] Capecitabine is an oral pro-drug that is converted to 5-fluorouracil.[18] This agent is also utilized with other drugs to prevent the return of pancreatic cancer.[17,18]

The investigation of isosteres and Bioisosteres of capecitabine has the potential for increasing the number of effective agents in the treatment of pancreatic cancer. Presented in Figure 3, are the structures of capecitabine and six structures of isosteres/bioisosters. The atoms or molecule groups constituting the isosteric/bioisosteric substitution are circled (see Fig. 3). Substitutions involved include: -CH_3, -NH_2, -Cl -OH, and -S- atoms.

The molecular properties for compounds 8 to 14, have been determined and shown in Table 3, with summary statistics compiled in Table 4. Immerdiately recognized is that compounds 8, 9, 10, 11, and 14 having PSA less than 140 Anstroms^2, and therefore, will have favorable cell permeation and oral bioavailability.[12] This observation is further substantiated by the zero violations of RO5 for all compounds, except for compound 13 which has only one violation.[13]

In addition, compound 10 could effectively cross the blood-brain barrier based on the PSA less than 90 Angstroms^2.[12] Summary statistics for these molecular properties are shown in Table 4, concise ranges for molecular weight, Log P, etc, helps define boundaries for potential analogs to capecitabine, allowing estimation of potential effectiveness of similar agents. The favorable values of RO5 at zero (or 1 for compound 13), substantiates that these compounds will have favorable oral bioavailability. Interestingly, there is considerable range in Log P (-0.40 to 3.33), hydrogen bond donors (1 to 4), and polar surface area (82.5 to 148.9 Angstroms^2). Hydrogen bond donors and Log P are an essential part of RO5.[13] The objective of one-way ANOVA statistical test, is to determine if there is any significant differences among the means of multiple independent groups (the eight groups molecular properties for each isostere/bioisostere in this study).[14]

The objective of one-way ANOVA statistical test, is to determine if there is any significant differences among the means of multiple independent groups (each group of eight molecular properties for each isostere/bioisostere in this study).[14] For this study the outcome of one-way ANOVA, produced the value of (***P*=1.0**), which indicates that the molecular properties mean of the parent compound (capecitabine here) are not statistically different from that of the same properties for each of the isosteres/Bioisosteres, and to each other, for Table 3.[14] The objective for ANOSIM (Analysis of Similarities) is to determine if the composition of multiple groups of data are different and that the difference has statistical significance.[14] For ANOSIM analysis in this study, resulted in the value of (***P*=.72**) and (**R= -.20**), for Table 3. This indicates that the group of molecular properties for each isostere/bioisostere are not different in composition, but are statistically alike. The value of (**R= -.20**) indicates these groups of molecular properties are statistically indistinguishable.

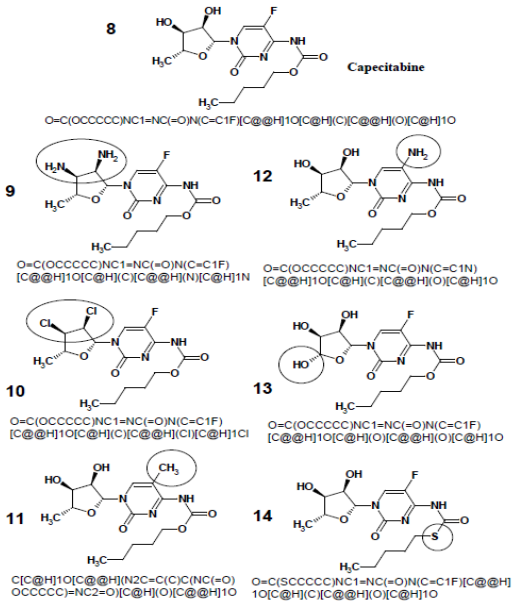

Figure 3: Isosteres and Bioisosteres of capecitabine. SMILES notation are adjacent to structures. The isosteric/bioisosteric substitutions are circled.

Table 3: Molecular Properties of Capecitabine Isoteres and Bioisosteres.

Compound	Molecular Weight	Log P	Polar Surface Area (A^2)	Hydrogen Bond Acceptors	Hydrogen Bond Donors	Number of Atoms	Refractivity	Rule of Five Fault
8 Capecitabine	359.3	0.833	122.9	10	3	47	85.3	0
9	357.4	2.17	134.5	10	3	49	88.3	0
10	396.2	3.33	82.5	8	1	45	92.5	0
11	355.4	1.00	122.9	9	3	50	90.3	0
12	356.4	0.86	148.9	10	4	49	89.8	0
13	361.3	-0.24	143.1	11	4	45	81.6	1
14	375.4	1.55	139.0	9	3	47	91.8	0

Table 4: Summare Statistics of Molecular Properties.

Statistic	Molecular Weight	Log P	Polar Surface Area (A^2)	Hydrogen Bond Acceptors	Hydrogen Bond Donors	Number of Atoms	Reractivity	Rule of Five Fault
Mean	365.9	1.36	127.7	10	3	47	88.5	0
Median	359.3	1	124.5	10	3	47	89.8	0
Standard Deviation	15	1.1	22	1	1	2	3.9	0
Range	355.4-396.2	-0.24-3.33	82.5-148.9	8-11	1-4	45-50	81.6-92.5	0-1

Underlying relationships of molecular properties presented in Table 3 and Table 4, can be elucidated with high resolution by utilizing neighbor joining cluster analysis.[14] By the definition the substitution utilizing isosteres and Bioisosteres, is to maintains vital characteristics of the parent compound in order to preserve effective clinical activity. This goal encompasses the beneficial modifications of the molecular properties (see Table 3 and Table 4) as well.

The use of neighbor joining cluster analysis makes it feasible to identify subtle underlying relationships within the molecular properties presented in Table 3.[14]

What is shown in Fig. 4, Plot A, is the results of neighbor joining cluster analysis of Table 3 molecular properties, where these seven compounds are plaed in groups having the greatest similarity based on their molecular properties. Here, clearly seen are that compound 8 (parent compound capecitabine) and compound 11 are most similar. Following this, compounds 12, 13, 14, and 9 have highest similarity. Note that compound 10 is considerably distinct from all the rest and has an extensive distance (long segment} from all the remaining compounds (see Figure 4). Plot B, Fig. 4, is a steep highly linear Shepard plot showing that the lower dimensional neighbor joining cluster plot is highly accurate data reduction scenario, and that distances in the lower dimensional space are an exact match to the original data, and representative of the data in Table 3.[14]

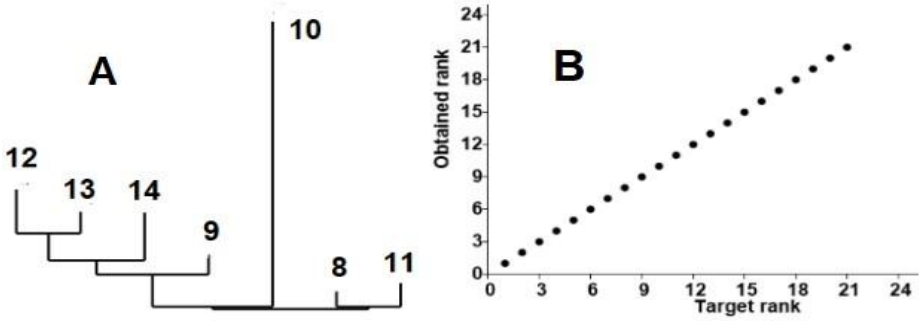

Figure 4: Plot (A) is neighbor joining cluster analysis of Table 3. This result with high resolution of analysis indicated compounds 8 and 11 to be most similar. Compounds 12, 13, 14, and 9 are clustered and more similar, but with compounds 9 somewhat distinct from 12, 13, and 14. Plot (B) is a highly linear Shepard plot onto a steep line, indicating the neighbor joining cluster plot is highly accurate and representative of the data in Table 3.

The Shepard Plot is a method for evaluating the "goodness of fit" of the lower dimensional analysis technique (neighbor joining cluster analysis here) to the actual distance between data points coming from the original higher dimensional data set.[14,16]

Paclitaxel Isosteres and Bioisosteres

Pancreatic cancer is highly lethal, in which many patients remain non-symptomatic until the cancer has reached an advanced condition.[19] Surgery remains the hope for potential for "curative" treatment.[19] The study of

isosteres and Bioisosteres of paclitaxel has the potential for increasing the number of effective agents in the treatment of pancreatic cancer. Paclitaxel has been utilized for the clinical treatment of pancreatic cancer, breast cancer, esophegeal cancer, lung cancer, Kaposi's sarcoma, ovarian cancer, and cervical cancer. It is generally administered by means of intravenous injection.[19]

Presented in Figure 5, are the structures of paclitaxel and four structures of isosteres/bioisosteres. The atoms or molecule groups constitiuting the isosteric/bioisosteric substitution are circled (see Fig. 5). Substitutions involved include: -CH3, -NH2, and -Cl atoms. A 2-methyl-1,3-oxazole (Cc1occn1) substituent is in place in compound 16 (see circled substituent).

The molecular properties for compounds 15 to 19, have been determined and shown in Table 5, with summary statistics compiled in Table 6. What can be immerdiately recognized is that compounds 15, 16, 17, 18, and 19 having PSA greater than 140 Anstroms^2, and therefore, will have not have favorable cell permeation and oral bioavailability.[12] This observation is further substantiated because all compounds 15 to 19 have more than one violation of RO5.[13] In addition, note that compounds 15 to 19 could not effectively cross the blood-brain barrier due to PSA values significantly greater than 90 Angstroms^2.[12]

In addition, this study presents the summary statistics for these molecular properties, and are shown in Table 6. The concise ranges for molecular weight, Log P, etc, helps define boundaries for potential analogs to paclitaxel, which can allow for successful estimation of potential effectiveness for the proposed similar agents. Interestingly, there is considerable ranges in Log P (range of 4.13 to 7.95) and hydrogen bond donors (range of 1 to 4) (see Table 5).

The objective of one-way ANOVA statistical test, is to determine if there is any significant differences among the means of multiple independent groups (the eight molecular properties for each isostere/bioisostere in this study).[14] The objective for ANOSIM (Analysis of Similarities) is to determine if the composition of multiple groups of data are different and that the difference has statistical significance.[14]

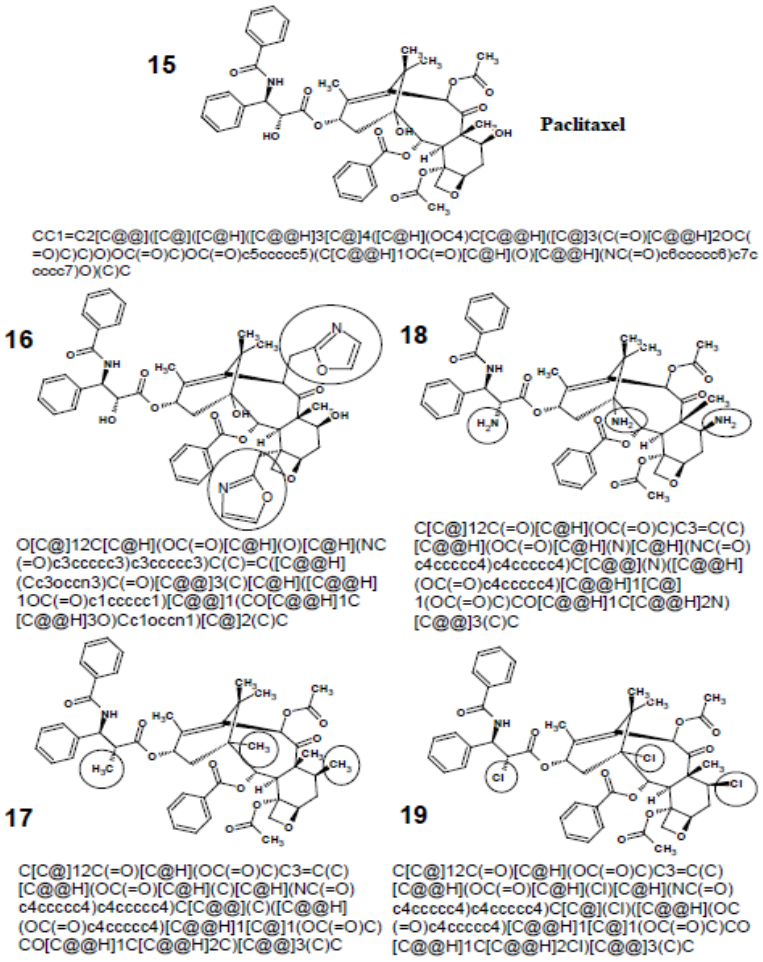

Figure 5: Iosteres and Bioisosteres of paclitaxel. SMILES notation is adjacent to the structures. The isosteric/bioisosteric substitutions are circled.

Table 5: Molecular Properties of Paclitaxel Isosteres and Bioisosteres.

Compound	Molecular Weight	Log P	Polar Surface Area (A^2)	Hydrogen Bond Acceptors	Hydrogen Bond Donors	Number of Atoms	Refractivity	Rule of Five Fault
15 Paclitaxel	853.9	4.13	221.3	15	4	113	219.0	2
16	900.0	5.96	220.8	15	4	119	235.6	3
17	848.0	7.95	160.6	12	1	119	229.6	3
18	851.0	6.13	238.7	15	4	116	223.6	3
19	909.2	7.87	160.6	12	1	110	229.9	3

Table 6: Summare Statistics of Molecular Properties.

Statistic	Molecular Weight	Log P	Polar Surface Area (A^2)	Hydrogen Bond Acceptors	Hydrogen Bond Donors	Number of Atoms	Refractivity	Rule of Five Fault
Mean	872.4	6.41	200.4	14	3	115	227.5	3
Median	853.9	6.13	220.8	15	4	116	229.69	3
Standard Deviation	30	1.6	37	2	2	4	6.4	0
Range	848.0-909.2	4.13-7.95	160.6-238.7	12-15	1-4	110-119	219.0-235.6	2-3

For one-way ANOVA, the value of (***P*=1.0**) obtained from analysis of Table 5, indicates that the molecular properties mean of the parent compound (paclitaxel here) are not statistically different from that of the same properties for each of the isosteres/Bioisosteres, and to each other, for Table 5.[14] For ANOSIM analysis, the value of (***P*=1.0**) and (**R= -.33**), for Table 5. This indicates that the group of molecular properties for each isostere/bioisostere are not different in composition, but are statistically alike. The value of (**R= -.33**) indicates these groups of molecular properties are statistically indistinguishable.[14]

Underlying relationships of molecular properties presented in Table 5 and Table 6, can be elucidated with high resolution by utilizing neighbor joining cluster analysis.[14] The definition of substitution utilizing isosteres and Bioisosteres, the vital characteristics of the parent compound are preserved in order to preserve the effectiveness of clinical application. This goal encompasses the beneficial modifications of the molecular properties as well (see Table 5 and Table 6). It is possible to identify subtle underlying relationships within the molecular properties by use of high resolution pattern recognition methods, such as neighbor joining cluster analysis.[14] Shown in Fig. 6, Plot A, is the results of neighbor joining cluster analysis of Table 5 molecular properties, where these five compounds are placed in groups having the greatest similarity based on their molecular properties. Here, clearly seen are that compound 15 (parent compound paclitaxel), 16, and 18 are most similar, however, compound 16 is determined to be somewhat distinct from compounds 15 and 18, with a considerable long segment. Following this, compounds 17 and 19, are most similar.

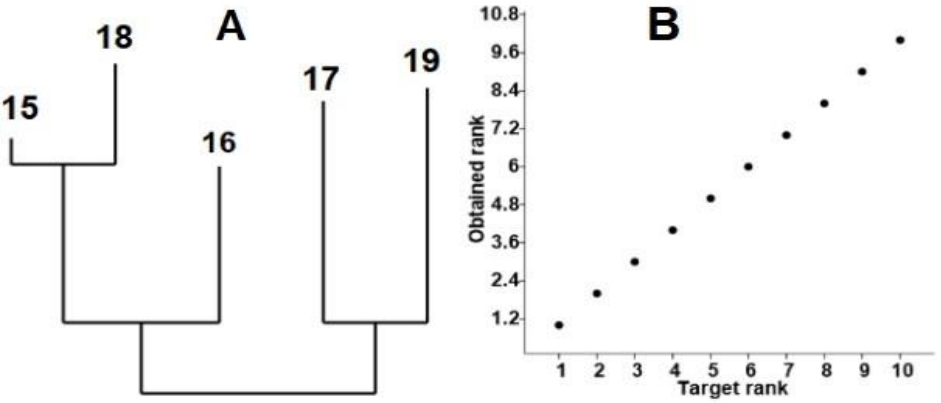

Figure 6: Plot (A) is neighbor joining cluster analysis of Table 5. This result with high resolution of analysis indicated compounds 17 and 19 to be most similar. Compounds 15, 16, and 18 are clustered and more similar, but with compounds 16 somewhat distinct from 15, and 18. Plot (B) is a highly linear Shepard plot onto a steep line, indicating the neighbor joining cluster plot is highly accurate and representative of the data in Table 5.

Plot B, Fig. 6, is a steep highly linear Shepard plot showing that the lower dimensional neighbor joining cluster plot is a highly accurate data reduction outcome, and that distances in the lower dimensional space are an exact match to the original data and representative of the multivariate data in Table 5.[14] The Shepard Plot is a method for evaluating the "goodness of fit" of the lower dimensional analysis technique (neighbor joining cluster analysis here) compared to the actual distance between data points coming from the original and higher dimensional data set.[14,16]

CONCLUSION

Isosteres and Bioisosteres have been presented for the three anticancer drugs gemcitabine, capecitabine, and paclitaxel, which are effective in the clinical treatment of pancreatic cancer. The molecular properties relevant to favorable drug-likeness were determined by heuristic platform. Statistical analysis, inclusive of summary statistics, were calculated for each group of compounds. ANOSIM results showed (***P*>.05**) within all three groups of compounds, indicating the compounds within their groups are statistically indistinguishable from easch other, based on molecular properties (note that accompaning **R** values lay between -0.33 to -0.2). Results of one-way ANOVA showed that (***P*=1.0**) for within each group of the three groups of compounds, showing there is no significant statistical difference in the means of the molecular properties between the parent compound and their particular isosteres/Bioisosteres presented. For compounds 1 to 14, all showed zero or one violation (compound 13) of RO5, indicating favorable oral bioavailability. These findings suggests that rational substitution within structures of each of the three parent compounds (gemcitabine, capecitabine, and paclitaxel) could produce measureable beneficial changes in molecular properties and potentially preserve and enhance their clinical efficacy. The implementation of isosteres and Bioisosteres in pharmaceutical development shows substantial success and high level of potential in the pursuit of new drugs for the treatment of cancer.

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