Dienogest Derivatives Show Increased Selectivity to the Progesterone Receptor

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ABSTRACT

Progestin, the synthetic progesterone in the combination birth control pill, functions to prevent pregnancy. Unfortunately, it also results in a wide range of side effects associated with the pill, including nausea, headaches, abdominal cramping, breakthrough bleeding, and mood changes. These side effects are due to the interactions that take place when the progestin binds not only to its desired target, the progesterone receptor, but also to other steroid receptors, namely the androgen receptor, estrogen receptor, glucocorticoid receptor, and mineralocorticoid receptor. In hopes of diminishing these side effects, in this study, one progestin, dienogest, was computationally altered to improve binding to the progesterone receptor while minimizing the binding to other receptors. The most successful derivative created involved the addition of a methyl and a methylene group, which significantly decreased binding to the five other receptors while maintaining a similar affinity for the progesterone receptor. Importantly, in an assessment of the social aspect of the birth control pill via an online survey released in the San Francisco Bay Area (n=73), the side effects of the birth control pill, which could be improved by minimizing off target interactions, are a major concern among women who consider this form of contraception.

Introduction

The combination birth control pill, which consists of both a progestin (synthetic progesterone) component and an estrogen component, works to prevent pregnancy. The progestin, similar to the natural progesterone, binds to the progesterone receptor, which prevents the increase in luteinizing hormone concentration that is required for the release of the ovum. It also results in the thickening of cervical mucus, thus making it difficult for sperm to access the egg.¹ The estrogen component of the pill works to improve cycle control and essentially makes menstrual bleeding predictable.²

The combination pill has been documented to cause a variety of side effects, including but not limited to: nausea, headaches, abdominal cramping, breast tenderness, increase in vaginal discharge, breakthrough bleeding (vaginal bleeding or spotting in between periods), decreased libido,³ increased acne, bloating or weight change,⁴ and mood changes.⁵ While progesterone receptors are the target receptors for progestins, these progestins also have the ability to bind to the androgen receptor, estrogen receptor, glucocorticoid receptor, and mineralocorticoid receptor. Side interactions with these receptors are thought to be the cause of many of the classic side effects associated with the combination birth control pill.

Modifying existing progestins to promote increased binding to the progesterone receptor and decreased binding to the other steroid receptors may result in a more desirable progestin. Fourth-generation progestins that have been developed within the last two decades and are currently in use, namely drospirenone, dienogest, nomegestrol acetate, and trimegestone, were considered for the subject of this study. Ultimately, dienogest was selected as it showed greatest potential for improvement in selectivity to the progesterone receptor.
Dienogest is extremely common in the birth control pill. The combined contraceptive of ethinylestradiol and dienogest, since being launched in 1995, has been one of the most frequently prescribed contraceptives to date. Not only this, but dienogest is also found in the birth control pill in combination with estradiol valerate, and has been known to aid with excessive menstrual bleeding. Given how frequently utilized dienogest is in combination birth control pills, and given what relief it can provide to those who face extreme menstrual bleeding, it is extremely important to improve its selectivity to the progesterone receptor. Doing so would allow for increased comfort for women around the world by reducing adverse side effects when utilizing dienogest-based birth control pills.

The social aspect of birth control was also investigated with the release of an online survey in the San Francisco Bay Area (n=73). The goal of this survey was to determine respondents’ beliefs regarding birth control, including prevalence of side effects, concerns over these effects, and reasons for cessation of use. Overall, this study will examine both how to best modify dienogest to decrease unwanted side effects and assess the participant’s desire for an improved birth control pill with minimal side interactions.

**Methods**

**Molecular Mechanics Optimization**

Avogadro, a cross-platform molecular editor, was used to visualize progesterone and dienogest, and to create the dienogest derivatives as three-dimensional models. Before running geometry optimization, all studied compounds were optimized using the Universal Force Field (UFF) method at 2500 steps.

**DFT Geometry Optimization**

Next, density functional theory (DFT) was used to calculate the most stable atomic arrangement of the studied molecules. DFT was completed with the use of ORCA, a quantum chemistry program package. After progesterone, dienogest, and derivatives were created in Avogadro, input files were created via ORCA. The following settings were used in creating these files: the B3LYP hybrid functional, def2-SVP basis set, normal print, default grid size for SCF iterations of 4, normal SCF settings, and 125 as the maximum number of iterations set for SCF.

**AutodockTools**

AutodockTools (ADT) is a part of the MGLTools package, which was developed to visualize and edit three-dimensional structures and to set up and run Autodock dockings. ADT was used to prepare the ligand and macromolecule files for docking. Ligand files previously created with Avogadro and ORCA were first opened in ADT before the
torsion tree roots were identified. No changes were made to the number of torsions, or rotatable bonds, that was set by the software when the ligand was first opened. The macromolecule files for the progesterone receptor, androgen receptor, estrogen receptor, glucocorticoid receptors (agonist and antagonist forms), and the mineralocorticoid receptor were chosen from the Protein Database Bank (PDB) with, respectively, the following PDB IDs: 1A28, 4OEA, 3OS8, 1P93, 1NHZ, and 3VHU. In preparing these files, the first step required removing any compounds in complex with the receptors. From there, any chains not corresponding to the receptors that were present in the PDB files were deleted as well. Next, water molecules were deleted and hydrogens were added. After the preparations for the ligand and receptors were complete, search grids were defined. The size of these search grids remained constant, with the number of points in the x-dimension being set at ninety-two, the number of points in the y-dimension being set at 92, and the number of points in the z-dimension being set at 126. With these measurements, it was ensured that the totality of the ligand-receptor complexes were included in the search grid, so that blind docking could take place.

**Autodock4**

Autodock4 (AD4) is a computational program that uses a semi-empirical force field to predict the binding affinities and conformations of small-molecule ligands to macromolecule targets. AD4 was utilized to generate ten binding poses of each of the studied molecules’ binding to the progesterone receptor, the androgen receptor, the estrogen receptor, the agonist form of the glucocorticoid receptor, the antagonist form of the glucocorticoid receptor, and the mineralocorticoid receptor. When comparing the binding affinities of progesterone and dienogest to the dienogest derivatives, only the highest binding affinities were compared and the affinities were estimated to the nearest tenth to account for any computational error.

**Derivative Scoring**

All derivatives created, along with progesterone, were assigned a score to determine how well they performed in selectively binding to the progesterone receptor when compared to each other and to dienogest. To calculate these scores, differences between the binding affinities of dienogest to the six receptors and the binding affinities of the other eight compounds to the receptors were calculated. The differences between the binding affinities to the progesterone receptor were calculated by subtracting the binding affinity of the derivatives from the binding affinity of dienogest. All derivatives created showed a negative value in terms of difference in binding affinity, indicating a decrease in binding affinity to the progesterone receptor. The differences between the binding affinities to the remaining receptors were calculated by subtracting the binding affinity of dienogest from the binding affinity of the created derivatives. This resulted in both positive and negative values: positive indicated desired results, decreases in binding affinity to the five receptors, and negative indicated undesired results, increases in binding affinities to the other five receptors. Using these same methods, six positive or negative smaller scores were created for every structure except dienogest, which couldn’t be compared to itself (a score of 0). These values were totaled to provide the final scores seen in the last column of Table 1.

**Results**

**Generation of Dienogest Derivatives**

In determining how to improve the binding affinity of dienogest to the progesterone receptor, previous literature regarding improvements made to various progestins’ binding was analyzed. A previous study showed that removal of the C-19 methyl group from progesterone resulted in improved binding to the progesterone receptor. Because dienogest only has one methyl, which is attached to location 13 on Figure 1, this methyl was removed to create one analog. When an OH was added to location 17 on progesterone, and then acetylated, enhanced progestational activity was shown. When this change was made, along with the addition of a methyl to C-6, relatively high progestational activity...
activity was also exhibited. Furthermore, when the OH mentioned prior was acetylated, when a chlorine atom was added to progesterone at location 6, and when the carbon bond between location 6 and 7 was changed to a double bond, higher progestational activity was also observed. To make the corresponding changes on dienogest, one analog was created so that the OH extending from location 17 was acetylated. Another derivative was created so that the OH was acetylated and so that a methyl was added to location 6. The fourth derivative in this study was created by again acetyllating the aforementioned OH, by adding a chlorine to location 6, and by making the carbon bond between locations 6 and 7 a double bond.

The introduction of an 18-methyl group in norethindrone, a progestin, and the introduction of this group with the introduction of a 11-methylene group have also resulted in two instances with increased binding to the progesterone receptor. To mimic these changes, one derivative was created by replacing one of the hydrogens on the methyl extended from location 13 with another methyl. Another analog was created by making this change and by adding a methylene group to location 11.

It was found that 21-fluoro-progesterone, 11β-hydroxyprogesterone, and 21-hydroxyprogesterone all showcased strong binding to the progesterone receptor when compared to progesterone. Hence, three more derivatives were created, one with the addition of a fluorne to location 1 (the carbon attached to the nitrogen), another with the addition of an OH to location 11, and a last analog with the addition of an OH to location 1 (the carbon attached to the nitrogen).

**Binding Affinity of Dienogest Derivatives**

Nine derivatives were created over the course of this study, and all underwent binding to six receptors: the progesterone receptor, androgen receptor, estrogen receptor, agonist glucocorticoid receptor, antagonist glucocorticoid receptor, and the mineralocorticoid receptor.

When comparing the created analogs to the binding affinities showcased by natural progesterone, two of the created derivatives demonstrated increased binding affinity to the progesterone receptor: dienogest with the addition of fluorine to location one of the acetonitrile, and dienogest with the addition of OH to location eleven. Both derivatives also showed decreased binding affinity to the androgen receptor, estrogen receptor, and the antagonist glucocorticoid receptor. When binding to the agonist glucocorticoid receptor, the derivative that was created via the introduction of fluorine showed a lower binding affinity than progesterone, whereas the derivative that was derived by the addition of OH to location eleven showed an equal binding affinity. For the mineralocorticoid receptor, both derivatives had an increased binding affinity when compared to progesterone.

Looking at the remaining seven derivatives created, all seven showed an overall better score than that of progesterone. Observing the scores in the last column of Figure 2, we see that progesterone had the lowest score of -0.1, and almost all the other derivatives had a much greater score, with the exception of the derivative created by the removal of a methyl, which had a greater score by only 0.1.

**Table 1:** Binding affinities of progesterone, dienogest, and all derivatives, and scores comparing the selectivity of progesterone and the created derivatives to that of dienogest are listed. A more negative number in terms of binding affinity indicates better binding to the respective receptors. In the last column of the table, higher scores indicate better selectivity to the progesterone receptor.
<table>
<thead>
<tr>
<th>Ligands (a-k)</th>
<th>Binding Affinity to Progesterone Receptor (kcal/mol)</th>
<th>Binding Affinity to Androgen Receptor (kcal/mol)</th>
<th>Binding Affinity to Estrogen Receptor (kcal/mol)</th>
<th>Binding Affinity to Agonist Glucocorticoid Receptor (kcal/mol)</th>
<th>Binding Affinity to Antagonist Glucocorticoid Receptor (kcal/mol)</th>
<th>Binding Affinity to Mineralocorticoid Receptor (kcal/mol)</th>
<th>Score (When Compound is Compared to Dienogest)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progesterone (a)</td>
<td>-10.3</td>
<td>-9.9</td>
<td>-9.2</td>
<td>-9.4</td>
<td>-8.5</td>
<td>-9.7</td>
<td>-0.2</td>
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<tr>
<td>Dienogest (b)</td>
<td>-10.7</td>
<td>-8.5</td>
<td>-9.5</td>
<td>-9.5</td>
<td>-8.1</td>
<td>-11.3</td>
<td></td>
</tr>
<tr>
<td>Dienogest with Removed Methyl from Location 13 (c)</td>
<td>-10.2</td>
<td>-9.9</td>
<td>-9.4</td>
<td>-8.7</td>
<td>-8.1</td>
<td>-10.4</td>
<td>-0.1</td>
</tr>
<tr>
<td>Dienogest with the Acetylation of the OH at Location 17 (d)</td>
<td>-9.1</td>
<td>-7.4</td>
<td>-7.3</td>
<td>-7.1</td>
<td>-8.9</td>
<td>-6.5</td>
<td>8.1</td>
</tr>
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<td>Dienogest with the Acetylation of the OH at Location 17 and with the Addition of a Methyl to Location 6 (e)</td>
<td>-7.6</td>
<td>-6.5</td>
<td>-9.5</td>
<td>-9.2</td>
<td>-6.8</td>
<td>-6.2</td>
<td>5.6</td>
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<td>Dienogest with Acetylation of the OH at Location 17, Addition of Chlorine to Location 6, and the Addition of a Carbon Bond between Locations 6 and 7 (f)</td>
<td>-7.3</td>
<td>-6.8</td>
<td>-6.8</td>
<td>-8.7</td>
<td>-8.5</td>
<td>-7.4</td>
<td>5.3</td>
</tr>
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<td>Dienogest with the Addition of a Methyl to the Methyl at Location 13 (g)</td>
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<td>-6.2</td>
<td>-8.6</td>
<td>-9.2</td>
<td>-7.9</td>
<td>-9.8</td>
<td>4.6</td>
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<tr>
<td>Dienogest with the Addition of a Methyl to the</td>
<td>-10.1</td>
<td>-6.4</td>
<td>-6.2</td>
<td>-9.7</td>
<td>-7.9</td>
<td>-7.1</td>
<td>9.0</td>
</tr>
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<td>Derivative Description</td>
<td>Score 1</td>
<td>Score 2</td>
<td>Score 3</td>
<td>Score 4</td>
<td>Score 5</td>
<td>Score 6</td>
<td>Score 7</td>
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<tr>
<td>--------------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>Methyl at Location 13 and with the Addition of a Methylene to Location 11 (h)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dienogest with the Addition of Fluorine to Location 1 of the Acetonitrile (i)</td>
<td>-10.6</td>
<td>-6.1</td>
<td>-6.7</td>
<td>-8.9</td>
<td>-7.6</td>
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<td>6.6</td>
</tr>
<tr>
<td>Dienogest with the Addition of OH to Location 11 (j)</td>
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<td>-6.5</td>
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<td>-7.6</td>
<td>-10.7</td>
<td>3.8</td>
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<tr>
<td>Dienogest with the Addition of OH to Location 1 of the Acetonitrile (k)</td>
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<td>-6.1</td>
<td>-8.2</td>
<td>-8.7</td>
<td>-6.5</td>
<td>-9.9</td>
<td>6.4</td>
</tr>
</tbody>
</table>

**Figure 2:** Visual Depiction of the scores of all structures studied.

When comparing the binding affinities of the created derivatives to those of dienogest, no derivatives had greater binding affinities to the progesterone receptor. Two derivatives came close, both of which had a binding affinity of -10.6 kcal/mol to the receptor, as compared to the -10.7 kcal/mol binding affinity displayed by dienogest. Both derivatives, dienogest with the addition of fluorine to location one of the acetonitrile and dienogest with the
addition of OH to location eleven, showed decreased binding to all of the remaining five receptors (Table 1). When comparing scores, the derivative created by the addition of fluorine performed significantly better, with a score of 6.6 versus 3.8 (Figure 2).

Furthermore, eight of the nine derivatives created showcased improved selectivity to the progesterone receptor. Unexpectedly, out of the eight derivatives with improved selectivity, dienogest with the addition of OH to location eleven had the lowest score of 3.8. Yet, its binding affinity of -10.6 kcal/mol was most similar to the binding affinity of dienogest. The derivative with the highest score of 9.0, and thus the derivative that was the most improved when compared to dienogest, was created by the addition of a methyl to the already existing methyl at location thirteen and of a methylene to location eleven. The binding affinity of this structure to the progesterone receptor was relatively close to that of dienogest, with it being -10.1 kcal/mol vs dienogest’s -10.7 kcal/mol. This derivative had decreased binding affinity to all the remaining receptors except the agonist glucocorticoid receptor, for which it showed an increase in binding affinity by 0.2 kcal/mol (Table 1).

Lastly, for the one derivative that had worsened selectivity to the progesterone receptor and a score of -0.1, binding affinity to the progesterone receptor was only somewhat decreased, with it being -10.2 kcal/mol vs -10.7 kcal/mol (Figure 1). Given this negative score, this derivative actually had a lower binding affinity than dienogest when binding to the estrogen receptor, agonist glucocorticoid receptor, and the mineralocorticoid receptor. However, it also demonstrated increased binding to the androgen receptor and an equal binding affinity to the antagonist glucocorticoid receptor (Table 1).

**Social Survey Results**

This survey received 73 responses total. Over half of the respondents answered that they had never taken the birth control pill prior to the survey, as seen in Figure 3. 34.2% of respondents had taken the pill at one point, yet had stopped doing so. Only 9.6% of respondents took the birth control pill at the time at which they filled out the survey.

![Figure 3: The proportion of participants who once took the birth control pill, who currently take the pill, or who once took the pill but no longer do.](image)

Of the seven respondents who took the birth control pill at the time of the survey, the side effects most commonly observed were breast tenderness, increase in vaginal discharge, and depression or mood changes. Other side effects also experienced by some included nausea, headaches, abdominal cramping, breakthrough bleeding, decreased libido, and bleeding. One participant responded not experiencing side effects at all. Three respondents felt that if their side effects were to become severe, they would stop taking the birth control pill. An equal number of respondents felt the opposite: even if their side effects were to become more severe, they would continue taking the birth control pill.
The proportion of participants who felt as if they would or would not stop taking the birth control pill if side effects were to become more severe.

Of the respondents who once took the birth control pill but had ceased at the time of survey completion, the most frequently highest ranked reason for why people stopped taking the pill was due to side effects. Shortly after that came the reason that the respondents wanted to switch to a different birth control method. The third most common reason for no longer taking the birth control pill was due to having reached the age of menopause.

Forty-one respondents selected the option that they had never and still do not take the birth control pill. Many respondents indicated they did not take the birth control pill because they were not sexually active, were concerned with side effects, or because they used a different birth control method. Participants were also given the option to choose “other” as a reason for why they do not take the pill, and those who did so listed that they chose not to take the pill because they were asexual, never felt like there was a need to use the pill, received a tubal ligation, or did not like the feeling of swallowing the pill, as seen in Figure 5.

![Figure 4](image.png)

**Figure 4:** The proportion of participants who felt as if they would or would not stop taking the birth control pill if side effects were to become more severe.

![Figure 5](image.png)

**Figure 5:** Representation of reasoning behind why participants chose not to take the birth control pill.

Of the participants who selected that one of the reasons they did not take the pill was due to the side effects commonly associated with it, the side effects of most concern were depression or mood changes, weight change, breast cancer, nausea, brain tumors, and heart trouble, as seen in Figure 6. It is important to note that result percentages shown may have been skewed due to the responses that filled in the “other” box to write that they did not take the pill.
or that they weren’t able to get pregnant if they did take the pill, as these are not side effects that come with use of the pill.

**Figure 6**: This image showcases participants who did not take the birth control pill’s concerns about specific side effects associated with the birth control pill.

**Discussion**

Examination of Created Derivatives

As shown in Table 1 and Figure 2, the derivative that was the most selective to the progesterone receptor, and thus the one that would ideally reduce the side effects caused by the birth control pill by the greatest amount, was the analog created by the addition of a methyl to the already existing methyl at location thirteen of dienogest and of a methylene to location eleven of dienogest. However, according to the source used as a reference for this modification, the introduction of the 18-methyl group to norethindrone along with the introduction of 11-methylene group should have resulted in a higher binding affinity to the progesterone receptor than when only an 18-methyl group was added. However, as Table 1 depicts, both derivatives showed identical binding affinities to the progesterone receptor, which is quite surprising. This source also explains that when only the 18-methyl group was added to norethindrone, the binding affinity to the androgen receptor actually increased, and when both the 18-methyl and 11-methylene group were added, binding affinity to the androgen receptor decreased\(^5\). Yet, this does not prove to be true, as in both derivatives created, the binding affinity to the androgen receptor decreased greatly. These results thus suggest that the modifications described in the sources of this study likely did not result in the same responses in terms of binding affinity to studied receptors when applied to dienogest, yet still almost always resulted in improved selectivity to the progesterone receptor.

The only derivative whose selectivity to the progesterone receptor decreased, dienogest with a removed methyl from location 13, showed similar findings. A recent study discusses that binding to the progesterone receptor
increased with this modification to progesterone. However, as shown in Table 1, binding affinity to the progesterone receptor for this created derivative actually did the opposite and decreased by 0.5 kcal/mol. However, unlike the prior derivatives mentioned, this may be due to the fact that this source focused on binding to the hamster uterine progesterone receptor, rather than the human progesterone receptor. The difference between these structures may have played a role in why this derivative appeared to be so unsuccessful in this study.

The next three derivatives, dienogest with an acetylated OH, dienogest with an acetylated OH and an addition of a methyl, and dienogest with an acetylated OH, an addition of a chlorine, and an addition of a single carbon bond, all showed similar results as well. Progestational activity was found to increase for the corresponding derivatives when modifications were made to progesterone, yet here, binding affinity for these derivatives to the progesterone receptor decreased by 1.6, 3.1, and 3.4 kcal/mol respectively (Table 1). The analog described by this paper as having the most increased progestational activity — progesterone with the acetylated OH, added chlorine, and added single carbon bond — actually showed the greatest decrease in binding affinity to the progesterone receptor of the three described.

Lastly, the final three derivatives, dienogest with the addition of fluorine, dienogest with the addition of OH to location 11, and dienogest with the addition of OH to location 1 of the acetonitrile, displayed some unexpected observations. Of the derivatives tested in a recent study, the addition of a fluorine to progesterone competed best with progesterone for binding to the progesterone receptor, and progesterone with the addition of OH to location 11 and 1 also showed decent competition with progesterone. Results in this study mostly support this claim, as the addition of fluorine and the addition of OH to location 11 only resulted in a decrease in binding affinity by 0.1 kcal/mol. Unfortunately, the addition of OH to location 1 of the acetonitrile depicted contrary results, with a great decrease in binding affinity to the receptor.

Observing all nine derivatives created, it appears as if seven of the nine analogs displayed contrary results as to what was expected given the sources studied. Binding affinity to the progesterone receptor only decreased due to the modifications that took place. This may have been in part due to the fact that some of the sources did not only study the human progesterone receptor, but also examined other animal receptors, like those of hamsters and chicks. These results may also be explained by the fact that the modifications described in the studied sources were made to progesterone or other progestins, all of whose structures are very different from that of dienogest. Thus, they perhaps could not be adequately applied to dienogest without resulting in contrary results.

Examination of the Social Aspect of Birth Control

Upon observing the results derived from the conducted survey, it was surprising to find that of the women who were taking the birth control pill at the time of the survey, an equal number of women noted that they would continue taking the pill regardless of whether the side effects they were experiencing were to get more severe. This contradicts research conducted by Reed et al in 2014, which suggests that women who report experiencing side effects are actually more likely to stop using the birth control pill regularly than women who experience little to no side effects. The reason for this discrepancy likely results from two variables — the first of which is that it has been almost seven year since this study was performed. However, the more likely reason lies behind the number of respondents who described that they were currently taking the birth control pill at the time of the survey. Only three women each stated that they would continue or discontinue taking the pill if its side effects were to get more severe. Such a small sample size may not be representative of the population and could skew our results. Around thirty-four percent of respondents described that they once took the birth control pill, yet stopped doing so for various reasons. The most highly ranked reason, concern over side effects associated with the pill, seems to align with prior literature in that, according to a study conducted in 2012, the greatest cited reason for discontinuation of the pill was due to the side effects users experienced. In fact, reported percentages regarding this ranged from as low as thirty percent to as high as sixty percent. Of the reasons for why respondents chose not to take the pill, the most frequently cited reason was that the respondent was not sexually active and thus had no use for the pill. This is not surprising, as eighty-six percent of women use the pill for pregnancy protection. A majority of those who partook in this study were young women, most likely under the age of eighteen, given the fact that the survey was distributed via the student researcher’s own
personal social media accounts on Instagram, Facebook, LinkedIn, etc. Because fewer American high schoolers than ever before are taking part in sexual intercourse, only around twenty-seven percent, it makes sense that many would not be using the birth control pill as a result, as they have no need to protect against contraception. This explains why a majority of respondents indicated that they do not take birth control as they are not sexually active, and allows for an explanation for why fewer respondents may have chosen that they do not take the pill because they are wary of side effects. Because these results may be skewed, simply by the fact that most respondents were younger women, side effects are still a major concern that need to be addressed. Thus, there is a need for improvements to the already existing dienogest in the birth control pill.

**Conclusion**

Over the course of this study, nine derivatives of the progestin dienogest were created to improve dienogest’s selectivity to the progesterone receptor, thus minimizing the side effects commonly associated with the birth control pill. Bindings of these analogs to the progesterone receptor, androgen receptor, estrogen receptor, glucocorticoid receptor, and mineralocorticoid receptor were conducted computationally, and all but one derivative showed improved selectivity to the progesterone receptor. This is of great importance, as in the survey conducted as a part of this study, side effects of the birth control pill were considered to be a major concern for respondents. Future studies should delve into whether the created derivatives are compatible with the synthetic estrogens commonly found in the birth control pill, and should examine whether the derivatives created can be safely taken in by the human body. Research should also study whether the modifications made in this study can be applied to other fourth-generation progestins as well, in hopes of improving a wide variety of birth control pills, not just those that contain dienogest.

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**References**


