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Construction of Substituted 1,2,3-Triazole Rings Containing Progesterone Moiety *via* Transition Metal-Free Cycloaddition

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Abstract

In this study, a one-pot synthesis method was utilized to prepare a series of novel progesterone derivatives featuring 1,2,3-triazole rings. The condensation of progesterone with ten different aromatic aldehydes through a Claisen-Schmidt reaction gave the desired α,β-unsaturated carbonyl derivatives as intermediates, which were treated directly with benzyl azide *via* a metal-free [3+2] cycloaddition reaction to furnish the target derivatives **1**-**10** in 58-81% yields. The structure of the synthesized compounds (**1**-**10**) was characterized using FT-IR, ^{1}H NMR, and ^{13}C NMR spectroscopy. The significant point of this work is combining two important moieties (the progesterone and 1,2,3-triazole) together to form new derivatives **1**-**10**. This novel design of derivatives could be tested in the future to investigate its biological studies, such as anti-oxidants and anti-bacterial activities.

Keywords: Cycloaddition, Metal-free, One-pot, Progesterone, 1,2,3-Triazole.

بناء حلقات 3،2،1–ترايازول معوضة تحتوي على جزء البروجسترون عن طريق الإضافة الحلقية الخالية من المعادن الانتقالية

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الخلاصة

في هذه الدراسة، تم استخدام وعاء تخليق واحد لتحضير سلسلة من مشتقات البروجيستيرون الجديدة التي تحتوي على حلقات 3،2،1–ترايازول. أعطى تكثيف البروجيستيرون مع عشرة ألدهيدات عطرية مختلفة من خلال تفاعل كلايسن–شميدت مشتقات الكاربونيل β,α–غير المشبعة المطلوبة كوسيطات، و التي تمت معالجتها مباشرة بأزيد البنزيل عن طريق تفاعل إضافة حلقية [3+2] خالية من المعادن لتوفير المشتقات المستهدفة **1–10** بنسبة إنتاج 58–81٪. تم التأكد من تركيب المركبات المحضرة **(1–10)** بواسطة مطيافية الاشعة تحت الحمراء و الرنين النووي المغناطيسي للهيدروجين و الكاربون. النقطة المهمة في هذا العمل هي الجمع بين جزأين مهمين (البروجيستيرون و 3،2،1–ترايازول) معًا لتكوين مشتقات جديدة **1–10**. يمكن اختبار هذا التصميم الجديد للمشتقات في المستقبل للتحقيق في دراساته البيولوجية، مثل مضادات الأكسدة والأنشطة المضادة للبكتيريا.

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1. Introduction

Progesterone (abbreviated as PNG or P4), alternatively referred to as pregnenedione or pregn-4-ene-3,20-dione, is a natural sex steroid hormone in the body that comprises a fused four-ring system: three six-membered rings and one five-membered ring with two ketone functional groups and a carbon-carbon double bond (21 carbon atoms) [1,2]. The discovery of progesterone was made by Allen in 1929, while the first isolation (*circa*. 20 mg) was by Butenandt and Westphal in 1934 from pure *corpus luteum* hormone [3-5]. The first semi-synthesis of progesterone was developed by Marker and Krueger in 1940, utilizing diosgenin, a steroid isolated from two Japanese source plants, *Dioscorea tokoro and Dioscorea mexicana* [6]. This was followed by two other semi-syntheses: Heyl and Herr in 1950 using 3-acetoxybisnor-5-cholenaldehyde [7], and Sundararaman and Djerassi in 1977 starting from stigmasterol [8]. The first total synthesis of progesterone was reported in 1971 by Johnson, Gravestock, and McCarry [9]. In humans, progesterone is naturally produced in both males and females, though females have a significantly higher concentration of this substance [10]. In females, it is related to reproductive activities such as pregnancy maintenance, ovulation, uterine preparation for embryo implantation, sexual behavior, and regulation of growth and differentiation of the uterus and mammary gland [11-15]. This hormone is also used in menopausal hormone replacement therapies and birth control pills [16,17]. Additionally, it is a medication for women with infertility problems, frequent pregnancy loss, and premenstrual syndrome (PMS) [18]. In males, the effects of progesterone include impotence and breast enlargement, as well as alterations in spermatogenesis, prostate, seminal vesicle, Cowper's gland, and accessory glands [19]. The first time for using progesterone as a medication *via* intramuscular injection was in 1939 [20,21], then as an oral medication in 1980 [21]. On the other hand, the 1,2,3-triazole ring is a five-membered ring with three atoms of nitrogen. The molecules bearing 1,2,3-triazole rings have been proven to possess a wide range of biological activities, such as antitumor [22,23], anti-inflammatory [24,25], antiplatelet [26,27], anti-tubercular [28], antiviral [29,30], antioxidant [31], antimalarial [32], antibacterial [33,34], anti-HIV-1 [35], antifungal [36], antiepileptic [37], and anticonvulsant [38]. Figure 1 shows some selected examples of compounds bearing 1,2,3-triazole rings that have been approved as medicines [39-41]. This study aims to prepare new progesterones bearing substituted 1,2,3-triazole rings using a one-pot procedure. The first step will include a treatment of progesterone with diverse aromatic aldehydes, resulting in the formation of corresponding α,β-unsaturated carbonyl derivatives as intermediates. In the second step, these intermediates will go through a metal-free [3+2] cycloaddition reaction with benzyl azide. This process will yield the desired progesterone derivatives. The feature in our structure design is combining two important scaffolds together (progesterone and 1,2,3-triazole rings), which was not reported in the literature.

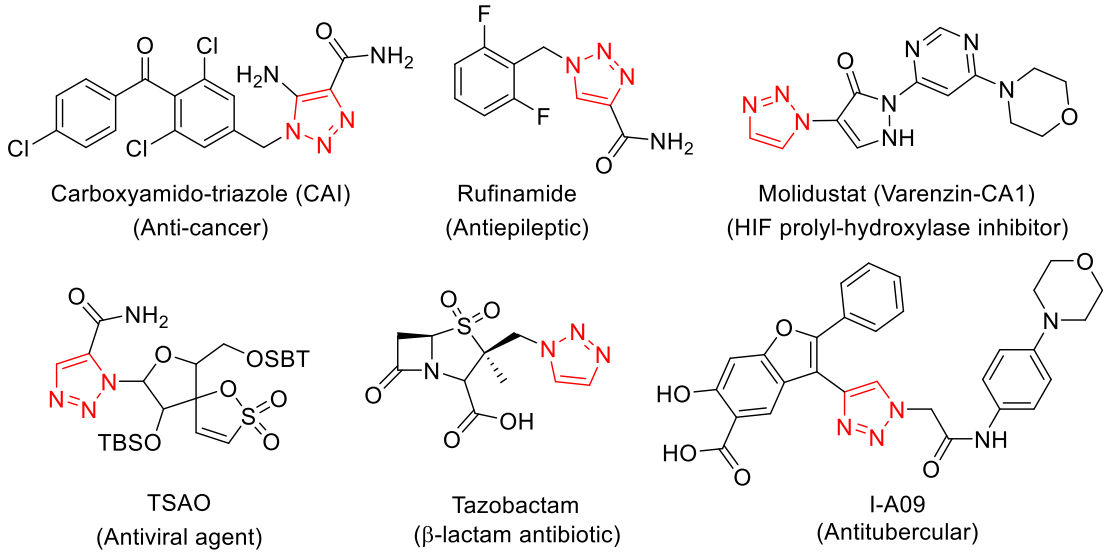


Figure 1: Examples of drugs incorporating 1,2,3-triazole rings

2. Experimental part

2.1. Chemicals and instruments

The chemicals were used exactly as received, without any additional purification after being procured from commercial sources. Thin layer chromatography (TLC) was conducted using silica gel 60 F_{254} (Merck Company). The spots of the products were visualized *via* exposure to ultraviolet (UV) light at 254 nm and then developed by the $KMnO_4$ solution. The silica gel employed in column chromatography was supplied by Merck Company (silica gel 60, 0.040-0.063 mm). The length and diameter of the column used are 32.5 and 2.2 cm, respectively. Melting points were recorded after purification by column silica gel on a Stuart Scientific SMP3 melting point apparatus. The FT-IR analysis data were measured on a Shimadzu 8400 FT-IR spectrometer. A Bruker AV400 spectrometer was employed to record the spectra of the ^{1}H NMR and ^{13}C NMR. The parts per million (ppm) downfield from tetramethylsilane (TMS), which is used as a standard, are used to report the chemical shifts (δ). Our reference was deuterated chloroform, which was set at 7.26 ppm for ^{1}H NMR and 77.16 ppm for ^{13}C NMR.

2.2. Synthesis

2.2.1. Preparation of benzyl azide [42,43]

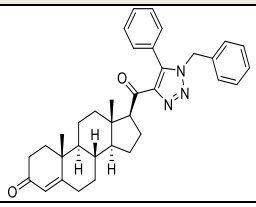
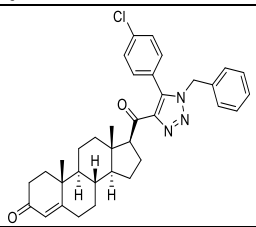
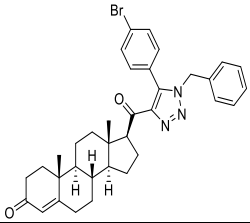
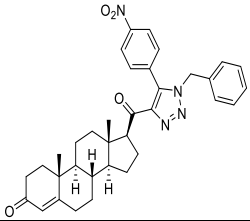
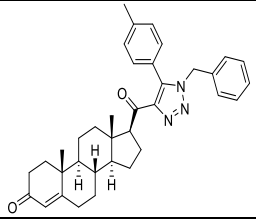
To a solution of benzyl bromide (10 mL, 84.2 mmol, 1.0 eq.) in DMSO (35 mL), sodium azide (8.2 g, 126.3 mmol, 1.5 eq.) was slowly added. The reaction mixture was then stirred for 26 hours at ambient temperature. Thereafter, H_2O (50 mL) was carefully added to the reaction mixture, and the organic layer was separated using Et_2O (2 × 25 mL), rinsed with brine (25 mL), and dried by anhydrous $NaSO_4$. The solvent was then evaporated *in vacuo* to give the crude mixture of colourless oil (8 mL, 64 mmol, 76%). The obtained product was used in our work without further purification in the next step.

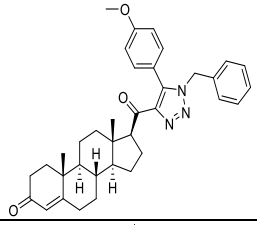
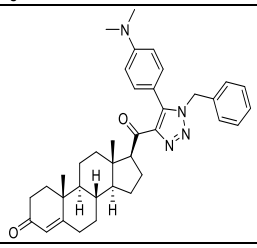
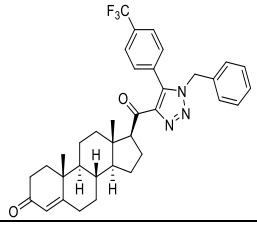
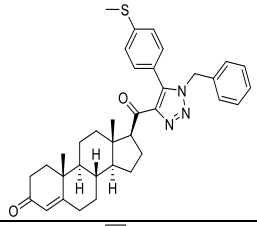
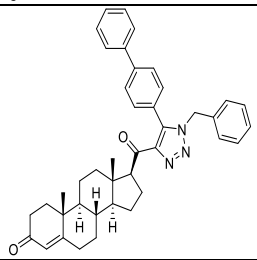
*2.2.2. The general procedure for the production of 1,4,5-trisubstituted 1,2,3-triazoles derived from progesterone **1-10** [44]*

A solution of progesterone (600 mg, 1.9 mmol, 1.0 eq.) in EtOH:MeCN (4:1, 25 mL) and K_2CO_3 (525 mg, 3.8 mmol, 2.0 eq.) was stirred for 5 minutes at ambient temperature before adding aromatic aldehydes (1.9 mmol, 1.0 eq.). After completion of the addition, the reaction mixture was heated to 65 °C and monitored by the TLC (petroleum ether/ethyl acetate) until

the starting materials were completely consumed (12-16 hours). Followed by the addition of BnN_3 (237 μL, 1.9 mmol, 1.0 eq.), K_2CO_3 (525 mg, 3.8 mmol, 2.0 eq.) and H_2O:dioxane (5:1, 20 mL) to the mixture in a one-pot reaction, before heating at 85 °C under an O_2 atmosphere. The reaction's conversion was monitored using TLC (petroleum ether/ethyl acetate) as long as the product that formed in the first stage was consumed (8-11 hours). The reaction mixture was subsequently permitted to cool down to ambient temperature before separating the organic layer using EtOAc (3 × 15 mL). After separation, the organic layer was dried with anhydrous $NaSO_4$, filtrated, and concentrated under reduced pressure. The crude organic material was subsequently purified using flash column chromatography using silica gel (eluting with petroleum ether/ethyl acetate) to furnish the title products (**1-10**). The FT-IR analysis data and physical properties of these products are shown in Tables 1 and 2, respectively.

Table 1: Certain physical properties of the synthesized products (**1-10**)

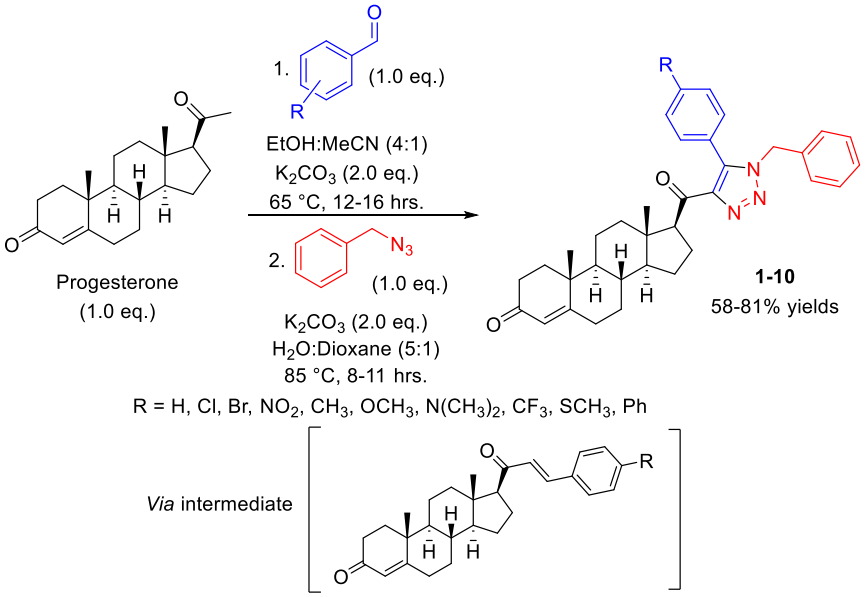
No	Structure	m.p. (°C)	Chemical formula	Color	Rf	Times (hour)	Yield (%)	Eluent ratio: Pet EtOAc
1		123-125	$C_{35}H_{39}N_3O_2$	White crystalline solid	0.27	$R^1 = 14$ $R^2 = 8$	70	6:1
2		102-104	$C_{35}H_{38}ClN_3O_2$	White crystalline solid	0.25	$R^1 = 14$ $R^2 = 9$	66	6:1
3		133-135	$C_{35}H_{38}BrN_3O_2$	White crystalline solid	0.28	$R^1 = 15$ $R^2 = 8$	65	6:1
4		N/A	$C_{35}H_{38}N_4O_4$	Yellow crystalline solid	0.25	$R^1 = 16$ $R^2 = 9$	77	5:1
5		144-146	$C_{36}H_{41}N_3O_2$	White crystalline solid	0.29	$R^1 = 16$ $R^2 = 10$	59	5:1

6		161-163	$C_{36}H_{41}N_3O_3$	White crystalline solid	0.29	$R^1 = 15$ $R^2 = 10$	60	6:1
7		133-135	$C_{37}H_{44}N_4O_2$	Brown crystalline solid	0.28	$R^1 = 14$ $R^2 = 10$	58	6:1
8		99-101	$C_{36}H_{38}F_3N_3O_2$	White crystalline solid	0.27	$R^1 = 12$ $R^2 = 10$	81	5:1
9		144-146	$C_{36}H_{41}N_3O_2S$	Yellow crystalline solid	0.26	$R^1 = 16$ $R^2 = 11$	64	6:1
10		171-173	$C_{41}H_{43}N_3O_2$	White crystalline solid	0.25	$R^1 = 15$ $R^2 = 9$	65	5:1

3. Results and discussion

The construction of the 1,2,3-triazole rings on the progesterone hormone was successfully accomplished to afford products **1**-**10** through a one-pot reaction, as displayed in Scheme 1. The first step in this reaction involved the formation of the corresponding α,β-unsaturated carbonyl derivatives for progesterone as intermediates. This was done *via* a Claisen-Schmidt condensation between progesterone and various types of aromatic aldehydes in the presence of K_2CO_3, which serves as a base to form the enolate of progesterone. The enolate form is more reactive towards the reaction with aldehydes. The TLC confirmed the conversion of starting materials into intermediates, which were then utilized in a second step to react with benzyl azide under metal-free [3+2] cycloaddition conditions. This afforded the desired targets of **1**-**10** in yields ranging from 58 to 81%. The products **4** and **8** were isolated with higher yields (77% for **4** and 81% for **8**) than the other eight products. This could be attributed to the electron-withdrawing groups at the aromatic aldehydes, which are considered more reactive to attack by the enolate form of progesterone. On the other hand, the derivatives **5**, **6**, and **7** were obtained with the lowest yields compared to the other derivatives. This could also be due to the presence of electron-donating groups at the aromatic aldehydes, which deactivated them when attacked by progesterone enolate. The FT-IR analysis data of products **1**-**10** showed new absorption bands between 3007 and 3098 cm^{-1} that are attributed

to aromatic C-H stretching [45]. Furthermore, indicating the existence of carbon-carbon double bonds in the aromatic rings of the produced compounds is the development of new stretching vibrations in the range of 1572-1596 cm^{-1} [45-48]. Table 2 shows all FT-IR analysis data for products **1-10**. In the ^{1}H NMR analysis data of compounds **5**, **6**, **7**, and **9**, the characteristic signals are the two protons of the benzyl moiety that formed at the triazole ring, which were observed in the normal range of the chemical shifts (5.49-5.51 ppm). Additionally, multiple signals due to the two aromatic ring protons were observed (**5** at 8.28-7.68, **6** at 8.27-7.60, **7** at 8.28-7.66, and **9** at 8.25-7.65 ppm [45]. The protons of the methyl groups in products **5**, **6**, **7**, and **9** appeared at 2.12, 3.73, 2.9, and 1.15 ppm, respectively, which are considered satisfactory evidence for the conversion. The ^{13}C NMR spectra of products **5**, **6**, **7**, and **9** showed the desired number of signals. All the ^{1}H NMR and ^{13}C NMR analysis data for products **5**, **6**, **7**, and **9** are listed in Table 3.

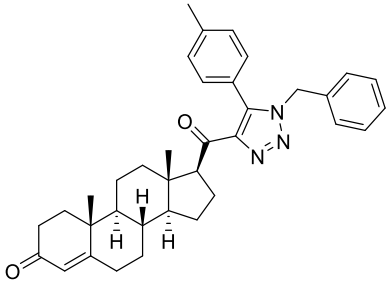
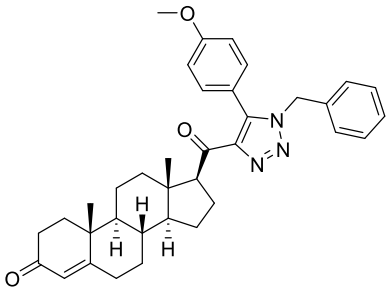
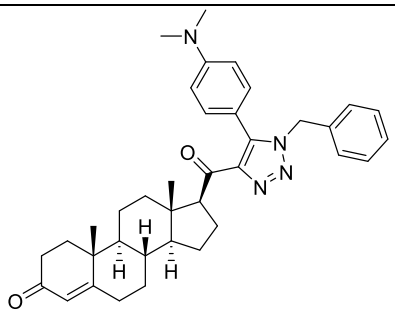
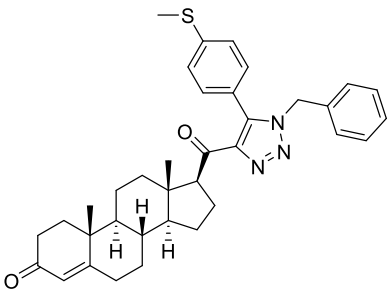


Scheme 1: Synthesis of progesterone linked to 1,2,3-triazole rings in a one-pot reaction

Table 2: Characteristic FT-IR analysis data (υ, cm^{-1}) of the products **1-10**

Compound number	C-H Aromatic	C-H Aliphatic	C=O Carbonyl	C=C Aliphatic	C=C Aromatic	N=N Triazole	Other bands
1	3064 3034	2986 2877	1717 1654	1613	1589	1453	-
2	3077 3034	2960 2863	1720 1653	1610	1583	1454	1050 (C-Cl)
3	3063 3033	2926 2854	1721 1652	1613	1593	1458	1066 (C-Br)
4	3062 3007	2978 2851	1730 1649	1602	1579	1449	1524 (NO_2 asym.) 1365 (NO_2 sym.)
5	3079 3054	2958 2873	1713 1641	1612	1596	1465	-
6	3064 3032	2977 2862	1727 1649	1612	1590	1458	1259 1029 (C-O-C)
7	3063 3033	2926 2854	1720 1651	1612	1592	1458	-
8	3063 3034	2927 2857	1719 1654	1612	1592	1455	1164 (C-F)
9	3068 3035	2980 2856	1714 1655	1607	1583	1455	727 C-S
10	3098 3033	2932 2852	1717 1654	1615	1572	1452	-

Table 3: ^{1}H NMR and ^{13}C NMR analysis data (δ, ppm) of products **5**, **6**, **7**, and **9**

No.	Compound structure	^{1}H NMR and ^{13}C NMR analysis data (δ, ppm)
5		**^{1}H NMR**: 8.28-8.14 (4H, m), 7.88-7.68 (5H, m), 5.73 (1H, s), 5.49 (2H, s), 2.55-2.51 (1H, m), 2.47-2.36 (3H, m), 2.30-2.25 (1H, m), 2.22-2.17 (1H, m), 2.12 (3H, s), 2.08-2.01 (2H, m), 1.88-1.83 (1H, m), 1.73-1.64 (4H, m), 1.61-1.57 (1H, m), 1.55-1.40 (3H, m), 1.35-1.23 (1H, m), 1.18 (3H, s), 1.09-1.00 (2H, m), 0.67 (3H, s). **^{13}C NMR**: 209.1, 170.8, 144.5, 135.7, 135.0, 134.4, 133.7, 132.3, 131.4, 130.6, 129.7, 128.1, 122.9, 111.2, 63.4, 55.9, 53.5, 51.7, 43.8, 38.6, 37.6, 36.4, 35.4, 33.9, 32.7, 31.8, 30.6, 23.5, 22.7, 20.9, 17.3, 13.3.
6		**^{1}H NMR**: 8.27-8.11 (4H, m), 7.90-7.60 (5H, m), 5.75 (1H, s), 5.51 (2H, s), 3.79 (3H, s), 2.57-2.53 (1H, m), 2.45-2.37 (3H, m), 2.32-2.26 (1H, m), 2.24-2.20 (1H, m), 2.19-2.04 (2H, m), 1.85-1.73 (1H, m), 1.71-1.68 (4H, m), 1.64-160 (1H, m), 1.57-1.51 (1H, m), 1.49-1.39 (2H, m), 1.28-1.22 (1H, m), 1.20 (3H, s), 1.10-1.02 (2H, m), 0.69 (3H, s). **^{13}C NMR**: 209.3, 171.0, 144.7, 135.9, 135.2, 134.6, 133.9, 132.5, 131.6, 130.8, 129.9, 128.3, 123.1, 111.4, 63.6, 56.1, 55.1, 53.7, 51.9, 44.0, 38.8, 37.8, 36.6, 35.6, 34.1, 32.9, 32.0, 30.8, 23.7, 21.1, 17.5, 13.5.
7		**^{1}H NMR**: 8.28-8.16 (4H, m), 7.90-7.66 (5H, m), 5.73 (1H, s), 5.50 (2H, s), 2.90 (6H, s), 2.55-2.50 (1H, m), 2.42-2.37 (3H, m), 2.35-2.29 (1H, m), 2.20-2.12 (1H, m), 2.08-2.02 (3H, m), 1.84-1.75 (1H, m), 1.71-1.68 (4H, m), 1.63-1.57 (1H, m), 1.48-1.40 (2H, m), 1.29-1.21 (1H, m), 1.18 (3H, s), 1.09-1.01 (2H, m), 0.67 (3H, s). **^{13}C NMR**: 209.0, 170.7, 144.4, 135.6, 134.9, 134.3, 133.6, 132.2, 131.3, 130.5, 129.6, 128.0, 122.8, 111.1, 63.3, 55.8, 53.4, 48.5, 43.7, 40.8, 38.5, 37.5, 36.3, 35.3, 33.8, 32.6, 31.7, 30.5, 23.4, 20.8, 17.2, 13.2.
9		**^{1}H NMR**: 8.25-8.11 (4H, m), 7.85-7.65 (5H, m), 5.70 (1H, s), 5.46 (2H, s), 2.52-2.41 (1H, m), 2.39-2.35 (3H, m), 2.32 (3H, s), 2.30-2.26 (1H, m), 2.23-2.17 (1H, m), 2.05-1.85 (3H, m), 1.72-1.64 (4H, m), 1.61-1.56 (1H, m), 1.52-1.48 (1H, m), 1.45-1.40 (2H, m), 1.27-1.20 (1H, m), 1.15 (3H, s), 1.07-0.96 (2H, m), 0.64 (3H, s). **^{13}C NMR**: 209.2, 170.9, 144.6, 135.7, 135.0, 134.4, 133.7, 132.3, 131.5, 130.6, 129.7, 128.1, 123.0, 111.3, 63.4, 56.0, 53.6, 51.7, 43.9, 38.6, 37.7, 36.4, 35.4, 33.9, 32.7, 31.9, 30.7, 23.6, 21.0, 17.3, 15.7, 13.3.

Conclusion

A successful method for the access of novel progesterone-1,2,3-triazole hybrids in a one-pot protocol has been accomplished. This approach offers high yields (up to 81%), a broad substrate scope, and proceeds under a cheap and metal-free catalytic manifold. The targeted progesterone derivatives are formed through aldol condensation and azide-enone [3+2] cycloaddition reactions.

References

[1] J. Elks. The dictionary of drugs: Chemical data: Chemical data, Structures and bibliographies, Springer, p. 1024, 2014.

[2] L. Kolatorova, J. Vitku, J. Suchopar, M. Hill, and A. Parizek, "Progesterone: A steroid with wide range of effects in physiology as well as human medicine, *International Journal of Molecular Sciences*", vol. 23, no. 14, article no. 7989 (36 pages), 2022.

[3] A. Butenandt and U. Westphal, "Isolation of progesterone", Forty years ago, *American Journal of Obstetrics and Gynecology*, vol. 120, no. 1, pp. 137-141, 1974.
[4] J. B. Josimovich, Gynecologic endocrinology, Springer science and business media, pp. 25-29, 2022.
[5] R. F. Witzmann, Steroidss keys to life; Van Norstrand Reinhold Co., 1st edition, New York, 1981.
[6] R. E. Marker and J. Krueger, "Sterols. CXII. Sapogenins. XLI. The preparation of trillin and its conversion to progesterone", *Journal of the American Chemical Society*, vol. 62, no. 12, pp. 3349-3350, 1940.
[7] F. W. Heyl and M. E. Herr, "Progesterone from 3-acetoxybisnor-5-cholenaldehyde and 3-ketobisnor-4-cholenaldehyde", *Journal of the American Chemical Society*, vol. 72, no. 6, pp. 2617-2619, 1950.
[8] P. Sundararaman and C. Djerassi, "A convenient synthesis of progesterone from stigmasterol", *The Journal of Organic Chemistry*, vol. 42, no. 22, pp. 3633-3634, 1977.
[9] W. S. Johnson, M. B. Gravestock, and B. E. McCarry, "Acetylenic bond participation in biogenetic-like olefinic cyclizations. II. Synthesis of dl-progesterone", *Journal of the American Chemical Society*, vol. 93, no. 17, pp. 4332-4334, 1971.
[10] J. Ricanyová, R. Gadzała-Kopciuch, K. Reiffova, Y. Bazel, and B. Buszewski, "Molecularly imprinted adsorbents for preconcentration and isolation of progesterone and testosterone by solid phase extraction combined with HPLC", *Adsorption*, vol. 16, pp. 473-483, 2010.
[11] S. P. Wu, R. Li, and F. J. DeMayo, "Progesterone receptor regulation of uterine adaptation for pregnancy", *Trends in Endocrinology and Metabolism*, vol. 29, no. 7, pp. 481-491, 2018.
[12] N. Wang, W. Zhu, and Y. Gong, "Association of raised serum progesterone level with ovulation trigger and histology of endometrium in stimulated cycles", *Brazilian Journal of Pharmaceutical Sciences*, vol. 58, article no. e20151 (7 pages), 2022.
[13] M. Cozzolino, I. Hervás, Y. Ergun, M. G. Massaro, N. Pellicer, F. D. Angelis, E. Labarta, and D. Galliano, "Higher serum progesterone level has no negative impact on live birth rate in frozen embryo transfer", *European Journal of Obstetrics and Gynecology and Reproductive Biology*, vol. 303, pp. 15-21, 2024.
[14] M. Jewson, P. Purohit, and M. A. Lumsden, "Progesterone and abnormal uterine bleeding/menstrual disorders" *Best Practice and Research Clinical Obstetrics and Gynaecology*, vol. 69, pp. 62-73, 2020.
[15] S. Inoue, Hormonal and circuit mechanisms controlling female sexual behavior, "*Frontiers in Neural Circuits*", vol. 18, article no. 1409349 (7 pages), 2024.
[16] J. M. Tian, B. Ran, C. L. Zhang, D. M. Yan, and X. H. Li, "Estrogen and progesterone promote breast cancer cell proliferation by inducing cyclin G1 expression", *Brazilian Journal of Medical and Biological Research*, vol. 51, no. 3, article no. e5612 (7 pages), 2018.
[17] C. K. Wagner, "The many faces of progesterone: A role in adult and developing male brain", *Frontiers in Neuroendocrinology*, vol. 27, no. 3, pp. 340-359, 2006.
[18] R. W. Lancaster, P. G. Karamertzanis, A. T. Hulme, D. A. Tocher, T. C. Lewis, and S. L. Price, "The polymorphism of progesterone: Stabilization of a 'disappearing' polymorph by co-crystallization", *Journal of Pharmaceutical Sciences*, vol. 96, no. 12, pp. 3419-3431, 2007.
[19] M. J. L. de Alda, A. Gil, E. Paz, and D. Barcelo, "Occurrence and analysis of estrogens and progestogens in river sediments by liquid chromatography-electrospray-mass spectrometry", *Analyst*, vol. 127, pp. 1299-1304, 2002.
[20] B. Seaman, The greatest experiment ever performed on women: Exploding the estrogen myth: Seven stories press, 2nd edition, p. 27, 2009.
[21] J. A. Simon, "Micronized progesterone: Vaginal and oral uses", *Clinical Obstetrics and Gynecology*, vol. 38, no. 4, pp. 902-914, 1995.
[22] F. Wang, B. Peng, T. Ren, S. Liu, J. Du, Z. Chen, T. Zhang, X. Gu, M. Li, S. Cao, and X. Xu, "A 1,2,3-Triazole derivative of quinazoline exhibits antitumor activity by tethering RNF168 to SQSTM1/P62", *Journal of Medicinal Chemistry*, vol. 65, no. 22, pp. 15028-15047, 2022.
[23] J. C. R. Gonçalves, T. H. Coulidiati, A. L. Monteiro, L. C. T. de Carvalho-Gonçalves, W. de Oliveira Valença, R. N. de Oliveira, C. A. de Câmara, and D. A. M. de Araújo, "Antitumoral activity of novel 1,4-naphthoquinone derivative involves L-type calcium channel activation in

human colorectal cancer cell line", *Journal of Applied Biomedicine*, vol. 14, no. 3, pp. 229-234, 2016.

[24] S. P. O. Assis, M. T. da Silva, R. N. de Oliveira, and V. L. M. Lima, "Synthesis and anti-inflammatory activity of new alkyl-substituted phthalimide 1*H*-1,2,3-triazole derivatives", *The Scientific World Journal*, vol. 2012, article no. 925925, 2012.

[25] K. K. Angajala, S. Vianala, R. Macha, M. Raghavender, M. K. Thupurani, and P. J. Pathi, "Synthesis, anti-inflammatory, bactericidal activities and docking studies of novel 1,2,3-triazoles derived from ibuprofen using click chemistry", *SpringerPlus*, vol. 5, article no. 423 (15 pages), 2016.

[26] A. C. Cunha, J. M. Figueiredo, J. L. M. Tributino, A. L. P. Miranda, H. C. Castro, R. B. Zingali, C. A. M. Fraga, M. C. B. V. De Souza, V. F. Ferreira, and E. J. Barreiro, "Antiplatelet properties of novel *N*-substituted-phenyl-1,2,3-triazole-4-acylhydrazone derivatives", *Bioorganic and Medicinal Chemistry*, vol. 11, no. 9, pp. 2051-2059, 2003.

[27] A. K. Jordao, V. F. Ferreira, E. S. Lima, M. C. B. V. De Souza, E. C. L. Carlos, H. C. Castro, R. B. Geraldo, C. R. Rodrigues, M. C. B. Almeida, and A. C. Cunha, "Synthesis, antiplatelet and in silico evaluations of novel *N*-substituted-phenylamino-5-methyl-1H-1,2,3-triazole-4-carbohydrazides", *Bioorganic and Medicinal Chemistry*, vol. 17, no. 10, pp. 3713-3719, 2009.

[28] S. Zhang, Z. Xu, C. Gao, Q. Ren, L. Chang, Z. Lv, and L. Feng, "Triazole derivatives and their anti-tubercular activity", *European Journal of Medicinal Chemistry*, vol. 138, pp. 501-513, 2017.

[29] N. Agouram, "1,2,3-triazole derivatives as antiviral agents", *Medicinal Chemistry Research*, vol. 32, no. 12, pp. 2458-2472, 2023.

[30] D. J. Viegas, V. D. Silva, C. D. Buarque, D. C. Bloom, and P. A. Abreu, "Antiviral activity of 1,4-disubstituted-1,2,3-triazoles against HSV-1 in vitro", *Antiviral Therapy*, vol. 25, no. 8, pp. 399-410, 2020.

[31] S. Aitha, V. Thumma, R. Matta, S. Ambala, K. Jyothi, S. Manda, and J. Pochampally, "Antioxidant activity of novel 4*H*-chromene tethered 1,2,3-triazole analogues: Synthesis and molecular docking studies", *Results in Chemistry*, vol. 5, article no. 100987, 2023.

[32] S. M. Abdul Rahman, J. S. Bhatti, S. Thareja, and V. Monga, "Current development of 1,2,3-triazole derived potential antimalarial scaffolds: Structure-activity relationship (SAR) and bioactive compounds", *European Journal of Medicinal Chemistry*, vol. 259, article no. 115699, 2023.

[33] B. Zhang, "Comprehensive review on the anti-bacterial activity of 1,2,3-triazole", *European Journal of Medicinal Chemistry*, vol. 168, pp. 357-372, 2019.

[34] Z. Xu, "1,2,3-Triazole-containing hybrids with potential antibacterial activity against methicillin-resistant staphylococcus aureus (MRSA)", *European Journal of Medicinal Chemistry*, vol. 206, article no. 112686 (15 pages), 2020.

[35] L. S. Feng, M. J. Zheng, F. Zhao, and D. Liu, "1,2,3-Triazole hybrids with anti-HIV-1 activity", *Archiv der Pharmazie,* vol. 354, no. 1, article no. 2000163 (10 pages), 2021.

[36] N. Nehra, R. K. Tittal, D. G. Vikas, Naveen, and K. La, "Synthesis, antifungal studies, molecular docking, ADME and DNA interaction studies of 4-hydroxyphenyl benzothiazole linked 1,2,3-triazoles", *Journal of Molecular Structure*, vol. 1245, article no. 131013 (11 pages), 2021.

[37] S. Ulloora, R. Shabaraya, and A. V. Adhikari, "Facile synthesis of new imidazo[1,2-a]pyridines carrying 1,2,3-triazoles *via* click chemistry and their antiepileptic studies", *Bioorganic and Medicinal Chemistry Letters*, vol. 23, no. 11, pp. 3368-3372, 2013.

[38] P. K. Kadaba, "Triazolines. 14. 1,2,3-Triazolines and triazoles, a new class of anticonvulsants. Drug design and structure-activity relationships", *Journal of Medicinal Chemistry*, vol. 31, no. 1, pp. 196-203, 1988.

[39] M. M. Matin, P. Matin, M. R. Rahman, T. B. Hadda, F. A. Almalki, S. Mahmud, M. M. Ghoneim, M. Alruwaily, and S. Alshehri, "Triazoles and their derivatives: Chemistry, synthesis, and therapeutic applications", *Frontiers in Molecular Biosciences*, vol. 9, article no. 864286 (8 pages), 2022.

[40] D. P. Vala, R. M. Vala, and H. M. Patel, "Versatile synthetic platform for 1,2,3-triazole chemistry", *ACS Omega*, vol. 7, no. 42, pp. 36945-36987, 2022.

[41] M. J. Vaishnani, S. Bijani, M. Rahamathulla, L. Baldaniya, V. Jain, K. Y. Thajudeen, M. M. Ahmed, S. A. Farhana, and I. Pasha, "Biological importance and synthesis of 1,2,3-triazole

derivatives: A review", *Green Chemistry Letters and Reviews*, vol. 17, no. 1, article no. 2307989, 2024.

[42] E. J. O'Neil, K. M. DiVittorio, and B. D. Smith, "Phosphatidylcholine-derived bolaamphiphiles *via* click chemistry", *Organic Letters*, vol. 9, no. 2, pp. 199-202, 2007.

[43] R. S. Dawood and A. S. Hamed, "Synthesis and characterization of new 1,3-nenzodioxole derivatives based on Suzuki-Miyaura coupling reaction", *Research Journal of Chemistry and Environment*, vol. 23, Special Issue I, pp. 14-21, 2019.

[44] W. Yang, T. Miao, P. Li, and L. Wang, "Regioselective synthesis of triazoles *via* base-promoted oxidative cycloaddition of chalcones with azides in aqueous solution", *RSC Advances*, vol. 5, no. 116, pp. 95833-95839, 2015.

[45] R. M. Silverstein, F. X. Webster, and D. J. Kiemle, "Spectrometric identification of organic compounds", 7th edition, John Wiley and Sons, USA, 2005.

[46] A. S. Hamed and R. S. Dawood, "Synthesis and identification of some new derivatives of benzoxazole bearing pyrazole and 1,2,4-triazine rings", *Journal of Global Pharma Technology*, vol. 12, no. 2, pp. 737-744, 2020.

[47] Ahlam Al-Azzawi and Kafa Hammud, "Synthesis and characterization of some new 1,3,4-oxadiazole and 1,2,4-triazole derivatives based on 3,4,5,6-tetrachlorophthalimide", *Iraqi Journal of Science*, vol. 54, no. 4, pp. 782-788, 2024.

[48] Amaal S. Sadiq and Entesar O. Al-Tamimi, "Synthesis and characterization of new polymers bearing tetrazole and triazole moieties with studying their corrosion protection of stainless steel surface in hydrochloric acid", *Iraqi Journal of Science*, vol. 61, no. 10, pp. 2467-2478, 2020.

[49] Hadeel A. K Hussien and Zainab A. K. Al-Messri, "Synthesis, characterization and evaluation of 5-alkylidene meldrum's acid derivatives as multifunction lubricating oil additives", *Eurasian Chemical Communications*, vol. 3, no. 9, pp. 598-605, 2021.

[50] Ahmad R. Salih and Zainab A. K. Al-Messri, "Synthesis of pyranopyrazole and pyranopyrimidine derivatives using magnesium oxide nanoparticles and evaluation as corrosion inhibitors for lubricants", *Eurasian Chemical Communications*, vol. 3, no. 8, pp. 533-541, 2021.