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Synthesis of new succinate-dihydrotestosterone-dihydropyrimidine conjugate

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A new steroid-dihydropyrimidine derivative has been synthesized. The route involves preparation of dihydrotestosterone-dihydropyrimidine derivative **4** using dihydrotestosterone **1**, benzaldheyde **2**, and thiourea **3** in presence of hydrochloric acid, followed by esterification of **4** with succinic acid **5** which results in the formation of succinate-dihydrotestosterone-dihydropyrimidine conjugate **6**.

Keywords: Dihydropyrimidine, steroid, dihydrotestosterone, succinic acid, succinate

In the past decades, several dihydropyrimidine derivatives were synthesized having a wide spectrum of biological activity[1] — as antibacterials[2,3], antivirals[4] as well as antitumor agents. In this context, there are reports of several multi-component reactions for synthesis of dihydropyrimidines. For example, the work reported by Hantzsch[5] which described the preparation of 1,4-dihydropyridine using three component (acetoacetic ester, benzaldehyde and ammonia or ammonium salts) coupling reaction in refluxing ethanol. Other reports by Bignelli[6] demonstrated the synthesis of dihydropyrimidine derivatives using ethyl acetoacetate, benzaldehyde and urea. In addition, dihydropyrimidin-2(1*H*)-one was synthesized recently using the three component system (urea/thiourea, ethyl acetoacetate/acetyl acetone) in presence of phosphorous pentoxide[7]. Additionally, work[8] carried out by Surya and co-workers demonstrated the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones under solvent-free conditions using ruthenium(III) chloride catalysis. In addition, Kappe[9] and co-workers showed a highly versatile solid-phase synthesis of biofunctional 4-aryl-3,4-dihydropyrimidine using resin-bound isothiourea building blocks and multi-directional resin cleavage. In addition, Shirini and coworkers[10] have used $Fe(HSO_4)_3$ as an efficient catalyst for the preparation of 3,4-dihydropyrimidin-2(1*H*)-ones using the three component system (β-ketoester, benzaldehyde and thiourea). Salehia[11] and co-workers have carried out the synthesis of dihydropyrimidinones using aldheyde-derivatives, dicarbonyl compounds and urea or thiurea in presence of diammonium hydrogen phosphate.

All these reports describe several protocols for synthesis of dihydropyrimidine-derivatives involved in Bignelli reaction. Nevertheless, the use of expensive reagents require special conditions. Therefore, in this work, the initial design includes a facile synthesis of a steroid-dihydropyrimidine derivative that contains the cyclopentene ring of dihydropyrimidine derivative nucleus, a spacer arm with both ester and acid functional groups. The route involves preparation of dihydrotestosterone-dihydropyrimidine derivative **4** using the three component system (5α-androstan-17β-ol-3-one, benzaldehyde and thiourea in presence of hydrochloric acid as catalyst, followed by esterification of steroid-dihydropyrimidine derivative with succinic acid and 1,3-dicyclohexylcarbodiimide to form succinate-dihydrotestosterone-dihydropyrimidine conjugate **6**.

Results and Discussion

It is important to mention that many methods for the formation of dihydropyrimidine derivatives are known in the literature. The most widely practiced method employs boric acid[12], silica sulfuric acid[13], poly(4-vinylpyridine-codivynylbenzene)-Cu(II) complex[14], H_2SO_4 (ref. 15), silica triflate[16] and phosphorus pentoxide[7]. Nevertheless, despite their wide scope, the former protocols suffer from several

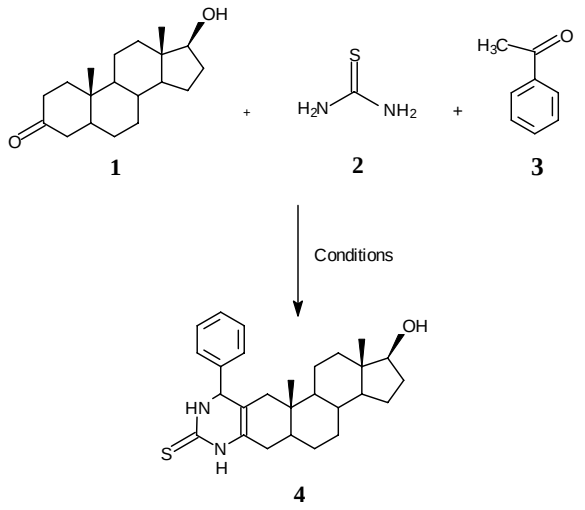

Figure 1 — Synthesis of dihydrotestosterone-dihydropyrimidine derivative **4**, using a multi-component system: dihydrotestosterone **1**, thiourea **2** and benzaldehyde **3**. Conditions = hydrochloric acid/ethanol.

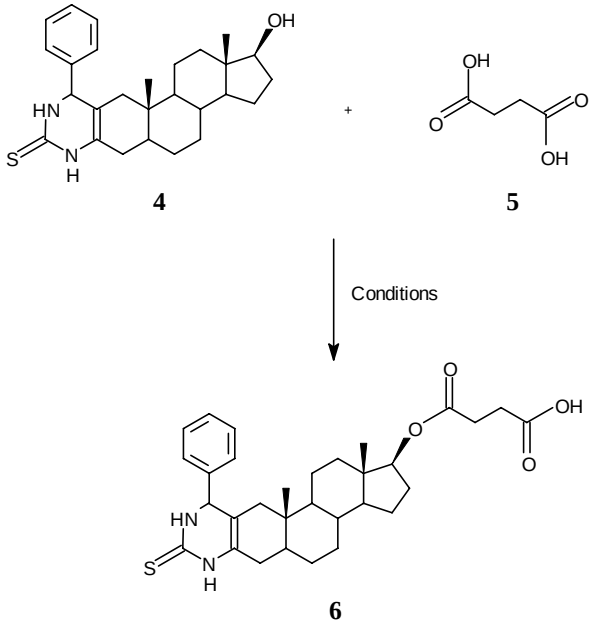

Figure 2 — Preparation of succinate-dihydrotestosterone-dihydropyrimidine **6** conjugate by esterification of **4** with succinic acid **5**. Conditions = dicyclohexylcarbodiimide / *p*-toluenesulfonic acid in acetonitrile/water.

drawbacks; some reagents have a limited stability and their preparation can be dangerous.

Therefore, in this work is reportd a straightforward route for synthesis of a new steroid-dihydropyrimidine derivative; the first step involves preparation of dihydrotestosterone-dihydropyrimidine derivative **4** using the three component system (5α-androstan-17β-ol-3-one, benzaldehyde and thiourea) in presence of hydrochloric acid as catalyst (**Figure 1**). The results indicate that the ^{1}H NMR spectrum of dihydrotestosterone-dihydropyrimidine derivative showed a signal at δ 0.74 and 0.78 for methyls present in the heterocyclic rings; at 4.83 for methylene involved in pyrimidine ring. At down-field there are several chemical shifts (δ 7.21-7.29 and 7.46) corresponding to aromatic protons. Finally, spectra display a similar chemical shift at δ 7.38 for NH (pyrimidine ring) and OH.

On the other hand, ^{13}C NMR spectra display chemical shifts at δ 11.94 and 12.11 for the carbons of the methyl groups present in the heterocyclic rings. The chemical shift of the methylene joined to pyrimidine ring were found at δ 109.01 (C–*C*=C) and 125.57 (C=*C*–N). At down-field there are several signals (δ 125.60, 127.38, 127.46, 128.33 and 139.31) corresponding to the carbons of aromatic ring. Additionally, the mass spectra displays a molecular ion at *m/z* 438.16 corresponding to M+ –Cl which confirms the structure of **4**.

The second step involves the esterification of the hydroxyl group of dihydrotestosterone-dihydropyrimidine derivative by the reaction of **4** with succinic acid **5** in presence of 1,3-dicyclohexylcarbodiimide and *p*-toluenesulfonic acid as catalysts. Although there are diverse reagents to produce esters derivatives[17,18], in this work carbodiimide-derivative as catalyst was used. Nevertheless, it is important to mention that when 1,3-dicyclohexylcarbodiimide is used as condensing agent in ester synthesis, the yield of ester is often unsatisfactory due to formation of N-acylurea derivative as by-product. Therefore, in this esterification reaction, the *p*-toluenesulfonic acid was used to increase the yield of succinate-dihydrotestosterone-dihydropyrimidine conjugate **6** (**Figure 2**). It is important to mention that this method is reported by Holmberg and Hansen[19] for esterification of steroid-derivatives with 1,3-dicyclohexylcarbodiimide enhanced by acid catalyst.

The ^{1}H NMR spectra of **6** showed a signal at δ 0.76 and 0.83 present in the heterocyclic ring and at 4.81 for methylene of the pyrimidine ring. In addition, down-field there are several chemical shifts (δ 7.24-7.43) corresponding to protons in aromatic ring. Finally, the spectra display a similar chemical shift at δ 8.60 for NH (pyrimidine ring) and CO_2H.

It is seen that the ^{13}C NMR spectrum of **6** displays chemical shifts at δ 11.98 and 12.13 for the carbons of

the methylene groups presents in the heterocyclic rings. The chemical shift of the methylene joined to pyrimidine ring were found at δ 108.02 (C–*C*=C) and 125.58 (C=*C*–N). At down-field there are several signals (δ 125.60, 127.39, 127.42, 128.35, 139.32 and 142.02) corresponding to the carbons of aromatic ring. Additionally, two chemical shifts were found at δ 172.81 (*C*O_2H) and 180.62 (N–*C*=S, pyrimidine ring). In addition, the mass spectra displays a molecular ion at *m/z* 583.31 corresponding to M+ –Cl which confirms the structure of **6**.

In conclusion, in this work is reported an efficient and simple method for synthesis of new steroid-dihydropyrimidine derivative **4**, using a multi-component system in presence of hydrochloric acid as catalyst. It is important to mention that this method showed a high versatility and excellent yields. Additionally, the esterification of dihydro-testosterone-dihydropyrimidine derivative using succinic acid in presence of 1,3-dicyclohexyl-carbodiimide/*p*-toluenesulfonic acid is a good method to increase the yield of **6**.

Experimental Section

Dihydrotestosterone (5α-androstan-17β-ol-3-one) and the other compounds used in this study were purchased from Sigma-Aldrich Co., Ltd. The melting points of the different compounds were determined on an Electrothermal (900 model) instrument and are uncorrected. Ultraviolet-visible spectroscopy (UV-Vis) were recorded in dry methanol on a Perkin-Elmer model 552 spectrophotometer and infrared spectra (IR) were recorded using KBr pellets on a Perkin-Elmer Lambda 40 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR-300/5 FT NMR spectrometer at 300 and 75.4 MHz respectively in $CDCl_3$ using TMS as internal standard. EIMS spectra were obtained with a Finnigan Trace GCPolaris Q spectrometer. Elemental analysis data were acquired from a Perkin-Elmer series II CHNS/0 2400 elemental analyzer.

Synthesis of 1-hydroxy-11*a*,13*a*-dimethyl-10-phenyl-1,2,3,3*a*,3*b*,4,5,5*a*,6,7,9,10,11,11*a*,11*b*,12,13,13*a*-octadecahydro-7,9-diaza-indeno[5,4-*a*]anthracene-8-thione, 4. A solution of dihydrotestosterone (118 mg, 0.41 mmole), thiourea (123.70 mg, 1.62 mmole) and benzaldehyde 172.44 mg (1.62 mmole) in 10 mL ethanol was stirred for 10 min at RT. Thereafter, 1 mL hydrochloric acid was added and the mixture was stirred for 48 hr at RT. The reaction-mixture was then concentrated to a smaller volume, diluted with water, and extracted with chloroform. The organic phase was evaporated to dryness under reduced pressure, the residue was purified by recrystallization from methanol:water (3:1) to give 235 mg (80%) product; m.p. 107°C; UV-Vis (MeOH): (log ε) 217 (0.18), 258 (0.09) nm; IR: 3330, 1620, 1470 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.74 (1H, s, C*H*$_3$), 0.78 (3H, s, C*H*$_3$), 0.87 (1H, m, H-7), 0.96-1.09 (m, 2H), 1.11-1.79 (m, 11H), 1.85-1.90 (m, 2H), 2.06-2.52 (m, 4H), 3.61 (m, 1H), 3.80 (m, 1H), 4.83 (s, 1H), 7.21-729 (m, 3H, ArH), 7.38 (m, NH pyrimidine ring and OH), 7.46 (m, 2H, ArH); ^{13}C NMR (74.5 MHz, $CDCl_3$): δ 11.94 (CH_3), 12.11(CH_3), 20.55, 23.56, 27.87, 27.89, 30.33, 34.93, 35.36, 35.38, 36.41, 42.66, 50.58, 50.77, 53.39, 53.43, 58.25, 61.32, 82.84 (*C*-OH), 109.01 (C–*C*=C), 125.57 (C=*C*–N), 125.60, 127.38, 127.46, 128.33, 139.31 (Ar), 179.30 (pyrimidine ring); EIMS: *m/z* 438.16 (M$^+$, 11). Anal. Calcd for $C_{27}H_{36}N_2OS$: C, 74.27; H, 8.31; N, 6.42; O, 3.66; S, 7.34. Found: C, 74.2; H, 8.29; N, 6.38%.

Synthesis of succinic acid mono-(11*a*,13*a*-dimethyl-10-phenyl-8-thioxo-2,3,3*a*,3*b*,4,5,5*a*,6,7,8,9,10,11,11*a*,11*b*,12,13,13*a*-octadecahydro-1*H*-7,9-diaza-inde-no[5,4-α]anthracen-1-yl)ester, 6. Dihydrotesto-sterone derivative **4** (100 mg, 0.24 mmole) was added to a solution of succinic acid **5** (85 mg, 0.72 mmole), 1,3 dicyclohexylcarbodiimide (100 mg, 0.48 mmole) in acetonitrile-water (15 mL, 3:1) and *p*-toluenesulfonyl chloride (69 mg, 0.36 mmole) was added and the mixture was stirred at RT for 72 hr. After the solvent was removed under vacuum and the crude product was purified by crystallization from methanol:hexane:water (3:2:1) yielding 48% of product; m.p. 121°C; UV-Vis (MeOH): (log ε) 218 (0.19), 261 (0.20) nm; IR: 3326, 1615, 1712 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.76 (s, CH_3), 0.83 (s, CH_3), 0.87 (m, 1H), 1.1 (m, 1H), 1.10-1.80 (m, 11H), 1.85-1.90 (m, 2H), 2.03-2.43 (m, 4H), 2.57 (m, 2H), 3.62 (m, 1H), 3.81 (m, 2H), 4.44 (m, 1H), 4.81 (s, 1H) 7.24-7.43 (m, 5H, ArH), 8.60 (1H, br, NH, pyrimidine ring and CO_2H); ^{13}C NMR (74.5 MHz, $CDCl_3$): δ 11.98 (*C*H$_3$-22), 12.13(*C*H$_3$-23), 20.55, 23.52, 27.85, 27.89, 29.73, 29.81, 30.31, 32.01, 34.96, 35.34, 35.36, 36.44, 42.69, 50.56, 50.71, 53.31, 53.45, 61.37, 82.83 (C–*C*–O, cyclopentene), 108.02 (C–*C*=C), 125.58 (N–*C*=C), 125.60, 127.39, 127.42, 128.35, 139.32, 142.02 (*C*–Ar), 172.81 *C*O_2H), 173.05(*C*O_2), 180.62 (N–*C*=S, pyrimidine ring); EIMS: *m/z* 538.31(M$^+$, 24). Anal. Calcd for $C_{31}H_{40}N_2O_4S$: C, 69.37; H, 7.51; N, 5.22; O, 11.92; S, 5.97. Found: C, 69.09; H, 7.50; N, 5.20%.

References

1 Cheng C I, *Prog Med Chem*, 6, **1969**, 67.

2 Mishra R, Mishra B & Moorthy H, *Trends in Appl Sci Res*, 3, **2008**, 203.

3 Padhy A, Bardhan M & Panda C, *Indian J Chem*, 42B, **2003**, 910.

4 Vishnevskii S, Pirozhenko V, Chentsova N, Antonenko S, Barbasheva E & Grin E, *Pharm Chem J*, 28, **1994**, 12.

5 Hantzsch A, *Ann Chem*, 215, **1892**,1.

6 Kappe O, *Acc Chem Res*, 33, **2000**, 879.

7 Deshmukh M, Anbhule P, Jadhav S, Mali A, Jagtap S & Deshmukh S, *Indian J Chem*, 46B, **2007**, 1545.

8 Surya K & Gibbs A, *Synthesis*, 11, **2005**, 1748.

9 Kappe C O, *Bioorg Med Chem Lett*, 10, **2000**, 49.

10 Shirinia F, Zolfigolb M & Abria A, *J Iran Chem Soc*, 5, **2008**, 96.

11 Salehia P, Dabirib M, Khosropour A & Roozbehniyab P, *J Iran Chem Soc*, 3, **2006**, 98.

12 Tu S, Fang F, Miao C, Jiang H, Feng Y & Shi D, *Tetrahedron Lett*, 44, **2003**, 6153.

13 Salehi P & Fard N, *Tetrahedron Lett*, 44, **2003**, 2889.

14 Yarapathi R, Kurva S & Tammishetti S, *Catal Commun*, 5, **2004**, 511.

15 Bussolari J & McDonnell P, *J Org Chem*, 65, **2005**, 6777.

16 Shirini F, Marjani K & Nahzomi H, *Arkivoc*, i, **2007**, 51.

17 Crossland R & Servis K, *J Org Chem*, 35, **1970**, 3195.

18 Zhu H, Yang F, Tang J & He M, *Green Chem*, 5, **2003**, 38.

19 Holmberg K & Hansen B, *Acta Chem Scand*, B33, **1979**, 410.