

Synthesis, Characterization and biological Study of some new derivatives from Pregnenolone via McMurry reaction

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Abstract

A series of some new Pregnenolone derivatives have been synthesized by McMurry reaction which include using of (Low-Valent) titanium from ($TiCl_4$) with (Zn-dust) as catalyst and (THF) as a solvent to convert the (ketonic carbonyl group) of Pregnenolone with a new aldehyde or ketone compound to a new aliphatic double bond connected each other. All the new synthesized derivatives were monitored by (TLC) and assigned by elemental analysis, melting points, FT-IR and (1H NMR, ^{13}C NMR and 2D-NMR) spectroscopy. The anti-bacterial and anti-fungi activity of these derivatives were also determined.

Key words: steroids, biological activity, Pregnenolone, McMurry reaction,

1- Introduction

Steroids are an important class of biological regulator that nearly always show dramatic physiological effects when they are administered to living organisms [1-3]. In addition to the many hundreds of steroids isolated from plants and animals, the thousands more have been synthesized in pharmaceutical laboratories in the search for new drugs [4-5].

Pregnenolone and its derivatives promote neuronal activity by enhancing learning and memory, relieving depression, enhancing

locomotors activity, and promoting neuronal cell survival [6-7], also used as an inhibitor of the enzyme 17- α -hydroxylase /C_{17,20}-lyase(CYP17A1) [8-13], for treating prostate cancer[14-17] .A new α -ester Pregnenolone derivatives(**Figure 1.**) show activity as (anti-HIV) [18].

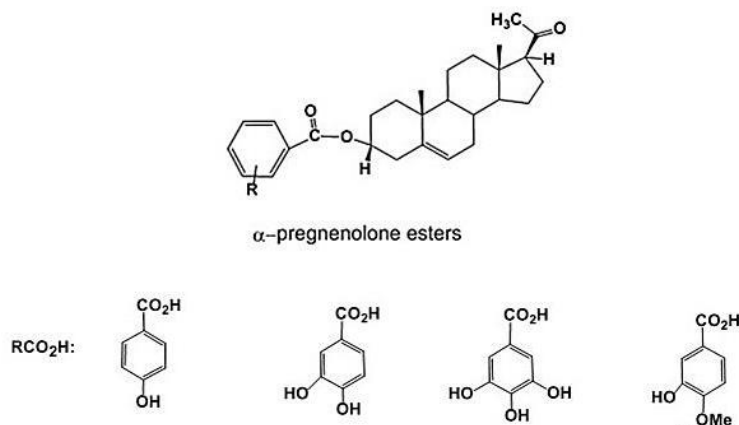
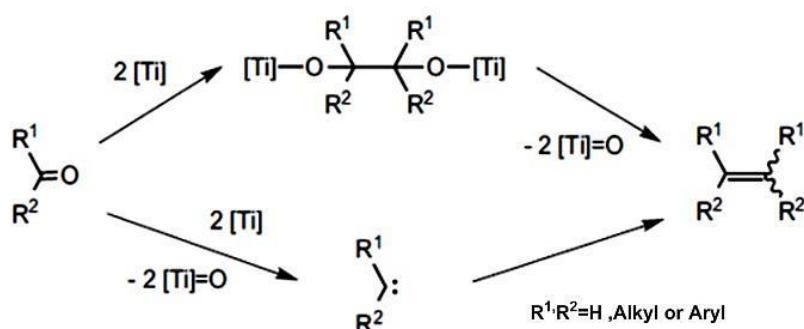


Figure 1. α -ester Pregnenolone derivatives

McMurry reaction used to convert aldehydes or ketones to aliphatic double bond by low valent titanium .

The reaction of carbonyl-coupling takes place in tow steps:(1) Reductive of ketone or aldehyde to form carbon-carbon double bond(dimerization) .
(2) Deoxygenation the intermediate to product the alkene.(**scheme 1**) [19,20].



Scheme 1. Mechanism of reductive aldehyde or ketone carbonyl to form carbon-carbon double bond with TiCl₄ via McMurry reaction

The aims of this study are synthesis of some a new series of Pregnenolone derivatives via McMurry reaction for reductive coupling of aldehydes or ketones and study the biological properties.

2- Experimental

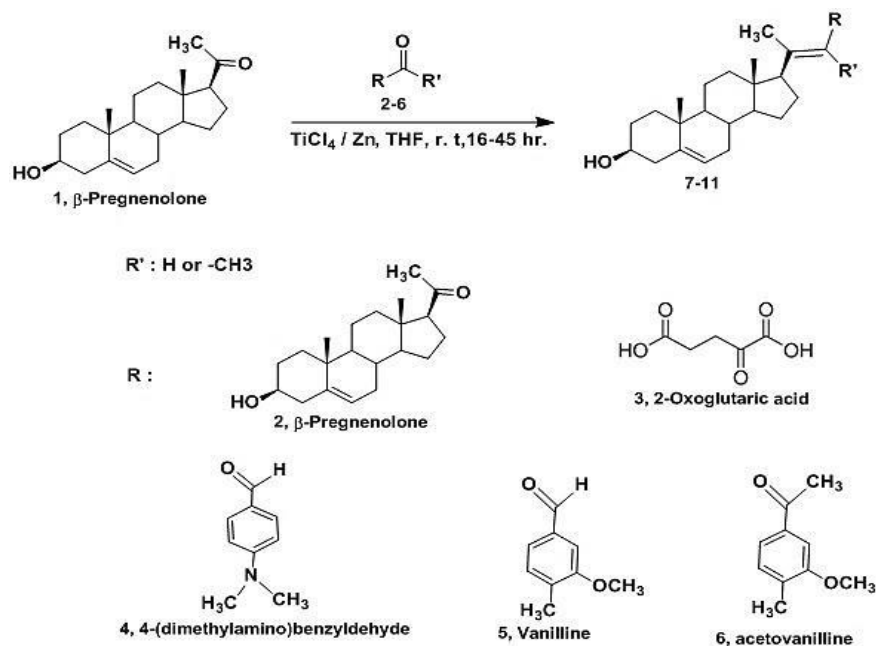
2-1- Instrumentation

Melting points were determined on (SMP/Steuart) melting point instrument, IR spectra were measured on FT-IR spectrophotometer (Shemadzu, Japan) using KBr disks , NMR spectra were obtained on (Avance III ,Bruker, Germany) spectrophotometer 300 MHz (^1H) and on 75 MHz (^{13}C) with TMS as internal standard and on the δ scale in ppm. Heteronuclear assignments were verified by ^1H , ^{13}C HMBC and ^1H , ^1H NOESY experiment. Microanalytical data were measured using Vario Elemental Analyzer (Shimadzu, Japan). TLC plates 60 F₂₅₄ were purchased from Merck. The chromatograms were visualized by iodine -solvent: (hexane-ethyl acetate)(3-2)(v-v).

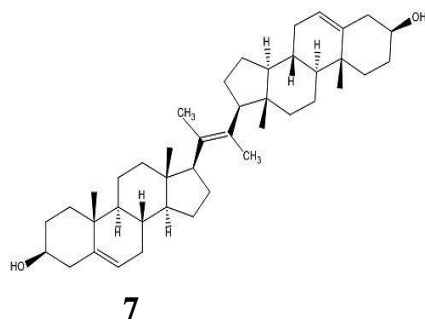
2-2- Synthesis

2-2-1 General procedure for synthesis Pregnenolone derivatives by applying McMurry reaction

Titanium tetrachloride (TiCl_4) (1 mL) was added under (N_2 gas)to mixture of zinc- dust (7.65mmol, 0.5gm) and tetrahydrofuran (THF) (50 mL) and the mixture was stirred at 65°C for 2 hours to prepared the catalyst .Tetrahydrofuran (10 mL) was added to Pregnenolone (200 mg,0.632 mmol) and aldehyde or ketone (**2-6**) and mixed with the prepared catalyst and stirred together at 65°C , the reaction monitored by TLC (*n*-hexane :ethyl acetate)(4:1)(v:v) ,the products purification were checked by silica– gel column chromatography(SiO_2 5gm)by mixture of(C_6H_{14} : EtCO_2H)(3:2)(v:v) as elution the to give final products (**Scheme 2**).



Scheme 2. Some a new series of Pregnenolone derivatives via McMurry reaction .



((E)- 2-3-di (5-pregnen-3 β -ol) 2-butene. (7).

Color: Yellow Sami-solid. Yield 74% .FT-IR (KBr, ν , cm^{-1}):

2952 ((C-H) sp^3), 1467(-CH₂), 1678(C=C), 3392(OH), 1357(CH₃ bending).

¹H NMR (300MHz, DMSO-*d*₆, δ , ppm):

5.28(s, 1H, H-6), 4.06(br. s, 1H, OH), 3.40(s, 1H, H-3), 2.49(s, 1H, H-17), 2.21(s, 1H, H-16), 2.05(d, 3H, Me-21), 1.98(s, 1H, H-7), 1.83(s, 1H, H-12), 1.78(s, 1H, H-1), 1.59(s, 1H, H-15), 1.48(s, 1H, H-14), 1.42(s, 1H, H-11), 1.39(s, 1H, H-8), 1.04(s, 1H, H-9), 0.96(s, 3H, Me-19), 0.88(s, 3H, Me-18).

¹³C NMR(75MHz, DMSO-*d*₆, ppm) δ = 140.68(C-5), 121.19(C-6), 71.45(C-3), 56.86(C-14), 49.95(C-9), 44.92(C-13), 43.97(C-4), 42.11(C-12), 38.78(C-1), 36.48(C-10), 31.82(C-7), 31.72(C-8), 31.46(C-1), 26.35(C-15), 24.44(C-

16),22.78(C-11),21.04(Me-19),19.34(Me-21),13.16(Me-18).

Anal .cale. : C 83.94, H 10.73 found: C 83.82, H 10.60.

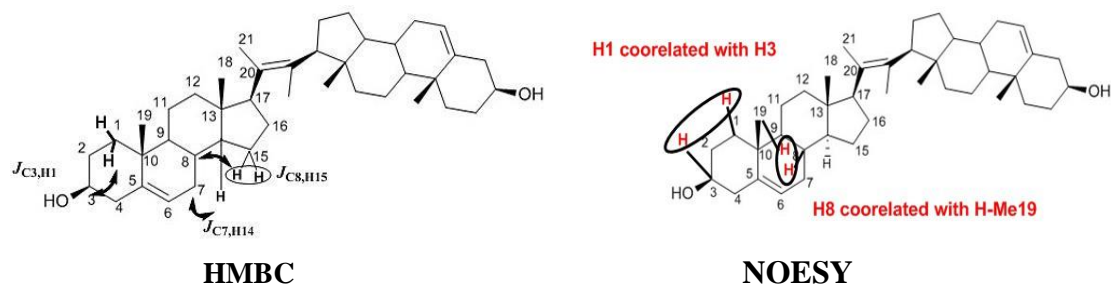
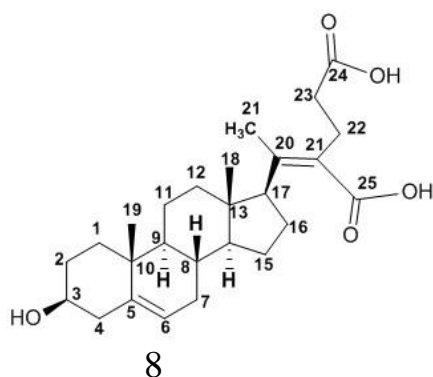


Figure 2. $J_{C,H}$ correlation in the HMBC and $J_{H,H}$ correlation in the NOESY of **7**

The HMBC spectrum showed $J_{C,H}$ coupling between H-14 proton at $\delta=1.48$ ppm with C-7 carbon at $\delta=31.82$ ppm and between H-15 proton at $\delta=1.60$ ppm with C=8 carbon at $\delta=31.72$ ppm. The NOESY spectrum showed the correlation between the proton H-8 at $\delta= 1.39$ ppm with the proton H-Me19 at $\delta=0.96$ ppm, and the proton H-1 at $\delta=1.78$ ppm with the proton H-3 at $\delta=3.40$ ppm. (**Figure 2.**)



(E)-1-(2-bentane-1-5-dioic)-2-(5-pregnen-3 β -ol)-propene.(8)

Color: Dark Sami-solid. Yield 64% .FT-IR (KBr, ν , cm^{-1}):1661(C=C), 1359(CH_3 bending),3505(OH),2862(OH_{carboxylic}).

1H NMR (300MHz, DMSO- d_6 , δ ,ppm): 11.80(s,1H-CO₂H),5.26(t,1H,H-6),3.55(br.s,2H,CH₂OH),3.38(s,1H,H-3),2.67(s,1H,H-17),2.19(m,1H,-

24)2.15(m,1H,H-16a),2.11(m,2H,CH₂-4),2.05(s,3H,Me-21),1.98(d,*J*=27.5 Hz,1H,H-7a),1.89(s,1H,H-12a),1.78(m,1H,H-19),1.58(s,1H,H-7b),1.55(s,1H,H-11a),1.45(m,1H,H-8),1.39(m,1H,H-11b),1.36(m,1H,H-2b),1.14(m,2H,H-14+H-15b),1.02(m,1H,H-1b),0.93(m,3H,Me-19),0.55(s,3H,Me-18).

¹³C-NMR(75MHz,DMSO-*d*₆,ppm)δ= 171.55(CO₂H),136.09(C-5).71.95(C-3),57.85(C-14),52.14(C-9),45.21(C-13),40.25(C-4),39.26(C-12),37.44(C-1),34.07(C-10),32.52(C-2),31.76(C-7),24.79(C-15),22.32(C-17),21.99(C-11),19.73(Me-19),16.32(Me-21),14.64(Me-18).

Anal. Cal. : C 72.53, H 8.90. **Found** C 72.35, H 8.71.

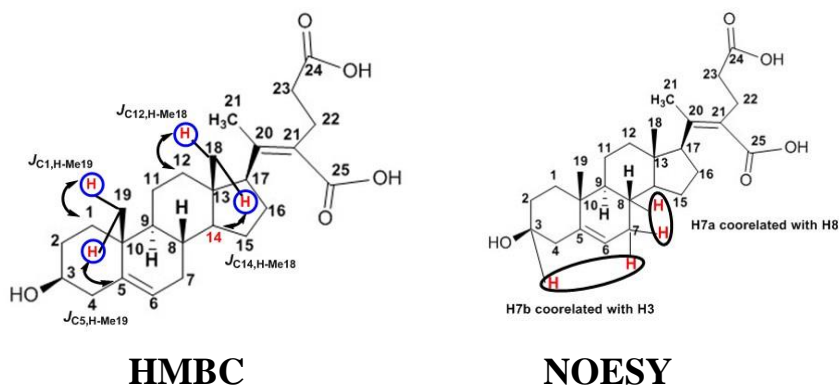
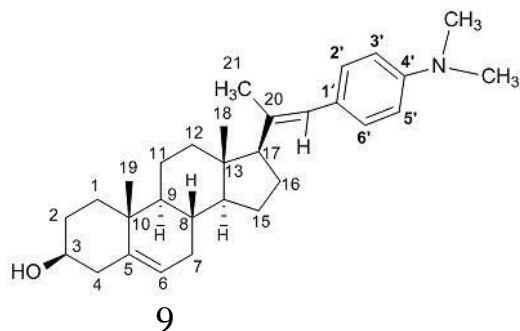


Figure. 3 $J_{C,H}$ correlation in the HMBC and $J_{H,H}$ correlation in the NOESY of **8**

The HMBC spectrum showed $J_{C,H}$ coupling between the proton H-Me19 at $\delta=0.93$ ppm with the carbon C-1 at $\delta=37.44$ ppm, the proton H-Me 18 at $\delta=0.55$ with the carbon C-12 at $\delta=39.26$ ppm, the proton H-Me 18 at $\delta=0.55$ ppm with the carbon C-14 at $\delta=57.85$ ppm and the proton H-Me19 at $\delta=0.93$ ppm with the carbon C-5 at $\delta=136.09$ ppm (**Figure. 3**)



(E)-1-(1-(4-dimethylamino)phenyl)-2-(5-pregnen-3 β -ol)-propene (9)

Color: Yellow Browne solid. Yield 61% .M.p: 196-198C°

FT-IR (KBr, ν , cm^{-1}):1666(C=C), 1590(C=C_{aromatic}), 1365(CH₃ bending), 3510(OH), 1288(CN)

¹H NMR (300MHz, DMSO-*d*₆, δ ,ppm): 7.29(s,3H,H_{arom}),5.31(s,1H,H-6),4.15(br.s,1H,OH),3.39(s,1H,H-3),2.51(d, J =8.3 Hz,1H,H-17),2.10(m,2H,CH₂-4),2.04(m,3H,Me-21),2.02(m,1H,H-7a),1.81(m,1H,H-1a),1.70(m,1H,H-2a),1.62(d, J =6.0 Hz,1H,H-16b),1.60(m,1H,H-7b),1.43(d, J =9.8 Hz,1H,H-8),1.41(s,1H,H-11b),1.17(d, J =6.6 Hz,2H,H-14+H-15b),0.98(s,1H,H-9),0.90(s,3H,Me-19),0.60(s,3H,Me-18).

¹³C NMR(75MHz,DMSO-*d*₆,ppm) δ = 136.09(C_{arom.}-4'),132.30(C_{arom.}-2'+C_{arom.}-6') 130.54(C_{arom.}-3'+C_{arom.}-5'),124.51(C-5),71.93(C-3),57.86(C-14),52.14(C-9),45.21(C-13),40.24(C-4),40.15(NCH₃),39.25(C-12),37.43(C-1),34.07(C-10),31.76(C-2),27.04(C-14),24.79(C-15),24.69(C-16),22.00(C-11),19.72(Me-19),18.05(Me-21),14.63(Me-18).

Anal. Calc.: C 83.09, H 9.99,N 2.23 . **Found :** C82.91, H 9.85, N 3.12

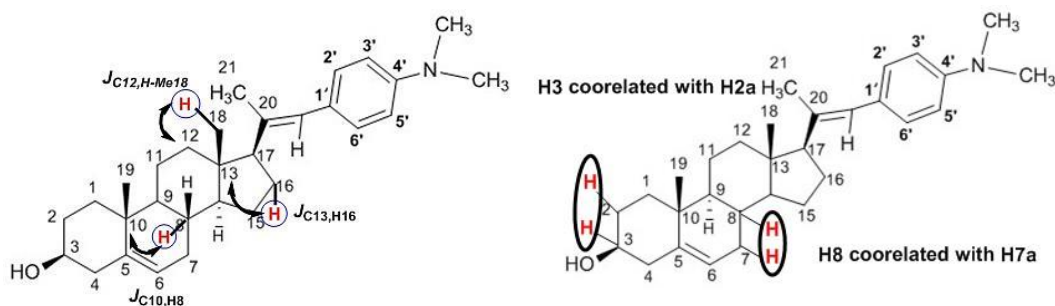
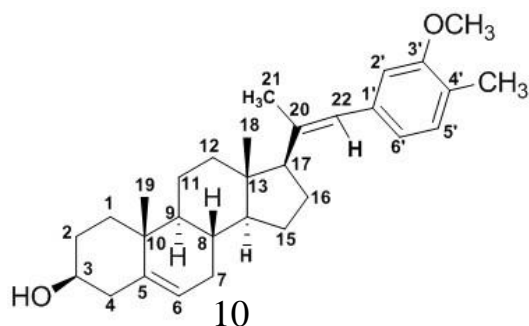


Figure. 4 $J_{C,H}$ correlation in the HMBC and $J_{H,H}$ correlation in the NOESY of **9**

The HMBC spectrum showed $J_{C,H}$ coupling between the proton H-8 at $\delta=1.43$ ppm and the carbon C-10 at $\delta=34.07$ ppm, the proton H-Me18 at $\delta=0.60$ ppm and the carbon C-12 at $\delta=39.25$ ppm, and the proton H-16b at $\delta=1.62$ ppm with C-13 at $\delta=45.21$ ppm. The NOESY spectrum showed the correlation between the proton H-3 at $\delta=3.39$ ppm and the proton H-2a at $\delta=1.70$ ppm and the correlation between the proton H-8 at $\delta=1.43$ ppm and H-7a at $\delta=2.02$ ppm (Figure 4.).



(E)-1-(3-methoxy-4-methylphenyl)-2-(5-pregnen-3 β -ol)-propene (10).

Color: Brown semi-oil. Yield 62%. FT-IR (KBr, ν , cm^{-1}): 1670(C=C), 1577(C=C_{aromatic}), 1366(CH₃ bending), 3510(OH), 2939(C-H_{sp³}).

¹H NMR (300MHz, DMSO-*d*₆, δ , ppm): 7.29 (t, 2H, H-3'+ H-6'), 5.31 (t, 1H, H-6), 3.74 (br. s, 1H, OH), 3.72 (s, 3H, -OCH₃), 2.54 (s, 1H, H-17), 2.17 (m, 1H, H-16a), 2.10 (m, 2H, CH₂-4), 2.04 (s, 3H, Me-21), 2.01 (m, 1H, H-7a), 1.79 (s, 1H, H-1a), 1.68 (m, 1H, H-2a), 1.61 (m, 1H, H-16b), 1.45 (m, 1H, H-8), 1.41 (m, 1H, H-11b), 1.18 (m, 2H, H-14 + H-15b), 1.07 (m, 1H, H-1b), 0.98 (m, 1H, H-9), 0.91 (s, 3H, Me-19), 0.61 (s, 3H, Me-18).

¹³C-NMR (75MHz, DMSO-*d*₆, ppm) δ = 136.07 (C_{arom.}-5'), 116.56, C_{arom.}-2'+C_{arom.}-6'), 72.77 (C-3), 63.20 (OCH₃), 57.88 (C-14), 52.14 (C-9), 45.21 (C-13), 40.26 (C-4), 40.16 (C-12), 39.26 (C-10), 37.43 (C-1), 34.07 (C-7), 32.51 (C-8), 31.76 (C-2), 24.94 (Me-21), 24.79 (C-15), 24.60 (C-16), 22.12 (C-

11), 19.73 (Me-19), 16.23 (Ar-CH₃), 14.64 (Me-18).

Anal. Calc. : C 82.90, H 9.74 . **Found :** C 82.74, C 9.59.

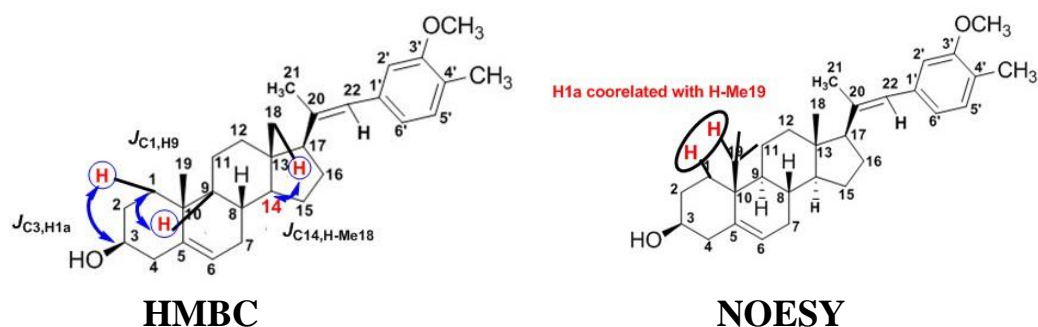
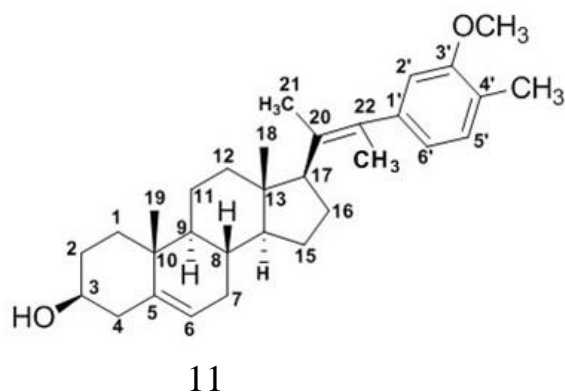


Figure 5. $J_{C,H}$ correlation in the HMBC and $J_{H,H}$ correlation in the NOESY of **10**

The HMBC spectrum showed $J_{C,H}$ coupling between the proton H-9 at $\delta=0.98$ ppm and the carbon C-1 at $\delta=37.43$ ppm, the proton H-1a at $\delta=1.79$ ppm with the carbon C-3 at $\delta=72.77$ ppm and between the proton H-Me18 at $\delta=0.61$ ppm and the carbon at C-14 at $\delta=57.88$ ppm.

The NOESY spectrum showed the correlation between the proton H-Me19 at $\delta=0.91$ ppm and the proton H-1a at $\delta=1.79$ ppm (Figure 5).



(E)-3-(3-methoxy-4-methylphenyl)-3-(5-pregnen-3 β -ol)-2-butene (11)

Color: Brown solid. Yield 73% .M.p:183-185 °C.FT-IR (KBr, ν , cm^{-1}):

1669(C=C), 1581(C=C_{aromatic}), 2494(OH), 1365(CH₃ binding), 2939(CH₃ SP³).

^1H NMR (300MHz, DMSO- d_6 , δ , ppm):

7.29(m, 1H, $\text{H}_{\text{arom.}-5'}$) 7.12(m, 1H, $\text{H}_{\text{arom.}-2'}$), 6.98(m, 1H, $\text{H}_{\text{arom.}-6'}$), 5.29(s, 1H, H-6), 4.51(br.s., 1H, OH) 3.67(s, 3H, OCH_3), 3.37(s, 1H, H-3), 2.49(s, 1H, H-17), 2.15(s, 2H, CH_2 -4), 2.08(s, 3H, Me-21), 2.05(d, $J=15.9\text{Hz}$, H, H-7a), 2.00(s, 1H, H-16a), 1.92(s, 1H, H-12a) 1.78(s, 1H, H-1a), 1.68(d, $J=3.9\text{Hz}$, 1H, H-2a), 1.67(s, 1H, H-15a), 1.59(d, $J=6.1\text{Hz}$, 1H, H-7b), 1.57(s, 1H, H-11a), 1.43(s, 1H, H-8), 1.15(d, $J=15.6\text{Hz}$, 2H, H-14+H-15b), 0.99(d, $J=7.7\text{Hz}$, 2H, H-1b+H-9), 0.96(s, 3H, Me-19), 0.58(s, 3H, Me-18).

^{13}C -NMR(75MHz, DMSO- d_6 , ppm) $\delta=140.83(\text{C}_{\text{arom.}-1'+\text{C}_{\text{arom.}-3'})$, 128.44(C-20+ $\text{C}_{\text{arom.}-5'}$), 128.14(C-21+ $\text{C}_{\text{arom.}-4'}$), 121.26(C-6), 71.51(C-3), 56.88(C-14), 49.95(C-9), 44.98(C-13), 42.15(C-4), 38.80(C-12), 37.25(C-1), 36.50(C-10), 31.84(C-7), 31.75(C-8), 31.53(C-1), 25.58(C-15), 24.47(C-16), 22.79(C-11), 21.07(Me-21), 19.38(Me-19), 13.21(Me-18).

Anal. Calc. : C 82.98, H 9.88. **Found** C 82.85, H 9.69.

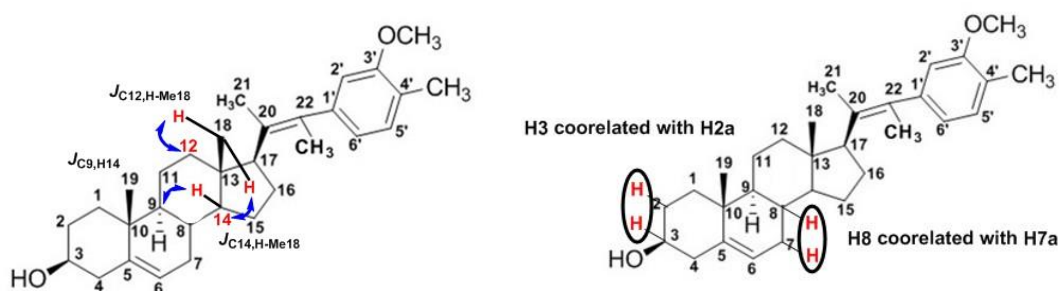


Figure. 6 $J_{\text{C,H}}$ correlation in the HMBC and $J_{\text{H,H}}$ correlation in the NOESY of **11**

The HMBC spectrum showed $J_{\text{C,H}}$ coupling between the proton H-Me18 at $\delta=0.58$ ppm and the carbon C-12 at $\delta=38.80$ ppm, the proton H-14 at $\delta=1.15$ ppm with the carbon C-9 at $\delta=49.95$ ppm, and the proton H-Me18 at $\delta=0.58$ ppm with the carbon C-14 at $\delta=56.88$ ppm.

The NOESY spectrum showed the correlation between the proton H-8 at $\delta=1.43$ ppm and the proton H-7a at $\delta=2.05$ ppm and the correlation between H-2a at $\delta=1.68$ ppm and H-3 at $\delta=3.37$ ppm (Figure 6.).

2-2-2 – Biological activity study

The method which was used to obtain the screening was (Agar diffusion method) by dissolve (20 mg) from each new derivatives in (10 mL) of ethanol, then (0.1mL) from every prepared sample was put in holes agar dishes that contained microorganisms, these dishes were incubated at 37 °C for 24 hours for bacteria and 72 hours for fungal, the inhibition zones were measured by ruler [21].

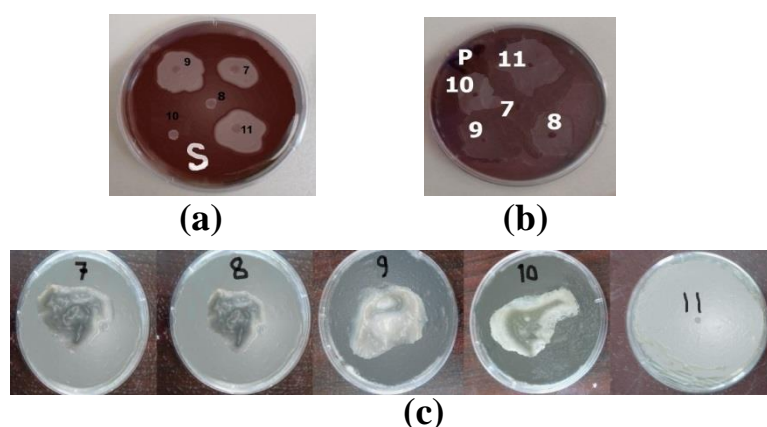


Figure 7. Inhibition zone of compounds against (a) *Streptococcus*, (b) *Proteus* ,
(c) *Alternaria alternata*

3- Results and discussion

3-1- Chemistry

The Pregnenolone derivatives (7-11) have been synthesized by McMurry reaction with use of Pregnenolone with aldehydes or ketones (2-6), in the presence of titanium tetrachloride, zinc –dust and tetrahydrofuran as catalysts under N₂ gas [22].

The reaction was reductive of carbonyl gropes by (Low-Valent) titanium, the first step was formed carbon –carbon bond and (1, 2 diolate)

as intermediate, the second step included deoxygenating of (1, 2 diolate) to form carbon-carbon double bond [23,24].

The compounds structures have been characterized by disappearance of carbonyl groups of Pregnenolone and (aldehyde or ketone) and appearance of new carbon-carbon double bond in the new prepared derivatives (7-11) by TLC, melting points, FT-TR, C.H.N. analysis, ¹H NMR, ¹³C NMR and 2D-NMR (HMBC & NOESY).

3-2-Biological activity

Antimicrobial activity of new synthesized derivatives were screened against bacteria (*Streptococcus*, *Proteus*) and fungal (*Alternaria alternata*) as shown in Figure 7, the results were represented in table 1 and the derivatives activity against *Streptococcus* showed that the compounds (9,11) gave high activity and compound (7) showed moderated activity, while compounds (8,10) showed no activity against this type of bacteria .

The derivatives activity against *proteus* was showed the compound (11) gave moderated activity while compounds (8, 9, and 10) showed slightly activity and compound (7) showed no activity against these bacteria.

The fungal activity against the (*Alternaria alternata*) showed the compounds (9, 10) gave high activity and compound (7) showed moderated activity, compound (8) showed slightly activity while compound (11) showed no activity against the fungal (*Alternaria alternata*).

Table 1. Antimicrobial activity

Comp.	Streptococcus	Proteus	Alternaria alternata
7	++	-	++
8	-	+	+
9	+++	+	+++
10	-	+	+++
11	+++	++	-

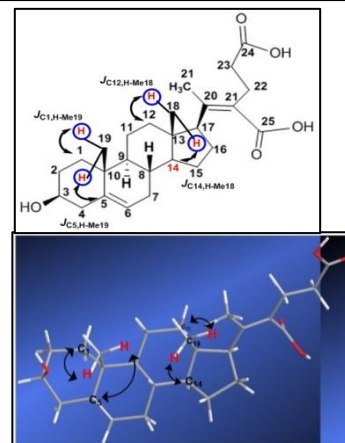
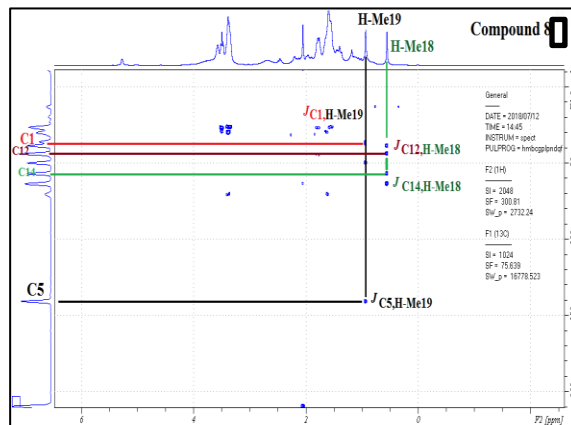
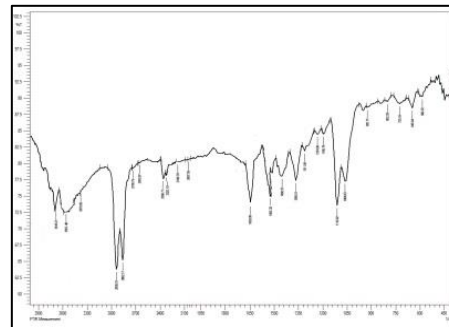
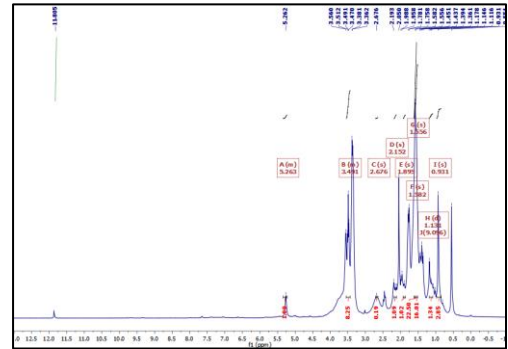
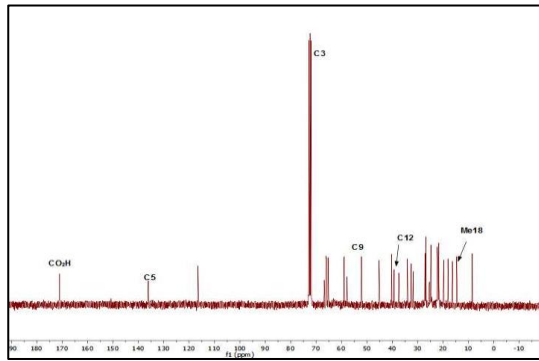
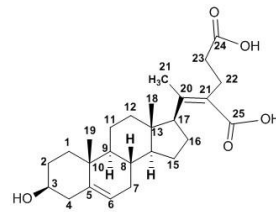
+= (0-4 mm), ++= (6-9mm), +++= (10-15 mm) and - =non active

4- Conclusion

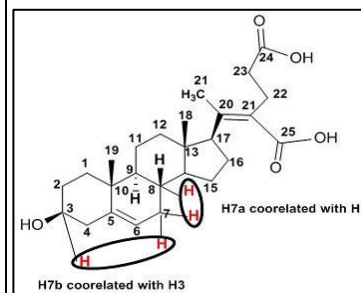
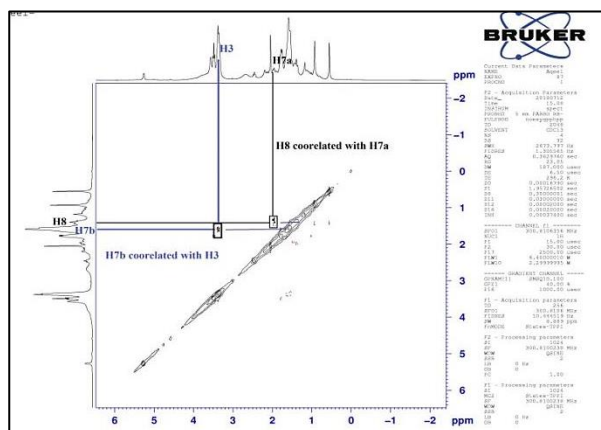
A series of some new Pregnenolone derivatives has been prepared by applying McMurry reaction, all these derivatives were achieved according to the measuring data of chemical analysis which included (TLC, FT-IR spectroscopy, melting points, elemental analysis and NMR spectroscopy (^1H , ^{13}C and 2D-NMR).

All the prepared compounds showed disappearing of carbonyl groups of Pregnenolone and (aldehydes or ketones) and appearing of new carbon-carbon double bonds. Most of new derivatives showed high antimicrobial activity against some types of bacteria and fungal.

Compound /8

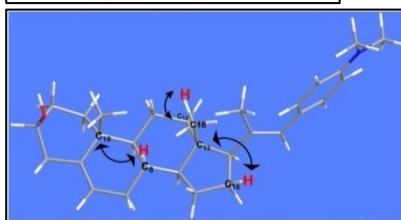
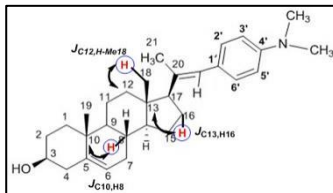
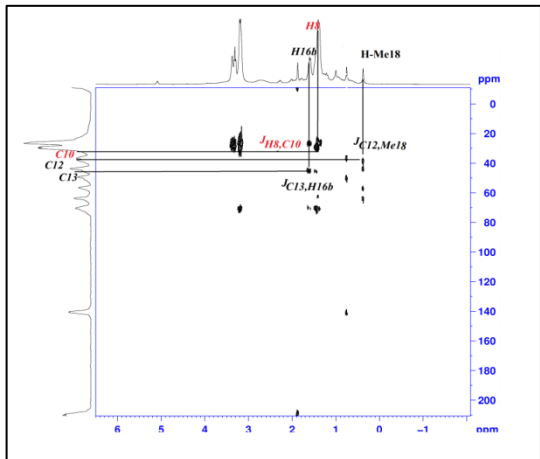
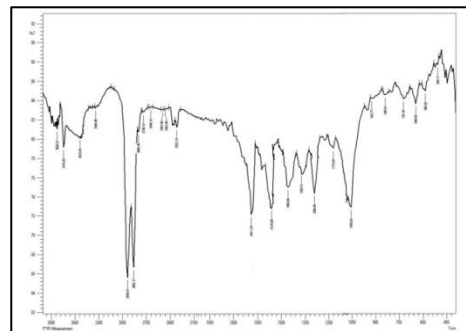
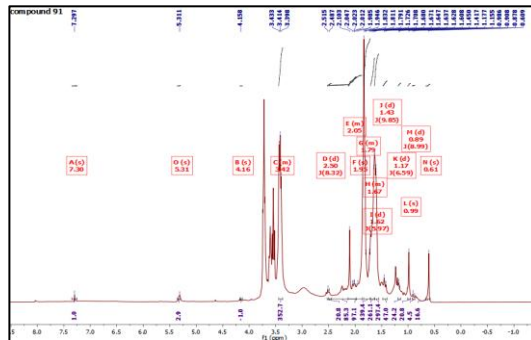
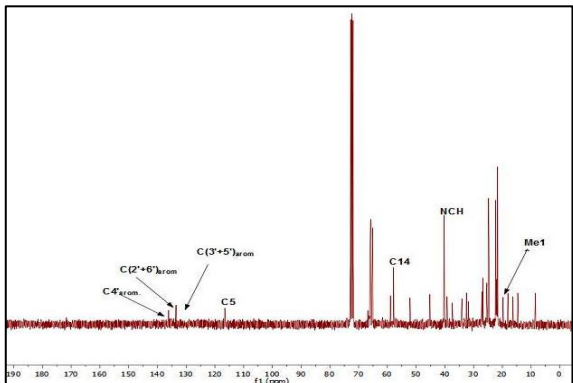
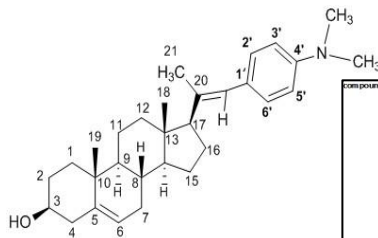


2D-NMR HMBC

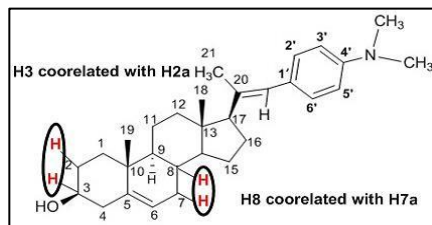
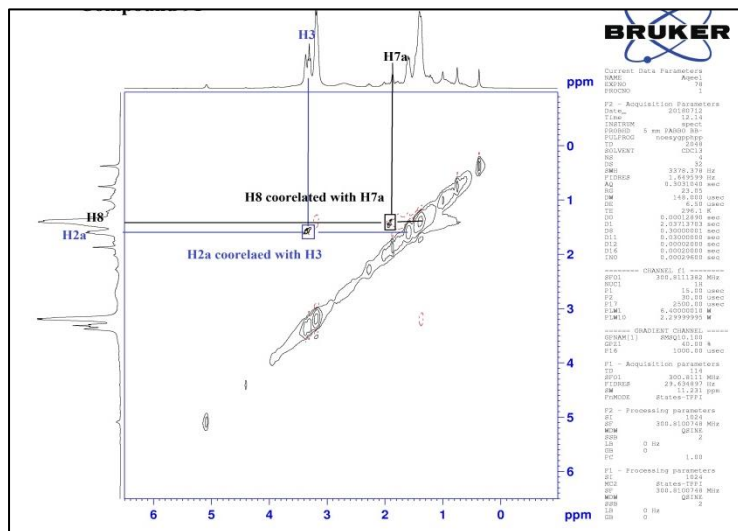


2D- NMR NOESY

Compound /9

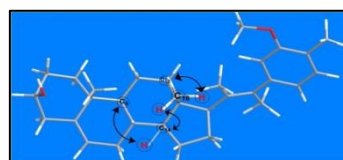
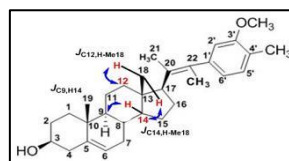
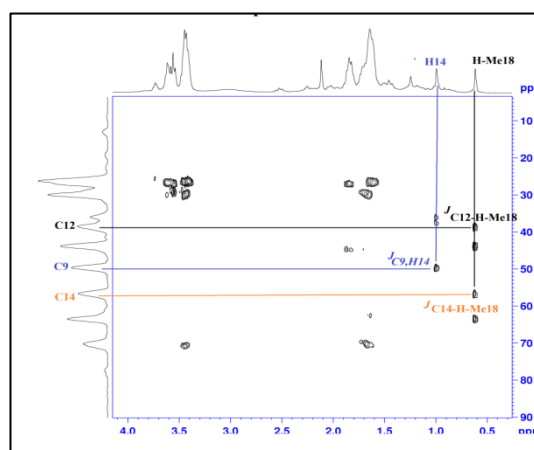
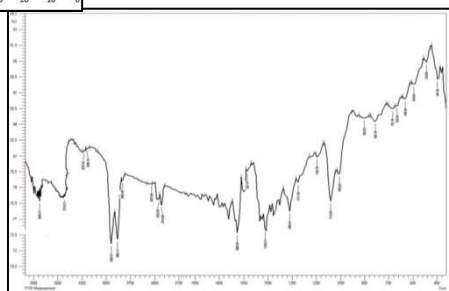
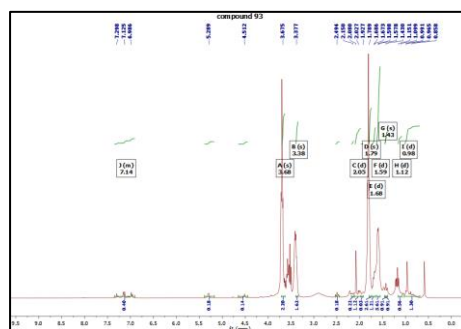
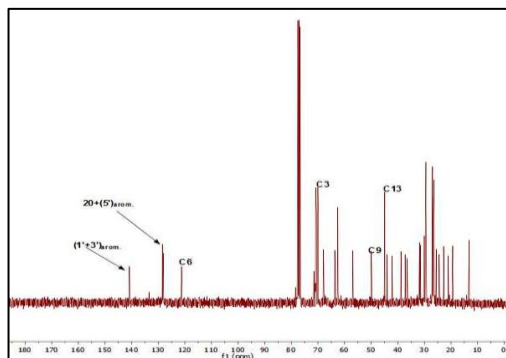
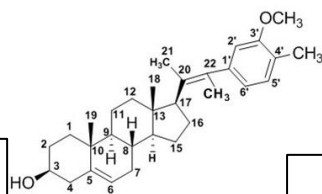


HMBC

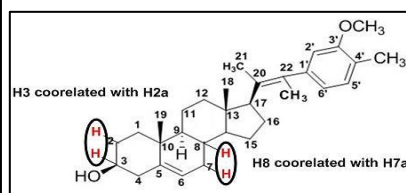
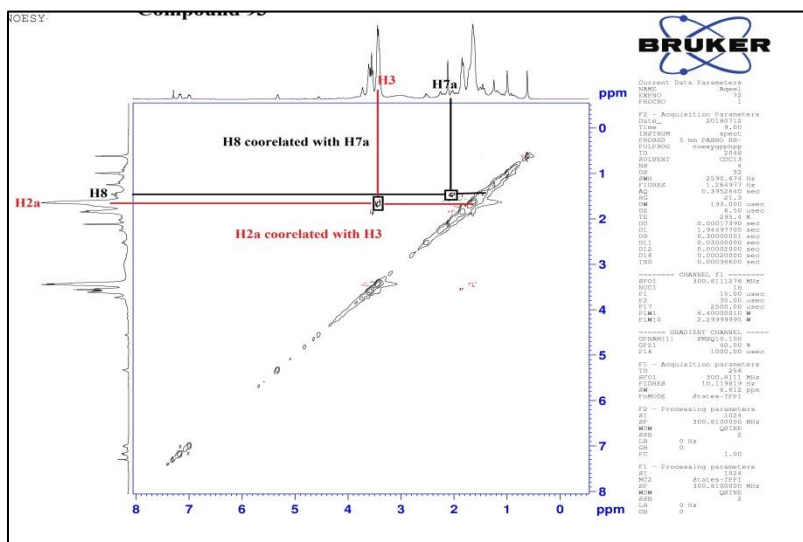


NOESY

Compound /11



HMBC



NOESY

References

1. T.W.G.Solomons, C.B.Fryhle,S.A.Snyder "Organic Chemistry" 12th Ed ,Willy & Sons,**2016**,p;1026.
2. Ibrahim-Ouali, M. *Steroids* **2007**, 72, 475-508.
3. Bhatti, H. N. Khera, R. A. *Steroids* **2012**, 77, 1267-1290.
4. J. McMurry " Organic Chemistry" 9th Ed,Change Learning ,**2016**. P; 930.
5. Moffat, L. E.; Kirk, D.; Tolley, D. A.; Smith, M. F.; Beastall, G. *British J.Urology* **1988**, 61, 439- 440.
6. Smith,P.HRT:The Answers, Healthy living Book .Inc,*Michigan:2003*
7. J.H.Wang, B.C.Chang, *Steroids***2016**, 111, 54-59.
8. Handratta, V. D.Vasaitis, T. S. Njar, V. C. Gediya, L. K. Kataria, R.Chopra, P.Newman, P.Farquhar, R. Guo, Z. Qiu, Y. Brodie, A. M. *J.Med. Chem.* **2005**, 48, 2972-2984.
9. Brodie, A. Njar, V. C. WO Patent **2006/093993**, 2006.
10. Vasaitis, T. S. Njar, V. C. O. *Future Med. Chem.* **2010**, 2, 667-680.
11. Molina, A.Belldegrun, A. *J. Urol.* **2011**, 185, 787-794.
12. de Bono, J. S. Logothetis, C. J. Molina, A.Fizazi, K.North, S. Chu, L.Chi, K. N. Jones, R. J.; *et al. N. Engl. J. Med.* **2011**, 364, 1995-2005.
13. Bryce, A. Ryan, C. J. *Clin. Pharma. Therap.* **2012**, 91, 101-108.
14. Potter, G. A. Barrie, S. E. Jarman, M. Rowlands, M. G. *J. Med. Chem.*
15. Moffat, L. E. Kirk, D. Tolley, D. A.; Smith, M. F. Beastall, G. *British J.Urology* **1988**, 61, 439-440.
16. Mahler, C. Verhelst, J. Denis, L. *Cancer* **1993**, 71, 1068-1073.
17. Lake-Bakaar, G. Scheuer, P. J. Sherlock, S. *British Med. J.* **1987**, 294,419-442.
18. K.M.Mahdi, N.A.Abdul-Reda, N.A.Al-Masoudi, *Europ.J.Chem.***2015**,6,1-7.
19. J.E.McMurry,C.N.Hodge,*J.Am.Chem.Soc.***1984**,106,6450.
20. M . Ephritikhine ,Chem. Commun,**1998**,2945-2954.
21. Manna,F.*J.Med.Chem.***1992**,27,633-639.
22. J. E. McMurry , American . *Chem. Soc, Rev*, **1989**, 89, 1513-1524.
23. T. Laue, A.Plagens" Named Organic Reactions " 2nd Ed , John Willy & Sons Ltd,**2005** , p; 196-199.
24. X. F. Duan , J. Zeng , J. W .Lü , Z . B. Zhang , *J .Org . Chem.* **2006**,71,9873-9876.