Qatar Univ. Sci. J. (2002), 22 : 107 - 117

Synthesis and Spectroscopic Studies of Atenolol Derivatives with Enhanced Lipophilicity as Potential Prodrugs

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تحضير ودراسات طيفية لمشتقات عقار الاتينولول ذات ذائبية متميزة في الليبيدات باعتبارها صيغ دوائية محتملة

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الأتينولول المستخدم انتقائياً لإيقاف مستقبلات الأدرينالين معروف بإنخفاض معدل استيعابه المتاح بيولوجيا. وقد جرى في هذا البحث تحضير عدد من المشتقات والصيغ الدوائية لهذا العقار لغرض تحسين ذائبيته في الليبيدات، وبالتالي يرتفع معدل إتاحته بيولوجيا. تتضمن هذه المشتقات مركبات تحتوي أوكسازوليدين-٢ثيون، ومركبات ١,٤- أوكسازين - ٢,٣ - دايون، ومركبات من مشتقات الأوكسازوليدين.
وقد تم التعرف على هذه المركبات من خلال تحليل العناصر وطيف الأشعة تحت الحمراء والرنين النووي المغناطيسي وطيف الكتلة، كذلك جرت مناقشة نتائج هذه التحاليل الطيفية من خلال هذا البحث.

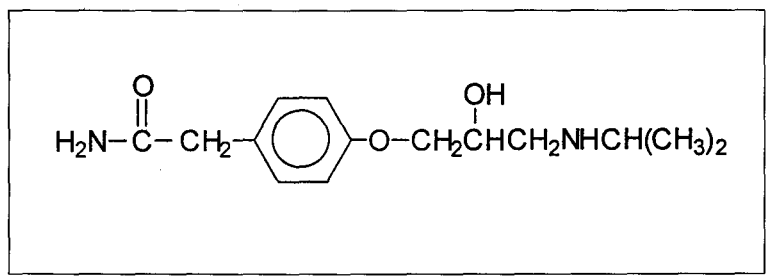
Key Words: *Atenolol, Oxazolidine-2-thione, 1,4-Oxazine-2,3-dione, Oxazolidine, Prodrugs.*

ABSTRACT

Atenolol, a selective β_1-adrenoceptor blocking agent is characterized by its low bioavailability. A number of atenolol prodrugs were synthesized to improve its lipid solubility and hence bioavailability. These compounds included an oxazolidine-2-thione derivative (II), a 1,4-oxazine-2,3-dione derivative (III), and a series of oxazolidine derivatives (IVa-m). The structure of each compound was characterized by elemental analysis, infrared (IR), protonnuclear magnetic resonance (^{1}H-NMR), and mass spectra (MS). The spectroscopic results for these compounds are discussed.

Introduction

Atenolol (I), 4-[2-hydroxy-3-{(1-methylethyl)amino}propoxy] benzeneacetamide ,CAS#2919\22-68-7 as an USP dictionary, is one of the commonly used b-adrenergic receptor blockers for treatment of the cardiovascular system and ocular hypertension. Clinical and pharmacological studies of atenolol had been reviewed by Florey.[1] This drug is characterized by low bioavailability (40 - 57%)[2,3] due to its low lipophilicity. Improvement of this prospect through the synthesis of appropriate prodrugs proved successful with other related drugs.



(I)

For instance, ester, amide[4], or oxazolidines prodrugs of propranolol[5] and timolol[6-8] have been evaluated. As it is usually the case, the profound stability of amide linkage (especially acyclic amides) renders them less significant for prodrug approaches. However, cyclic amides might show less prominent stability. To examine this prospect, the cyclic amide (1,4-oxazine-2,3-dione) and the cyclic thioamide (oxazolidine-2-thione) are prepared. In addition, synthesis of oxazolidine derivatives of β-aminoalcohol functionalized drugs have been well documented[9-12]. We considered the cyclization of the β-aminoalcohol function in atenolol into various oxazolidines by undertaking condensation of atenolol with a group of carefully selected aldehydes comprising aliphatic, aromatic, or aromatic substituted substrates with various fuctionalities.

The aim of the present study is to synthesize nitrogen and alkylated, cyclic amide esters, and oxazolidine prodrugs of atenolol and to discuss their IR, NMR and MS spectroscopic data related to their structural studies on their stablities, lipid solubilities and their bioavailabilities is underway.

Materials and Method

Apparatus

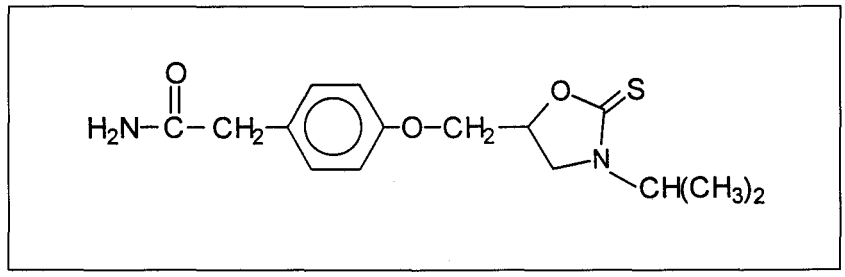
The synthesized prodrugs are characterized by a variety of analytical techniques. ^{1}H-NMR spectra were run on Bruker WP80, using the suitable deuteriated solvent and tetramethylsilane (TMS) as the internal reference. Mass spectra were measured on 7070-E VG Analytical mass Spectrometer. Infrared spectra were recorded on Shimadzu IR 435 spectrometer as KBr disc. Ultraviolet-Visible spectra were measured on Varian DMS-100 spectrometer. Melting points were determined using an electrothermal melting point apparatus and were not corrected. Elemental analyses were done at MHW laboratories, Phenix, Arizona-U.S.A.

Chemicals

Atenolol (I) was supplied by Al-Hikma Pharmaceuticals-Amman Jordan and was employed without any further purification. The solvents methylene chloride and petroleum ether used in this study, were freshly distilled and dried according to Perrin[13] procedure.

- Synthetic Procedure

- [3-(1-methylethyl)-5-(4-amidomethylphenoxy)methyl-1,3-oxazolidine-2-thione (II)



(II)

To atenolol (1.0g,3.75 mmole) dissolved in chloroform (250 ml), thiophosgene is added dropwise (0.45g,3.90 mmole), followed by triethylamine (1ml). Nitrogen gas is passed through the reaction. The reaction mixture is stirred at room temperature for 3 hours prior to heating in a water bath at 50°C for 1 hour. The solvent is then evaporated (water-benzene azeotrope) and an additional amount of benzene (20 ml) is added to remove any remaining traces of water. The gummy residue is treated with a solution of ethyl acetate and 1M aqueous HCl (50 : 50 mixture). The ethyl acetate layer is dried over (anhydrous), sodium sulfate then filtered, and the solvent evaporated to leave behind a white solid product which is recrystallized from absolute ethanol to give compound (II) in 45% yield (m.p. 183-184°C). Elemental Analyses: %C, H, N Calculated (found) 56.78 (56.60), 6.62 (6.63), 8.83 (8.96).

IR ($\bar{\nu}$ cm^{-1}):

3360(s), 3160(m), 2960-2900(w), 1732(m), 16529s), 1632(sh), 1610(m), 1580(m), 1510(s), 1480(s), 1450(m), 1425(m), 1410-1390(m), 1400(s), 1340(s), 1156(s), 1000(w), 820-808(m), 788(m).

^{1}H-NMR (δ-ppm): ($CDCL_3$)

6.78-7.25(dd, 4H), 4.85-5.23(m,1H), 4.12-4.29(m,2H), 3.70-4.00(m,2H), 3.46(s,2H), 3.24-3.25(m,1H), 1.21-1.40(d,6H).

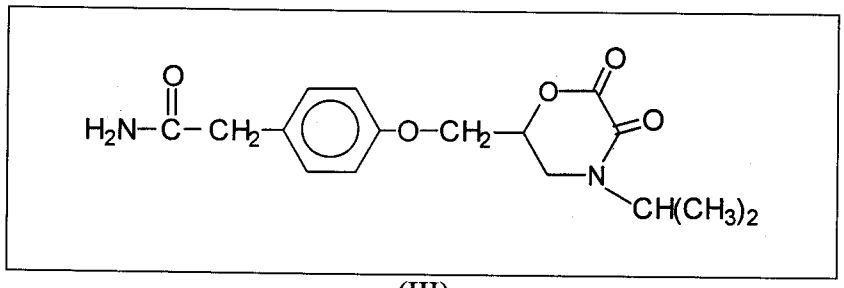
MS (m/z) : 308(M.+), 290, 274, 259, 158, 107, 86.

4-[(1-methylethyl)-6-(4-amidomethylphenoxy)methyl-5,6-dihydro-1,4 oxazine-2,3dione) (III)]

similar procedure as described above for compound (II), using oxalyl dichloride in place of thiophos-

gene. The title compound was obtained in 50% yield (m.p. 187-188°C). Elemental Analyses: %C, H, N Calculated (found) 60.00(59.85), 6.25 (6.49), 8.75 (8.56).

This compound is prepared by a



(III)

IR ($\bar{\nu}$ cm^{-1}):

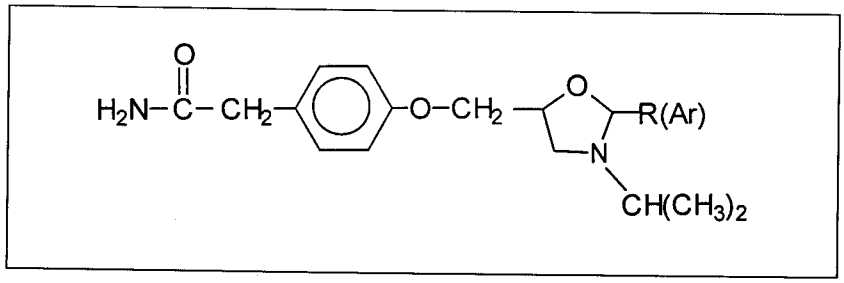
3360(s), 3160(m), 2980-2900(w), 1752(s), 1680(s), 1656(s), 1624(m), 1610(m), 1510(m), 1472(m), 1448(m), 1372(s), 1336(m), 1240(s), 1224(m), 1188(m), 1172(s), 1156(s), 1100(m), 810(m), 788(m).

^{1}H-NMR (d-ppm) : ($CDCL_3$)

6.82-7.26(dd,4H), 4.85-5.11(m,1H), 4.22-4.38(d,2H), 5.73-3.91(d,2H), 3.44(s,2H), 3.26-3.40 (m,1H), 1.08-1.35(dd,6H).

MS (m/z) : 320[M^+], 302, 276, 259, 170, 107

Oxazolidine derivatives (IV a - m) oxazolidines having the general structure given in figure (1) are synthesized according to the following general procedure:



(IV)

a. R = H
b. R = CH_3
c. R = $CH_2CH_2CH_3$
d. R = $-C_6H_5$
e. R = 2-ClC_6H_4
f. R = 3-ClC_6H_4
g. R = 4-ClC_6H_4
h. R = 4-BrC_6H_4
i. R = 4-CH_3-C_6H_4
j. R = 4-$CH_3OC_6H_4$
k. R = 4-$NO_2C_6H_4$
l. R = 2,4-$Cl_2C_6H_3$
m. R = 2,4-$(CH_3)_2C_6H_3$

Figure 1: Structures of synthesized oxazolidine derivatives

Atenolol (11.3 mmole) is slurried in benzene (15 ml) and the required aldehyde (13 mmole) is added using a syringe (when liquid) or as solution in benzene (when solid).The mixture is stirred for 30 minutes at ambient temperature and then heated in a steam bath at 98°C (In the case of using low boiling aldehydes, Dean and Stark trap is not connected and the temperature should not exceed 70°C). The resulting water is withdrawn from the reaction mixture using Dean and Stark trap as water-benzene azeotrope. Reflux was continued for a period of 10-20 hours. and (anhydrous) Na_2SO_4 was added afterwords, then reflux continued for an additional 1 hour.

The mixture is then filtered while hot and the solvent evaporated in vacuo. The residue is triturated with ether and petroleum ether before being recrystallized from the appropriate solvent.

When employing solid aldehydes, atenolol (11.3 mmole) is slurried with only (6 ml) of benzene, and the aldehyde (12 mmole) is dissolved in (6 ml) of benzene before being added to atenolol.

The physical and spectroscopic data of the oxazolidines IVa-m are given below. The elemental analysis (C, H, N) for all compounds were found to be within ± 0.4 % of the calculated values).

5-(4-amidomethylphenoxy)methyl-3-(methylethyl)-1,3-oxazolidine (IV a).

Yield, 90%; mp, IR 180-182°C; (cm^{-1}) 3340,3140,1628,1510,1410,1240,1184,824,792; 1H-NMR ($CDCl_3$):(6.66-7.37(dd,4H),4.93-5.73(bs,2H), 4.22-4.56(m,3H), 3.92 4.13(d,2H), 3.51(s,2H),3.00-3.32 (dd,2H), 2.40-3.00(m,1H), 0.96-1.25(d,6H):

MS (m/z):278(M+), 26,226,143,128;Molecular formula,$C_{15}H_{22}N_2O_3$.

5-(4-amidomethylphenoxy)methyl-2-methyl-3-(methylethyl)- 1,3-oxazolidine (IV b).

Yield, 66%; mp,98-100°C; IR (cm^{-1}) 3340, 3160,1652,1632,1510,1240,1110-1088, 810,788; 1H-NMR ($CDCl_3$) (6.76-7.33 (dd,4H), 5.04-5.81 (bs, 2H).4.42-4.68 (q,1H), 4.11-4.42 (m,1H), 3.93-4.12 (d,2H), 3.51 (s,2H), 2.53-3.39 (m,3H),1.23-1.39 (dd,4H),0.93-1.23(m,6H);

MS (m/z)277(M+ -15),248,222,107. Molecular formula, $C_{16}H_{24}N_2O_3$.

5-(4-amidomethylphenoxy)methyl-3-(methylethyl)-2-propyl-1,3-oxazolidine (IV c).

Yield, 68%; mp,69-71°C;IR (cm^{-1}) 3340, 3160,1652,1510,1240,1172,1080,1028,880,810,788; 1H-NMR($CDCl_3$) (6.75-7.31(dd,4H),5.00-5.72 (bs,2H), 4.34-457(m,1H),4.06-4.34(m,1H), 3.89-06(dd,2H), 3.52 (s,2H),3.07-3.30 (dd,2H), 2.25-3.07 (m,1H), 1.52-1.66(m,4H),0.73-1.25 (dd,9H);MS (m/z) 277(M+-43), 226, 143,107; Molecular formula, $C_{18}H_{28}N_2O_3$.

5-(4-amidomethylphenoxy)methyl-3-(methylethyl)-2-phenyl-1,3oxazolidine (IV d).

Yield, 90% ; mp,96-99°C; IR (cm^{-1}) 3340,3160, 1649,1610,1508,1244,1172,1024, 820, 800, 752, 692, 672 1H-NMR($CDCl_3$) (6.77-7.58 (m,9H),5.00-5.81 (bs,2H), 5.20 (s,1H),4.18 -4.72(m,1H),3.86-4.19

(dd,2H), 3.49 (s,2H),3.24-3.40 (s,2H), 2.65-3.19 (dd,2H), 0.80-1.21 (dd,6H); MS (m/z) 354 (M+), 277,251,222,107; Molecular formula , $C_{21}H_{26}N_2O_3$.

5-(4-amidomethylphenoxy)methyl -2-(2-chlorophenyl)-3-(methylethyl)-1,3-oxazolidine (IVe).

Yield, 88% ; mp,103-105°C; IR(cm^{-1}) 3340,3160, 1654,1608,1508,1243,1174,1027, 856,817,787,695-665.; 1H-NMR($CDCl_3$) (6.77-7.51(m,8H),5.08-5.81(bs,2H), 5.22(s,1H),4.22-4.66(m,1H), 3.36-4.22 (dd, 2H), 3.53 (s,2H),3.00-3.42 (dd,2H),2.64-3.04 (m,1H),0.91-1.15(dd, 6H); MS(m/z) 388,390(M^+), 372, 374, 353, 277, 107; Molecular formula , $C_{21}H_{25}N_2O_3Cl$.

5-(4-amidomethylphenoxy)methyl-2-(3-chlorophenyl)-3-(methylethyl)-1,3-oxazolidine (IV f).

Yield, 85% ; mp 111-114°C ; IR (cm^{-1}) 3340, 3168,1666,1612,1508,1276,1248,1196-1171, 1024, 896, 876, 780, 678; 1H-NMR ($CDCl_3$) ((6.79-7.68 (m,8H), 5.00-5.72 (bs,2H),5.22(s,1H), 4.20-4.70 (m,1H),3.86-4.20 (m,2H), 3.04-3.29(dd,2H), 2.52-3.04 (m,1H),0.81-1.16 (dd,6H); MS(m/z)388,390 (M^+), 372, 374,277,107,.; Molecular formula , $C_{21}H_{25}N_2O_3Cl$.

5-(4-amidomethylphenoxy)methyl-2-(4-chlorophenyl)-3-(methylethyl)-1,3-oxazolidine (IV g).

Yield, 83% ; mp, 118-120 oC ; IR (cm^{-1}) 3340, 3160, 1650, 1610, 1510, 1278, 1234, 1078, 1026, 865, 813; 1H-NMR ($CDCl_3$) (6.75-7.46 (m,8H),5.00-5.73 (bs,2H), 5.20(s,1H), 4.17-4.66(m,1H),3.84-4.17 (m,2H), 3.52(s,2H),3.04-3.42 (dd,2H),2.62-300(m,1H), 0.9-1.19 (m,6H); MS (m/z)388, 390(M+),372, 374, 277, 107; Molecular formula, $C_{21}H_{25}N_2O_3Cl$.

5-(4-amidomethylphenoxy)methyl-2-(4-bromophenyl)-3-(methylethyl)-1,3-oxazolidine (IV h).

Yield, 79% ; mp 124-125°C ; IR (cm^{-1}) 3340,3160, 1608 1508,1240,1176,1088, 1028,868,812; 1H-NMR ($CDCl_3$) (6.76-7.54 (m,8H),5.00-5.91 (bs,2H), 5.17(s,1H),4.17-4.65 (m,1H),3.85-4.17 (m,2H), 3.50 (s,2H),3.04-3.39 (dd,2H), 2.52-3.04 (d,1H), 0.91-1.45 (m,6H; MS (m/z)432,434 (M+), 416,418,399,401,277, 259, 223, 183 , 169; Molecular formula , $C_{21}H_{25}N_2O_3$ Br.

5-(4-amidomethylphenoxy)methyl-3-(methylethyl)-2-(4-methylphenyl)-1,3-oxazolidine (IV i).

Yield, 94% ; mp, 106-108 oC ; IR (cm^{-1}) 3328, 3160, 1394, 1280, 1296, 1280, 1248, 1210, 1172, 1028, 876, 804; 1H-NMR($CDCl_3$) (6.67-7.55 (m,8H),5.88(bs,2H),5.17 (s,1H), 4.18-4.74 (m,1H), 3.85-4.18 (dd,2H), 3.50 (s,2H), 3.02-3.40 (dd,2 H), 2.48-3.02 (m,1H), 2.35 (s,3H), 0.75-1.20 (d,6H); MS (m/z) 368 (M^+),352,277,216, 107; Molecular formula , $C_{22}H_{28}N_2O_3$.

5-(4-Amidomethylphenoxy) methyl-2-(4-methoxyphenyl)-3-(methylethyl)-1,3-oxazolidine (IV j).

Yield, 90% ; mp, 85-90°C; IR(cm^{-1}) 3340,3160,1380, 1296,818,800 ; 1H-NMR ($CDCl_3$) (6.72-7.60 (m,8H), 5.00-5.76(bs,2h), 4.15-4.71 (m,1H), 3.86-4.15 (dd, 2H), 3.80 (s,3h),3.51 (s,2H), 3.03-3.41

(dd,2H), 2.52-3.03 (m,1H), 0.78-1.20 (m,6H); MS (m/z) 384 (M^+),368,366, 277, 259, 190, 149, 135, 121, 107,; Molecular formula, $C_{22}H_{28}N_2O_3$.

5-(4-amidomethylphenoxy)methyl-3-(methylethyl)-2-(4-nitrophenyl)-1,3-oxazolidine (IV k).

Yield, 95%; mp, 121-122°C;IR (cm^{-1}) 3360, 3180 , 1520, 1344, 1280, 1234, 1084, 1028, 872 840, 816, 740; 1H-NMR ($CDCl_3$) (7.55-8.35 (m,4H),6.68-7.30 (m,4H), 500-5.68 (bs, 2H), 5.34 (s,1H), 5.37 (s,1H), 4.20-4.70-(m,1H), 3.85-4.20 (dd,2H), 3.51 (s,2H), 3.04-3.40 (dd, 2H), 2.66-3.02 (m,1H), 0.82-1.22 (m,6H); MS (m/z)399 (M^+), 383,365,350,163,145,107; Molecular formula, $C_{21}H_{25}N_3O_5$

5-(4-amidomethylphenoxy)methyl-2-(2,4-dichlorophenyl)-3-(methylethyl)-1,3-oxazolidine (IV l).

Yield, 100% ; mp,109-110°C; IR (cm^{-1}) 3340, 3180, 1654, 1580, 1508, 1460, 1396,1372,1240, 1172, 1080, 1022, 848,810; 1H-NMR ($CDCl_3$) (6.77-7.97 (m,8H), 5.00-5.72 (bs,2H), 5.63 (s,1H), 5.58 (s,1H), 4.21-4.73 (m,1H), 3.87- 4.19 (dd,2H), 3.52(s,2H),3.14-3.48) (dd,2H),2.60-3.04 (m,1H),0.83-1.24 (m,6H); MS (m/z) 422,424,426 (M^+) , 406,389 , 271, 258, 190, 159,145,107; Molecular, formula $C_{21}H_{24}N_2O_3Cl_2$

5-(4-amidomethylphenoxy)methyl-3-(methylethyl)-2-(2,4-dimethylphenyl)-1,3-oxazolidine (IV m).

Yield, 100% ; mp 101-103°C; IR (cm^{-1}) 3340, 3160, 1656,1610,1510,1400,1288, 1236,1172, 1024,864,810,788; 1H-NMR ($CDCl_3$) (6.74-7.62 (m,8H), 5.00-5.75 (bs,2H), 5.36 (s,1H), 4.20-4.69 (m,1H), 3.88-4.20 (dd,2H), 3.51 (s,1H), 3.14-3.49 (dd,2H), 2.41 (s,3H), 2.30 (s,3H), 0.83-1.22 (dd,6H); MS (m/z) 382 (M^+) 366, 349, 178, 107; Molecular formula, $C_{23}H_{30}N_2O_3$.

Results and Discussion :

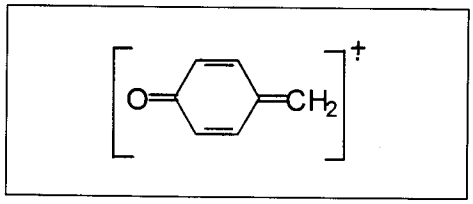
1. Preparation and spectroscopy of the oxazolidine-2-thione derivative (II)

In earlier work, Bundgaard etal.[4] and Chang etal.[19] reported that esters of timolol (another non-selective β-adrenergic receptor blocker) enhanced corneal permeability. Characteristics, with slight reduction in systemic absorption, and concluded that they are promising timolol prodrugs for ocular delivery. However, they suffered from instability in aqueous solutions. To elaborate further on this prospect, Buur etal.[6] synthesized and tested the hydrolysis and aminolysis of various oxazolidine-2-one derivatives of propranolol. Unfortunately, theses derivatives showed to be highly stable in aqueous solutions as well as in the presence of human plasma, thus rendering them unsuitable prodrug form. We anticipate here to introduce the oxazolidine-2-thione (II) and the six membered 1,4-oxazine-2,3-dione (III) which might lead to endeavors of suitably balanced stability.

A modification of the synthesis procedure reported by Giuliana[15], and Buur[4] in their synthesis of oxazolidine-2-one of propranolol had to be done. Unlike the relatively concentrated solutions of the amino alcohol they used, the diacid halide had to be added to dilute solution of atenolol, in order to enhance the intramolecular cyclization reaction and to avoide the formation of dimers or polymers of esters and

amides. The addition of triethylamine helps in liberating a free amino group of the drug so that amides can be obtained. The IR spectrum shows the C=S at 1732(m) and 1156(s) cm^{-1}. The appearance of these two peaks might be due to coupling of the C=S bond with the neighbouring C-N and C-O bonds[16].

Elemental analysis and appearance of M^+ at m/z of 308 confirm the formation of the desired cyclic compound rather than the dimeric product. The fragment ions of m/z 290, 274, and 259 are due to (M^+ - H_2O), (M^+ - H_2O - NH_2), and (M^+-H_2O-NH_2-CH_3) respectively. Moreover, the highly abundant fragment of m/z 107, due to the ion shown below was also detected.



2. Preparation and spectroscopy of the 1,4-oxazine-2,3-dione derivative (III)

Lalonde etal.[17] and Speziale etal.[18,19] reported the preparation of barbituric acid by condensation of malonic ester and urea. However upon trial to prepare the five membered cyclic compound using oxalyl chloride in place of malonic ester, an acyl isocyanate (R-CO-N=C=O) is formed. However, unlike the acylation reaction which was not successful with acetyl chloride, oxalyl chloride reacts with atenolol (dilute solution), in presence of $(CH_3CH_2)_3N$ and yields 1,4-oxazine-2,3-dione derivative. IR and NMR spectral data are in full agreement with the assigned structure. The mass spectrum shows very low abundance of M^+ peak at m/z 320 followed by more abundant M^+-18 at m/z 302 due to loss of water. Loss of isopropyl group 43 mass units leads to the ion m/z 259 as the base peak in a difference from the parent compound (atenolol base peak is m/z 72). In addition, a fragment ion at m/z of 276 corresponding to loss of amide (-CO-NH_2) was also observed (M^+-44).

Again, elemental analysis and mass spectral data eliminates the possibility of acyclic dimeric product formation.

3. Preparation and spectroscopy of the oxazolidine derivatives (IV a-m)

Oxazolidines were synthesized according to literature procedure[11,20], by the condensation of aldehydes with b-amino alcohols. The variations aimed towards adjusting the reaction conditions to obtain higher yield. In brief, variations included the use of slight excess of aldehyde, reaction temperature and time, and withdrawal of water generated during the reaction by the use of Dean-Stark trap, or drying agent (sodium sulfate is recommended). In our general experimental procedure the technique of azeotropic distillation with Dean-Stark trap was adopted and showed to reach satisfactory yields.

Our intention towards a prodrug implies the careful selection of the incorporated aldehyde due to the fact that hydrolysis of the synthesized oxazolidine back to the parent atenolol drug takes place with reasonable rate which depend largely on the nature of the alkyl or aryl moiety of the aldehyde. This group

would appear on C-2 of the oxazolidine ring. In their study of oxazolidine hydrolysis, Fife and Hagopian[21] studied the effect of aryl substituent on the rate of ring opening and concluded that electron withdrawing groups retard the process, while opposite effect is seen due to electron donating substituents (particularly at acidic pH). Accordingly, our list of synthesized oxazolidines (IVa-m) included aliphatic (R = H, CH_3, or $CH_3CH_2CH_2$), unsubstituted aromatic (Ar = C_6H_5), deactivated aromatic (with chloro, bromo, or nitro-substituted phenyl), and activated aromatic (with methyl or methoxy-substituted phenyl). Furthermore, our selection emphasizes the position (*ortho, meta, or para*) of the activating or deactivating group, as well as the number of activating or deactivating units. The mechanism by which oxazolidines hydrolyzes back to the aldehyde and amino alcohol was studied and proposed by Johansen[9], and Bundgaard[22] to follow the path displayed in figure-2.

The ^{1}H-NMR spectra of these oxazolidines show general features in agreement with the assigned structures in each case the four protons capable of H-bonding (namely NH_2 , OH , NH) in the parent compound,

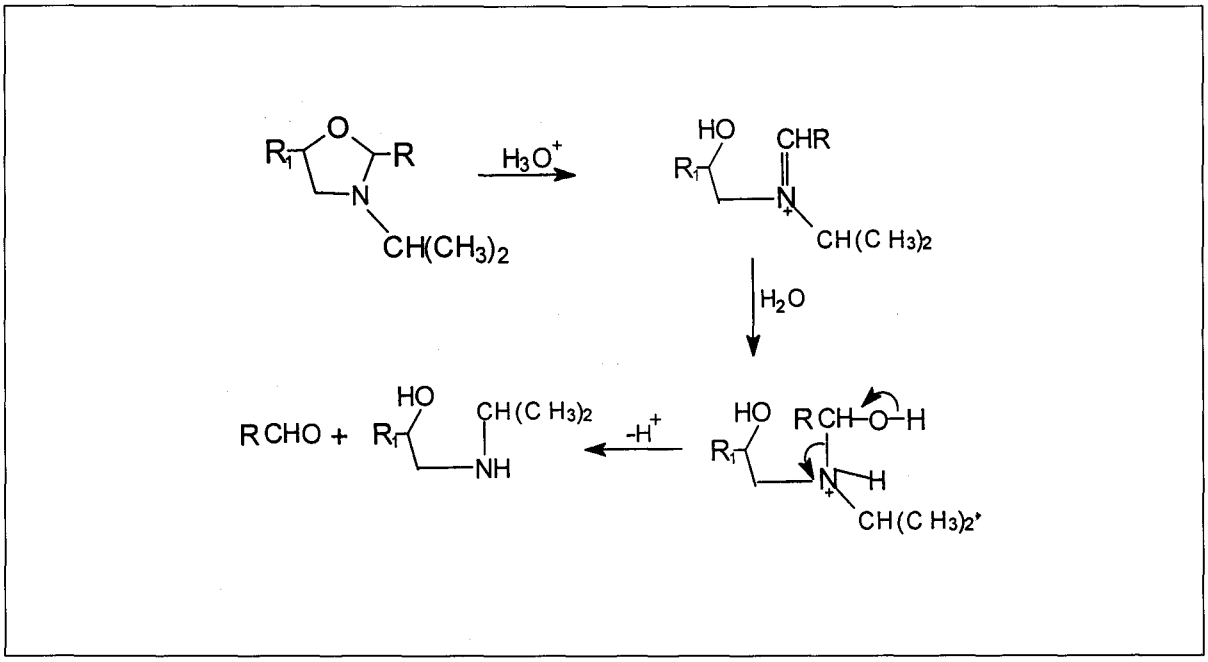


Figure 2

atenolol, are changed to a broad peak integrating to two-NH_2 protons of oxazolidine derivatives (disappear upon D_2O addition). This is indicative of the disapearance of NH and OH protons involved in the condensation process. In addition, the integrations of the incorporated aldehyde protons agree with atenolol: aldehyde (1:1) condensation ratio. Detailed analysis of all 1H-NMR spectra of synthesized oxazolidines and comparison with that of atenolol agree with the variations expected due to the new compound structure.

The main features in IR spectra of these compounds are characterized by a theme of bands, namely : 1175-1190 cm^{-1} due to O-C-N; 1035-1060 cm^{-1} due to C-O-C; ~ 1580 cm^{-1} C-N. These bands are characteristic of the oxazolidine ring according to well documented literature.[15,23,24]

Additional peaks representing the other functional groups e.g. 3050 cm^{-1} for aromatic C-H, 3400 and

3160 for amide -$CONH_2$, were also observed.

The mass spectra showed the molecular ion (M^+), and a pattern of fragmentation including primarily most of the following ions : M^+-18 due to loss of water or M^+-16 due to cleavage of amide NH2; M^+-43 or M^+-44 due to cleavage of isopropyl or -$CONH_2$, respectively. The ions M+-150, due to cleavage of the amide-$CONH_2$ and the directly connected m/z of 107 ion described for the 2-thione (II) (*vide supra*). Cleavage of methyl group, leading to M^+-15 ion is seen in some cases. Collectively the NMR, IR and MS spectral data agree with the assigned structures. Evaluation of the prepared compounds as prodrugs of a tenolol is under investigation.

Acknowledgment

The authors wish to thanl the financial support and research grants of the Deanships of Jordan University of Scientific Research and Technology and Yarmouk University are highly acknowledge.

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