Synthesis , Spectroscopic and Antibacterial Investigation of New Molecular hybridized 4-Aminoantipyrine Derivatives of pharmaceutical Interest.

***Vian Jawher, **Nuha S. Al-Baytii, ***Hatif.A.Y. Alshirayda**
***Department of Organic chemistry, College of Science, University of Koya, Koya, Iraq**
****,***Department of Pharaceutical Chemistry, College of Pharmacy, Tikrit , University of Tikrit, Iraq**

Received 10/4 /2010 Accepted 6/6/2011

Abstract

A new series of a hybridized 4-(N- substituted) aminoantipyrine derivatives with amide linkage backbone aminoantipyrine, series (A),compounds [13a- g] and secondary amine linkage, series(B), compounds [l4a-20a] were prepared through systematic sequence coupling reaction of 4-aminoantipyrine (4-AA) and well established active nitrogen bases moieties of phthalimide,piperidine and substituted aniline derivatives with chloroacetylchloride of actively different chlorine functions. . The antibacterial activity of some selected products was reported.

تصنيع والكشف عن الفحص الطيفي والفعالية البايولوجية لمشتقات ا لمهجنة4- أمينوأنتي يايرين الجزيئية الجديدة واهميتها في مجال الصيدلانيات

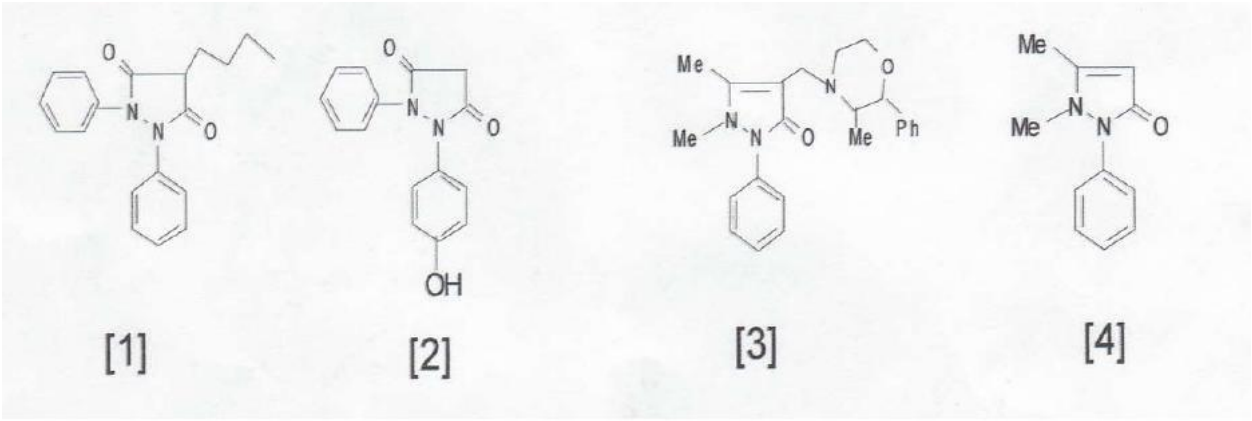
فيان جوهر نهى سليم البياتي هاتف عبدالرزاق الشريدة

الملخص

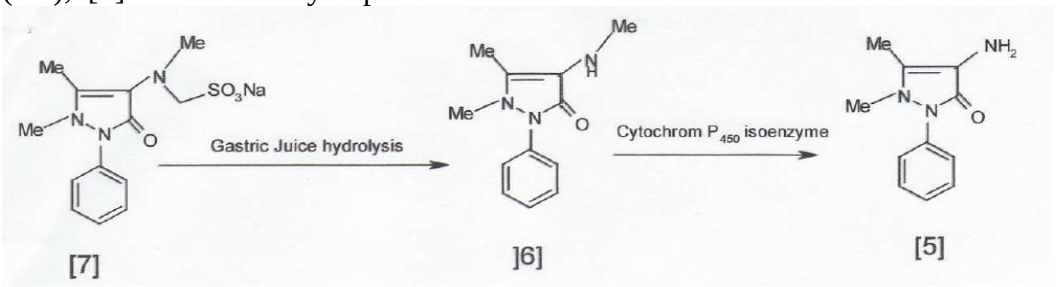
يتضمن البحث تحضير سلسلة من مشتقات 4(ن – مءوضات)أمينو انتي بايرين المهجنة مع رابطة الامايد التابعة لمنظومة امينو انتيبايرين ،سلسلة (أي) والمكونة من المركبات (3 أي –جي) ورابطة الامين الثانوي ،سلسلة (بي) والمكونة من مركبات (14 أي-20 أي)وذلك من خلال تفاعل الازدواج المتعاقب المنظم ل 4- امينو انتيبا يرين(4-أي أي) والمؤلفة من قواعد النتروجين الفعالة للفثال ايمايد ،ببريدين،ومشتقات الانلين المعوضة ب كلوروأسيتايل كلورايد التي لها وظائف مختلفة لذرة الكلور النشطة وتم تدوين الفعالية البايولوجية لبعض المركبات المحضرة.

Introduction

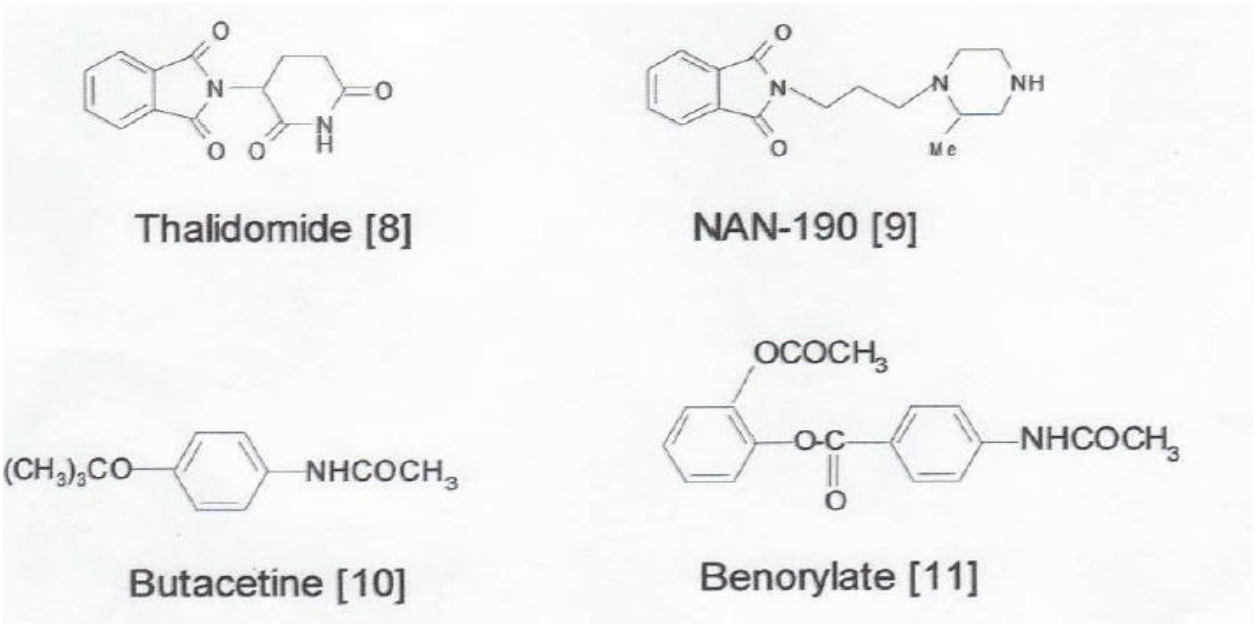
Organic molecules owe their biological activities to verity of structural features; some activities are associated with the structural backbone of parent molecule others associated with the type and orientation of additives modification. However, many compounds containing the pyrazolone ring moiety have been prepared and reported to posses varied pharmacological activities [1-5]. They used in the treatment of arthritis , musculoskeletal and joint disorders[6].Also, the term pyrazolone some time refer to the non steroidal anti-inflammatory drug (NSAID). e.g Phenylbutazone [1], Oxyphenbutazone [2]. and Morazone[7], [3]. Additionally, analgesic and anti-pyretic activities were found to be associated with the pyazolone derivative, antipyrine[4].



The pyrazolone derivative 4-Aminoantipl.ren(4-AA),[5] have been used as intermediate for the Synthesis of pharmaceutically active ingredients e.g. .Aminopyrine[6] and Dipyrone (DP), [7]. Recent study reported that (4-AA) was as a metabolite of dipyrone(DP) , scheme I ,which was found to be associated with a property of delaying the gastric emptying (GE) of liquid meal in rats[8-9].



Scheme 1, On the other hand., the phthalimide moiety play a great role in the pharmacological activity of the alpha tumor necroses factor(α -TNF) secretion inhibitor[10] , Thalidomide[8] and the 5-HTIA anti stimulant[11] NAN-190,[9], Additionally, acetanilide moieties are well known for their antiinflamatory and analgesic properties,e.g. Paracetemol, butacetin[12][10] and hybridized benorylale [11].



On the basis of the above finding ,encouraged us to prepare new modified antipyrine derivatives, compounds series (A)and (B) as shown in scheme 2 and 3, hoping that such companion affect the pyrazolone ring bassist, hydrophilicity hexing a new biologically active pharmacophore.

Experimantal

Melting point were determined on digital electro thermal apparatus and are uncorrected. The IR spectra were recorded by FT-IR-8400s Shimadzu as KBr disc.U:V spectra were recorded by using CECIC-CE3021 spectrophotometers' ^{I}NMR spectra were recorded on Bruker AC-250 using TMS as internal stander .Elemental analysis were done by the analytical service unit, Faculat for chemi.Konstans University.

General procdure for the preparation of the new 4-(N-substituted) aminoantipyrin.
dervatives, compounds [13a-13g1 and [14a-20a].

Equimolar mixture of 0.02 mol. of nitrogen amine base and 0.02 mol. Of freshly distilled chloroacetylchloride in 40 ml of cold dry benzene and in the presence of 0.9 g,0.00lmol. Of potassium carbonate was stirred at room temperature for l-3 hrs .The solution mixture was filtered , evaporated and residue was collected and recrystalized from ethanol afforded the pure intermediates of 4-N-(chloroacetyl) amine base derivatives. Equimolar of the prepared. 4-N-(chloroacetyl) arrine base 0.001 mol, .and desired nitrogen amine base 0.001mol.in 4o ml of dry benzene and the presence of 0.9 g, 0.001 mol. K2CO3 was stirred under refluxes for 4-8 hrs .The solution then filtered , evaporated and the precipitate collected and recrystalized from ethanol.

4-N-(anilinoacetyl) aminoantipyrine [13a]

The compound was obtained as white powder ,mp.; .224 -226 C ,71Yield%, elem. anal. ; Calc. ,For $C_{19}H_{20}N_4O_2$, (336 .4): C,67 .86,H,5.95, N,16.66. Found: C,67,76; H,5.93; N,l6.58. ^{I}H

NNR(250MHz,$CDCI_3$); δ 2.28 (S,2H),2.80 (S,3H,C-CH3), 2.84 (S,3HN-CH3).UV.λmax(EtOH) ,227 nm.IR. KBrdisc Cm_{-1} ; 1660 (C=O,lactam ring), 1605 (C=O, amid), 3481(b,NH amine), 3361(b,NHCOC).

4-N-(4-chloroanilinoacetyl)aminoantipyrine [13b]

The compound was collected as white solid,mp.; 96-98C, 61 yield%,elem.anal.;Ca1c.;

For $C_{19}H_{19}N_4$ O_2 Cl (370.6); C,61.62,H,5.13, N,15.13. Found: C, 61,68, H,5,44, N,14.89.

^{I}HNMR (250 MHz,$CDCI_3$); δ 7.22-7.65 (m,9H-Ar), 2.33(S,CH2),2.70(S,H3,C-CH3),2.82(S, 3H,N-CH3).UV.;λmax(EtOH) 224 nm.IR.KBr disc; Cm^{-1}, 1665(C=O lactam ring),1610(C=O ,amide),3483 (b , NH amin), 3360 (b, NHCO).

4-N-(4-methoxyanilinoacetyl) aminoantipyrine [13c]

The compound was obtained as pale brown solid.mp, 87-89 C, 57yieldYo, elem.anal.Calc.; For $C_{20}H_{22}N_4O_3$,(360.5), CaLc. :C,65,57,H,6.01,N,15,30. Found; C,65.44,H,5.89, 15.43.

^{I}HNMR(250 MHz, $CDCl_3$); δ 7.33-7.48 (m,9H,Ar),2.40 (S,cH2),2.66(S,3H,C-CH3t),2.79 (S,3HN-CH3), 3.11(S,3H,OCH3).UVλmax,(EtOH)223 nm. IR. KBr disc cm-1, 1668(C=O, lactam ring), 1615 (C=O,amide),3475(b , NH,amin), 3370(b , NHCO).

4-N-(4-nitroanilinoacetyl) aminoantipyrine[13d]

The compound was obtained as pale yellowish crystals,mp.:67-69 C,67 yield%,elem.anal.,

For $C_{19}H_{19}$ N_5O_4 (381.4).Calc. C,59.84, H,4.99N,18.32. Found: C,59.77,H,5.11,N,18.37.

^{I}H NMR (250MHz,$CDCl_3$); δ 7 .42-7 .22 (m, 9H, Ar); 2.62 (S, CH2),2.60(S,3H,C-CH3), 2.80 (S, 3H,N-CH3).UV.λmax,(EtOH ,229 nm.IR. KBr disc.Cm^{-1} 1636 (C=o.lactam ring), 1700 (C=O,amaide),), 3481 (b, NH amine). 3361(b, NHCO).

4-N-(4-methyl-3-chloro anilinoacetyl) aminoantipyrine [13e]

The compound was obtained as white powder, mp. 87-91 C, 60 Yield %,e1em.anal.For C_{20} $H_{21}N_4O_{2tt}Cl$ (384.6), Calc.; C,62.50, H,5.47, N,l4.58.found. C,62.67, H,5.03, N,14.22.

^{I}H NMR (250 Mhz,$CDCl_3$); δ 7.33-7.21(complex mult .,Ar),2.60(CH2),2.40(S,3H,Ar-CH3), 2.64(S,3H,C-CH3),2.76(S,3H,NCH3).UV).λmax(EtOH) 226 nm.IR.KBr disc Cm^{-1} 1640 (C=O,lactamring),1705 (C=O,amide), and3475 (b,NH amine),3365 (b,NHCO).

4-N-fuipiridinoacetyl) aminoantipyrine [13f]

The compormd was obtaind as white powder,mp .:218-220 C, 62 Yield% ,.elem.anal. For $C_{18}H_{24}N_4O_2$(328.4).Calc., C,65.85, H,7.31, N,l7.07. Found: C,65.44, H,7.23,N,17,37.

^{I}H1 NMR (250 Mhz,$CDCl_3$);δ 7 .2-7 .4(m,5H,Ar), 2.19(S,2H,CH2CO),2.78(S,3H,C-CH3) 3.25(S,3HN-CH3),3.12(m,4H),1.90(m,4H),1.65(m, 2H) for pipiridinne ring.UV. λmax (EtOH). 228,nm.IR. Kbr disc. 1660(C=O lactam ring), 1630 (C=O,amide),3360(b,NHCO).

4-N-(phthalinidoacetyl) arninoantipyrine [13g]

The compound obtained as pail yellowish crystals ,mp.: 178-180 C,57 Yreld%.elem.anal.

For $C_{21}H_{18}N_4O_4$(390.2). Calc.: C,64.61,H,4.61,N,14.36. Found: C,64,44, H,4.57, N,14.01.
^{I}H NMR (250 Mhz,DMSO) δ 7 .7-7.8(m,2H,Ar of phthalimide),7 .2-7.4(m,5H,Ar),2.2(CH2), 2.79(s,3h,C-C3),2.95(s,3H,N-CH3).UV , λmax (EtOH),229,223,280 nm.IR Kbr disc; 1668(C=O lactam ring),1635(C=O amide),1620(C=O phthalimide ring).3355(NHCO).

4-N-(acetanilidyl) aninoantipyrine [1 4a]

The compound obtained as white crystal.mp.; 60-62 C,65 yield%, elem.anal. For $C_{19}H_{20}N_4O_2$ (336.4).Calc.C,67.11,H5.95N,l6.66.Found;C,67.45,H5.68,N,16.23.^{I}HNMR.(250MHz,$CDCl_3$) δ7.2-7.4 (m,l0H,Ar), 2.3 (S,2H,CH2),2.66 (s,3H, C-CH3),3.22(s,3H,N-CH3)UV . λmax (EtOH); 238 nm. IRKBr disc 1635 (C=O,lactam ring),1625(C=O,amid)3465 (NH amine),3350 (NHCO).

4-N-(4-chloroacetanilidyl)aminoantipyrin [1 5a]

The compound was obtained as white solid.mp.86-88 C,62Yeld%. elem.anal. For $C_{19}H_{19}N_4O_2Cl$(370.2). Calc.: C,61.62, H,5.13, N,15.13. Found: C,61,11, H,4.98, N,15.01. ^{I}H1 NNR. (250 MHz,$CDCl_3$),δ 7.20-7.40 (m, Ar.), 2.26(s, CH2),2.58 (s, C-CH3),3.32 (s,NCH3).UV. λmax(EtOH) 245,.IR.KBrdisc 1660(C=O,lactam ring), 1620(C=O amide),3450 and 3325 broad bands assigned for amine and amide NH respectively.

4-N-(4-methoxyactanilidyl) aminoantipyrine[16a]

The compound was obtained as brown solid,mp.: 53-55C, 64Yield%. elem.anal.
For $C_{20}H_{22}tN_4O_3$(366.2), Calc., N,15,31 %. Found; N%,15.52. ^{I}HNMR (250 MHz, $CDCl_3$); δ 7.25-7.68 (m, ,Ar), 2.42 (5,2H,-CH2),2.62(S,3H,C-CH3), 2.78 (S, 3H, NCH3); 3.16 (S, 3H, OCH3).UV.λmax (EtOH); 239.1R. KBr disc. 1665 (C=O,lactam ring), 1625(C=O, amid). 3446(b,NH,amine);3320 (b, NHCO).

4-N-(4-Nitroacetanilidyl) aminoantipyrine[l 7a]

The compound obtained as yellow solid,mp,96-98C,61 Yield%. elem.anal.for $C_{19}H_{19}N_5O_4$. Calc.: N%, 16.84 .found; 17,32. ^{I}H NMR(250MHz,$CDCl_3$);δ 7,46-7 .20(m,,Ar), 2.70 (s,2H,CH 2), 2.5 8 (s,3H,C-CH3), 2.76 (s,3H,N-CH3). UV.λmax (EtOH), 231 nm. IR. KBr disc.1632(C=O,lactam ring), 1659 (C=O,amide), 3482 NH-amine, 3362 (NHCO).

4-N-(4-Methyl-3-chloroactanilidyl) aminoantipyrine [18a]

The compound was obtained as brown solid.mp; 60-62 C,6l Yield %. elem.anal.
For $C_{20}H_{20}N_4O_2Cl$. Calc. : N% 15.13 . found N% 15.23 . ^{I}HNMR(250MHz,$CDCI_3$) δ 7 .46-7 .22 (m, Ar), 2.50 (s, 2H, CH2), 2.44 (s, 3H, C-CH3), 2.66 (s,3H,N-CH3). 1.86(s,.3H, Ar-CH3).UV. λmax (EtOH), 241nm.IRKBr disc.l635(C=O,lactam), 1655 (C=O, amide), 3445 (NH amine), 3354 (NHCO).

4-N-(pipiridinoylmethyl) aminoantipyrine [1 9a]

The compound was obtained as pail yellow solid .mp. 94-96 C,67 yield% elmen.anal. For $C_{18}H_{24}N_{t4}O_2$, Calc.for N%(ll.23), found(l l.9l).^{I}H NMR

(250MHz,$CDCl_3$);δ 7.27.4(m,5H,Ar),2.21(s,CH2),2.79(s,3 HCCH3),2.95(s,3H,NCH3), (1.66, m ,2H),(1.92,m,4H) and (3.13,m,4H) forpipiridinyl ring protonsUV. λmax (EtOH), 242IR. KBr disc.1632(C=O,lactam ring),1659(C=O,amide),3351(NHCO).

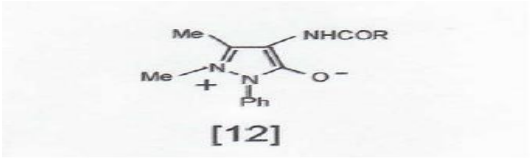
4-N-(phthalinidoylnethyl) aminoantipyrine [20a]

The compound obtained as yellowish crystalls,mp,l53-156C, 64Yeld%, elem.anal. For $C_{21}H_{18}N_4O_4$.Calc. : for N% (l 4.3 6), found,(1 4.67). ^{I}HNMR. (250MHz,DMSO) δ 7.76-7.87(m,4H,Ar),7.25-7.40(m,5H,Ar),2.27(s,CH2),2.80 (s, CH3),2.86(s,N-CH3). UV. λmax (EtOH) 215 nm. IR. KBr disc.l700 (C=O.lactam rng), 17 32 (C=O,amide), 346 1 (NHCO).

Results and Discussion

The new antipyrine derivatives compounds of series (A) ,and series (B) were prepared through a multistep reaction as outlined in scheme 2 and 3. Due to the highly active acetoyl chlorine the reaction of the chloroacetylchloride with the required amine in dry benzene and the presence of potassium carbonate at room temperature afford the N-(chloroacetyl) derivatives [13-19] '. In case of aniline derivatives was observed to be greatly affected by the substituent .Generally, substituent, electron withdrawing substituent showed the slower reaction time and that agree with the expected variation of aniline bassist and nucleophilicity .In case of the phthalimide derivative [20] was prepared by using sodium salt due to the slow and poor yield . reaction with the free phthalimide base Coupling of the prepared N-chloroaetyl derivatives with the corresponding amine in refluxing dry benzene and the presence of potassium carbonate afforded the required compounds of series (A),[13a-g] and [l4a-20a), seies(B). The prepared compounds were characterized by UV , IR ,^{I}H NMRand elemental analysis. The UV spectral were carried out in ethanol and the. λmax for the pyrazolone ring were determined according to the comparison with that observed for the pure 4-aminoantipyrine[5]- of λ max (EtoH),236nm. Interestingly, in exception of the phthalimide derivatives, compounds of series (A) of amide link aminoantipyrine showed λ max at range of (223 - 229 nm),while compounds of series (B) of amine link antipl,rine showd λ max at range of (231-245nm).The bathochromic shift in compounds of series (A) comparing to the parent aminoantipyrine may be due to formation of less stable conjugation chromophore consisted of rhe C3-C4 double bond,nitrogen lone pair and the carbonyl group in a extended resonance in the pyrazolone ring ,structure[12].by the inductive effect of amide carbonyl group

.



[12]

The IR spectra (KBr disc) of both series showed a common carbonyl absorption as sharp strong band in the region 1650-1700) cm^{-1} and 1600-1650 cm^{-1} assigned for amide and ring carbonyl stretching respectably. The spectra also exhibited. two broad band at 33 6l-3362cm^{-1} and3481-3482 cam assayed for the NH of amide and secondary amine stretching respectively. The ^{l}H NMR spectra of the prepared compounds showed pattern almost in good agreement with the required structure. Peaks of each proton was assigned according to their electronic. Environment (shielded-desheilded) and comparison with that obtained for starting material and some intermediate. The spectra showed correct aliphatic/aromatic protons ratio supporting the stichiometry and the purity of the prepared compounds. However, the ^{l}H NMR spectrum of compound [13f] showed a remarkable up field shift signal at δ 2.88 ppm for the methylene protons compare to that observed for tire intermediate [19] which showed signal for the same protons at δ 4.22ppm supporting the replacement of the cblorine by piperidyl group, δ the spectrum a.tso showed three signal as multiple are δ 1.66,1.89 andδ 3.12 ppm assigned for ring methylene protons.Also,the presence of aromatic protons signal as two multiple at δ 7.13-7 .42 ppm supporting the right structure.

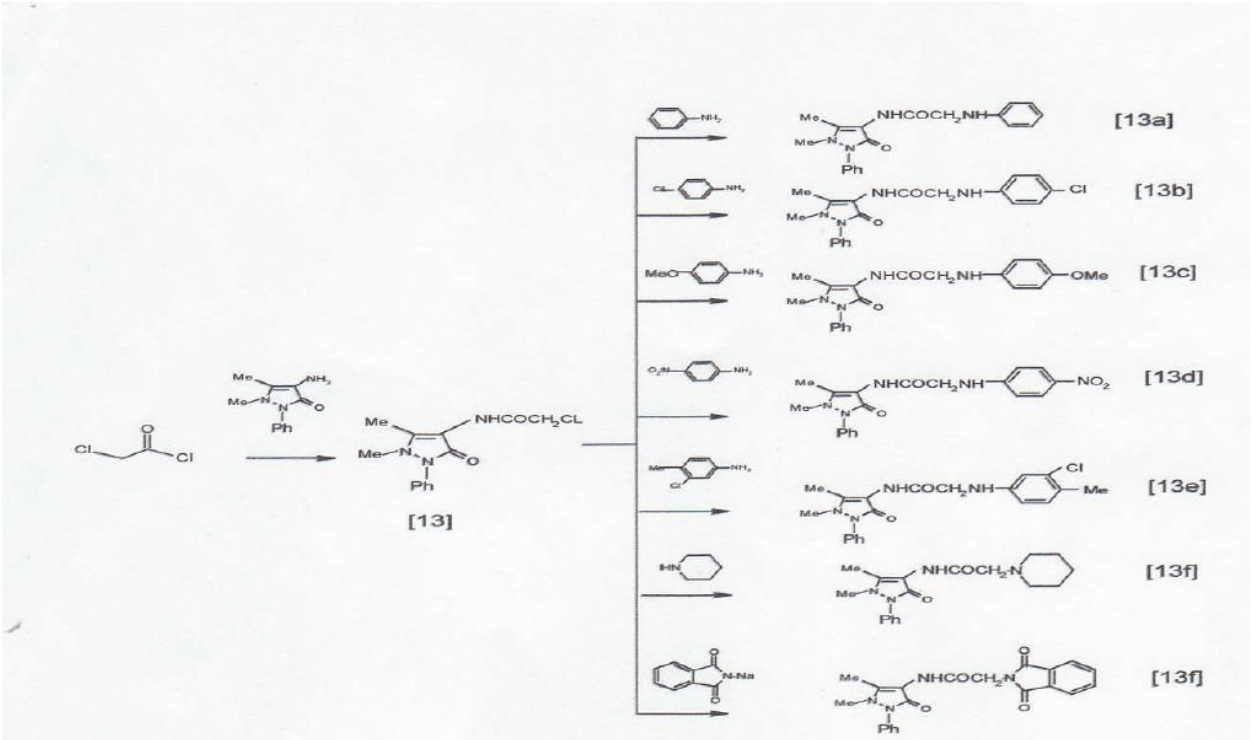
Preliminary antibacterial screening

Four of the synthesized new 4-AA derivatives , compounds (13f,13g) and (19ap0a) were selected for comparison in preliminary antibacterial screening (Table l).The agar diffusion technique(l3'ra) was applied The organism tested were a *Staphylococcus aureus*. *Escherichia coli* and,*Klebsiella sp*. The agar media were incubated with the tested organisms and a solution of testedcompound in sterile water and ethanol (lmg/ml) was placed separately in discks (8mm. diameter)in the agar medium. The resulting inhibition zones were measured after 24 hrs incubation.A0.l% solution . Ciprofloxacin was used as reference., as shown in Table l. It could be concluded, that there were no effect of tested compounds 13f,13gr19a and 20a on the

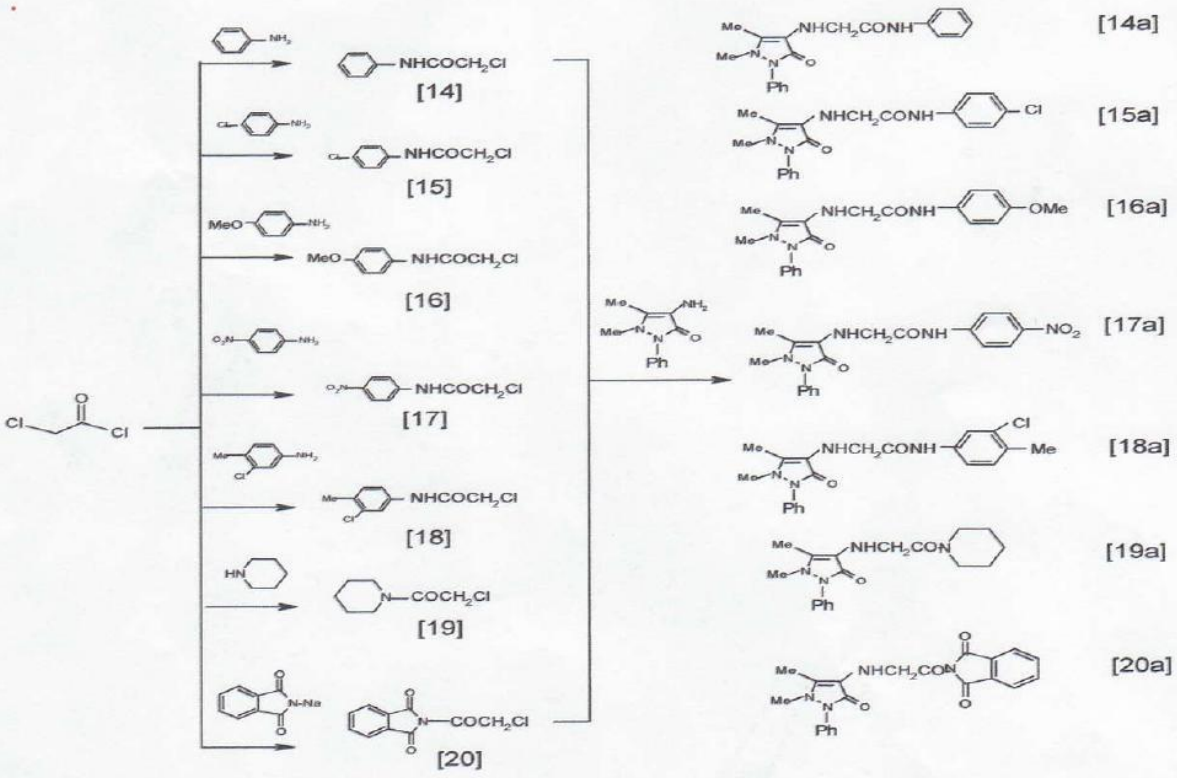
different bacterial strains, compared to the reference antibiotic. Other pharmacological evaluation is under investigation.

Table (l):- The inhibition zones in mm.of compounds 13f,13g,19a and 20a and the antibiotics control against *S. aureus, E.coli* and *klebsiella sp.*

Comp.No.	S.aureus	E.coli	Klebsiella sp.
13f	1mm	0.5mm	1mm
13g	0.5mm	1mm	0.5mm
19a	zero	0.5mm	zero
20a	0.6mm	zero	0.5mm
Ciprofloxacin	30mm	27mm	32mm



Scheme 2: Reactions step for series (A),compounds[13a-13g]



Scheme 3:Reactions step for series (B),compounds [14a-20a]

References

l- Silvio & co-workers ; J.Molecular structure, vol.(752),issues l-3,p 32-39,(2005).
2-
D.Burdulen,A.Palaim4Z.stumbryavich yute; J. pharmaceutical chem., vol.33(4),
P 191-193,(1999).-
3- L.A.Shabrova and G.M.stepnova; J.Khimiya Geterotsiklicheskikh Soedinenii,
Vol.3(1),P 1 3 s -1 37,(1967).
4- Tripathi.M.verna, M.Palit and G.shanker.k; Arzreimettelforscung, Vol.43(10),
p 104s-1049,(1993).
5- A.E Rubtsov and co-workers; J. Pharmaceutical chemistry,vo1.36 ,11,(2002).
6- Y.Shibaia K.Sasaki, Y.Hashimoto and Siwasaki; J.Chem.pharm.Bull. 44,156,(1996).
7- O.Hengen, H.Siemer and A.Doppstadt; J.Arzneimittel forschoung., 9,421,(195g).
8- R.N. Brogden, Drugs Text book,32,4,60,(1986'1.
9- M.Leq, E.ZylbetKatz,and, B.Rosenkranz;
Clin.pharmacokilent;29,216,(1995).
10- E.P.Sampio, E.N.Samo, R.Galilty and Z.A.Cohn and G.J.Kaplan;Exp.Med.;137,699,(1991).
ll- R.K.Rahupthi,L.Rydellek, M.Titler,and R.A.Glennon; J.Med.Chem.;34,2633,(1991).
12- K.Bowden and P.N. Green; J.chem.Soc.l954 (1975).
13- A.M. Vinagre and E.F.Collares; Braz. J.Med.,Biol.Res.40,7,903,(2007).
l4- R.J.Debs,H.J.Fuche, R.Philip, E.N.Brunette, N.Duzgunes, J.E.Shallito and D.Liggitt; J.cancer Res.,50,375,(1990).