Synthesis of new derivative containing (lactam and bis-lactam) and (tetrazole and bis-tetrazol) from aldo-imine

Amera .H.Hamed
Isam.Sh.Hamza
Mohammad.M.Saleh
Chemistry Dept.College of Science for women
University of Baghdad.

Abstract:

Some new β-Lactam and tetrazol derivatives were prepared from Schiff bases which the reaction of different substitution aromatic aldehyde with urea followed by cycloaddition reaction with chloroacetyl chloride and triethylamine to give β-Lactam .while reaction Schiff base with sodium azide give tetrazole .

Also prepare bis lactam and tetrazol from the reaction of substitution aromatic acid with thionyl chloride to give substituted aromatic acid chloride followed by reaction with urea to give amide which followed cycloaddition reaction with chloroacetyl chloride and triethylamine to give bis β-Lactam .while reaction amid with sodium azide give bistetrazole .

Key words: β-Lactam, tetrazole. Schiff base, azetodinone.

Introduction:

β-Lactams are a large class of antibiotics having an azetidine-2-one ring, which is the core of their biological activity.[(1)]They have been widely used as chemotherapeutic agents for treating microbial diseases.[(2)]They also show many other interesting biological properties, such as cholesterol absorption inhibitors,[(3)]human cytomegalovirus protease inhibitors,[(4)]thrombin inhibitors,5antihyperglycemic,[(6)]antitumor,[(7)]anti-HIV,([(8)]anti-inflammatory, analgesic activities[(9),] antimalarial activities,[(10)]and serine-dependent enzyme inhibitors.[(11)]

However, microorganisms have built up resistance against most b-lactam antibiotics due to the overuse of these drugs. Therefore, the phenomenon of bacterial resistance forces the continuous modification of structure of b-lactams and the development of the new ones[(12)].

the design and synthesis of hybrid molecules, from two or more different classes of biologically active compounds of natural and/or synthetic origin has attracted the attention of synthetic chemists in the past few years,

owing to the enhanced possibility of discovering new biologically active therapeutic agents[13].Tetrazole and its derivatives have attracted much attention because of their unique structure and applications as antihypertensive, anti- alergic, antibiotic and anticonvulsant agents.[14-21] Synthesis of tetrazole derivatives is obviously an important task in modern medicinal chemistry. Although anumber of synthetic methods are available, there still exists a demand for improved protocol which allows an effective transformation in the presence of a wide range of functional groups.the substituted tetrazole derivatives development of tetrazole chemistry has been largely associated with wide scale of applications of these classes of compounds in medicine, biochemistry, agriculture [14-25]; and also a large number of medicinally important tetrazole heterocyclic incorporated drugs approved by the FDA.13-14 The tetrazole functionality plays an important role in medicinal chemistry, primarily due to its ability to serve as bioequivalent of the carboxylic acid group.[17-27] Heterocyclic derivative is the first approved treatment for the partial agonist of dopamine D2 receptors; and also heterocyclic derivatives are widely used as antibacterial agents in human and veterinary medicines.[30-31] Some of tetrazole containing compounds have been used both as anticancer and antimicrobial agents[16]. 1-Substituted tetrazole derivatives are used as antibiotics and optically active tetrazole containing antifungal preparations of azole type. [32-33] there is always a need for new and effective antifungal and antibacterial agents with broad spectrum antibacterial and antifungal activities.

The objective of the present study was to synthesize new substituted lactam and tetrazole derivatives and to evaluate their antibacterial and antifungal properties.

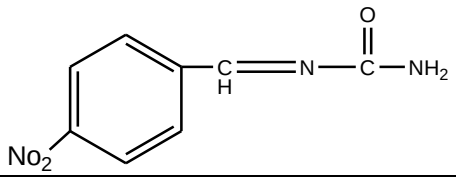
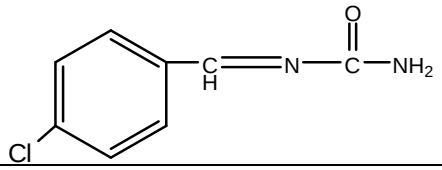
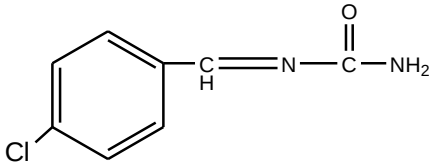
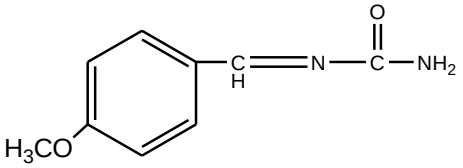
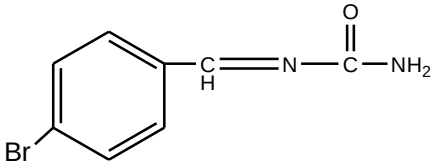
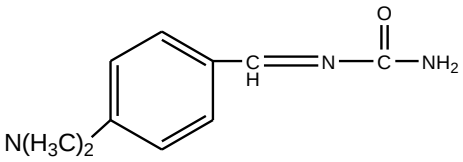
Experimental:

Melting points were recorded with Gallen Kamp MFB-600-Melting Point apparatus and were uncorrected .Infra-red spectra (FT-IR) were recorded on Shimadzu FT-IR-8300 spectrophotometer in Ibn Sina State Company (ISSC).Uv. /vis. spectra were recorded on Uv/vis Varian Uv-Cary-100. 1H-NMR spectra were recorded operating at 400 MHZ with tetramethylsilane as internal standard in CDCl3 and DMSO-d6 as a solvent, measurements were made at Chemistry Department ,in China .Thin layer Chromatography (TLC) was carried out by using alumina plates percolated with silica–gel, supplied by Merck. Spots were detected with iodine vapor.

1-Synthesis of 1-((N-Substituted benzylidine) urea [34, 35].

A mixture of equimolar amounts (0.09 mol) of aromatic aldehyde substitution with urea and using ethanol absolute as a solvent with (2) drops of glacial acetic acid was refluxed for 3 hours. The reaction mixture was then allowed to cool at room temperature, and the precipitate was filtered and dried, recrystallized from ethanol. Condensation of substituted aromatic aldehyde with urea has been described in Scheme (1) the following

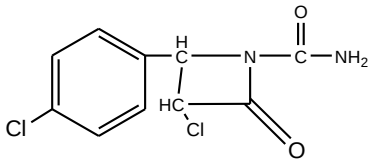
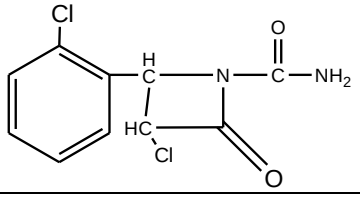
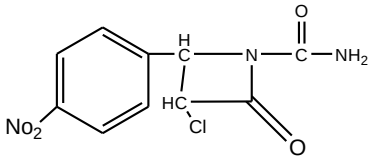
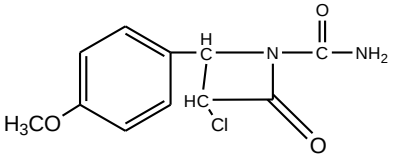
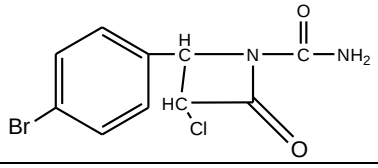
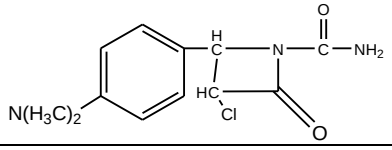
Table No. (1) Shows the physical properties of Schiff bases.

Comp .No	M.P.˚C	R	Structure product	Yield %	Color	Recry. Solvent
A1	145-147	p-NO_2		66%	Yellow	Ethanol
A2	127-129	o-Cl		72%	White	Ethanol
A3	120-122	p-Cl		71%	White	Ethanol
A4	97-99	p-OCH_3		60%	White	Dichloro methane
A5	111-113	P-Br		73%	Yellow	Ethanol
A6	87-89	p-$(CH_3)_2N$		84%	Orange	Ethanol

2-Synthesis of [4-(N-substituted2-oxozete-1(2H) carboxamide (36)

A mixture of equimolar amounts (0.005 mol) of Schiff base with chloroacetyl chloride and triethylamine using Dmf as a solvent was refluxed for 4 hours. The mixture was then allowed to cool at room temperature, and the precipitate was filtered. After it is taken to the filtrate and the monument of ice Greiche Then dried precipitate formed and recrystallized in ethanol.

Table No. (2) Shows the physical properties of lactam

Comp. No.	M.P.˚C	R	Structure product	Yield %	Color	Recry. Solvent
A7	142-144	p-Cl		70%	White	Ethanol
A8	133-135	O-Cl		68%	White	Ethanol
A12	160-162	p-NO_2		62%	Yellow	Ethanol
A13	112-114	P-OCH_3		83%	Bile yellow	ethylacetate
A14	134-136	p-Br		80%	Yellow	Ethanol
A15	102-104	p-$N(CH_3)_2$		78%	Dark brown	Ethanol

3-Synthesis of 5-(N-Substituted phenyl)-4, 5dihydro-5-methyltetrazol-1-carboxamide [37, 38]

A mixture of equimolar amounts (0.05 mol) of Schiff base with sodium azide using Dmf as a solvent was heated in water bath at (50-60)C^0 for 10 hr. The mixture was then allowed to cool at room temperature, and the precipitate was filtered. Then dried precipitate formed and recrystallized in ethanol.

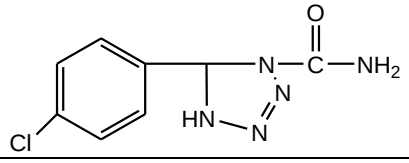
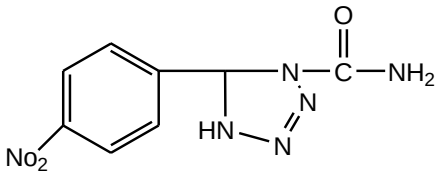
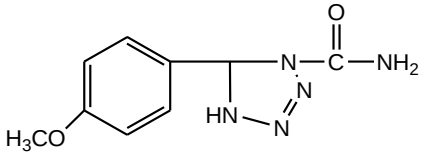
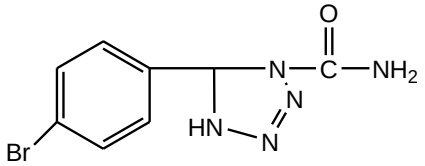
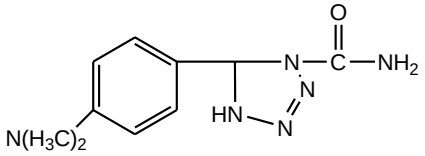
Com. No.	M.P.˚C	R	Structure product	Yield %	Color	Recry. Solvent
A16	144-146	p-Cl		74%	Orange	Ethanol
A17	169-171	p-No2		68%	Red	Ethanol
A18	120-122	O-CH3		62%	Bile yellow	Ethanol
A19	125-127	p-Br		71%	Yellow	Ethanol
A20	107-109	P-$N(CH_3)_2$		69%	Brown	Ethanol

Table No. (3) Shows the physical properties of tetrazole.

Preparation of acid chloride [39]

A mixture of equimolar amounts (0.05 mol) of thionyl chloride with substitution benzoic acid using Dmf as a solvent was refluxed for 3hr**.** The mixture was then allowed to cool at room temperature, and the precipitate was filtered. Then dried precipitate formed and recrystallized in ethanol.

Preparation of amide. [40]

A mixture of (0.005mol) of urea with (0.01mol) of acid chloride ratio (1:2) using Dmf as a solvent was refluxed for (4) hours. The mixture was then allowed to cool at room refluxed for (4) hours the mixture was then

allowed to cool at room temperature, and the precipitate was filtered. Then dried precipitate formed and recrystallized in ethanol

4-Synthesis of 1,2-bis(N-Substituted -5-phenyl -4,5-dihydrotetrazole-1-yl)ethanone . And Synthesis of 1,2-bis(N-Substituted -5-phenyl-4,5-dihydroazetidine-1-yl) ethanone(41)

A mixture of (0.005mol) of amide with (0.01mol) of chloroacetyl chloride and triethylamine using Dmf as a solvent was refluxed for (4) hours. Then the mixture was allowed to cool at room temperature, and the precipitate was filtered after it is taken to the filtrate and the monument of ice greiche. Then dried precipitate formed and recrystallized in ethanol .The condensation of substituted amide has been described. (Scheme 2)

Table No.(4) shows the physical properties of bis lactam .

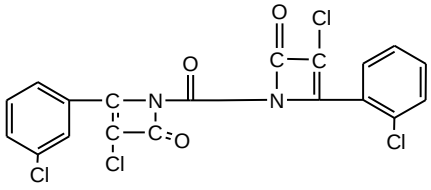
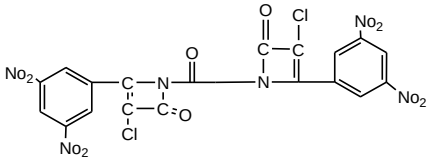
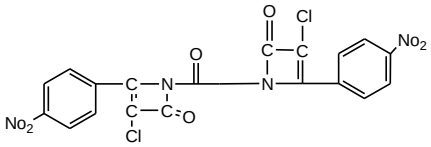
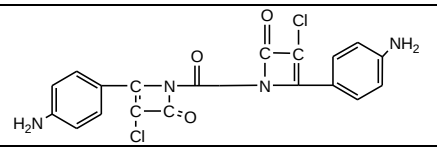
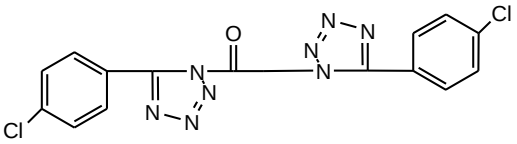
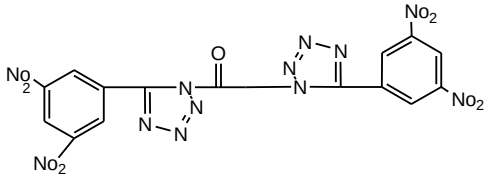
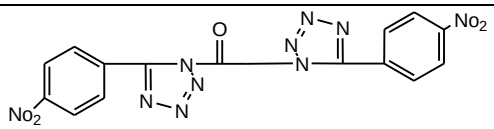
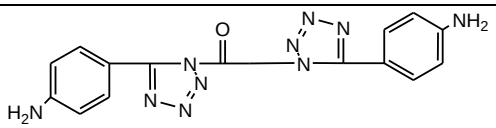
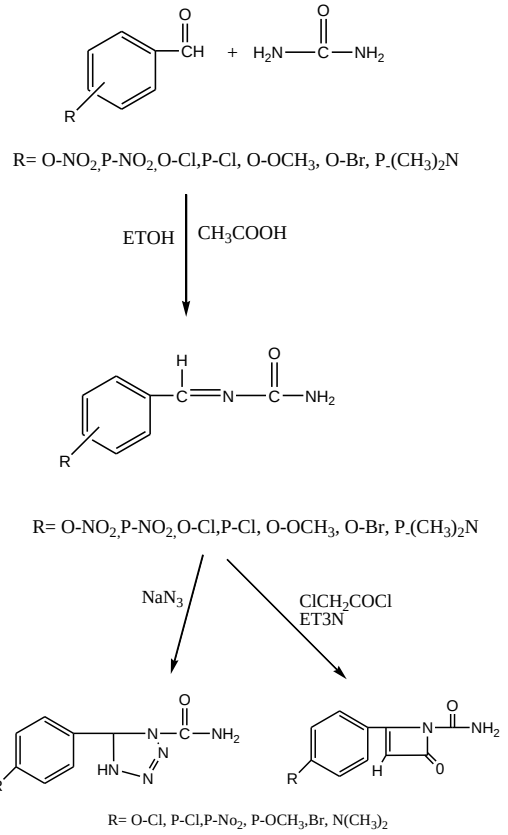
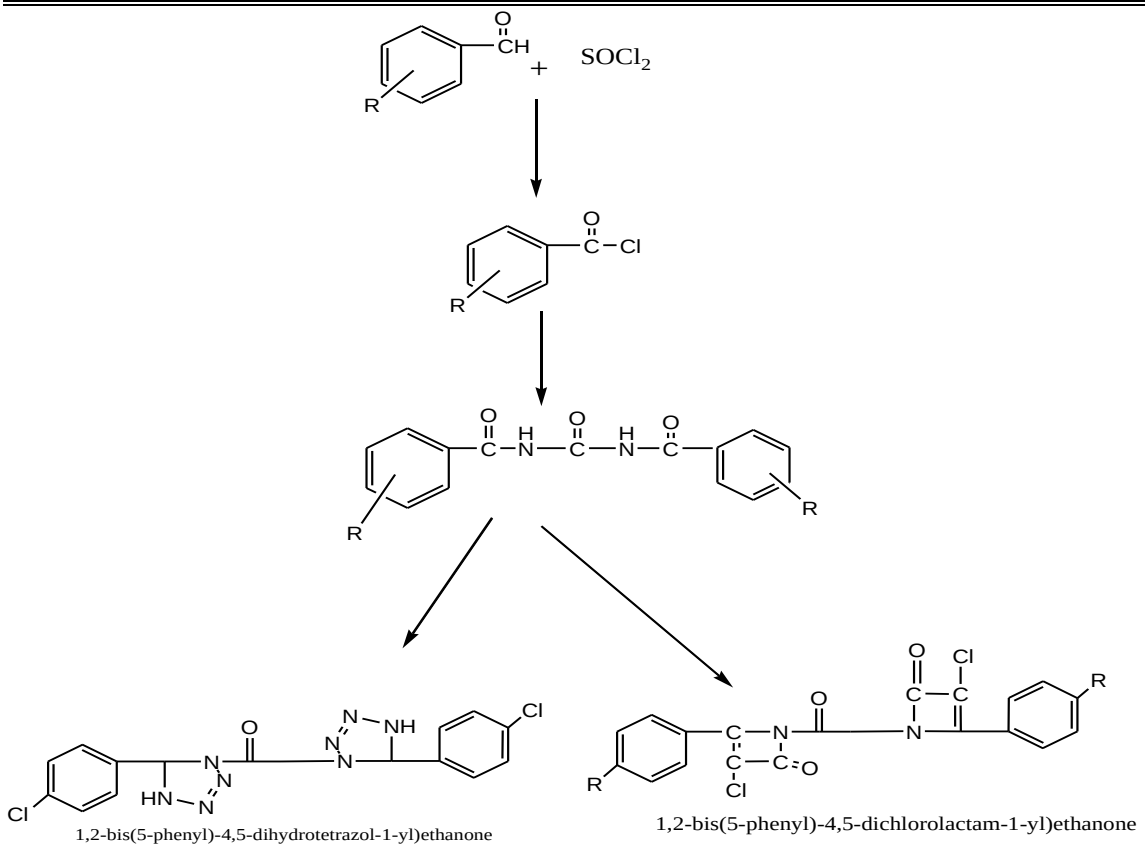
Comp. No.	M.P.˚C	R	Structure product	Yield %	Color	Recry.Solvent
A33	192-195	P-Cl		69%	White	Ethanol
A34	198-201	m,m-NO2		79%	Yellow	Ethanol
A35	196-198	P-NO2		71%	Yellow	Ethanol
A36	197-199	P-NH2		80%	Brown	Ethanol

Table No. (5) Shows the physical properties of tetrazole.

Comp No.	M.P.˚C	R	Structure product	Yield %	Color	Recry. Solvent
A37	**189-191**	**P-Cl**		**68%**	**Dark yellow**	**Ethanol**
A38	**190-192**	**m,m-NO2**		**72%**	**Red**	**Ethanol**
A39	**175-177**	**P-NO2**		**70%**	**orange**	**Ethanol**
A40	**174-176**	**P-NH2**		**73%**	**Bile yellow**	**Ethanol**



Scheme -1-



Scheme -2-

Result and Discussion:

1- Synthesis of 1-(N-Substituted benzylidine) urea

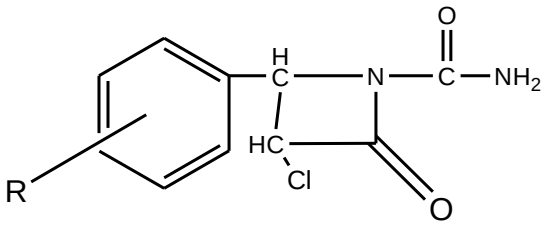
The FT-IR spectrum of compound [A1-A_6], Fig. (7) exhibited significant two bands in the range (3444-3352$cm^{-1)}$ which could be attributed to asymmetric and symmetric stretching vibrations of NH_2group. Besides this, band at about range (1604-1579 cm^{-1}) due to (C=N) stretching is also observed carbonyl group at range (1654-1681cm^{-1}) a. The Uv/vis. Spectrum of compound [A_6] Fig. (9) Showed the absorption bands at (276 nm), (262) due to (n → π*) and (π-π*) transitions. All. ^{1}H-NMR spectrum of compound [A_6], Fig. (31) Shows the following characteristic chemical shifts (DMSO-d_6, ppm).

The five aromatic protons appear at: (δ 6.675-7.693) were due to aromatic protons. Amino protons (NH_2) absorbed at (δ 5.428) and the signal at (δ 10.1) attributed to (C-H) proton. The signal at (δ3.037) due to (C-NMe_2) proton. Furthermore, the small peak at (δ 2.5) was due to DMSO. The spectral data for other compounds are listed in table (6)

Table (6): FT-IR spectral data of compounds (A_1-A_6).

Comp.No.	ν(C-H) al	ν(C-H)$_{Ar}$	ν(C=O)	ν(C=N)	.ν(C-NH_2)	Others
A_1	2974	3060	1657	1600	3439-3309	ν(C- No_2) 1558
A_2	2974	3066	1654	1579	3433-3313	Ortho ν(C-Cl) 752
A3	2954	3070	1678	1651	3390-3217	ν(C-Cl) 729
A4	2970	3004	1681	1600	3448-3348	ν(C-OCH_3) 1026
A5	2974	3032	1685	1604	3433-3313	ν(C-Br) 590
A6	2920	2993	1662	1593	3444-3352	ν[C-N(CH3)2] 3201

Synthesis of 4-(N-Substituted phenyl)-2-oxozete-1(2H)-carboxamide .



4-(N-Substituted phenyl)-2-oxozete-1(2H)-carboxamide

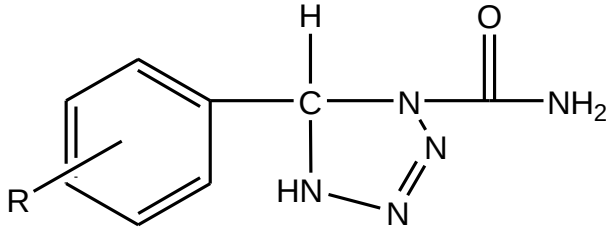
The FT-IR spectrum of compound [A7-A13], shows the appearance of band at range (1699-1716 cm^{-1}) due to (C=O) of lactams ring and disappearance of the absorption band (C=N)at range (1597-1604cm^{-1}).

The Uv/vis. Spectrum of compound [A_{10}] Fig. (28) Showed the absorption bands at (283-264 nm), due to (n → π*)and (π → π*) transitions. . ^{1}H-NMR spectrum of compound [A_{12}], Fig. (32), shows the following characteristic chemical shifts (DMSO-d_6) ppm. Signal of (C-H) and (NH_2) proton absorbed at (δ 9.993) and (δ 5.502), respectively. Protons of *P*-substituted, aromatic ring appeared at the range δ (7.321–7.943) as a multiple peaks. All the spectral data for other compounds are listed in table (7)

Table (7): FT-IR spectral data of compounds (A_7-A_{13})

Comp. No.	υ(C-H) aromatic cm^{-1}	υ(C-H) aliphatic cm^{-1}	υ(C=O) exocyclic cm^{-1}	υ(C=O) endocyclic cm^{-1}	υ(C-NH_2) cm^{-1}	Others cm^{-1}
A7	3070	2954	1666	1701	3390-3217	υ(C-Cl) cm-1 752
A8	3035	2985	1654	1708	3394-3356	υ(C-Cl) cm-1 729
A9	3001	2953	-	1699	-	$\upsilon(C\text{-}No_2)_{str.}$ 3211
A10	3082	2951	1604	1708	3379-3313	$\upsilon(C\text{-}No_2)_{str.}$ 1527
A11	3023	2970	1681	1716	3433-3400	$\upsilon(C\text{-}OCH_3)_{bend}$ cm-1 1026
A12	3093	2937	1666	1693	3394-3217	υ(C-Br) cm-1 763
A13	2993	2920	1662	1698	3486-3223	υ [C-$N(CH_3)_2$] 3201 cm-1

Synthesis and characterization of 5-(N-Substituted phenyl)-4, 5dihydro-5-methyltetrazol-1-carboxamide.



R= O-Cl, P-Cl,P-No_2, P-OCH_3,Br, $N(CH_3)_2$

5-(N-substituted phenyl)-4, 5dihydro-5-methyltetrazol-1-carboxamide

The FT-IR absorption bonds of [A_{14}- A_{18}], was utilized to characterize the specific structure of the synthesized compounds. The disappearance of band at (1597-1604 cm^{-1}), attributed to (C=N) (imine

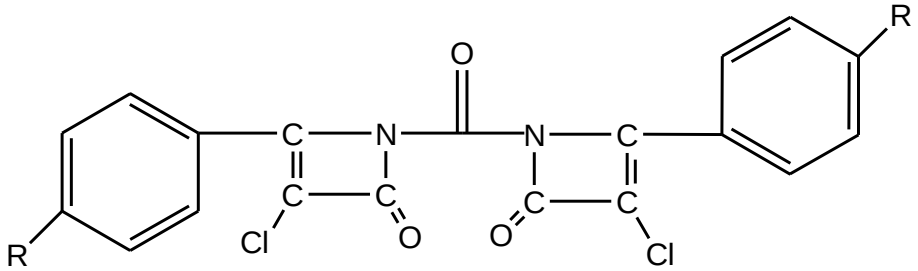
group) stretching frequency is good evidence for the success of this step of reaction. It also, the IR spectra for these compounds were devoid of a strong band at (2120–2160) cm^{-1} attributed stretching frequency of a zide group. A band at range (1593-1533 cm^{-1}) was due to the cyclic (N=N) stretching of tetrazole ring [98]. And a sharp band at range (1371-1388cm^{-1}) due to the cyclic (C-N).). ^{1}H-NMR spectrum of compound [A_{14}-A_{17}], in table (8), shows the following characteristic chemical shifts the aromatic ring protons appear at (δ 7.320-8.554 ppm.) (N-H) proton (tautomer proton) absorbed at (δ 6.809 -6.830). Signal at (δ 9.994) due to the (C-H) proton. And signal at (δ5.398) due to the (C-NH) proton of NH_2

Table (8): FT-IR spectral data of compounds (A_{14}-A_{19})

Comp. No.	υ(C-H) aliphatic cm^{-1}	υ(C-H) aromatic cm^{-1}	υ(N=N) cm^{-1}	υ(C-N) cm^{-1}	Others Bands cm^{-1}
A14	2981	3024	1593	1377	υ(C-Cl) 729
A15	2982	3093	1537	1371	υ(C-No_2)1500
A16	2905	2942	1573	1388	4-(O-me) 1311 υ(N-H) 1442
A17	3023	2974	1533	1373	υ(C-Br) 590
A18	2993	2920	1546	1373	4-(N-me)3201

Synthesis and characterization of 1,2-bis[5-(4-Chloro,2-Chloro,2-Nitro,4-Nitro,4-methoxy,2-bromo,or dimethylamin phenyl)-4,5-dihydroazetidine-1-yl]ethanone

These compounds [A_{19}-A_{22}] were synthesized from the reaction of amide with chloroacetyl chloride and triethylamine using dimethylformamide.



R=P-Cl, m,m-NO_2, P-NO_2, P-NH_2,

The FT-IR spectrum of compound [A_{20}] figure (13) as example shows appearance the band at(1732cm^{-1}) belong to carbonyl group which is presence lactam cyclic. Besides the disappearance band at (3425cm-1) stretching frequency belong to (C-NH)is good evidence for the success of this step of reaction.

Also show in compound [A_{21}] appearance the band (C=O) at (1716cm-1) belong to endocyclic carbonyl of lactam and in compound

[A36] figure(15) appearance the band (C=O) at(1693cm-1) and disappearance the the band(C-NH) at(3417cm-1) . ^{1}H-NMR spectrum of compound [A_{20}], Fig. (34), shows the following characteristic chemical shifts ($CDCl_3$-d_6, ppm). The aromatic protons appear at (7.473-7.960).

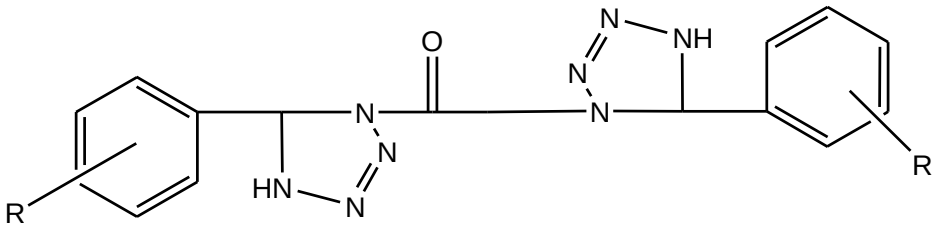
Uv/vis. Spectrum of compound [A_{34}] Fig. (25) Showed the absorption bands at (293 nm), due to ($n \rightarrow \pi^*$) transitions the characteristic data are reported in Table (3.1.8).

Table (9): FT-IR spectral data of compounds (A_{20}-A_{23})

Comp. No.	υ(C-H) aromatic cm^{-1}	υ (C=C) cm^{-1}	$υ(C=O)_{endo}$ cm^{-1}	$υ(C=O)_{exo}$ cm^{-1}	Other band
A19	2935	1519	1712	1658	(C-Cl) 790
A20	3001	1635	1732	1651	(C-No_2)1546
A21	3097	1534	1716	1658	(C-No_2)1519
A22	3062	1543	1693	1604	(C-NH_2)3425-3113

5- Synthesis and characterization of 1,2-bis[5-(4-Chloro,2-Chloro,2-Nitro,4-Nitro,4-methoxy,2-bromo,or dimethylamin phenyl)-4,5-dihydrotetrazole-1-yl]ethanone.

These compounds [A_{24}-A_{27}] were synthesized from the reaction of amide with sodium azide and using dimethylformamide.



1,2-bis(5-(4,2-substituted phenyl)-4,5-dihydrotetrazol-1-yl)ethanone

The FT-IR spectrum of compound [A37] fig (20)as example shows appearance the band at(1535cm-1) belong to(N=N) and appearance band at(3324cm-1) stretching frequency belong to (C-NH) and band at (1369cm-1) belong to band (C-N) .The characteristic data are reported in Table (9).

Table (10): FT-IR spectral data of compounds (A_{23}-A_{26})

Comp. No.	υ(C-H) aromatic cm^{-1}	υ(C-H) alephatic cm^{-1}	υ (N=N) cm^{-1}	υ(C-N) cm^{-1}	υ(C-NH) cm^{-1}	Other band cm^{-1}
A23	3051	2904	1535	1361	3163	(C-Cl) 721
A24	3090	2923	1592	1384	3402	(C-No_2)1565
A25	3079	2945	1580	1360	3211	(C-No_2)1553
A26	3070	2870	1577	1381	3213	(C-NH_2)3421-3340

References:

1. Broccolo, F.; Cainelli, G.; Caltabiano, G.; Cocuzza, C. E. A.; Fortuna, C. G.; Galletti, P; Giacomini, D.; Musumarra, G.; Musumeci, R.; Quintavalla, A. J. Med. Chem. 2006, 49, 2804e2811 and references cited therein.
2. Halve, A. K.; Bhadauria, D.; Dubey, R. Bioorg. Med. Chem. Lett. 2007, 17, 341e345 and references cited therein.
3. Rosenblum, S. B.; Huynh, T.; Afonso, A.; Davis, H. R., Jr.; Yumibe, N.; Clader, J.W.; Burnett, D. A. J. Med. Chem. 1998, 41, 973-980.
4. Borthwick, A. D.; Weingarte, G.; Haley, T. M.; Tomaszewski, M.; Wang, W.; Hu, Z.; Bedard, J.; Jin, H.; Yuen, L.; Mansour, T. S. Bioorg. Med. Chem. Lett. 1998, 8,36 5-370.
5. Han, W. T.; Trehan, A. K.; Wright, J. J. K.; Federici, M. E.; Seiler, S. M.; Meanwell, N. A. Bioorg. Med. Chem. 1995, 3, 1123-1143.
6. Goel, R. K.; Mahajan, M. P.; Kulkarni, S. K. J. Pharm. Pharm. Sci. 2004, 7, 80-83.
7. Veinberg, G.; Shestakova, I.; Verma, M.; Kenepe, I.; Lukevics, E. Bioorg. Med. Chem. Lett. 2004, 14, 147-150.
8. Sperka, T.; Pitlik, J.; Bagossi, P.; Tozser, J. Bioorg. Med. Chem. Lett. 2005, 15, 3086-3090.
9. Saturnino, C.; Fusco, B.; Saturnino, P.; De Martino, G.; Rocco, F.; Lanceolat, J. C. Biol. Pharm. Bull. 2000, 23, 654-656.
10. Jarrahpour, A.; Ebrahimi, E.; De Clercq, E.; Sinou, V.; Latour, C.; DjouhriBouktab, L.; Brunel, J. M. Tetrahedron 2011, 67, 8699-8704.
11. (a) Konaklieva, M. I. Curr. Med. Chem. Anti-Infective Agents 2002, 1, 215e236; (b) Clemente, A.; Domingos, A.; Grancho, A. P.; Iley, J.; Moreira, R.; Neres, J.; Palma, N.; Santana, A. B.; Valente, E. Bioorg. Med. Chem. Lett. 2001, 11, 1065-1068.

12.(a) Fisher, J. F.; Meroueh, S. O.; Mobashery, S. Chem. Rev. 2005, 105, 395e424; (b) Ritter, T. K.; Eong, C.-H. Angew. Chem., Int. Ed. 2001, 40, 3508-3533.
13.Mehta, G.; Singh, V. Chem. Soc. Rev. 2002, 31, 324-334.
14.Myznikov, L. V.; Hrabalek, A.; Koldobskii, G. I. Drugs in tetrazole series. Chem. Het.Compounds.2007, 43, 1-9.
15.Schocken, M. J.; Creekmore, R.W.; Theodoridis, G.; Nystrom, G. J.; Robinson, R. A. Microbialtransformation of the tetrazolinone herbicide F5231. Appl. Environ. Micobiol. 1989, 55, 1220-1222.
16.Butter, R. N. Comprehensive heterocyclic chemistry, Katritzky, A. R.; Rees, C. W. Vol. 5: Part 4A, 1984, 791-838.
17.Mavromoustakos, T.; Kolocouris, A.; Zervou, M.; Roumelioti, P.; Matsoukas, J.;Weisemann, R. An effort to understand the molecular basis of hypertension through the study of conformational analysis of losartan and sarmesin using a combination of nuclear magnetic resonance spectroscopy and theoretical calculations. J. Med. Chem. 1999, 42, 1714-1722.
18.Mekni, N.; .; Bakloiti, A.. Synthesis of new 1-substituted 4-perfluoroalkyl tetrazol-5-ones. J. Fluorine Chem. 2008, 129, 1073-1075.
19.Toney, J. H.; Fitzgerald, P. M.D.; Grover-Sharma, N.; Olson, S. H.; May, W. J.;Sundelof, J. G.; Venderwall, D. E.; Cleary, K. A.; Grant, S. K.; Wu, J. K.; Kozarich, J. W.; Pompliano, D. L.; Hammond, G. G. Antibiotic sensitization using biphenyl tetrazoles as potent inhibitors of bacteroidesfragilismetallo-b-lactamase. Chem. Biol. 1998, 5, 185-196.
20.Tamura, Y.; Watanabe, F.; Nakatani, T.; Yasui, K.; Fuji, M.; Komurasaki, T.; Tsuzuki, H.; Maekawa, R.; Yoshioka, T.; Kawada, K.; Sugita, K.; Ohtani, M. Highly selective and orally active inhibitors type IV collagenase (MMP-9 and MMP-2): N-sulfonylamino acid derivatives. J. Med. Chem. 1998, 41, 640-649.
21.Lim, S. J.; Sunohara, Y.; Matsumoto, H. Action of fentrazamide on protein metabolism and cell divisionin plants. J. Pestic. Sci. 2007, 32, 249-254.
22.Butler, R. N. Recent advances in tetrazole chemistry. Advances in Heterocyclic Chemistry. 1977, 21, 323-435.
23.Singh, H.; Chawla, A. S.; Kapoor, V. K.; Paul, D.; Malhotra, R. K. Medicinal chemistry of tetrazoles. Progr. Med. Chem. 1980, 17, 151-183.

24. Jun, H. W. Pharmacokinetics studies of pentylenetetrazole in dogs. J. Pharma. Sci., 1976, 65,1038-1041.
25. ModarresiAlam, A. R.; Nasrollahzadeh, M. Synthesis of s-arylamino-1H(2H)-tetrazoles and 5-amino-1-aryl-1H-tetrazoles from secondary arylcyanamides in glacial acetic acid: A Simple and EfficientMethod. Turk J. Chem. 2009, 33, 267-280.
26. Katritzky, A. R.; Jain, R.; Petrukhin, R.; Denisenko, S.; Schelenz, T. QSAR correlations of the algistatic activity of 5-amino-1-aryl-1H-tetrazoles. SAR QSAR Environ. Res., 2001, 12, 259-266.
27. Hiriyanna, S. G.; Basavaiah, K.; Dhayanithi, V.; Bindu, A.; Sudhaker, P.; Pati, H. N.Simultaneous Determination Of Several Angiotensin-II-Receptor Antagonists By Liquid Chromatography. Anal.Chem. Indian J. 2008, 7, 568-572.
28. Burger, A. Isosterism and bioisosterism in drug design. Prog. Drug Res. 1991, 37, 287-371.
29. Lawler, C. P.; Prioleau, C.; Lewis, M.M.; Mak, C.; Jiang, D.; Schetz, J. A. Interactions of the novel antipsychotic aripiprazole (OPC-14597) with dopamine and serotonin receptor subtypes. Neuropsychopharmacol., 1999, 20, 612-627.
30. Burris, K. D.; Molski, T. F.; Xu, C.; Ryan, E.; Tottori, K.; Kikuchi, T.; Yocca, F. D.; Molinoff, P. B. Aripiprazole, a novel antipsychotic, is a high-affinity partial agonist at human dopamine D2 receptor. J.Pharmacol. Exp.Ther. 2002, 302, 381-389.56 substituted tetrazole derivatives
31. Ichikawa, T.; Kitazaki, T.; Matsushita, Y.; Hosono, H.; Yamada, M.; Mizuno, M.; ItohK.Optically active antifungal azoles. XI. An alternative synthetic route for 1. Chem. Pharm. Bull. 2000, 48, 1947-1953.
32. Ichikawa, T.; Kitazaki, T.; Matsushita, Y.; Yamada, M.; Hayashi, R.; Yamaguchi, M.; Kiyota, Y.; Okonogi, K.; Itoh, K. Optically active antifungal azoles. XII. Synthesis and antifungal activity of the water-soluble prodrugs of 1-[(1R,2R)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol- 1-yl)propyl]-3-[4-(1H-1-tetrazolyl)phenyl]-2-imidazolidinone.Chem. Pharm. Bull. 2001, 49, 1102-1109.
33. D.R.Laurance, P.N. Bennett, M.J. Brown, Clinical Pharmacology, 8th ed., P.237 (1997).
34. M. J. Mahmoud, Z. M. Al-Rnbaiy, R. K. Al-Kubaisy, M. M. Al-Najafi and H. M. Al-Jumaily, IBN-AL-HAITHAM. J. for pure and Appl. Sci., vol. 17(1) 103-110 (2004).

35.H.I.El-Subbagh, M.Y.Yousif, A.A.El-Emam and M.M.El-Kardawy,Arch Pharm. Rsi. 12. 344 (1989).
36. Staudinger, H. Liebigs Ann. Chem. 1907, 356, 51e123
37.S.B. Mandal , V.S.G iri, M.S.Sabeena ,and S.C.Pakrashi Indian Institute of chemical Biology, Jadaupur, calcutt-700 023,India Received March1 (1988) .
38.European Journal of Medicinal ChemistryVolume 45, Issue 7, July 2010, Pages 2739–2747.
39.NanyanFw, Thomas.T Tidwell (Preparation of β-lactams by [2+2] cycloaddition of ketenes and imines) Tetrahedron,vol.64,155 ue 46,10 November (2008),pag. 10465-10496 .
40. K. Venkataraman, and D. R. Wagle (1979). "Cyanuricchloride : a useful reagent for converting carboxylic acids into chlorides, esters, amides and peptides". Tet. Lett. 20 (32): 3037–3040
41.William Reusch. "Carboxylic Acid Derivatives". VirtualText of Organic Chemistry. Michigan State University
42.Xiao-Lan Tong , Duo-Zhi Wang , Tong-Liang Hu ,Wei-Chao Song
43. (Zinc and Cadmium Coordination Polymers with Bis(tetrazole) Ligands Bearing Flexible Spacers: Synthesis, Crystal Structures, and Properties) March 12,(2009), 9 (5), pp 2280–2286

الخلاصة :

بعض المشتقات الجديدة من بيتالاكتام والتترازول تم تحضيرها من قواعد شف والتي حضرت من تفاعل مختلف الالديهايدات الاروماتية المعوضة مع اليوريا والتي يتبعها تفاعل غلق الحلقة مع كلورو اسيتايل كلورايد مع ثلاثي اثيل امين ليعطينا مركب البيتالاكتام بينما تفاعل قواعد شف مع ازيد الصوديوم ليعطينا مركب التترازول.كذلك تم تحضير ثنائي بيتا لاكتام وثنائي تترازول من تفاعل الاحماض الاروماتية مع كلوريد الثايونيل بعدها يتم تكثيف كلوريد الحامض الاروماتي مع اليوريا لتعطينا الامايد بعدها يتم تفاعل الامايد مع ازيد الصوديوم ليعطينا ثنائي تترازول بينما تفاعل الامايد مع كلورو اسيتايل كلورايد ليعطينا ثنائي بيتالاكتام.