Synthesis And Characterization Of New Imidazole derivatives

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Abstract

Synthesis new compounds of 1,3-oxazole 5(H) one by cyclization of amino acid (Glycine) with acetic anhydride and then react the compound (1) with different substituted aldehyde to give the oxazole derivatives compound (2 a-c) .Imidazole was synthesized by reaction of compounds (2 a-c] with hydrazine hydrate (95%) to give compounds (3a-c). imidazole derivatives reaction with chloro ethyl acetate to give ester derivatives (4 a-c),after that added thiosemicarbazid to the ester derivatives to formed compounds (5a-c) the last react with H_2SO_4 and NH_3 to give thiadiazole derivatives (6 a-c). The synthesized compounds were elucidated using some spectral data: FTIR,^{1}HNMR.

Introduction

1,3-oxazole moiety has found as a subunit of many biological active natural product[1] .Clinical trials have shown that many of them have are mark ably broad spectrum[2].anti tubercular[3],anti hypertensive [4] andanti inflammatory actives[5] .The imidazole are an important class of heterocyclic and many naturally occurring imidazoles are known to possess biological activity[6] , anti fungal, anti bacterial [7] , anti thelminitic [8] , anti-neoplastic[9] , anti-pyretic[10] and anti-spasmolytic activities[11] . 1,3,4-thiadaizole fused heterocyclic ring compound have many biological activities as antimicrobial activity[12], anti-inflammatory [13] , anti fungal and antibiotic activities [14].

Experimental

Melting point were determined in open capillary tubes on a Gallen Kamp melting point apparatus and are uncorrected .The IR Spectra were recorded by KBr discs were recorded with Shimadzu-2N,FTIR-8400 S. HNMR Spectra were recorded on a Varian on a Varian-Mercury 300MHZ Spectrometer.

Synthesis of 1,3- oxazole 5 (4H)- one(1).

To a solution of Glycine (0.06 mole, 5g) with 15 ml of acetic anhydride was reflux 3 hrs. And the excess of acetic anhydride was evaporated. After evaporation, the product was collected, table 1.

Synthesis of 4(arylidine)1,3-oxazole 5(4H) one (2a-c).

To a stirring solution of compound [1] (0.005 mole,0.42 g) with different substituted aldehyde (0.005mole)and anhydrous sodium acetate (0.005mole,0.45g)in glacial acetic acid and acetic anhydride (30+10) ml was reflux 3 hrs. After that proud into ice water, recrystilization by benzene, table 1.

Synthesis of 3-amino-5-(arylidene)-3,5-dihydro-4H-imidazole -4-one(3a-c) .

To a solution of compound [2a-c] (0.0lmole) in 50 ml of absolute ethanol and hydrazine hydrate (0.03 mole), was added and the reaction mixture was refluxed for 6hrs. On cooling, the precipitate formed was filtered off, recrystilization by ethanol, table 1.

Synthesis of Ethyl 2-(4-aryl benzylidene)-5-oxo-4,5-dihydro-1-H-imidazol-1-yl amino) acetate (4a-c).

Ethyl chloro acetate (0.01 mol) was add dropwise to stirred solution of compound (3a-c) (0.01 mol), KOH (0.01mol) in 20 ml absolute ethanol. The reaction was refluxed for 7 hours, after that filtered the product and recrystilization from chloroform, table 1.

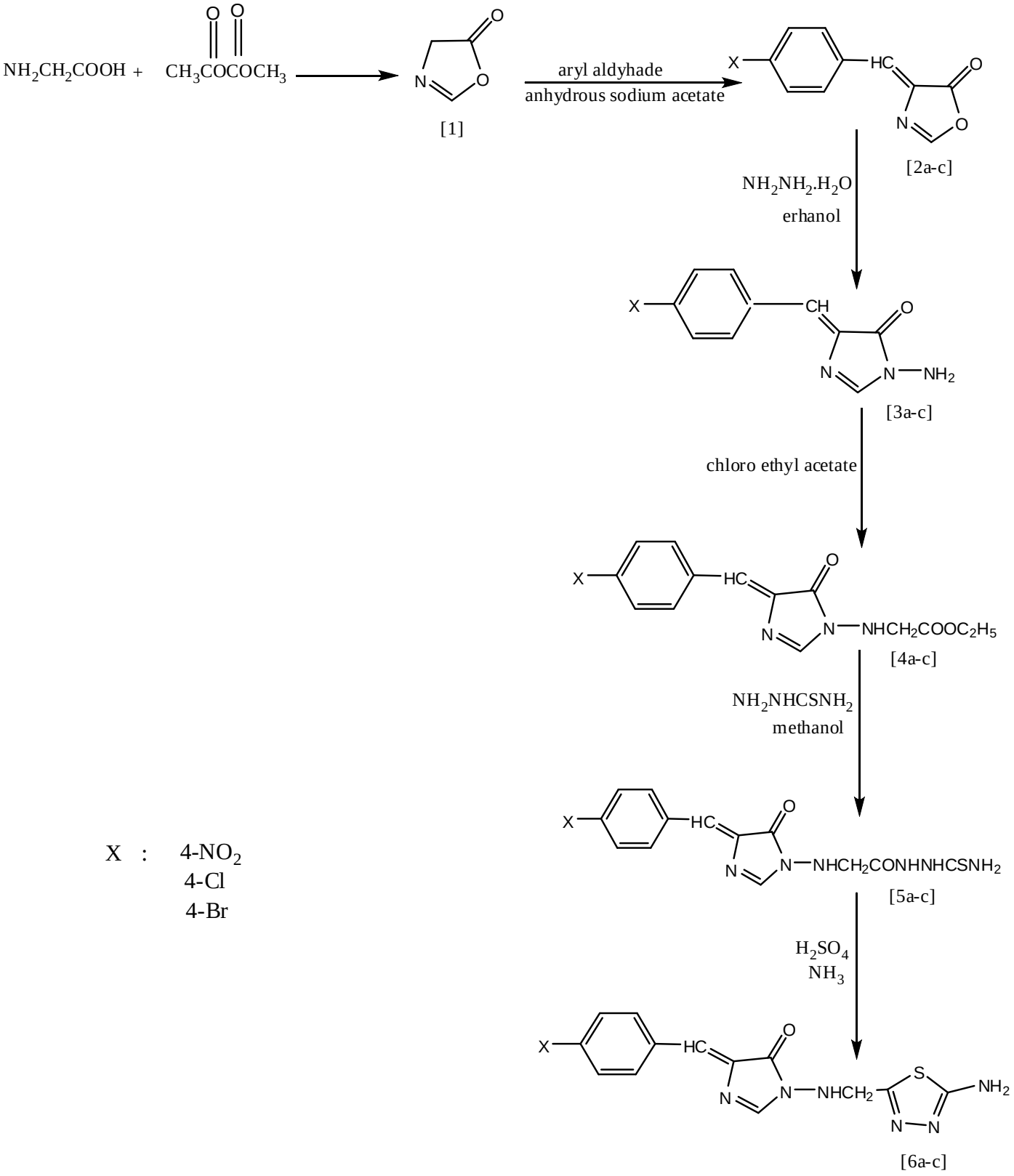
Synthesis of 2-(4-(aryl benzylidene)-5-oxo-4,5 dihydro-1-H-imidazol-1-yl amino)acetyl)hydrazine carbothio amide(5a-c).

The mixture of compound (4a-c) (0.025 mol) and thiosemicarbazide (0.025 mol) in methanol 60 ml was refluxed for 10 hours. The solvent was removed under reduced pressure and the product was poured over ice cold water, filtered and recrystallised from methanol to give compound (5a-c) , table 1.

Synthesis of 1-((5- amino -1,3,4 - thiadiazol-2-yl) methy lamino)- 4- (aryl benzylidene) 1-H-imidazol-5-(4H)one (6a-c).

A mixture of compound (5a-c) (0.01 mol) and conc. H_2SO_4 (25 ml) was kept over night at room temperature. The reaction mixture was then poured into ice cold water and neutralized with liquid ammonia and then filtered, recrystallised by methanol, table 1.

Scheme I


NH2CH2COOH +
CH3COCOCH3
[1]
aryl aldyhade
anhydrous sodium acetate
[2a-c]
NH2NH2.H2O
erhanol
[3a-c]
chloro ethyl acetate
[4a-c]
NH2NHCSNH2
methanol
[5a-c]
H2SO4
NH3
[6a-c]
X : 4-NO2
4-Cl
4-Br

Results and Discussion

The new derivatives of oxazole, imidazole, ester and thiazdiazole were prepared following the reaction sequences outlined in scheme I.

Compound [1] 1, 3-oxazole was synthesized by treatment of Glycine with acetic anhydride .The reaction is followed by the appearance of (ν C=O) absorption band at (1703cm^{-1}) in their spectra 1,3-oxazole 5(4H) one, table 2.

compounds[2a-c] have been synthesized by the reaction of aryl aldehyde in presence of acetic acid and acetic anhydride led to the formation of 4(arylidine)1,3-oxazole 5(4H) one [2a-c] have been identified by IR spectrum which it show the appearance of characteristic absorption band near (1759-1766)cm^{-1}which belonged to the oxazole 5(4H)one carbonyl group oxazole, ν C=O, and at (3010-3095)cm^{-1}due to (aromatic ν CH); table 2. ^{1}HNMR (DMSO_d_6) ς (ppm) compound **2a:** 8.71 (s, 1H, C=C<u>H</u>) and at 6.2-7.8 which belonged to aromatic protons.

Treatment compounds [2a-c] with hydrazine hydrate offered good yield of the imidazole [3a-c]. The IR spectra of compounds [3a-c] displaced peaks at (1622-1647) cm^{-1}, (3201-3456) $cm^{-1}$for (imidazole, ν C=O) and ν NH_2 functions respectively, table 2. ^{1}HNMR (DMSO_ d_6) ς (ppm) compounds **3a:**8.4(s, 2H, NH2), 8.8 (s, 1H, C=C<u>H</u>) and at 6.7-8.1ppm which belonged to aromatic protons.

Compounds [3a-c] react with chloro ethyl acetate in absolute ethanol to form ester derivatives (4a-c) .The IR. Spectra presence appearance the band of carbonyl of ester at (1730-1741 cm^{-1}), NH stretching band at (3201-3362 cm^{-1}), table 2. ^{1}HNMR (DMSO_d_6)ς (ppm) compound **4a** : 1.2 (t,3H,$COOCH_2C\underline{H_3}$),4.0 (q, 2H,$COOC\underline{H_2}CH_3$),5.1 (d,2H,$NHC\underline{H_2}$) , 8.7 (s,1H,$N\underline{H}CH_2$) , 7.5-8.1 aromatic proton .

When the ester derivatives (4a-c) react with thiosemicarbazide in methanol to give the 2-(4-(aryl benzylidene)-5-oxo-4, 5 dihydro-1-H-imidazol-1-yl amino) acetyl) hydrazine carbothio amide (5a-c). The IR. Spectra presence appearance the band of carbonyl amide at (1647-1670 cm^{-1}) and disappearance the carbonyl of ester at (1730-1741 cm^{-1}), C=S band appearance at (1180-1193cm^{-1}), table 2. ^{1}HNMR (DMSO_ d_6) ς (ppm) compounds **5a** : 4.0 (d,2H,$NHC\underline{H_2}$) , 8.75 (m,4H,$N\underline{H}N\underline{H}CSN\underline{H_2}$) , 10.5 (s,1H, $N\underline{H}CH_2$) , 6.8-7.9 Aromatic proton .

Compounds (5a-c) react with H_2SO_4 and NH_3 to give thiadiazole derivatives compound (6a-c). The formation of these derivatives was indicated by the presence in their IR spectra of the appearance the C-S-C at (663-690 cm^{-1}), N-N at (1205-1292 cm^{-1}), table 2. ^{1}HNMR (DMSO_d_6) ς (ppm) compounds **6a** : 3.7 (d,2H,$NHC\underline{H_2}$) , 10.5 (s,1H,$N\underline{H}CH_2$) , 8.5 (s,1H,$N\underline{H_2}$) , 6.8-7.9 Aromatic proton.

Table [1]: Physical properties

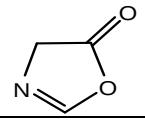
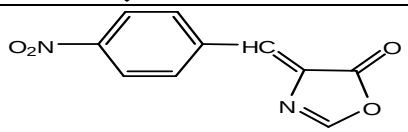
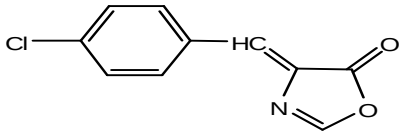
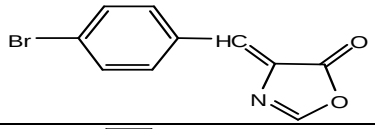
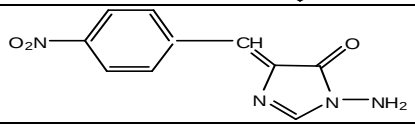
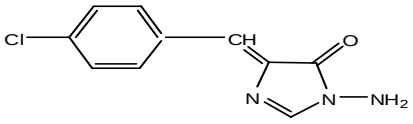
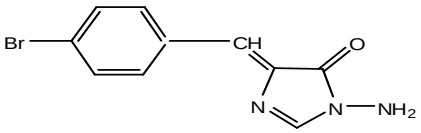
NO.	***Compound***	***Yield %***	***m.p C°***	***Recrystallization***
		80	190-192	Benzene
2a		70	120-122	Benzene
2b		65	99-101	Benzene
2c		65	140-142	Benzene
3a		65	200-202	Ethanol
3b		60	210-212	Ethanol
3c		60	240-242	Ethanol

Table [1]: Physical properties

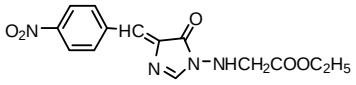
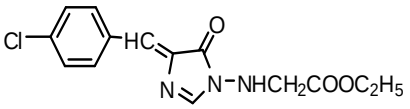
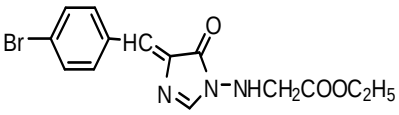
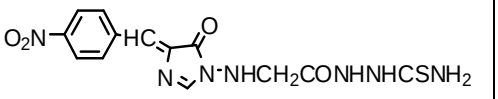
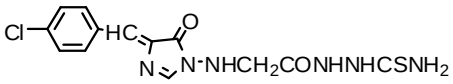
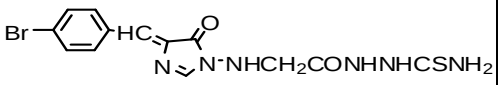
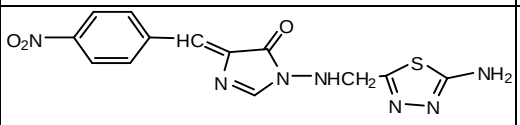
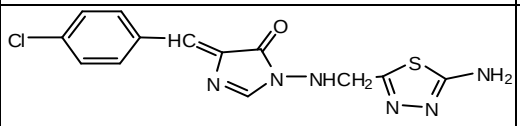
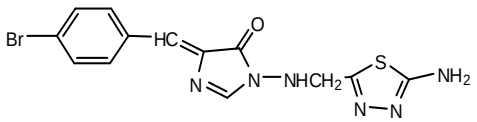
NO.	***Compound***	***Yield %***	***m.p C°***	***Recrystallization***
4a		83	108-110	Chloroform
4b		75	118-120	Chloroform
4c		66	140-142	Chloroform
5a		60	180-182	Methanol
5b		65	202-204	Methanol
5c		60	188-190	Methanol
6a		70	222-224	Methanol
6b		75	240-242	Methanol
6c		66	210-212	Methanol

Table [2] : Spectral data

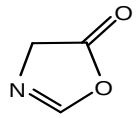
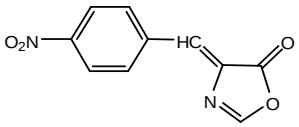
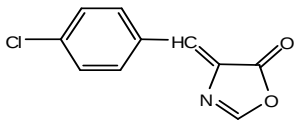
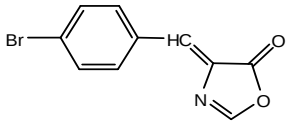
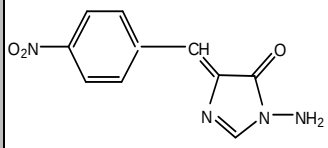
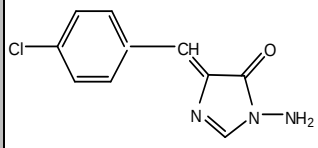
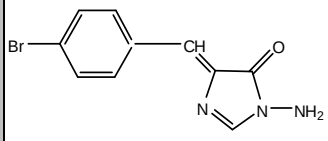
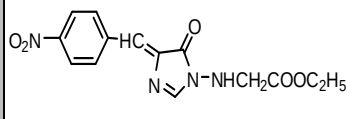
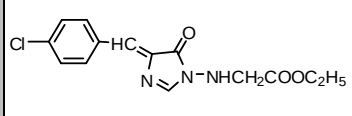
NO.	***Compound***	***IR. Cm^{-1}***						
		CH Ar.	***CH Alph.***	***C=O***	***NH_2***	***C=C***	***C=N***	***Others***
1		3049	2999	1703 oxazole	-----	1531	1593	C-O 1284
2a		3095	2904	1766 oxazole	-----	1570	1604	C-O 1269 , 877 para substitution
2b		3090	2933	1759 oxazole	------	1514	1643	C-O 1238, 877 para substitution
2c		3020	2874	1764 oxazole	-----	1568	1614	C-O 1207, 881 para substitution
3a		3005	2999	1641 imidazol	3420-3201	1527	1566	C-N 1485, 856 para substitution
3b		3022	2935	1637 imidazol	3330-3205	1527	1577	C-N 1483 , 856 para substitution
3c		3010	2914	1647 imidazol	3394-3230	1554	1589	C-N 1438, 840 para substitution
4a		3039	2993	1730 ester, 1674 imidazol	3360-3302	1521	1597	C-N 1481, 844 para substitution
4b		3039	2895	1735 ester , 1676 imidazol	3362-3304	1521	1597	C-N 1411, 844 para substitution

Table [2]: spectral data

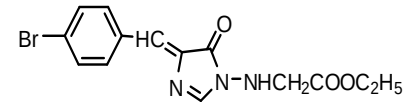
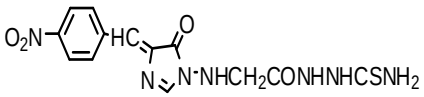
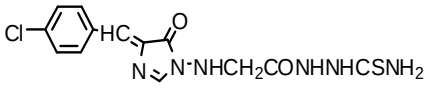
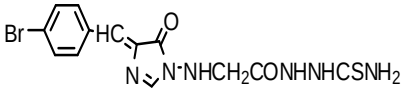
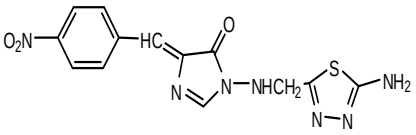
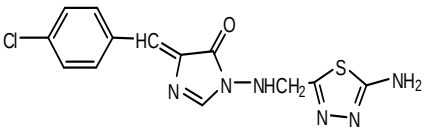
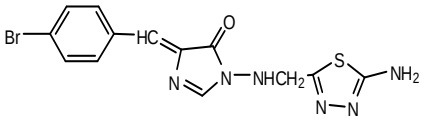
NO.	Compound	IR. Cm^{-1}						
		CH Ar.	CH Alph.	C=O	NH_2	C=C	C=N	Others
4c		3043	2831	1741 ester 1654 imidazol	3252-3201	1523	1585	C-N 1467 , 881 para substitution
5a		3186	2999	1658 amide, 1647 imidazole	3381-3288	1564	1604	C=S 1193 C-N 1433 842 para substitution
5b		3055	2856	1685 amide, 1653 imidazole	3333-3230	1519	1606	C=S 1180 C-N 1491 852 para substitution
5c		3043	2890	1668 amide, 1635 imidazole	3379-3246	1510	1573	C=S 1184 C-N 1419 821 para substitution
6a		3064	2829	1654 imidazole	3265	1525	1585	C-S-C 688, N-N 1294, C-N 1467, 844 para substitution
6b		3043	2837	1653 imidazole	3250	1523	1589	C-S-C 663, N-N 1292, C-N 1467, 885 para substitution
6c		3043	2943	1653 imidazole	3252	1523	1585	C-S-C 690, N-N 1205, C-N 1419, 858 para substitution

Table -3: Chemical shifts ^{1}HNMR spectra

NO.	***^{1}HNMR (DMSO_d_6) ς ppm***
2a	8.71 (s, 1H, C=C<u>H</u>), 6.2-7.8 which belonged to aromatic protons.
3a	8.4(s, 2H ,N<u>H</u>$_2$) , 8.8 (s, 1H,C=C<u>H</u>) and at 6.7-8.1ppm which belonged to aromatic protons .
4a	1.25 (t,3H,COOCH$_2$C<u>H</u>$_3$),4.0 (q, 2H,COOC<u>H</u>$_2$CH$_3$),5.1 (d,2H,NHC<u>H</u>$_2$) , 8.7 (s,1H,N<u>H</u>CH$_2$) , 7.5-8.1 aromatic proton .
5a	4.0 (d,2H,NHC<u>H</u>$_2$) , 8.75 (m,4H,N<u>H</u>N<u>H</u>CSN<u>H</u>$_2$) , 10.5 (s,1H, N<u>H</u>CH$_2$) , 6.8-7.9 Aromatic proton .
6a	3.7(d,2H,NHC<u>H</u>$_2$), 10.5 (s,1H,N<u>H</u>CH$_2$),8.5 (s,1H,N<u>H</u>$_2$), 6.8-7.9 Aromatic proton.

Reference

1- Eunjung Choi and Daeock Choi "synthesis of 5-(2-hydroxyphenyl-1,3-oxazole and N-(2-hydroxyphenacyl) Benz amides .Bull Korean Chem.Soc:24 ,2,249***(2003).***

2- Justyna Zwawlak ,Dorota Olender,Zofia Zwdska, Ewa Augus tynowicz-kopec and Lucjusz Zaprutko" synthesis of 2,3-dihydro-7- nitroimidazole[5,1-b]oxazoles as potential tubercul ostatic Agents.Acta poloniae, Pharmaceuti ca-Drug Research :65,2,229-233***(2008).***

3- Mohamed Kaspady, Venugopola Katharigatta ,Narayana Swamy , Mohana Raju and Gopal Krishuna Rao " synthesis Anti bacterial Activity of 2,4-Disubstit oxazole Thiazole as Bioi sosteres-Lettersin Drug Design and Discovery: 6,21-28***,(2009).***

4- Ann .C.G Helena, I MB.;Scott,G.F.;Clifton,E.B.;Brent,R.C.A "Anti mycobacterial natural products synthesis and preliminary-biological evaluation of oxazole-Cortainig alkaloid texaline. Tetrahedron Lett:46,7355-57 ***(2005).***

5- Gorge,C.Michael,J.F "derivatives of 2-amino oxazoles showing anti-inflammatory activity ,J.Med.Chem :14,1075-77***(1971).***

6- R.Kalirajan, leela Rathore , S. Jubie, B. Gowramma, S.Gomathy,S.Sankar and K.Elango;" Micro Wave assisted and biological Evaluation of pyrazole derivatives of Benz imidazoles .Indian J. Pharm. Educ.Res: 44 ,4 ***(2010).***

7- Ashutosh K Bhatt,Hasanali Karadiya Palak shah, Manish P Parmar, patal HD." Synthesis of Benz imidazol derivatives and their anti bacterial and anti fungal activites . Indian J heterocyclic chem.: 13,187-189 ***(2003).***

8- Ayman El-faham,Mohammed Chebbo , Mohamed Abdul-Ghani, Ghassan Yunes. "Chloro formamidinium salt: Efficient reagents for preparation of 2-amino benzimidazole,2 amino benzoxazole and 2-amino benzothiazole derivatives .J.heterocycl chem. :43,599-606 ***(2006).***

9- Gernot A Eller,Barbara Datterl,Wolfgang Holzer." Pyrazolo[41,31:5,6]pyrano[2,3,b]Quin oxalin4(H): synthesis and characterization of a novel tetra cyclic ring system J.heterocycl chem. :44,1139-1143***(2007).***

10- Primofiore G, Marini AM, Salerno S,Dasettimof, Bertini D,L.Dalla Via, " synthesis and anti proliferative evaluation of new aryl substituted pyridothio pyrano [g,3c] pyrazoles , J heterocyclic chem. :42,1357-1361 ***(2005).***
11-Jyoti pandey, Vinod K.Tiwari,Shyam S. Verma Vinita chaturredi , S.Bhatnar S. Sinha, A.N.Gaik wad and Rama P.Tripathi "synthesis and anti tubercular screeing of imidazole derivatives " European Journal of Medicinal:44,3350-3355 ***(2009).***
12- Arvind k. Singh, Geeta Mishra and Kshitiz Jyoti "Review on Biological Activities of 1,3,4-ThiadiazoleDerivatives" Journal of Applied Pharmaceutical Science :5 , 44-49 ***(2011).***
13- Mohammad Asif ,Chhaviasthana "2, 4- Di substituted-5-Imino-1, 3, 4-Thiadiazole Derivatives: Synthesis and Biological Evaluation of Anti-inflammatory Activities" International Journal of Chem. Tech Research.:4, 1200-1205, ***(2009)***.
14- Chatrasal Singh Rajput, Sanjeev Sharma and Yashovardhan "synthesis of new pyridine derivatives as potent antifungal agents"International Journal of Pharma and Bio Sciences:2,0975-6299 ***(2011).***

تحضير وتشخيص مشتقات جديدة لمركب الاميدازول

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الخلاصة

حضرت مركبات جديدة لمركب 1,3-oxazole 5 (4H) one من تفاعل الحامض الاميني الكلايسين مع الاستيك انهايرايد (1) وفاعل المركب (1) مع بعض الالديهايدات المعوضة لتعطي مشتق oxazole (2a-c) , مركبات imidazole حضرت من تفاعل المركب (2 a-c) مع الهيدرازين المائي(95%) , فاعلت imidazole مع chloro ethyl acetate لتعطي مشتق الاستر (4a-c) وتم اضافة ثايو سمي كاربزايد الى مشتق الاستر ليعطي مركب (5 a-c) والذي فعل الاخير مع حامض الكبريتيك المركز والامونيا ليعطي مشتق الثاياديازول (6a-c). وشخصت هذه النواتج بالاعتماد على بعض الخواص الطيفية ^{1}HNMR,FTIR .