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Synthesis, characterization and anthelmintic activity of some novel imidazolidinone derivatives

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Abstract
A series of some novel imidazolidinone were synthesized by the aminolysis of oxazolones with amines, obtained by the condensation of aromatic aldehydes with benzoyl glycine in the presence of acetic anhydride and anhydrous sodium acetate. The so formed oxazolones were condensed with 2, 4-dinitrophenylhydrazine in dry pyridine to obtain a series of (Z)-N-(4-benzylidene-1-((2, 4-dinitrophenyl) amino)-2-phenyl-1H-imidazol-5(4H) one (3a-g). The compounds synthesized were identified and characterized by TLC, IR, ^{1}H NMR and MS spectroscopy and screened for anthelmintic activity.
All the compounds showed significant dose dependant anthelmintic activity. Among them compound 3g showed most potent activity. Compounds 3b, 3d, 3f demonstrated paralysis as well as death of worms at a time as that of albendazole.

Keywords: oxazolones, imidazole, anthelmintic, albendazole

Introduction
Heterocyclic synthesis has emerged as powerful technique for generating new molecules useful for drug discovery. Since many decades, active heterocyclic compounds are one of the main topic of interest for the medicinal chemists as it displays a number of pharmacological activities. Nitrogen, sulphur, oxygen containing five and six membered heterocyclic compounds have occupied enormous significance in the field of medicinal chemistry [1]. Oxazolones are heterocyclic compounds which perform an important role in the synthesis of several organic molecules including amino acids [2], amino alcohols, thiamine [3], amides [4], peptides [5, 6, 7] and polyfunctional compounds [8]. Certain natural and synthetic oxazolones also including benzoxazolone [9, 10, 11, 12, 13] derivatives possess important biological activities; such as antimicrobial [14, 15, 16], anti-inflammatory [10, 17, 18], anticancer [19, 20], anti-HIV [21, 22, 23], antiangiogenic [24], anticonvulsant [25], antitumor, antagonistic, sedative [26, 27, 28] and cardio tonic activity [12, 29]. The imidazole ring occurs largely in the context of the natural amino acid histidine. In addition, the imidazole ring appears as a component of unnatural cyclic peptides and is used as an ester isostere in peptidomimetic studies. The imidazole ring has potential therapeutic agents for thrombosis, cancer, and inflammatory diseases. The imidazolidinone are one of five families of herbicides that inhibit the enzyme acetohydroxy acid syntheses (AHAS). All imidazolidinone herbicides (imazapyr, imazapic, imazethapyr, imazamox, imazamethabenz and imazaquin) have a chiral, imidazole moiety in their molecular structure, but differ in the second heterocyclic in the structure. Imazapyr and imazethapyr have a pyridine ring and imazquin have a quinoline moiety. A common characteristic of all imidozolines herbicides is the presence of two enantiomers that derive from the chiral centre of imidozolidinone ring. The inhibitory activity of the R (+) enantiomer for AHAS is nearly eight times greater than that of the S (-) enantiomer (lao and gen, 2005). It is worthy to mention that this substitution formulated a unique structure with potent biological activities.

Experimental work
Melting points were taken in open capillary tubes using Arson digital melting point apparatus and uncorrected. ^{1}H NMR spectra were recorded on BRUKER 400 MHz obtained from IIS-Bangalore. IR spectra were recorded on BRUKER Alpha FTIR Spectrometer with universal sampling model using KBr pellets from CES, Kurnool. A MASS spectrum was obtained from Apex Mass spectra from IIT Madras.

Synthesis of benzyl glycine: (1)
Benzyl glycine was prepared by dissolving 25gm of glycine in 25 ml of 10% sodium hydroxide solution to which 45 ml of benzoyl chloride was added in 5 portions, shaken vigorously after each addition until all chlorides get reacted. This reaction mixture was then transferred in to a beaker containing few grams of crushed ice. Concentrated hydrochloric acid was added slowly by stirring until the mixture was acidic to red litmus. The resulting crystalline precipitate of benzyl glycine was filtered washed with cold water and drained well. The solid was boiled gently with 100 ml of CCl_4 for 10 min to extract benzoic acid which may be present the mixture and was allowed to cool. The product was filtered, washed with 10-20ml of CCl_4, dried and recrystallized from boiling water.

Synthesis of 4-Benzylidine-2-phenyl oxazolone-5-one: (2)
The mixture of 8.6 gm's of compound 1 (0.0478mmol), benzaldehyde (5ml) (0.0476mmol), acetic anhydride (14ml) (0.146mmol), and anhydrous sodium acetate (3.9gm) (0.0476mmol) in a 250 ml conical flask were heated on electric hot plate with constant shaking. As soon as the mixture liquefies completely transfer the flask was transferred

to water bath and heated for 2 hrs. Then added (10ml) ethanol slowly to contents of flask and mixture was allowed to stand for overnight (Sammie Fozooni *et al*, (2008). The crystalline precipitate was filtered with suction and washed with 2 portion of ice-cold alcohol (6ml) and finally with 2 portions of boiling water. The product was dried and recrystallized from benzene.

Yield = 3.6g (72%), M.P = 156-158^{0}c.

Various 2-phenyl-4-(substituted benzylidine)-oxazole-5ones were synthesised by similar procedure. After drying they were used for subsequent reaction.

Synthesis of-N-(4-benzylidene-1-((2, 4dinitrophenyl) amino)-2-phenyl-1H-imidazol-5(4H)-one: (3)

A mixture of compound 2 (0.01mol) and different substituted 4-benzylidene-2-phenyl Oxazol-5-one (0.01mol) in pyiridine (15ml) were refluxed for 48 hrs. The excess of solvent was removed under reduced pressure and reaction mixture was poured in to crushed ice, filtered, dried and recrystallized from methanol. The completion of reaction was monitored by Thin Layer Chromatography.

Various (Z)-N-(4-benzylidene-1-((2, 4dinitrophenyl) amino)-2-phenyl-1H-imidazol-5(4H)-one were prepared in a similar manner.

Scheme of work

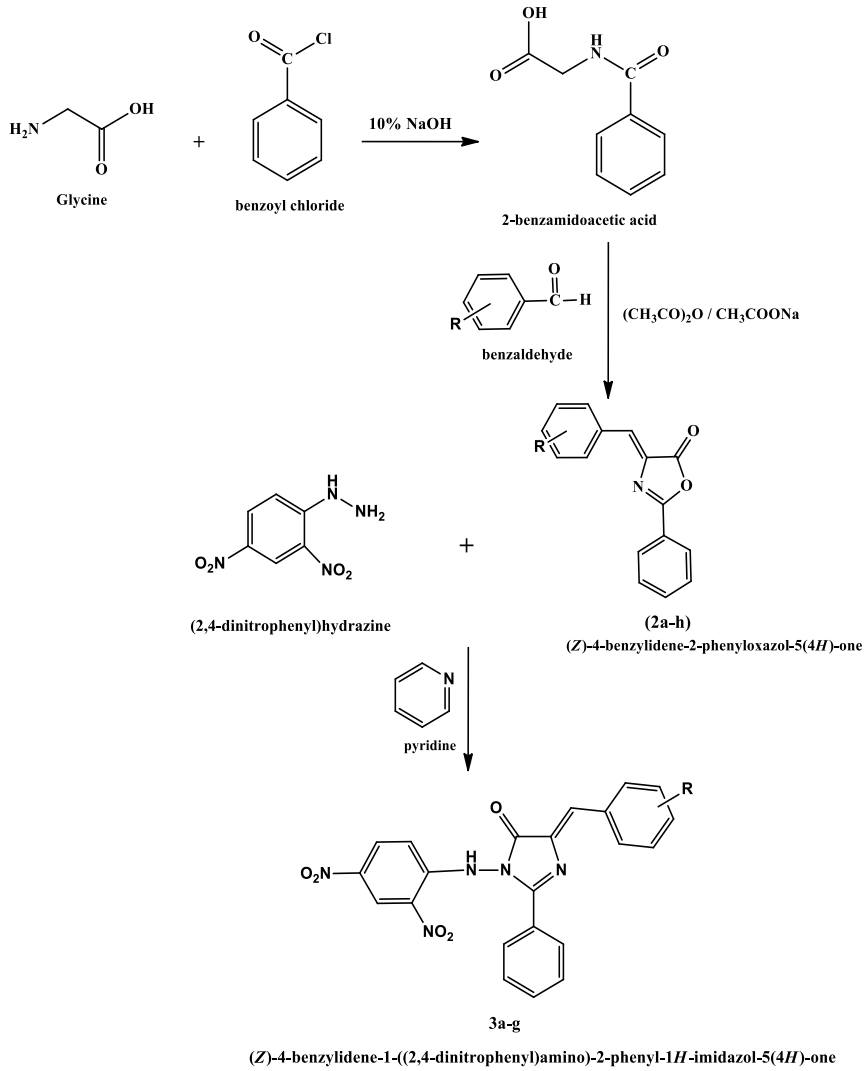

Table 1: Physico-chemical data of Substituted Imidazolinone derivatives (3a-3g)

S.No.	Compound code	Melting Point(^{0}C)	molecular Formula	Molecular weight	Appearance	Yield (%)
1	3a	140-189 ^{0}C	$C_{22}H_{15}N_5O_5$	429.11	Brown yellowish	35
2	3b	125-160 ^{0}C	$C_{25}H_{21}N_5O_8$	519.14	Reddish Brown	60
3	3c	136-156 ^{0}C	$C_{23}H_{17}N_5O_6$	459.12	Yellowish brown	40
4	3d	130-170 ^{0}C	$C_{22}H_{14}ClN_5O_5$	463.07	Pale Brown	50
5	3e	130-167 ^{0}C	$C_{24}H_{19}N_5O_7$	489.13	Yellowish brown	60
6	3f	200-220 ^{0}C	$C_{22}H_{15}N_5O_6$	445.10	Yellowish cream	20
7	3g	140-175 ^{0}C	$C_{22}H_{14}N_6O_7$	474.09	Reddish brown	50

Compound 3a

(Z)-N-(4-benzylidene-1-((2,4dinitrophenyl)amino)-2-phenyl-1H-imidazol-5(4H)-one

IR (kBr cm^{-1}): 3338.07(N-H str), 3224.18(Ar C-H str), 1801.77(C=O str), 1493(Ar- NO_2), 1273 (C-N). ^{1}H NMR spectral data (δ, DMSO) : 6.57-6.59(m, 5H, Ar H), 7.23-7.32(m, 4H, Ar-H), 7.41-7.62(m, 5H, Ar-H), 8.33-8.35(S, 1H, NH), 8.02-8.04(S, 1H, C=H). MASS (GC-MS**):** 429.4 (M+)

Compound 3b

(Z)-1-((2,4dinitrophenyl)amino)-2-phenyl-4-(3,4,5-trimethoxybenzylidine)-1H-imidazol-5(4H)-one

IR (KBr, cm^{-1}) : 3440.58(N-H str), 3110.32(Ar C-H str), 1641.82(C=O str), 1502.82(C=N str in ring) 1333.28(Ar-NO_2), 1128.88(C-O str in C-O-C), 1018.03(C-N str). ^{1}HNMR spectral data (δ, DMSO):3.368-3.994(m, 9H, tri -OCH_3), 4.108(S, 1H, NH). 6.73-6.738(m, 2H, Ar-H), 7.53-8.096 (m, 5H, Ar- H), 7.99-8.01(S, 1H, C=CH).

Compound 3c

((Z)-1-((2,4dinitrophenyl)amino)-4-(4-methoxybenzylidine)-2-phenyl-1H-imidazol-5(4H)-one

IR (kBr cm^{-1}):34450.80 (N-H str), 3016.91 (Ar C-H str), 2974.91 (C-H str in methyl), 1783.03(Ar C=C str), 1644.12 (C=O str), 1611.71(Ar-NO_2), 1448.72(C=N in ring), 1388.80 (C-O str in C-O-C), 1182.88(C-N). ^{1}HNMR spectral data (δ, DMSO):3.368-3.994(m, 3H, -OCH_3), 4.108(S,1H, NH). 6.73-6.738(m, 2H, Ar-H), 7.53-8.096 (m, 5H, Ar- H), 7.99-8.01(S, 1H, C=CH).

Compound 3d

((Z)-4-(4-chlorobenzylidene-1-((2,4dinitrophenyl)amino)-2-phenyl-1H-imidazol-5(4H)-one

IR (kBr cm^{-1}):3382.62(N-H str Amines), 3322.12(N-H str Amides),2823.34(C-H str in methylene),1622.87(C=O str), 1480.22(C=N str), 1238.08(C-N), 838.18(C-Cl).^{1}H NMR spectral data (δ, DMSO):6.56-6.63(m, 4H, Ar-H),7.09(m, 1H, Ar-H), 7.25-7.59(m, 4H, Ar-H),7.62-7.68(m, 4H, Ar-H), 8.03-8.38(S,1H, C=CH), 8.87(S, 1H, NH).

Compound 3e

(Z)-4-(3,4-dimethoxybenzylidene)-1-((2,4dinitrophenyl)amino)-2-phenyl-1H-imidazol-5(4H)-one

IR s (kBr cm^{-1}):3484.21(N-H str Amines), 3286.73(N-H str Amide), 1618.28(C=O str), 1483.80(C=N str), 1328.47(Ar-NO_2), 1272.37(C-O in C-O-C str), 1138.83(Ar C-H str), 1020.87(C-N). ^{1}HNMR spectral data (δ, DMSO):3.368-3.994(m, 6H, -OCH_3), 4.108(S, 1H, NH), 6.73-6.738(m, 2H, Ar-H), 7.53-8.096 (m, 5H, Ar- H), 7.99-8.01(S, 1H, C=CH).MASS (GC-MS): m/z 490.75 (M+ peak).

Compound 3f

(Z)-1-((2, 4dinitrophenyl) amino)-4- (2-hydroxy benzylidine) -2-phenyl-1H-imidazol-5(4H)-one

IR (kBr cm^{-1}): 3383.38 (O-H str), 1687.78(C=O str), 1538.70(Ar C=C), 1501.87(C=N in ring), 1383.10(Ar-NO_2), 1357.70(Ar C-H str),1030.38(C-N str).^{1}H NMR spectral data (δ, DMSO) : 6.51-6.77(m, 3H,Ar-H)6.79-6.99(m,4H, Ar-H), 7.04(s, 1H, C=CH),7.42-7.6(m, 4H Ar-H), 9.95(S, 1H, NH),3.80-3.87(S, 6H, CH_3),

Anthelmintic activity

All the newly synthesized compounds were screened for anthelmintic activity on adult earthworms (*Pheritima posthuma*) [30-34].Adult earthworm *Pheritima posthuma* were collected (due to its anatomical and physiological resemblance with the intestinal roundworm parasites of human being) from moist soil, obtained from agricultural fields. Three test groups were taken each containing six earth worms of approximately equal size (8 ± 1 cm). Albendazole was taken as standard drug and different concentrations (62.5µg/ml, 125µg/ml, 250µg/ml, 500µg/ml &1000µg/ml) were prepared in normal saline containing 1% tween 80. The synthesized compounds of different concentrations were prepared by dissolving in minimum quantity of tween 80 and making up to the final volume with normal saline to obtain 62.5µg/ml, 125µg/ml, 250µg/ml, 500µg/ml &1000µg/ml concentrations. One of the groups is taken as control group, which was treated with normal saline containing 1% tween 80. Paralysis onset time and death time of individual worms were noted. Paralysis was said to occur when the worms do not revive even in normal saline. Death was concluded when the worms lost their motility followed by fading away of color of worm.

Results and Discussion

Table 2: Anti-helminthic activity of different substituted imidazolinone derivatives

S. No.	Compound	Concentration (µg/mL)	Paralysis time (min.)	Death Time (min.)
1.	Normal Saline	-	-	-
2.	Albendazole	62.5	2.34±0.53	3.95±0.24
		125	1.69±0.47	2.37±0.62
		250	1.43±0.21	1.62±0.52
		500	1.11±0.38	1.42±0.29
		1000	0.39±0.82	0.52±0.51
3.	3a	62.5	8.11±0.23	8.78±0.35
		125	8.36±0.52	8.56±0.24
		250	6.34±0.25	7.12±0.52
		500	5.61±0.37	6.82±0.42
		1000	4.56±0.82	4.78±0.51
4.	3b	62.5	3.13±0.51	3.95±0.21
		125	2.71±0.37	3.18±0.23

		250	2.13±0.25	2.53±0.28
		500	1.12±0.36	1.87±0.91
		1000	0.79±0.42	0.92±0.21
5.	3c	62.5	5.91±0.67	6.24±0.42
		125	5.37±0.82	5.91±0.56
		250	4.84±0.19	5.15±0.92
		500	3.91±0.25	4.35±0.83
		1000	2.28±0.73	2.96±0.28
6.	3d	62.5	3.89±0.51	4.15±0.52
		125	3.71±0.32	4.24±0.43
		250	2.84±0.25	3.13±0.31
		500	1.98±0.36	2.17±0.82
		1000	1.09±0.42	1.42±0.72
7.	3e	62.5	4.91±0.67	5.24±0.46
		125	4.37±0.82	4.71±0.51
		250	3.84±0.19	4.12±0.72
		500	2.91±0.25	3.15±0.51
		1000	2.28±0.73	2.46±0.48
8.	3f	62.5	2.84±0.53	4.15±0.14
		125	1.89±0.47	3.12±0.42
		250	1.43±0.21	1.92±0.37
		500	1.15±0.38	1.62±0.53
		1000	0.69±0.82	0.81±0.42
9.	3g	62.5	2.54±034	4.56±0.57
		125	1.89±0.67	2.57±0.91
		250	1.53±0.34	1.72±0.57
		500	1.21±0.27	1.42±0.39
		1000	0.47±0.79	0.62±0.34

Result are expressed as Mean ± SEM for six observations, when compared with albendazole as standard reference

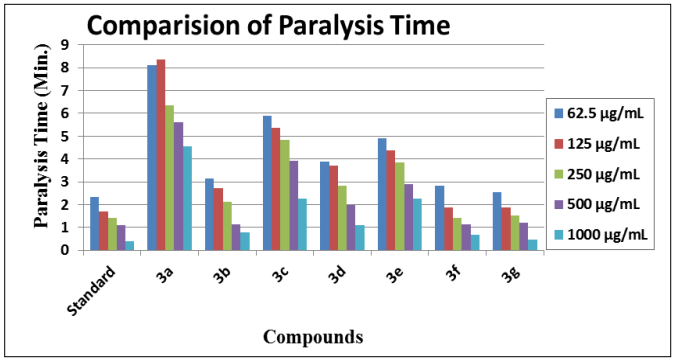

Fig 1: Comparison of paralysis time at different conc. of compound

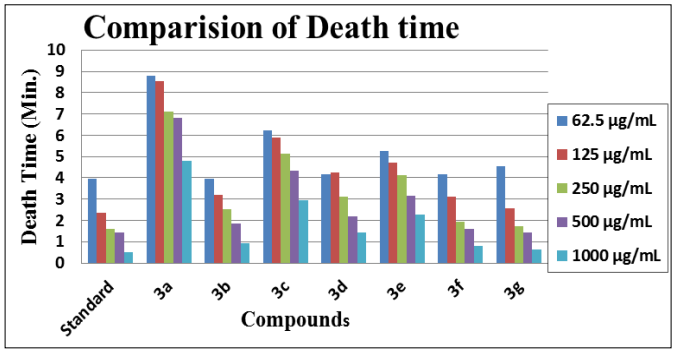

Fig 2: Comparison of death time at different conc. of compound

Conclusion

A set of seven imidazolidinone derivatives were designed and synthesized using appropriate synthetic scheme. The synthesized compounds were purified and well characterized by TLC, IR, 1HNMR and CG-MS data. Among the tested compounds tested for anthelmintic activity, compound 3g showed most potent activity. The compound 3b, 3d, 3f demonstrated paralysis as well as death of worms at a time comparable to albendazole at 62.5µg/ml, 125µg/ml, 250µg/ml, 500µg/ml &1000µg/ml concentrations. Our present study makes it an intresting compound when compared to the present therapeutic agents and are considered the candidates to investigate for the same purpose.

References

1. Aaglawe MJ, Dhule SS, Bahekar SS, Wakte PS, Shinde DB. Synthesis and antibacterial activity of some oxazolone derivatives, Journal of the Korean Chemical Society. 2003; 47:133-136.
2. Lamb J, Robson W. The Erlenmeyer synthesis of amino-acids, Biochemical Journal. 1931; 25:1231-1236.
3. Ismail MI. Physical characteristics and polarographic reduction mechanism of some oxazolones, Canadian Journal of Chemistry. 1991; 69:1886-1892.
4. Park BS, Min Oh C, Chun KH, Lee JO. Photoinduced one pot transformation of 2-phenyl-4-ethylidene-5(4H)-oxazolone and allylic alcohols to γ, δ-unsaturated N-benzoyl amides, Tetrahedron Letters, 1998; 39:9711-9714.
5. Palcut M. Spectral properties of novel 1, 3- oxazol-5(4*H*)-ones with substituted benzylidene and phenyl rings, Acta Chimica Slovenica. 2009, 56:362-368.
6. Seebach D, Jaeschke G, Gottwald K, Matsuda K, Formisano R, Chaplin DA. Resolution of racemic carboxylic acid derivatives by Ti-TADDO Late mediated esterification reactions: a general method for the

preparation of enantiopure compounds, Tetrahedron. 1997; 53:7539-7556.
7. Gottwald K, Seebach D. Ring opening with kinetic resolution of azlactones by Ti- TADDO Lates, Tetrahedron. 1999; 55:723-738.
8. Matsunaga H, Ishizuka T, Kunieda T. Synthetic utility of five-membered heterocycles-chiral functionalization and applications, Tetrahedron, 2005; 61:8073-8094.
9. Ellaithy MM, El-Ragehy NA, El-Ghobashy MA. Kinetic study of alkaline induced hydrolysis of the skeletal muscle relaxant chlorzoxazone using ratio spectra first derivative Spectrophotometry, IL Farmaco. 2003; 58:337-342.
10. Goksen US, Kelekci NG, Goktas O, Koysal Y, Kilic E, Isik S, *et al*. 1-Acylthiosemicarbazides, 1,2,4-triazole-5(4H)- thiones, 1, 3, 4-thiadiazoles and hydrazones containing 5-methyl-2-benzoxazolinones: synthesis, analgesic-anti-inflammatory and antimicrobial activities, Bioorganic & Medicinal Chemistry. 2007; 15:5738-5751.
11. Dogruer DS, Unlu S, Sahin MF, Yesilada E. Anti-nociceptive and anti-inflammatory activity of some (2-benzoxazolone-3-yl and 2-benzothiazolone-3yl) acetic acid derivatives, IL Farmaco. 1998; 53:80-84.
12. Pasha MA, Jayashankara VP, Venugopala KN, Rao GK. Zinc Oxide (ZnO): an efficient catalyst for the synthesis of 4-arylmethylidene-2-phenyl-5-(4H)-oxazolones having antimicrobial activity, Journal of Pharmacology and Toxicology. 2007; 2:264-270.
13. Schnurch M, Hammerle J, Stanetty P. Product class: benzoxazoles and other annulated oxazoles, In Science of Synthesis Updates, by Georg Thieme Verlag, 2010, 1-54.
14. Brownlee G, Woodbine M. The antibacterial activity of some synthetic compounds related to penicillin, British Journal of Pharmacology. 1948; 3:305-308.
15. Siddiqui SA, Bhusare SR, Jarikote DV, Pawar RP, Vibhute YB. New novel synthesis and antibacterial activity of 1-(substituted phenyl)-2-phenyl-4-(3'-halo, 4'-hydroxy 5'-methoxy benzylidene)-imidazole-5-ones, Bulletin of the Korean Chemical Society. 2001; 22:1033-1036.
16. Desai NC, Bhavsar AM, Baldaniya BB. Synthesis and antimicrobial activity of 6-imidazolinone derivatives, Indian Journal of Pharmaceutical Sciences, 2009; 71:90-94.
17. Abdel-Aty AS. Pesticidal effects of some imidazolidine and oxazolone derivatives, World Journal of Agricultural Sciences. 2009; 5:105-113.
18. Argade ND, Kalrale BK, Gill CH. Microwave assisted improved method for the synthesis of pyrazole containing 2,4,-disubstitute oxazole-5-one and their antimicrobial activity, European Journal of Chemistry. 2008; 5:120-129.
19. Sanchez C, Mendez C, Salas JA. Indolocarbazole natural products: occurrence, biosynthesis and biological activity, Natural Product Reports. 2006; 23:1007-1045.
20. Gaenzler, Corbo F. Part I. A 2-nitroimidazole indocyanine green dyederivative tumor imaging agent. Part II. Adichlorination-reductive-dechlorination route toN-acetyl-2-oxazolone. Part III. IntramolecularDiels-Alder approach to the synthesis of pancratistatin, Pro Quest and Dissertations Theses, 2007, 163.
21. Witvrouw M, Pannecouque C, Clercq ED, Fernandez-Alvarez E, Marco JL, Inhibition of human immunodeficiency virus type (HIV-1) replication by some diversely functionalized spirocyclopropyl derivatives, Arch. Pharm. Pharm. Med. Chem. 1999; 352:163-166.
22. Pinto IL, West A, Debouckm CM, DiLella A, Gorniak JG, O'Donnell KC, O'Shannessy DJ, *et al*. Novel, selective mechanism-based inhibitors of the herpes proteases, Bioorganic & Medicinal Chemistry Letters. 1996; 6:2467-2472.
23. Siddiqui IR, Singh PK, Srivastava V, Singh J. Facile synthesis of acyclic analogues of carbocyclic nucleoside as potential anti-HIV prodrug, Indian Journal of Chemistry. 2010; 49B:512-520.
24. Sierra FMP, Pierre A, Burbridge M, Guilbaud N. Novel bicyclic oxazolone derivatives as anti-angiogenic agents, Bioorganic & Medicinal Chemistry Letters. 2002; 12:1463-1466.
25. Madkour HMF. Simple one-step syntheses of heterocyclic systems from (4*Z*)-2-phenyl-4-(thien-2-ylmethylene)-1,3(4H)-oxazol-5-one, Chemical Papers. 2002; 56:313-319.
26. Khan KM, Mughal UR, Khan MTH, Ullah Z, Perveen S, Choudhary MI. Oxazolones new tyrosinase inhibitors; synthesis and their structure–activity relationships, Bioorganic & Medicinal Chemistry. 2006; 14:6027-6033.
27. Tikdari AM, Fozooni S, Hamidian H. Dodecatungsto phosphoric acid (H3PW12O40), samarium and ruthenium (iii) chloride catalyzed synthesis of unsaturated 2-phenyl-5(4H)-oxazolone derivatives under solvent-free conditions, Molecules. 2008; 13:3246-3252.
28. Mesaik MA, Rahat S, Khan KM, Ullah Z, Choudhary MI, Murad S, *et al*. Synthesis and immunomodulatory properties of selected oxazolone derivatives, Bioorganic & Medicinal Chemistry. 2004; 12:2049-2057.
29. Schnettler. Cardiotonic heterocyclic oxazolones, United States Patent, Patent No US, 1987.
30. Thorn GW, Adams RD, Baunwald E, Isselbacher KJ, Petersdorf RG. Harrison's Principle of Internal Medicine, Mc-Graw Hill Co., New York, 1977, 1088.
31. Vigar Z. Atlas of Medical Parasitology, P. G. Publishing House, Singapore, 1984, 216.
32. Nirmal SA, Malwadkar G, Laware RB. Anthelmintic Activity of Pongamia Glabra Songklanakarin, Sci. Technol. 2007; 29(3):755-757.
33. Raut DN, Pal SC, Mandal SC. Anthelmintic Potential of Dendrophthoe Falcate Etting. (l.f) Leaf, IJPRD. 2009; 6:1603-1608.
34. Borkar VS, Gangurde HH, Gulecha VS, Bhoyar PK, Mundada AS. Evaluation of *In Vitro* Antihelmintic Activity of Leaves of Butea Monosperma, Int. J Phytomedicine. 2010; 6:31-35.