Journal Of Harmonized Research (JOHR)

Journal Of Harmonized Research in Pharmacy
2(3), 2013, 181-189

ISSN 2321 – 0958

Original Research Article

SYNTHESIS OF SOME NOVAL PARACETAMOL INCORPORATED THIAZOLIDINONE DERIVATIVES AND THEIR ANTIMICROBIAL ACTIVITY

Vivek Gupta[1]*, A. Pandurangan[2]

1. Charak Institute of Pharmacy, Mandleshwar Dist. Khargone (M.P.)
2. College of Pharmacy, MM University, Mullana, Ambala (Haryana)

Abstract:

4-acetamidophenoxyacetylhydrazide is synthesized from paracetamol which on reaction with various aldehyde gives Schiff bases. Schiff bases treated with mercaptoaceticacid to produce thiazolidinenone derivatives. The entire synthesized compound characterized by physical and analytical data. The chemical structures of synthesized compound were confirmed by means of IR, 1HNMR and MS. Antimicrobial activity of synthesized compounds evaluated by cup-plate method. Synthesized compound showed good antimicrobial activity.

Key word: Schiff bases, paracetamol, antimicrobial, thiazolidine-4-one.

Introduction:

A **Schiff base**, named after Hugo Schiff, is a compound with a functional group that contains a carbon-nitrogen double bond with the nitrogen atom connected to an aryl or alkyl group, not hydrogen. Schiff bases in a broad sense have the general formula $R^1R^2C=NR^3$, where R is an organic side chain. In this definition, Schiff base is synonymous with **azomethine**. Some restrict the term to the secondary aldimines (azomethines where the carbon is connected to a hydrogen atom), thus with the general formula RCH=NR.

For Correspondence:
Vivekg_srm06@yahoo.co.in
Received on: June 2013
Accepted after revision: August 2013

Material and Method:

Melting point is determine by open capillary tube method and uncorrected. The IR spectrum was recorded by using KBr disc on FTIR 8010 Shimadzu model. The ^{1}H-NMR spectra of the synthesized compounds were recorded on Brucker Spectrospin DPX 300 spectrophotometer. The solutions of the test compounds were prepared in dimethyl sulfoxide DMSO-d_6. Tetra Methyl Silane (TMS) was used as internal standard. Molecular weight weights of the synthesized

compounds were identified by Mass Spectrophotometer, LC-MSD-TrapSL (6300 Series Ion Trap LC/MS).

Procedure for the synthesis of ethyl-4-acetamidophenoxyacetate:

A mixture of paracetamol (1.51g, 0.01mol) and ethylchloroacetate (1.22ml, 0.01mol) was refluxed in dry acetone in presence of anhydrous K_2CO_3 (1.38g, 0.01mol) for 6 hr and was then poured onto the crushed ice. Solid product obtained was crystallized from ethanol.

Percentage yield: 80%, Melting point : 197- 199 ^{O}C

Procedure for the synthesis of 4-acetamidophenoxyacetylhydrazide:

A mixture of ethyl-4-acetamidophenoxyacetate (2.835g, 0.01mol) and hydrazine hydrate (2.0 ml, 0.04 mol) in ethanol was refluxed for 5 hr. The solution was then poured onto crushed ice. The separated solid was crystallized from ethanol.

Percentage yield: 70%, Melting point : 155- 157 ^{0}C

Procedure for Synthesis of Schiff bases: (1a-1l): In a round bottomed flask, 4-acetamidophenoxyacetylhydrazide (2.23 gm, 0.01mol), various aldehyde (5 ml) and ehanol (30-35 ml) was taken and refluxed for three hours. The solution was cooled at room temperature and allowed to stand for 5 hours. Solid product was separated out, filtered, washed with ice cooled distilled water, dried and crystallized with ethanol. The Schiff Base was obtained.

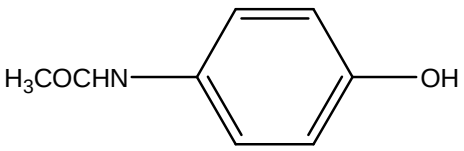
Percentage yield: 78% , Melting point : 146-148 ^{O}C

Procedure for Synthesis of 4-Oxo-thiazolidin derivatives (2a-2l):

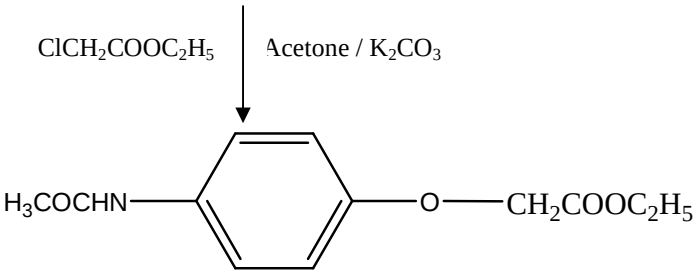
Schiff bases (1a-1l) (0.01 mol) was dissolved in 1:4 dioxane (25ml) with constant stirring. Thioglycolic acid (1ml) was added slowly with stirring. The content was transferred to round bottom flask and heated under reflux for 8 hours. The mixture was allowed to cool and poured into aqueous solution of sodium bicarbonate to remove un- reacted thioglycolic acid. The solid product was filtered, dried and re-crystallised from ethanol.

SCHEME

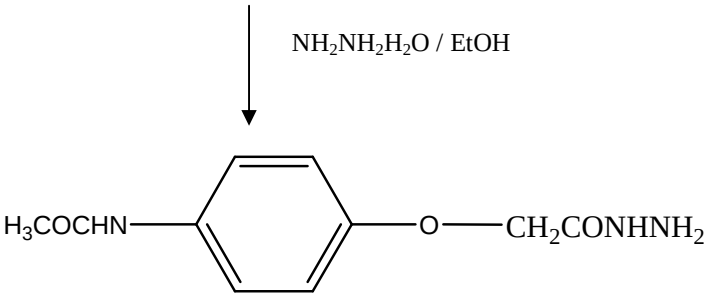
Step I: Synthesis of 4-acetamidophenoxyacetylhydrazide



Paracetamol

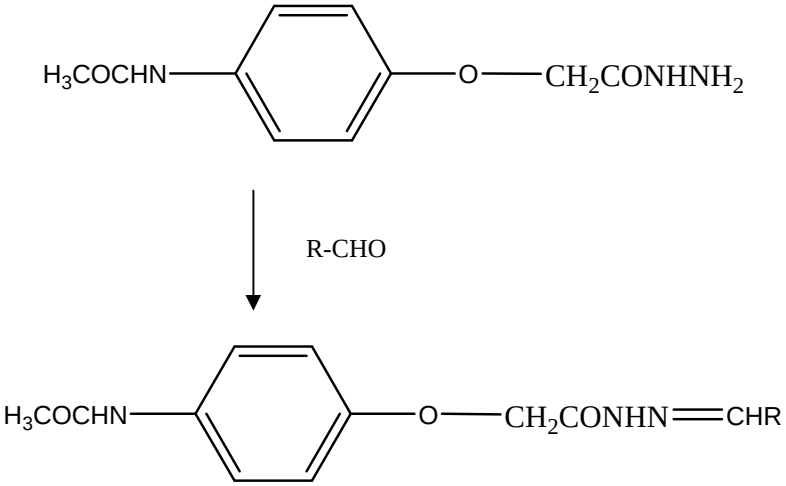


Ethyl-4-acetamidophenoxyacetate

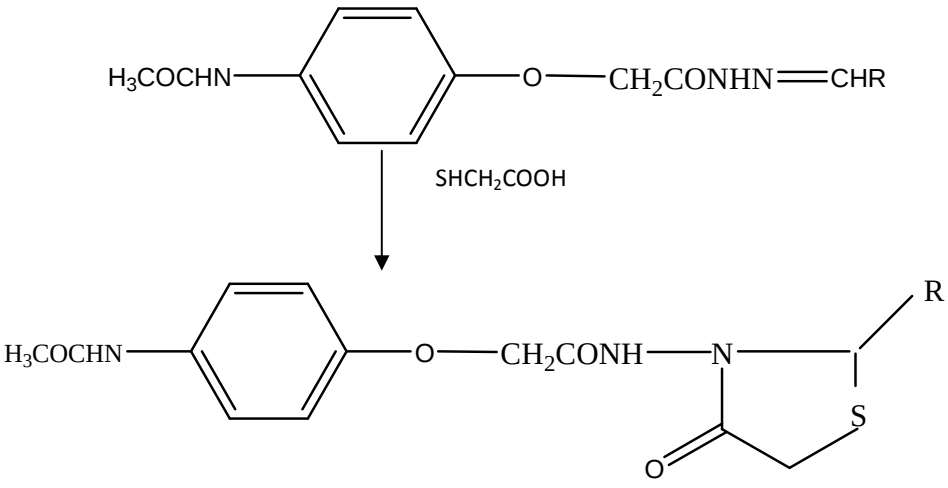


4-acetamidophenoxyacetylhydrazide

Step II: Synthesis of Schiff bases



Step III: Synthesis of 4-oxo-thiazolidine derivatives



2a-2l, R = Various aromatic aldehyde

Physical characterization:

Compound	% Yeild	Appearance	Melting Point (°C)	Molecular Formula	Molecular Weight
2a	59	White crystal	211-212	$C_{19}H_{19}O_4N_3S$	385
2b	63	Brown Crystals	229-231	$C_{19}H_{19}O_5N_3S$	401
2c	73	White Crystals	235-237	$C_{19}H_{18}O_4N_3SCl$	419
2d	71	White Crystals	223-225	$C_{19}H_{20}O_4N_4S$	400
2e	69	Brown Crystals	226-227	$C_{20}H_{21}O_5N_3S$	429
2f	67	Yellow crystals	243-245	$C_{20}H_{21}O_4N_3S$	415
2g	73	Brown Crystals	228-229	$C_{19}H_{18}O_6N_4S$	430
2h	78	Yellow crystals	247-249	$C_{19}H_{19}O_6N_3S$	417
2i	72	Brown Crystals	232-234	$C_{19}H_{17}O_4N_3SCl_2$	453
2j	68	Brown Crystals	251-253	$C_{19}H_{21}O_4N_5S$	415
2k	68	White Crystals	256-257	$C_{19}H_{17}O_8N_5S$	475
2l	66	White crystals	286-287	$C_{19}H_{18}O_4N_3SCl$	419

Thin layer chromatography:

The purity of synthesized compound was ascertained by TLC

Absorbent -
Precoated silica gel plate

Mobile phase -
Benzene: Methanol (8:2 v/v)

Detecting agent -
Iodine vapour

R_f = Distance run by solute / Distance run by solvent

TABLE - R_f Value of the synthesized compounds

S. No.	Code of compounds	R_f Value
1.	2a	0.81
2.	2b	0.71
3.	2c	0.67
4.	2d	0.69
5.	2e	0.81
6.	2f	0.86
7.	2g	0.72
8.	2h	0.71
9.	2i	0.72
10.	2j	0.78
11.	2k	0.77
12.	2l	0.74

Comp	IR**(cm^{-1})**	NMR**(ppm)**	MASS **(M/Z)**
2a	(N-H Stre. Secondary Amide), 3050 (Aromatic -C-H Stre.), 1690 (C=O Stre thiazolidine ring), 1600 (C=O stre.), 1370 (CH-N), 830 (-C-S-C).	8.1 (s, 1H, NH amide), 7.7-7.8 (m, 8H, Ar-CH), 3.3 (s, 2H, -CH_2- aromatic), 2.5 (m, 1H, aromatic –CH-), 2.2 (d, 3H, CH_3).	383
2b	3490(OH stre.), 3310 (N-H Stre. Secondary Amide), 3050 (Aromatic -C-H Stre.), 1690 (C=O Stre thiazolidine ring), 1600 (C=O), 1370 (CH-N), 830 (-C-S-C), 800 (C-H Stre Phenyl).	8.1 (s, 1H, NH amide), 7.7-6.3 (m, 8H, Ar-CH), 5.2 (s, 1H, OH), 3.3 (s, 2H, -CH_2- aromatic), 2.2 (s, 3H, CH_3).	400
2c	3460 (N-H Stre. Secondary Amide), 3040 (Aromatic -C-H Stre.), 1690 (C=O Stre thiazolidine ring), 1600 (acyclic C=O stre.), 1370 (CH-N), 830 (-C-S-C), 810 (C-H Stre Phenyl).	8.1 (s, 1H, NH amide), 7.7-7.2 (m, 8H, Ar-CH), 3.3 (s, 2H, -CH_2- aromatic).	418
2d	3490 (N-H stre Primary amine), 3390 (N-H Stre. Secondary Amide), 3040 (Aromatic -C-H Stre.), 1690 (C=O Stre thiazolidine ring), 1600 (acyclic C=O stre.) 1370 (CH-N), 830 (-C-S-C), 810 (C-H Stre Phenyl).	8.1 (s, 1H, NH amide), 7.7-7.4 (m, 8H, Ar-CH), 4.2 (d, 2H, NH_2), 3.3 (s, 2H, -CH_2- aromatic), 2.5 (s, 1H, aromatic –CH-).	399.7
2e	3460 (N-H Stre. Secondary Amide), 3040 (Aromatic -C-H Stre.), 2820 (C-H Stre OCH_3), 1690 (C=O Stre thiazolidine ring), 1600 (acyclic C=O stre.),1370 (CH-N), 830 (-C-S-C), 810 (C-H Stre Phenyl).	8.1 (s, 1H, NH amide), 7.7-7.2 (m, 8H, Ar-CH), 3.3 (s, 2H, -CH_2- aromatic), 3.1 (s, 3H, OCH_3), 2.5 (s, 1H, aromatic –CH-).	429
2f	3360 (N-H Stre. Secondary Amide), 3046 (Aromatic -C-H Stre.), 2928(Aliphatic C-H stre.)1690 (C=O Stre thiazolidine ring), 1600 (acyclic C=O stre.) 1370 (CH-N), 830 (-C-S-C), 810 (C-H Stre Phenyl).	8.1 (s, 1H, NH amide), 7.7-7.3 (m, 8H, Ar-CH), 3.3 (s, 2H, -CH_2- aromatic), 3.1 (t, 3H, CH_3), 2.5 (s, 1H, aromatic –CH-).	415

2g	3440 (N-H Stre. Secondary Amide), 3060 (Aromatic -C-H Stre.), 1690 (C=O Stre thiazolidine ring), 1600 (acyclic C=O stre.), 1490 (N-O Stre,), 1370 (CH-N), 830 (-C-S-C), 810 (C-H Stre Phenyl).	8.1 (s, 1H, NH amide), 7.7-7.3 (m, 8H, Ar-CH), 3.3 (s, 2H, -CH_2- aromatic), 2.5 (s, 1H, aromatic –CH-).	429
2h	3450 (O-H Stre.) 3390 (N-H Stre. Secondary Amide), 3020 (Aromatic -C-H Stre.), 1690 (C=O Stre thiazolidine ring), 1600 (acyclic C=O stre.), 1370 (CH-N), 830 (-C-S-C), 810 (C-H Stre Phenyl).	8.1 (s, 1H, NH amide), 7.7-7.2 (m, 8H, Ar-CH), 5.1 (s, 1H, OH) 3.3 (s, 2H, -CH_2- aromatic), 2.5 (s, 1H, aromatic –CH-).	416
2i	3390 (N-H Stre. Secondary Amide), 3060 (Aromatic -C-H Stre.), 1690 (C=O Stre thiazolidine ring), 1600 (acyclic C=O stre.), 1370 (CH-N), 830 (-C-S-C), 825 (C-Cl), 810 (C-H Stre Phenyl).	8.1 (s, 1H, NH amide), 7.7-7.3 (m, 8H, Ar-CH), 3.3 (s, 2H, -CH_2- aromatic), 2.5 (s, 1H, aromatic –CH-).	452
2j	3430 (N-H Stre. Secondary Amide), 3142 (Aromatic -C-H Stre.), 1670 (C=O Stre thiazolidine ring), 1640, 1370 (CH-N), 830 (-C-S-C), 810 (C-H Stre Phenyl).	8.1 (s, 1H, NH amide), 7.7-7.3 (m, 8H, Ar-CH), 4.3 (d, 2H,NH_2), 3.3 (s, 2H, -CH_2- aromatic), 2.5 (s, 1H, aromatic –CH-).	414
2k	3380 (N-H Stre. Secondary Amide), 3050 (Aromatic -C-H Stre.), 1690 (C=O Stre thiazolidine ring), 1600 (acyclic C=O stre.),1370 (CH-N), 830 (-C-S-C), 810 (C-H Stre Phenyl), 770 (N-H wag).	8.1 (s, 1H, NH amide), 7.7-7.2 (m, 8H, Ar-CH), 3.3 (s, 2H, -CH_2- aromatic), 2.5 (s, 1H, aromatic –CH-).	474
2l	3420 (N-H Stre. Secondary Amide), 3020 (Aromatic -C-H Stre.), 1690 (C=O Stre thiazolidine ring), 1600 (acyclic C=O stre.), 1370 (CH-N), 1320 (C-S Stre thiophene), 830 (-C-S-C), 810 (C-H Stre Phenyl).	8.1 (s, 1H, NH amide), 7.7-7.2 (m, 8H, Ar-CH), 3.3 (s, 2H, -CH_2- aromatic), 2.5 (s, 1H, aromatic –CH-	418

TABLE - IR, MASS, NMR Spectral data of the synthesized compounds

Antimicrobial Method:

The *in vitro* antimicrobial activity was carried out against 24 h old cultures of two bacteria and two fungi by cup-plate method [15]. The compounds **2a-2l** has been investigated for their antibacterial activity against *S. aureus*, *E. Coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* and antifungal activity against *Aspergillus niger* and *Curvularia lunata*. Chloramphenicol and fluconazole were used as standards 20 µg/mL for antibacterial and antifungal activity respectively. The compounds were tested at a concentration of 20 µg/mL in DMF against all organisms. The zone

of inhibition was compared with the standard drug after 24 h of incubation at 25 ^{o}C for antibacterial activity and 48 h at 30 ^{o}C for antifungal activity.

TABLE – Zone of inhibition of the synthesized compounds

Antibacterial screening data of compound 2a-2l

Compounds	Zone of Inhibition (in mm) at concentration of 20 µg/mL)			
	S. aureus	*E. Coli*	*P. Aeruginosa*	*K. pneumonia*
2a	12	16	20	23
2b	14	15	23	15
2c	21	22	24	23
2d	16	19	27	22
2e	22	26	24	24
2f	21	22	26	24
2g	22	18	23	25
2h	23	27	31	09
2i	17	19	26	12
2j	19	21	29	21
2k	16	23	32	36
2l	18	19	25	23
Chloramphenicol	27	28	26	26

Table: Antifungal screening data of compounds 2a-2l.

Comp.	Std.	2a	2b	2c	2d	2e	2f	2g	2h	2i	2j	2k	2l
C. albicans	28	12	19	22	-	22	21	13	17	15	14	-	12
A. niger	27	13	13	24	19	20	21	15	14	11	-	-	19

Result and Discussion:

The present study reports the synthesis of some paracetamol incorporated 4-oxo-thiazolidine derivatives. The synthesized compound were re-crystallized and identified by TLC, the R_f values were calculated and tabulated. The melting point of the product were found and are presented uncorrected in the table. Synthesized compound confirm by IR, NMR & Mass data. The compounds **2a-2l** has been investigated for their antibacterial activity against *S. aureus, E. Coli, Pseudomonas aeruginosa* and *Staphylococcus aureus* and antifungal activity against *Aspergillus niger* and *C. albicans* Chloramphenicol and fluconazole were used as standards for antibacterial and antifungal activity respectively. Compound 2c, 2e, 2g and 2f shows good activity against bacterium strain.

Conclusion:

A series of paracetamol contending 4-oxo-thiazolidine derivatives **(2a-2l)** were synthesized and characterized by analytical and spectral studies. The newly synthesized compounds were evaluated for antibacterial & antifungal. The results obtained here indicated, that ring systems enhances the activity to a considerable extent. In many cases, presence of electron withdrawing group results in increase of activity. Hence further structural modifications and screening has to be done to confirm the more and still better activity.

However it is interesting field of studding which can taken for more systematic studies under controlled condition.

Reference:

1. Ahmed F.S.M., El-Gazzar A.M., Shedid S.A. and El-Sharkawy K.A. "Synthesis and Antimicrobial Activity of Some Amino Acid Derivatives of Thiazolidine-4- Carboxylic Acid" Egypt. J. Biomed. Sci. Vol. 25, November, 2007.
2. Nazar Trotsko, Maria Dobosz and Ewa Jagiello-Wojtowicz "Cyclization of Thiosemicarbazide Derivatives of 5-Arylidene-2, 4-Dioxothiazolidine-3-Acetic Acids to 1, 3, 4-Thiadiazoles and their Pharmacological Properties" Acta Poloniae Pharmaceutica - Drug Research, Vol. 64 (3) 227-231 (2007).
3. Weng Jian-Quan, Shen De-Long and Tan Cheng-Xia "Synthesis, Structure and Biological Activities of1, 3-Thiazolidine Derivatives" Chin. J. Org. Chem., Vol. 27 (01) 126-130 (2007).
4. Masaru Mori, Masaru Takagi, Chikako Noritake and Shinzo Kagabu "2, 4-Dioxo-1, 3-thiazolidine derivatives as a lead for new fungicides" J. Pestic. Sci., 33(4), 357–363 (2008).
5. Abdullah G.M. Al-Sehemi "Preparation and Structure Studies of Thiazolidine and Bisthiazolidine Derivatives" JKAU: Sci., Vol. 21 (1), 79-88 (2009).
6. Ludmyla Mosula, Borys Zimenkovsky, Dmytro Havrylyuk, Alexandru-Vasile Missir, Ileana Cornelia Chirita and Roman Lesyk "Synthesis and Antitumor Activity of Novel 2-Thioxo-4-thiazolidinones with Benzothiazole Moieties" Farmacia, , Vol. 57 (3) 321-330 (2009).
7. Iro Argyropoulou, Athina Geronikaki, Paola Vicini and Franca Zanib "Synthesis and biological evaluation of sulfonamide thiazole and benzothiazole derivatives as antimicrobial agents" ARKIVOC-(vi), 89-102 (2009).
8. Rama Ganesh C K, Yadav D Bodke and venkatesh K B "Synthesis and Biological Evalution of Some Ennovative Coumarin Derivative Containing Thiazolidine-4-one Ring" Indian Journal of Chemistry Vol 49B, 1151-1154 (2010).
9. Srikanth L., Raghunandan N., Srinivas P.and Amarender G. Reddy "Synthesis and Evaluation of newer Quinoline Derivatives of Thiazolidinediones for their Antidiabetic Activity" International Journal of Pharma and Bio Sciences, Vol.1 (4) 120-131(2010).
10. Ramachandran S. and Shanmugapandiyan P. "Synthesis, characterisation, antimicrobial evaluation of Thiazolidine-4-one derivatives" IJPI's Journal of Medicinal Chemistry Vol 1 (1) 2-6 (2010).
11. Soleiman H. A. "Some Fused/Isolated Heterocyclic of Pyrimidine, β-Lactam,

Thiazolidine and Triazine Derivatives" The Open Catalysis Journal, , 4, 18-26 (2011).
12. Verma Smita, Srivastava S.K. and Samadhiya Pushkal "Synthesis and Antimicrobial Activity of Thiazolidine Derivatives of Thiazole" IJPRD Vol 2 (11) 73-81 (2011).
13. Pandey Yashshree, Singh Ankita, Sharma Pramod Kumar and Kumar Nitin "Biological Activities of Thiazolidine – A Review" Current Pharma Research, 1(2), 192-196 (2011).
14. Prasad Davinder, Kumar Awanit, Shukla Praveen Kumar and Nath Mahendra "Design, synthesis and antimicrobial evaluation of novel 2-aryl-thiazolidin-4-one derivatives" Organic and Medicinal Chemistry Letters 1(4) 1-7 (2011).
15. Malik Sachin, Upadhyaya Prabhat Kumar and Miglani Sandeep "Thiazolidinediones: A Plethro of Biological Load" International Journal of PharmTech Research Vol. 3 (1) 62-75, (2011).
16. Amrita A Zagade and Senthilkumar G. P. "Thiazole: A valuable insight into recent advances, synthesis and biological activities" Der Pharma Chemica, 3(1), 523-537 (2011).
17. Sadaf J. Gilani, Suroor A. Khan, Ozair Alam, Vijender Singh and Alka Arora "Thiazolidin-4-one, azetidin-2-one and 1,3,4-oxadiazole derivatives of isonicotinic acid hydrazide: synthesis and their biological evaluation" J. Serb. Chem. Soc. 76 (8) 1057–1067 (2011).
18. LI Hong-xin, CHEN Xiao-tao and XU Liang-zhong "Design and Synthesis of 3-(1-Phenylethyl) thiazolidine-2-thione Derivatives with Potential Biological Activities" Chem. Res. Chinese Universities, 27(3), 431—434 (2011).
19. Sho Nishida, Hiroshi Maruoka, Yuki Yoshimura,Takao Goto, Ryoko Tomita, Eiichi Masumoto, Fumi Okabe, Kenji Yamagata, Toshihiro Fujioka "Synthesis and biological activities of some new thiazolidine derivatives containing pyrazole ring system" Journal of Heterocyclic Chemistry, published online: 22 NOV 2011.