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RESEARCH ARTICLE

Microwave Assisted Multicomponent Synthesis of Promising Insulin Inhibitor and Mcl-1 Antagonist Thiazolidinone & Pyrazolo Thiazolidine Derivatives Khot SS, Kapase VS, Kenawade S, Dhongade SR^{*}

Research Laboratory in Heterocyclic Chemistry, Devchand College, Arjunnagar, Maharashtra, India. Manuscript No: IJPRS/V3/I1/00068, Received On: 08/02/2014, Accepted On: 12/02/2014

ABSTRACT

This work involves synthesis of thiazolidinone derivatives by condensation of various amines with carbon disulfide and chloro acetic acid in presence of NaHCO₃ with *microwave assisted multicomponent reactions* with microwaves (140watts) in a scientific microwave oven, which on further condensation in another MCR with different aromatic aldehydes and hydrazides furnish the 1,3,6-Triaryl-hexahydro-pyrazolo[3,4-d]thiazole-5-thione derivatives [I (a-g)]. Library of such pyrazolo thiazolidine derivatives has been generated and the structures were subjected to PASS for finding their probabilities of being active biologically. QSAR study of the libraries was done to find out most active molecules. 3-Phenyl-2-thioxo-thiazolidin-4-one. (I A) is found most active compound as *insulin inhibitor and* Mcl-1 antagonist.

KEYWORDS

Thiazolidinone, Insulin Inhibitor, Pyrazolo Thiazolidine

INTRODUCTION

Thiazolidinone, a saturated form of thiazole with carbonyl group on fourth carbon, has been considered as a very important moiety which possess almost all types of biological activities. This diversity in the biological response profile has attracted the attention of organic chemists to explore this skeleton to its multiple potential against biological activities. The chemistry of heterocycles lies at the heart of drug discovery¹ 4-thiazolidinone is one of the most intensively classes investigated of five member heterocycles.^{2,3} The biological significance of this class of compounds attracted us to work on the synthesis of new thiazolidinone derivatives in the hope that synthesized compounds will be biologically active.

*Address for Correspondence: Savita R. Dhongade Research Laboratory in Heterocyclic Chemistry, Devchand College, Arjunnagar, Maharashtra (India). E-Mail Id: savitadesai2010@gmail.com

4-thiazolidinones are the heterocyclic compounds having nitrogen and sulfur atoms and are known for a long time for their wide range of interesting biological activities namely anticonvulsant activity, anti-inflammatory activity, anti-tubercular activity, anthelmintic activity, antiviral activity, antifungal activity, antibacterial activity, anticancer activity and anti - HIV activity⁴⁻¹² etc. There are many protocols for the synthesis of 4-thiazolidinone.¹³⁻²² 4thiazolidinone can be synthesized either by cyclisation of acyclic compounds or by simple condensation of thioglycolic acid with Schiff's bases. The reaction undergoes by the attack of the mercapto acetic acid upon the C = N group, with the - S - CH_2 – COOH adding to the carbon atom followed by the capture of a proton by nitrogen and subsequent cyclisation. The nucleophilic attack of mercaptoacetic acid anion on carbon of azomethine, which has got positive character while nitrogen has negative character, is evidenced. Simultaneous removal of Chandra

Kant Belwal et al /Int.J.ChemTech Res.2012, 4(4) 1759 water as it forms in reaction helps in condensation and determination of the reaction time. The constitution of all the products has been characterized using elemental analyses, IR, 1H NMR and mass spectral study.

PASS

PASS is a software application that predicts 565 possible biological activities of a user selected (set of) compound(s). These activities include 5hydroxytryptamine antagonists, neuromuscular blocking agents. Antibiotics, antidepressants, antiviral agents(AIDS), contraceptives, tumor necrosis factor antagonists and many others. Using PASS predictions, novel pharmaceutical agents have been discovered with anxiolytic, anti-inflammatory, antihypertensive, anticancer and other actions. PASS is applicable to chemical libraries containing millions of compounds.

The biological activities of chemical compounds are related to their physicochemical properties by some functions as shown in equation (1).

Biological activity = f (physicochemical properties)......(1)

Thus, "the biological activity spectrum" is defined as the "intrinsic" property of a compound depending only on its structure and physico-chemical characteristics. Prediction of this spectrum by PASS is based on SAR analysis of the training set containing thousands of compounds which have many kinds of biological activities. In PASS *biological activities* are described qualitatively ("active" or "inactive").

Importance of PASS

- 1. Experimental determination of biological activity of a drug is time and cost consuming procedure, so making the use of PASS is generally important.
- 2. PASS can be effectively used for finding of compounds with required properties and without undesirable side effects.

- 3. It used for selecting the most prospective compounds from the set of available samples for specific screening.
- 4. For determining of more relevant screens for particular compound.

Due to this significance of PASS, it is used in the present study as a tool to design the drug with highest probable activity.

EXPERIMENTAL

Melting points were determined in open capillary tubes and were uncorrected. The IR spectra were recorded in KBr pellets on a Nicolet 400D spectrometer and¹H NMR spectra were recorded in CDCl₃ with TMS as internal standard on a Bruker spectrometer at 400 MHz. LC-MS of selected samples taken on LC-MSD-Trap-SL_01046 Purity of the compounds were checked by TLC on silica- G plates. Antimicrobial activities are checked by using pass software.

Preparation of 3-Phenylamino-2-thioxothiazolidin-4-one

Aniline 1.86 g (0.02 mol), carbon disulfide 1.52 g (0.02 mol) and chloroacetic acid 1.88g were mixed in ethanol (20mL) in 100 mL RBF, 10% NaHCO₃ solution (2mL) was added and the reaction mixture was irradiated with microwaves at 20% microwave power (140 W) for 5 mins. The reaction mixture was cooled solid separated and the separated product was filtered, washed with ethanol (5 mL) and recrystallized from ethanol. The yields, melting points and other characterization data of these compounds are given in Table-1, 2.

Preparation of 3-Benzyl-2-thioxo-thiazolidin-4-one

Benzyl amine 2.16 g (0.02 mol), carbon disulfide 1.52 g (0.02 mol) and chloroacetic acid 1.88g was taken in 100 mL RBF with 20 ml ethanol10% NaHCO₃ solution (2mL) was added and subjected to microwave irradiations at 20% microwave power (140 W) for 5 mins. The reaction mixture was cooled and poured in ice to

obtain yellow solid which was filtered, washed with little water and recrystallized from 30% ethanol. The yields, melting points and other characterization data of these compounds are given in Table-1, 2.

Preparation of 3-(4-Chloro-phenyl)-2-thioxothiazolidin-4-one

4-chloro aniline 2.54 g (0.02 mol), carbon disulfide 1.52 g (0.02 mol) and chloro acetic acid 1.88g was taken in 100 mL RBF with 30 ml ethanol10% NaHCO₃ solution (2mL) was added and subjected to microwave irradiatates at 20% microwave power (140 W) for 5 mins. The reaction mixture was cooled and poured in ice to obtain white solid which was filtered, washed with little water and recrystallized from 50% ethanol. The yields, melting points and other characterization data of these compounds are given in Table-1, 2.

Preparation of 3-(2-Methyl-cyclohexa-2,4dienyl)-2-thioxo-thiazolidin-4-one

o-Tolyl amine 2.16 g (0.02 mol), carbon disulfide 1.52 g (0.02 mol) and chloroacetic acid 1.88g was taken in 100 mL RBF with 30 ml ethanol10% NaHCO₃ solution (2mL) was added and subjected to microwave irradiations at 20% microwave power (140 W) for 5 mins. The reaction mixture was cooled and poured in ice to obtain yellow solid which was filtered, washed with little water and recrystallized from 30% ethanol. The yields, melting points and other characterization data of these compounds are given in Table -1,2.

Preparation of 3-Phenylamino-2-thioxothiazolidin-4-one

Phenyl hydrazine 2.16 g (0.02 mol), carbon disulfide 1.52 g (0.02 mol) and chloroacetic acid 1.88g was taken in 100 mL RBF with 30 ml ethanol 10% NaHCO₃ solution (2mL) was added and was irradiated at 20% microwave power (140 W) for 4 mins. The reaction mixture was cooled and poured in ice to obtain brawn solid which was filtered, washed with little water and recrystallized from 50% ethanol. The yields, melting points and other characterization

data of these compounds are given in Table -1, 2.

Preparation of 3-Phenylamino-2-thioxothiazolidin-4-one

Phenyl hydrazine 2.16 g (0.02 mol), carbon disulfide 1.52 g (0.02 mol) and chloroacetic acid 1.88g was taken in 100 mL RBF with 25 ml ethanol10% NaHCO₃ solution (2mL) was added and subjected to microwave irradiations at 20% microwave power (140 W) for 4 mins. The reaction mixture was cooled and poured in ice to obtain black solid which was filtered, washed with little water and recrystallized from 50% ethanol. The yields, melting points and other characterization data of these compounds are given in Table -1, 2.

Preparation of 3(2,4-diamino-phenylamino)-2-thioxo-thiazolidin-4-one

2,4Dinitrophenylhydrazine 2.96 g (0.02 mol), carbon disulfide 1.52 g (0.02 mol) and chloroacetic acid 1.88g was taken in 100 mL RBF with 20 ml ethanol 10% NaHCO₃ solution (2mL) was added and subjected to microwave irradiations at 20% microwave power (140 W) for 9 min. The reaction mixture was cooled and poured in ice to obtain brawn solid which was filtered, washed with little water and recrystallized from 50% ethanol. The yields, melting points and other characterization data of these compounds are given in Table -1, 2.

Preparation of 3-(2,Benzoyl-4-chlorophenyl)-2-thioxo-thiazolidin-4-one

2 amino 5 chloro benzo acetophenone 4.65 g (0.02 mol), carbon disulfide 1.52 g (0.02 mol) and chloroacetic acid 1.88g was taken in 100 mL RBF with 30 ml ethanol 10% NaHCO₃ solution (2mL) was added and was irradiated at 20% microwave power (140 W) for 8 min. The reaction mixture was cooled and poured in ice to obtain brawn solid which was filtered, washed with little water and recrystallized from 20% ethanol. The yields, melting points and other characterization data of these compounds are given in Table -1, 2.



Table 1: Analytical Data and Elemental Analysis of Compounds (1A-G)

Comp.	Molecular formula	Yield	LC- MS data	M.P. ⁰ C	%C		% H		%N		%S	
					Found	Cal.	Found	Cal.	Found	Cal.	Found	Cal.
IA	C ₉ H ₇ NOS ₂	90	215	101	51.65	51.65	3.59	3.6	6.09	6.09	30.64	30.64
I B	C ₁₀ H ₉ NOS ₂	86.33	230	112	53.79	53.75	4.06	4.06	6.27	6.28	28.72	28.7
I C	C ₉ H ₈ ClNOS ₂	87.54	218	90	43.99	43.96	3.28	3.28	5.7	5.7	27.05	27.05
I D	$C_{10}H_{11}NOS_2$	71.94	235	96	53.3	53.3	4.92	4.95	6.22	6.2	28.46	28.45
ΙE	$C_9H_8NOS_2$	85.6	220	98	48.19	48.18	3.37	3.39	12.06	12.03	28.59	28.61
ΙF	$C_9H_{10}N_4OS_2$	75.3	246	138	42.5	42.7	3.96	3.96	22.03	22	25.21	25.21
I G	C ₁₆ H ₁₀ ClNOS ₂	80.6	238	158	55.6	55.5	2.9	2.11	4.03	4.03	18.44	18.46

RESULTS AND DISCUSATION

It was observed that Aniline carbon disulfide and chloro acetic acid on condensed in scientic 3-Phenyl-2-thioxomicrowoven yields thiazolidin-4-one. (I A). The structures of (IA) were confirmed by elemental analysis and IR spectra showing an absorption band at 1310(C=S),1590 C-C=C(AR), 3050 C=C-H, 1340 C-Nstr, 755 C-Sstr,1634 C=Nstr, 1780 C=Ostr 2980 H-C-H. ¹HNMR: 7.40-7.30(5H m) δ 4.49(2H s)-CH2 of Thizolidinone1.8.92(1H d) -CH of Thizolidinone, 3.85-3.75-S-CH2 -Cof Thizolidinone, MS m/z (M+):209 The C, H, N analysis data of all compounds are presented in Table-1.

The examination of elemental analytical data reveals that the elemental contents are consistence with the predicted structure shown in Scheme. The IR data also direct for assignment of the predicted structure. The final structure of all compounds is confirmed by LC-MS. LC-MS data of Samples Ia and gives the molecular ion peak (m/z) at 209 and respectively. These values are corresponds to their molecular weight.

QSAR Analysis of Activities with PASS

The relationship between structure and different biological activities was studied using computer programme PASS. The structures of derivatives [I(a-g)] were studied for the predictions of their probabilities of being active [Pa] and inactive [Pi] for the selected activities. The following five activities were predicted with top probability for the series of compounds [I(a-g)]

- 1. Insulin inhibitor
- 2. Mcl-1 antagonist
- 3. Hepatic disorders treatment
- 4. Dual specificity phosphatase
- 5. Thiol protease inhibitor

Insulin Inhibitor

Diabetes mellitus type 2 (formerly noninsulindependent diabetes mellitus (NIDDM)or adultonset diabetes) is a metabolic disorder that is characterized by high blood glucose in the

of insulin resistance and context relative insulin deficiency.¹¹ This is in contrast to diabetes mellitus type 1, in which there is an absolute insulin deficiency due to destruction of is let cells in the pancreas.¹² The classic symptoms are excess thirst, frequent urination, and constant hunger. Type 2 diabetes makes up about 90% of cases of diabetes with the other 10% due primarily to diabetes mellitus type 1 and gestational diabetes. Obesity is thought to be the primary cause of type 2 diabetes in people who are genetically predisposed to the disease. Type 2 diabetes is initially managed by increasing exercise and dietary modification. If blood glucose levels are not adequately lowered by these measures, medications such as metformin or insulin may be needed. In those on insulin, there is typically the requirement to routinely check blood sugar levels.

Rates of type 2 diabetes have increased markedly over the last 50 years in parallel with obesity: As of 2010 there are approximately 285 million people with the disease compared to around 30 million in 1985.^{[4][5]} Long-term complications from high blood sugar can include heart disease, strokes, diabetic retinopathy where eyesight is affected, kidney failure which may require dialysis, and poor circulation in the limbs leading to amputations. The acute complication of ketoacidosis, a feature of type 1 diabetes, is uncommon.¹⁴⁻¹⁵ However, nonketotichyperosmolar coma may Thiazolidinone improve sensitivity, occur. inhibit the release of glucose from the liver and slightly increase high density lipoprotein(HDL)or good cholesterol.

Mcl-1 Antagonist

Mcl-1 is frequently associated with advanced human PCa (high-Gleason-grade primary tumors and metastases)¹⁸, as well as other carcinomas and leukemia¹⁸. Mcl-1 is a highly regulated antiapoptotic member of the Bcl-2 protein family known to antagonize the function of many proapoptotic BH and BH3-only proteins¹⁷. Elevated expression of Bcl-2 family of proteins is a key mechanism resulting in evasion of mitochondrial-dependent apoptosis by cancer cells¹⁸. Previous studies from our laboratories and from others^{16–22} have reported that the natural product Gossypol is a potent Bcl-2, $Bcl-X_I$ and inhibitor of Mcl-1, functioning as a BH3 mimic, is currently in clinical trials, displaying single-agent antitumor activity in patients with advanced malignancies. However, we anticipated that the two reactive aldehyde groups could render Gossypol intrinsically toxic and was thus eliminated to lead to the compound Apogossypol^{23–26}. Further modifications on Apogossypol were made to improve potency and efficacy. These studies culminated in Sabutoclax, with increased potency *in vitro* against Bcl-2 family proteins ²⁵⁻ ⁷. Here we report the use of Sabutoclax (SBX, also known as BI-97C1) to inhibit prostate tumor progression. We used multiple PCa models to specifically test late stage disease that can involve castrate resistance, bone metastasis, and docetaxel resistance. In our studies, Sabutoclax caused the regression of CRPC transgenic and xenograft models at both primary and bone microenvironments. A mediator of PCa castrate resistance and metastasis, the HGF/c-Met signaling, was downregulated by Sabutoclax treatment in *in* vitro and in vivo models. Sabutoclax restored sensitivity of PCa epithelial cells to intracellular apoptotic signaling, both alone and with docetaxel, resulting in substantial reduction in tumor progression.

Hepatic Disorders Treatment

There are many kinds of liver diseases. Viruses cause some of them, like hepatitis A, hepatitis B and hepatitis C. Others can be the result of drugs, poisons or drinking too much alcohol. If the liver forms scar tissue because of an illness, it's called cirrhosis. Jaundice, or yellowing of the skin, can be one sign of liver disease.

Cancer can affect the liver. You could also inherit a liver disease such ashemochromatosis. Liver failure occurs when large parts of the liver become damaged beyond repair and the liver is no longer able to function. Liver failure is a lifethreatening condition that demands urgent medical care. Most often, liver failure occurs

gradually and over many years. However, a more rare condition known as acute liver failure occurs rapidly (in as little as 48 hours) and can be difficult to detect initially. The most common causes of chronic liver failure (where the liver fails over months to years) include: Hepatitis B Hepatitis C, Long term alcohol consumption, Cirrhosis Hemochromatosis (an inherited disorder that causes the body to absorb and store too much iron) Malnutrition The causes of acute liver failure, when the liver fails rapidly, however, are often different. These include Acetaminophen (Tylenol) overdose. Viruses including hepatitis A, B, and C (especially in children). Reactions to certain prescription and herbal medications. Ingestion of poisonous wild mushrooms.

Dual-Specificity Phosphatase

of phosphatase that can Is a form act upon tyrosine or serine threonine residues? There are several families of Dual-Specificity Phosphatase (DUSP) enzymes in mammals. All share a similar catalytic mechanism, by which a conserved cysteine residue forms a covalent intermediate with the phosphate group to be eliminated. The residues surrounding their calatytic core obey a rather strict consensus: His-Cys-x-x-x-x-Arg-Ser. The serine side chain and an additional conserved aspartate play a central role in the elimination of the Cyslinked intermediate, thus completing their enzymatic cycle.² The main difference between tyrosine-specific phosphatases and dualspecificity phosphatases lies in the width of the latter enzymes' catalytic pocket: thus they can accommodate phosphorylated serine or threonine side chains as well as phosphorylated (dual-specificity tyrosines. DUSPs phosphatases) are a heterogeneous group of protein phosphatases that can dephosphorylate phosphotyrosine both and phosphoserine/phosphothreonine residues within the one substrate. DUSPs have been implicated as major modulators of critical signalling pathways that are dysregulated in various diseases. DUSPs can be divided into six subgroups on the basis of sequence similarity that include slingshots, PRLs (phosphatases of

regenerating liver), Cdc14 phosphatases (Cdc is cell division cycle), PTENs (phosphatase and tensin homologues deleted on chromosome 10), myotubularins, **MKPs** (mitogen-activated protein kinase phosphatases) and atypical DUSPs. Of these subgroups, a great deal of research has focused on the characterization of the MKPs. As their name suggests, MKPs (mitogen-activated dephosphorylate MAPK protein kinase) proteins ERK (extracellularsignal-regulated kinase), JNK (c-Jun N-terminal kinase) and p38 with specificity distinct from that of individual MKP proteins. Atypical DUSPs are mostly of low-molecular-mass and lack the N-terminal CH2 (Cdc25 homology 2) domain common to MKPs. The discovery of most atypical DUSPs has occurred in the last 6 years, which has initiated a large amount of interest in their role and regulation. In the past, atypical DUSPs have generally been grouped together with the MKPs and characterized for their role in MAPK signalling cascades. Indeed, some have been shown to dephosphorylate MAPKs. The current literature hints at the potential of the atypical DUSPs as important signalling regulators, but is crowded with conflicting reports. The present review provides an overview of the DUSP family before focusing on atypical DUSPs, emerging as a group of proteins with vastly diverse substrate specificity and function.

Thiol Protease Inhibitor

Biological thiol-dependent enzymes have recently received extensive attention in the literature because of their involvement in a variety of physiopathological conditions. The active thiol groups of these enzymes are derived from the cysteine residues present. Hence, in a biological system, the selective reversible or irreversible inhibition of the activity of these enzymes by modification of the thiol moiety may potentially lead to the development of a chemotherapeutic treatment. Despite all the research efforts involved in the attempt to develop potential chemotherapeutic treatments for the major diseases involving cysteine proteases, there are in fact no such treatments available yet. However, AG7088 (1) an inhibitor

of rhinovirus-3C is in phase II/III clinical trial for the treatment of common cold and VX-740 (2, pralnacasan) an inhibitor of caspase-1 is in phase II clinical trial as an anti-inflammatory agent for rheumatoid arthritis. Several other cysteine protease inhibitors (i.e., cathepsin K, and S) are in pre-clinical evaluation or preclinical development. Structure-based drug design approaches have been instrumental in the development of these inhibitors. Intensive biochemical studies on the cysteine proteases have shed some light on some potential targets for therapeutic development. In addition, new techniques and new ideas are constantly emerging. As such, an up-to-date review of the literature on thiol-dependent enzymes as potential targets and their inhibitors designed peptidic. from modified peptidomimetic scaffolds and from small heterocyclic molecules is presented.



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Comp	\mathbf{R}^{1}	Insulin inhibitor	Mcl-1 antagonist	Hepatic disorders treatment	Dual specificity phosphatase inhibitor	Thiol protease inhibitor
ΙA	$C_6H_5NH_2$	0.85	0.887	0.821	0.777	0.713
I B	C ₆ H ₅ -CH ₂ -NH ₂	0.747	0.765	0.601	0	0
I C	4-Cl- C ₆ H ₅ NH ₂	0.827	0.828	0.774	0.695	0.644
I D	2-Methyl-C ₆ H ₅ NH ₂	0.867	0.798	0.685	0.667	0.582
ΙE	C ₆ H ₅ NH-NH ₂	0.766	0.841	0	0	0
ΙF	2,4Dinitrophenylhydrazine	0.608	0.854	0.621	0.540	0.650
IG	2amino5chlorobenzoacetoph enone	0.837	0.765	0.634	0.652	0.544

Table 2: Results of biological activities along with pa predicted by PASS are described







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