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Thiazolidine-4-carbonitriles and analogues and their use as dipeptidyl-peptidase inhibitors

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(54) **Title:** THIAZOLIDINE-4-CARBONITRILES AND ANALOGUES AND THEIR USE AS DIPEPTIDYL-PEPTIDAS INHIBITORS

(57) **Abstract:** The invention discloses a novel series of compound represented by general formula (I), its derivatives, analogs, tautomeric forms, stereoisomers, polymorphs, pharmaceutically acceptable salts, solvates wherein X, n, k, z, R₁, R₂, R₃, R₄, R₅ and R₆ are as defined in the specification that are useful in (i) normalizing elevated blood glucose levels in diabetes, (ii) treating disorders related to glucose intolerance and (iii) for scavenging free radicals of mammals. The invention also discloses pharmaceutically acceptable composition comprising these compounds, method for preparation of the compounds as defined above and method of treating mammals including human beings by administering an effective amount of said compounds to a subject in need thereof. The invention further discloses use of these compounds in the manufacture of a medicament useful for treatment of different disease conditions as stated above.

CROSS REFERENCE TO RELATED APPLICATIONS

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This application claims benefit from U.S. provisional application No.60/370,224 filed April 08, 2002 which is incorporated herein by reference in its entirety.

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BACKGROUND OF THE INVENTION

1. FIELD OF THE INVENTION

10 The present invention relates to novel heterocyclic compounds useful for normalizing elevated blood glucose levels in diabetics and in treating disorders related to glucose intolerance.

15 These compounds inhibit the enzyme DPP-IV, that degrade the peptide GLP-1, providing for enhanced levels of active GLP-1, a peptide which normalizes elevated blood glucose levels.

20 These compounds are useful to control blood glucose level in diabetic patients and thereby delay the onset of vascular complications in diabetic patients and also transition to type II diabetes in impaired glucose tolerant patients.

25 These compounds are also useful in treating disorders related to glucose intolerance like Cushing's syndrome, hyperthyroidism, obesity, hyperglucagonemia, diseases like ulcers, HIV infection, disorders related to increased gastric emptying, acid secretion and hunger, autoimmune disorders like multiple sclerosis, rheumatoid arthritis and Grave's disease (Sedo and Kraml, 1994).

30 These compounds also exhibit free radical scavenging activity which is useful in treatment of various disease condition caused by accumulation of free radicals in the body cells.

2. DESCRIPTION OF THE RELATED ART

Diabetes mellitus is a clinically and genetically heterogenous group of disorders characterized by abnormally high levels of glucose in the blood. The
5 hyperglycemia is due to deficiency of insulin secretion or to resistance of body cells to the action of insulin, or to a combination of these. Chronic hyperglycemia is a cause of heavy burden of morbidity and premature mortality from diabetic complications. These long-term complications can be delayed by improving glycemetic control. None of the currently used medications is capable of reversing an ongoing
10 failure of β -cell function and reduction in post prandial glucose peak represents an important target for therapeutic strategies.

Although pancreatic insulin secretion is predominantly controlled by blood glucose levels, incretins like the peptide GLP-1 derived from enteroinsular axis have
15 an effect on insulin secretion and therefore on the blood glucose level. It is released from the gut in response to ingested nutrients, which acts on the pancreas to potentiate glucose-induced insulin secretion. GLP-1 has beneficial effects in diabetic patients in normalizing elevated blood glucose levels (Holst J and Deacon C, 1998). GLP-1 has multifaceted actions, which include stimulation of insulin gene expression, trophic
20 effects on β -cells, inhibition of glucagon secretion, promotion of satiety, and slowing of gastric emptying. Because of glucose dependency of the peptide and glucagonostatic actions, the glucose lowering effect is self-limiting, and the hormone, therefore does not cause hypoglycemia regardless of the dose.

25 The pathogenesis of type-2 diabetes ordinarily involves the development of insulin resistance associated with compensatory hyperinsulinaemia followed by progressive beta-cell impairment that results in decreasing insulin secretion and hyperglycemia. Hyperglycemia itself causes additional inhibition of insulin secretion and more insulin resistance (glucose toxicity), which further accentuates the
30 hyperglycemia. (Augustyns K. et al. The unique properties of Dipeptidyl-peptidase IV (DPP-IV/ CD 26) and the therapeutic potential of DPP - IV inhibitors. Current Medical Chemistry 1999; 6:311-327)

Most therapies used at present ultimately fail to control blood sugar level after 3-5 years. This is due to the progressive β -cell failure in the course of the disease and insulin is finally required in most type-2 diabetic patients.

5

Impaired glucose tolerance and impaired fasting glucose is present in a large population. These abnormalities progress to a large extent to overt diabetes. No therapy has been approved for the prevention or delay of type-2 diabetes in these patients.

10

Dipeptidyl Peptidase IV (DPP-IV) inhibitors addresses to a large extent the inadequacies of the presently available therapies. It targets not only the β -cell dysfunction but also insulin resistance and increased hepatic glucose output by liver. Thus, it has a more holistic approach towards the treatment of type-2 diabetes.

15 Furthermore, by stabilizing / reversing the progressive β -cell dysfunction, it would prevent the progression of the disease and for the same reason, it has the potential to prevent or delay the occurrence of overt diabetes in subjects with impaired fasting glucose and impaired glucose tolerance. (Pathogenesis of type-2 Diabetes; Harold E Lebovitz, Drug Benefit Trends 12 (supp A):8-16, 2000).

20

The presently used antihyperglycemic drugs target either insulin resistance or β -cell dysfunction. Hence, there is a need to address both these pathologies together.

25 The homeodomain transcription factor, PDX-1 is essential for the early development of the pancreas and the maintenance of the β -cell phenotype. PDX-1 is known to regulate insulin, GLUT2 and islet amyloid precursor. Under conditions of sustained hyperglycemia, such as in the diabetic state, there is a downregulation of PDX-1 expression and a decrease in insulin secretion (Doyle and Egan, 2001). GLP-1 induces the differentiation of PDX-1 positive pancreatic epithelial cells into insulin-secreting cells. GLP-1 stimulates the expression of transcription factor PDX-1 while
30 stimulating β -cell neogenesis and may thereby be an effective treatment for diabetes. GLP-1 and a long acting GLP-1 analogue exendin-4, stimulates both β -cell replication

and neogenesis, resulting in increased β -cell mass and improved glucose tolerance in partial pancreatectomy rat model of type 2 diabetes (Gang et al, 1999).

GLP-1₇₋₃₆ is one of the substrate for the circulating exopeptidase dipeptidyl
5 peptidase IV (EC 3.4.14.5), a post proline cleaving enzyme with a specificity for
removing Xaa-Pro or Xaa-Ala dipeptides from the N-terminus of polypeptides and
proteins. DPP-IV is widely distributed in tissues like kidney, intestine and placenta,
hepatocytes, epithelial cells of pancreatic duct, central nervous system, peripheral
nervous system, endothelial cells of blood vessels (Rolf, 1999), and found as soluble
10 enzyme in blood plasma. About 50% of the GLP-1₇₋₃₆ amide released from the L cells
is inactivated in the capillary bed surrounding these cells by DPP-IV. Furthermore,
single pass through the liver inactivates a large fraction of the remaining active GLP –
1 (>40%) (Bork and Xue, 2000). Thus these two processes together with inactivation
in the circulatory system and in other organs can be expected to inactivate or remove
15 most of the GLP-1 released from the duodenum and intestine before the peptide can
reach the pancreas in the active form. Hydrolysis of GLP-1₇₋₃₆ by DPP-IV yields the
truncated oligopeptide GLP-1₉₋₃₆ and the dipeptide His-Ala. This N- terminally
truncated form is not insulinotropic and acts as an antagonist at GLP-1 receptor. GLP-
1 is rapidly degraded in the circulation, which results in clearance that exceeds cardiac
20 output and an apparent half-life of 1-1.5 min. The truncated metabolite is eliminated
more slowly, with half-lives of 4-5 min for GLP-1₉₋₃₆. It has been speculated that
DPP-IV-mediated hydrolysis is the primary mechanism of inactivation of this
hormone in vivo (Tina et al, 2001).

25 Because of rapid degradation, the effects of single injections of GLP-1 are
short lasting and for a full demonstration of its anti-diabetogenic effects, continuous
intravenous infusion is required. Therefore, it is proposed that the inhibition of DPP-
IV, that elevate the levels of active GLP-1 and reduce the level of antagonistic
metabolite, may be useful to treat impaired glucose tolerance and perhaps transition to
30 type 2 diabetes.

(Siegel et al (1999) reported that analogues of GLP-1 resistant to degradation by DPP-IV might help to realize the potential of GLP-1 in diabetes therapy.

DPP-IV inhibitor, Isoleucine thiazolidide (P-32/98), completely inhibited the formation of GLP-1₉₋₃₆, an antagonist at GLP-1 receptor, when it was incubated with 30 mM/L GLP-1₇₋₃₆ and serum for 21 hours. Inhibition of circulating DPP-IV enhanced insulin secretion and improved glucose tolerance in response to oral glucose challenge in lean and obese fatty (fa/fa) rats. (Raymond et al, 1998). Also it has improved glucose tolerance in Zucker fatty rats (Robert et al, 1999)

10

It is reported that a DPP-IV inhibitor NVP-DPP-728 i.e. 1-[-2-[(5-cyanopyridin-2-yl) amino]ethylamino]acetyl-2-cyano-(S)-pyrrolidine inhibits DPP-IV activity and improves insulin secretion and glucose tolerance, through augmentation of the effects of endogenous GLP-1. The improvement in prandial glucose homeostasis during DPP-IV inhibition by this molecule suggests that inhibition of this enzyme is a promising target for treating type 2 diabetes (Balkan et al, 2000) Also this molecule showed potentiation of insulinotropic effects of GLP-1 in anaesthetized pig (Carolyn et al, 1998).

20

These data support a therapeutic approach of drug manipulation of plasma incretin activity by lowering glucose levels in NIDDM and other disorders involving glucose intolerance.

Dipeptidyl Peptidase IV (DPP – IV) is a proline specific protease and is involved in breaking peptide bonds before or after a proline residue. It plays an important role in the regulation of the life-time of biological active peptides like growth hormone releasing factor (GRF), Glucagon-like peptide – I (GLP-I), Gastric Inhibitory Polypeptide (GIP), Glucagon-like peptide – II (GLP-II), β -Casomorphin, morphiceptin, Human Neuropeptide Y, Human Peptide YY (Augustyns K. et al. 1999) DPP – IV is present on the surface of a subset of T-cells (lymphocytes) and has been recognized as CD 26 antigen.

30

Dipeptidyl peptidase-IV (DPP-IV) is a serine protease, which cleaves N-terminal dipeptides from a peptide chain containing, preferably, a proline residue in the penultimate position. DPP-IV is responsible for inactivating glucagon-like peptide-1 (GLP-1). More particularly, DPP-IV cleaves the amino-terminal His-Ala dipeptide of GLP-1, generating a GLP-1 receptor antagonist, and thereby shortens the physiological response to GLP-1. Since the half-life for DPP-IV cleavage is much shorter than the half-life for removal of GLP-1 from circulation, a significant increase in GLP-1 bioactivity (5- to 10-fold) is anticipated from DPP-IV inhibition. Since GLP-1 is a major stimulator of pancreatic insulin secretion and has direct beneficial effects on glucose disposal, DPP-IV inhibition appears to represent an attractive approach for treating non-insulin-dependent diabetes mellitus (NIDDM). GLP-1 has multifaceted actions, which include stimulation of insulin gene expression, trophic effects on β -cells, inhibition of glucagon secretion, promotion of satiety, and slowing of gastric emptying, all of which contribute to normalizing elevated blood glucose levels (Holst and Deacon, 1998). Because of glucose dependency of the peptide and glucagonostatic actions, the glucose lowering effect is self-limiting, and the hormone, therefore does not cause hypoglycemia regardless of the dose.

The exact biological functions of DPP – IV / CD 26 are still under investigation, but considerable evidence exists for the therapeutic potential of DPP-IV inhibitors.

Although a number of DPP-IV inhibitors have been described, all have limitations relating to potency, stability or toxicity. Accordingly, a great need exists for novel DPP-IV inhibitors, which do not suffer from the above-mentioned limitations.

30 **Type – II Diabetes Mellitus:** -

DPP – IV is involved in the degradation of GIP and GLP-I. GIP and GLP-I are considered to be most important insulin-releasing hormones (incretins) comprising the enteroinsular axis. The term enteroinsular axis refers to the signaling pathways between the gut and pancreatic islets that amplify the insulin response to absorbed

nutrients. Inhibition of circulating DPP – IV with orally administered tetrahydrozoline
[DPP-IV inhibitor] enhanced insulin secretion and improved glucose tolerance in
response to an oral glucose challenge in lean and obese Zucker rats. The enhanced
incretin response was greater in obese than in lean animals, with a more profound
5 improvement in glucose tolerance (Pederson R. A, 1998). This was attributed to
disruption of DPP – IV inactivation of GIP and GLP-I, resulting in amplification of
enteroinsular axis.

DPP-IV inhibitors would have very little effect on subjects with normal blood
10 glucose levels regardless of dose because its actions are glucose dependent
(Qualmann C et al. 1995).

Hyperthyroidism and glucose intolerance

15 In patients with preexisting type I or type II diabetes mellitus, the presence of
hyperthyroidism renders blood glucose management more difficult. Influences of
thyroid hormone on insulin secretion and cellular metabolism have been implicated
on the basis of *in vitro* and animal studies. In rats, thyroxine and triiodothyronine
treatment inhibits the delayed phase of glucose-mediated insulin secretion-
20 triiodothyronine being fivefold more potent than thyroxine.

In hyperthyroid states, gluconeogenic precursor (lactate and glycerol) are
present in increased concentration in plasma. In rats, increased activity of
mitochondrial glycerol, phosphate oxidase increases the capacity for gluconeogenesis
25 from glycerol. It has also been shown in rats and pigs that hyperthyroidism leads to an
increase in futile cycling of glucose, which could contribute to hyperglycemia.
Increased activity of several enzymes that could be implicated in the increase in
gluconeogenesis have been seen in response to thyroid hormone, including
glucokinase, pyruvate carboxylase, phospho-enolpyruvate carboxykinase, and
30 glucose-6-phosphatase. Studies in hyperthyroid patients report impairment in insulin
suppression of hepatic glucose production. A recent study has also shown the
inability to increase the insulin response appropriately to hyperglycemia and increased
proinsulin levels, both fasting and in response to a meal (Michael Berelowitz and

Lone A Kourides, 2000). Glucose intolerance as a result of hyperthyroidism can be better managed by enhancing the levels of GLP-1 a glucose dependent insulinotropic agent.

5 Obesity and glucose intolerance

Obesity has been related to insulin resistance and hyperinsulinemia. Visceral obesity is associated with specific changes in skeletal muscle morphology that correlate with insulin resistance and hyperinsulinemia, namely a reduction in capillary density and an increase in the proportion of 'white' or 'glycolytic' fibers which are less insulin sensitive than red (glycolytic) fibers. TNF-alpha is secreted by adipose tissue and its circulating levels parallel total body fat mass. Circulating non-esterified fatty acid (NEFA) levels are raised in obese subjects, especially those with visceral obesity. In the liver, NEFA are oxidised to acetyl CoA, which stimulates pyruvate carboxylase and therefore gluconeogenic production of glucose from pyruvate; hepatic glucose production therefore increases. High NEFA level may also inhibit glucose utilization by skeletal muscle. Increased acetyl CoA levels inhibit pyruvate dehydrogenase, thus decreasing glucose oxidation. The combination of increased hepatic glucose output and reduced peripheral uptake effectively antagonises and would ultimately lead to hyperglycemia (Ronald T Jung, 1997). Glucose intolerance as a result of the above conditions can be managed better by the elevation of GLP-1 levels (as a result of DPP-IV inhibition).

25 Cushing's syndrome and glucose level

Cushing's syndrome represents a distinctive constellation of clinical features associated with prolonged overproduction of impaired glucose tolerance, overt diabetes (in approximately 20%), loss of libido and impotence. Some of these abnormalities such as obesity, deranged glucose metabolism are directly attributable to increased glucocorticoids. These glucocorticoids stimulate gluconeogenesis in diabetes. Also, they increase amino acid uptake by the liver and kidney and increase

the activity of enzymes required for gluconeogenesis and may lead to hyperglycemia
(Ronald A DeLellis, 1989)

Glucose metabolism under the above conditions can be managed better by
5 treatment with DPP-IV inhibitors.

Role of DPP- IV in HIV infection

Prevention and treatment of HIV infection

10

The role of CD26 in HIV infection is also not completely clear yet, but seems
to be important. Some DPP-IV inhibitors are reported to inhibit HIV infection such
as pyrrolidine-2-nitriles and an irreversible cyclopeptide inhibitor (Nguyen C et al.
1998).

15

DPP-IV has been originally described to be a marker of activated T
lymphocytes and lately DPP-IV/CD26 molecular identity has been proven
CD26/DPP-IV serves as an essential cofactor for HIV entry into CD⁴⁺ cells and that
its enzyme activity is an important condition for this function (Sedo A and Kraml J,
20 1994). Hence inhibition of DPP-IV could prove useful in the management of HIV
infection.

Immunosuppressant

25 It has been shown that DPP-IV / CD26 plays an important role in the immune system
by a number of possible mechanisms. The exact mechanism remains to be elucidated,
but a few examples are reported where DPP-IV inhibitors are useful
immunosuppressants *in vivo*. A dipeptide diphenyl phosphonate ester was able to
abrogate acute rejection and prolong allograft cardiac survival (Korom S. et al. 1997).

30

Role of DPP-IV inhibitors in ulcers, hyperglucagonemia, gastric emptying and hunger

DPP-IV inhibitors increase the level of GLP-1. GLP-1 has multifaceted actions, which include stimulation of insulin gene expression, inhibition of glucagon secretion, promotion of satiety, inhibition of food intake and slowing of gastric emptying (Holst JJ and Deacon CF, 1998).

10 GLP-1 also reduces gastric acid secretion (Michael A Nauck, 1999). Increase in gastric acid secretion is one the main reason for duodenal ulcers. By inhibiting gastric acid secretion, GLP-1 and therefore DPP-IV inhibitors may prove useful for the treatment of ulcers or can be used in combination with other antiulcer agents.

15 **Diarrhea**

DPP-IV is involved in metabolic processing of morphiceptin. Co-administration of a DPP-IV and the opiate peptide morphiceptin could be used in case of diarrhoea, as the experiment with DPP-IV deficient rats showed (Tirupathi, C., et al., Am. J. Physiol. 1993).

20 **Mucosal Regeneration in patient with Intestinal Disease**

DPP-IV hydrolysis of GLP-2 is responsible for its inactivation. GLP-2 has recently been shown to display intestinal growth factor activity in rodents, raising the possibility that GLP-2 may be therapeutically useful for enhancement of mucosal regeneration in patients with intestinal disease (Drucker, D.J. et al. Diabetes 1998; 47:159). The use of [Gly²] GLP-2, resistant to DPP-IV hydrolysis, increases small bowel weight in mice, predominantly due to a significant increase in villous height (Brubaker P.L. et al. Am. J. Physiol. 1997).

Growth Hormone Deficiency

5 Since GRF is also degraded by DPP-IV, the use of a DPP-IV inhibitor together with GRF could be useful to treat children with growth hormone deficiency (Augustyns K. et al. 1999)

Neurological and Neuropsychological Disorders

10 Administration of a suitable DPP-IV inhibitor leads as a causal consequence to a reduced degradation of the neuropeptide Y(NPY) in the brain of mammals. Such treatment will result in a reduction or delay in the decrease of the concentration of functionally active neuronal NPY (1-36). As a consequence of the resulting enhanced stability of the endogenous NPY (1-36), NPY activity is prolonged thereby resulting
15 among other things in functionally active NPY Y1 receptor activity thereby facilitating antidepressive, anxiolytic, analgesic, antihypertension and other neurological effects (WO 02/34243 dated 02 May 2002 by PROBIODRUG AG).

Cancers and Tumours

20 DPP-IV is able to bind proteins of the extracellular matrix as a cell adhesion molecule. This has been interpreted from the observation that the DPP-IV inhibitors interfere *in vitro* with the initial spreading of rat hepatocytes on a matrix consisting of fibronectin and collagen. Thus the DPP-IV inhibitors could also be used for the
25 prevention/treatment of cancer metastasis and tumour colonization (WO 03/002595 dated 09 Jan 2003 by PROBIODRUG AG).

Free Radical Scavenging Activity

30 It has been reported that compounds exhibiting free radical scavenging activity are useful in treatment of Neurodegenerative disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Motor Neuron Disease, Prion Disease etc, (b) Diabetes and Diabetic Vascular Complications, (c) Intestinal Diseases such as Intestinal Ischemia, Radiation Enteritis, Inflammatory Bowel Disease, Gastric and

Colorectal Cancers etc., (d) Liver Diseases such as Alcoholic Liver Disease, Chronic Hepatitis C etc., (e) Cancers such as Lung Cancer, Colorectal Cancer, Cervical Cancer, Breast Cancer, Malignant Melanoma etc, (f) Cardiac Diseases such as Atherosclerosis, Myocardial Infarction, Ischemic Stroke, Endothelial Dysfunction etc., (g) Ophthalmic Disorders such as Cataract formation, Macular degeneration etc., (h) HIV Diseases, (i) Respiratory Diseases such as Chronic Obstructive Pulmonary Diseases, Asthma etc., (j) Renal Diseases such as Glomerulonephritis, Acute Renal Failure etc.

Neuro-degenerative disorders such as Alzheimer's disease (A.D.), Parkinson's disease (P. D.), Huntington's disease (H.D.), Motor neuron disease (M.N.D), Prion disease

As people age, their antioxidant levels diminish and these low levels are directly linked to the many diseases associated with aging such as Alzheimer's and Parkinson's disease. One of the leading hypotheses is that oxidative stress induced by ROS damages essential components of the neurons, resulting ultimately in the neuronal death. Oxidative stress is involved in various divergent events leading to neuronal damage, including an increase in membrane rigidity, DNA strand break, and impairment in glucose uptake. Several potential sources of oxidative stress in different neurodegenerative disorders have been well identified (Munch G, et al. 1998).

In A.D. mitochondrial dysfunction, amyloid beta mediated processes; transition metal accumulation and genetic factors are responsible for the redox imbalance (Smith MA, et al. 2000).

Point mutations in Superoxide Dismutase enzymes are known in the familial form of MND.

Disturbances of neuronal energy metabolism have been implicated as a pathogenetic mechanism for H.D. (Browne SE, et al. 1999)

Diabetes and Diabetic Vascular Complications (DVCs)

The cause of oxidative stress in diabetes is not yet fully understood but is
5 thought to be due to mitochondrial dysfunction, direct enzyme inhibition by
hyperglycemia, auto-oxidation of glucose, and activation of nicotinamide-adenine
dinucleotide phosphate (NADPH)-oxidase. Oxidative stress in diabetes is also
increased due to weakened defenses due to reduced endogenous antioxidants. The
oxidative stress manifests itself as elevated concentrations of lipid peroxidation
10 products, erythrocyte fragility, and decreases in the antioxidant enzyme systems
(CAT, GSH Px, SOD). Recent studies also have shown a positive correlation between
blood glucose concentration and oxidant-induced lymphocyte DNA damage (E.J.
Harper The 24th Annual WALTHAM®/OSU SYMPOSIUM).

15 ROS are generated during glucose oxidation and formation of advanced
glycation end products (AGE). Evidence has accumulated indicating that the
generation of ROS plays an important role in the development of DVCs. Many
biochemical pathways associated with hyperglycemia such as advanced glycosylation,
glucose auto oxidation, and polyol pathway can increase the production of free
20 radicals. Hyperglycemia in diabetic patients leads to excess auto-oxidation of glucose
thereby reducing molecular oxygen and yielding oxidizing intermediates such as
superoxide ions (O_2^-), hydroxyl radicals ($\cdot OH$), and hydrogen peroxide (H_2O_2). Free
radicals accelerate the formation of advanced glycosylation end products (AGE),
because fragmentation and conformational changes occurring during glycosylation
25 and glucose oxidation have been shown to be dependent upon free radicals. AGEs in
turn supply more free radicals; this process is termed as oxidative glycosylation or
glycooxidation. These free radicals impair vascular relaxation by inactivating or
quenching nitric oxide (NO) and also adversely affect the endothelial function.
Evidence also suggests that Maillard reaction acts as an amplifier of oxidative damage
30 in aging and diabetes.

Intestinal diseases

5

Oxidative stress is an important cause of tissue injury that occurs in inflammation and ischemia. *Intestinal ischemia, radiation enteritis, inflammatory bowel disease*, and promotion of *gastric and colorectal cancers* are some of the gastro-intestinal conditions where oxidative stress is implicated in the pathogenesis.

10

Liver diseases

Alcoholic liver disease- Ethanol induces an increase in lipid peroxidation either by enhancing ROS or decreasing the level of endogenous antioxidants. Ethanol also induces variety of cytochrome P450 enzymes in microsomes and xanthine oxidases in cytosol. The role of these enzymes in the generation of oxidative stress has been well established in various studies (Ishii H, et al. 1997).

15

Chronic hepatitis C- Enhanced oxidative stress initiates a fibrogenesis cascade in the liver of patients with chronic hepatitis C. Evidences are coming up supporting an oxidative stress pathway leading to active fibrogenesis in chronic hepatitis C. This fibrogenesis cascade characteristic of severe chronic hepatitis C (e.g., oxidative stress, induction of c-myb, activation of stellate cells, and collagen gene expression) is stimulated by ROS.

20

25

Cancers

Oxidative damage to DNA is a result of interaction of DNA with ROS, in particular the hydroxyl radical. The hydroxyl radicals produce multiple modifications in DNA. Oxidative attack by OH radical on the deoxyribose moiety leads to the release of free bases from DNA, generating strand breaks with various sugar modifications and simple abasic (AP) sites

30

ROS also interact with and modify cellular protein, lipid, and DNA, which results in altered target cell function. The accumulation of oxidative damage has been implicated in both acute and chronic cell injury including possible participation in the formation of cancer. Acute oxidative injury may produce selective cell death and a compensatory increase in cell proliferation. This stimulus may result in the formation of newly initiated preneoplastic cells and/or enhance the selective clonal expansion of latent initiated preneoplastic cells. Similarly, sublethal acute oxidative injury may produce unrepaired DNA damage and result in the formation of new mutations and, potentially, new initiated cells. ROS, therefore, can have multiple effects in the initiation stage of carcinogenesis by mediating carcinogen activation, causing DNA damage, and interfering with the repair of the DNA damage.

15 Benefits of various antioxidants in preventing or treating following cancers have been extensively studied.

- 1) Lung cancer
- 2) Colorectal cancer
- 3) Cervical cancer
- 20 4) Breast cancer
- 5) Malignant melanoma

Oxidative stress in cardiac diseases

25 Lifelong high levels of antioxidant nutrients are supposed to protect against the development of heart disease. High doses of antioxidants in the month following an acute heart attack have been shown to significantly reduce the number of deaths, as well as the extent of cardiac damage in non-fatal cases.

30 It is currently thought that increase in oxidative stress is involved in the pathophysiology of endothelial dysfunction that accompanies a number of cardiovascular risk factors including hypercholesterolemia, hypertension and cigarette

smoking. It also plays a pivotal role in the evolution of clinical conditions such as atherosclerosis and heart failure. Oxidative stress can activate redox-sensitive kinase cascades and transcription factors such as NF κ B and AP-1, with resulting increases in the expression of factors associated with an inflammatory response and cellular proliferation. There are three enzyme systems producing reactive oxygen species in the vascular wall: NADH/NADPH oxidase, xanthine oxidoreductase, and endothelial nitric oxide synthase (Zalba G. et al, 2000, Rosenfeld ME, 1998).

Atherogenesis is regarded as the outcome of interactions among multiple stimuli. Endothelial dysfunction plays a key role in the development of atherosclerosis. Elevated homocysteine concentrations are associated with rapid onset endothelial dysfunction, which is another mechanism by which increased oxidative stress contributes to atherosclerosis. Oxidation of low-density lipoprotein plays an important role at several steps in atherogenesis. Oxidative stress also activates NF κ B, which induces expression of genes controlling cytokine expression and leukocyte adhesion to vascular wall. (Maxwell, et al. 1997).

Animal studies have provided evidence by suggesting that free radicals may promote thrombosis, directly damage vascular cells and other tissues, and interfere with vasomotor regulation with the clinical sequelae of **myocardial infarction and ischemic stroke**.

In tissues where oxygen supply becomes used up following ischemia, as in myocardial ischemia, the enzyme xanthine oxidase is changed to a form that has potential to reduce oxygen to superoxides. On readmission of oxygen e.g. by reperfusion there is a burst of free radical generation. ROS are formed at an accelerated rate in post-ischemic myocardium. Thus biochemical damage due to free radicals contributes to the ischemic injury.

Oxidative stress also seems to be one of the mechanisms that may produce membrane defects and result in intracellular calcium overload, and cardiac contractile dysfunction in the stunned myocardium.

5 *Macular degeneration and cataract*

Oxidative damage to lens of the eye with increase in age has a major contribution in cataract formation. Macular degeneration is also being recognized as a consequence of oxidative damage.

10

HIV disease

Perturbation of anti-oxidant defense system has been observed in various tissues in HIV patients. Oxidative stress may contribute to several aspects of HIV disease pathogenesis such as viral replication, inflammatory response, and decreased immune cell proliferation, loss of immune function, apoptosis, chronic weight loss. Antioxidants may offer a promising treatment to HIV patients.

Chronic obstructive pulmonary diseases (COPD)

20

Alteration in the alveolar and lung metabolism of glutathione is widely recognized as a central feature of many inflammatory lung diseases including COPD. These changes are a result of the alteration in the gene expression of the gamma-glutamyl cystine synthase (Gamma-GCS), the rate-limiting enzyme in glutathione synthesis. Oxidative stress is implicated in the pathogenesis of COPD, since it results in inactivation of anti proteinases, airspace epithelial injury, mucus hypersecretion, increased influx of neutrophils into the lungs, transcription factor activation and gene expression of pro-inflammatory mediators (MacNee W, et al. 2001).

30 *Renal Disease*

ROS have been implicated not only in the genesis of different forms of renal disease, predominantly experimentally induced **glomerulonephritis**, but also in different forms of **acute renal failure**.

5

Asthma

Although the pathogenesis of asthma is not fully defined, a typical feature is an increase in the number of inflammatory cells in the lung. Such cells generate ROS, which are involved in the pathophysiology of asthma, including airway smooth
10 muscle contraction, increased airway reactivity, and increased vascular permeability.

Effect of antioxidant status on immunologic function

The immune system is particularly sensitive to oxidative stress, primarily
15 because immune cells rely heavily on cell-to-cell communication to work effectively. Peroxidation of cell membranes compromises membrane integrity and disrupts intracellular signaling.

Cataract:

20

Oxidative damage to lens of eye with increase in age has been a major contribution in cataract formation.

Thus, by scavenging the free radicals, the following diseases can be treated or
25 controlled :

- 1) Neurodegenerative disorders
 - (a) Alzheimer's Disease
 - (b) Parkinson's Disease
 - (c) Huntington's Disease
 - (d) Motor Neuron Disease
 - (e) Prion Disease
- 30

-
- 2) Diabetes and Diabetic Vascular Complications

 - 3) Intestinal Diseases
 - (a) Intestinal Ischemia
 - (b) Radiation Enteritis
 - (c) Inflammatory Bowel Disease
 - (d) Gastric and Colorectal Cancers

 - 4) Liver Diseases
 - (a) Alcoholic Liver Disease
 - (b) Chronic Hepatitis C

 - 5) Cancers
 - (a) Lung Cancer
 - (b) Colorectal Cancer
 - (c) Cervical Cancer
 - (d) Breast Cancer
 - (e) Malignant Melanoma

 - 6) Cardiac Diseases
 - (a) Atherosclerosis
 - (b) Myocardial Infarction
 - (c) Ischemic Stroke
 - (d) Endothelial dysfunction

 - 7) Ophthalmic Disorders
 - (a) Cataract formation
 - (b) Macular degeneration

 - 8) HIV Disease
 - 9) Respiratory Diseases
 - (a) Chronic Obstructive Pulmonary Diseases (COPD)

(b) Asthma

10) Renal Diseases

(a) Glomerulonephritis

5 (b) Acute Renal failure

OBJECTS OF THE INVENTION

10 The first object of the present invention is to provide a new class of compounds which normalize elevated blood glucose levels in diabetic patients thereby delaying diabetic complications and preventing transition to type II diabetes in impaired glucose tolerant patients.

15 These compounds exhibit in vitro DPP-IV inhibitory activity. DPP-IV inhibitors enhance the level of active GLP-1, which would be advantageous in treating hyperglycemia. Added advantage is that there is no risk of hypoglycemia, since GLP-1 increases glucose mediated insulin secretion. Due to non-peptide nature of the compounds, they can be conveniently administered orally. The increase in
20 GLP-1 level in the active form provides for multifaceted action in respect of increase in insulin level, decrease in glucagon level, neogenesis of pancreatic β -cell, stimulation of insulin gene expression, and promotion of satiety, all of which contribute to beneficial effects in a diabetic patient.

25 Another object of the invention is to provide a method of treatment of a diabetic patient with glucose intolerance by administration of the compounds of the invention or pharmaceutically acceptable salts thereof either singly or in combination with drugs for anti-diabetic or other therapies for Cushing's syndrome, hyperthyroidism, HIV infection, obesity, ulcers, disorders related to
30 hyperglucagonemia, gastric emptying and hunger in required dosage in admixture with pharmaceutically acceptable diluents, solvents, excipients, carriers or other media as may be appropriate for the purpose.

A further object of the invention is to provide a class of compounds having free radical scavenging activity which are useful for treatment of (a) Neurodegenerative disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Motor Neuron Disease, Prion Disease etc, (b) Diabetes and Diabetic Vascular Complications, (c) Intestinal Diseases such as Intestinal Ischemia, Radiation Enteritis, Inflammatory Bowel Disease, Gastric and Colorectal Cancers etc., (d) Liver Diseases such as Alcoholic Liver Disease, Chronic Hepatitis C etc., (e) Cancers such as Lung Cancer, Colorectal Cancer, Cervical Cancer, Breast Cancer, Malignant Melanoma etc., (f) Cardiac Diseases such as Atherosclerosis, Myocardial Infarction, Ischemic Stroke, Endothelial Dysfunction etc., (g) Ophthalmic Disorders such as Cataract formation, Macular degeneration etc., (h) HIV Diseases, (i) Respiratory Diseases such as Chronic Obstructive Pulmonary Diseases, Asthma etc., (j) Renal Diseases such as Glomerulonephritis, Acute Renal Failure etc.

15

Yet another object of the present invention is to provide a method of preparation of these compounds.

A still further object of the invention is to provide a pharmaceutical composition comprising said compound in association with a pharmaceutical acceptable carrier, diluent or excipients.

Yet another object of the invention is to provide a method of treatment and/or prophylaxis of mammals including human beings for diseases relating to glucose intolerance and/or disease conditions caused by accumulation of free radicals in the body cells.

25

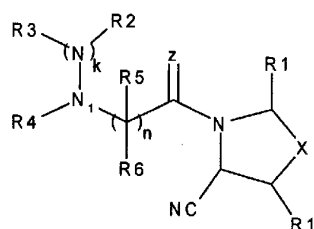
SUMMARY OF THE INVENTION

The present invention provides novel compounds represented by general formula (I), its derivatives, analogs, tautomeric forms, stereoisomers, polymorphs, pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, which are useful for one or more of (i) normalizing elevated blood glucose levels in diabetes,

30

(ii) treating disorders related to glucose intolerance and (iii) scavenging free radicals from body cells.

5



(I)

wherein

10

X is O, S, SO, SO₂, NR₇ or CHR₁;

n is null or 1;

15 k is 1;

Z is O, S, and NR₇;

20 R₁ at two positions are independently selected from hydrogen or a substituted or unsubstituted group selected from linear or branched (C₁-C₁₂)alkyl, (C₂-C₁₂)alkenyl, (C₃-C₇)cycloalkyl, (C₅-C₇)cycloalkenyl, bicycloalkyl, bicycloalkenyl, heterocycloalkyl, aryl, aryloxy, aralkyl, aralkoxy, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, wherein one or more heteroatoms are independently selected from O, N or S;

25

R₂, R₃, R₄ and R₇ are independently selected from hydrogen, perhaloalkyl, -(CO)NR₈R₉, -(CO)R₈, -(CO)OR₈, -SO₂R₈, -SOR₈, substituted or unsubstituted

30

groups selected from linear or branched (C₁-C₁₂)alkyl, (C₂-C₁₂)alkenyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkenyl, bicycloalkyl, amidino bicycloalkenyl, heterocycloalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, wherein one or more heteroatoms are independently selected from O, N or S;

5

R5 and R6 are independently selected from by hydrogen or a substituted or unsubstituted group selected from linear or branched (C₁-C₁₂)alkyl, (C₂-C₁₂)alkenyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkenyl, bicycloalkyl, bicycloalkenyl, heterocycloalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, wherein one or more
10 heteroatoms are independently selected from O, N or S;

R8 and R9 are independently selected from hydrogen or a substituted and unsubstituted group selected from linear or branched (C₁-C₁₂)alkyl, alkoxyaryl, alkoxyalkyl, alkoxycycloalkyl, alkoxyaryl, perhaloalkyl, (C₂-C₁₂)alkenyl, (C₃-C₇)
15 cycloalkyl, perhalocycloalkyl, haloheterocycloalkyl, cyanoheterocycloalkyl, perhaloheterocycloalkyl, (C₃-C₇) cycloalkenyl, bicycloalkyl, bicycloalkenyl, heterocycloalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, perhaloaryl, perhaloheteroaryl;

20 wherein in the groups represented by R1, R2, R3, R4, R5, R6, R7, R8 and R9 when substituted, the substituents are optionally and independently bridged by -(CO)-, -(CO)O-, -(CO)NH-, -NH-, -NR8-, -O-, -S-, -(SO)-, -(SO₂)-, -(SO₂)NH-, -NH(SO₂)-, -O(CO)- or -NH(CO)-; and are selected from halogen, hydroxy, nitro, cyano, amino, oxo, oxime, unsubstituted or substituted by R10 for the groups selected from linear or
25 branched (C₁-C₈) alkyl, (C₃-C₇)cycloalkyl, alkylcycloalkyl, perhaloalkyl, perhalocycloalkyl, aryl, aralkyl, alkylaryl, alkylheteroaryl, aralkoxyalkyl, perhaloaryl, alkylheterocycloalkyl, heterocycloalkyl, perhaloheterocycloalkyl, heteroaryl, heteroaralkyl, alkylaryl, perhaloheteroaryl, acyl, acyloxy, acylamino, alkylamino, arylamino, aralkoxy, alkoxyalkyl, alkylthio, thioalkyl, arylthio, thioaryl,
30 carboxylic acid or its derivatives, or sulfonic acid or its derivatives wherein the groups / substituents present on same or adjacent atoms such as carbon or nitrogen, together optionally and independently may form a five or a six or a seven membered

ring, optionally containing one or more double bonds and optionally containing one or more heteroatoms selected from O,N or S;

5

and wherein

10 R10 is independently selected from halogen, hydroxy, nitro, cyano, amino, oxo or oxime, and pharmaceutically usable hydrates and salts thereof ;

As used herein, aryl and heteroaryl ring includes up to two conjugated or fused ring systems.

15

Pharmaceutically acceptable salts forming part of this invention are intended to include not limited to salts of the carboxylic acid moiety such as alkali metal salts like Li, Na and K salts; alkaline earth metal salts like Ca and Mg salts; salts of organic bases such as lysine, arginine, guanidine, diethanolamine, choline, trimethamine and
20 the like; ammonium or substituted ammonium salts and aluminum salts. Salts may be acid addition salts which defines but not limited to sulfates, nitrates, phosphates, perchlorates, borates, hydrohalides, acetates, perhaloacetates, tartrates, maleates, citrates, succinates, palmoates, methanesulfonates, benzoates, salicylates, hydroxynaphthoates, benzensulfonates, ascorbates, glycerophosphates, ketoglutarates
25 and the like.

The invention also provides a process for preparation of the compounds as defined above.

30

The invention further provides pharmaceutical composition comprising compounds of the invention in association with a pharmaceutically acceptable carrier, diluent or excipient.

- 5 The invention also provides a method of treatment of mammals including human beings in disease conditions resulting from glucose intolerance and/or accumulation of free radical in the body cells by administering an effective compound of compounds of the invention to the subject in need thereof.
- 10 The invention further provides use of the compounds of invention in the manufacture of a medicament useful for treatment of diseases conditions resulting from glucose intolerance and/or accumulation free radical in the body cells.

BRIEF DESCRIPTION OF ACCOMPANYING DRAWINGS

15

Fig 1 : This shows the effect of test compound (compound No. 95) on AUC in OGTT for the glucose load of 1 gm/kg in nSTZ induced diabetic rat.

- 20 Fig. 2: This shows the effect of test compound (compound No.95) pre-treatment on the glucose excursion.

DETAILED DESCRIPTION OF THE INVENTION

25

The representative compounds of formula (I) as referred above are listed in Table I below which can be conveniently prepared, by methods as described hereinafter. These compounds may exist both as diastereomeric mixtures or as the diastereomerically pure or enantiomerically pure compounds.

Table-1 : Representative Compounds

Comp.No.	R1	R2	R3	- R4 - R6 - -CH ₂ -CH ₂ -NH- CH ₂ -	R4	R5	R6	k	n	X	Z	Salt
1	H	-	-	-	*	H	*	0	1	-CH ₂	O	2 CF ₃ COOH
2	H	-	-	-CH ₂ -CH ₂ - N(isopropyl)- CH ₂ -	*	H	*	0	1	-CH ₂	O	2 CF ₃ COOH
3	H	H	H	-	Ph	H	H	1	1	-CH ₂	O	CF ₃ COOH
4	H	H	H	-	H	H	H	1	1	-CH ₂	O	CF ₃ COOH
5	H	H	-CO(O)tBu	-	H	H	H	1	1	S	O	-
6	H	H	-CO(O)tBu	-	Ph	H	H	1	1	-CH ₂	O	-
7	H	H	-CO(O)tBu	-	H	H	H	1	1	-CH ₂	O	-
8	H	H	H	-	p-nitrobenzyl	H	H	1	1	-CH ₂	O	CF ₃ COOH
9	H	H	H	-	Ph	H	H	1	1	S	O	CF ₃ COOH
10	H	H	H	-	CH ₂ CH(CH ₃) ₂	H	H	1	1	CH ₂	O	-
11	H	H	H	-	Benzyl	H	H	1	1	-CH ₂	O	CF ₃ COOH
12	H	H	H	-	CH(CH ₃) ₂	H	H	1	1	-CH ₂	O	CF ₃ COOH
13	H	Ethyl	Ethyl	-	H	H	H	1	1	S	O	-
14	H	H	H	-	Ethyl	H	H	1	1	-CH ₂	O	CF ₃ COOH
15	H	H	H	-	H	H	H	1	1	S	O	CF ₃ COOH
16	H	H	H	-	Benzyl	H	H	1	1	S	O	CF ₃ COOH
17	H	H	H	-	p-nitrobenzyl	H	H	1	1	S	O	CF ₃ COOH
18	H	H	H	-	Cyclopentyl	H	H	1	1	S	O	CF ₃ COOH
19	H	H	H	-	Cyclopentyl	H	H	1	1	-CH ₂	O	CF ₃ COOH
20	H	H	H	-	Cyclohexyl	H	H	1	1	S	O	CF ₃ COOH
21	H	H	H	-	Cyclohexyl	H	H	1	1	-CH ₂	O	CF ₃ COOH
22	H	H	H	-	CH(CH ₃)CH ₂ CH ₃	H	H	1	1	S	O	CF ₃ COOH
23	H	H	H	-	CH(CH ₃)CH ₂ CH ₃	H	H	1	1	-CH ₂	O	CF ₃ COOH

Comp No.	R1	R2	R3	- R4 - R6 -	R4	R5	R6	k	n	X	Z	Salt
24	H	H	H	-	SO ₂ Ph	H	H	1	1	-CH ₂	O	CF ₃ COOH
25	H	H	H	-	4-CH ₃ -cyclohexyl	H	H	1	1	S	O	CF ₃ COOH
26	H	H	H	-	4-CH ₃ -cyclohexyl	H	H	1	1	-CH ₂	O	CF ₃ COOH
27	H	H	H	-	2-pyridyl	H	H	1	1	-CH ₂	O	2CF ₃ COOH
28	H	H	H	-	-cycloheptyl	H	H	1	1	S	O	CF ₃ COOH
29	H	H	H	-	4-CH ₃ -cyclohexyl	H	H	1	1	S	O	CF ₃ COOH
30	H	H	H	-	-cycloheptyl	H	H	1	1	-CH ₂	O	CF ₃ COOH
31	H	H	H	-	CH(CH ₃) ₂	-	-	1	0	S	O	HCl
32	H	H	H	-	-cyclohexyl	-	-	1	0	-CH ₂	O	HCl
33	H	H	H	-	-cyclohexyl	-	-	1	0	S	O	HCl
34	H	H	-cyclohexyl	-	H	H	H	1	1	-CH ₂	O	CF ₃ COOH
35	H	H	H	-	Phenyl	-	-	1	0	S	O	CF ₃ COOH
36	H	H	-isopropyl	-	-cyclohexyl	H	H	1	1	S	O	HCl
37	H	H	H	-	4-CH ₃ -cyclohexyl	H	H	1	1	-CH ₂	O	CF ₃ COOH
38	H	H	-isopropyl	-	-cyclohexyl	H	H	1	1	-CH ₂	O	-
39	H	H	H	-	4-CH ₃ -cyclohexylmethyl	H	H	1	1	-CH ₂	O	CF ₃ COOH
40	H	H	H	-	4-chlorophenyl	H	H	1	1	-CH ₂	O	CF ₃ COOH
41	H	H	H	-	H	H	- isopro pyl	1	1	-CH ₂	O	CF ₃ COOH
42	H	H	-ethyl	-	4-CH ₃ -cyclohexyl	H	H	1	1	S	O	-
43	H	H	H	-	-morpholino-carbonyl	H	H	1	1	S	O	CF ₃ COOH
44	H	H	-isopropyl	- *	4-CH ₃ -cyclohexyl	H	H	1	1	S	O	CF ₃ COOH

Comp No.	R1	R2	R3	-R4 - R6 -	R4	R5	R6	k	n	X	Z	Salt
45	H	H	-2-oxo-2-(2'-cyanopyridino-1-yl)-ethyl	-	-cyclohexyl	H	H	1	1	-CH ₂	O	CF ₃ COOH
46	H	H	-N(2-(2-pyridyl)ethyl)amino carbonyl	-	-N(2-(2-pyridyl)ethyl)amino carbonyl	H	H	1	1	S	O	2CF ₃ COOH
47	H	H	H	-	-4-tertbutyl-cyclohexyl	H	H	1	1	S	O	CF ₃ COOH
48	H	H	H	-	-1-tetralino	H	H	1	1	-CH ₂	O	CF ₃ COOH
49	H	H	H	-	-4-tertbutyl-cyclohexyl	H	H	1	1	S	O	CF ₃ COOH
50	H	-cyclo-hexyl	-2-oxo-2-(2'-cyanopyridino-1-yl)-ethyl	-	H	H	H	1	1	S	O	-
51	H	H	H	-	1-isopropyl-4-piperidinyl	H	H	1	1	S	O	CF ₃ COOH
52	H	H	H	-	1-(4-cyanobenzyl)-4-piperidinyl	H	H	1	1	S	O	2CF ₃ COOH
53	H	H	1(3-pyridinylmethyl)-4-piperidinyl	-	4-CH ₃ -cyclohexyl	H	H	1	1	S	O	-
54	H	H	1-isopropyl-4-piperidinyl	-	4-CH ₃ -cyclohexyl	H	H	1	1	S	O	-
55	H	H	H	-	1(p-tolunesulfonyl)-4-piperidinyl	H	H	1	1	S	O	CF ₃ COOH
56	H	H	1(p-tolunesulfonyl)-4-piperidinyl	-	-methyl	H	H	1	1	S	O	CF ₃ COOH
57	H	H	H	-	1(3-pyridinylmethyl)-4-piperidinyl	H	H	1	1	S	O	3CF ₃ COOH

Comp No.	R1	R2	R3	-R4 - R6 -	R4	R5	R6	k	n	X	Z	Salt
58	H	H	1-(4-cyanobenzyl)-4-piperidinyl	-	-methyl	H	H	1	1	S	O	2CF ₃ COOH
59	H	H	1(3-pyridinylmethyl)-4-piperidinyl	-	-methyl	H	H	1	1	S	O	3CF ₃ COOH
60	H	H	H	-	4-n-propyl-cyclohexyl	H	H	1	1	S	O	CF ₃ COOH
61	H	H	H	-	1-(4-nitrobenzyl)-4-piperidinyl	H	H	1	1	S	O	CF ₃ COOH
62	H	H	H	-	1(4-chlorobenzene-sulfonyl)-4-piperidinyl	H	H	1	1	S	O	CF ₃ COOH
63	H	H	H	-	2-norcamphoryl	H	H	1	1	S	O	CF ₃ COOH
64	H	H	H	-	4-n-propyl-cyclohexyl	H	H	1	1	S	O	CF ₃ COOH
65	H	H	H	-	1(4-methylcyclohexylcarbonyl)-4-piperidinyl	H	H	1	1	S	O	3CF ₃ COOH
66	H	H	H	-	1(acetyl)-4-piperidinyl	H	H	1	1	S	O	CF ₃ COOH
67	H	H	H	-	4-methylcyclo-hexyl	H	H	1	1	SO ₂	O	CF ₃ COOH
68	H	H	4-methylcyclo-hexyl	-	methyl	H	H	1	1	S	O	-
69	H	H	4-methylcyclo-hexyl	-	methyl	H	H	1	1	S	O	-
70	H	H	H	-	1(2,3-dichlorophenylcarbonyl)-4-piperidinyl	H	H	1	1	S	O	CF ₃ COOH
71	H	H	1(4-chlorobenzene-sulfonyl)-4-piperidinyl	-	methyl	H	H	1	1	S	O	CF ₃ COOH

Comp No.	R1	R2	R3	- R4 - R6 -	R4	R5	R6	k	n	X	Z	Salt
72	H	H	H	-	4-piperidinyl	H	H	1	1	S	O	2CF ₃ COOH
73	H	H	H	-	1(4-chlorobenzene-sulfonyl)-4-piperidinyl	H	H	1	1	-CH ₂	O	CF ₃ COOH
74	H	H	Acetyl	-	4-CH ₃ -cyclohexyl	H	H	1	1	S	O	-
75	H	H	H	-	2-adamantyl	H	H	1	1	S	O	CF ₃ COOH
76	H	H	H	-	1(terbutylcarbonyl)-4-piperidinyl	H	H	1	1	S	O	CF ₃ COOH
77	H	H	H	-	1(5-trifluoro-methyl-2-pyridyl)-4-piperidinyl	H	H	1	1	S	O	2CF ₃ COOH
78	H	H	H	-	4-methane-sulfonamido-cyclohexyl	H	H	1	1	S	O	CF ₃ COOH
79	H	H	H	-	3,3,5-trimethyl-cyclohexyl	H	H	1	1	S	O	CF ₃ COOH
80	H	H	-ethyl	-	-isopropyl	H	H	1	1	S	O	CF ₃ COOH
81	H	H	H	-	1-benzyl-4-piperidinyl	H	H	1	1	S	O	CF ₃ COOH
82	H	H	H	-	4-(4-chlorophenyl-sulfonamido)-cyclohexyl	H	H	1	1	S	O	CF ₃ COOH
83	H	#	H	-	#	H	H	1	1	S	O	-
84	H	H	-isopropyl	-	4-methane-sulfonamido-cyclohexyl	H	H	1	1	S	O	CF ₃ COOH
85	H	H	H	-	1(morpholinocarbonyl)-4-piperidinyl	H	H	1	1	S	O	CF ₃ COOH
86	H	H	H	-	1(methylsulphonyl)-4-piperidinyl	H	H	1	1	S	O	CF ₃ COOH
87	H	H	-isopropyl	-	1(methylsulphonyl)-4-piperidinyl	H	H	1	1	S	O	CF ₃ COOH
88	H	H	-ethyl	-	1(methylsulphonyl)-4-piperidinyl	H	H	1	1	S	O	CF ₃ COOH

Comp No.	R1	R2	R3	- R4 - R6 -	R4	R5	R6	k	n	X	Z	Salt
89	H	H	-ethyl	-	1(morpholinocarbonyl)-4-piperidinyl	H	H	1	1	S	O	CF ₃ COOH
90	H	H	H	-	1(ethyl methyl aminocarbonyl)-4-piperidinyl	H	H	1	1	S	O	CF ₃ COOH
91	H	H	H	-	1(4-methoxy benzene-sulphonyl)-4-piperidinyl	H	H	1	1	S	O	CF ₃ COOH
92	H	H	H	-	4-(4-methoxy phenyl-sulfonamido)-cyclohexyl	H	H	1	1	S	O	CF ₃ COOH
93	H	H	H	-	4-fluorobenzyl amino cyclohexyl	H	H	1	1	S	O	2CF ₃ COOH
94	H	H	H	-	N-(4-fluoro benzyl) piperidine-4-yl	H	H	1	1	S	O	2CF ₃ COOH
95	H	H	H	-	1-[[5-chloro pyridin-2-yl carbonyl]-methyl]-piperidine-4-yl	H	H	1	1	S	O	CF ₃ COOH
96	H	H	H	-	1-trimethylacetamido cyclohexan-4-yl	H	H	1	1	S	O	CF ₃ COOH
97	H	H	C ₂ H ₅	-	4-methyl sulfonamido cyclohexyl	H	H	1	1	S	O	-
98	H	H	H	-	1-trimethylacetamido cyclohexan-4-yl	H	H	1	1	S	O	CF ₃ COOH
99	H	H	H	-	N-[[4-cyanophenyl Carbonyl] Methyl]piperidin-4-yl	H	H	1	1	S	O	2CF ₃ COOH

Comp No.	R1	R2	R3	-R4 - R6 -	R4	R5	R6	k	n	X	Z	Salt
100	H	H	H	-	4-(fluorophenyl carbomoyl)cyclohexyl	H	H	1	1	S	O	CF ₃ COOH
101	H	H	C ₂ H ₅	-	N-[(5-chloro Pyridin-2-yl Carbomoyl) methyl] piperidine-4-yl	H	H	1	1	S	O	3HCl
102	H	H	H	-	1-[(4-trifluoromethyl-phenylcarbomoyl)-methyl]-piperidin-4-yl	H	H	1	1	-S-	O	2CF ₃ COOH
103	H	H	H	-	1-(adamantan-1-yl-carbamoyl)-methyl]-piperidin-4-yl	H	H	1	1	-S-	O	2CF ₃ COOH
104	H	H	H	-	1-[(2,3-dihydro-benzo[1,4]dioxin-6-yl-carbamoyl)-methyl]-piperidin-4-yl	H	H	1	1	-S-	O	2CF ₃ COOH
105	H	H	H	-	1-[(4-chlorophenyl carbamoyl)-methyl]-piperidin-4-yl	H	H	1	1	-S-	O	2CF ₃ COOH
106	H	H	H	-	1-[(pyrimidin-2-yl-carbamoyl)-methyl]-piperidin-4-yl	H	H	1	1	-S-	O	3CF ₃ COOH
107	H	H	H	-	1-(2-morpholin-4-yl-2-oxo-ethyl)-piperidin-4-yl	H	H	1	1	-S-	O	2CF ₃ COOH
108	H	H	H	-	1-(cyclopropyl carbamoyl)-methyl-piperidin-4-yl	H	H	1	1	-S-	O	2CF ₃ COOH
109	H	H	H	-	1-(2'-cyano-biphenyl-4-yl-methyl) piperidine-4-yl	H	H	1	1	-S-	O	2CF ₃ COOH

Comp.No.	R1	R2	R3	-R4-R6-	R4	R5	R6	k	n	X	Z	Salt
110	H	H	H	-	1-(morpholin-4-ylacetyl) piperidine-4-yl	H	H	1	1	-S-	O	2CF ₃ COOH
111	H	H	H	-	4-{{(5-chloropyridin-2-ylcarbonyl)amino} cyclohex-1-yl}	H	H	1	1	-S-	O	3CF ₃ COOH
112	H	H	H	-	4-{{(4-cyanophenylcarbonyl)met hyl } amino} cyclohex-1-yl}	H	H	1	1	-S-	O	2CF ₃ COOH
113	H	H	H	-	4-{{(4-chlorophenylcarbonyl)met hyl } amino} cyclohex-1-yl}	H	H	1	1	-S-	O	2CF ₃ COOH
114	H	H	H	-	4-methane-sulfonamido-cyclohex-1-yl	H	H	1	1	S	O	HCl
115	H	H	H	-	1-{{(5-chloro pyridin-2-yl carbonyl)-methyl}- piperidine-4-yl}	H	H	1	1	S	O	HCl

* : This is part of the cyclic structure -R4 -R6 -

** : This compound is obtained by reacting with lower isomer obtained during the reduction step.

*** : This compound is obtained by reacting with the upper isomer obtained during the reduction step.

: R2-R4 combine together to give -CH₂-CH₂-CH₂-CH₂-

The representative compounds of the invention listed in Table I can be identified by their following chemical names :-

- 5
- (a) [2-Cyano-1-(piperazine-2-yl)-carbonyl pyrrolidine bis-trifluoroacetate] (Compound No. 1).
- 10 (b) [2-Cyano-1-(4-isopropyl-2-piperazinyl)-carbonyl-pyrrolidine bis trifluoroacetate] (Compound No. 2)
- (c) 1-[1-Oxo-2-((1-phenyl)-hydrazino)]ethyl-2-cyano pyrrolidine trifluoroacetate (Compound No. 3)
- 15 (d) 1-[1-Oxo-2-(1-hydrazino)]ethyl-2-cyano pyrrolidine trifluoroacetate (Compound No. 4)
- (e) 3-[1-Oxo-2-((2-(1,1-dimethyl ethyl oxy carbonyl))hydrazino)]ethyl-4-cyano thiazolidine (Compound No. 5)
- 20 (f) 1-[1-Oxo-2-((2-(1,1-dimethylethoxy carbonyl))-1-phenyl hydrazino)]ethyl-2-cyano pyrrolidine (Compound No. 6)
- (g) 1-[1-Oxo-2-((2-(1,1-dimethylethyl oxy carbonyl))hydrazino)]ethyl-2-cyano pyrrolidine (Compound No. 7).
- 25 (h) 1-[1-Oxo-2-((1-(4-nitrophenylmethyl))hydrazino)]ethyl-2-cyano pyrrolidine trifluoroacetate (Compound No. 8)
- 30 (i) 3-[1-Oxo-2-((1-phenyl)hydrazino)]ethyl-4-cyano thiazolidine trifluoroacetate (Compound No. 9)
- (j) 1-[1-Oxo-2-(1-(2-methylpropyl)hydrazino)]ethyl-2-cyano pyrrolidine trifluoroacetate (Compound No. 10)
- 35 (k) 1-[1-Oxo-2-((1-phenylmethyl)hydrazino)]ethyl-2-cyano pyrrolidine trifluoroacetate (Compound No. 11)
- (l) 1-[1-Oxo-2-((1-(1-methyl)ethyl)hydrazino)]ethyl-2-cyano pyrrolidine trifluoroacetate (Compound No. 12)
- 40 (m) 1-[1-Oxo-2-((2,2-diethyl)-hydrazino)]ethyl-2-cyano thiazolidine (Compound No. 13)
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- (n) 1-[1-Oxo-2-((1-ethyl)hydrazino)]ethyl-2-cyano pyrrolidine trifluoroacetate
(Compound No. 14)
- 5 (o) 3-[1-Oxo-2-(1-hydrazino)]ethyl-4-cyano thiazolidine trifluoroacetate (Compound
No. 15)
- (p) 3-[1-Oxo-2-((1-phenylmethyl)hydrazino)]ethyl-4-cyano thiazolidine
trifluoroacetate (Compound No. 16)
- 10 (q) 3-[1-Oxo-2-((1-(4-nitrophenylmethyl))hydrazino)]ethyl-4-cyano thiazolidine
trifluoroacetate (Compound No. 17)
- (r) 1-[1-Oxo-2-((1-Cyclopentyl)-hydrazino)]ethyl-2-cyano pyrrolidine trifluoroacetate
(Compound No. 18)
- 15 (s) 3-[1-Oxo-2-((1-Cyclopentyl)-hydrazino)]ethyl-4-cyano thiazolidine
trifluoroacetate (Compound No. 19)
- (t) 1-[1-Oxo-2-((1-Cyclohexyl)-hydrazino)]ethyl-2-cyano pyrrolidine trifluoroacetate
20 (Compound No. 20)
- (u) 3-[1-Oxo-2-((1-Cyclohexyl)-hydrazino)]ethyl-4-cyano thiazolidine
trifluoroacetate (Compound No. 21)
- 25 (v) 1-[1-Oxo-2-((1-methylpropyl)hydrazino)]ethyl-2-cyano pyrrolidine
trifluoroacetate (Compound No. 22)
- (w) 3-[1-Oxo-2-((1-methylpropyl)hydrazino)]ethyl-4-cyano thiazolidine
trifluoroacetate (Compound No. 23)
- 30 (x) 1-[1-Oxo-2-((1-Phenyl sulphonyl)hydrazino)]ethyl-2-cyano pyrrolidine
trifluoroacetate (Compound No. 24)
- (y) 3-[1-Oxo-2-((1-(4-methyl)cyclohexyl)hydrazino)]ethyl-4-cyano thiazolidine
35 trifluoroacetate (Compound No. 25).
- (z) 1-[1-Oxo-2-((4-Methyl)cyclohexyl)hydrazino)]ethyl-2-cyano pyrrolidine
trifluoroacetate (Compound No. 26)
- 40 (aa) 1-[1-Oxo-2-(1-(2-Pyridyl)-hydrazino)]ethyl-2-cyano pyrrolidine bis-
trifluoroacetate (Compound No. 27).
- (ab) 3-[1-Oxo-2-((1-Cycloheptyl)-hydrazino)] ethyl-4-cyano thiazolidine
trifluoroacetate (Compound No. 28)
- 45 (ac) 3-[1-Oxo-2-((1-(4-methyl) cyclohexyl)-hydrazino)] ethyl-4-cyano thiazolidine
trifluoroacetate (Compound No. 29)

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- ad) 1-[1-Oxo-2-((1-Cycloheptyl)-hydrazino)] ethyl-2-cyano pyrrolidine trifluoroacetate (Compound No. 30)
- 5 ae) [4-Cyano-3-(1-isopropylhydrazino)carbonyl thiazolidine hydrochloride] (Compound No. 31)
- af) [2-Cyano-1-(1-cyclohexyl hydrazino)carbonyl pyrrolidine hydrochloride] (Compound No. 32)
- 10 ag) [4-Cyano-3-(1-cyclohexylhydrazino)carbonyl thiazolidine hydrochloride] (Compound No. 33)
- ah) 1-[1-Oxo-2-(2-cyclohexyl) hydrazino] ethyl-2-cyanopyrrolidine trifluoroacetate (Compound No. 34)
- 15 ai) [4-Cyano-3-(1-phenyl hydrazino) carbonyl thiazolidine trifluoroacetate] (Compound No. 35)
- 20 aj) 3-[1-Oxo-2-(1-cyclohexyl-2-isopropyl) hydrazino] ethyl-4-cyanothiazolidine hydrochloride (Compound No. 36)
- ak) 1-[1-Oxo-2-(4-methylcyclohexyl)hydrazino]ethyl-2-cyanopyrrolidine trifluoroacetate (Compound No. 37)
- 25 al) 1-[1-Oxo-2-(1-cyclohexyl-2-isopropyl)hydrazino]ethyl-2-cyano pyrrolidine (Compound No. 38)
- am) 1-[1-Oxo-2-(1-(4-methylcyclohexylmethyl) hydrazino)]ethyl-2-cyanopyrrolidine trifluoroacetate (Compound No. 39)
- 30 an) 1-[1-Oxo-2-(4-chlorophenyl) hydrazino] ethyl-2-cyanopyrrolidine trifluoroacetate (Compound No. 40)
- ao) 1-[1-Oxo-2-isopropyl-2-hydrazino] ethyl-2-cyano pyrrolidine trifluoroacetate (Compound No. 41)
- 35 ap) 3-[1-Oxo-2-(1-(4-methylcyclohexyl)-2-ethyl) hydrazino] ethyl-4-cyanothiazolidine trifluoroacetate (Compound No. 42)
- 40 aq) 3-[1-Oxo-2-(1-(4-morpholinocarbonyl) hydrazino) ethyl]-4-cyanothiazolidine trifluoroacetate (Compound No. 43)
- ar) 3-[1-Oxo-2-(1-(4-methylcyclohexyl)-2-isopropyl) hydrazino] ethyl-4-cyanothiazolidine trifluoroacetate (Compound No. 44)
- 45 as) 1-[1-Oxo-2-[(1-cyclohexyl)-2-(2-cyano-1-pyrrolidino acetyl)] hydrazino] ethyl-2-cyanopyrrolidine trifluoroacetate (Compound No. 45)

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- at) 3-[1-Oxo-2- (1,2-bis- (2-(2-pyridyl) ethylaminocarbonyl) hydrazino)] ethyl-4-cyano thiazolidine bis trifluoroacetate (Compound No. 46)
- 5 au) 3-[1-Oxo-2- (1-(4-tert-butyl cyclohexyl) hydrazino)] ethyl-4-cyanothiazolidine trifluoro acetate (Compound No. 47)
- av) 1-[1-Oxo-2- (1-tetralinyl) hydrazino] ethyl-2-cyanopyrrolidine trifluoroacetate (Compound No. 48)
- 10 aw) 3-[1-Oxo-2- (1-(4-tertbutylcyclohexyl) hydrazino)] ethyl-4-cyanothiazolidine trifluoroacetate (Compound No. 49)
- ax) 1-[1-Oxo-2- (1-cyclohexyl)-2-(4-cyano-3-thiazolidino acetyl)] hydrazino] ethyl-2-cyano pyrrolidine (Compound No. 50)
- 15 ay) 3-[1-Oxo-2- (1-isopropyl-4-piperidinyl) hydrazino)] ethyl-4-cyano thiazolidine trifluoroacetate (Compound No. 51)
- az) 3-[1-Oxo-2- (1-(1-(4-cyanophenylmethyl)-piperidin-4-yl) hydrazino)] ethyl-4-cyanothiazolidine bis trifluoroacetate (Compound No. 52)
- 20 ba) 3-[1-Oxo-2-[1-(4-methylcyclohexyl)-2-(1-(3-pyridinylmethyl)-4-piperidinyl)]hydrazino]ethyl-4-cyanothiazolidine (Compound No. 53)
- 25 (a) 3-[1-Oxo-2- [1-(4-methylcyclohexyl)-2-(1-isopropyl-4-piperidinyl)] hydrazino] ethyl-4-cyanothiazolidine (Compound No. 54)
- bc) 3-[1-Oxo-2- (1-(1-(4-methylphenylsulphonyl)-4-piperidinyl)-hydrazino)] ethyl-4-cyanothiazolidine trifluoroacetate (Compound No. 55)
- 30 bd) 3-[1-Oxo-2- [1-methyl-2- (1-(4-methylphenylsulphonyl)-piperidin-4-yl)] hydrazino] ethyl-4-cyanothiazolidine trifluoroacetate (Compound No. 56)
- be) 3-[1-Oxo-2- (1-(1-(3-pyridinemethyl)-4-piperidinyl) hydrazino)] ethyl-4-cyanothiazolidine tris trifluoroacetate (Compound No. 57)
- 35 bf) 3-[1-Oxo-2- [1-methyl-2- (1-(4-cyanophenylmethyl) piperidin-4-yl)] hydrazino] ethyl-4-cyanothiazolidine bis trifluoroacetate (Compound No. 58)
- 40 bg) 3-[1-Oxo-2- [1-methyl-2- (1-(3-pyridinylmethyl)-piperidin-4-yl)] hydrazino] ethyl-4-cyanothiazolidine tris trifluoroacetate (Compound No. 59)
- bh) 3-[1-Oxo-2- (1-(4-n propylcyclohexyl) hydrazino)] ethyl-4-cyanothiazolidine trifluoro acetate (Compound No. 60)
- 45 bi) 3-[1-Oxo-2- (1-(1-(4-nitrophenylmethyl)-piperidin-4-yl) hydrazino)] ethyl-4-cyanothiazolidine trifluoroacetate (Compound No. 61)

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- bj) 3-[1-Oxo-2-[1-(1-(4-chlorophenylsulphonyl)-piperidin-4-yl)] hydrazino] ethyl-4-cyanothiazolidine trifluoroacetate (Compound No. 62)
- 5 bk) 3-[1-Oxo-2-(1-(1-norcamphoranyl) hydrazino)] ethyl-4-cyanothiazolidine trifluoroacetate (Compound No. 63)
- bl) 3-[1-Oxo-2-(1-(4-n propylcyclohexyl) hydrazino)] ethyl-4- cyanothiazolidine trifluoroacetate (Compound No. 64)
- 10 bm) 3-[1-Oxo-2-[1-(1-(4-methylcyclohexyl carbonyl)-piperidin-4-yl)] hydrazino] ethyl-4-cyanothiazolidine trifluoroacetate (Compound No. 65)
- bn) 3-[1-Oxo-2-(1-(1-acetyl)-piperidin-4-yl)hydrazino] ethyl-4-cyanothiazolidine trifluoroacetate (Compound No. 66)
- 15 bo) 1,1-Dioxo-3-[1-oxo-2-(1-(4-methylcyclohexyl) hydrazino)] ethyl-4-cyanothiazolidine trifluoroacetate (Compound No. 67)
- bp) 3-[1-Oxo-2-(1-methyl-2-(4-methylcyclohexyl) hydrazino)] ethyl-4-cyanothiazolidine (Compound No. 68)
- 20 bq) 3-[1-Oxo-2-(1-methyl-2-(4-methylcyclohexyl) hydrazino)] ethyl-4-cyanothiazolidine (Compound No. 69)
- br) 3-[1-Oxo-2-(1-(1-(2,3-dichlorophenyl carbonyl)-piperidin-4-yl) hydrazino)] ethyl-4-cyanothiazolidine trifluoroacetate (Compound No. 70)
- bs) 3-[1-Oxo-2-[1-methyl-2-(1-(4-chlorophenylsulphonyl)-piperidin-4-yl)]-hydrazino] ethyl-4-cyanothiazolidine (Compound No. 71)
- 30 bt) 3-[1-Oxo-2-(1-(4-piperidiny)l) hydrazino]ethyl-4-cyanothiazolidine bis trifluoroacetate (Compound No. 72)
- bu) [1-Oxo-2-(1-(1-(4-chlorophenylsulphonyl)-piperidin-4-yl)-hydrazino)] ethyl -2-cyanopyrrolidine trifluoroacetate (Compound No. 73)
- 35 bv) 3-[1-Oxo-2-(1-(4-methylcyclohexyl)-2-acetyl) hydrazino]ethyl-4-cyanothiazolidine (Compound No. 74)
- bw) 3-[1-Oxo-2-(1-(1-adamantanyl) hydrazino)] ethyl-4-cyanothiazolidine trifluoroacetate (Compound No. 75)
- 40 bx) 3-[1-Oxo-2-(1-(1-(tert-butyl carbonyl)-piperidin-4-yl) hydrazino)] ethyl-4-cyanothiazolidine trifluoroacetate (Compound No. 76)
- 45 by)3-[1-Oxo-2-(1-(1-(5-trifluoromethyl-2-pyridiny)l)-piperidin-4-yl) hydrazino)] ethyl-4-cyano thiazolidine bis trifluoroacetate (Compound No. 77)
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- bz) 3-[1-Oxo-2-(1-(1-methanesulphonylamino-4-cyclohexyl) hydrazino)] ethyl-4-cyanothiazolidine trifluoroacetate (Compound No. 78)
- 5 ca) 3-[1-Oxo-2-(1-(3,3,5-trimethyl cyclohexyl)-hydrazino)] ethyl-4-cyanothiazolidine trifluoroacetate (Compound No. 79)
- cb) 3-[1-Oxo-2-(1-isopropyl-2-ethyl)-hydrazino]-ethyl-4-cyanothiazolidine trifluoroacetate (Compound No. 80)
- 10 (cc) 3-[1-Oxo-2-[1-(1-phenylmethyl-piperidin-4-yl)]-hydrazino]-ethyl-4-cyanothiazolidine trifluoroacetate (Compound No. 81)
- cd) 3-[1-Oxo-2-(1-(4-chlorophenyl sulphonylamino-4-cyclohexyl) hydrazino)] ethyl-4-cyanothiazolidine trifluoroacetate (Compound No. 82)
- 15 ce) 3-[1-Oxo-2-(pyridazin-1-yl)] ethyl-4-cyanothiazolidine (Compound No. 83)
- cf) 3-[1-Oxo-2-(1-(1-methanesulphonylamino-4-cyclohexyl)-2-isopropyl) hydrazino]ethyl-4-cyanothiazolidine trifluoroacetate (Compound No. 84)
- 20 cg) 3-[1-oxo-2-[1-(1(morpholinocarbonyl)-piperidin-4-yl)]hydrazino]ethyl-4-cyanothiazolidine trifluoroacetate (Compound No. 85)
- ch) 3-[1-oxo-2-[1-(1-(methylsulphonyl)-piperidin-4-yl)]hydrazino]ethyl-4-cyanothiazolidine trifluoroacetate (Compound No. 86)
- 25 ci) 3-[1-oxo-2-[1-(1(methylsulphonyl)-piperidin-4-yl)-2-isopropyl]hydrazino]ethyl-4-cyanothiazolidine trifluoroacetate (Compound No. 87)
- 30 cj) 3-[1-oxo-2-[1-(1-(methylsulphonyl)-piperidin-4-yl)-2-ethyl]hydrazino]ethyl-4-cyanothiazolidine trifluoroacetate (Compound No. 88)
- ck) 3-[1-oxo-2-[1-(1-(morpholinocarbonyl)-piperidin-4-yl)-2-ethyl]hydrazino] ethyl-4-cyanothiazolidine trifluoroacetate (Compound No. 89)
- 35 cl) 3-[1-oxo-2-[1-(1-(N-ethylmethylaminocarbonyl)-piperidin-4-yl)]hydrazino]ethyl-4-cyanothiazolidine trifluoroacetate (Compound No. 90)
- 40 cm) 3-[1-oxo-2-[1-(1-(4-methoxyphenylsulphonyl)-piperidin-4-yl)]hydrazino]ethyl-4-cyanothiazolidine trifluoroacetate (Compound No. 91)
- cn) 3-[1-oxo-2-[1-(1-(4-methoxyphenylsulphonyl)aminocyclohexan-4-yl)]hydrazino]ethyl-4-cyanothiazolidine trifluoroacetate (Compound No. 92)
- 45 co) 3-[1-oxo-2-[1-(1-(4-fluorobenzyl)aminocyclohexan-4-yl)]hydrazino]ethyl-4-cyanothiazolidine bis-trifluoroacetate (Compound No. 93)

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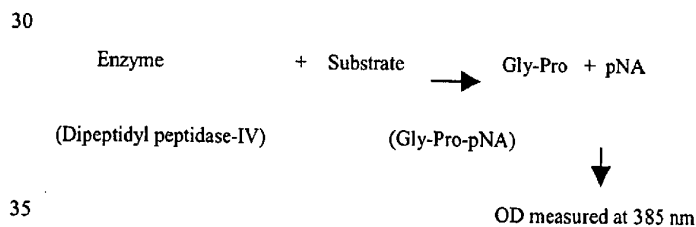
- cp) 3-[1-oxo-2-[1-(1-(4-fluorobenzyl)-piperidin-4-yl)]hydrazino]ethyl-4-cyanothiazolidine bis-trifluoroacetate (Compound No. 94)
- 5 cq) 3-[1-oxo-2-[(1-(1-(2-oxo-2-(5-chloropyridin-2-yl)aminoethyl)piperidin-4-yl)]hydrazino]ethyl-4-cyanothiazolidine tris-trifluoroacetate (Compound No. 95)
- cr) 3-[1-oxo-2-[1-(1-(trimethyl acetamido)cyclohexan-4-yl)]hydrazino]ethyl-4-cyanothiazolidine trifluoroacetate (Compound No. 96)
- 10 cs) 3-[1-oxo-2-[1-(1-(methanesulphonyl)aminocyclohexan-4-yl)-2-ethyl]]hydrazino]ethyl-4-cyanothiazolidine (Compound No. 97)
- ct) 3-[1-oxo-2-[(1-(1-(trimethyl acetamido) cyclohexan-4-yl)]hydrazino]ethyl-4-cyanothiazolidine trifluoroacetate (Compound No. 98)
- 15 cu) 3-[1-oxo-2-[1-(1-(2-oxo-2-(4-cyanophenyl)aminoethyl)piperidin-4-yl)]hydrazino]ethyl-4-cyanothiazolidine bis-trifluoroacetate (Compound No. 99)
- cv) 3-[1-oxo-2-[1-(1-(4-fluorobenzoyl)aminocyclohexan-4-yl)]hydrazino]ethyl-4-cyanothiazolidine trifluoroacetate (Compound No. 100)
- 20 cw) 3-[1-oxo-2-[1-(1-(2-oxo-2-(5-chloropyridin-2-yl)aminoethyl)piperidin-4-yl)]-2-ethyl]hydrazino]ethyl-4-cyanothiazolidine tris-hydrochloride (Compound No. 101)
- 25 cx) 3-[1-oxo-2-[1-(1-(2-oxo-2(4-trifluorophenyl)aminoethyl)piperidin-4-yl)]hydrazino]ethyl-4-cyanothiazolidine bis-trifluoroacetate (Compound No. 102)
- cy) 3-[1-oxo-2-[1-(1-(2-oxo-2(-adamant-1-yl)amino ethyl)piperidin-4-yl)]hydrazino]ethyl-4-cyanothiazolidine bis-trifluoroacetate (Compound No. 103)
- 30 cz) 3-[1-oxo-2-[1-(1-(2-oxo-2(2,3-dihydrobenzo(1,4)dioxan-6-yl) aminoethyl) piperidin-4-yl)]hydrazino]ethyl-4-cyano-thiazolidine bis-trifluoroacetate (Compound No. 104)
- 35 da) 3-[1-oxo-2-[1-(1-(2-oxo-2(4-chlorophenyl)aminoethyl)piperidin-4-yl)]hydrazino]ethyl-4-cyanothiazolidine bis-trifluoroacetate (Compound No. 105)
- db) 3[2-oxo-2-[1-(1-(2-oxo-2(pyrimidin-2-yl)aminoethyl)piperidin-4-yl)]hydrazino]ethyl-4-cyanothiazolidine tris-trifluoroacetate (Compound No. 106)
- 40 dc) 3-[1-oxo-2-[1-(1-(2-oxo-2(morpholin-4-yl)ethyl)piperidin-4-yl)]hydrazino]ethyl-4-cyanothiazolidine bis-trifluoroacetate (Compound No. 107)
- 45 dd) 3[1-oxo-2-[1-(1-(2-oxo-2(cyclopropyl)aminoethyl)piperidin-4-yl)]hydrazino]ethyl-4-cyanothiazolidine bis-trifluoroacetate (Compound No. 108)

- de) 3-[1-oxo-2-[1-(1-(2-cyanobiphenyl-4-yl)methyl)piperidine-4-yl]hydrazino]ethyl-4-cyanothiazolidine bis-trifluoroacetate (Compound No. 109)
- 5 df) 3-[1-oxo-2-[1-(1-(1-oxo-2-(morpholin-4-yl)ethyl)piperidin-4-yl)]hydrazino]ethyl-4-cyanothiazolidine bis-trifluoroacetate (Compound No. 110)
- dg) 3-[1-oxo-2-[1-(4-(2-oxo-2-(5-chloropyridin-2-yl)aminoethyl)amino cyclohex-1-yl)]hydrazino]ethyl-4-cyanothiazolidine tris-trifluoroacetate (Compound No. 111)
- 10 dh) 3-[1-oxo-2-[1-(4-(2-oxo-2-(4-cyanophenyl)aminoethyl)aminocyclohex-1-yl)]hydrazino]ethyl-4-cyanothiazolidine bis-trifluoroacetate (Compound No.112)
- di) 3-[1-oxo-2-[1-(4-(2-oxo-2-(4-chlorophenyl)aminoethyl)aminocyclohex-1-yl)]hydrazino]ethyl-4-cyanothiazolidine bis-trifluoroacetate (Compound No.113)
- 15 dj) 3-[1-oxo-2-(1-(1-methanesulphonylamino-4-cyclohexyl)hydrazino)]ethyl-4-cyanothiazolidine hydrochloride (Compound No. 114)
- 20 dk)3-[1-oxo-2-[1-(1-(2-oxo-2-(5-chloropyridin-2-yl)aminoethyl)piperidine-4-yl)]hydrazino]ethyl-4-cyanothiazolidine trihydrochloride (Compound No. 115)

Assay of DPP-IV enzyme inhibitory activity.

The assay method is a modified method (as described by Welch et al, 1998) based on spectrophotometric determination of the product formed by penultimate proline cleaving activity of the enzyme.

The following equation explains the principle of the assay method:



Gly-Pro-pNA: Glycine-Proline-p-nitroanilide

Assay protocol involves incubation of the enzyme dipeptidyl peptidase IV with the test substance at 30° C for 30 min followed by addition of this reaction mixture to the substrate Gly-Pro-pNA that was equilibrated at 30° C for 2 min. The enzyme cleaves the substrate at penultimate proline and releases p-nitroanilide, the optical density of which is measured at 385 nm. The formation of p-nitroanilide will be reduced in the presence of inhibitor. Optical density is measured for 2 hours for every 10min using a spectrophotometer and V_{max} is calculated to find the activity of new chemical entities. The activity of molecule is expressed in terms of % inhibition. Atleast three different concentrations were tried out for each of the test substances. The percentage inhibitions for each of the concentrations were plotted and an IC_{50} of the test compound was worked out. The enzyme inhibitory activity of different test compounds were compared based on the IC_{50} values.

The percentage inhibition %I, is calculated using the formula:

$\% I = [(1 - v_i/v_0)] * 100$ where v_i and v_0 are the V_{max} values with and without the test substance, respectively.

Reagents and their preparation:

Substrate solution: 0.5 mM in 45 mM phosphate buffer

Substrate used: Gly-Pro-p-nitroanilide (Source: Sigma-Aldrich Co. Germany)
M. Wt of Gly-Pro-p-nitroanilide =328.8

3.288 mg substrate in 1 ml 45 mM phosphate buffer was prepared as stock solution. 0.25 ml of this stock solution was diluted to 5 ml to get 0.5 mM substrate solution (90 μ l to be added in each well). The stock solution of the substrate was used within three days of preparation.

Enzyme solution: Porcine DPP-IV (Sigma-Aldrich Germany) was used throughout the study. 0.4 mU in 80 μ l of Tris. HCl buffer was prepared. Fresh solutions were prepared everyday for the assays.

Inhibitor solution:

The compounds of the present invention were dissolved in their respective vehicles. E.g. 1. Compound No.95 (in MilliQ water)

Mol. Wt. of Compound No.95 : 779

Various concentrations of inhibitor were used: 0.391 μ M, 0.781 μ M, and 3.125 μ M.

Solutions of inhibitor were prepared and used on the same day.

5 Experimental Procedure:

Different concentrations of inhibitor (compound 95), vehicle, substrate and enzyme were prepared as per standard procedures. 280 μ l of enzyme solution (0.4-mU/80 μ l in Tris HCl buffer) was added to the eppendorf containing 70 μ l solution of inhibitor or vehicle and mixed. This reaction mixture was incubated for 30 min at 30 $^{\circ}$ C. The 96 well plate containing substrate solution was thermally equilibrated in the spectrophotometer for 2 min at 30 $^{\circ}$ C. Later 100 μ l of the enzyme-inhibitor pre-incubation solution was added to respective wells in a 96 well plate. Each concentration of the inhibitor was tested in triplicates.

15

The rate of change in UV absorbance (in presence of various concentrations of the inhibitor) was measured at 385 nm, with respect to wells containing only 0.5 mM substrate in 45 mM phosphate buffer as blank at every 10 min for 2 hours after adding enzyme-inhibitor mixture to wells containing substrate solution.

20

Table 2:

The inhibitory activity of the compounds on DPP-IV enzyme activity

Compound No.	IC ₅₀ (μ M) Mean \pm SD
1	47.56 \pm 2.72
3	34.11 \pm 4.57
4	88.60 \pm 18.05
9	6.18 \pm 0.88
10	69.84 \pm 17.48
12	61.29 \pm 4.55
13	57.05 \pm 3.76
14	93.72 \pm 5.54
15	41.92 \pm 11.56

Compound No.	IC ₅₀ (μM) Mean ±SD
16	9.29±0.64
17	35.80±1.03
18	32.07±1.65
19	1.46±0.16
20	33.71±0.99
21	2.01±0.16
22	76.52±7.51
23	2.94±0.15
25	0.67±0.03
26	10±0.79
27	42.96±2.76
28	2.29±0.11
29	0.80±0.15
30	35.07±2.66
34	30.31±5.50
36	23.33±2.54
37	28.26±4.60
38	96.90±23.03
39	50.42±4.59
41	48.27±1.75
42	0.53±0.09
43	38.18±2.56
44	2.86±0.18
45	43.99±1.92
46	78.62±4.58
47	1.14±0.09
48	45.18±1.21
49	1.04±0.25
50	60.06±5.50

Compound No.	IC ₅₀ (μM) Mean ±SD
51	3.50±0.06
52	0.71±0.06
53	16.74±2.07
54	6.43±0.15
55	2.70±0.16
56	44.23±1.36
57	4.77±0.41
58	17.07±0.30
59	9.27±0.42
60	0.69±0.03
61	0.70±0.03
62	1.54±0.34
63	0.73±0.02
64	0.34±0.07
65	0.87±0.06
66	1.53±0.01
67	72.49±7.05
68	45.26±3.03
69	68.99±10.07
70	1.79±0.12
71	86.16±5.30
72	12.08±0.13
73	48.87±1.81
74	97.74±13.12
75	0.31±0.05
76	4.15±0.29
77	0.67±0.06
78	0.25±0.02
79	0.92±0.03

Compound No.	IC ₅₀ (μM) Mean ±SD
80	2.27±0.19
81	1.63±0.15
82	0.66±0.10
83	81.97±18.04
84	5.78±0.18
85	0.79 ± 0.072
86	1.46 ± 0.22
87	18.26 ± 3.2
88	3.755 ± 0.101
89	0.985 ± 0.086
90	1.23 ± 0.3
91	6.7 ± 0.4
92	1.33 ± 0.124
93	5.56 ± 0.18
94	2.23 ± 0.08
95	0.12 ± 0.013
96	4.0 ± 0.144
97	1.03 ± 0.07
98	0.71 ± 0.01
99	0.2 ± 0.04
100	0.93 ± 0.015
101	0.488 ± 0.017
102	0.308±0.06
103	0.523±0.017
104	0.222±0.023
105	0.258±0.027
106	0.143±0.02
107	0.525±0.098
108	0.236±0.025
109	1.022±0.14

Compound No.	IC ₅₀ (μM) Mean ±SD
110	0.830±0.05
111	0.563±0.077
112	1.471±0.07
113	1.065±0.3
114	0.397±0.02
115	0.088±0.006

(Values are mean ± SD of the three experiments)

- 5 **Note :** The IC₅₀ values for compounds 1-32 as reported in the provisional specification No.60/370,224, which is incorporated in the instant patent application by reference, were subjected to same experimental procedure as reported here to determine IC₅₀ values. However, in view of an erroneous dilution factor taken for calculation of IC₅₀ values in the provisional specification, the reported figures, though showing the same trend of activity are 9.5 times of the figures reported above for the compounds 1,3,4,9,10,12-23 and 25-30 recalculated by using the correct dilution factor.

In vivo oral glucose tolerance studies

- 15 The anti-hyperglycemic effect of compound no. 95 (8mg/ml/kg, i.v) after an oral glucose load of 1gm/kg was studied in STZ induced diabetic rats (modified method of Balkan et al 1999).

- 20 **Animals:** Male STZ induced diabetic rats aged 10-12 weeks and weighing between 200-250gm were used for the study. These rats were treated with streptozotocin administered intraperitoneally on the day of birth at a dose of 90 mg/kg. They were maintained under standard conditions till the age of 10-12 weeks when they were used for the study.

- 25 **Materials:** Glucose solution (1gm/4ml of saline), Diethyl ether compound no. 95 (8mg/ml/kg), vehicle (1ml/kg), Heparinized saline (100IU/ml), glucometer and strips

Method: Animals were divided into two groups

5 Group I: 8 hours fasted rats were treated with compound no. 95 vehicle (1 ml/kg, i.v.)
5 min before administration of glucose load.

10 Group II: 8 hours fasted rats were treated with compound no. 95 (8mg/ ml/kg, i.v) 5
min before administration of glucose load.

In both groups, blood samples were taken before administration of vehicle/
15 compound no. 95 and glucose load for blood glucose estimation. Blood glucose level
before administration of compound no. 95 or its vehicle was considered as -5 min
reading. Blood glucose level before administration of glucose was considered as 0
min reading.

20 After 10, 20, 30, 45, 60, 75, 90, 120, 150 and 180 min of glucose
administration, blood glucose level was estimated by the glucose oxidase method
using a LifeScan glucometer (Ca, USA). Blood glucose level at various time points
was subtracted from the basal (0 min) reading. This was done to avoid changes in
AUC because of variation in basal glucose level. The glucose excursion at various
time points was plotted against time and the AUC was calculated.

25 The activity of compound no. 95 was expressed as % reduction in AUC as
compared with that of its vehicle.

30 RESULTS:

The AUC for the group treated with compound no. 95 was found to be
413.3±134.6 mM*min and the AUC for the group treated with vehicle for compound
no. 95 was found to be 1070.5±342.4 mM*min. compound no. 95 significantly
35 (p<0.05) reduced the AUC values as compared to the group treated with their
corresponding vehicle.

Table A: Effect of compound no. 95 on AUC of glucose excursion in nSTZ induced diabetic rats.

5

Table - A

GROUP (n)	DOSE	AUC values mM*min
compound no. 95 (7)	8 mg/ml/kg	413.3±134.6a
Vehicle for (compound no. 95) (5)	1 ml/kg	1070.5±342.4

Values of AUC are Mean ±SD

10

a = P<0.05 vs Vehicle for compound no. 95 group

Table B: Effect of compound no. 95 (8mg/ml/kg; i.v) pre-treatment on glucose excursions after a 1 gm/kg glucose load in nSTZ induced diabetic rats

15

Table - B

TIME	Glucose excursions after a 1gm/kg glucose load	
	compound no. 95 (n=7)	Vehicle for compound no. 95 (n=5)
0	0.0	0.0
10	3.9	2.7
20	5.9	5.2
30	7.8	7.8
45	6.2	8.0
60	4.1	8.8
75	2.7	7.9
90	0.5	7.4
120	-2.8	5.4
150	-4.1	4.5
180	-3.9	3.9

20

The results of the above analysis are also depicted in Figure 1 and Figure 2 of the drawings.

Free Radical Scavenging activity:

1.Aim:

5

To determine the in-vitro free radical scavenging activity of compounds of general formula-I on 2,2,-diphenyl-1-picrylhydrazyl (DPPH)radical (Ref: W. Brand- Williams, M.E.Cuvelier, C. Berset "Use of a free radical method to evaluate antioxidant activity", Lebensm.- Wiss.u. Technol.,1995,28,Nr.1:25-30).

10

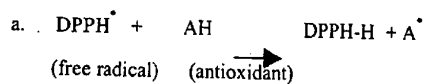
2.Principle involved:

To evaluate the free radical scavenging activity of compounds they are allowed to react with stable radical DPPH[•]. In its radical form, DPPH[•] absorbed at the characteristic wave length of 515nm, but upon reduction by an antioxidant or radical scavenger (AH), the absorption disappears.

15

Equation:

20



3. Reagents and Chemicals:

25

DPPH[•] (Sigma Aldrich)
Methanol (Merck)

4. Instrument used:

30

UV-visible spectrophotometer (Jasco)
Quartz Microcuvette (1ml capacity)

5. Procedure:

Preparation of DPPH[•] solution:

5 10⁻⁴M solution of DPPH[•] was prepared in methanol.

Preparation of drug solution:

10 Various concentrations (10mM,1mM, 0.5mM,0.25mM and 0.125mM) of drug solutions were prepared in methanol.

Preparation of Control solution:

15 900µl of DPPH[•] radical solution was added to an eppendorf tube. To it was added 100µl of methanol.

Preparation of Test solution:

20 900µl of DPPH[•] radical solution was added to an eppendorf tube. To it was added 100µl of various concentrations of drug solutions in methanol.

Measurement of absorbance (O.D):

25 The absorbance of control and test samples was recorded after incubation at 30°C for 30 minutes, at 515nm taking methanol as blank.

6. Calculation:

The percent antioxidant activity was calculated according to the formula:

30 % Antioxidant activity = 100-[O.D of test sample/O.D of control*100]

TABLE - 3

IN-VITRO FREE RADICAL SCAVENGING ACTIVITY OF THE MOLECULES USING DPPH FREE RADICAL

5

Control/Compound No.	Concentration (µM)	% Activity
ASCORBIC ACID (Control)	12.5	28.01
	25	54.10
	50	95.31
	100	96.18
25	100	95.66
19	100	94.55
21	100	95.71
29	100	93.70
85	12.5	15.25
	25	30.67
	50	49.97
	100	67.23
86	12.5	22.72
	25	45.27
	50	70.18
	100	88.14
87	12.5	12.87
	25	30.88
	50	44.03
	100	55.94
88	12.5	14.49
	25	44.12
	50	56.11
	100	69.34
89	12.5	10.37
	25	20.74
	50	36.94
	100	55.07
90	12.5	21.81
	25	42.93
	50	62.91
	100	82.75
91	12.5	17.16
	25	38.11
	50	58.87
	100	85.69
92	12.5	10.07
	25	30.36
	50	58.48
	100	78.77

93	12.5	15.18
	25	28.08
	50	44.13
	100	64.24
94	12.5	9.34
	25	24.05
	50	39.04
	100	55.85
95	12.5	22.06
	25	36.87
	50	44.81
	100	65.52
96	12.5	19.11
	25	34.43
	50	48.83
	100	63.26
97	12.5	18.06
	25	38.30
	50	66.99
	100	91.67
98	12.5	21.99
	25	40.77
	50	59.21
	100	73.35
99	12.5	15.12
	25	24.87
	50	39.13
	100	53.33
100	12.5	31.14
	25	41.49
	50	59.54
	100	77.75
101	12.5	20.41
	25	31.00
	50	32.19
	100	61.15
102	12.5	20.90
	25	29.56
	50	34.26
	100	50.15
103	12.5	20.41
	25	40.80
	50	44.09
	100	54.81
104	12.5	19.40
	25	36.23
	50	42.20
	100	50.14

105	12.5	24.03
	25	35.27
	50	49.25
	100	49.63
106	12.5	24.86
	25	42.52
	50	70.39
	100	72.86
108	12.5	20.19
	25	26.25
	50	34.71
	100	52.72
114	12.5	19.23
	25	39.37
	50	78.16
	100	92.76
115	12.5	19.46
	25	26.94
	50	46.24
	100	75.84

The test compounds listed in the Table 3 above exhibit *invitro* (antioxidant) free radical scavenging activity. Excessive production of free radicals; reactive oxygen species (ROS) results in oxidative stress. Therefore, these molecules would be very effective in reducing oxidative stress by their ability to trap ROS. Antioxidants (free radicals scavengers) are reported to be effective in the management of various diseases linked with oxidative stress.

Also, the novel compounds show Free Radical Scavenging Activity which is useful for (a) Neurodegenerative disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Motor Neuron Disease, Prion Disease etc, (b) Diabetes and Diabetic Vascular Complications, (c) Intestinal Diseases such as Intestinal Ischemia, Radiation Enteritis, Inflammatory Bowel Disease, Gastric and Colorectal Cancers etc., (d) Liver Diseases such as Alcoholic Liver Disease, Chronic Hepatitis C etc., (e) Cancers such as Lung Cancer, Colorectal Cancer, Cervical Cancer, Breast Cancer, Malignant Melanoma etc., (f) Cardiac Diseases such as Atherosclerosis, Myocardial Infarction, Ischemic Stroke, Endothelial Dysfunction

etc., (g) Ophthalmic Disorders such as Cataract formation, Macular degeneration etc.,
(h) HIV Diseases, (i) Respiratory Diseases such as Chronic Obstructive Pulmonary
Diseases, Asthma etc., (j) Renal Diseases such as Glomerulonephritis, Acute Renal
Failure etc.

5

Discussion of Test Results :

Oral glucose tolerance test is one of the methods to test pre-diabetic or
diabetic condition and to evaluate insulin secretagogues and/or releasers. Glucose
10 level in the body is mainly controlled by insulin although many other factors
contribute to insulin release. Administration of glucose by oral route will increase the
glucose level in the blood, which induces the release of insulin. This glucose
stimulated insulin release is impaired in diabetes. By pretreatment with drugs that
releases or stimulates insulin release before taking food/glucose, the rise in glucose
15 level can be controlled.

Figure-2 and Table-2 show a distinct decrease in the compound no. 95 treated
animal's blood glucose values as compared to the corresponding vehicle treated
group. This is also reflected in the decrease in AUC of glucose in compound no. 95
20 treated group as compared to vehicle group. From the graphs shown in figures 1 and 2
it is evident that compound no. 95 controls hyperglycemia and brings the glucose
levels to normoglycemic range. Please note that the negative values do not represent
hypoglycemia; it is only a fall below the basal hyperglycemic level. This could be
explained by an increase in glucose mediated insulin secretion by compound no. 95.
25 Hence, it is concluded that compound no. 95 would be a useful in the management of
hyperglycemia in type II diabetes.

Free radicals along with AGE formation contributes to macroangiopathic
(atherosclerosis, coronary artery disease) and microangiopathic (neuropathy,
30 retinopathy, nephropathy) complication of diabetes.

The test compounds listed in Table-3 exhibit *in vitro* (antioxidant) free radical scavenging activity. The novel compounds show free radical scavenging activity, which would be useful for treatment of diabetes and diabetic vascular complications (DVCs).

5

The DPP-IV inhibitors under study are preferably expected to not only control diabetes, but also to prevent diabetic complications by their antioxidant actions.

10

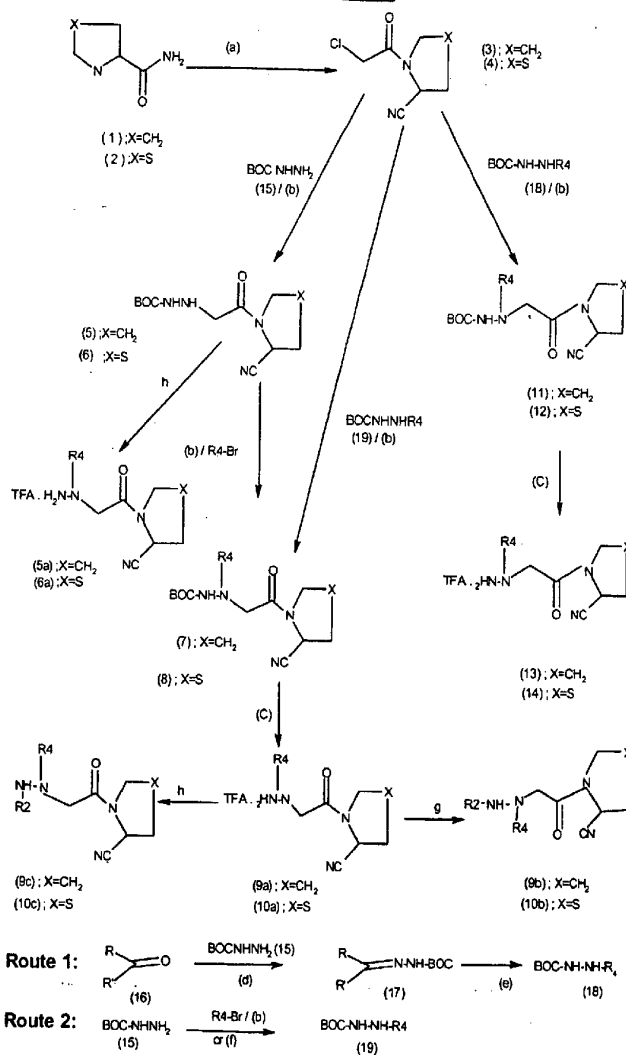
Compound numbers 78, 95, 99, 104, 108 and 115 showed prominent dipeptidyl peptidase-IV inhibitory actions with their IC_{50} 's in the range of 88 to 250 nM. These compounds could be used to prevent the degradation of the insulinotropic hormone GLP-1; and thereby elevate their circulating levels. These
15 compounds are expected to exert their anti-hyperglycemic action in a glucose dependent way and hence the usual side effect of hypoglycemia observed with the classical sulphonylureas would not be observed.

20 **Preparation of representative compounds of the invention :**

The compounds of the invention may be prepared by alternative synthetic routes as per Scheme I, II or III as described below:

25

SCHEME 1



Reagents and conditions for Scheme - I :

- [a] (I) Et₃N, THF, K₂CO₃, ClCH₂COCl, 0-20°C, 2.5-3.0 hrs. (II) (CF₃CO)₂O / THF ;
[b] K₂CO₃, KI, THF, Reflux, 6-20 hrs.
[c] CF₃COOOH, Room Temp., 10-20 min.
5 [d] Hexane / Reflux, 2-4 hrs.
[e] NaBH₄, MeOH, Reflux, 4-20 hrs.
[f] Neat, Reflux.
[g] (i) Aldehyde/ketone, MeOH, Reflux, (ii) NaCNBH₃, TiCl₄, MeOH
[h] (i) R₈NHCOCl or R₈SO₂Cl or R₈COCl, TEA, THF, 0-20°C (ii) [c]

10 **Description:**

The compounds of present invention may be prepared by the general methods as depicted in Scheme (I). The starting amide compound of formula (1) i.e L - prolinamide is prepared in four steps from L-proline following the same methods as
15 described in literature for the synthesis of (R)-(-)-thiazolidine-4-amide of formula (2) from the corresponding acid.

Ref. US pat-6110949 dated 29.8.00, Doreen M et al, Bio.Org. Med. Chem. Lett. 6(22), 1996, 2745-48]. L-prolinamide (1) is then converted to 1-chloroacetyl-2-cyanopyrrolidine of formula (3) in two steps which involves chloroacylation of the
20 amide followed by dehydration [Ref. US pat -6124305 dated 26.09.00, WO-0034241 dated 15.06.00 and US pat 6011155 dated 01.04.00].

In a similar manner, the another starting material 3-chloroacetyl-4-cyano thiazolidine of formula (4) is prepared by following two step reactions sequence. Step-1 involves the reaction of thiazolidine amide of formula (2) with
25 chloroacetylchloride in presence of a base such as potassium carbonate and an inert organic solvent like tetrahydrofuran at a temperature of from 0 °C to 20 °C for 2.5 to 3 hrs. Step 2 involves the dehydration of 3-chloroacetyl-thiazolidine-4-amide prepared in step-1, with 2-equivalents of trifluoroacetic anhydride conducted in presence of an inert organic solvent such as tetrahydrofuran at a temperature preferably at 20 °C.

30 The second major component of the present invention i.e. N-2-substituted - tertbutyl carbazates of formulae (18) and (19), is prepared by the conventional manner. The tert-butyl alkylidene carbazates of formula (17) is prepared by refluxing hexane or tetrahydrofuran solution of tert-butyl carbazate (15) with appropriate

aldehyde or ketone of formula (16) in 1:1 molar ratio for 2-4 hrs. [Ref. Dutta Anand S et.al., J.Chem. Soc.Perkin I, 1975, 1712-1720. Ghali N.I et al, J.Org.Chem. 46, 1981, 5413-5414].

5 The alkyldine carbazates thus formed in the previous step is reduced to N-2 substituted -tert-butyl carbazates of formula (18) using metal hydrides like sodium borohydride or lithium aluminium hydride, preferably sodium borohydride and Sodium cyanoborohydride. The solvent used in the reaction is organic solvent like methanol or tetrahydrofuran at a temperature ranging from 25°C to 70°C for 4 to 20

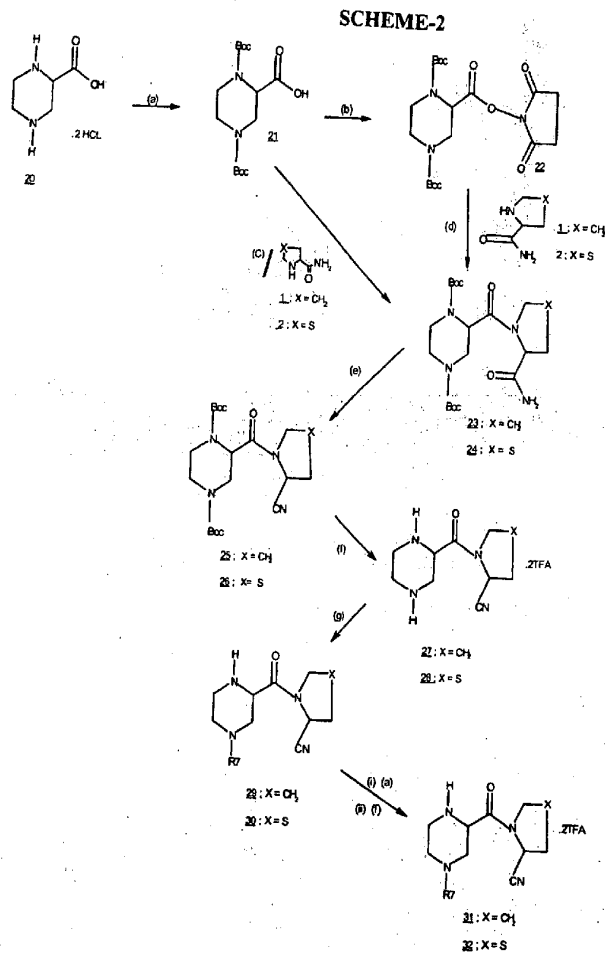
10 hrs.

On the other hand, direct alkylation of tert-butyl carbazate with alkyl or aryl halides preferably with the corresponding chlorides or bromides either in neat reaction condition or in presence of an inorganic base such as potassium carbonate and a catalyst such as potassium iodide in presence of THF provides carbazate derivatives of formula (19). Coupling of chloroacyl derivatives of formula (3) or (4) with the tert-butyl carbazate derivatives (18) or (19) in presence of K_2CO_3 /KI in THF gives rise to hydrazinoacyl derivatives (11),(7),(12) or (8) which on deprotection using trifluoroacetic acid provides the final compounds (13), (9a),(14) or (10a) respectively as trifluoroacetate salts and further reaction of 9(a) or 10(a) with appropriate aldehyde followed by reduction using metal hydride like sodium borohydride or sodium cyanoborohydride in presence of catalytic compound of $TiCl_4$ (Titanium tetrachloride) gives rise to compounds 9(b) or 10(b).

Similar reaction of 9(a) or 10(a) with appropriate acid chloride or sulfonyl chloride gives rise to respective compounds 9(c) or 10(c).

25 Alternatively, the hydrazino derivatives (5) or (6) can be prepared from the corresponding chloroacyl derivatives (3) or (4) by reaction with tert-butyl carbazate itself. Alkylation of (5) or (6) with alkyl halides gives rise to penultimate intermediates (7) or (8) respectively.

30 Also, the reaction of compound (5) or (6) with appropriate carbamoyl chloride, sulphonyl chloride or acid chloride followed by deprotection with trifluoroacetic acid gives rise to compound 5(a) or 6(a) respectively.

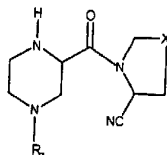


Reagents and conditions for Scheme - II:

- [a] : $(\text{Boc})_2\text{O}$, NaOH, Dioxan, H_2O , $0^\circ\text{-}25^\circ\text{C}$, 2-4 hrs;
 [b] : NOSU, DCC, DCM, THF, $0^\circ\text{-}15^\circ\text{C}$, 3-5 hrs;
 [c] : HOBT, DCC, DIEA, DCM, $-5^\circ\text{-}25^\circ\text{C}$, 6-16 hrs;
 [d] : DCM or THF, $5^\circ\text{-}25^\circ\text{C}$, 12-22 hrs;
 [e] : $(\text{CF}_3\text{CO})_2\text{O}$, DCM or THF, Room Temp., 1-3 hrs;
 [f] : CF_3COOH , CH_3CN , Room Temp., 3-4 hrs;

[g] : R7Br, Et₃N, K₂CO₃, THF, CH₃CN or RBr, Et₃N, THF, 0^o-60^oC, 1-25 hrs.

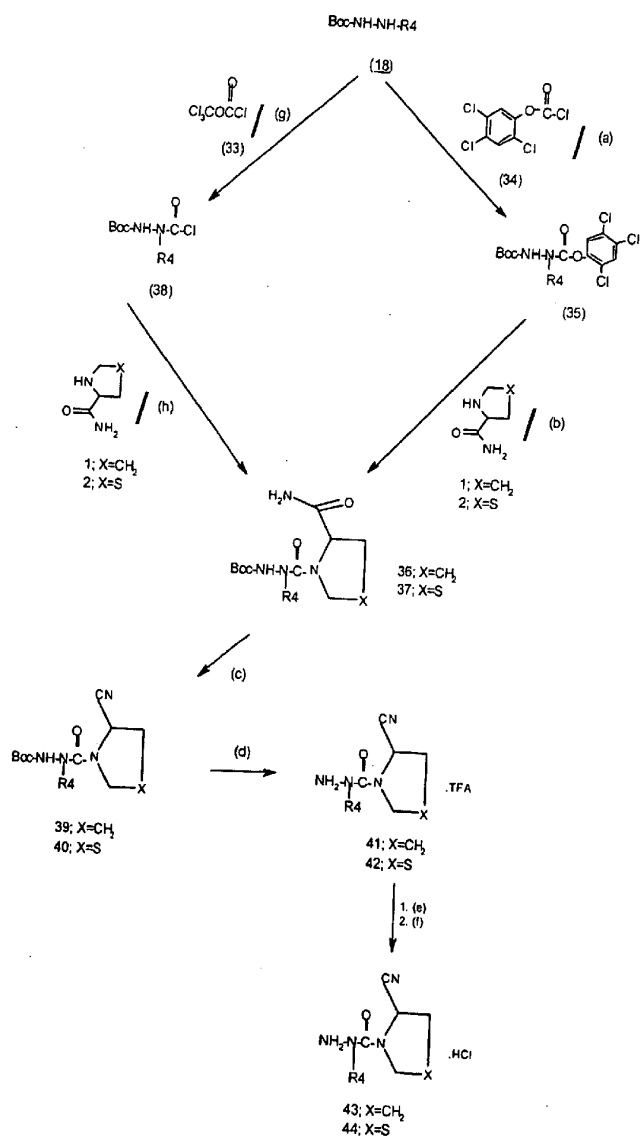
In an another embodiment of the present invention in which compounds, wherein the value of "k" mentioned in the general formula (I) is "null", then R₄ and R₆ together form optionally six or seven membered ring optionally containing two or three heteroatoms independently selected from O, S and NR₇, with R₁ is hydrogen, and N₁ is attached to hydrogen. As described represented by the formula (II), compounds may be prepared by the general methods as depicted in Scheme-II.



(II)

10 Piperazine-2-carboxylic acid dihydrochloride (20) is first protected by using usual protecting groups like Boc (tert-butyloxycarbonyl) or CBZ (benzyloxycarbonyl). The protected acid (21) is subjected to coupling with L-prolinamide (1) or (R)-(-)-thiazolidine-4-amide (2) to give the coupled products (23) or (24). This can either be done by first dicyclohexylcarbodiimide (DCC) mediated
15 coupling of the acid (21) with N-hydroxysuccinimide (NOSU) to form the active ester (22) followed by its reaction with the amides (1 or 2), or by direct coupling of the protected acid (21) with the amides (1 or 2) in presence of 1-hydroxybenzotriazole (HOBT), DCC and the tertiaryamine like, diisopropylethyl amine (DIEA). Dehydration of the coupled products (23 or 24) using trifluoroacetic anhydride as
20 dehydrating agent provides the corresponding cyano derivatives (25 or 26). Deprotection of the compounds (25 or 26) in presence of trifluoroacetic acid followed by regioselective functionalization of the deprotected compounds (27 or 28) at N-4 of piperazine ring using alkyl or aryl halides, or with acyl or sulphonyl halides yield the target compounds as represented by formula (29,30). They (29,30) can optionally be
25 purified by reprotecting them at N-1 of the piperazine ring with a non-polar protecting group like Boc group, thereby, making these compounds more non polar, followed by deprotection of Boc group of this column purified intermediate using trifluoroacetic acid results in the formation of final compounds as trifluoroacetate salts (31,32).

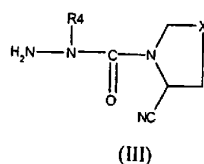
SCHEME-3



Reagents and Conditions for Scheme -III:

- 5 i. Et₃N, THF or DCM, -25⁰ to 4⁰C, N₂, 10-16 hrs.
ii. Et₃N, THF or DCM, Reflux, 6-10 hrs.
iii. (CF₃CO)₂O, THF, Room temp. 2-4 hrs.,
iv. CF₃COOH, THF, 5⁰C to Room temp. 0.5 to 2 hrs.,
v. Aqueous NaHCO₃,
vi. MeOH.HCl
10 vii. Et₃N, THF, -5⁰ to 0⁰C, 1-2 hrs., N₂,
viii. Et₃N, THF, 5⁰ to 60⁰C, 12-18 hrs.

In a yet another embodiment of the present invention in which compounds described represented by the formula (III), wherein the value of "n" mentioned in the
15 formula (I) is "null", may be prepared by the general methods as depicted in Scheme-III.



20 N-2-substituted tert-butyl carbazate (18) on reaction with 2,4,5-trichlorophenyl chloroformate (34), prepared from 2,4,5-trichlorophenol and trimethyl chloroformate (33) by the method as described in the literature, in presence of triethylamine as base results in the formation of carbazate derivatives (35). [Ref. Konakahara T et al, Synthesis, 1993, 103-106.]

25 The carbazate derivatives (35) on coupling with L-prolinamide (1) or thiazolidine amide (2) in presence of a tertiary amine as a base preferably triethylamine in an organic solvent like THF under reflux for 4-10 hrs. give the coupled products (36,37). These amide derivatives (36,37) can also be obtained by
30 chlorocarbonylation of tert-butyl-carbazates (18) with trichloromethyl chloroformate

(33) in presence of Et₃N at a low temperature(-5^o to 0^o C), followed by coupling of the amides (1,2) with the chlorocarbonyl derivative of carbazates (38) in presence of Et₃N / THF at a temperature ranging from 25^o to 60^oC for 8-12 hrs.

5 Subsequently usual dehydration of the amide derivatives (36,37) with trifluoroacetic anhydride in THF at a temperature from 5^o to 30^oC for 2-4 hrs. followed by deprotection of the corresponding cyano derivatives (39,40) with a deprotecting agent like trifluoroacetic acid at a temperature in the range of 5^oC to 30^oC for 0.5 to 2 hrs, results in the formation of the final compounds (41,42) as
10 trifluoroacetate salts. They can optionally be purified by neutralizing with an aqueous alkali like sodium bicarbonate (aqueous), purifying the free base thus obtained by column chromatography followed by converting to hydrochloride salts (43,44) by
15 treating with methanolic hydrochloric acid at 10^oC to 20^oC for 1 to 2 hrs.

15 **Representative example of Scheme I:**

Example - 1

3-[1-Oxo-2-(-(1-cyclohexyl)hydrazino)] ethyl-4-cyano thiazolidine
trifluoroacetate [Compound No.21].

20

Step: 1

A solution of tert-butyl cyclohexylidene (8.0g, 37.7 mmol) in methanol
(50ml) was warmed to 50^oC and then added sodium borohydride (11.4g, 301.6
25 mmol) in portions over a period of 20 minutes. Refluxed for 8 hrs. Reaction mixture is concentrated in vacuo. Reaction mixture diluted with water and extracted with ethylacetate. Ethylacetate layer washed with water, dried (Na₂ SO₄), evaporated to dryness yielding the crude mass which is purified by column chromatography (5% ethyl acetate /hexane) gives N-cyclohexyl tert-butyl carbazate. (Yield 5.81g, 71.95
30 %).

Step: 2

To a solution of carbazate derivative (0.535g, 2.5 mmol) thus formed in Step1, and 3-chloroacyl-4 – cyanothiazolidine (0.475g, 2.5 mmol) (prepared in analogous
5 manner as for corresponding pyrrolidine derivative) in THF (30 ml) is added
K₂CO₃ (1.03g, 7.5 mmol) and KI (0.29g, 1.75 mmol). Reaction mixture is then
refluxed for 6 hrs. Cooled, filtered, filtrate evaporated to dryness and the crude
material purified by column chromatography (5 % ethylacetate/hexane). (Yield 0.45g,
48.9 %).

10

Step: 3

Product obtained in step-2 (0.25g, 0.68 mmol) is taken with
trifluoroacetic acid (2.0 ml) at 0°C and allowed to stir at 5-10°C for 10 minutes.
15 Trifluoroacetic acid removed in vacuo and final traces of trifluoroacetic acid removed
by stripping off with toluene and methanol respectively, gives white solid as a
trifluoroacetate salt, final product. (Yield 0.179g, 69 %).

Example-2

20

3-[1-oxo-2-(1-cyclohexyl-2-isopropyl)hydrazino]ethyl-4-cyanothiazolidine
hydrochloride (Compound No. 36)

Product obtained in step-2 of example-1 (0.6g, 1.57 mmol) was stirred with
25 trifluoroacetic acid (5 ml) at 5-10°C for 10 minutes. Trifluoro acetic acid removed in
vacuo. To the residue, added 5ml water and 5 ml saturated sodium carbonate
solution, extracted with ethylacetate, evaporated to dryness yielded a mass.
Resulting mass was refluxed in acetone (10ml) for 2 hrs. Excess solvent was
removed in vacuo. Obtained mass was taken in methanol (15ml), cooled to 0°C,
30 added sodium cyanoborohydride (8.1mmol, 0.30g) in portions, and stirred for 1 hr.
Reaction mixture was concentrated in vacuo, treated with water, extracted with
ethylacetate. Dried organic layer was evaporated to dryness, yielding a mass, which
is purified by column chromatography (15% ethylacetate / hexane). Free base was

stirred with methanolic hydrochloric acid (2ml) for 15 min, solvent was removed in vacuo yielded hydrochloride salt. (200 mg, yield: 40%).

Example-3

5 1,1-dioxo-3-[1-oxo-2-(1-methylcyclohexyl)hydrazino]ethyl-4-cyanothiazolidine trifluoroacetate (Compound No. 67).

Title compound is prepared by same method described in example-1 using N-(4-methyl-cyclohexyl)ter-butyl carbazate and 3-chloro-acyl-4-cyanothiazolidine-1,1-dioxide (prepared as followed).

10 To stirred solution of 3-chloroacyl-4-cyanothiazolidine (0.50g, 2.6mmol) in dichloromethane added meta-perchlorobenzoic acid (0.91g, 5.2 mmol) in portions at 5-10°C. Reaction mixture was then stirred for 30 minutes and evaporated to dryness. Resulting crude mass was column chromatographed (20% ethylacetate / hexane) yielded desired compound (0.2g, yield: 30%).

15 **Example-4**

3-[1-oxo-2-(pyridizin-1yl)ethyl-4-cyanothiazolidine (Compound No. 83).

The solution of N⁺-benzyloxycarbonyl-N-ter-butylloxycarbonyl hydrazine (4g, 15mmol) and 1,4-diabromobutane (5.8g, 25.9mmol) in acetonitrile (50ml) was refluxed for 15 hrs in presence of potassium carbonate (4.2g, 30mmol). Reaction mixture was filtered, evaporated to dryness, purified by column chromatography (10% ethylacetate-hexane, 4g, yield: 83%). The solution of obtained solid in 50% methanol-water (100ml) was stirred with 5% palladium-charcoal (400mg) at 50 psi for 6 hrs, filtered evaporated, and purified by column chromatography (ethylacetate 1.9g, yield: 82%). The solution of obtained N-ter-butylloxypyridazine (1g, 5.3mmol) 25 was stirred with 3-chloroacyl-4-cyanothiazolidine (1.5g, 7.8mmol) in tetrahydrofuran (60ml) at room temperature for 5 hrs in presence of cesium carbonate (2.6g, 7.8mmol) and then heated at 55°C for 30 hrs. Reaction mixture was filtered, evaporated, column chromatographed (35% ethylacetate-hexane) yielded desired product (0.4g, yield: 20%). Obtained product stirred with trifluoroacetic acid for 10 minutes at 5-

10°C. Trifluoroacetic acid removed in vacuo neutralised with aqueous sodium carbonate, extracted with ethylacetate. Dried organic layer was evaporated to dryness, purified by column chromatography (2% methanol / dichloromethane) yielded 90ml final compound (yield: 30%).

5

Representative example of Scheme II:

Example - 5

10 2-Cyano-1-(4-isopropyl-2-piperazinyl)-carbonyl pyrrolidine trifluoroacetate (Compound No.2).

Step-1

15 To an aqueous (100 ml) sodium hydroxide (4.0g, 100 mmol) solution of piperazine-2-carboxylic acid dihydrochloride (5g, 24.63 mmol) is added a solution of di-tert-butyl dicarbonate (11.0g, 50.45 mmol) in dioxan (50 ml) at 0°C over a period of half an hour. The reaction mixture is stirred at 0°C for 1 hr. followed by stirring at room temperature (25°C) for another 2 hrs. Neutralized (pH 6-7) with aqueous 2N
20 HCl, extracted with ethyl acetate. Organic layer washed with brine solution, dried (Na₂SO₄) and evaporated in vacuo to yield an oil which solidifies on cooling. (Yield 8.02g, 98.76%).

Step-2

25

Method-A

(i) To a dichloromethane (DCM, 40ml) solution of Boc-protected acid (5.01g, 15.18 mmol) as prepared in step-1 is added a solution of N-hydroxysuccinimide
30 (1.75g, 15.21 mmol) in THF (20ml) and a solution of DCC (3.6g, 17.47 mmol) in DCM (20ml) at 0°C in the order specified. Reaction mixture stirred at 0-5°C for 4-5 hrs, filtered, filtrate washed successively with water, aqueous sodium bicarbonate

solution and finally with brine. Organic layer dried (Na_2SO_4) evaporated in vacuo to give the product as white solid. (Yield 5.8g, 86.05%).

(ii) To a solution of the succinimide derivative (1.92g, 4.49 mmol) in DCM (20ml) as prepared in (i) of step-2, is added a solution of L-prolinamide (0.6g, 5.26 mmol). Reaction mixture stirred at 25°C for 16 hrs. washed with aqueous NaHCO_3 solution and brine, dried (Na_2SO_4), evaporated in vacuo yielding a crude residue. Desired coupled product was isolated by column chromatography (40% ethyl acetate/hexane), (Yield 0.53g, 27.74%).

Method-B

Alternatively the above prolinamide derivative can be prepared by the following method.

DIEA (1.35g, 10.46 mmol), HOBT (1.40g, 10.37 mmol) sequentially added to piperazine acid (3.30g, 10 mmol) and L-prolinamide (1.14g, 10 mmol) in DCM (40ml) at 0°C . A solution of DCC (2.40g, 11.65 mmol) in DCM (30ml) is added slowly at 0°C over a period of 1 hr. Stirred another 1 hr. at 0°C and then at 25°C for 14 hrs. Filtered, DCM distilled off, diluted with ethyl acetate, washed sequentially with saturated aqueous solution of NaHCO_3 and brine. Organic layer dried (Na_2SO_4), evaporated in vacuo purified by column chromatography (ethyl acetate). (Yield 2.6g, 61.03%).

25 Step-3

Prolinamide derivative (0.8g, 1.87 mmol) in THF (15 ml) is stirred with trifluoroacetic anhydride (TFAA) (1.5g, 7.14 mmol) at room temperature (25°C) for 4 hrs. Excess TFAA and THF is distilled off in vacuo, diluted with ethyl acetate, washed with aqueous sodium bicarbonate solution and brine. Organic layer dried (Na_2SO_4), evaporated in vacuo and the required cyano compound purified by column chromatography (50% ethyl acetate/hexane). (Yield 0.6g, 78.32%).

Step-4

Deprotection of the above compound as obtained in step-3 is done by stirring a solution of the compound (0.5g, 1.22 mmol) in CH₃CN (10ml) with TFA (7ml) at room temperature for 2 hrs. Excess TFA and CH₃CN removed in vacuo followed by stripping off with toluene and methanol respectively results in the formation of deprotected product as trifluoroacetate salt. (Yield 0.52g, 97.32%).

Step-5

To a solution of the deprotected compound (0.64g, 1.46 mmol) as obtained in step-4, in acetone (30ml), was added triethylamine (0.45g, 4.45 mmol), K₂CO₃ (0.3g, 2.17 mmol) and isopropyl bromide (0.23g, 1.88mmol) and refluxed for 15 hrs. The reaction mixture is filtered and the filtrate is evaporated in vacuo to give the product as an oily residue. (Yield 0.2g, 54.51%).

The crude material thus obtained is purified as follows:

The compound is protected using di-tert-butyl dicarbonate (0.18g, 0.82 mmol) and NaOH (0.05g, 1.25 mmol) in the same way as described in step-1 and purified by column chromatography (50% ethyl acetate/hexane). (Yield 0.15g, 53.57%). This is finally deprotected using trifluoroacetic acid (2ml) resulting in the formation of the final product as trifluoroacetate salt. (Yield 0.11g, 53.92%).

25 Representative example of Scheme III:

Example - 6

[4-Cyano-3-(1-cyclohexylhydrazino) carbonyl thiazolidine hydrochloride]
30 (Compound No. 33).

Step-1

A solution of trichloromethyl chloroformate (3.43g, 17.50 mmol) in THF (15ml) is added slowly at 0°C to a stirred solution of tert-butyl-cyclohexyl carbazate (2.5g, 11.68 mmol) in THF (15ml) under N₂ atmosphere. Triethylamine (1.77g, 17.52 mmol) in THF (15ml) is next added at 0°C slowly over a period of 20 minutes. Stirred at 0°C for 1.5 hrs, THF distilled off, diluted with DCM (30ml), washed sequentially with water and 5% aqueous citric acid solution. Organic layer dried (Na₂SO₄) and removed in vacuo to give the product. (Yield 3.10g, 96.27%).

10 **Step-2**

To a solution of thiazolidine amide (0.66g, 5.0 mmol) and the product obtained in step-1 (1.96g, 7.10 mmol) in THF (30ml) is added a solution of triethylamine (1.6g, 15.84 mmol) in THF (10ml) dropwise at 5°C over a period of half an hr. Stirred at room temp. for 15 hrs, followed by refluxing for 1 hr. THF distilled off, diluted with ethyl acetate, washed successively with water and 5% aqueous citric acid, organic layer dried (Na₂SO₄), evaporated in vacuo and crude material purified by column chromatography (50% ethyl acetate/hexane). (Yield 0.85g, 45.70%).

Step-3

20 Trifluoroacetic anhydride (0.54g, 2.57 mmol) is added to a solution of the amide compound (0.80g, 2.15 mmol) as obtained in step-2, in THF (15ml) at 5°C and stirred at 30°C for 3 hrs. Excess solvents removed in vacuo, diluted with ethyl acetate, washed with aqueous 5% NaHCO₃ solution, dried (Na₂SO₄) and concentrated. Crude material purified by column chromatography (20% ethyl acetate/ hexane). (Yield 25 0.43g, 56.48%).

Step-4

The deprotection is done by stirring a solution of the cyano compound (0.43g, 1.21 mmol) with TFA (5ml) in THF (5ml) at 5°C for 1 hr. Excess solvents distilled 30 off in vacuo, diluted with ethyl acetate, washed with saturated aqueous solution of NaHCO₃. Organic layer dried (Na₂SO₄), evaporated and the required pure compound

is isolated as a free base after column chromatography (35% ethyl acetate/ hexane).
(Yield 0.10g, 32.46%).

This is converted to its hydrochloride salt by treating with methanolic HCl at
5 10⁰C for 1 hr. and removing excess solvents in vacuo followed by crystallization from
ether.

The following representative compounds may be prepared by following the
synthetic route of Scheme I.

10

Example - 7

15 1-[1-Oxo-2- ((1-Cycloheptyl)-hydrazino)] ethyl-2-cyano pyrrolidine
trifluoroacetate (Compound No. 30)

Yield : 60.6%;
m.p. : 138-140⁰ C ;
Mass (m/z) : 265 (M⁺+1), 287 (M⁺+Na) ;
20 ¹HNMR (400 MHz, CDCl₃) δ: 4.88-4.90 (m, 1H), 4.10-4.34 (m, 3H), 3.58-3.79
(m, 2H), 2.19-2.29 (m, 6H), 1.73-1.81(m, 4H), 1.54-1.57 (m, 6H);
IR. (KBr, cm.⁻¹) : 3460, 3170, 2270, 1673, 1605, and 1524.

Example - 8

25

3-[1-Oxo-2- ((1-(4-methyl) cyclohexyl)-hydrazino)] ethyl-4-cyano thiazolidine
trifluoroacetate (Compound No. 29)

Yield : 58.2%;
30 m.p. : 140-142⁰ C ;
Mass (m/z) : 283 (M⁺+1), 267 ;
¹HNMR (400 MHz, CDCl₃) δ: 5.27-5.29 (m, 1H), 4.13-4.57 (m, 4H), 3.49-3.75
(m, 4H), 1.82 (bs, 4H), 1.38 (bs, 4H), 0.98 (d, 3H, J=8Hz);
IR (KBr, cm.⁻¹) : 3460, 3175, 2250, 1670, 1605, and 1523.

Example - 9

3-[1-Oxo-2-((1-Cycloheptyl)-hydrazino)] ethyl-4-cyano thiazolidine trifluoroacetate (Compound No. 28)

5

Yield : 72.8%;
m.p. : 141-142^o C ;
Mass (m/z) : 283 (M⁺+1) ;
¹HNMR (400 MHz, d₄-MeOH) δ : 5.34-5.36 (t,1H,J=4Hz), 4.72-4.74 (d,1H,J=8Hz), 4.64-4.66(d,1H,J=8Hz), 4.06-4.18 (m,2H), 3.39-3.50(m,2H),2.04(bs,2H), 1.82(bs,2H), 1.70-1.73 (m,2H), 1.56-1.63 (m,7H) ;
IR (KBr, cm.⁻¹) : 3477, 3408, 2340, 1672, 1626, 1562, 1524.

15 **Example - 10**

1-[1-Oxo-2-(1-(2-Pyridyl)-hydrazino)]ethyl-2-cyano pyrrolidine bis-trifluoroacetate (Compound No. 27)

20 Yield : 36.50% ;
Mass (m/z) : 246 (M⁺+1),150,167 ;
¹HNMR (400 MHz, d₄-MeOH)δ : 8.65-8.67 (d,1H, J=8Hz), 8.48-8.52 (t,1H, J=8Hz), 7.79-7.81 (d,1H, J=8Hz), 7.58-7.62 (t,1H, J=8Hz),4.69-4.73 (t,1H, J=8Hz), 3.40-3.51(m, 4H), 2.20-2.33 (m, 4H) ;
25 IR (CCl₄, cm.⁻¹) : 3445, 2248, 1677, 1519.

Example - 11

1-[1-Oxo-2-((4-Methyl)cyclohexyl)hydrazino)]ethyl-2-cyano pyrrolidine trifluoroacetate (Compound No. 26)

30 Yield : 87.70% ;

Mass (m/z) : 265 (M⁺+1), 287 (M⁺+Na);

¹HNMR (400 MHz, d₄-MeOH) δ : 4.04 (bs, 1H), 3.65-3.71 (m, 1H),
 3.48-3.55 (m, 1H), 3.15-3.17 (m, 1H), 2.26-2.31 (m, 2H), 2.18-2.22 (t, 2H, J=8Hz), 2.03-
 5 2.05 (m, 2H), 1.86-1.89 (m, 2H), 1.30-1.45 (m, 7H),
 0.92-0.94 (d, 3H, J=8Hz);
 IR (CCl₄, cm⁻¹) : 3400, 2248, 1676, 1454.

Example - 12

10

3-[1-Oxo-2-((1-(4-methyl)cyclohexyl)hydrazino)]ethyl-4-cyano thiazolidine
 trifluoroacetate (Compound No. 25). [** This compound obtained by reacting with
 lower isomer obtained during the reduction step]

15 Yield : 73.9%;
 m.p. : 89-90⁰ C;
 Mass (m/z) : 283 (M⁺+1), 305 (M⁺+Na),
 266;
¹HNMR (400 MHz, d₄-MeOH) δ : 5.33-5.35 (t, 1H, J=4Hz), 4.71-
 20 4.73 (d, 1H, J=8Hz), 4.64-4.66 (d, 1H, J=8Hz), 4.05-4.16 (m, 2H), 3.38-3.40 (m, 2H),
 3.12-3.18 (m, 1H), 2.01-2.03 (m, 2H), 1.86-1.89 (m, 2H), 1.36-1.43 (m, 3H), 1.01-1.10
 (m, 2H), 0.93-0.95 (d, 3H, J=8Hz);
 IR (KBr, cm⁻¹) : 3477, 3403, 2340, 1670, 1629,
 1567, 1523.

25

Example - 13

1-[1-Oxo-2-((1-Phenyl sulphonyl)hydrazino)]ethyl-2-cyano pyrrolidine
 trifluoroacetate (Compound No. 24)

30

Yield : 80.6%;
 Mass (m/z) : 331 (M⁺+Na), 283;

¹HNMR (400 MHz, d₄-MeOH) δ : 7.36-7.84 (m,5H), 4.72-4.75 (m,1H), 3.55-3.70(m,2H), 2.12-2.33 (m,6H);
IR (CCl₄, cm.⁻¹) : 3444, 2337, 1639, 1424.

5 **Example - 14**

3-[1-Oxo-2-((1-methylpropyl)hydrazino)]ethyl-4-cyano thiazolidine trifluoroacetate
(Compound No. 23)

Yield : 90.3% ;
10 Mass (m/z) : 243 (M⁺+1),225 ;
¹HNMR (400 MHz, d₄-MeOH) δ : 5.34-5.36 (t,1H,J=4Hz), 4.75-4.77 (d,1H,J=8Hz), 4.67-4.69 (d,1H,J=8Hz), 4.04 (bs,2H), 3.39-3.47 (m,3H), 1.36-1.42(m,2H), 1.26-1.28 (d,3H,J=8Hz), 0.99-1.03 (t,3H,J=8Hz)
IR (CCl₄, cm.⁻¹) : 3470,2340,1676,1632,1521

15

Example - 15

1-[1-Oxo-2-((1-methylpropyl)hydrazino)]ethyl-2-cyano pyrrolidine trifluoroacetate
(Compound No. 22)

20 Yield : 86.9% ;
Mass (m/z) : 225 (M⁺+1) ;
¹HNMR (400 MHz, d₄-MeOH) δ : 4.79-4.80 (bs,1H), 3.98 (bs,2H),3.67-3.72 (m,1H), 3.49-3.56 (m,1H),2.18- 2.31(m,3H),1.77-1.80(m,1H),1.52-1.54(m,1H), 1.35-1.38(m,2H), 1.28-1.30 (d,3H,J=8Hz), 1.00-1.04 (t,3H,J=8Hz) ;
25 IR (CCl₄, cm.⁻¹) : 3441, 2280,1676, 1521.

Example - 16

3-[1-Oxo-2-((1-Cyclohexyl)-hydrazino)]ethyl-4-cyano thiazolidine trifluoroacetate
30 (Compound No. 21)

Yield : 69% ;
m.p. : 154 -155^o C ;

Mass (m/z) : 269 (M⁺ +1), 291 (M⁺ +Na) ;

¹HNMR (400 MHz, d₄-MeOH) δ : 5.33 (t,1H,J=4Hz), 4.72-4.74 (d,1H,J=8Hz),4.64-4.66 (d,1H,J=8Hz), 4.02-4.12 (m,2H), 3.38-3.40 (d,2H,J=8Hz),
5 3.19-3.26 (m,1H), 1.92-2.01 (m,4H),1.69- 1.72 (m,1H),1.32-1.38 (m,4H), 1.22-1.24 (m,1H) ;
IR (KBr, cm.⁻¹) : 3172, 2342, 1676, 1608,1521.

Example - 17

10 1-[1-Oxo-2-((1-Cyclohexyl)-hydrazino)]ethyl-2-cyano pyrrolidine trifluoroacetate (Compound No. 20)

Yield : 81.7%:

15 m.p. : 148 -150⁰ C ;

Mass (m/z) : 251 (M⁺ +1), 273 (M⁺ +Na), 225 ;

¹HNMR (400 MHz, d₄-MeOH)δ : 4.81-4.84 (bs,1H), 3.99-4.03 (m,2H),
3.66-3.70 (m,1H), 3.50-3.55 (m,1H), 3.33-3.36 (m,1H), 3.18-3.22 (m,1H), 2.26-2.29 (m,1H), 2.18-2.23 (m,2H), 2.00-2.02 (m,2H), 1.90-1.90 (m,2H), 1.69-1.73 (m,1H),
20 1.35-1.41 (m,5H);
IR (KBr, cm.⁻¹) : 3159, 2241, 1676, 1607, 1519.

Example - 18

25 3-[1-Oxo-2-((1-Cyclopentyl)-hydrazino)]ethyl-4-cyano thiazolidine trifluoroacetate (Compound No. 19)

Yield : 48.3%:

m.p. : 136-137⁰ C ;

Mass (m/z) : 255 (M⁺ +1), 277 (M⁺ +Na) ;

30 ¹HNMR (400 MHz, d₄-MeOH)δ : 5.34-5.36 (t,1H,J=4Hz), 4.73-4.75 (d,1H,J=8Hz), 4.63-4.65 (d,1H,J=8Hz), 4.02-4.14 (m,2H), 3.65-3.69 (m,1H), 3.38-3.39 (d,2H,J=4Hz), 1.98-2.02 (m,2H), 1.81-1.85 (m,2H), 1.65-1.69 (m,4H);
IR (KBr, cm.⁻¹) : 3180, 2365, 1677, 1602, 1524.

Example - 19

1-[1-Oxo-2-((1-Cyclopentyl)-hydrazino)]ethyl-2-cyano pyrrolidine trifluoroacetate
5 (Compound No. 18)

Yield : 64.1%
m.p. : 118-119^o C ;
Mass (m/z) : 237 (M⁺ +1), 259(M⁺ +Na) ;
10 ¹HNMR (400 MHz, d₄-MeOH)δ : 4.71-4.75 (bs,1H), 3.97-4.01 (m,2H),
3.66-3.69 (m,2H), 3.48-3.52 (m, 1H), 2.18-2.29 (m,4H), 1.98-2.02 (m,2H),1.80-1.85
(m,2H), 1.65-1.69 (m,4H);
IR (KBr, cm.⁻¹) : 3169, 2241, 1679, 1605, 1522.

15 **Example - 20**

3-[1-Oxo-2-((1-(4-nitrophenylmethyl))hydrazino)]ethyl-4-cyano thiazolidine
trifluoroacetate (Compound No. 17)

20 Yield : 76.9%
Mas (m/z) : 322 (M⁺ +1);
¹HNMR (400 MHz, d₄-MeOH)δ : 8.24-8.31 (dd,2H,J=8Hz, 12Hz), 7.63-
7.70(dd,2H,J=8Hz, 12Hz), 5.35-5.37 (t,1H,J=4Hz), 4.66-4.79 (m,2H), 4.01-4.41
(m,4H), 3.37-3.38 (m,2H);
25 IR (CCl₄, cm.⁻¹) : 3422, 2338, 1655, 1510.

Example - 21

3-[1-Oxo-2-((1-phenylmethyl)hydrazino)]ethyl-4-cyano thiazolidine trifluoroacetate
30 (Compound No. 16)

Yield : 64.3% ;
Mass (m/z) : 277 (M⁺ +1), 299(M⁺ +Na), 261 ;

^1H NMR (400 MHz, d_4 -MeOH) δ : 7.35-7.46 (m,5H), 5.33-5.35 (t,1H, $J=4\text{Hz}$), 4.43-4.49 (m,2H), 4.25 (s,2H), 3.90 (s,2H), 3.36-3.37(d,2H, $J=4\text{Hz}$);
IR (KBr, cm^{-1}) : 3470, 2340, 1671, 1620, 1508.

5 **Example - 22**

3-[1-Oxo-2-(1-hydrazino)]ethyl-4-cyano thiazolidine trifluoroacetate (Compound No. 15)

10 Yield : 63.7%;
Mass (m/z) : 187 ($M^+ + 1$);
 ^1H NMR (400 MHz, d_4 -MeOH) δ : 5.04 (bs,1H), 4.41-4.49 (m,2H), 3.58-3.62 (dd,2H, $J=5.6\text{Hz}$, 4.8Hz), 3.26-3.33 (m,2H);
IR (CCl_4 , cm^{-1}) : 3460, 2260, 1676, 1508.

15

Example - 23

1-[1-Oxo-2-((1-ethyl)hydrazino)]ethyl-2-cyano pyrrolidine trifluoroacetate (Compound No. 14)

20

Yield : 38.2% ;
Mass (m/z) : 197 ($M^+ + 1$), 219 ($M^+ + \text{Na}$);
 ^1H NMR (400 MHz, d_4 -MeOH) δ : 4.82-4.84 (bs,1H),4.22-4.24 (bs,1H),3.98-4.00 (m,1H), 3.65-3.70 (m,1H),3.48-3.54 (m,1H), 3.17-3.23 (q,2H, $J=8\text{Hz}$), 2.13-2.31(m,4H), 1.26-1.30 (t,3H, $J=8\text{Hz}$);
IR (CCl_4 , cm^{-1}) : 3424, 2247, 1676, 1521.

Example -24

30 1-[1-Oxo-2-((2,2-diethyl)-hydrazino)]ethyl-2-cyano thiazolidine (Compound No. 13)

Yield : 52.3% ;

Mass (m/z) : 243 (M⁺ +1);
¹HNMR (400 MHz, d₄-MeOH)δ : 5.36-5.38 (t, 1H, J=4Hz), 4.75-4.77
(d, 1H, J=8Hz), 4.61-4.63 (d, 1H, J=8Hz), 3.82-3.85 (dd, 1H, J=4Hz, 4Hz), 3.75-3.78
5 (dd, 1H, J=4Hz, 4Hz), 3.40-3.41 (d, 2H, J=4Hz), 3.20-3.26 (q, 4H, J=8Hz), 1.31-1.35
(t, 6H, J=8Hz);
IR (CCl₄, cm.⁻¹) : 3440, 2253, 1678, 1460.

Example - 25

10

1-[1-Oxo-2-((1-(1-methyl)ethyl)hydrazino)]ethyl-2-cyano pyrrolidine trifluoroacetate
(Compound No. 12)

Yield : 38.3% ;
15 Mass (m/z) : 211 (M⁺ +1), 233 (M⁺ +Na);
¹HNMR (400 MHz, d₄-MeOH)δ : 4.83-4.86 (t, 1H, J=4Hz), 4.05-4.11
(m, 2H), 3.67-3.72 (m, 1H), 3.50-3.61 (m, 2H), 2.28-2.32 (m, 2H), 2.16-2.23 (m, 2H),
1.30-1.32 (d, 6H, J=8Hz);
IR (CCl₄, cm.⁻¹) : 3280, 2250, 1675, 1522.

20

Example - 26

1-[1-Oxo-2-((1-phenylmethyl)hydrazino)]ethyl-2-cyano pyrrolidine trifluoroacetate
25 (Compound No. 11)

Yield : 67.6% ;
Mass (m/z) : 259 (M⁺ +1), 281 (M⁺ +Na), 158;
¹HNMR (400 MHz, d₄-MeOH)δ : 7.37-7.44 (m, 5H), 4.82-4.84
(t, 1H, J=4Hz), 4.26 (s, 2H), 3.79 (s, 2H), 3.39-3.45 (m, 1H), 3.27-3.32 (m, 1H), 2.22-
30 2.27 (m, 2H), 2.09-2.16 (m, 2H);
IR (CCl₄, cm.⁻¹) : 3470, 2340, 1676, 1451.

Example - 27

1-[1-Oxo-2-(1-(2-methylpropyl)hydrazino)]ethyl-2-cyano pyrrolidine trifluoroacetate
5 (Compound No. 10)

Yield : 88% ;
Mass (m/z) : 225 (M⁺ +1), 247 (M⁺ +Na);
1HNMR (400 MHz, d₄-MeOH)□ : 4.82-4.84 (t,1H,J=4Hz), 3.83-3.89
10 (m,2H), 3.64-3.69 (m,1H), 3.47-3.53 (m,1H), 2.84-2.86 (d,2H,J=8Hz), 2.25-2.30
(m,2H), 2.16-2.21 (m,2H), 1.30-1.37 (m,1H), 0.99-1.00 (d,6H,J=4Hz)
IR (CCl₄, cm.⁻¹) : 3443, 2280, 1675, 1557, 1453.

15

Example - 28

3-[1-Oxo-2-((1-phenyl)hydrazino)]ethyl-4-cyano thiazolidine trifluoroacetate
20 (Compound No. 9)

Yield : 56.4% ;
Mass (m/z) : 263 (M⁺ +1), 285 (M⁺ +Na), 235;
1HNMR (400 MHz, d₄-MeOH)δ : 7.22-7.40 (m,3H), 6.77-6.94 (m,2H),
4.95-4.97 (m,1H), 4.62-4.82 (m,2H), 4.12-4.20 (m,2H), 3.32-3.36 (m,2H);
25 IR (CCl₄, cm.⁻¹) : 3440, 2339, 1677, 1436.

Example - 29

1-[1-Oxo-2-((1-(4-nitrophenylmethyl)hydrazino)]ethyl-2-cyano pyrrolidine
30 trifluoroacetate (Compound No.8)

Yield : 52% ;

m.p. : 107-108⁰C;
 Mass (m/z) : 304 (M⁺ +1), 326 (M⁺ +Na);
¹HNMR (400 MHz, d₄-MeOH)δ : 8.29-8.31 (d,2H,J=8Hz), 7.68-
 7.70 (d,2H,J=8Hz), 4.84-4.86(t,1H,J=4Hz), 4.39 (s,2H), 3.90-3.91(d,2H,J=4Hz),3.50-
 5 3.54 (m,2H), 2.24-2.28 (m,2H), 2.14-2.18 (m,2H);
 IR (KBr, cm.⁻¹) : 3420, 3180, 2339, 1675, 1604, 1515.

Example - 30

10 1-[1-Oxo-2-((2-(1,1-dimethylethyl oxy carbonyl))hydrazino)]ethyl-2-cyano
 pyrrolidine (Compound No.7)
 Yield : 45.3% ;
 Mass (m/z) : 269 (M⁺ +1), 291 (M⁺ +Na), 213;
¹HNMR (400 MHz, d₄-MeOH)δ : 4.77-4.79 (t,1H,J=4Hz),3.61-3.74
 15 (m,3H), 3.46 -3.54 (m,1H), 2.23-2.28 (m,2H), 2.13-2.20 (m,2H), 1.46 (s,9H);
 IR (CCl₄, cm.⁻¹) : 3306, 2979, 2242, 1678, 1530.

Example - 31

20
 1-[1-Oxo-2-((2-(1,1-dimethylethoxy carbonyl))-1-phenyl hydrazino)]ethyl-2-cyano
 pyrrolidine (Compound No. 6)
 Yield : 53.7% ;
 Mass (m/z) : 345 (M⁺ +1), 367 (M⁺ +Na), 267;
 25 ¹HNMR (400 MHz, CDCl₃)δ : 7.22-7.26(m,2H),6.75-6.89 (m,3H), 6.37
 (bs,1H), 4.77-4.80(t,1H,J=8Hz), 4.07 (s,2H), 3.72-3.76 (m,1H), 3.60-3.66 (m,1H),
 2.20-2.37 (m,4H), 1.35 (s,9H);
 IR (CCl₄, cm.⁻¹) : 3470, 3333, 2242, 1663, 1602, 1496.

30 **Example - 32**

3-[1-Oxo-2-((2-(1,1-dimethyl ethyl oxy carbonyl))hydrazino)]ethyl-4-cyano
thiazolidine (Compound No. 5)

Yield : 33.3% ;
5 Mass (m/z) : 287 (M⁺ +1), 309 (M⁺ +Na) , 231;
¹HNMR (400 MHz, CDCl₃) δ: 7.44-7.48(m,1H), 7.20-7.24 (m,1H), 5.24-5.34
(m,1H), 4.68-4.75 (m,1H), 4.55 (s,1H), 3.84 (bs,1H), 3.46-3.56 (m,1H), 3.30-3.35
(m,2H), 1.48 (s,9H);
IR (CCl₄, cm.⁻¹) : 3401, 2241, 1733, 1578, 1540.

10

Example - 33

1-[1-Oxo-2-(1-hydrazino)]ethyl-2-cyano pyrrolidine trifluoroacetate (Compound No.
4)

15

Yield : 42.3% ;
Mass (m/z) : 168 (M⁺ +1), 191 (M⁺ +Na);
¹HNMR (400 MHz, d₄-MeOH)δ : 4.79-4.81(m,1H), 3.88 (s,2H), 3.62-3.69
(m,2H), 2.24-2.29(m,2H), 2.12-2.20 (m,2H);
20 IR (CCl₄, cm.⁻¹) : 3470, 3250, 2240, 1678, 1435.

Example - 34

1-[1-Oxo-2-((1-phenyl)-hydrazino)]ethyl-2-cyano pyrrolidine trifluoroacetate
25 (Compound No. 3)

Yield : 96.1% ;
Mass (m/z) : 245 (M⁺ +1), 267 (M⁺ +Na), 228;
¹HNMR (400 MHz, CDCl₃) δ: 7.00-7.42(m,5H), 4.78-4.80 (b,s), 4.08 (s,2H),
30 3.64-3.83(m,2H), 2.24-2.34 (m,4H);
IR (CCl₄, cm.⁻¹) : 3441, 2339, 1679, 1432.

Example-35

1-[1-Oxo-2- (2-cyclohexyl) hydrazino] ethyl-2-cyanopyrrolidine trifluoroacetate (Compound No. 34)

- 5 Yield : 97% .
- Mass : 251 ($M^+ + 1$), 273 ($M^+ + Na$);
- 1H NMR ($CDCl_3$) δ : 4.70 (bs, 1H), 3.97-4.01 (d, 1H, J=16 Hz), 3.81-3.85 (d, 1H, J=16 Hz), 3.58-3.65 (m, 2H), 3.45-3.53 (m, 2H), 3.14-3.20 (m, 3H), 2.18-2.21 (m, 4H), 1.86-1.89 (m, 4H), 1.68-1.71 (m, 2H);
- 10 IR (Neat, cm^{-1}) : 2938, 2246 and 1670

Example-36

15 [4-Cyano-3-(1-phenyl hydrazino)carbonyl thiazolidine trifluoroacetate] (Compound No. 35)

- Yield : 37.8%.
- 20 Mass : 249 ($M^+ + 1$), 271 ($M^+ + Na$);
- 1H NMR ($CDCl_3$) δ : 7.51-7.54 (d, 2H, J=12 Hz), 7.35-7.39 (dd, 2H, J=8Hz, 8Hz), 7.19-7.23 (dd, 1H, J=8Hz, 8Hz) 5.36-5.38 (d, 1H, J=8Hz), 4.31-4.33 (d, 1H, J=8Hz), 4.22-4.26 (dd, 1H, J=6Hz, 6Hz), 4.08 (bs, 2H), 3.33-3.37 (dd, 1H, J=8Hz, 8Hz), 3.08-3.14 (t, 1H, J=12Hz);
- 25 IR (Neat, cm^{-1}) : 2935, 2244 and 1663

Example-37

30 3-[1-Oxo-2- (1-cyclohexyl-2-isopropyl) hydrazino] ethyl-4-cyanothiazolidine hydrochloride (Compound No. 36)

- Yield : 40%.
- 35 Mass : 311 ($M^+ + 1$);
- 1H NMR (d_4 -MeOH) δ : 5.60 (bs, 1H), 3.71-3.74(d, 1H, J=12Hz), 3.61-3.64 (d, 1H, J=12Hz), 3.01 (s,1H), 2.28-2.35 (m,7H), 1.30 (m, 1H), 0.83-1.06 (m, 3H), 0.67-0.82 (m, 10H);

IR (Neat, Cm^{-1}) : 2931, 2497, 1654

5 **Example-38**

1-[1-Oxo-2-(4-methylcyclohexyl)hydrazino]ethyl-2-cyanopyrrolidine trifluoroacetate
(Compound No. 37)

10 Yield : 50%.
Mass : 265 ($\text{M}^+ + 1$), 287 ($\text{M}^+ + \text{Na}$);
 $^1\text{HNMR}$ ($\text{d}_4\text{-MeOH}$) δ : 4.84 (bs, 1H), 4.01-4.03 (m, 2H), 3.66-3.70
(m, 1H), 3.50-3.53 (m, 1H), 2.26-2.29 (m, 2H), 2.18-2.22 (m, 2H), 1.74-1.77 (m, 6H),
1.51-1.58 (m, 4H), 0.99-1.01 (d, 3H, $J=8\text{Hz}$);

15 IR (KBr, Cm^{-1}) : 3169, 2917, 2240, 1673

Example-39

20 1-[1-Oxo-2-(1-cyclohexyl-2-isopropyl)hydrazino]ethyl-2-cyano pyrrolidine (Compound
No. 38)

Yield : 30%.
Mass : 293 ($\text{M}^+ + 1$), 315 ($\text{M}^+ + \text{Na}$);
25 $^1\text{HNMR}$ (CDCl_3) δ : 4.75 (bs, 1H), 3.85-3.87 (m, 1H),
3.64-3.71 (m, 2H), 3.29-3.35 (m, 3H), 2.83-2.90 (m, 2H), 2.61-2.65 (m, 2H), 2.11-2.22
(m, 6H), 1.78-1.88 (m, 4H), 0.96-0.98 (d, 6H, $J=8\text{Hz}$);

IR (Neat, Cm^{-1}) : 3263, 2924, 2241, 1645

30

Example-40

1-[1-Oxo-2-(1-(4-methylcyclohexylmethyl) hydrazino)]ethyl-2-cyanopyrrolidine
trifluoroacetate (Compound No. 39)

35 Yield : 5%.
Mass : 279 ($\text{M}^+ + 1$), 301 ($\text{M}^+ + \text{Na}$);
 $^1\text{HNMR}$ (CDCl_3) δ : 4.79 (bs, 1H), 3.96-3.98 (m, 1H),
40 3.53-3.61 (m, 2H), 3.06-3.10 (m, 1H), 2.25-2.29 (m, 3H), 1.84-1.88 (m, 1H), 1.72-

1.75 (m, 1H), 1.51-1.55 (m, 4H), 1.35-1.37 (m, 1H), 1.22-1.35 (m, 4H), 0.89-0.96 (m, 5H);

5 IR (Neat, Cm^{-1}) : 2856, 2248, 1669, 1513

Example-41

1-[1-Oxo-2- (4-chlorophenyl) hydrazino] ethyl-2-cyanopyrrolidine trifluoroacetate
10 (Compound No. 40)

Yield : 35.3%.
Mass : 279 ($\text{M}^+ + 1$), 301 ($\text{M}^+ + \text{Na}$);
15 $^1\text{HNMR}$ (CDCl_3) δ : 7.16-7.18 (d, 2H, $\text{J}=8\text{Hz}$), 6.86-
6.88 (d, 2H, $\text{J}=8\text{Hz}$), 4.76 (bs, 1H), 3.55-3.84 (m, 4H), 2.11-2.33 (m, 4H);

IR (Neat, Cm^{-1}) : 2244, 1650, 1597

20 **Example-42**

1-[1-Oxo-2-isopropyl-2-hydrazino] ethyl-2-cyano pyrrolidine trifluoroacetate
(Compound No. 41)

25 Yield : 66.6%.
Mass : 211 ($\text{M}^+ + 1$), 233 ($\text{M}^+ + \text{Na}$);
 $^1\text{HNMR}$ ($\text{d}_4\text{-MeOH}$) δ : 5.01 (bs, 1H), 3.62-3.64 (m, 1H), 3.60-
3.61 (m, 1H), 2.28-2.31 (m, 2H), 2.08-2.18 (m, 4H), 0.99-1.01 (d, 6H, $\text{J}=8\text{Hz}$);

30 IR (Neat, Cm^{-1}) : 2877, 2251, 1651, 1555

Example-43

3-[1-Oxo-2- (1-(4-methylcyclohexyl)-2-ethyl) hydrazino] ethyl-4- cyanothiazolidine
trifluoroacetate (Compound No. 42)

35 Yield : 21.8%.
Mass : 311 ($\text{M}^+ + 1$), 333 ($\text{M}^+ + \text{Na}$);
 $^1\text{HNMR}$ (CDCl_3) δ : 5.31-5.33 (bs, 1H), 4.70-4.72 (d,
1H, $\text{J}=8\text{Hz}$), 4.63-4.65 (d, 1H, $\text{J}=8\text{Hz}$), 4.02-4.15 (m, 2H), 3.30-3.42 (m,

4H), 2.14-3.12 (m, 3H), 1.82-1.90 (m, 5H), 1.32-1.42 (m, 3H), 1.05-1.08(m, 2H),
0.92-0.94 (d, 3H, J=8Hz);

IR (KBr, Cm^{-1}) : 3470, 3403, 2340, 1665, 1630.

5

Example-44

3-[1-Oxo-2- (1-(4-morpholinocarbonyl) hydrazino) ethyl]-4-cyanothiazolidine
trifluoroacetate (Compound No. 43)

10

Yield : 10.5%.
Mass : 300 (M^+1), 322 (M^+Na);
 $^1\text{HNMR}$ (CDCl_3) δ : 4.62 (bs, 1H), 3.68-3.72 (m, 5H),
3.44-3.55 (m, 2H), 3.18-3.40 (m, 7H)

15 IR (KBr, Cm^{-1}) : 2828, 1670, 1429

Example-45

20 3-[1-Oxo-2- (1-(4-methylcyclohexyl)-2-isopropyl) hydrazino] ethyl-4-
cyanothiazolidine trifluoroacetate (Compound No. 44)

Yield : 40%.

Mass : 325 (M^+1);

25 $^1\text{HNMR}$ (CDCl_3) δ : 5.28 (bs, 1H), 4.57-4.59 (m, 2H),
3.88-4.10 (dd, 2H, J=16Hz, 16Hz), 3.60-3.63 (t, 1H, J=6Hz), 3.22-3.33 (m, 2H), 1.96-
2.08 (m, 2H), 1.80-1.83 (m, 2H), 1.41-1.44 (t, 6H, J=5.5 Hz), 1.27-1.37 (m, 4H),
1.01-1.06 (m, 2H), 0.87-0.90 (d, 3H, J=11Hz);

30 IR (Neat, Cm^{-1}) : 2249, 1673, 1560

Example-46

35 1-[1-Oxo-2- [(1-cyclohexyl)-2-(2-cyano-1-pyrrolidino acetyl)] hydrazino] ethyl- 2-
cyanopyrrolidine trifluoroacetate (Compound No. 45)

Yield : 66.6%.

Mass : 385 ($M^+ - 1$);
 $^1\text{HNMR}$ (CDCl_3) δ : 4.84 (bs, 1H), 4.76 (bs, 1H),
4.05-4.19 (m, 4H), 3.98-4.01 (m, 1H), 3.80-3.87 (m, 1H), 3.61-3.68 (m, 7H), 1.42-
4.48 (m, 6H), 1.31-1.34 (m, 8H);
5 IR (Neat, Cm^{-1}) : 2933, 2239, 1669, 1609, 1534.

10 **Example-47**

3-[1-Oxo-2- (1,2-bis- (2-(2-pyridyl) ethylaminocarbonyl) hydrazino)] ethyl-4-cyano
thiazolidine bis trifluoroacetate (Compound No. 46)

15 Yield : 96%.
Mass : 483 ($M^+ + 1$), 505 ($M^+ + \text{Na}$);
 $^1\text{HNMR}$ (d_4 -MeOH) δ : 8.71-8.75 (dd, 2H, $J=8\text{Hz}$, 8Hz),
8.44-8.52 (m, 2H), 7.85-7.99(m, 4H), 5.25(bs, 1H), 4.56-4.58 (d, 1H, $J=8.5\text{Hz}$), 3.94-
3.99 (dd, 1H, $J=9\text{Hz}$, 9Hz), 3.61-3.66(m, 4H), 3.36-3.39(m, 3H), 3.22-3.26(m, 5H);
20 IR (Neat, Cm^{-1}) : 2362, 1673, 1524

Example-48

25 3-[1-Oxo-2- (1-(4-tert-butyl cyclohexyl) hydrazino)] ethyl-4-cyanothiazolidine
trifluoro acetate (Compound No. 47)

Yield : 82.2%.
30 Mass : 325 ($M^+ + 1$), 347 ($M^+ + \text{Na}$);
 $^1\text{HNMR}$ (d_4 -MeOH) δ : 5.33-5.36 (t, 1H, $J=4\text{Hz}$), 4.72-4.74 (d,
1H, $J=8\text{Hz}$), 4.63-4.65 (d, 1H, $J=8\text{Hz}$), 4.06-4.09 (m, 2H), 3.47-3.51 (m, 1H), 3.36-
3.40 (m, 2H), 1.95-2.10 (m, 4H), 1.04-1.21 (m, 5H), 0.90 (s, 9H);
IR (KBr, Cm^{-1}) : 3025, 2964, 2207, 1678, 1610.

35

Example-49

1-[1-Oxo-2-(1-tetralinyl) hydrazino] ethyl-2-cyanopyrrolidine trifluoroacetate
(Compound No. 48)

5

Yield	:	69.4%.
Mass	:	299 (M ⁺ +1), 321 (M ⁺ +Na);
¹ HNMR (CDCl ₃)δ	:	7.47-7.51 (d, 1H, J=14Hz), 7.33-7.35 (d,
10 1H, J=8Hz), 7.19-7.21 (d, 2H, J=8Hz), 4.71 (bs, 1H), 3.74-4.00 (m, 3H), 3.42-3.55 (m,		
3H), 2.77-2.92 (m, 2H), 2.05-2.21 (m, 7H);		
IR (Neat, Cm ⁻¹)	:	3414, 2950, 2246, 1675

15 **Example-50**

3-[1-Oxo-2-(1-(4-tertbutylcyclohexyl) hydrazino)] ethyl-4-cyanothiazolidine
trifluoroacetate (Compound No. 49)

20

Yield	:	71%.
Mass	:	325 (M ⁺ +1), 347 (M ⁺ +Na);
¹ HNMR(d4-MeOH) δ	:	5.32-5.34 (t, 1H, J=4Hz), 4.67-4.74 (dd, 2H,
J=8Hz, 8Hz), 4.08-4.11 (d, 2H, J=12Hz), 3.47-3.51 (m, 1H), 3.37-3.38 (d, 2H, J=4Hz),		
25 1.95-2.05 (m, 2H), 1.57-1.60 (m, 4H), 1.32-1.38 (m, 3H), 0.90 (s, 9H);		
IR (KBr, Cm ⁻¹)	:	2942, 2867, 2247, 1662, 1498.

Example-51

30 1-[1-Oxo-2-(1-cyclohexyl)-2-(4-cyano-3-thiazolidino acetyl)] hydrazino] ethyl- 2-
cyano pyrrolidine (Compound No. 50)

35

Yield	:	17.7%.
Mass	:	403 (M ⁺ -1);

¹HNMR (CDCl₃) δ : 5.32 (bs, 1H), 4.71-4.87 (m, 3H), 4.11-4.23 (m, 2H), 3.75-3.79 (m, 2H), 3.51-3.64 (m, 4H), 3.27-3.36 (m, 4H), 1.86-1.90 (m, 2H), 1.77-1.80 (m, 4H), 1.30-1.35 (m, 5H);
IR (Neat, Cm⁻¹) : 2936, 2247, 1675, 1540.

5

Example-52

3-[1-Oxo-2- (1-isopropyl-4-piperidiny)l hydrazino)] ethyl-4-cyano thiazolidine trifluoroacetate (Compound No. 51)

10

Yield : 43.9%.
Mass : 312 (M⁺+1);
¹HNMR (d₆-DMSO) δ : 5.32 (bs, 1H), 4.58-4.80 (m, 4H), 4.28-4.49 (m, 2H), 3.93-4.05 (m, 4H), 2.99-3.01 (m, 2H), 1.24-1.25 (d, 6H, J=6Hz);
IR (KBr, Cm⁻¹) : 2934, 2245, 1669, 1512.

15

Example-53

20 3-[1-Oxo-2- (1-(1-(4-cyanophenylmethyl)-piperidin-4-yl) hydrazino)] ethyl-4-cyanothiazolidine bis trifluoroacetate (Compound No. 52)

25

Yield : 55%.
Mass : 385 (M⁺+1);
¹HNMR (d₄-MeOH) δ : 7.88-7.90 (d, 2H, J=8Hz), 7.71-7.73 (d, 2H, J=8Hz), 5.31-.5.33 (t, 1H, J=4Hz), 4.77-4.78 (d, 1H, J=8Hz), 4.70-4.72 (d, 1H, J=8Hz), 4.41-4.44 (m, 3H), 4.0-4.12 (m, 1H), 3.46-3.53 (m, 4H), 3.37-3.39 (m, 3H), 1.42-1.46 (m, 4H);
IR (Neat, Cm⁻¹) : 3416, 2946, 2234, 1676, 1541.

30

91

35

Example-54

3-[1-Oxo-2-[1-(4-methylcyclohexyl)-2-(1-(3-pyridinylmethyl)-4-piperidinyl)]hydrazino]ethyl-4-cyanothiazolidine (Compound No. 53)

5

Yield : 45.7%.

Mass : 457 ($M^+ + 1$), 479 ($M^+ + Na$);

10 1H NMR (d_4 -MeOH) δ : 8.70-8.72 (d, 2H, $J=8$ Hz), 8.04-8.09 (t, 1H, $J=9$ Hz), 7.59-7.61 (t, 1H, $J=4$ Hz), 5.25-5.28 (t, 1H, $J=4.5$ Hz), 4.68-4.70 (d, 1H, $J=8$ Hz), 4.35-4.45 (m, 2H), 3.38-3.71 (m, 4H), 3.01-3.09 (m, 3H), 1.70-1.86 (m, 6H), 1.22-1.36 (m, 11H), 0.88-0.90 (d, 3H, $J=8$ Hz);

IR (Neat, Cm^{-1}) : 3418, 2925, 2246, 1651

15

Example-55

20 3-[1-Oxo-2-[1-(4-methylcyclohexyl)-2-(1-isopropyl-4-piperidinyl)] hydrazino] ethyl-4-cyanothiazolidine (Compound No. 54)

Yield : 36%.

25 Mass : 408 ($M^+ + 1$);

1H NMR ($CDCl_3$) δ : 5.23 (bs, 1H), 4.76-4.78 (d, 1H, $J=8$ Hz), 4.68-4.70 (d, 1H, $J=8$ Hz), 4.51-4.53 (d, 1H, $J=8$ Hz), 3.47-3.52 (m, 1H), 3.30-3.37 (m, 4H), 3.10-3.17 (m, 2H), 2.90-2.94 (m, 2H), 2.75-2.78 (m, 1H), 2.64-2.68 (m, 1H), 2.33-2.36 (m, 1H), 2.03-2.11 (m, 2H), 1.75-1.86 (m, 5H), 1.41-1.43 (d, 3H, $J=8$ Hz), 1.38-1.40 (d, 3H, $J=8$ Hz), 1.12-1.22 (m, 4H), 0.89-0.91 (d, 3H, $J=8$ Hz);

30 IR (Neat, Cm^{-1}) : 3423, 2931, 2340, 1636

35

92

Example-56

3-[1-Oxo-2- (1-(1-(4-methylphenylsulphonyl)-4-piperidinyl)-hydrazino)] ethyl- 4-
5 cyanothiazolidine trifluoroacetate (Compound No. 55)

Yield : 65.5%.
Mass : 424 (M⁺+1), 446 (M⁺+Na);
10 ¹HNMR (d₄-MeOH) δ : 7.67-7.69 (d, 2H, J=8Hz), 7.44-7.46 (d,
2H, J=8Hz), 5.29-5.31 (t, 1H, J=4Hz), 4.67-4.69 (d, 1H, J=8Hz), 4.60-4.62 (d, 1H,
J=8Hz), 3.99-4.01 (d, 2H, J=8Hz), 3.75-3.78 (m, 2H), 3.36-3.37 (d, 2H, J=8Hz), 3.10-
3.16 (m, 1H), 2.46 (s, 3H), 2.38-2.41 (m, 2H), 1.98-2.01 (m, 2H), 1.62-1.72 (m, 2H);
IR (KBr, Cm⁻¹) : 3464, 2842, 2111, 1672, 1606

15

Example-57

20 3-[1-Oxo-2- [1-methyl-2- (1-(4-methylphenylsulphonyl)-piperidin-4-yl)] hydrazino]
ethyl-4-cyanothiazolidine trifluoroacetate (Compound No. 56)

25 Yield : 16%.
Mass : 438 (M⁺+1), 460 (M⁺+Na);
¹HNMR (CDCl₃) δ : 7.65-7.67 (d, 2H, J=8Hz), 7.33-
7.35 (d, 2H, J=8Hz), 5.24-5.26 (t, 1H, J=4Hz), 4.68-4.70 (d, 1H, J=8Hz), 4.58-4.60
(d, 1H, J=8Hz), 3.49-3.57 (m, 5H), 3.26-3.27 (d, 2H, J=4Hz), 2.56-2.60 (m, 6H), 2.46
30 (s, 6H);
IR (Neat, Cm⁻¹) : 3424, 2939, 2251, 1666, 1599.

Example-58

35 3-[1-Oxo-2- (1-(1-(3-pyridinemethyl)-4-piperidinyl) hydrazino)] ethyl-4-
cyanothiazolidine tris-trifluoroacetate (Compound No. 57)

Yield : 68.2%.

Mass : 361 ($M^+ + 1$);
1HNMR(d_4 -MeOH) δ : 8.98-9.00 (d, 2H, J=8Hz), 8.72-8.74 (d, 1H, J=8Hz), 8.23-8.29 (dd, 1H, J=8Hz, 8Hz), 4.74-4.78 (t, 1H, J=8Hz), 4.32-4.35 (d, 1H, J=8Hz), 4.23-4.25 (d, 1H, J=8Hz), 3.42-3.70 (m, 5H), 3.02-3.10 (m, 6H),
5 2.17-2.20 (m, 4H);
IR (Neat, Cm^{-1}) : 3392, 2949, 2250, 1676.

Example-59

10 3-[1-Oxo-2- [1-methyl-2- (1-(4-cyanophenylmethyl) piperidin-4-yl)] hydrazino] ethyl-4-cyanothiazolidine bis-trifluoroacetate (Compound No. 58)

Yield : 33.6%.
Mass : 399 ($M^+ + 1$);
15 1HNMR (d_4 -MeOH) δ : 7.87-7.89 (d, 2H, J=8Hz), 7.69-7.71 (d, 2H, J=8Hz), 5.25-5.27 (t, 1H, J=4Hz), 4.69-4.71 (d, 2H, J=8Hz), 4.35-4.39 (m, 2H), 3.49-3.64 (m, 4H), 3.06-3.22 (m, 2H), 3.02-3.04 (m, 1H), 2.49-2.58 (m, 2H), 1.35 (s, 3H);
20 IR (CCl_4 , Cm^{-1}) : 3354, 2236, 1678.

Example-60

25 3-[1-Oxo-2- [1-methyl-2- (1-(3-pyridinylmethyl)-piperidin-4-yl)] hydrazino] ethyl-4-cyanothiazolidine tris-trifluoroacetate (Compound No. 59)

Yield : 32.7%.
Mass : 375 ($M^+ + 1$);
30 1HNMR ($CDCl_3$) δ : 8.70-8.72 (d, 2H, J=8Hz), 8.04-8.08 (t, 1H, J=8Hz), 7.59-7.61 (t, 1H, J=8Hz), 5.25-5.27 (t, 1H, J=4Hz), 4.68-4.70 (d, 1H, J=8Hz), 4.35-4.43 (m, 3H), 3.51-3.71 (m, 2H), 3.09-3.15 (m, 3H), 2.01-2.03 (m, 4H), 1.36 (s, 3H);
35 IR (CCl_4 , Cm^{-1}) : 3358, 2142, 1678.

Example-61

5 3-[1-Oxo-2- (1-(4-n-propylcyclohexyl) hydrazino)] ethyl-4-cyanothiazolidine trifluoroacetate (Compound No. 60)

Yield : 97.5%.
10 Mass : 311 ($M^+ + 1$), 333 ($M^+ + Na$);
 1H NMR (d_4 -MeOH) δ : 5.33-5.35 (t, 1H, J=4Hz), 4.72-4.74 (d, 1H, J=8Hz), 4.64-4.68 (d, 1H, J=8Hz), 4.05-4.20 (m, 2H), 3.38-3.47 (m, 3H), 1.70-1.74 (m, 5H), 1.52-1.60 (m, 4H), 1.33-1.39 (m, 4H), 0.92-0.96 (t, 3H, J=8Hz);
15 IR (KBr, Cm^{-1}) : 3461, 2942, 2117, 1670, 1640.

Example-62

20 3-[1-Oxo-2- (1-(1-(4-nitrophenylmethyl)-piperidin-4-yl) hydrazino)] ethyl-4-cyanothiazolidine trifluoroacetate (Compound No. 61)

Yield : 56%.
Mass : 405 ($M^+ + 1$);
25 1H NMR (d_4 -MeOH) δ : 8.35-8.37 (d, 2H, J=8Hz), 1.77-1.79 (d, 2H, J=8Hz), 5.31-5.33 (t, 1H, J=4Hz), 4.78-4.80 (d, 1H, J=8Hz), 4.63-4.65 (d, 1H, J=8Hz), 4.45 (s, 2H), 3.44-3.50 (m, 3H), 3.37-3.38 (m, 4H), 3.11-3.15 (m, 2H), 1.88-2.20 (m, 4H);
30 IR (KBr, Cm^{-1}) : 2939, 2679 and 1652

Example-63

35 3-[1-Oxo-2- [1-(1-(4-chlorophenylsulphonyl)-piperidin-4-yl)] hydrazino)] ethyl-4-cyanothiazolidine trifluoroacetate (Compound No. 62)

Yield : 55.5%.
Mass : 444 ($M^+ + 1$);
40

- $^1\text{HNMR}$ (d_4 -MeOH) δ : 7.78-7.80 (d, 2H, $J=8\text{Hz}$), 7.65-7.67 (d, 2H, $J=8\text{Hz}$), 5.29-5.31 (t, 1H, $J=4\text{Hz}$), 4.68-4.70 (d, 1H, $J=8\text{Hz}$), 4.60-4.62 (d, 1H, $J=8\text{Hz}$), 4.00-4.01 (d, 1H, $J=8\text{Hz}$), 3.77-3.81 (dd, 2H, $J=4\text{Hz}$, 6Hz), 3.31-3.36 (m, 2H), 3.06-3.18 (m, 2H), 2.44-2.49 (m, 2H), 1.99-2.05 (m, 2H), 1.65-1.72 (m, 2H);
- 5 IR (KBr, Cm^{-1}) : 3171, 2357, 1674, 1605, 1534, 1440

Example-64

3-[1-Oxo-2-(1-(1-norcamphoranyl) hydrazino)] ethyl-4-cyanothiazolidine trifluoroacetate (Compound No. 63)

- 10 Yield : 58.3%.
- Mass : 281 (M^+), 303 ($M^+ + \text{Na}$);
- $^1\text{HNMR}$ (d_4 -MeOH) δ : 5.33-5.35 (t, 1H, $J=4\text{Hz}$), 4.71-4.72 (d, 1H, $J=6\text{Hz}$), 4.64-4.65 (d, 1H, $J=6\text{Hz}$), 3.93-3.97 (dd, 2H, $J=4\text{Hz}$, 8Hz), 3.50-3.54 (m, 2H),
- 15 3.37-3.39 (d, 2H, $J=6\text{Hz}$), 2.38-2.40 (m, 1H), 2.28-2.32 (m, 1H), 1.78-1.88 (m, 2H), 1.60-1.63 (m, 1H), 1.42-1.54 (m, 4H);
- IR (KBr, Cm^{-1}) : 2950, 216, 1675, 1628, 1511.

Example-65

20 3-[1-Oxo-2-(1-(4-n-propylcyclohexyl) hydrazino)] ethyl-4-cyanothiazolidine trifluoroacetate (Compound No. 64)

- Yield : 85.3%.
- Mass : 311 (M^+);
- 25 $^1\text{HNMR}$ (d_4 -MeOH) δ : 5.33-5.35 (t, 1H, $J=4\text{Hz}$), 4.71-4.73 (d, 1H, $J=8\text{Hz}$), 4.63-4.65 (d, 1H, $J=8\text{Hz}$), 4.11-4.16 (m, 1H), 3.38-3.39 (d, 2H, $J=4\text{Hz}$), 3.12-3.16 (m, 1H), 1.92-2.05 (m, 4H), 1.39-1.41 (m, 1H), 1.32-1.38 (m, 4H), 1.20-1.23 (m, 3H), 0.90-0.94 (t, 3H, $J=8\text{Hz}$);
- 30 IR (KBr, Cm^{-1}) : 3496, 2328, 1667, 1551.

Example-66

3-[1-Oxo-2-[1-(1-(4-methylcyclohexyl carbonyl)-piperidin-4-yl)] hydrazino] ethyl-4-cyanothiazolidine trifluoroacetate (Compound No. 65)

- 5 Yield : 61%.
Mass : 394 ($M^+ + 1$), 416 ($M^+ + Na$);
 1H NMR ($CDCl_3$) δ : 5.31-5.33 (t, 1H, J=4Hz), 4.68-4.70 (d, 1H, J=8Hz), 4.52-4.54 (d, 1H, J=8Hz), 4.01-4.05 (m, 4H), 3.51-3.63 (m, 5H), 2.56-2.68 (m, 2H), 2.11-2.20 (m, 2H), 1.71-1.80 (m, 4H), 1.44-1.53 (m, 6H), 0.90-0.92 (d, 3H, J=8Hz);
10 IR (CCl_4 , cm^{-1}) : 3372, 2944, 2240, 1679.

Example-67

- 15 3-[1-Oxo-2-(1-(1-acetyl)-piperidin-4-yl)hydrazino] ethyl-4-cyanothiazolidine trifluoroacetate (Compound No. 66)

- Yield : 43%.
Mass : 312 ($M^+ + 1$), 334 ($M^+ + Na$);
20 1H NMR (d_4 -MeOH) δ : 5.32-5.35 (t, 1H, J= 4Hz), 4.71-4.73 (d, 1H, J=8Hz), 4.64-4.66 (d, 1H, J=8Hz), 4.54-4.57 (m, 1H), 4.05-4.15 (m, 2H), 3.38-3.51 (m, 4H), 3.15-3.19 (m, 1H), 2.70-2.83 (m, 1H), 2.13 (s, 3H), 1.97-2.05 (m, 2H), 1.44-1.55 (m, 1H), 1.24-1.29 (m, 1H);
IR (Neat, cm^{-1}) : 2922, 1680 and 1651

25 **Example-68**

1,1-Dioxo-3-[1-oxo-2-(1-(4-methylcyclohexyl) hydrazino)] ethyl-4-cyanothiazolidine trifluoroacetate (Compound No. 67)

- 30 Yield : 70.5%.
Mass : 315 ($M^+ + 1$), 337 ($M^+ + Na$);

¹HNMR (CDCl₃) δ : 5.62-5.65 (dd, 1H, J=4Hz, J=4Hz),
4.95-4.97 (d, 1H, J=8Hz), 4.73-4.75 (d, 1H, J=8Hz), 3.97-4.08 (m, 2H), 3.79-3.93 (m,
2H), 3.11-3.15 (m, 1H), 1.98-2.05 (m, 2H), 1.85-1.89 (dd, 2H, J=4Hz, 4Hz), 1.36-1.41
(m, 3H), 1.0-1.09 (m, 2H), 0.93-0.95 (d, 3H, J=8Hz);
5 IR (Neat, Cm⁻¹) : 3398,2252,1678,1530.

Example-69

3-[1-Oxo-2-(1-methyl-2-(4-methylcyclohexyl) hydrazino)] ethyl-4-cyanothiazolidine
(Compound No. 68)

10 Yield : 15%.
Mass : 297 (M⁺+1), 319 (M⁺+Na);
¹HNMR (CDCl₃) δ : 5.32 (bs, 1H), 4.64-4.66 (d, 1H,
15 J=8Hz), 4.61-4.63 (d, 1H, J=1H), 3.51 (s, 3H), 3.32-3.36 (m, 3H), 2.96-2.99 (m, 1H),
2.84-2.87 (m, 1H), 2.03-2.06 (m, 1H), 1.92-1.94 (m, 1H), 1.23-1.36 (m, 5H), 1.03-1.11
(m, 2H), 0.94-0.96 (d, 3H, J=8Hz);
IR (Neat, Cm⁻¹) : 3302,2923,2244,1667.

20 **Example-70**

3-[1-Oxo-2-(1-methyl-2-(4-methylcyclohexyl) hydrazino)] ethyl-4-cyanothiazolidine
(Compound No. 69)

25 Yield : 15%.
Mass : 297 (M⁺+1), 319 (M⁺+Na);
¹HNMR (d₄-MeOH) δ : 5.26-5.28 (t, 1H, J=4Hz), 4.75-4.77 (d, 1H,
J=8Hz), 4.57-4.59 (d, 1H, J=8Hz), 3.41-3.50 (m, 2H), 2.64-2.67 (m, 1H), 2.54-2.60 (m,
2H), 2.19 (s, 3H), 1.85-1.88 (m, 2H), 1.70-1.73 (m, 2H), 1.28-1.32 (m, 2H), 1.03-1.12
30 (m, 3H), 0.89-0.91 (d, 3H, J=8Hz);
IR (Neat, Cm⁻¹) : 3421, 2244, 1660.

Example-71

3-[1-Oxo-2-(1-(1-(2,3-dichlorophenyl carbonyl)-piperidin-4-yl) hydrazino)] ethyl-4-cyanothiazolidine trifluoroacetate (Compound No. 70)

5

Yield : 60%.
Mass : 442 (M⁺+1), 464(M⁺+Na);
¹HNMR (d₄-MeOH) δ : 7.65-7.68 (dd, 1H, J=4Hz, 4Hz),
7.42-7.45 (dd, 1H, J=4Hz, 4Hz), 7.31-7.35 (dd, 1H, J=4Hz) 4Hz), 5.34 (bs, 1H), 4.71-
10 4.73 (d, 1H, J=8Hz), 4.62-4.64 (d, 1H, J=8Hz), 4.02-4.08 (m, 1H), 3.25-3.53 (m, 4H),
2.84-3.15 (m, 3H), 2.07-2.13 (m, 1H), 1.88-1.95 (m, 1H), 1.62-1.65 (m, 1H), 1.48-1.51
(m, 1H), 1.21-1.31 (m, 1H);

IR (Neat, Cm⁻¹) : 3351,2227,1676,1629.

15

Example-72

3-[1-Oxo-2-[1-methyl-2-(1-(4-chlorophenylsulphonyl)-piperidin-4-yl)]-hydrazino] ethyl-4-cyanothiazolidine (Compound No. 71)

20

Yield : 23.5%.
Mass : 458 (M⁺+1), 480 (M⁺+Na);
¹HNMR (CDCl₃) δ : 7.76-7.78 (d, 2H, J=8Hz), 7.62-7.64
(d, 2H, J=8Hz), 5.17-5.19 (t, 1H, J=4Hz), 4.83-4.85 (d, 1H, J=8Hz), 4.71-4.73 (d, 1H,
J=8Hz), 4.63 (s, 1H), 4.51-4.57 (m, 1H), 3.66-3.69 (d, 1H, J=12Hz), 3.50-3.53 (m, 1H),
25 3.41-3.47 (m, 4H), 3.35-3.39 (m, 1H), 2.52 (s, 3H), 1.84-1.88 (m, 2H), 1.43-1.47 (m,
2H);
IR (Neat,Cm⁻¹) : 2943, 2240, 1728, 1666, 1584.

30

Example-73

3-[1-Oxo-2-(1-(4-piperidinyl) hydrazino)]ethyl-4-cyanothiazolidine bis-trifluoroacetate (Compound No. 72)

- 5 Yield : 52.8%.
Mass : 270 ($M^+ + 1$);
 $^1\text{HNMR}$ (d_4 -MeOH) δ : 5.32-5.34 (t, 1H, $J=4\text{Hz}$), 4.74-4.76 (d, 1H, $J=8\text{Hz}$), 4.62-4.64 (d, 1H, $J=8\text{Hz}$), 3.36-3.53 (m, 8H), 2.17-2.21 (m, 3H), 1.77-1.86 (m, 2H);
10 IR (Neat, Cm^{-1}) : 3394, 2250, 1679.

Example-74

[1-Oxo-2-(1-(1-(4-chlorophenylsulphonyl)-piperidin-4-yl)-hydrazino)] ethyl -2-cyanopyrrolidine trifluoroacetate (Compound No. 73)

- Yield : 67%.
15 Mass : 426 ($M^+ + 1$), 448 ($M^+ + \text{Na}$);
 $^1\text{HNMR}$ (d_4 -MeOH) δ : 7.78-7.80 (d, 2H, $J=8\text{Hz}$), 7.65-7.67 (d, 2H, $J=8\text{Hz}$), 4.79-4.81 (t, 1H, $J=4\text{Hz}$), 3.92 (s, 2H), 3.79-3.82 (m, 2H), 3.62-3.66 (m, 1H), 3.47-3.51 (m, 1H), 3.14-3.17 (m, 1H), 2.43-2.49 (t, 2H, $J=8\text{Hz}$), 2.16-2.29 (m, 4H), 2.01-2.03 (d, 2H, $J=8\text{Hz}$), 1.61-1.68 (m, 2H);
20 IR (KBr, Cm^{-1}) : 3415, 2332, 1663, 1580.

Example-75

3-[1-Oxo-2-(1-(4-methylcyclohexyl)-2-acetyl) hydrazino]ethyl-4- cyanothiazolidine (Compound No. 74)

- Yield : 47.6%.
Mass : 325 ($M^+ + 1$), 347 ($M^+ + \text{Na}$);
 $^1\text{HNMR}$ (CDCl_3) δ : 5.18-5.20 (t, 1H, $J=4\text{Hz}$), 4.76-4.78 (d, 1H, $J=8\text{Hz}$), 4.67-4.70 (d, 1H, $J=9.6\text{Hz}$), 4.56-4.58 (d, 1H, $J=8\text{Hz}$), 4.42-4.44 (d, 1H, $J=9\text{Hz}$), 3.96-3.99 (m, 1H), 3.81-3.92 (m, 1H), 3.77-3.81 (m, 2H), 3.52-3.55

(m, 2H), 3.30-3.35 (m, 4H), 2.85-2.92 (m, 1H), 2.63-2.67 (m, 1H), 1.89 (s, 3H), 0.90-0.92 (d, 3H, J=8Hz);

IR (Neat, Cm^{-1}) : 3343, 2248, 1676, 1570.

Example-76

5 3-[1-Oxo-2-(1-(1-adamantanyl) hydrazino)] ethyl-4-cyanothiazolidine trifluoroacetate (Compound No. 75)

Yield : 38.9%.

Mass : 321 ($\text{M}^+ + 1$), 343 ($\text{M}^+ + \text{Na}$);

10 $^1\text{HNMR}$ (d_4 -MeOH) δ : 5.32-5.34 (t, 1H, J=4Hz), 4.70-4.72 (d, 1H, J=8Hz), 4.61-4.63 (d, 1H, J=8Hz), 4.04-4.06 (d, 1H, J=8Hz), 3.53 (bs, 1H), 3.47-3.50 (m, 1H), 3.37-3.38 (d, 2H, J=4Hz), 1.92-2.12 (m, 6H), 1.85-1.94 (m, 2H), 1.76-1.82 (m, 4H), 1.58-1.61 (m, 2H);

IR (KBr, Cm^{-1}) : 2927, 2242, 1663, 1508.

15

Example-77

3-[1-Oxo-2-(1-(1-(tert-butyl carbonyl)-piperidin-4-yl) hydrazino)] ethyl-4-cyanothiazolidine trifluoroacetate (Compound No. 76)

20 Yield : 76.4%.

Mass : 354 ($\text{M}^+ + 1$), 376 ($\text{M}^+ + \text{Na}$);

$^1\text{HNMR}$ (d_4 -MeOH) δ : 5.33-5.35 (t, 1H, J=4Hz), 4.76-4.78 (d, 1H, J=8Hz), 4.63-4.65 (d, 1H, J=8Hz), 4.47-4.50 (d, 2H, J=12 Hz), 4.08-4.10 (d, 2H, J=8Hz), 3.33-3.53 (m, 5H), 2.01-2.03 (m, 2H), 1.48-1.54 (m, 2H), 1.30 (s, 9H);

25 IR (KBr, Cm^{-1}) : 3427, 2248, 1673, 1614.

Example-78

3-[1-Oxo-2-(1-(1-(5-trifluoromethyl-2-pyridinyl)-piperidin-4-yl) hydrazino)] ethyl-4-cyano thiazolidine bis trifluoroacetate (Compound No. 77)

30

Yield : 63.3%.

Mass : 415 ($\text{M}^+ + 1$), 437 ($\text{M}^+ + \text{Na}$);

¹HNMR (d₄-MeOH) δ : 8.36 (s, 1H), 7.73-7.77 (dd, 1H, J=4Hz, 8Hz), 6.94-6.96 (d, 1H, J=8Hz), 5.34-5.36 (t, 1H, J=4Hz), 4.71-4.73 (d, 1H, J=8Hz), 4.63-4.65 (d, 1H, J=8Hz), 4.54-4.58 (d, 2H, J= 13Hz), 4.09-4.13 (t, 2H, J=8Hz), 3.36-3.40 (m, 1H), 3.01-3.04 (m, 3H), 2.03-2.07 (m, 2H), 1.58-1.62 (m, 2H);
5 IR (Neat, Cm⁻¹) : 2943, 2248 and 1672

Example-79

3-[1-Oxo-2-(1-(1-methanesulphonylamino-4-cyclohexyl) hydrazino)] ethyl-4-
10 cyanothiazolidine trifluoroacetate (Compound No. 78)

Yield : 66.6%.
Mass : 362 (M⁺+1), 384 (M⁺+Na);
¹HNMR (d₄-MeOH) δ : 5.33-5.35 (t, 1H, J=4Hz), 4.73-
15 4.75 (d, 1H, J=8Hz), 4.59-4.61 (d, 1H, J=8Hz), 4.02-4.14 (m, 2H), 3.19-3.24 (m, 4H),
2.97 (s, 3H), 2.14-2.17 (d, 2H, J=10Hz), 2.05-2.07 (d, 2H, J=8Hz), 1.36-1.44 (m, 4H);
IR (KBr, Cm⁻¹) : 2940, 2248, 1677, 1437.

Example-80

20 3-[1-Oxo-2-(1-(3,3,5-trimethyl cyclohexyl)-hydrazino)] ethyl-4-cyanothiazolidine
trifluoroacetate (Compound No. 79)

Yield : 48.5%.
Mass : 311 (M⁺+1);
25 ¹HNMR (d₄-MeOH) δ : 5.34 (bs, 1H), 4.73-4.75 (d, 1H, J=8Hz),
4.65-4.67 (d, 1H, J=8Hz), 4.04-4.14 (m, 2H), 3.61-3.64 (m, 1H), 3.38-3.39 (d, 2H,
J=4Hz), 1.95-1.99 (m, 1H), 1.77-1.80 (m, 1H), 1.62-1.65 (m, 1H), 1.46-1.49 (m, 4H),
1.10-1.12 (d, 3H, J=8Hz), 0.99 (s, 6H);
IR (KBr, Cm⁻¹) : 3099, 2246, 1665, 1628, 1516.

30

Example-81

3-[1-Oxo-2-(1-isopropyl-2-ethyl)-hydrazino]-ethyl-4-cyanothiazolidine
trifluoroacetate (Compound No. 80)

- 5 Yield : 97%.
Mass : 257 ($M^+ + 1$), 279 ($M^+ + Na$);
 1H NMR ($CDCl_3$) δ : 5.27 (bs, 1H), 4.71-4.73 (d, 1H,
J=8Hz), 4.55-4.57 (d, 1H, J=8Hz), 3.84-3.90 (m, 2H), 3.66-3.69 (t, 1H, J=6Hz), 3.28-
3.37 (m, 4H), 1.35-1.37 (t, 3H, J=4Hz), 1.26-1.27 (d, 6H, J=6Hz);
10 IR (Neat, cm^{-1}) : 2983, 2251, 1670.

Example-82

3-[1-Oxo-2-[1-(1-phenylmethyl-piperidin-4-yl)]-hydrazino]-ethyl-4-cyanothiazolidine
15 trifluoroacetate (Compound No. 81)

- Yield : 56%.
Mass : 360 ($M^+ + 1$);
20 1H NMR (d_4 -MeOH) δ : 7.52 (bs, 5H), 5.43 (bs, 1H),
4.69-4.71 (d, 1H, J=8Hz), 4.61-4.63 (d, 1H, J=8Hz), 4.31-4.42 (m, 2H), 4.05-4.11 (m,
2H), 3.58-3.61 (m, 2H), 3.40-3.51 (m, 3H), 3.01-3.15 (m, 2H), 2.21-2.24 (m, 2H),
1.96-2.02 (m, 2H);
IR (Neat, cm^{-1}) : 3411, 2249, 1675.
25

Example-83

3-[1-Oxo-2-(1-(1-(4-chlorophenyl sulphonylamino-4-cyclohexyl) hydrazino))] ethyl-4-
cyanothiazolidine trifluoroacetate (Compound No. 82)

- 30 Yield : 41%.
Mass : 458 ($M^+ + 1$), 480 ($M^+ + Na$);

- ¹HNMR (d₄-MeOH) δ : 7.85-7.87 (d, 2H, J=8Hz), 7.58-7.60 (d, 2H, J=8Hz), 5.31 (bs, 1H), 4.72-4.74 (d, 1H, J=8Hz), 4.60-4.62 (d, 1H, J=8Hz), 3.96-4.07 (m, 2H), 3.45-3.53 (m, 2H), 3.06-3.08 (m, 2H), 1.86-1.97 (m, 4H), 1.26-1.38 (m, 4H);
- 5 IR (KBr, Cm⁻¹) : 2943, 2240, 1673, 1435.

Example-84

- 10 3-[1-Oxo-2-(pyridazin-1-yl)] ethyl-4-cyanothiazolidine (Compound No. 83)

Yield : 30%.
Mass : 241 (M⁺+1);

- 15 ¹HNMR (d₄-MeOH) δ : 5.25-5.27 (t, 1H, J=4Hz), 4.78-4.81 (d, 1H, J=10Hz), 4.72-4.74 (d, 1H, J=8Hz), 3.50-3.56 (m, 2H), 3.30-3.37 (m, 2H), 2.95-2.98 (t, 2H, J=5.5Hz), 2.72-2.83 (m, 2H), 1.25-1.34 (m, 4H);
IR (Neat, Cm⁻¹) : 2925, 2244, 1737, 1663.

20 **Example-85**

3-[1-Oxo-2-(1-(1-methanesulfonylamino-4-cyclohexyl)-2-isopropyl)hydrazino]ethyl-4-cyanothiazolidine trifluoroacetate (Compound No. 84)

- Yield : 75%.
25 Mass : 404 (M⁺+1), 426 (M⁺+Na);
¹HNMR (d₄-MeOH) δ : 5.32-5.34 (t, 1H, J=4Hz), 4.79-4.81 (d, 1H, J=8Hz), 4.65-4.67 (d, 1H, J=8Hz), 4.03-4.13 (m, 2H), 3.57-3.59 (t, 1H, J=4Hz), 3.48-3.53 (q, 2H, J=8Hz), 3.38-3.39 (d, 2H, J=4Hz), 3.21-3.26 (m, 1H), 2.96-2.97 (d, 3H, J=6.5Hz), 2.11-2.14 (m, 2H), 1.98-2.04 (m, 2H), 1.71-1.80 (m, 2H), 1.44-1.50 (m, 2H), 1.35-1.37 (d, 6H, J=8Hz);
- 30

IR (KBr, cm^{-1}) : 2945, 2245, 1676, 1435.

Example-86

5 3-[1-oxo-2-[1-(1(morpholinocarbonyl)-piperidin-4-yl)]hydrazino]ethyl-4-cyanothiazolidine trifluoroacetate (Compound No. 85)

10 Yield : 80%
Mass : 383 ($M^+ + 1$), 405 ($M^+ + \text{Na}$)

$^1\text{H NMR}$ (d_4 -MeOH): δ 5.32-5.34 (t, 1H), 4.71-4.73 (d, 1H), 4.63-4.65 (d, 1H), 4.03-4.12 (m, 2H), 3.78-3.81 (m, 2H), 3.66-3.68 (t, 4H), 3.47-3.49 (m, 1H), 3.38-3.39 (d, 2H), 3.27-3.29 (t, 4H), 2.87-2.94 (t, 2H), 1.95-2.03 (m, 2H), 1.55-1.61 (m, 2H)

15 IR (KBr, cm^{-1}) : 2888, 2246, 1670, 1542

20 **Example-87**

3-[1-oxo-2-[1-(1-(methylsulphonyl)-piperidin-4-yl)]hydrazino]ethyl-4-cyanothiazolidine trifluoroacetate (Compound No. 86)

25 Yield : 70%
Mass : 348 ($M^+ + 1$)
 $^1\text{H NMR}$ (d_4 -MeOH) δ : 5.32-5.34 (t, 1H), 4.72-4.74 (d, 1H), 4.59-4.61 (d, 1H), 4.07-4.09 (m, 2H), 3.78-3.81 (m, 2H), 3.43-3.48 (m, 1H), 3.38-3.39 (d, 2H), 2.86 (s, 3H), 2.80-2.85 (m, 2H), 2.03-2.08 (m, 2H), 1.63-1.73 (m, 2H)

30 IR (KBr, cm^{-1}) : 3426, 2929, 2248, 2110, 1679

5 **Example-88**

3-[1-oxo-2-[1-(methylsulphonyl)-piperidin-4-yl]-2-isopropyl]hydrazino]ethyl- 4-cyanothiazolidine trifluoroacetate (Compound No. 87)

- 10 Yield : 80%
- Mass : 390 ($M^+ + 1$), 412 ($M^+ + Na$)
- 1H NMR (d_4 -MeOH) δ : 5.31-5.34 (t, 1H), 4.75-4.76 (d, 1H),
15 4.58-4.61 (d, 1H), 4.08-4.10 (d, 2H), 3.80-3.83 (m, 2H), 3.53-3.61 (m, 1H), 3.38-3.39 (d, 2H), 2.86 (s, 3H), 3.44-3.48 (m, 1H), 2.78-2.85 (m, 2H), 2.03-2.06 (m, 2H), 1.60-1.72 (m, 2H), 1.36-1.37 (d, 6H)
- IR (KBr, cm^{-1}) : 3399, 2937, 2248, 1672

20

Example-89

3-[1-oxo-2-[1-(methylsulphonyl)-piperidin-4-yl]-2-ethyl]hydrazino]ethyl-4-cyanothiazolidine trifluoroacetate (Compound No. 88)

- 25 Yield : 80%
- Mass : 376 ($M^+ + 1$), 398 ($M^+ + Na$)
- 30 1H NMR (d_4 -MeOH) δ : 5.31-5.34 (t, 1H), 4.74-4.76 (d, 1H),
4.65-4.67 (d, 1H), 4.03-4.25 (m, 2H), 3.80-3.82 (m, 2H), 3.44-3.48 (m, 1H), 3.25-3.29 (q, 2H), 3.38-3.39 (d, 2H), 2.86 (s, 3H), 2.80-2.85 (m, 2H), 2.03-2.05 (m, 2H), 1.64-1.70 (m, 2H), 1.30-1.34 (t, 3H)
- IR (KBr, cm^{-1}) : 3501, 2933, 2246, 1672

35

Example-90

3-[1-oxo-2-[1-(1-(morpholinocarbonyl)-piperidin-4-yl)-2-ethyl]hydrazino]ethyl- 4-cyanothiazolidine trifluoroacetate (Compound No. 89)

- 5
Yield : 80%
- Mass : 411 ($M^+ + 1$), 433 ($M^+ + Na$)
- 10 1H NMR (d_4 -MeOH) δ : 5.32-5.33 (t, 1H), 4.73-4.78 (d, 1H),
4.64-4.66 (d, 1H), 4.03-4.11 (m, 2H), 3.77-3.81 (m, 2H), 3.66-3.69 (t, 4H), 3.48-3.51
(m, 1H), 3.38-3.39 (d, 2H), 3.26-3.29 (m, 6H), 2.88-2.90 (m, 2H), 1.92-1.96 (m, 2H),
1.53-1.56 (m, 2H), 1.31-1.36 (t, 3H)
- IR (KBr, cm^{-1}) : 3361, 2929, 2247, 1675

15
Example-91

3-[1-oxo-2-[1-(1-(N-ethylmethylaminocarbonyl)-piperidin-4-yl)]hydrazino]ethyl-4-cyanothiazolidine trifluoroacetate (Compound No. 90)

- 20
Yield : 80%
- Mass : 355 ($M^+ + 1$), 377 ($M^+ + Na$)
- 25 1H NMR (d_4 -MeOH) δ : 5.33-5.35 (t, 1H), 4.71-4.74 (d, 1H),
4.63-4.66 (d, 1H), 4.08-4.12 (m, 2H), 3.71-3.74 (m, 2H), 3.44-3.48 (m, 1H), 3.38-3.39
(d, 2H), 3.22-3.27 (q, 2H), 2.82-2.88 (m, 2H), 2.88 (s, 3H), 1.95-1.97 (m, 2H), 1.53-
1.62 (m, 2H), 1.14-1.19 (t, 3H)
- IR (KBr, cm^{-1}) : 3398, 2935, 2245, 1675

30
Example-92

3-[1-oxo-2-[1-(1-(4-methoxyphenylsulphonyl)-piperidin-4-yl)]hydrazino]ethyl- 4-cyanothiazolidine trifluoroacetate (Compound No. 91)

- 35
Yield : 80%
- Mass : 440 ($M^+ + 1$), 462 ($M^+ + Na$)

- ¹HNMR (d₄-MeOH) δ : 7.72-7.74 (d, 2H), 7.12-7.15 (d, 2H),
5.29-5.31 (t, 1H), 4.67-4.69 (d, 1H), 4.59-4.61 (d, 1H), 4.05-4.07 (m, 2H), 3.90 (s, 3H),
3.72-3.77 (m, 2H), 3.35-3.37 (d, 2H), 3.17-3.19 (m, 1H), 2.38-2.44 (m, 2H), 1.99-2.03
(m, 2H), 1.65-1.71 (m, 2H).
- 5 IR (KBr, cm⁻¹) : 3471, 2954, 2246, 1665

Example-93

- 3-[1-oxo-2-[1-(1-(4-methoxyphenylsulphonyl)aminocyclohexan-4-yl)]hydrazino]ethyl-4-
10 cyanothiazolidine trifluoroacetate (Compound No. 92)

- Yield : 90%
- Mass : 453 (M⁺+1)
- 15 ¹HNMR (d₄-MeOH) δ : 7.79-7.82 (d, 2H), 7.07-7.09 (d, 2H),
5.30-5.32 (t, 1H), 4.67-4.69 (d, 1H), 4.59-4.61 (d, 1H), 4.01-4.03 (m, 2H), 3.36-3.37 (d,
2H), 3.08-3.11 (m, 1H), 2.97-3.01 (m, 1H), 1.96-2.03 (m, 2H); 1.85-1.88 (m, 2H), 1.25-
1.38 (m, 4H)
- 20 IR (KBr, cm⁻¹) : 2942, 2247, 1673, 1596

Example-94

- 25 3-[1-oxo-2-[1-(1-(4-fluorobenzyl)aminocyclohexan-4-yl)]hydrazino]ethyl-4-
cyanothiazolidine bis-trifluoroacetate (Compound No. 93)

- Yield : 90%
- 30 Mass : 392 (M⁺+1)
- ¹HNMR (d₄-MeOH) δ : 7.53-7.56 (t, 2H), 7.20-7.24 (t, 2H), 5.32-
5.34 (t, 1H), 4.72-4.74 (d, 1H), 4.63-4.65 (d, 1H), 4.24-4.25 (s, 2H), 4.07-4.14 (m, 2H),
3.64-3.70 (m, 1H), 3.38-3.39 (d, 2H), 3.18-3.22 (m, 1H), 2.32-2.36 (m, 2H), 2.18-2.22
35 (m, 2H), 1.52-1.58 (m, 4H)
- IR (KBr, cm⁻¹) : 2963, 2248, 1673, 1513

Example-95

3-[1-oxo-2-[1-(1-(4-fluorobenzyl)-piperidin-4-yl)]hydrazino]ethyl-4-cyanothiazolidine bis-trifluoroacetate (Compound No. 94)

5

Yield : 95%

Mass : 387 ($M^+ + 1$), 400 ($M^+ + Na$)

10 1H NMR (d_4 -MeOH) δ : 7.55-7.58 (t, 2H), 7.23-7.25 (t, 2H),
5.31-5.33 (t, 1H), 4.70-4.72 (d, 1H), 4.59-4.61 (d, 1H), 4.35 (s, 2H), 4.02-4.14 (m, 2H),
3.46-3.59 (m, 3H), 3.37-3.38 (d, 2H), 3.07-3.15 (m, 2H), 2.18-2.24 (m, 2H), 1.83-1.87
(m, 2H).

15 IR (KBr, cm^{-1}) : 3364, 2955, 2251, 1675

Example-96

3-[1-oxo-2-[(1-(1-(2-oxo-2-(5-chloropyridin-2-yl)aminoethyl)piperidin-4-yl)]hydrazino]ethyl-4-cyanothiazolidine tris-trifluoroacetate (Compound No. 95)

20

Yield : 87%

Mass : 438 ($M^+ + 1$), 460 ($M^+ + Na$)

25

1H NMR (d_4 -MeOH) δ : 8.332-8.338 (d, 1H), 8.16-8.18 (d,
1H), 7.83-7.86 (dd, 1H), 5.32-5.34 (t, 1H), 4.72-4.74 (d, 1H), 4.64-4.66 (d, 1H), 4.01-
4.14 (m, 4H), 3.66-3.68 (m, 2H), 3.47-3.49 (m, 1H), 3.37-3.38 (d, 2H), 3.21-3.23 (m, 2H),
2.23-2.26 (m, 2H), 2.01-2.05 (m, 2H)

30

IR (KBr, cm^{-1}) : 2954, 2249, 1674, 1539

Example-97

35 3-[1-oxo-2-[1-(1-(trimethyl acetamido)cyclohexan-4-yl)]hydrazino]ethyl-4-cyanothiazolidine trifluoroacetate (Compound No. 96)

Yield : 90%

40

109

Mass : 368 (M⁺+1), 390 (M⁺+Na)
¹HNMR (d₄-MeOH) δ : 5.53-5.35 (t, 1H), 4.74-4.76 (d, 1H), 4.63-4.65 (d, 1H), 4.04-4.16 (m, 2H), 3.64-3.70 (m, 1H), 3.38-3.41 (d, 2H), 3.18-3.22 (m, 1H),
5 2.05-2.08 (m, 2H), 1.96-1.99 (m, 2H), 1.36-1.52 (m, 4H), 1.2 (s, 9H)
IR (KBr, cm⁻¹) : 3342, 2949, 2242, 1693, 1534

Example-98

10 3-[1-oxo-2-[1-(1-(methanesulphonyl)aminocyclohexan-4-yl)-2-ethyl]hydrazino]ethyl-4-cyanothiazolidine (Compound No. 97)

Yield : 45%
15 Mass : 390 (M⁺+1), 412 (M⁺+Na)
¹HNMR (d₄-MeOH) δ : 5.27-5.28 (t, 1H), 4.71-4.83 (m, 2H), 3.42-3.82 (m, 2H), 3.27-3.34 (m, 3H), 2.80 (s, 3H), 2.76-2.80 (m, 2H), 2.12-2.15 (m,
20 2H), 1.90-1.93 (m, 2H), 1.25-1.44 (m, 4H), 1.02-1.07 (t, 3H).
IR (KBr, cm⁻¹) : 3587, 3218, 2243, 1739, 1677

Example-99

25 3-[1-oxo-2-[(1-(trimethyl acetamido) cyclohexan-4-yl)]hydrazino]ethyl-4-cyanothiazolidine trifluoroacetate (Compound No. 98)

Yield : 60%
30 Mass : 367 (M⁺+1)
¹HNMR (d₄-MeOH) δ : 5.33-5.35 (t, 1H), 4.72-4.74 (d, 1H), 4.68-4.70 (d, 1H), 4.02-4.15 (m, 2H), 3.76-3.80 (m, 1H), 3.38-3.48 (m, 1H), 3.32-3.33 (d, 2H),
35 1.75-1.78 (m, 8H), 1.2 (s, 9H).
IR (KBr, cm⁻¹) : 3408, 2933, 2159, 1672

Example-100

3-[1-oxo-2-[1-(1-(2-oxo-2-(4-cyanophenyl)aminoethyl)piperidin-4-yl)]hydrazino]ethyl-4-cyanothiazolidine bis-trifluoroacetate (Compound No. 99)

Yield : 90%

Mass : 428 (M^+ +1), 450 (M^+ +Na)

¹HNMR (d_4 -MeOH) δ : 7.80-7.83 (d, 2H), 7.73-7.75 (d, 2H), 5.53-5.35 (t, 1H), 4.72-4.74 (d, 1H), 4.63-4.65 (d, 1H), 4.20 (s, 2H), 4.10-4.18 (m, 2H), 3.48-3.75 (m, 3H), 3.38-3.39 (d, 2H), 3.25-3.27 (m, 2H), 2.26-2.29 (m, 2H), 2.03-2.05 (m, 2H).

IR (KBr, cm^{-1}) : 3411, 2934, 2248, 1675, 1647

Example-101

3-[1-oxo-2-[1-(4-fluorobenzoyl)aminocyclohexan-4-yl]]hydrazino] ethyl-4-cyanothiazolidine trifluoroacetate (Compound No. 100)

Yield : 75%

Mass : 428 (M^+ +Na)

¹HNMR (d_4 -MeOH) δ : 7.86-7.89 (t, 2H), 7.18-7.22 (t, 2H), 5.32-5.34 (t, 1H), 4.72-4.74 (d, 1H), 4.60-4.62 (d, 1H), 4.09-4.20 (m, 2H), 3.46-3.50 (m, 2H), 3.39-3.40 (d, 2H), 1.77-1.89 (m, 8H).

IR (KBr, cm^{-1}) : 3273, 2949, 2248, 1675, 1644

Example-102

3-[1-oxo-2-[1-(1-(2-oxo-2-(5-chloropyridin-2-yl)aminoethyl)piperidin-4-yl)]-2-ethylhydrazino]ethyl-4-cyanothiazolidine tris-hydrochloride (Compound No.101)

Yield : 87%

Mass : 466(M⁺+1), 488 (M⁺+Na)
¹HNMR (d₄-MeOH) δ : 8.332-8.338 (d, 1H), 8.16-8.18 (d, 1H),
5 7.83-7.86 (dd, 1H), 5.35-5.37 (t, 1H), 4.64-4.82 (m, 4H), 4.05-4.24 (m, 4H), 3.78-
3.82 (m, 2H), 3.47-3.49(m,1H),3.32-3.40 (m, 4H), 2.22-2.30 (m, 3H), 2.01-2.05 (m,
3H),1.35-1.39(t,3H).
10 IR (KBr, cm⁻¹) : 2946, 2247, 1696, 1667

15 **Example-103**

3-[1-oxo-2-[-1-(1-(2-oxo-2(4-trifluorophenyl)aminoethyl)piperidin-4-
yl)]hydrazino]ethyl-4-cyanothiazolidine bis-trifluoroacetate (Compound No. 102)

20 Yield : 59%
Mass : 471 (M⁺+1)
¹HNMR (d₄-MeOH) δ : 7.81-7.83 (d, 2H), 7.66-7.68 (d,
25 2H), 5.32-5.34 (t, 1H), 4.73-4.75 (d, 1H), 4.65-.467 (d, 1H), 4.1 (S, 2H), 4.03-4.06
(m, 2H), 3.53-3.69 (m, 2H), 3.46-3.50 (m, 1H), 3.38-3.39 (d, 2H), 3.46-3.50 (m, 1H),
2.23-2.26 (m, 2H), 2.01-2.05 (m, 2H)
IR (KBr, cm⁻¹) : 2945, 2249, 1674, 1613

30

Example-104

3-[1-oxo-2-[1-(1-(2-oxo-2(-adamant-1-yl)amino ethyl)piperidin-4-
yl)]hydrazino]ethyl-4-cyanothiazolidine bis-trifluoroacetate (Compound No. 103)

35

Yield : 53%
Mass : 461 (M⁺+1)

¹HNMR (d4-MeOH) δ : 5.32-5.34 (t, 1H), 4.71-4.73 (d, 2H), 4.63-4.65 (d, 1H), 4.05-4.08 (m, 2H), 3.8 (s, 2H), 3.48-3.50 (m, 3H), 3.37-3.39 (d, 2H), 3.32-3.33 (m, 2H), 2.03-2.09 (m, 2H), 1.85-2.02 (m, 11H), 1.72-1.75 (m, 6H)

5 IR (KBr, cm⁻¹) : 2910, 1674, 1558

Example - 105

10 3-[1-oxo-2-[1-(1-(2-oxo-2(2,3-dihydrobenzo(1,4)dioxan-6-yl)aminoethyl)piperidin-4-yl)]hydrazino]ethyl-4-cyano-thiazolidine bis-trifluoroacetate (Compound No. 104)

15 Yield : 80%

Mass : 461 (M⁺+1), 483 (M⁺+Na)

¹HNMR (d4-MeOH) δ : 7.22-7.23 (d, 1H), 6.94-6.97 (dd, 1H), 6.79-6.82 (d, 2H), 5.32-5.34 (t, 1H), 4.73-4.75 (d, 1H), 4.64-4.67 (d, 1H), 4.24 (s, 1H), 4.00-4.05 (m, 4H), 3.50-3.51 (m, 2H), 3.46-3.47 (m, 1H), 3.38-3.39 (d, 2H), 3.15-3.32 (m, 2H), 2.21-2.23 (m, 2H), 2.03-2.05 (m, 2H)

25 IR (KBr, cm⁻¹) : 2949, 1677, 1620

Example-106

30 3-[1-oxo-2-[1-(1-(2-oxo-2(4-chlorophenyl)aminoethyl)piperidin-4-yl)]hydrazino]ethyl-4-cyanothiazolidine bis-trifluoroacetate (Compound No. 105)

Yield : 60%

Mass : 437 (M⁺+1), 459 (M⁺+Na)

35 ¹HNMR (d4-MeOH) δ : 7.60-7.62 (d, 2H), 7.35-7.37 (d, 2H), 5.32-5.33 (t, 1H), 4.73-4.76 (d, 1H), 4.65-4.67 (d, 1H), 4.07- (s, 1H), 3.92-4.00 (m, 2H), 3.59-3.64 (m, 2H), 3.51-3.52 (m, 1H), 3.17-3.38 (d, 2H), 3.15-3.32 (m, 2H), 2.18-2.21 (m, 2H), 1.99-2.05 (m, 2H)

40 113

IR (KBr, cm⁻¹) : 2924, 1677, 1620

5

Example-107

3[2-oxo-2-[1-(1-(2-oxo-2(pyrimidin-2-yl)aminoethyl)piperidin-4-yl)]hydrazino]ethyl-4-cyanothiazolidine tris-trifluoroacetate (Compound No. 106)

10

Yield : 66%

Mass : 408 (M⁺+1), 427 (M⁺+Na)

15

¹HNMR (d4-MeOH) δ : 8.66-8.67 (d, 2H), 7.20-7.23 (t, 1H), 5.32-5.34 (t, 1H), 4.68-4.72 (d, 1H), 4.63-4.67 (d, 1H), 4.60-4.62 (m, 2H), 4.09-4.19 (m, 2H), 3.72-3.74 (m, 2H), 3.47-3.53 (m, 3H), 3.38-3.39 (d, 2H), 2.25-2.28 (m, 2H), 2.03-2.05 (m, 2H)

20

IR (KBr, cm⁻¹) : 2978, 1678, 1517

Example-108

25

3-[1-oxo-2-[1-(1-(2-oxo-2(morpholin-4-yl)ethyl)piperidin-4-yl)]hydrazino]ethyl-4-cyanothiazolidine bis-trifluoroacetate (Compound No. 107)

Yield : 86%

30

Mass : 397 (M⁺+1), 419 (M⁺+Na)

35

¹HNMR (d4-MeOH) δ : 5.32-5.34 (t, 1H), 4.72-4.74 (d, 1H), 4.63-4.65 (d, 1H), 4.28 (s, 2H), 4.02-4.14 (m, 2H), 3.70-3.71 (t, 4H), 3.61-3.63 (m, 2H), 3.47-3.51 (m, 1H), 3.42-3.43 (m, 2H), 3.38-3.39 (d, 2H), 3.32 (t, 4H), 2.21-2.24 (m, 2H), 1.99-2.03 (m, 2H)

IR (KBr, cm⁻¹) : 2977, 1676, 1539

40

Example-109

5 3[1-oxo-2-[1-(1-(2-oxo-2-(cyclopropyl)aminoethyl)piperidin-4-yl)]hydrazino]ethyl-4-cyanothiazolidine bis-trifluoroacetate (Compound No. 108)

10 Yield : 40%
Mass : 367 ($M^+ + 1$), 389 ($M^+ + Na$)
 1H NMR (d4-MeOH) δ : 5.31-5.33 (t, 1H), 4.72-4.75 (d, 1H), 4.63-4.66 (d, 1H), 4.01-4.09 (m, 2H), 3.87 (s, 2H), 3.51-3.53 (m, 2H), 3.48-3.50 (m, 1H), 3.37-3.38 (d, 2H), 3.14-3.16 (m, 2H), 2.73-2.77 (m, 1H), 2.20-2.23 (m, 2H), 2.01-2.03 (m, 2H), 0.76-0.79 (m, 2H), 0.52-0.56 (m, 2H)
15 IR (KBr, cm^{-1}) : 2994, 1677, 1541

20 **Example-110**

3-[1-oxo-2-[1-(1-(2-cyanobiphenyl-4-yl)methyl)piperidine-4-yl]hydrazino]ethyl- 4-cyanothiazolidine bis-trifluoroacetate (Compound No. 109)

25 Yield : 80%
Mass : 461 ($M^+ + 1$), 483 ($M^+ + Na$)
30 1H NMR (d4-MeOH) δ : 7.59-7.90 (m, 8H), 5.31-5.33 (d, 1H), 4.71-4.73 (d, 2H), 4.61-4.64 (d, 1H), 4.45 (s, 2H), 4.01-4.12 (2H), 3.59-3.66 (m, 2H), 3.50-3.53 (m, 1H), 3.37-3.38 (d, 2H), 3.15-3.32 (m, 2H), 2.25-2.27 (m, 2H), 2.03-2.05 (m, 2H)
35 IR (KBr, cm^{-1}) : 2944, 2247, 1676

40

Example-111

3-[1-oxo-2-[1-(1-(1-oxo-2-(morpholin-4-yl)ethyl)piperidin-4-yl)]hydrazino]ethyl-4-cyanothiazolidine bis-trifluoroacetate (Compound No. 110)

5

Yield	:	51%
Mass	:	397 (M ⁺ +1), 419 (M ⁺ +Na)

10

¹ HNMR (d4-MeOH) δ	:	5.32-5.33 (t, 1H), 4.72-4.74 (d, 1H), 4.64-4.66 (d, 1H), 4.51-4.54 (m, 1H), 4.24-4.34 (m, 2H), 4.03-4.05 (m, 2H), 3.96 (t, 4H), 3.78-3.82 (m, 1H), 3.48-3.51 (m, 1H), 3.38-3.39 (d, 2H), 3.32-3.34 (t, 4H), 3.07-3.19 (m, 1H), 2.84-2.90 (m, 1H), 2.03-2.05 (m, 2H), 1.51-1.64 (m, 2H)
IR (KBr, cm ⁻¹)	:	2949, 2247, 1673

15

Example-112

3-[1-oxo-2-[1-(4-(2-oxo-2-(5-chloropyridin-2-yl)aminoethyl)amino cyclohex-1-yl)]hydrazino]ethyl-4-cyanothiazolidine tris-trifluoroacetate (Compound No. 111)

20

Yield	:	66%
Mass	:	452 (M ⁺ +1), 474 (M ⁺ +Na)

25

¹ HNMR (d4-MeOH) δ	:	8.32-8.33 (d, 1H), 8.14-8.16 (d, 1H), 7.83-7.85 (dd, 1H), 5.32-5.33 (t, 1H), 4.72-4.74 (d, 1H), 4.59-4.63 (d, 1H), 3.98-4.08 (m, 4H), 3.38-3.39 (t, 2H), 3.21-3.23 (m, 2H), 2.28-2.30 (m, 2H), 2.19-2.20 (m, 2H), 1.53-1.62 (m, 4H)
IR (KBr, cm ⁻¹)	:	2977, 1676, 1539

30

Example-113

3-[1-oxo-2-[1-(4-(2-oxo-2-(4-cyanophenyl)aminoethyl)aminocyclohex-1-yl)]hydrazino]ethyl-4-cyanothiazolidine bis-trifluoroacetate (Compound No. 112)

35

Yield	:	75%
Mass	:	442 (M ⁺ +1)

40

¹HNMR (d4-MeOH) δ : 7.80-7.82 (d, 1H), 7.72-7.74 (d, 1H), 5.32-5.33 (d, 1H), 4.71-4.73 (d, 1H), 4.53-4.65 (d, 1H), 4.02-4.13 (m, 4H), 3.38-3.39 (d, 2H), 3.07-3.15 (m, 2H), 2.29-2.31 (m, 2H), 2.18-2.20 (m, 2H), 1.56-1.63 (m, 4H).

5 IR (KBr, cm⁻¹) : 2946, 2226, 1676

Example-114

10 3-[1-oxo-2-[1-(4-(2-oxo-2-(4-chlorophenyl)aminoethyl)aminocyclohex-1-yl)]hydrazino]ethyl-4-cyanothiazolidine bis-trifluoroacetate (Compound No.113)

Yield : 85%

15 ¹HNMR (d4-MeOH) δ : 7.60-.762 (d, 2H), 7.34-7.36 (d, 2H), 5.32-5.33 (t, 1H), 4.72-4.74 (d, 1H), 4.65-4.67 (d, 1H), 3.98-4.09 (m, 4H), 3.37-3.38 (d, 2H), 3.07-3.15 (m, 2H), 2.29-2.31 (m, 2H), 2.17-2.19 (m, 2H), 1.53-1.59 (m, 4H)

20 Mass : 451 (M⁺+1)

IR (KBr, cm⁻¹) : 2948, 1677, 1544

Example-115

25 3-[1-oxo-2-(1-(1-methanesulphonylamino-4-cyclohexyl)hydrazino)]ethyl-4-cyanothiazolidine hydrochloride (Compound No. 114)

30 Yield : 70%

Mass : 362 (M⁺+1), 384 (M⁺+Na)

¹HNMR (d4-MeOH) δ : 5.33-5.35 (t, 1H), 4.73-4.76 (d, 1H), 4.64-4.66 (d, 1H), 4.06-4.14 (m, 2H), 3.38-3.40 (d, 2H), 3.15-3.25 (m, 2H), 2.97 (s, 3H), 2.14-2.16 (m, 2H), 2.01-2.03 (m, 2H), 1.36-1.50 (m, 4H).

35 IR (KBr, cm⁻¹) : 2936, 1664 and 1444

Example-116

5 3-[-1-oxo-2-[1-(1-(2-oxo-2-(5-chloropyridin-2-yl)aminoethyl)piperidine-4-yl)]hydrazino]ethyl-4-cyanothiazolidine trihydrochloride (Compound No. 115)

10 Yield : 70%

Mass : 438 (M⁺+1), 460 (M⁺+Na)

¹HNMR (d4-MeOH) δ : 8.32-8.33 (d, 1H), 8.18 (s, 1H),
7.84-7.86 (d, 1H), 5.34-5.35 (t, 1H), 4.73-4.75 (d, 1H), 4.66-4.68 (d, 1H), 4.11-4.28
15 (m, 4H), 3.81-3.83 (m, 2H), 3.67-3.69 (m, 1H), 3.48-3.49 (m, 2H), 3.38-3.39 (d, 1H),
2.27-2.29 (m, 2H), 2.03-2.11 (m, 2H)

IR (KBr, cm⁻¹) : 2940, 2246 and 1695

20 Examples of Scheme 2:

Example -117

[2-Cyano-1-(piperazine-2-yl)-carbonyl pyrrolidine bis-trifluoroacetate]
25 (Compound No. 1).

Yield : 97.32% ;

m.p. : 126-128^oC;

Mass (m/z) : 209 (M⁺ +1), 231 (M⁺ +Na);

¹HNMR (400 MHz, d₄-MeOH)δ : 4.79-4.82 (m, 1H), 4.27-4.30
30 (dd, 1H, J=4Hz, 4Hz), 3.91-3.94 (m, 1H), 3.59-3.62 (m, 1H), 3.22-3.39 (m, 6H), 2.19-
2.31 (m, 4H);

IR (KBr, cm⁻¹) : 3000, 2364, 1673, 1430.

Example -118

35 [2-Cyano-1-(4-isopropyl-2-piperazinyl)-carbonyl-pyrrolidine bis trifluoroacetate]
(Compound No. 2)

Yield : 53.92% ;

Mass (m/z)	:	251 (M ⁺ + 1);
¹ HNMR (400 MHz, d ₄ -MeOH)δ	:	4.79-4.82 (m, 1H), 4.28-4.30 (m, 1H), 3.56-3.74 (m, 2H), 2.41-3.47 (m, 7H), 2.21-2.37 (m, 4H), 1.31-1.33 (d, 6H, J=8Hz);
5 IR (CCl ₄ , cm. ⁻¹)	:	3480, 2962, 2302, 1677, 1453.

Examples of Scheme 3:

Example - 119

10	[4-Cyano-3-(1-isopropylhydrazino)carbonyl thiazolidine hydrochloride] (Compound No. 31)	
	Yield	: 52.63% ;
	m.p.	: 148-150 ^o C (dec.);
	Mass (m/z)	: 215 (M ⁺ + 1), 199;
15	¹ HNMR (400 MHz, d ₄ -MeOH)δ	: 5.13-5.15 (d, 1H, J=8Hz), 4.59-4.62 (m, 1H), 4.24-4.28 (m, 2H), 3.42-3.46 (dd, 1H, J=6Hz, 4Hz), 2.96-3.00 (t, 1H, J=8Hz), 1.22-1.26 (t, 6H, J=8Hz);
	IR (KBr, cm. ⁻¹)	: 3646, 2940, 2355, 1649.

20

Example 120

	[2-Cyano-1-(1-cyclohexyl hydrazino)carbonyl pyrrolidine hydrochloride] (Compound No. 32)	
	Yield	: 22.62% ;
25	m.p.	: 160-162 ^o C (dec.);
	Mass (m/z)	: 237 (M ⁺ + 1), 155;
	¹ HNMR (400 MHz, CDCl ₃)δ	: 8.75-8.77 (bs, 2H), 4.14-4.25 (bs, 2H), 3.53-3.65 (bs, 1H), 3.50-3.52 (bs, 1H), 2.60-2.80 (bs, 1H), 2.06-2.27 (m, 3H), 1.79-1.90 (m, 6H), 1.65-1.68 (m, 1H), 1.23-1.29 (m, 3H);
30	IR (KBr, cm. ⁻¹)	: 3646, 3245, 2931, 2360, 1666.

Example - 121

[4-Cyano-3-(1-cyclohexylhydrazino)carbonyl thiazolidine hydrochloride]
5 (Compound No. 33)

Yield : 32.46% ;
m.p. : 166-168^oC (dec.);
Mass (m/z) : 255 (M⁺+1), 173;
¹HNMR (400 MHz, d₄-MeOH)δ : 4.863-4.88(d,1H,J=8Hz),4.18-
10 4.20 (d,2H,J=8Hz),3.29-3.32(m,1H),3.16-3.20 (t,1H,J=8Hz), 2.92-2.96
(t,1H,J=8Hz),1.66-1.73 (m,2H),1.54-1.64 (m,4H), 1.49-1.53
(m,1H), 1.18-1.23 (m,2H),1.04-1.10 (m,1H);
IR (KBr, cm.⁻¹) : 3748, 3226, 2934, 2345, 1656.

15

Pharmaceutical Compositions

Pharmaceutical compositions may be prepared with a pharmaceutically effective quantity of compounds of general formula I, individually or in combination.

20 It is common practice to administer the compounds in the form of pharmaceutical dosage forms comprising pharmaceutically acceptable excipient(s) and at least one active ingredient. These dosage forms may be administered by a variety of routes including oral, topical, transdermal, subcutaneous, intramuscular, intravenous, intranasal, pulmonary etc.

25

The following pharmaceutical formulations suggested are by way of example alone and in no way restrict the forms in which they can be used.

Oral formulations

30

Oral formulations may be administered as solid dosage forms for example pellets, powders, sachets or discreet units such as tablets or capsules and like. Other orally administered pharmaceutical preparations include monophasic and biphasic

liquid dosage forms either in ready to use form or forms suitable for reconstitution such as mixtures, syrups, suspensions or emulsions. The preparations in addition may contain diluents, dispersing agents, buffers, stabilizers, solubilizers, surfactants, preservatives, chelating agents and/ or other pharmaceutical additives as are used.

5 Aqueous or non-aqueous vehicle or their combination may be used and if desired may contain suitable sweetener, flavoring agent or similar substances. In case of suspension or emulsion a suitable thickening agent or suspending agent or emulsifying agent may be present in addition. Alternatively, the compounds may be administered as such in their pure form unassociated with other additives for example as capsules or sachets. It
10 may also be administered with a vehicle. Pharmaceutical preparations can have a slow, delayed or controlled release of active ingredients as is provided by a matrix or diffusion controlled system.

When the present invention or its salts or suitable complexes is presented as a
15 discrete unit dosage form like tablet, it may contain in addition medically inert excipients as are used in the art. Some example of suitable excipients include lactose, cellulose and its derivatives such as microcrystalline cellulose, methylcellulose, hydroxy propyl methyl cellulose, ethylcellulose, dicalcium phosphate, mannitol, starch, gelatin, polyvinyl pyrrolidone, various gums like acacia, tragacanth, xanthan, alginates & its derivatives,
20 sorbitol, dextrose, xylitol, magnesium stearate, talc, colloidal silicon dioxide, mineral oil, glyceryl mono stearate, glyceryl behenate, sodium starch glycolate, Cross Povidone, crosslinked carboxymethylcellulose, various emulsifiers such as polyethylene glycol, sorbitol, fattyacid esters, polyethylene glycol alkylethers, sugar esters, polyoxyethylene polyoxypropyl block copolymers, polyethoxylated fatty acid monoesters, diesters and
25 mixtures thereof.

Preparation of oral dosage form:

A typical tablet can have the following compositions:

30

Oral formulation

A tablet formulation may be prepared as per the following compositions.

5 **Example - 122**

	Ingredients	Qty. (mg / tablet)
	Active ingredient of formula I	20.0 mg
	Microcrystalline Cellulose	200.0 mg
	Starch	50.0 mg
10	Magnesium Stearate	5.0 mg
	Talc	2.0 mg

Example - 123

15	Ingredients	Qty. (mg / tablet)
	Active ingredient of formula I	10 mg
	Lactose	75 mg
	Starch	50 mg.
20	Polyvinyl pyrrolidone (10% solution in water)	5 mg
	Sodium starch glycolate	5 mg
	Magnesium Stearate	2 mg
	Colloidal Silicon-dioxide	5 mg

25 **Example 124**

	Ingredients	Qty. (mg / tablet)
	Active ingredient	5.0 mg
	Microcrystalline Cellulose	80.5 mg
30	Starch	8.0 mg.
	Talc	3.3 mg
	Magnesium Stearate	1.6 mg
	Colloidal Silicon-dioxide	1.6 mg

Active ingredient, lactose and starch are screened through 40 # sieve and blended. The blend is then granulated with polyvinyl pyrrolidone solution. Resultant mass is screened through number 16 sieve. The granules produced are then dried at 50
5 - 60 °C and passed through 16-mesh sieve. Sodium starch glycolate, magnesium Stearate and colloidal silicon dioxide are sifted through 60-mesh sieve and blended with the granules. The resultant blend is then compressed into tablets.

The above ingredients may be blended into tablets by any other conventional
10 materials.

Parenteral Formulations

15 For parenteral administration, the compounds or their salts or suitable complexes thereof may be present in a sterile vehicle which may be an aqueous or non-aqueous vehicle or a combination thereof. The examples of vehicles are water, ethyl oleate, oils and derivatives of polyols, glycols and their derivatives. It may
20 contain additives common in injectable preparations like stabilizers, solubilizers, pH modifiers, buffers, antioxidants, cosolvents, complexing agents, tonicity modifiers, etc.

Some suitable additives are for example tartrate, citrate or similar buffers,
25 alcohol, sodium chloride, dextrose and high molecular weight polymers. Another alternative is sterile powder reconstitution. The compound may be administered in the form of injection for more than once daily administration, or intravenous infusion/ drip or suitable depot preparation.

30 For injectable administration, the active ingredient or its salt is dissolved or dispersed in a sterile vehicle. The vehicle may be aqueous or non-aqueous and may contain suitable surfactants, solubilizers, buffers, stabilizers, surfactants, antioxidants,

cosolvents, chelating agents, tonicity modifiers etc. Various excipients commonly used include propylene glycol, polythene glycol, mannitol, sodium chloride, ethyloleate, polyethylene glycol fatty acid esters, polyethylene glycol castor oil, polyethylene glycol sarbitan fatty acid esters, sugar esters, various buffers such as phosphate, succinate, citrate, borate, antioxidants such as sodium metabisulphite etc.

An injectable formulation containing the following ingredient may be prepared:

Example 125

10	Ingredients	Qty.
	Active ingredient of formula I	1 mg
	Polythylene glycol	0.1 ml
15	Isotonic Saline / WFI	to 1 ml
	Sodium metabisulphite	

OTHER FORMULATIONS

20 For the dermatological application and for the buccal delivery, the recommended formulations are gel, ointment, creams, patches, liniment, lotions, oral rinse, gurgles and toothpaste containing appropriate compounds of the compounds of the general formula I.

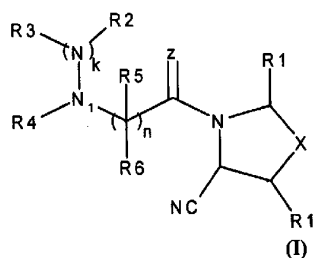
25 The above examples are presented by way of illustration alone and in no way limit the scope of the invention.

30 It is to be understood that, if any prior art publication is referred to herein, such reference does not constitute an admission that the publication forms a part of the common general knowledge in the art, in Australia or any other country.

35 In the claims which follow and in the preceding description of the invention, except where the context requires otherwise due to express language or necessary implication, the word "comprise" or variations such as "comprises" or "comprising" is used in an inclusive sense, i.e. to specify the presence of the stated features but not to preclude the presence or addition of further features in various embodiments of the invention.

CLAIMS

1. A compound represented by general formula (I), its derivatives, analogs, tautomeric forms, stereoisomers, polymorphs, pharmaceutically acceptable salts, their
 5 pharmaceutically acceptable solvates



wherein

- 10 X is O, S, SO, SO₂, NR₇ or CHR₁ ;

n is null or 1;

k is 1;

15

Z is O, S, and NR₇ ;

R₁ at two positions are independently selected from hydrogen or a substituted or unsubstituted group selected from linear or branched (C₁-C₁₂)alkyl, (C₂-C₁₂)alkenyl,
 20 (C₃-C₇)cycloalkyl, (C₅-C₇)cycloalkenyl, bicycloalkyl, bicycloalkenyl, heterocycloalkyl, aryl, aryloxy, aralkyl, aralkoxy, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, wherein one or more heteroatoms are independently selected from O, N or S;

- 25 R₂, R₃, R₄ and R₇ are independently selected from hydrogen, perhaloalkyl, -(CO)NR₈R₉, -(CO)R₈, -(CO)OR₈, -SO₂R₈, -SOR₈, substituted or unsubstituted groups selected from linear or branched (C₁-C₁₂)alkyl, (C₂-C₁₂)alkenyl, (C₃-C₇)cycloalkyl, (C₅-C₇)cycloalkenyl, bicycloalkyl, amidino bicycloalkenyl,

30

heterocycloalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, wherein one or more heteroatoms are independently selected from O, N or S;

5 R5 and R6 are independently selected from by hydrogen or a substituted or unsubstituted group selected from linear or branched (C₁-C₁₂)alkyl, (C₂-C₁₂)alkenyl, (C₃-C₇)cycloalkyl, (C₅-C₇)cycloalkenyl, bicycloalkyl, bicycloalkenyl, heterocycloalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, wherein one or more heteroatoms are independently selected from O, N or S;

10 R8 and R9 are independently selected from hydrogen or a substituted and unsubstituted group selected from linear or branched (C₁-C₁₂)alkyl, alkoxyaryl, alkoxyalkyl, alkoxyalkenyl, alkoxyaryl, perhaloalkyl, (C₂-C₁₂)alkenyl, (C₃-C₇) cycloalkyl, perhalocycloalkyl, haloheterocycloalkyl, cyanoheterocycloalkyl, perhaloheterocycloalkyl, (C₅-C₇) cycloalkenyl, bicycloalkyl, bicycloalkenyl,
15 heterocycloalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, perhaloaryl, perhaloheteroaryl;

wherein in the groups represented by R1, R2, R3, R4, R5, R6, R7, R8 and R9 when substituted, the substituents are optionally and independently bridged by -(CO)-, -
20 (CO)O-, -(CO)NH-, -NH-, -NR8-, -O-, -S-, -(SO)-, -(SO₂)-, -(SO₂)NH-, -NH(SO₂)-, -O(CO)- or -NH(CO)-; and are selected from halogen, hydroxy, nitro, cyano, amino, oxo, oxime, unsubstituted or substituted by R10 for the groups selected from linear or branched (C₁-C₈) alkyl, (C₃-C₇)cycloalkyl, alkylcycloalkyl, perhaloalkyl, perhalocycloalkyl, aryl, aralkyl, alkylaryl, alkylheteroaryl, aralkoxylalkyl,
25 perhaloaryl, alkylheterocycloalkyl, heterocycloalkyl, perhaloheterocycloalkyl, heteroaryl, heteroaralkyl, alkylaryl, perhaloheteroaryl, acyl, acyloxy, acylamino, alkylamino, arylamino, aralkoxy, alkoxyalkyl, alkylthio, thioalkyl, arylthio, thioaryl, carboxylic acid or its derivatives, or sulfonic acid or its derivatives wherein the groups / substituents present on same or adjacent atoms such as carbon or nitrogen,
30 together optionally and independently may form a five or a six or a seven membered ring optionally containing one or more double bonds and optionally containing one or more heteroatoms selected from O, N or S;

and wherein

R10 is independently selected from halogen, hydroxy, nitro, cyano, amino, oxo or oxime, and pharmaceutically usable hydrates and salts thereof;

5

2. A compound which is selected from the group consisting of :

1-[1-Oxo-2-((1-phenyl)-hydrazino)]ethyl-2-cyano pyrrolidine trifluoroacetate,

10 1-[1-Oxo-2-(1-hydrazino)]ethyl-2-cyano pyrrolidine trifluoroacetate,

3-[1-Oxo-2-((2-(1,1-dimethyl ethyl oxy carbonyl))hydrazino)]ethyl-4-cyano thiazolidine,

15 1-[1-Oxo-2-((2-(1,1-dimethylethoxy carbonyl))-1-phenyl hydrazino)]ethyl-2-cyano pyrrolidine,

1-[1-Oxo-2-((2-(1,1-dimethylethyl oxy carbonyl))hydrazino)]ethyl-2-cyano pyrrolidine,

20 1-[1-Oxo-2-((1-(4-nitrophenylmethyl))hydrazino)]ethyl-2-cyano pyrrolidine trifluoroacetate,

3-[1-Oxo-2-((1-phenyl)hydrazino)]ethyl-4-cyano thiazolidine trifluoroacetate,

25 1-[1-Oxo-2-(1-(2-methylpropyl)hydrazino)]ethyl-2-cyano pyrrolidine trifluoroacetate,

1-[1-Oxo-2-((1-phenylmethyl)hydrazino)]ethyl-2-cyano pyrrolidine trifluoroacetate,

1-[1-Oxo-2-((1-(1-methyl)ethyl)hydrazino)]ethyl-2-cyano pyrrolidine trifluoroacetate,

30

1-[1-Oxo-2-((2,2-diethyl)-hydrazino)]ethyl-2-cyano thiazolidine,

1-[1-Oxo-2-((1-ethyl)hydrazino)]ethyl-2-cyano pyrrolidine trifluoroacetate,

35 3-[1-Oxo-2-(1-hydrazino)]ethyl-4-cyano thiazolidine trifluoroacetate,

- 3-[1-Oxo-2-((1-phenylmethyl)hydrazino)]ethyl-4-cyano thiazolidine trifluoroacetate,
- 3-[1-Oxo-2-((1-(4-nitrophenylmethyl))hydrazino)]ethyl-4-cyano thiazolidine trifluoroacetate,
- 5 1-[1-Oxo-2-((1-Cyclopentyl)-hydrazino)]ethyl-2-cyano pyrrolidine trifluoroacetate,
- 3-[1-Oxo-2-((1-Cyclopentyl)-hydrazino)]ethyl-4-cyano thiazolidine trifluoroacetate,
- 10 1-[1-Oxo-2-((1-Cyclohexyl)-hydrazino)]ethyl-2-cyano pyrrolidine trifluoroacetate,
- 3-[1-Oxo-2-((1-Cyclohexyl)-hydrazino)]ethyl-4-cyano thiazolidine trifluoroacetate,
- 15 1-[1-Oxo-2-((1-methylpropyl)hydrazino)]ethyl-2-cyano pyrrolidine trifluoroacetate,
- 3-[1-Oxo-2-((1-methylpropyl)hydrazino)]ethyl-4-cyano thiazolidine trifluoroacetate,
- 1-[1-Oxo-2-((1-Phenyl sulphonyl)hydrazino)]ethyl-2-cyano pyrrolidine trifluoroacetate,
- 20 3-[1-Oxo-2-((1-(4-methyl)cyclohexyl)hydrazino)]ethyl-4-cyano thiazolidine trifluoroacetate,
- 1-[1-Oxo-2-((4-Methyl)cyclohexyl)hydrazino)]ethyl-2-cyano pyrrolidine trifluoroacetate,
- 25 1-[1-Oxo-2-(1-(2-Pyridyl)-hydrazino)]ethyl-2-cyano pyrrolidine bis-trifluoroacetate,
- 3-[1-Oxo-2- ((1-Cycloheptyl)-hydrazino)] ethyl-4-cyano thiazolidine trifluoroacetate,
- 30 3-[1-Oxo-2- ((1-(4-methyl) cyclohexyl)-hydrazino)] ethyl-4-cyano thiazolidine trifluoroacetate,
- 1-[1-Oxo-2- ((1-Cycloheptyl)-hydrazino)] ethyl-2-cyano pyrrolidine trifluoroacetate,
- 35 [4-Cyano-3-(1-isopropyl)hydrazino]carbonyl thiazolidine hydrochloride],

- [2-Cyano-1-(1-cyclohexyl hydrazino)carbonyl pyrrolidine hydrochloride],
- [4-Cyano-3-(1-cyclohexylhydrazino)carbonyl thiazolidine hydrochloride],
- 5 1-[1-Oxo-2- (2-cyclohexyl) hydrazino] ethyl-2-cyanopyrrolidine trifluoroacetate,
- [4-Cyano-3-(1-phenyl hydrazino) carbonyl thiazolidine trifluoroacetate],
- 3-[1-Oxo-2- (1-cyclohexyl-2-isopropyl) hydrazino] ethyl-4-cyanothiazolidine
- 10 hydrochloride,
- 1-[1-Oxo-2-(4-methylcyclohexyl)hydrazino]ethyl-2-cyanopyrrolidine trifluoroacetate,
- 1-[1-Oxo-2-(1-cyclohexyl-2-isopropyl)hydrazino]ethyl-2-cyano pyrrolidine,
- 15 1-[1-Oxo-2-(1-(4-methylcyclohexylmethyl) hydrazino)]ethyl-2-cyanopyrrolidine trifluoroacetate,
- 1-[1-Oxo-2- (4-chlorophenyl) hydrazino] ethyl-2-cyanopyrrolidine trifluoroacetate,
- 20 1-[1-Oxo-2-isopropyl-2-hydrazino] ethyl-2-cyano pyrrolidine trifluoroacetate,
- 3-[1-Oxo-2- (1-(4-methylcyclohexyl)-2-ethyl) hydrazino] ethyl-4-cyanothiazolidine trifluoroacetate,
- 25 3-[1-Oxo-2- (1-(4-morpholinocarbonyl) hydrazino) ethyl]-4-cyanothiazolidine trifluoroacetate,
- 3-[1-Oxo-2- (1-(4-methylcyclohexyl)-2-isopropyl) hydrazino] ethyl-4-
- 30 cyanothiazolidine trifluoroacetate,
- 1-[1-Oxo-2- [(1-cyclohexyl)-2-(2-cyano-1-pyrrolidino acetyl)] hydrazino] ethyl- 2-cyanopyrrolidine trifluoroacetate,
- 35 3-[1-Oxo-2- (1,2-bis- (2-(2-pyridyl) ethylaminocarbonyl) hydrazino)] ethyl-4-cyano thiazolidine bis trifluoroacetate,

- 3-[1-Oxo-2- (1-(4-tert-butyl cyclohexyl) hydrazino)] ethyl-4-cyanothiazolidine trifluoro acetate,
- 5 1-[1-Oxo-2- (1-tetralinyl) hydrazino] ethyl-2-cyanopyrrolidine trifluoroacetate,
- 3-[1-Oxo-2- (1-(4-tertbutylcyclohexyl) hydrazino)] ethyl-4-cyanothiazolidine trifluoroacetate,
- 10 1-[1-Oxo-2- (1-cyclohexyl)-2-(4-cyano-3-thiazolidino acetyl)] hydrazino] ethyl- 2-cyano pyrrolidine,
- 3-[1-Oxo-2- (1-isopropyl-4-piperidiny) hydrazino)] ethyl-4-cyano thiazolidine trifluoroacetate,
- 15 3-[1-Oxo-2- (1-(1-(4-cyanophenylmethyl)-piperidin-4-yl) hydrazino)] ethyl-4-cyanothiazolidine bis trifluoroacetate,
- 3-[1-Oxo-2-[1-(4-methylcyclohexyl)-2-(1-(3-pyridinylmethyl)-4-piperidiny)]hydrazino]ethyl-4-cyanothiazolidine,
- 20 3-[1-Oxo-2- [1-(4-methylcyclohexyl)-2-(1-isopropyl-4-piperidiny)] hydrazino] ethyl-4-cyanothiazolidine,
- 3-[1-Oxo-2- (1-(1-(4-methylphenylsulphonyl)-4-piperidiny)-hydrazino)] ethyl-4-cyanothiazolidine trifluoroacetate,
- 25 3-[1-Oxo-2- [1-methyl-2- (1-(4-methylphenylsulphonyl)-piperidin-4-yl)] hydrazino] ethyl-4-cyanothiazolidine trifluoroacetate,
- 30 3-[1-Oxo-2- (1-(1-(3-pyridinemethyl)-4-piperidiny) hydrazino)] ethyl-4-cyanothiazolidine tris trifluoroacetate,
- 3-[1-Oxo-2- [1-methyl-2- (1-(4-cyanophenylmethyl) piperidin-4-yl)] hydrazino]ethyl-4-cyanothiazolidine bis trifluoroacetate,
- 35 3-[1-Oxo-2- [1-methyl-2- (1-(3-pyridinylmethyl)-piperidin-4-yl)] hydrazino] ethyl-4-cyanothiazolidine tris trifluoroacetate,

- 3-[1-Oxo-2-(1-(4-n propylcyclohexyl) hydrazino)] ethyl-4-cyanothiazolidine trifluoroacetate,
- 3-[1-Oxo-2-(1-(4-nitrophenylmethyl)-piperidin-4-yl) hydrazino] ethyl-4-cyanothiazolidine trifluoroacetate,
- 5 3-[1-Oxo-2-[1-(1-(4-chlorophenylsulphonyl)-piperidin-4-yl)] hydrazino] ethyl- 4-cyanothiazolidine trifluoroacetate,
- 3-[1-Oxo-2-(1-(1-norcamphoranyl) hydrazino)] ethyl-4-cyanothiazolidine trifluoroacetate,
- 10 3-[1-Oxo-2-(1-(4-n propylcyclohexyl) hydrazino)] ethyl-4- cyanothiazolidine trifluoroacetate,
- 15 3-[1-Oxo-2-[1-(1-(4-methylcyclohexyl carbonyl)-piperidin-4-yl)] hydrazino]ethyl-4-cyanothiazolidine trifluoroacetate,
- 3-[1-Oxo-2-(1-(1-acetyl)-piperidin-4-yl)hydrazino] ethyl-4-cyanothiazolidine trifluoroacetate,
- 20 1,1-Dioxo-3-[1-oxo-2-(1-(4-methylcyclohexyl) hydrazino)] ethyl-4- cyanothiazolidine trifluoroacetate,
- 3-[1-Oxo-2-(1-methyl-2-(4-methylcyclohexyl) hydrazino)] ethyl-4-cyanothiazolidine,
- 25 3-[1-Oxo-2-(1-methyl-2-(4-methylcyclohexyl) hydrazino)] ethyl-4-cyanothiazolidine,
- 3-[1-Oxo-2-(1-(1-(2,3-dichlorophenyl carbonyl)-piperidin-4-yl) hydrazino)] ethyl-4-cyanothiazolidine trifluoroacetate,
- 30 3-[1-Oxo-2-[1-methyl-2-(1-(4-chlorophenylsulphonyl)-piperidin-4-yl)]-hydrazino] ethyl-4-cyanothiazolidine,
- 3-[1-Oxo-2-(1-(4-piperidinyl) hydrazino)]ethyl-4-cyanothiazolidine bis trifluoroacetate,
- 35 [1-Oxo-2-(1-(1-(4-chlorophenylsulphonyl)-piperidin-4-yl)-hydrazino)] ethyl -2-cyanopyrrolidine trifluoroacetate,

- 3-[1-Oxo-2-(1-(4-methylcyclohexyl)-2-acetyl) hydrazino]ethyl-4- cyanothiazolidine,
- 3-[1-Oxo-2-(1-(1-adamantanyl) hydrazino)] ethyl-4-cyanothiazolidine trifluoroacetate,
- 5 3-[1-Oxo-2-(1-(1-(tert-butyl carbonyl)-piperidin-4-yl) hydrazino)] ethyl-4-
cyanothiazolidine trifluoroacetate,
- 3-[1-Oxo-2-(1-(1-(5-trifluoromethyl-2-pyridinyl)-piperidin-4-yl) hydrazino)] ethyl-4-
cyano thiazolidine bis trifluoroacetate,
- 10 3-[1-Oxo-2-(1-(1-methanesulphonylamino-4-cyclohexyl) hydrazino)] ethyl-4-
cyanothiazolidine trifluoroacetate,
- 3-[1-Oxo-2- (1-(3,3,5-trimethyl cyclohexyl)-hydrazino)] ethyl-4- cyanothiazolidine
15 trifluoroacetate,
- 3-[1-Oxo-2-(1-isopropyl-2-ethyl)-hydrazino]-ethyl-4-cyanothiazolidine
trifluoroacetate,
- 20 3-[1-Oxo-2-[1-(1-phenylmethyl-piperidin-4-yl)]-hydrazino]-ethyl-4-cyanothiazolidine
trifluoroacetate,
- 3-[1-Oxo-2-(1-(1-(4-chlorophenyl sulphonylamino-4-cyclohexyl) hydrazino)]ethyl-4-
cyanothiazolidine trifluoroacetate,
- 25 3-[1-Oxo-2-(1-(1-methanesulphonylamino-4-cyclohexyl)-2-isopropyl) hydrazino]
ethyl-4-cyanothiazolidine trifluoroacetate,
- 3-[1-oxo-2-[1-(1(morpholinocarbonyl)-piperidin-4-yl)]hydrazino]ethyl-4-cyano-
30 thiazolidine trifluoroacetate,
- 3-[1-oxo-2-[1-(1-(methylsulphonyl)-piperidin-4-yl)]hydrazino]ethyl-4-
cyanothiazolidine trifluoroacetate,
- 35 3-[1-oxo-2-[1-(1(methylsulphonyl)-piperidin-4-yl)-2-isopropyl]hydrazino]ethyl-4-
cyanothiazolidine trifluoroacetate,

- 3-[1-oxo-2-[1-(1-(methylsulphonyl)-piperidin-4-yl)-2-ethyl]hydrazino]ethyl-4-cyanothiazolidine trifluoroacetate,
- 5 3-[1-oxo-2-[1-(1-(morpholinocarbonyl)-piperidin-4-yl)-2-ethyl]hydrazino]ethyl-4-cyanothiazolidine trifluoroacetate,
- 10 3-[1-oxo-2-[1-(1-(N-ethylmethylaminocarbonyl)-piperidin-4-yl)]hydrazino]ethyl-4-cyanothiazolidine trifluoroacetate,
- 15 3-[1-oxo-2-[1-(1-(4-methoxyphenylsulphonyl)aminocyclohexan-4-yl)] hydrazino]ethyl-4-cyanothiazolidine trifluoroacetate,
- 20 3-[1-oxo-2-[1-(1-(4-fluorobenzyl)aminocyclohexan-4-yl)]hydrazino]ethyl-4-cyanothiazolidine bis-trifluoroacetate,
- 25 3-[1-oxo-2-[(1-(1-(2-oxo-2-(5-chloropyridin-2-yl)aminoethyl)piperidin-4-yl)]hydrazino]ethyl-4-cyanothiazolidine tris-trifluoroacetate,
- 30 3-[1-oxo-2-[1-(1-(trimethyl acetamido)cyclohexan-4-yl)]hydrazino]ethyl-4-cyanothiazolidine trifluoroacetate,
- 35 3-[1-oxo-2-[1-(1-(2-oxo-2-(4-cyanophenyl)aminoethyl)piperidin-4-yl)] hydrazino]ethyl-4-cyanothiazolidine bis-trifluoroacetate,

- 3-[1-oxo-2-[1-(4-fluorobenzoyl)aminocyclohexan-4-yl]]hydrazino] ethyl-4-cyanothiazolidine trifluoroacetate,
- 5 3-[1-oxo-2-[1-(1-(2-oxo-2-(5-chloropyridin-2-yl)aminoethyl)piperidin-4-yl))-2-ethylhydrazino] ethyl-4-cyanothiazolidine tris-hydrochloride,
- 3-[1-oxo-2-[1-(1-(2-oxo-2(4-trifluorophenyl)aminoethyl)piperidin-4-yl))] hydrazino] ethyl-4-cyanothiazolidine bis-trifluoroacetate,
- 10 3-[1-oxo-2-[1-(1-(2-oxo-2(-adamant-1-yl)amino ethyl)piperidin-4-yl))] hydrazino] ethyl-4-cyanothiazolidine bis-trifluoroacetate,
- 3-[1-oxo-2-[1-(1-(2-oxo-2(2,3-dihydrobenzo(1,4)dioxan-6-yl)aminoethyl) piperidin-4-yl))] hydrazino] ethyl-4-cyano-thiazolidine bis-trifluoroacetate,
- 15 3-[1-oxo-2-[1-(1-(2-oxo-2(4-chlorophenyl)aminoethyl)piperidin-4-yl))] hydrazino] ethyl-4-cyanothiazolidine bis-trifluoroacetate,
- 3[2-oxo-2-[1-(1-(2-oxo-2(pyrimidin-2-yl)aminoethyl)piperidin-4-yl))] hydrazino]ethyl -
- 20 4-cyanothiazolidine tris-trifluoroacetate,
- 3-[1-oxo-2-[1-(1-(2-oxo-2(morpholin-4-yl)ethyl)piperidin-4-yl))] hydrazino]ethyl- 4-cyanothiazolidine bis-trifluoroacetate,
- 25 3[1-oxo-2-[1-(1-(2-oxo-2(cyclopropyl)aminoethyl)piperidin-4-yl))]hydrazino] ethyl-4-cyanothiazolidine bis-trifluoroacetate,
- 3-[1-oxo-2-[1-(1-(2-cyanobiphenyl-4-yl)methyl)piperidine-4-yl]]hydrazino]ethyl-4-cyanothiazolidine bis-trifluoroacetate,
- 30 3-[1-oxo-2-[1-(1-(1-oxo-2-(morpholin-4-yl)ethyl)piperidin-4-yl))] hydrazino] ethyl-4-cyanothiazolidine bis-trifluoroacetate,
- 35 3-[1-oxo-2-[1-(4-(2-oxo-2-(5-chloropyridin-2-yl)aminoethyl)amino cyclohex-1-yl))]hydrazino]ethyl-4-cyanothiazolidine tris-trifluoroacetate,

3-[1-oxo-2-[1-(4-(2-oxo-2-(4-cyanophenyl)aminoethyl)aminocyclohex-1-yl)]hydrazino]ethyl-4-cyanothiazolidine bis-trifluoroacetate,

5 3-[1-oxo-2-[1-(4-(2-oxo-2-(4-chlorophenyl)aminoethyl)aminocyclohex-1-yl)]hydrazino]ethyl-4-cyanothiazolidine bis-trifluoroacetate,

3-[1-oxo-2-(1-(1-methanesulphonylamino-4-cyclohexyl)hydrazino)]ethyl-4-cyanothiazolidine hydrochloride and

10 3-[1-oxo-2-[1-(1-(2-oxo-2-(5-chloropyridin-2-yl)aminoethyl)piperidine-4-yl)]hydrazino]ethyl-4-cyanothiazolidine trihydrochloride,

or derivatives, analogs, tautomeric forms, stereoisomers, polymorphs, pharmaceutically acceptable salts and pharmaceutically acceptable solvates thereof.

15

3. A pharmaceutical composition comprising compound of formula (1) as defined in claim 1, its derivatives, analogs, tautomeric forms, stereoisomers, polymorphs, pharmaceutically acceptable salts and pharmaceutically acceptable solvates in association with a pharmaceutically acceptable carrier, diluent or excipient.

20

4. A pharmaceutical composition comprising a compound as defined in claim 2 or derivatives, analogs, tautomeric forms, stereoisomers, polymorphs, pharmaceutically acceptable salts and pharmaceutically acceptable solvates thereof in association with a pharmaceutically acceptable carrier, diluent or excipient.

25

5. A method of inhibiting the enzyme DPP-IV in the body tissue of a mammal including human being which comprises administering an effective amount of compound of general formula I as defined in claim 1 or derivatives, analogs, tautomeric forms, stereoisomers, polymorphs, pharmaceutically acceptable salts and pharmaceutically acceptable solvates thereof in association with a pharmaceutically acceptable carrier, diluent or excipient to a mammal in need thereof.

30

6. A method of inhibiting the enzyme DPP-IV in the body tissue of a mammal including human being which comprises administering an effective amount of a compound as defined in claim 2 or derivatives, analogs, tautomeric forms, stereoisomers, polymorphs, pharmaceutically acceptable salts and pharmaceutically

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acceptable solvates thereof in association with a pharmaceutically acceptable carrier, diluent or excipient to a mammal in need thereof.

5 7. A method of scavenging free radicals from the body tissue of a mammal including human being which comprises administering an effective amount of compound of general formula I as defined in claim 1 or derivatives, analogs, tautomeric forms, stereoisomers, polymorphs, pharmaceutically acceptable salts and pharmaceutically acceptable solvates thereof in association with a pharmaceutically acceptable carrier, diluent or excipient to a mammal in need thereof.

10 8. A method of scavenging free radicals from the body tissue of a mammal including human being which comprises administering an effective amount of compound as defined in claim 2 or derivatives, analogs, tautomeric forms, stereoisomers, polymorphs, pharmaceutically acceptable salts and pharmaceutically acceptable solvates thereof in association with a pharmaceutically acceptable carrier, diluent or excipient to a mammal in need thereof.

15 9. A method of treatment and/or prophylaxis of diabetes in a mammal including human being which comprises administering an effective amount of compound of general formula I as defined in claim 1 or derivatives, analogs, tautomeric forms, stereoisomers, polymorphs, pharmaceutically acceptable salts and pharmaceutically acceptable solvates thereof in association with a pharmaceutically acceptable carrier, diluent or excipient to a mammal in need thereof.

20 10. A method of treatment and/or prophylaxis of diabetes in a mammal including human being which comprises administering an effective amount of compound as defined in claim 2 or derivatives, analogs, tautomeric forms, stereoisomers, polymorphs, pharmaceutically acceptable salts and pharmaceutically acceptable solvates thereof in association with a pharmaceutically acceptable carrier, diluent or excipient to a mammal in need thereof.

25 11. A method of treatment and/or prophylaxis of disorders associated with DPP-IV in a mammal including human being which comprises administering an effective amount of a compound of general formula I as defined in claim 1 or derivatives, analogs, tautomeric forms, stereoisomers, polymorphs, pharmaceutically acceptable salts and pharmaceutically acceptable solvates thereof in association with a

pharmaceutically acceptable carrier, diluent or excipient to a mammal in need thereof, wherein the said disorders are selected from the group consisting of:

- 5 a) Cushing's syndrome;
- b) Hyperthyroidism;
- c) Obesity;
- d) Hyperglucagonemia;
- e) Diseases including ulcers and HIV infection;
- f) Disorders related to increased gastric emptying, acid secretion and hunger;
- 10 g) Autoimmune disorders including multiple sclerosis;
- h) Rheumatoid arthritis;
- i) Grave's disease;
- j) Diarrhoea;
- k) Mucosal regeneration in patients with intestinal disease;
- 15 l) Growth hormone deficiency;
- m) Neurological and neuropsychological disorders; and
- n) Cancers and tumors.

12. A method of treatment and/or prophylaxis of disorders associated with DPP-IV
20 in a mammal including human being which comprises administering an effective amount of a compound as defined in claim 2 or derivatives, analogs, tautomeric forms, stereoisomers, polymorphs, pharmaceutically acceptable salts and pharmaceutically acceptable solvates thereof in association with a pharmaceutically acceptable carrier, diluent or excipient to mammal in need thereof, wherein the said disorders are selected
25 from the group consisting of:

- a) Cushing's syndrome;
- b) Hyperthyroidism;
- c) Obesity;
- 30 d) Hyperglucagonemia;
- e) Diseases including ulcers and HIV infection;
- f) Disorders related to increased gastric emptying, acid secretion and hunger;
- g) Autoimmune disorders including multiple sclerosis;
- h) Rheumatoid arthritis;

- i) Grave's disease;
- j) Diarrhoea;
- k) Mucosal regeneration in patients with intestinal disease;
- l) Growth hormone deficiency;
- 5 m) Neurological and neuropsychological disorders; and
- n) Cancers and tumors.

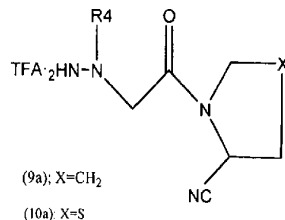
13. A method of treating a disease condition caused by accumulation of free radicals
in the body cells of a mammal including human being which comprises administering
10 an effective amount of a compound of general formula I as defined in claim 1 or
derivatives, analogs, tautomeric forms, stereoisomers, polymorphs, pharmaceutically
acceptable salts and pharmaceutically acceptable solvates thereof in association with a
pharmaceutically acceptable carrier, diluent or excipient to a mammal in need thereof,
wherein the said disease condition is selected from the group consisting of (a)
15 Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Motor Neuron Disease
or Prion Disease, (b) Diabetes or Diabetic Vascular Complications, (c) Intestinal
Ischemia, Radiation Enteritis, Inflammatory Bowel Disease, Gastric or Colorectal
Cancers, (d) Alcoholic Liver Disease or Chronic Hepatitis C, (e) Lung Cancer,
Colorectal Cancer, Cervical Cancer, Breast Cancer or Malignant Melanoma, (f)
20 Atherosclerosis, Myocardial Infarction, Ischemic Stroke or Endothelial Dysfunction, (g)
Cataract formation or Macular degeneration, (h) HIV Diseases, (i) Chronic Obstructive
Pulmonary Diseases or Asthma and (j) Glomerulonephritis or Acute Renal Failure.

14. A method of treating a disease condition caused by accumulation of free radicals
25 in the body cells of a mammal including human being which comprises administering
an effective amount of a compound as defined in claim 2 or derivatives, analogs,
tautomeric forms, stereoisomers, polymorphs, pharmaceutically acceptable salts and
pharmaceutically acceptable solvates thereof in association with a pharmaceutically
acceptable carrier, diluent or excipient to a mammal in need thereof, wherein the said
30 disease condition is selected from the group consisting of (a) Alzheimer's Disease,
Parkinson's Disease, Huntington's Disease, Motor Neuron Disease or Prion Disease, (b)
Diabetes or Diabetic Vascular Complications, (c) Intestinal Ischemia, Radiation
Enteritis, Inflammatory Bowel Disease, Gastric or Colorectal Cancers, (d) Alcoholic
Liver Disease or Chronic Hepatitis C, (e) Lung Cancer, Colorectal Cancer, Cervical
35 Cancer, Breast Cancer or Malignant Melanoma, (f) Atherosclerosis, Myocardial
Infarction, Ischemic Stroke or Endothelial Dysfunction, (g) Cataract formation or

Macular degeneration, (h) HIV Diseases, (i) Chronic Obstructive Pulmonary Diseases or Asthma and (j) Glomerulonephritis or Acute Renal Failure.

15. A process for preparation of compounds of formula 9a and 10a

5



wherein

10 R4 has the same meaning as defined in claim 1 and "Boc" in process step (a) below stands for "tertiary Butyloxy Carbonyl",

comprising the steps of :

15 a) reacting chloroacyl-2-cyanopyrrolidine or chloroacyl-4-cyanothiazolidine with appropriate N-substituted Boc-carbazate using aprotic solvents in presence of a base at 40-110°C for 8-50 hrs , wherein N-substituted Boc-carbazate obtained from alkyl halide and

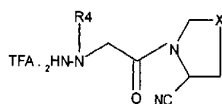
20 b) deprotecting resulting coupled product using trifluoroacetic acid at 5-30°C for 0.25-2 hrs to obtain the desired product.

16. The process as claimed in claim 15, wherein in step (a) of the process said aprotic solvent used is selected from acetonitrile, tetrahydrofuran, dimethylformamide or dioxane and said base used is selected from tertiary amine or alkali carbonate.

25

17. The process as claimed in claim 16 wherein in step (a) of the process said aprotic solvent used is tetrahydrofuran and said base used is potassium carbonate in presence of catalytic amount of potassium iodide.

18. A process for preparation of compounds of formula 13 and 14



(13); X=CH₂
(14); X=S

- 5 wherein

R4 has the same meaning as defined in claim 1 and "Boc" in process step (a) below stands for "tertiary Butyloxy Carbonyl",

- 10 comprising the steps of :

a) reacting chloroacyl-2-cyanopyrrolidine or chloroacyl-4-cyanothiazolidine with appropriate N-substituted Boc-carbazate using aprotic solvents in presence of a base at 40-110°C for 8-50 hrs , wherein said N-substituted Boc-carbazate is obtained from aldehyde and ketone and

15

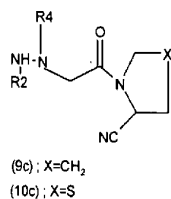
b) deprotecting resulting coupled product using trifluoroacetic acid at 5-30°C for 0.25-2 hrs to obtain the desired product.

- 20 19. The process as claimed in claim 18, wherein in step (a) of the process said aprotic solvent used is selected from acetonitrile, tetrahydrofuran, dimethylformamide or dioxane and said base used is selected from tertiary amine or alkali carbonate.

- 25 20. The process as claimed in claim 19 wherein in step (a) of the process said aprotic solvent used is tetrahydrofuran and said base used is potassium carbonate in presence of catalytic amount of potassium iodide.

21. A process for preparation of compounds of formula 9c and 10c

30

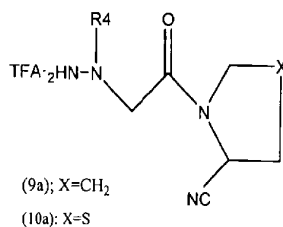


wherein

- 5 R4 and R2 have the same meaning as defined in claim 1,
comprising the steps of :

a) reacting N-1-substituted hydrazinoacyl derivative of cyanothiazolidine (formula-9a) or cyanopyrrolidine (formula-10a).

10



with acid chlorides/sulfonyl chloride in presence of a base in an aprotic solvent at 0-30°C for 1-8 hrs and

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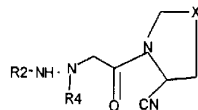
b) isolating compounds of formula 9c or 10c thus produced.

22. The process as claimed in claim 21, wherein in step (a) of the process said base used is selected from tertiaryamine or pyridine and said aprotic solvent used is selected from acetonitrile tetrahydrofuran, dimethylformamide, dioxane, dichloromethane or chloroform.

23. The process as claimed in claim 22 wherein in step (a) of the process said base used is triethylamine and aprotic solvent used is tetrahydrofuran .

25

24. A process for preparation of compounds of formula 9b and 10b



(9b): X=CH₂
 (10b): X=S

wherein

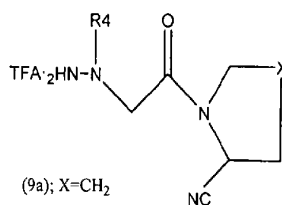
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R4 and R2 have the same meaning as defined in claim 1,

comprising the steps of :

10

a) reacting a substituted aldehyde or ketone required to form R2 as defined in Claim 1 with compound of formula 9a and 10a



(9a); X=CH₂
 (10a); X=S

15

at 20-70°C for 0.5-6 hrs in alcoholic solvents to give rise to corresponding Schiff base and

20

b) reduction of the Schiff base using metal hydride in presence of catalytic amount of titanium tetrachloride in alcoholic solvent to give the corresponding target compound.

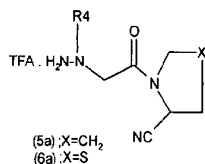
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The process as claimed in claim 24, wherein in step (a) of the process said alcoholic solvent used is selected from methanol, ethanol or isopropanol and in step (b) of the process said metal hydride used is selected from sodium cyanoborohydride or sodium borohydride.

26. The process as claimed in claim 24 wherein in step (a) of the process said alcoholic solvent is methanol and said schiff base used is sodium cyanoborohydride.

27. A process for preparation of compounds of formula 5a and 6a

5



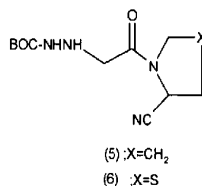
wherein

10 R4 has the same meaning as defined in claim 1 and "Boc" in process step (a) below stands for "tertiary Butyloxy Carbonyl",

comprising the steps of :

15 a) reacting chloroacyl-2-cyanopyrrolidine or chloroacyl-4-cyanothiazolidine with Boc-carbazate using aprotic solvents in presence of a base with catalytic amount of potassium iodide at 40-110°C for 6-50 hrs to give compound of formula 5 or 6 respectively,

20



b) reacting compound of formula 5 or 6 from step 1 above, with appropriate carbonyl chloride or acid chloride or sulphonyl chloride in presence of a base in an aprotic solvent at 0-30°C for 0.5-6 hrs and

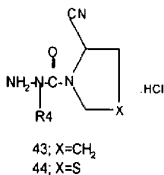
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c) deprotecting compounds obtained in step (b) using trifluoroacetic acid at 0-30°C for 0.25-2 hrs to give the corresponding target compound of formula 5a or 6a respectively.

5 28. The process as claimed in claim 27, wherein in step (a) of the process said aprotic solvent used is selected from acetonitrile, tetrahydrofuran, dimethylformamide or dioxane and the said base used is selected from alkali or alkali earth metal carbonates or tertiaryamine and in step (b) of the process the said base used is selected from tertiaryamine, pyridine and said aprotic solvent is selected from acetonitrile,
10 tetrahydrofuran, dimethylformamide or dioxane.

29. The process as claimed in claim 28 wherein in step (a) of the process said aprotic solvent used is tetrahydrofuron and said base used is potassium carbonate in presence of catalytic amount of potassium iodide and in step (b) of the process said base
15 used is triethylamine and said aprotic solvent used is tetrahydrofuran.

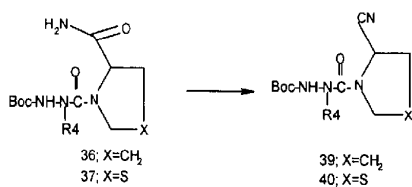
30. A process for preparation of compounds of formula 43 and 44



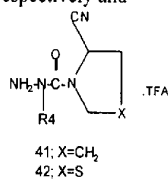
20 wherein

R4 has the same meaning as defined in claim 1, comprising steps of :

25 a) reacting tert-butyloxycarbonyl protected formula 36 or 37 with trifluoroacetic anhydride in aprotic solvent at 10-40°C for 2-4 hrs to give corresponding cyano compound of formula 39 or 40,



5 b) deprotecting compounds obtained in step (a) using trifluoroacetic acid in an aprotic solvent at 5 – 40°C for 0.25 - 2 hrs to give compound of formula no. 41 or 42 as trifluoroacetate salt respectively and



10 c) purifying the compound so obtained by neutralizing with an aqueous alkali followed by purification of free base thus obtained by column chromatography and then converting the product thus obtained into a pharmaceutically acceptable hydrochloride salt by treating with methanolic hydrochloride at 0 – 20°C for 0.5 - 2 hrs.

15 31. The process as claimed in claim 30, wherein in step (a) of the process the said aprotic solvent as used is selected from acetonitrile, tetrahydrofuran, dimethylformamide, dioxane, dichloromethane, diethyl ether or chloroform, in step (b) of the process the said aprotic solvent as used is selected from dichloromethane, diethylether, dioxane, tetrahydrofuran, acetonitrile, and in step (c) of the process the said aqueous alkali solvent as used is aqueous sodium bicarbonate and wherein steps(a) 20 and (b) of the process are carried out at 25^oC and 20^oC respectively.

32. The process as claimed in claim 31 wherein in step (a) and (b) the said aprotic solvent is tetrahydrofuran.

25 33. A method of inhibiting enzyme DPP-IV in the body cell of mammal including human beings to enhance level of active GLP I which comprises administering an effective amount of a compound of formula I as defined in claim 1 or derivatives, analogs, tautomeric forms, stereoisomers, polymorphs, pharmaceutically acceptable

salts and pharmaceutically acceptable solvates thereof in association with a pharmaceutically acceptable carrier, diluent or excipient to mammal in need thereof.

34. A method of inhibiting enzyme DPP-IV in the body cell of mammal including human beings to enhance level of active GLP I which comprises administering an effective amount of a compound as defined in claim 2 or derivatives, analogs, tautomeric forms, stereoisomers, polymorphs, pharmaceutically acceptable salts and pharmaceutically acceptable solvates thereof in association with a pharmaceutically acceptable carrier, diluent or excipient to mammal in need thereof.
35. Use of a compound as defined in claim 1 or derivatives, analogs, tautomeric forms, stereoisomers, polymorphs, pharmaceutically acceptable salts and pharmaceutically acceptable solvates thereof for manufacture of medicament useful for the treatment of diabetes in a mammal including human being.
36. Use of a compound as defined in claim 2 or derivatives, analogs, tautomeric forms, stereoisomers, polymorphs, pharmaceutically acceptable salts and pharmaceutically acceptable solvates thereof for the manufacture of a medicament useful for the treatment of diabetes in a mammal including human being.
37. Use of compound as defined in claim 1 or derivatives, analogs, tautomeric forms, stereoisomers, polymorphs, pharmaceutically acceptable salts and pharmaceutically acceptable solvates thereof in the manufacture of a medicament useful in the treatment of a mammal including human being in disease conditions caused by accumulation of free radicals in the body cell of a mammal including human being.
38. Use of compound as claimed in claim 2 or derivatives, analogs, tautomeric forms, stereoisomers, polymorphs, pharmaceutically acceptable salts and pharmaceutically acceptable solvates thereof in the manufacture of a medicament useful in the treatment of a mammal including human being in disease conditions caused by accumulation of free radicals in the body cell of a mammal including human being.
39. Use of compound of general formula I as defined in claim 1 or derivatives, analogues, tautomeric forms, stereoisomers, polymorphs, pharmaceutically acceptable salts and pharmaceutically acceptable solvates thereof in the manufacture of a

medicament useful in the treatment and/or prophylaxis of disorders associated with DPP-IV in a mammal including human being.

5 40. Use of compound as defined in claim 2 or derivatives, analogues, tautomeric forms, stereoisomers, polymorphs, pharmaceutically acceptable salts and pharmaceutically acceptable solvates thereof in the manufacture of a medicament useful in the treatment and/or prophylaxis of disorders associated with DPP-IV in a mammal including human being.

10 41. Use of a compound of formula I as defined in claim 1 or derivatives, analogues, tautomeric forms, stereoisomers, polymorphs, pharmaceutically acceptable salts and pharmaceutically acceptable solvates thereof in the manufacture of a medicament useful in inhibiting the enzyme DPP-IV in the body cells of a mammal including human beings to enhance level of active GLP-I.

15 42. Use of a compound as defined in claim 2 or derivatives, analogues, tautomeric forms, stereoisomers, polymorphs, pharmaceutically acceptable salts and pharmaceutically acceptable solvates thereof in inhibiting the enzyme DPP-IV in the body cells of a mammal including human beings to enhance level of active GLP-I.

20 43. Compounds represented by general formula I, pharmaceutical compositions containing them, methods or uses involving them or processes for their preparation substantially as hereinbefore described with reference to the accompanying examples and/or drawings.

25 Dated this 3rd day of August 2006
TORRENT PHARMACEUTICALS LTD

By their Patent Attorneys
GRIFFITH HACK

30 Fellows Institute of Patent and
Trade Mark Attorneys of Australia

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Effect of Compound No. 95 on AUC of glucose excursion after OGTT (glucose 1gm/kg) in nSTZ induced diabetic rat

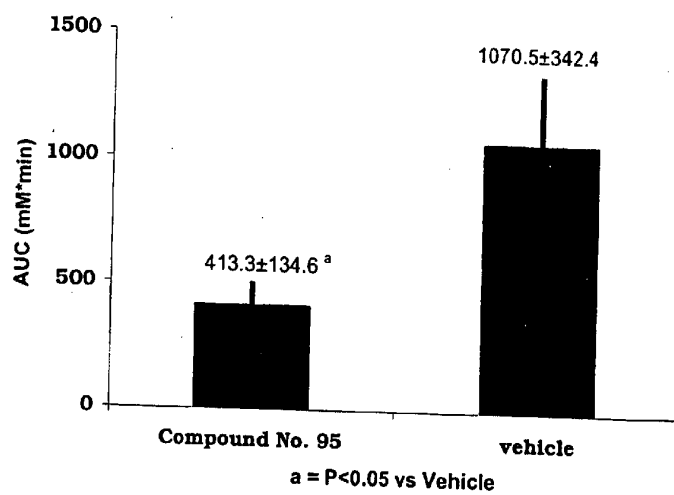


Fig. 1

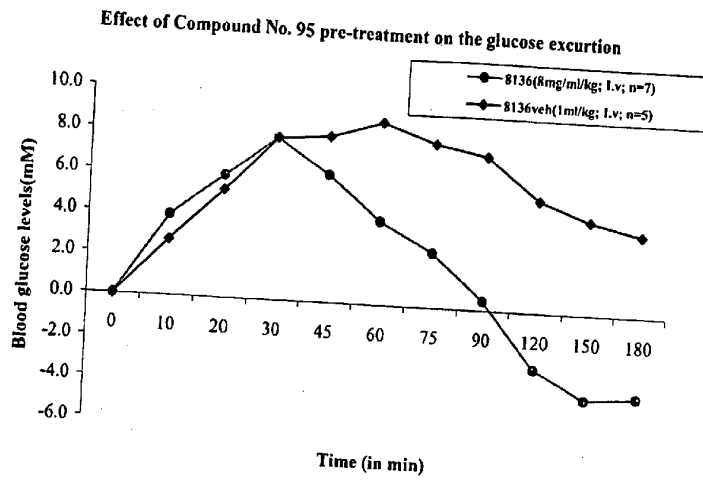


Fig. 2