Medicinal chemistry

Aboul-Enein and El Rashedy. Med chem 2015, 5:7
DOI: 10.4172/2161-0444.1000280

Review Article Open Access

Benzimidazole Derivatives as Antidiabetic Agents

Hassan Y Aboul-Enein[1]* and Ahemd A El Rashedy[2]

[1]Pharmaceutical and Medicinal Chemistry Department, Pharmaceutical and Drug Industries Research Division, National Research Centre, Dokki, Cairo 12311, Egypt
[2]Natural and Microbial Department, National Research Centre, Dokki, Giza 12622, Egypt

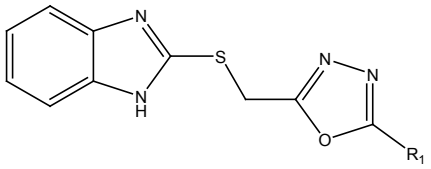
Abstract

Benzimidazole is an important pharmacophore which was included in several biologically active compounds resulted in the development of several classes of drugs. This review discusses the synthesis of benzimidazole derivatives as a target agents for antidiabetic by different mechanism such as peroxisome proliferator – activated receptor α transcriptional activity, glycosidases receptor, dipeptidyl peptidase IV, glucokinase, human glucagon receptor (hGCGR) antagonist , aldose reductase enzyme and stearoyl- CoA desaturase .

Keywords: Benzimidazole derivatives; Antidiabetic agents; Pharmacological activity; Mechanism of action; Synthesis

Diabetes mellitus (DM) is a chronic metabolic disease which result due to no production of insulin causing type 1 DM or due to partial and/or insufficient production of insulin causing type 2 DM. Furthermore , insulin resistance cause hyperglycemia and diabetes due to the inability of the cells to use insulin properly and efficiently. Some to the serious complication of diabetes include nephropathy, retinopathy, neuropathy, foot ulcers among other symptoms [1]. One of the most widely used antidiabetic agents are the sulfonylureas which act through the stimulation of the pancreatic β-cells for the secretion of insulin. Another class of antidiabetic agents are thiazolidinediones e.g. glibenclamide, ciglitazone and troglitazone. These drugs stimulate insulin secretion and therefore are effective in treatment of in a type-2 diabetic patients. Metformin which belongs to the biguanides group which enhance insulin action at the post receptor level in peripheral tissues such as muscle [2].

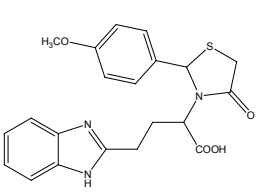
"Shingalapur et al. [3] synthesized a series of 1,3,4-oxadiazoles derivatives containing 2-mercapto benzimidazole moiety and screened for in vivo antidiabetic activity using oral glucose tolerance test (OGTT)". Some of these derivatives showed improved reduction in blood–glucose levels compared with glibenclamide (Scheme 1).

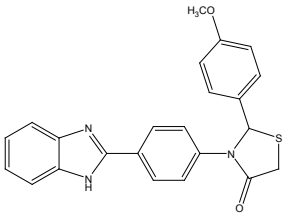


1

R= 4-OH,2-OH,Fufurayl, naphthalen-2-ol

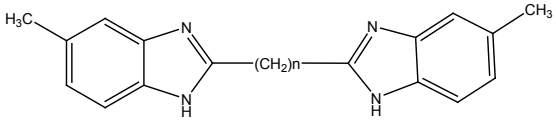
Some new benzimidazole containing thiazolidinone 2, 3 were also reported for anti-diabetic activity. Both compounds were found to be more potent in hyperglycemic and normoglycemic models at a dose of 50 mg/kg [4].





3

A series of bis-benzimidazole derivatives were synthesized and found that compound 4 has showed significant antidiabetic activity when compared to glibenclamide as standard drug [5] (Scheme 2).

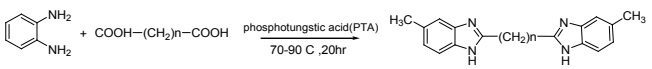


n=2, 3,6 ,7

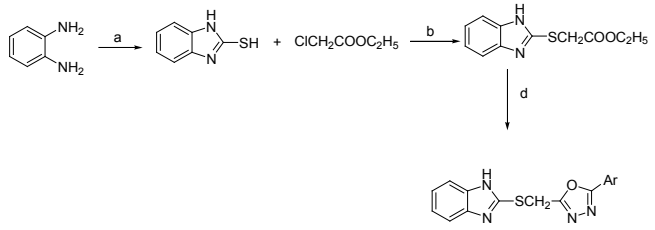
4

Type 2 diabetes mellitus (T2DM) is characterized by defects in insulin secretion and insulin sensitivity [6,7]. Insulin resistance by itself will not result in T2DM unless β-cell secretion of insulin is decreased. Based on the Centers for Disease Control and Prevention National Diabetes Fact Sheet in 2007 [8], there were 23.6 million Americans with diabetes, of whom 90% to 95% have T2DM.

Peroxisome Proliferator Activated Receptors (PPARs) act as regulators of lipid and glucose metabolism. This resulted in the development of synthetic drugs which represent a potential tool for



Scheme 2: Benzimidazole as Peroxisome proliferator



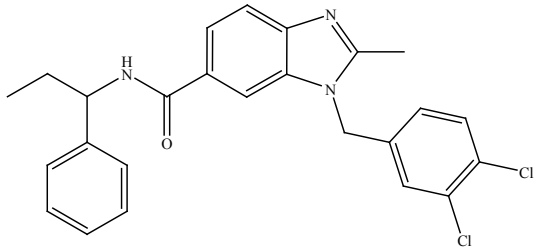
Scheme 1: Reagent and condition: (a) CS_2, NaOH, EtOH; (b) EtOH (c) EtOH, $NH_2NH_2.H_2O$ (d) Ar -COOH , $POCl_3$

***Corresponding author:** Hassan Y. Aboul-Enein, Pharmaceutical and Medicinal Chemistry Department, National Research Centre, Dokki, Cairo 12311, Egypt, Tel: +201003678948; Fax: +20233370931; E-mail: haboulenein@yahoo.com

Received June 01, 2015; **Accepted** July 17, 2015; **Published** July 25, 2015

Citation: Aboul-Enein HY, El Rashedy AA (2015) Benzimidazole Derivatives as Antidiabetic Agents. Med chem 5: 318-325. doi: 10.4172/2161-0444.1000280

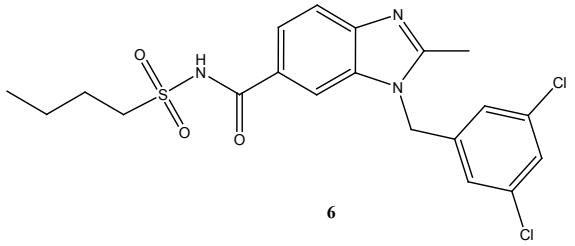
therapeutic intervention in type 2 diabetes mellitus (T2DM). PPARα 5 is ligand belonging to the nuclear receptor superfamily. The target genes of PPARα are group of genes that participate in various aspects of lipid catabolism such as (a) fatty acid uptake through membranes, (b) fatty acid binding in cells, (c) fatty acid oxidation in microsomes, peroxisomes and mitochondria, and (d) lipoprotein assembly and transportation [9]. The significance of PPARα in physiological and pathophysiological states is the fact that they are considered as a molecular targets for the lipid-lowering fibrate drugs and insulin-sensitizing thiazolidinedione (TZD), respectively [10] .



5

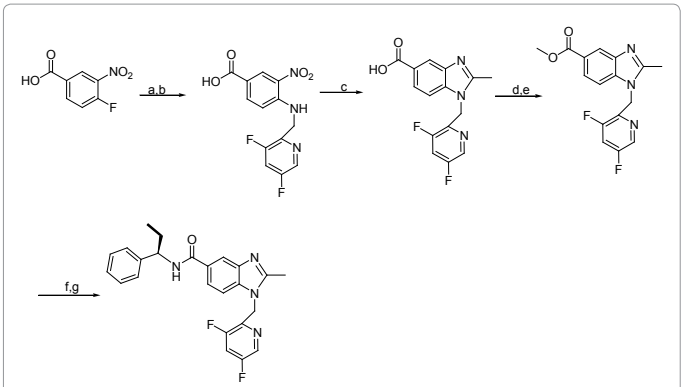
PPARα

"Minoura et al found that 3-(2,4-dichlorobenzyl)-2methyl-N-(pentylsulphonyl)-3H-benzimidazole-5-carboxamide,6, improve insulin resistance in mammalian animal model through activation of PPAR-GAMA (Peroxisome proliferator-activated receptor)-mediated transcripational activity thus compound 6 is considered as a novel therapeutic candidate for treatment of type 2 diabetic patients" [11]

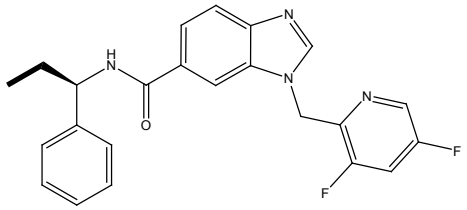


6

Sime et al. [12] carried out an optimization study of PPAR gamma activity which lead to the identification of GSK1997132B , **7** as shown in scheme 3**,** which it is a potent, metabolically stable and centrally penetrate PPAR γ - partial agonist .



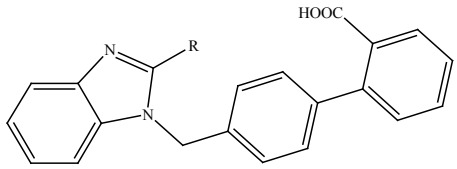
Scheme 3: Reagents and conditions: (a) $SOCl_2$, MeOH, 24 h, reflux; (b) (3,5-difluoropyridin-2-yl)methanamine , DIPEA, THF, 17 h, reflux; (c) $SnCl_2.2H_2O$, EtOAc, 2 h, reflux; (d) CH_3COCl, DIPEA, 30 min, 0°C to rt; (e) AcOH, 18 h, reflux; (f) (i) LiOH, THF/water, 18 h, reflux; (ii) HCl; (g) (*R*)-1-phenylpropan-1-amine, HATU, DIPEA, DMF, 18 h, rt.



GSK1997132B

7

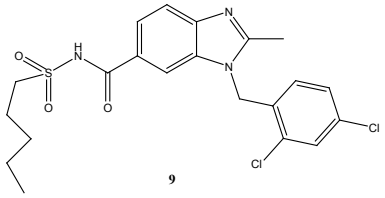
Goebel et al. [13] introduced different substitution on C-2 of the central benzimidazole ring of telmisartan for PPARγ activation. Compounds 8 a-i were evaluated in a differentiation assay using 3T3-L1 preadipocytes and a luciferase assay with COS-7 cells, transiently transfected with pGal4-hPPARγDEF, pGal5-TK-pGL3 and pRL-CMV, as established models for the assessment of cellular PPARγ activation." The alkyl series: iso-butyl (8b) ≤ tert-butyl (8c) <butyl (8a) demonstrated an increase in activity of the luciferase assay. Compound 8d with a phenyl group at C-2 was the most active compound with an EC_{50} value of 0.27 μM. 4-Hydroxylphenyl analog (8i) caused a drastic decrease in the activity. (EC_{50}=5.8 μM) presumably due to hydrophilic repulsion. This assumption was verified by O-methylation as shown in compound 8h , which retained the activity (EC_{50}=0.29 μM). The weak activity of the benzyl derivative 8e (EC_{50}=1.4 μM) was abolished by an additional hydrophobic 4-chloro substituent (8g; EC_{50}=0.55 μM) or an increase of the alkyl chain between the phenyl and the benzimidazole rings (8f; EC_{50}=0.31 μM) [13].



8

R = (a) butyl ,(b) iso-butyl , (c) tert-butyl , (d) phenyl , (e) benzyl , (f) phenethyl ,(g) 4-chlorobenzyl , (h) 4-methoxyphenyl , (i) 4-hydroxyphenyl .

Insulin resistance in C57BL/KSJ-db/db mice (db/db mice) animal models was improved by 3-(2,4-dichlorobenzyl)-2-methyl-N-(pentylsulphonyl)-3Hbenzimidazole- 5-carboxamide (FK614), 9, through activation of PPARc-mediated transcriptional activity. Accordingly compound 9 is considered a lead and a novel therapeutic agent for treatment of type 2 diabetic patients [14].



9

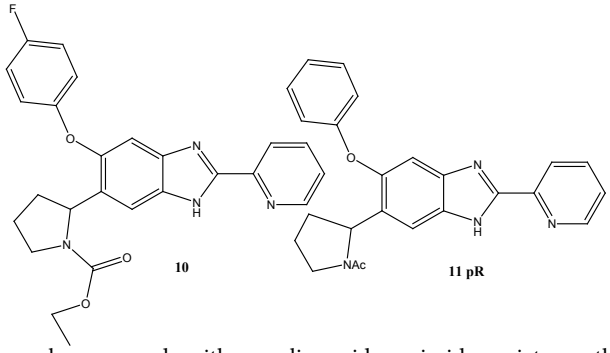
Benzimidazole as Glycogen Activator

The regulation of hepatic glucose production is controlled mainly by glucagon and insulin [15], thus a fall in the plasma glucose levels cause the secretion of glucagon by the pancreatic alpha-cells. Glucagon activates its receptor which is a G-protein coupled receptor located in the liver, causing an increase of the hepatic glucose production through glycogenolysis and gluconeogenesis. In db/db [16] and ob/ob [17] diabetic mouse models, reduction of glucagon receptor expression

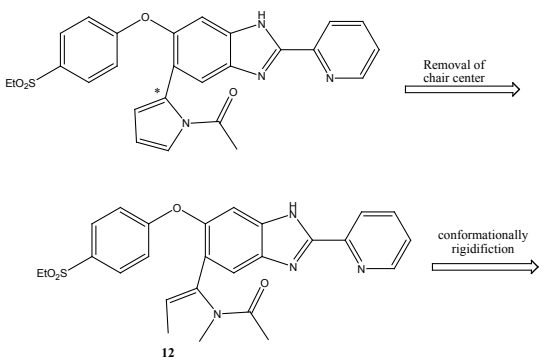
with antisense oligonucleotides result in the antidiabetic effect. In type 2 diabetic patients, elevated glucagon levels lead to an increae of the hepatic glucose output causing hyperglycemia. Accordingly, both macromolecules and small molecules glucagon receptor antagonists have been investigated as potential treatments for type 2 diabetes [18]. As a result Bayer developed the small molecule BAY-27-9955 which blocked glucagon-induced glucose production in healthy human volunteers [19].

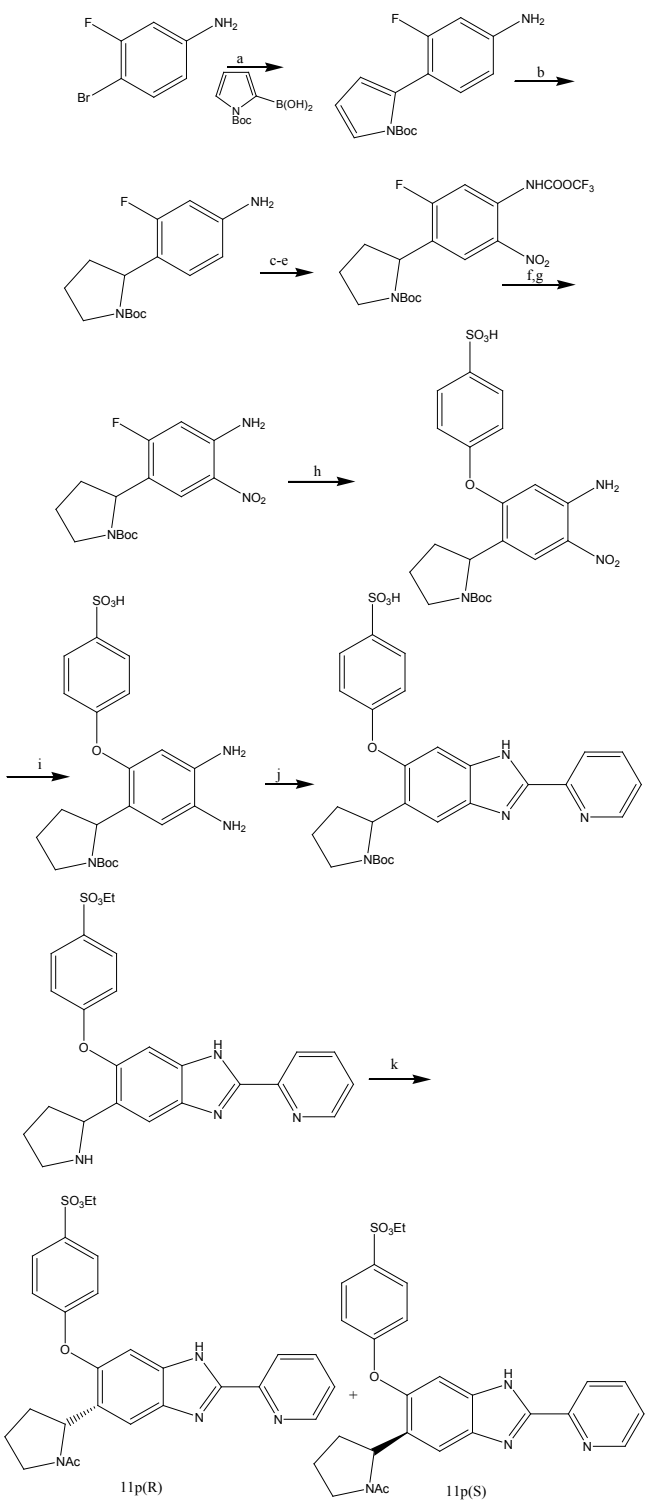
Glucokinase (GK) is an enzyme which facilitate the phosphorylation of glucose to glucose-6-phosphateand occurs predominantely in the liver and pancreatic beta-cells [20]. Glucokinase plays an important role in carbohydrate metabolism.Thus GK activation causes an increase in hepatic glucose uptake and utilization. It is of interest to mention that GK activity is related to increase insulin secretion in beta cells [21,22]. Accordingly, GK activators (GKAs) can act as hypoglycemic agents through the following mechanisms: i) an increase in the glucose uptake by the liver and ii) stimulating insulin secretion from pancreatic beta-cells. Based on this rationale, various small molecules were synthesized as GKAs [23–29].

New 2-(pyridine-2-yl)-1H-benzimidazole glucokinase activators were investigated. Through structural modification of benzimidazole lead to compound 11p(R) 10 which as identified from a high-throughput screening. Compound 11-p(R) 10 found to be a potent glucokinase activator 11p(R) (scheme 4). The compound also possesses an acute oral glucose lowering efficacy in rat OGTT model [30].

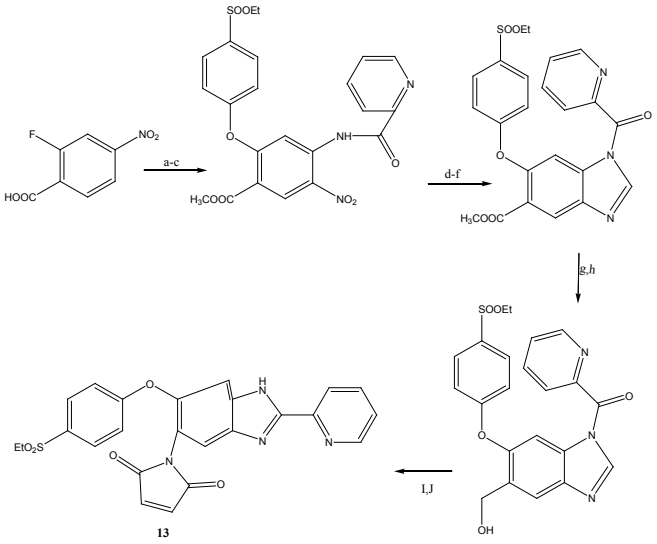


Several compounds with a cyclic amide or imide moiety on the benzimidazole ring were synthesized as potent GK activators [31]. These compounds, exemplified by 13 were designed by removing the chiral center of (N-acetylpyrrolidin-2-yl)benzimidazole and lead to compound 12. Succinimide derivative 13 caused a significant decrease of the plasma glucose when administered at 1mg/kg po in rat OGTT, and demonstrated acceptable pharmacokinetic profiles in beagle dogs. Furthermore, X-ray crystallographic analysis of the GKA 3g/GK protein complex revealed that compound 12 binds to the allosteric binding site of GK (Scheme 5).

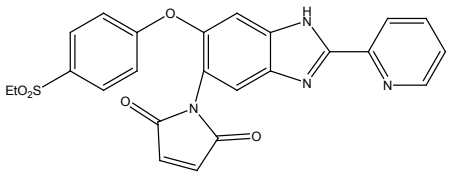




Scheme 4: Reagents and conditions: (a) $Pd(PPh)_2Cl_2$, Na_2CO_3, 80 °C, DME, H_2O, 63%; (b) Pt/C, H_2, MeOH, 85%; (c) TFA; (d) $(CF_3CO)_2O$, pyridine; (e) HNO_3, 87% for three steps; (f) K_2CO_3, MeOH-H2O; (g) Boc_2O, Et_3N, $CHCl_3$, 67% for two steps; (h) Cs_2CO_3, 4-fluorophenol, NMP, 80 °C, 85%; (i) Raney-Ni, NH_2NH_2, MeOH, 90%; (j) 2-pyridinecarboxaldehyde, EtOH, AcOH, 80 °C, 65%;(k) chiral separation by HPLC eluted with n-hexane/iPrOH (9/1v/v)/0.1% Et_2NH; (b) Ac_2O, pyridine



Scheme 5: Reagents and conditions: (a) cat H_2SO_4, MeOH, reflux, 94%; (b) H_2 (balloon), Raney Ni (cat), MeOH, THF, rt, 99%; (c) 2-picolinic acid, WSCI, pyridine, rt, 92%; (d) fuming HNO_3, 0°C to rt, 85%; (e) phenol , K2CO3, DMF, 80 °C, 82%; (f) $SnCl_2$2H2O, HCl, MeOH, DMF, 80 °C; (g) SEMCl, NaH, DMF, rt, 73% in two steps; (h) $LiAlH_4$, THF, 0°C, 80%;(i) imides, 40 wt % DEAD in toluene, PPh_3, THF, rt. (J) TFA, H2O, rt.

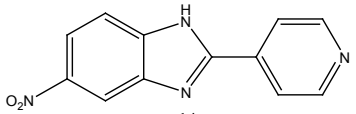


13

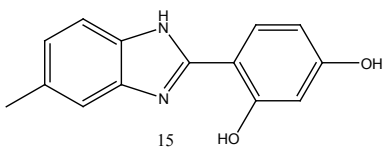
Benzimidazole as Target for Glycosidases Receptor

Glycosidases are group of enzymes responsible for the hydrolysis of gylcosidic bonds in complex carbohydrates. They recently became potential targets for the development of antidiabetic drugs.

2-Substituited benzimidazole derivatives were prepared by Jaladi et al. [32] and evaluated for their activity on yeast and rat intestinal α-glucosidase inhibition. Compound 14 exhibited 95.6% inhibition of yeast and rat intestinal α-glucosidase enzyme while compound 15 displayed 76% inhibition. Compound 14 was found to be the most potent inhibitor for intestinal α-glucosidase with IC_{50} value of be 99.4 μM. Compounds 14, 15 displayed significant antihyperglycemic activity in starch-induced postprandial hyperglycemia in rats [32].



14



15

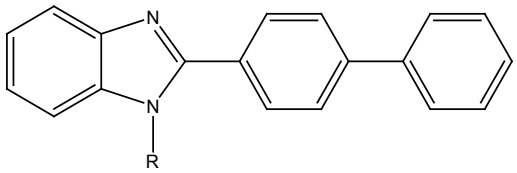
Benzimidazole as Target for Dipeptidyl Peptidase IV

Dipeptidyl peptidase IV (DPP-4) is a serine protease which has an intrinsic membrane glycoprotein and a serine exopeptidase that X-proline dipeptides from the N-terminus of polypeptides [33]. DPP-4 rapidly cleaves and inactivates the incretin glucagon-like peptide 1 (GLP-1) in the blood. Drucker et al. [34] and Herman et al. [35] published reports indicating that the active form of GLP-1 stimulates insulin release from beta cells in the pancreas , accordingly inhibition of DPP-4 can increase the levels of circulating GLP- 1 thus causing an increase insulin secretion and therefore can regulate blood glucose levels effectively.

Since the active form of GLP-1 stimulates insulin release from beta cells in the pancreas, inhibition of DPP-4 can increase the levels of circulating GLP- 1 thus causing an increase insulin secretion and effectively regulate blood glucose levels [34-36].

Structure-activity relationships (SAR) development led to the discovery of multiple compounds which are potent and selective for example 16, 17 [37] (Scheme 6).

A series of substituted benzimidazole derivatives were synthesized and evaluated for their potential anti-diabetic properties [38]. All the tested compounds showed anti-diabetic activity against DPP-IV and PTP-IB. Compound 17 showed inhibitory activity against PTP-IB (1.64 %, 2.42 %) at 30 Mm doses and exhibited inhibitory activity against DPP-IV (3%) at 0.3 Mm doses.

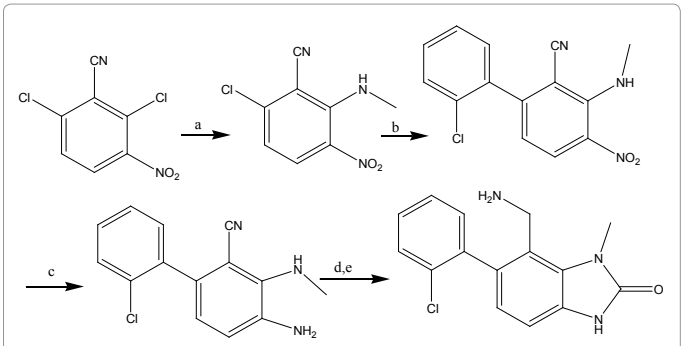


R= H,C_2H_5,$CH_2CH_2CH_3$

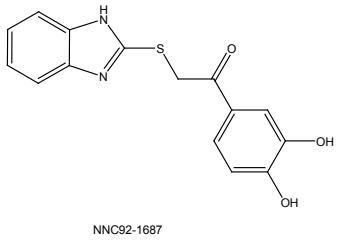
17

Benzimidazole as Glucagon Receptor Antagonists

Currently, research is focused on the development of non-peptide glucagon receptor antagonists. 2-(Benzimidazol-2-ylthio)-1-(3, 4-dihydroxyphenyl)-1-ethan one, NNC 92-1687 , 18 is the first non-peptide competitive antagonist to human glucagon receptor which specifically bind to the glucagon receptor, and thus causing inhibition of glucagon-stimulated cAMP accumulation in cells expressing the glucagon receptor [39].

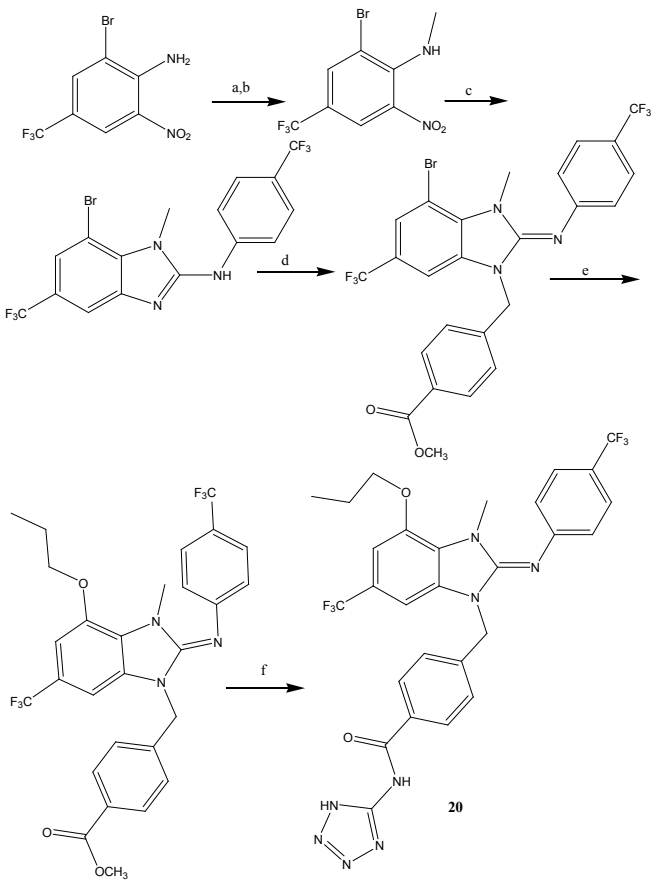


Scheme 6: Reagent and condition : (a) CH_3NH_2, THF; (b) R-Ph-B(OH)$_2$, Pd_2dba_3, DavePhos, K_3PO_4, DMA, 68 °C; (c) H_2, Pd/C, MeOH; or Fe, HOAc; (d) CDI, THF.,(e) 1-BH_3ÆTHF, reflux, 1 h; 2 –HCl

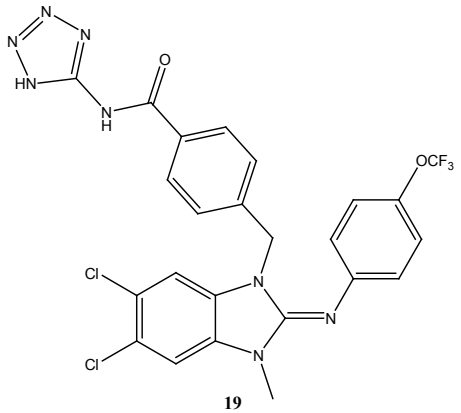


18

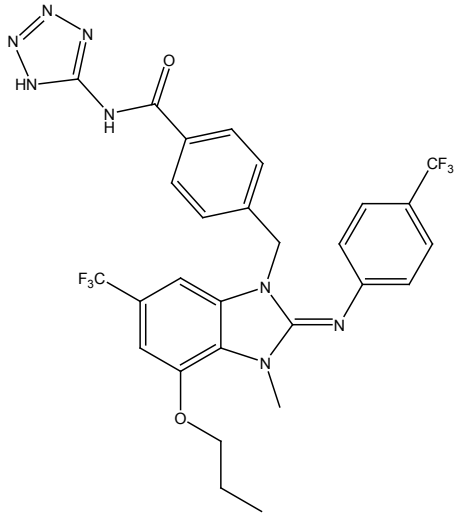
Compound 19 was the lead compound for this series which displayed promising in vitro potency and efficacy in vivo however it suffered from unacceptable pharamcokinetic profiles in preclinical animal studies and also poor human liver microsome stability, largely due to metabolic N-demethylation. Therefore, research was aimed at improving metabolic stability by introducing steric bulk near the site of metabolism resulted in a series of 4,6- disubstituted cyclic guanidine analogs which demonstrate improved metabolic stability, good rodent pharmacokinetic profiles, and excellent pharmacodynamic activity. Cyclic guanidine human glucagon receptor antagonists represented by the discovery of compound 20 which effectively caused blockade of glucagon induced glucose excursion in murine model, and also caused significant reduction in glucose levels in ob/ob/hGCGR efficacy model [39] (Scheme 7).



Scheme 7: Reagents and conditions: (a) NaH, MeI, DMF, rt; (b) $SnCl_2$, $2H_2O$, DMF/water, 40 ° C (c) 4-trifluoromethylphenyl isothiocyanate, CH2Cl2, 40 °C, then Hg(OTFA)2, DMF, rt; d. methyl 4-bromomethylbenzoate, CH_3CN, 110 ° C (e) n-propanol, Cs_2CO_3, $Pd(OAc)_2$, 2-(di-tert-butylphosphino-1,1·-binaphthyl, toluene, 70 ° C; (f) (i) LiOH, dioxane/ water, 40 °C; (ii). 5-aminotetrazole, EDC, HOBt, DIEA, DMF.



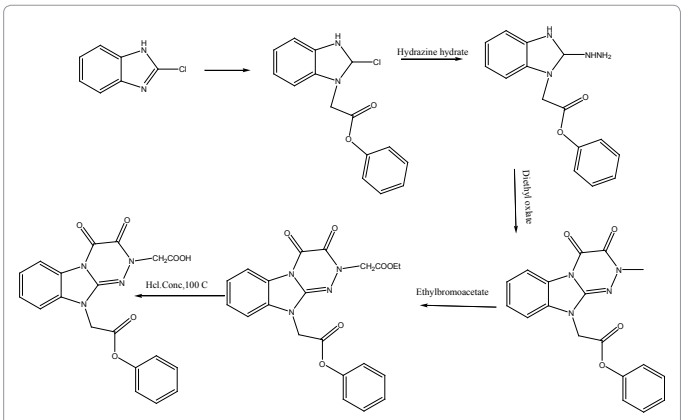
19



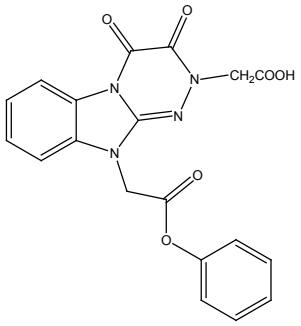
20

Benzimidazole as a Target for Aldose Reductase Enzyme

Several acetic acid derivatives of [1,2,4]triazino[4,3-a] benzimidazole (TBI) were prepared and evaluated both in vitro and in vivo as selective aldose reductase (ALR2) inhibitors [40]. Compound PS11, 21, possessed the highest inhibitory activity (IC_{50}) 0.32 mM and was found to be effective in preventing cataract development in severely galactosemic rats when administered as an eye drop solution. Although all the compounds investigated were selective for ALR2, yet none of them inhibited appreciably aldehyde reductase, sorbitol dehydrogenase, or glutathione reductase [40] (Scheme 8).



Scheme 8: Benzimidazole as a target for aldose reductase enzyme



PS11

21

Benzimidazole As A Target For Stearoyl- CoA desaturase

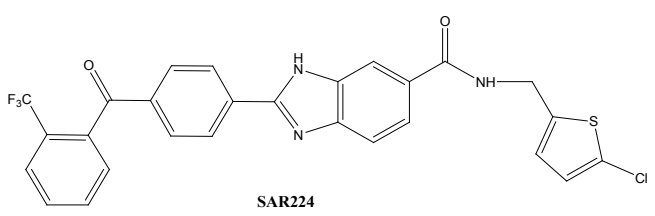
Increasing obesity and other metabolic disorders such as type 2 diabetes in Western societies focused on the necessity to discover new pharmaceuticals for the treatment of these conditions [41,42]. An increase of the activity of stearoyl- CoA desaturase (SCD1), one of the essential enzymes in lipogenesis, which has been linked to the pathogenesis of obesity, metabolic disorders, dyslipidemia and type 2 diabetes [43,44]. SCD1 catalyzes the formation of a cis-double bond at the carbon-9 position of saturated fatty acyl-Coenzyme-A esters which is the rate-limiting step in the synthesis of mono-unsaturated 16:1 n-7 and 18:1 n-9 fatty acyl-CoAs [43]. Different nutritional and pharmacological stimuli regulate the SCD1 expression [45,46]. SCD1-deficient mice were reported to exhibit reduced body weight, body fat mass, increased oxygen consumption and improved insulin sensitivity in a glucose tolerance test [47]. Substantial research have been directed to develop small-molecule SCD1 inhibitors for the treatment of metabolic disorders.

Through computational drug design search a series of potent SCD1 inhibitors were developed which resulted in the discovery of SAR224 which possessed favorable vivo pharmacokinetics and pharmacology studies after oral administration to male Zucker diabetic fatty (ZDF) rats. Hence SAR224, represents a promising lead compound for further investigation of SCD1 inhibitors as potential treatments of diabetes and related diseases [48] (Scheme 9).

Reagents and conditions: (a) AcOH/H_2O 80/20, 65 °C, 90 min, 73%; (b) $Na_2S_2O_5$ (1.3 equiv), DMF, 100 °C, 1 h, 79%; (c) tert-Bt OH, EDC·HCl, DIEA, DMF, rt, 18 h, 95% (d) 2-aminomethyl-5-chlorothiophene.

Benzimidazole as a Target for Diacylglycerol Acyltransferase

Triglyceride (TG) synthesis is involved in several biochemical processes, such as energy storage in adipose tissue, muscle, and assembly of lipoprotein particles in the liver and small intestine. However, excess accumulation of TG can cause several disorders, such as dyslipidemia, obesity, insulin resistance, and hepatic steatosis. Therefore, inhibition of the synthesis of TG is considered as an efficient rationale for treatment of obesity and type 2 diabetes [52,53].



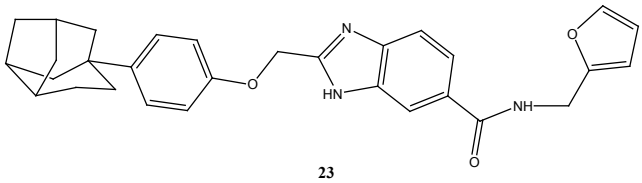
SAR224

22

Scheme 9: Reagents and conditions: (a) AcOH/H_2O 80/20, 65 °C, 90 min, 73%; (b) $Na_2S_2O_5$ (1.3 equiv), DMF, 100 °C, 1 h, 79%; (c) tert-Bt OH, EDC·HCl, DIEA, DMF, rt, 18 h, 95% (d) 2-aminomethyl-5-chlorothiophene.

TG is produced by two biochemical pathways: the major glycerol phosphate pathway and the minor monoacylglycerol pathway. Diacylglycerol acyltransferase (DGAT) catalyzes acyl residue transfer from acyl-CoA to diacylglycerol (DAG), is considered the exclusive key enzyme for the final step required for both pathways as described by Cases et al. [54], Kennedy [55] and Yen et al. [56]. Therefore, DGAT became an attractive target for the control of obesity and other related disorders such as type 2 diabetes [57].

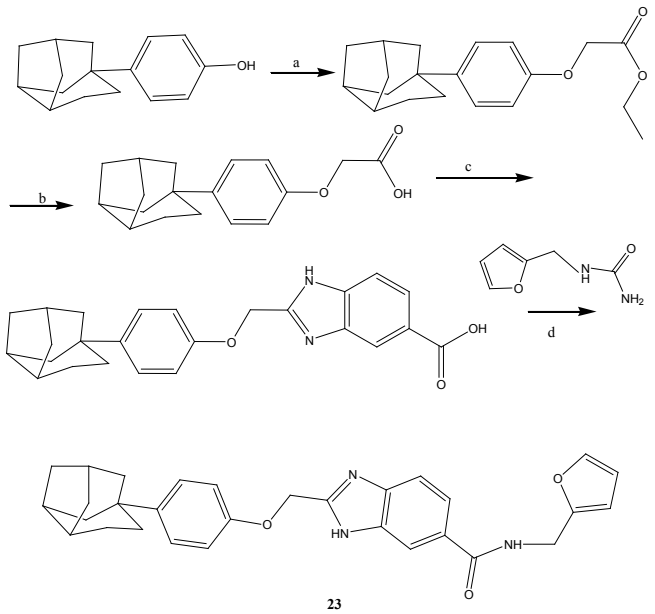
Several benzimidazole derivatives was prepared and evaluated for their DGAT inhibitory activity using rat liver microsome. Furfurylamine containing benzimidazole carboxamide 23 was among the newly synthesized compounds which showed the most potent DGAT inhibitory effect (IC_{50}=4.4 lM) and inhibited triglyceride formation in HepG2 cells. Furthermore, compound 23 reduced body weight gain in mice which are fed a high-fat diet. This was associated with decreased levels of triglyceride, cholesterol, and LDL-cholesterol in the blood accompanied with a significant increase in HDL-cholesterol level [58] (Scheme 10).



23

Benzimidazole as a Target for Carbonic Anhydrases

Carbonic anhydrases are zinc-containing metalloenzymes [59].



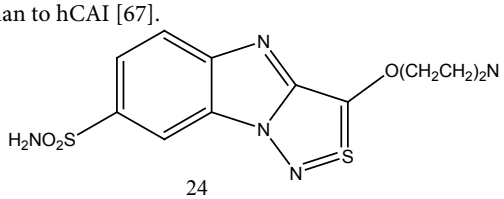
23

Scheme 10: Reagents and conditions: (a) ethyl chloroacetate, K2CO3, DMF, 12 hr, r.t., 96%; (b) LiOH, H_2O, THF/H_2O, 8 hr, r.t., 94%; (c) methyl-3,4-diaminobezoate, PPSE, 140 °C, 5 h, 90%; (d) AcOH/HCl, reflux, 4 hr, 84%; (e) HATU, DIPEA, DMF, 1–12 hr, rt., 50–86%.

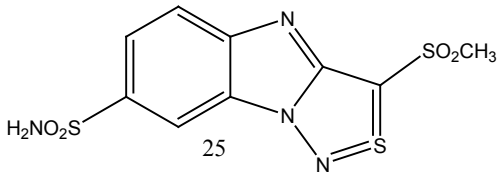
Several investigators identified fifteen carbonic anhydrase isoforms in humans which are located which possess different catalytic activity and subcellular localization [60-61]. Pastorekova et al. [60] and Supuran et al. [62] showed that these enzymes are involved in essential biochemical processes involving the hydration of carbon dioxide to bicarbonate and vice versa. Therefore these enzymes are involved in physiological processes such as lipogensis ,gluconeogenesis among other processes. Therefore, carbonic anhydrases are considered important targets for design of inhibitors with potential therapeutic applications. Aromatic/heterocyclic sulfonamides are the most important class of CA inhibitors studied for the development of antiglaucoma, antitumor, antiobesity or anticonvulsant drugs [63,64].

Benzimidazo[1,2-c][1,2,3]thiadiazole-7-sulfonamides were synthesized and their binding to two carbonic anhydrase isozymes measured by isothermal titration calorimetry (ITC). The observed association constants between human carbonic anhydrase I (hCAI) and bovine carbonic anhydrase II (bCAII) and the inhibitors where in the range from 1.1 × 106 to 2.6 × 107 M^{-1} respectively.

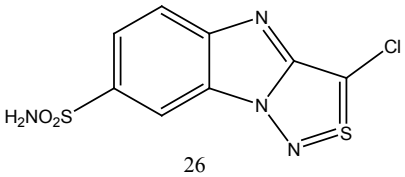
Compound 24 bound strongly to both isozymes of carbonic anhydrase with the observed Kd of about 0.04 lM. Compound 25 was the most specific binder of hCAI that bound about four fold stronger to hCAI than to bCAII while compound 26 bound threefold tighter to bCAII than to hCAI [67].



24



25



26

Conclusion

This review discusses several novel benzimidazole derivatives that possess antidiabetic activity.

Several agents demonstrated potential activities that they were marketed as useful agents for the treatment of type 2 diabetes operating on various mechanism(s) of actions. Efforts are still going on in the search of new benzimidazole derivatives that are pharmacologically effective and safe as antidiabetic agents [68-72].

References

1. Keane WF, Brenner BM, de Zeeuw D, Grunfeld JP, McGill J, et al. (2003) The risk of developing end-stage renal disease in patients with type 2 diabetes and nephropathy: the RENAAL study. Kidney Int 63: 1499-1507.
2. Cusi K, DeFronzo RA (1998) Metformin: a review of its metabolic effects. Diabetes Rev 6: 89-131.
3. Shingalapur RV, Hosamani KM, Keri RS, Hugar MH (2010) Derivatives of benzimidazole pharmacophore: synthesis, anticonvulsant, antidiabetic and DNA cleavage studies. Eur J Med Chem 45: 1753-1759.
4. Subudhi BB, Panda PK, Kundu T, Sahoo S, Pradhan D (2007) Synthesis and biological evaluation of benzimidazole and thiazolidinone derivatives. J Pharm Res 6: 114-118.
5. Hugar HM, Hosamani MK, Suresh DK (2010) Synthesis and investigation of anticonvulsant and antidiabetic activities of newly synthesized bis-benzimidazole derivatives. International Journal of Drug Formulation & Research 1: 240-262.
6. DeFronzo RA (1988) Lilly lecture 1987. The triumvirate: beta-cell, muscle, liver. A collusion responsible for NIDDM. Diabetes 37: 667-687.
7. Defronzo RA (2009) Banting Lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. Diabetes 58: 773-795.
8. Centers for Disease Control. National Diabetes Fact Sheet; 2007.
9. Lemberger T, Desvergne B, Wahli W (1996) Peroxisome proliferator-activated receptors: a nuclear receptor signaling pathway in lipid physiology. Annu Rev Cell Dev Biol 12: 335-363.
10. Evans RM, Barish GD, Wang YX (2004) PPARs and the complex journey to obesity. Nat Med 10: 355-361.
11. Minoura H, Takeshita S, Ita M, Hirosumi J, Mabuchi M, et al. (2004) Pharmacological characteristics of a novel nonthiazolidinedione insulin sensitizer, FK614. Eur J Pharmacol 494: 273–281.
12. Sime M, Allan AC, Chapman P, Fieldhouse C, Giblin GM, et al. (2011) Discovery of GSK1997132B a novel centrally penetrant benzimidazole PPARÎ³ partial agonist. Bioorg Med Chem Lett 21: 5568-5572.
13. Goebel M, Staels B, Unger T, Kintscher U, Gust R (2009) Characterization of new PPARgamma agonists: benzimidazole derivatives - the importance of position 2. Chem Med Chem 4: 1136-1142.
14. Minoura H, Takeshita S, Ita M, Hirosumi J, Mabuchi M, et al. (2004) Pharmacological characteristics of a novel nonthiazolidinedione insulin sensitizer, FK614. Eur J Pharmacol 494: 273-281.
15. Kurukulasuriya R, Link JT, Madar DJ, Pei Z, Rohde JJ, et al. (2003) Prospects for pharmacologic inhibition of hepatic glucose production. Curr Med Chem 10: 99-121.
16. Liang Y, Osborne MC, Monia BP, Bhanot S, Gaarde WA, et al. (2004) Reduction in glucagon receptor expression by an antisense oligonucleotide ameliorates diabetic syndrome in db/db mice. Diabetes 53: 410-417.
17. Sloop KW, Cao JX, Siesky AM, Zhang HY, Bodenmiller DM, et al. (2004) Hepatic and glucagon-like peptide-1-mediated reversal of diabetes by glucagon receptor antisense oligonucleotide inhibitors. J Clin Invest 113: 1571-1581.
18. Kim RM, Chang J, Lins AR, Brady E, Candelore MR, et al. (2008) Discovery of potent, orally active benzimidazole glucagon receptor antagonists. Bioorg Med Chem Lett 18: 3701-3705.
19. Petersen KF, Sullivan JT (2001) Effects of a novel glucagon receptor antagonist (Bay 27-9955) on glucagon-stimulated glucose production in humans. Diabetologia 44: 2018-2024.
20. Wallace MB, Feng J, Zhang Z, Skene RJ, Shi L, et al. (2008) Structure-based design and synthesis of benzimidazole derivatives as dipeptidyl peptidase IV inhibitors. Bioorg Med Chem Lett 18: 2362-2367.
21. Printz RL, Magnuson MA, Granner DK (1993) Mammalian glucokinase. Annu Rev Nutr 13: 463-496.
22. Matschinsky FM (1996) Banting Lecture 1995. A lesson in metabolic regulation inspired by the glucokinase glucose sensor paradigm. Diabetes 45: 223-241.
23. Matschinsky FM, Glaser B, Magnuson MA (1998) Pancreatic beta-cell glucokinase: closing the gap between theoretical concepts and experimental realities. Diabetes 47: 307-315.
24. Sarabu R, Grimsby J (2005) Targeting glucokinase activation for the treatment of type 2 diabetes--a status review. Curr Opin Drug Discov Devel 8: 631-637.
25. Castelhano AL, Dong H, Fyfe MC, Gardner LS, Kamikozawa Y, et al. (2005) Glucokinase-activating ureas. Bioorg Med Chem Lett 15: 1501-1504.
26. McKerrecher D, Allen JV, Bowker SS, Boyd S, Caulkett PWR, et al. (2005) Discovery, synthesis and biological evaluation of novel glucokinase activators. Bioorg Med Chem Lett 15: 2103-2106.

27. Guertin KR, Grimsby J (2006) Small molecule glucokinase activators as glucose lowering agents: a new paradigm for diabetes therapy. Curr Med Chem 13: 1839-1843.

28. Sarabu R, Berthel SJ, Kester RF, Tilley JW (2008) Glucokinase activators as new type 2 diabetes therapeutic agents. Expert Opin Ther Patents 18: 759-768.

29. Bertram LS, Black D, Briner PH, Chatfield R, Cooke A, et al. (2008) SAR, pharmacokinetics, safety, and efficacy of glucokinase activating 2-(4-sulfonylphenyl)-N-thiazol-2-ylacetamides: discovery of PSN-GK1. J Med Chem 51: 4340-4345.

30. Ishikawa M, Nonoshita K, Ogino Y, Nagae Y, Tsukahara D, et al. (2009) Discovery of novel 2-(pyridine-2-yl)-1H-benzimidazole derivatives as potent glucokinase activators. Bioorg Med Chem Lett 19: 4450-4454.

31. Takahashi K, Hashimoto N, Nakama C, Kamata K, Sasaki K, et al. (2009) The design and optimization of a series of 2-(pyridin-2-yl)-1H-benzimidazole compounds as allosteric glucokinase activators. Bioorg Med Chem 17: 7042–7051.

32. Kumar JA, Tiwari AK, Ali AZ, Madhusudhana K, Reddy BS, et al. (2010) New antihyperglycemic, alpha-glucosidase inhibitory, and cytotoxic derivatives of benzimidazoles. J Enzyme Inhib Med Chem 25: 80-86.

33. Yaron A, Naider F (1993) Proline-dependent structural and biological properties of peptides and proteins. Crit Rev Biochem Mol Biol 28: 31-81.

34. Drucker DJ, Nauck MA (2006) The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet 368: 1696-1705.

35. Herman GA, Bergman A, Liu F, Stevens C, Wang AQ, et al. (2006) Pharmacokinetics and pharmacodynamic effects of the oral DPP-4 inhibitor sitagliptin in middle-aged obese subjects. J Clin Pharmacol 46: 876-886.

36. Ahre´n B, Gomis R, Standl E, Mills D, Schweizer A (2004) Twelve- and 52-week efficacy of the dipeptidyl peptidase IV inhibitor LAF237 in metformin-treated patients with type 2 diabetes, Diabetes Care 27: 2874-2880.

37. Wallace MB, Feng J, Zhang Z, Skene RJ, Shi L, et al. (2008) Structure-based design and synthesis of benzimidazole derivatives as dipeptidyl peptidase IV inhibitors. Bioorg Med Chem Lett 18: 2362-2367.

38. Neelamma M, Kumar BB, Rao PV (2006) Synthesis and Structural Studies on Transition Metal Complexes Derived from 1-(2- Thienyl)-1-ethanole-1Hbenzimidazole-2-yl-hydrazone. Asian J Chem 18: 3060-3064.

39. Sinz C, Chang J, Lins AR, Brady E, Candelore M, et al. (2011) Discovery of cyclic guanidines as potent, orally active, human glucagon receptor antagonists. Bioorg Med Chem Lett 21: 7131-7136.

40. Sahoo PK, Behera P (2010) Synthesis and biological evaluation of [,2,4] triazino[4,3-a] benzimidazole acetic acid derivatives as selective aldose reductase inhibitors. Eur J Med Chem 45: 909-914.

41. Smyth S, Heron A (2006) Diabetes and obesity: the twin epidemics. Nat Med 12: 75-80.

42. Dobrzyn P, Dobrzyn A (2010) Novel substituted heteroaromatic compounds as inhibitors of stearoyl-CoA desaturase. Expert Opin Ther Pat 20: 849-853.

43. Enoch HG, Catala A, Strittmatter P (1976) Mechanism of rat liver microsomal stearyl-CoA desaturase. Studies of the substrate specificity, enzyme-substrate interactions, and the function of lipid. J Biol Chem 251: 5095-5103.

44. Miller CW, Ntambi JM (1996) Peroxisome proliferators induce mouse liver stearoyl-CoA desaturase 1 gene expression. Proc Natl Acad Sci USA 93: 9443-9448.

45. Ntambi JM (1992) Dietary regulation of stearoyl-CoA desaturase 1 gene expression in mouse liver. J Biol Chem 267: 10925-10930.

46. Ntambi JM (1995) The regulation of stearoyl-CoA desaturase (SCD). Prog Lipid Res 34: 139-150.

47. Abu-Elheiga L, Matzuk MM, Abo-Hashema KA, Wakil SJ (2001) Continuous fatty acid oxidation and reduced fat storage in mice lacking acetyl-CoA carboxylase 2. Science 291: 2613-2616.

48. Matter H, Zoller G, Herling AW, Sanchez-Arias JA, Philippo C, et al. (2013) Benzimidazole-carboxamides as potent and bioavailable stearoyl-CoA desaturase (SCD1) inhibitors from ligand-based virtual screening and chemical optimization. Bioorg Med Chem Lett 23: 1817-1822.

49. Wu W, Brunett DA, Caplen MA, Domalski MS, Bennet C, et al. (2006) Design and synthesis of orally efficacious benzimidazoles as melanin-concentrating hormone receptor 1 antagonists. Bioorg Med Chem Lett 16: 3674–3678.

50. Sasmal PK, Sasmal S, Rao PT, Venkatesham B, Roshaiah M, et al. (2010) Discovery of novel, orally available benzimidazoles as melanin concentrating hormone receptor 1 (MCHR1) antagonists. Bioorg Med Chem Lett 20: 5443-5448.

51. Shen HC, Ding FX, Zhou C, Xiong Y, Verras A, et al. (2011) Discovery of benzimidazole pyrrolidinyl amides as prolylcarboxypeptidase inhibitors. Bioorg Med Chem Lett 21: 1299-1305.

52. Chen HC, Farese RV Jr (2005) Inhibition of triglyceride synthesis as a treatment strategy for obesity: lessons from DGAT1-deficient mice. Arterioscler Thromb Vasc Biol 25: 482-486.

53. Kayden HJ, Senior JR, Mattson FH (1967) The monoglyceride pathway of fat absorption in man. J Clin Invest 46: 1695-1703.

54. Cases S, Smith SJ, Zheng YW, Myers HM, Lear SR, et al. (1998) Identification of a gene encoding an acyl CoA:diacylglycerol acyltransferase, a key enzyme in triacylglycerol synthesis. Proc Natl Acad Sci USA 95: 13018-13023.

55. Kennedy EP (1957) Metabolism of lipides. Annu Rev Biochem 26: 119-148.

56. Yen CL, Stone SJ, Koliwad S, Harris C, Farese RV Jr (2008) Thematic review series: glycerolipids. DGAT enzymes and triacylglycerol biosynthesis. J Lipid Res 49: 2283-2301.

57. Hubbard BK, Enyedy I, Gilmore TA, Serrano-Wu MH (2007) Antisense and small-molecule modulation of diacylglycerol acyltransferase. Expert Opin Ther Pat 17: 1331-1339.

58. Lee K, Goo JI, Jung HY, Kim M, Boovanahalli SK, et al. (2012) Discovery of a novel series of benzimidazole derivatives as diacylglycerol acyltransferase inhibitors. Bioorg Med Chem Lett 22: 7456-7460.

59. Liljas A, Laurberg M (2000) A wheel invented three times. The molecular structures of the three carbonic anhydrases. EMBO Rep 1: 16-17.

60. Pastorekova S, Parkkila S, Pastorek J, Supuran CT (2004) Carbonic anhydrases: current state of the art, therapeutic applications and future prospects. J Enzyme Inhib Med Chem 19: 199-229.

61. Kivela AJ, Kivela J, Saarnio J, Parkkila S (2005) Carbonic anhydrases in normal gastrointestinal tract and gastrointestinal tumours. World J Gastroenterol 11: 155-163.

62. Supuran CT, Vullo D, Manole G, Casini A, Scozzafava A (2004) Designing of novel carbonic anhydrase inhibitors and activators. Curr Med Chem Cardiovasc Hematol Agents 2: 49-68.

63. Pastorekova S, Parkkila S, Zavada J (2006) Tumor-associated carbonic anhydrases and their clinical significance. Adv Clin Chem 42: 167-216.

64. Clare BW, Supuran CT (2006) A perspective on quantitative structure-activity relationships and carbonic anhydrase inhibitors. Expert Opin Drug Metab Toxicol 2: 113-137.

65. Thiry A, Ledecq M, Cecchi A, Dogne JM, Wouters J, et al. (2006) Indanesulfonamides as carbonic anhydrase inhibitors. Toward structure-based design of selective inhibitors of the tumor-associated isozyme CA IX. J Med Chem 49: 2743-2749.

66. De Simone G, Vitale RM, Di Fiore A, Pedone C, Scozzafava A, et al. (2006) Carbonic anhydrase inhibitors: Hypoxia-activatable sulfonamides incorporating disulfide bonds that target the tumor-associated isoform IX. J Med Chem 49: 5544-5551.

67. Dudutiene V, Baranauskiene L, Matulis D (2007) Benzimidazo[,2-c][,2,3] thiadiazole-7-sulfonamides as inhibitors of carbonic anhydrase. Bioorg Med Chem Lett 17: 3335-3338.

68. Taha M, Ismail NH, Imran S, Selvaraj M, Rashwan H, et al. (2015) Synthesis of benzimidazole derivatives as potent Î²-glucuronidase inhibitors. Bioorg Chem 61: 36-44.

69. Zawawi NKN, Taha M, Ahmat N, Ismail AN, Rahim F, et al. (2015) Novel 2,5-disubtituted-,3,4-oxadiazoles with benzimidazole backbone: A new class of ß-glucuronidase inhibitors and in silico studies. Bioorg Med Chem 23: 3119-3125.

70. Taha M, Ismail NH, Jamil W, Rashwan H, Kashif SM, et al. (2014) Synthesis of novel derivatives of 4-methylbenzimidazole and evaluation of their biological activities. Eur J Med Chem 84: 731-738.

71. Saify ZS, Kamel A, Akhter S, Taha M, Khan A, et al. (2014) 2-(2'-Pyridyl) benzimidazole derivatives and their urease inhibitory activity. Med Chem Res 23: 4447-4454.

72. Khan KM, Khan M, Saleem M, Taha M, Perveen S, et al. (2013) Benzimidazoles: A New Class of Carbonic Anhydrase. J Pak Chem Soc 35: 901-904.