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Quantitative Structure –Activity Relationship Studies on Antidiabetic Agents

Raghu Raj Parihar
Assistant Professor,
Deptt. of Chemistry,
Govt. College,
Kota, Rajasthan

Abstract

Diabetes mellitus is an entity of considerable morbidity comprising a spectrum of multisystem dysfunctions stemming from the combination of insulin resistance and inadequate insulin secretion.Type 1 diabetes is usually caused by immune destruction of pancreatic islet cells while type 2 is associated with insulin resistance, hyperglycemia and other metabolic conditions such as hypertension, obesity and hyperlipidemia. Management of diabetes, akin to a tightrope walk, requires a comprehensive understanding of various factors such as over-all clinical picture, adverse effect profile, the complex of inter-play of drugs, etc.

Keywords: Diabetes Mellitus, Insulin, Type 1, Type 2, Dipeptidyl Peptidase IV, Glucokinase, Fibrates, Bromocriptine

Introduction

For several thousand years, man has used Herbs as medicines, until serious efforts were made to isolate and purify the active principles of these remedies in the mid-nineteenth century. Since then a large variety of biologically active compounds have been obtained and their structures were determined. This, in practice, is achieved by molecular modifications using the "trial-and-error" process aided by intuition, not by proper information. Information consists all types of data -qualitative as well as quantitative- which may be processed or unprocessed. It may have been designed to address a simple event or a more complex situation emerged from a statistically defined quantity with a probability of occurrence, ete.In the hierarchy of information flow, notion qualifies as the first qualitative, irregular and vague estimation of information In this flow, parameters and measurements take the center stage with intuitions (the amorphous state of information) at the origin of the flow line and the inferences and decisions at its crystalline end.In it, a parameter is a composition of set of rules designed to define a concept, property or any other relevant information. In the hierarchy of information, a parameter takes precedence over measurement. In this scenario, the origin of the concept of parameterization is time immemorial and it goes along with the conseciousness.

Aim of the Study

1. Explain the behavior of new compounds as antidiabetic agents.
2. Establish the exact relationship between the biological activity and different quantitative parameters.
3. Provide a basis of substituents selection in designing more perfect congener.
4. Help in understanding the mechanism of action at the sites of a given receptor at molecular level.
5. Extrapolate to find new active compounds whose activities are not evaluated so far.
6. Serve as a guide to understand the conformational changes that occur during
7. Interaction at a receptor site.
8. Help in identifying the behavior of different antidiabetic agents on various receptor sites

Antidiabetic Agents

Diabetes mellitus is an entity of considerable morbidity comprising a spectrum of multisystem dysfunctions stemming from the combination of insulin resistance and inadequate insulin secretion.Type 1 diabetes is

usually caused by immune destruction of pancreatic islet cells while type 2 is associated with insulin resistance, hyperglycemia and other metabolic conditions such as hypertension, obesity and hyperlipidemia.Management of diabetes, akin to a tightrope walk, requires a comprehensive understanding of various factors such as over-all clinical picture, adverse effect profile, the complex of inter-play of drugs, etc.

The various types of antidiabetic agents belonging to different classes are given below:

1. Sodium-glucose transport proteins-2 (SGLT2) inhibitors
2. Dipeptidyl peptidase IV (DPP IV) inhibitors
3. Glucagon-like peptide (GLP-1) analogues
4. Glucokinase activators
5. Peroxisome proliferator-activated receptor (PPAR)
6. Monoclonal antibodies
7. Dopamine-2 receptor agonist

Sodium-Glucose Transport Proteins-2 (SGLT2) Inhibitors

Sodium-dependent glucose co-transporters (SGLT) are found in the intestinal mucosa of the small intestine and the proximal tubules of the nephrons.Two types of SGLT ($SGLT_1$ and $SGLT_2$) are of considerable importance in diabetes[22] Intestines predominantly sport $SGLT_1$, whereas the proximal tubules of the nephrons display both $SGLT_2$: and $SGLT_1$. A sodium-to-glucose transport ratio of $SGLT_1$, is 2:1and that of $SGLT_2$ is 1 : 1 and while the former contributes 2 % to glucose reabsorption , the latter contributes 98%[1] Hence $SGLT_2$ inhibition enables us to considerably reduce transcellular epithelial glucose reabsorption. $SGLT_2$ inhibition is independent of glucose-dependent insulin secretion by the pancreatic β cells.

DPP IV Inhibitors

Dipeptidyl peptidase IV (DPP IV) inhibitors act primarily by blocking incretin degradation.These inhibit the breakdown of glucagon-like peptide (GLP-1) and glucose- concentrations of the same.This results in stimulation of insulin secretion, reduction in plasma glucose and glucagon levels, and inhibition of gastric emptying.Incretins also govern β-cell differentiation, mitogenesis and survival which is how DPP IV inhibition can preserve β-cell mass and improve their secretory function.[2]

GLP-1 Analogues

Glucagon-like peptide (GLP-1) analogues are synthesized by small intestinal L cells.They heighten glucose-dependent insulin secretion, reduce glucagon secretion promote weight loss, slow gastric emptying, decrease appetite, and promote B-cell regeneration.They do not cause hypoglycemia, in the absence of therapies that otherwise cause hypoglycemia.They also seem to play a role in halting the progression of more aggressive lesions from underlying steatosis in Nonalcoholic Fatty Liver Disease (NAFLD)[3]

Glucokinase Activators

Glucokinase (also called hexokinase IV or D) owing to its glucose sensor role inpancreatic β-cells and being the rate-controlling enzyme for hepatic glucose clearance and glycogen synthesis is known to have an exceptionally high impact on glucose homeostasis.Glucokinase activators ($GKA_{s)}$ stimulate insulin biosynthesis and secretion and augment glucose metabolism and related processes in other glucokinase-expressing cells via GKA-mediated increase in the affinity of glucokinase for glucose and its maximal catalytic rate[4] .GKA_s mediate their antidiabetic effects via generalized enhancement of B-cell function and through fasting restricted changes in glucose turn over.Piragliatin, a GKA, has shown an acute glucose-lowering action in patients with mild type 2 diabetics[5].An experimental GKA molecule ZYGK, showed promising efficacy in controlling both fasting and non-fasting blood glucose[6] . The side effects, although rare, of GKAs are hypoglycemia, fatty liver, and hyperlipidemia.,

Dual PPAR Agonists

Inhibition of PPARα-agonists (Fibrates) lowers plasma triglycerides and VLDL particles and increase HDL cholesterol while PPARγ-agonists (thiazolidinediones) influence free fatty acid flux and reduce insulin resistance and blood glucose levels. Although muraglitazar a similar molecule showed efficacy as an add-ontherapy for poorly controlled diabetics, excess incidence of death, major Ki adverse cardiovascular events (MI, Stroke, TIA), and heart failure were noted with it and hence withdrawn[55].

Monoclonal Antibodies

To include immune tolerance via monoclonal antibodies has been tried as a way to prevent and effectively treat diabetes. Otelixizumab, an anti-CD_3, monoclonal antibody, is known to stimulate C-peptide levels and reduce insulin requirement in type 1 diabetes[7]. Similarly studies with teplizumab are also reassuring. Other monoclonal antibodies such asanti-CD20 anti-CTGF[8] ,anti-IL-1β[9] have shown promising results and are yet to be approved.

Dopamine-2 Receptor Agonist

Timed bromocriptine (centrally-acting dopamine D_2 receptor agonist) is believed to act on circadian neuronal activities within the hypothalamus to reset abnormally elevated hypothalamic drive for increased plasma glucose, triglyceride, and free fatty acid levels in fasting andpostprandial states in insulin-resistant patients.Its use as monotherapy and in combination with other oral hypoglycemic agents (OHA_s) is shown to reduce HbA_{1c}, plasma triglyceride, and FFA concentrations in type 2 diabetic patients[10]

Interpretation

It is commonly believed that the closer the value to unity, the better the model is. However, R is just a measure of the quality of the fit between calculated and experimental activity values and not hits for the predictive power of the model at all ie, it is possible that a QSAR model with high R' could be a poor predictor. Standard crror of estimate (s):This is defined as

$$s = \sqrt{\frac{(Y_{calc} - \bar{Y})^2}{n-p-1}}$$

....(1)

The value of standard enor of estimate shouild be minimized for a better model. Variance ratio (F): It gives an indication about the stability of the regression coefficients. It should be maximized for goodness of fit.

$$s = \frac{\frac{\sum(Y_{calc}-\bar{Y})^2}{p}}{\frac{\sum(Y_{calc}-\bar{Y})^2}{n-p-1}}$$

df=p, n-p-1 …(2)

Where *df* is degree of freedom, always expessed with F and indicate mean activity value. A number of models are developed by using each training set of n-1 objects and predicting each excluded object in the test set.The formula for the calculation is:

$$Q^2_{L00} = 1 - {}^{PRESS}/_{SSY}$$

…(3)

Where PRESS is the squared difference between predicted and actual values, are added give the predictive residual sum of squares and SSY represents the variance of the observed responses of data-points around the mean value and expressed as:

$$PRESS = \sum(Y_1-\hat{Y}_1)^2 \;;$$
$$SSY=\sum(Y_1-\hat{Y}_1)^2$$

…(4)

Where y, y and y are, respectively, the measured, predicted, and averaged (over the entire dataset) values of the dependent variable;the summations run over all compounds in the training set.

The mathematical expression for this parameter is given below

$$R^2_{Test}=1-\frac{\sum(Y_{pred(Test)}-Y(Test)]^2}{Y(Test)] \;-Y_{(Training)}]^2}$$

…(5)

Where, $Y_{pred(Test)}$ and $Y_{(Test)}$ indicate predicted and observed activity values, respectively of the test-set compounds and $\check{y}_{(Training)}$ indicate mean activity value of set.For a predictive QSAR model, the value of predicted r^2_{Test} should be more than 0.5.

Thus, two novel parameters, r_p^2 and r_m^2 have been introduced further to account for the acceptability of a predictive QSAR model The modified r^2 [$r_m^2{}_{(Test)}$] is given by the Equation (1.6)

$$r^2_{m(Test)}=r^2 \times \left(1-\sqrt{r^2+r_0^2}\right)$$

…(6)

Where r_0 is squared correlation coefficient between the observed and predicted values of the test set compounds. with intercept set to zero.

Another modified parameter is R_p^2 , which penalizes the model R^2 for the difference between squared mean correlation coefficient (R_r^2) of randomized models and squared correlation coefficient (R^2) of the non- randomized model.This parameter may be calculated using following Equation

$$R_p^2=R^2 \times \sqrt{R^2+R_r^2}$$

…(7)

This parameter ensures that the models this developed are not obtained by chance an the value greater than 0.5 accounts for an acceptable model[11] The *AIC*, corresponding to total variable p, is given by Equation

$$AIC = SSY.\ (n+p)/(n-p) \quad \ldots(8)$$

A model which gives the minimum *AIC* value is considered potentially the mostu useful.The index FIT is closely related to the F-value is given by Equation

$$FIT = r^2.\ (n-k-1)/(n+k^2)(1-r^2) \quad \ldots(9)$$

The relation for *LOF* parameter is given by Equation (1.10)

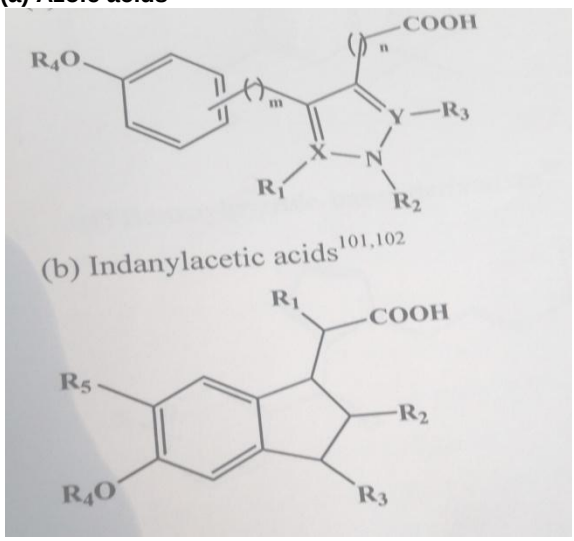
$$LOF=SSY/[n\ \{1-k\ (d+1)/n\}^2] \quad \ldots(10)$$

Where *d* is smoothing parameter

Scaffolds for the Present Qsar Study

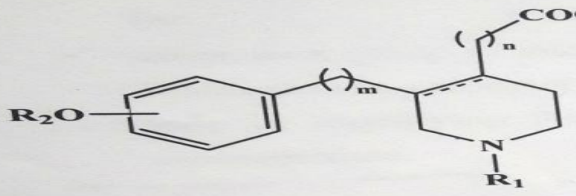
The data set for the present QSAR studies will be taken from the public domain.All these data sets have reported biological activities and established structure activity- relationships.An attempt will be made to rationalize the structural features ina molecule to furnish optimum antidiabetic activity.The following series will be considered for the present QSAR study

(a) Azole acids[100]

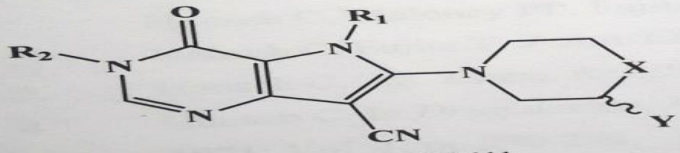


(b) Indanylacetic acids[101,102]

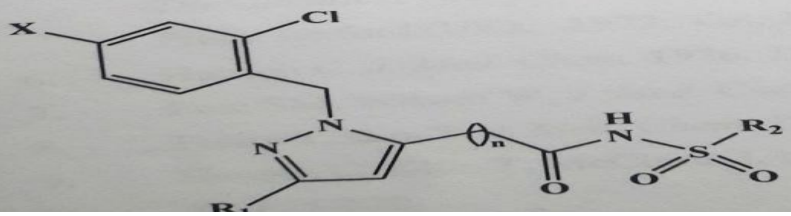
(g) Piperidine and dehydropiperidine carboxylic acids[10



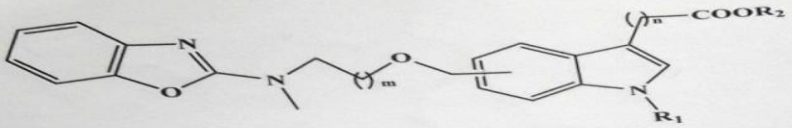
(h) 7-Cyanodeazahypoxanthine derivatives[109]



(i) Acylsulfonamides[110,111]

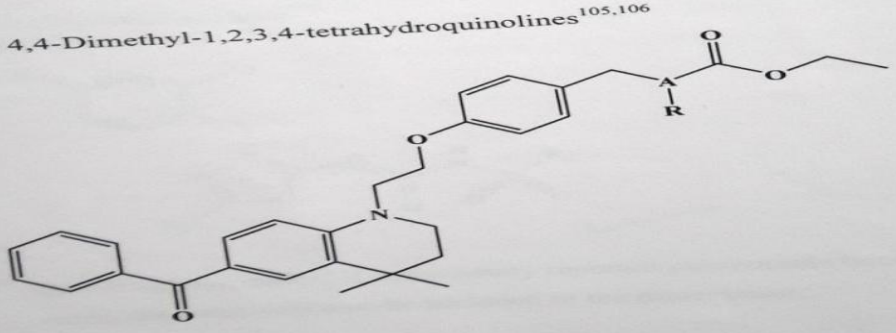


(c) Benzoxazole containing indole analogs[103]

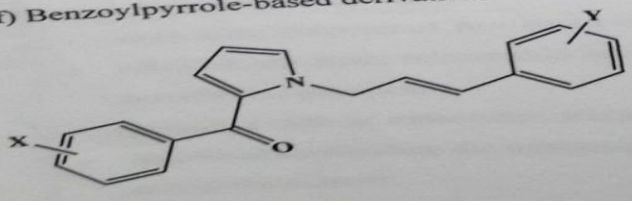


(d) 3-{4-[3-(2-Aryl-phenoxy)butoxy]-phenyl}propionic acids[104].

(e) 4,4-Dimethyl-1,2,3,4-tetrahydroquinolines[105,106]



(f) Benzoylpyrrole-based derivatives[107]



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