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Pharmacophore Modeling And 3D QSAR Analysis of Pyrazole-3-Carbohydrazone Derivatives as Dipeptidyl Peptidase IV Inhibitors for Type II Anti-Diabetic Therapy

Krishna sarma Pathy[1]*, Pathy saihithi sarma[2] and Rachna chaturvedi[2]

[1]*Ipl research , Ashbaugh . Lucknow , India*

[2]*Amity Institute of biotechnology, Amity University, Uttar Pradesh, Lucknow, India*

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***Corresponding author:** Krishna Sarma Pathy, Ipl research , Ashbaugh, Lucknow, India

Abstract

This study delves into the design of promising Type II anti-diabetic agents acting as inhibitors of Dipeptidyl Peptidase-IV (DPP-IV). Given the significance of Type 2 Diabetes Mellitus (T2DM) as a prevalent metabolic disorder, the pursuit of improved therapies is essential. Leveraging 3D QSAR and pharmacophore Modeling techniques, this research identifies critical structural elements pivotal to the biological efficacy of cyan pyrrolidine derivatives. The objective is to provide invaluable insights fostering the development of potent Type II anti-diabetic agents.

Keywords: Diabetes Mellitus; Pyrrolidine Derivatives; Hypoglycemia; Cyan Pyrrolidines; Anti-Diabetic Agents; Drug Development; Saxagliptin

Abbreviations: T2DM: Type 2 Diabetes Mellitus; DPP-IV: Dipeptidyl Peptidase-IV; QBD: Quality by Design; CPP: Critical Process Parameters; KPP: Key Process Parameters; CQAS: Critical Quality Attributes; API: Active Pharmaceutical Ingredient; AMB: Cyclic Amidine; OXAMD: Oxamidine

Introduction

Type 2 Diabetes Mellitus (T2DM) is a widely recognized chronic metabolic ailment associated with heightened morbidity and mortality. Notable trials such as the Diabetes Control and Complications Trial, the Stockholm Diabetes Intervention Study, and the United Kingdom Prospective Diabetes Study have substantiated the advantages of enhanced glucose control in reducing complications. Underlying T2DM are three core anomalies: insulin resistance, diminished insulin secretion, and excessive hepatic glucose production. Current therapeutic options encounter limitations encompassing safety concerns, efficacy sustainability, and dosing inconveniences. Adverse effects commonly linked to existing agents encompass hypoglycemia, weight gain, and gastrointestinal intolerance. Dipeptidyl peptidase-4 (DPP-4) inhibitors, exemplified by saxagliptin, offer distinctive mechanisms with potential for improved safety, tolerability, and effectiveness. Approved agents such as sitagliptin (Januvia®) and vildagliptin (Galvus®) exemplify this class [1-10].

Methods

This article presents a comprehensive exploration involving 3D QSAR and pharmacophore modeling applied to substituted cyan pyrrolidines as potential Type II anti-diabetic agents and DPP-IV inhibitors. Cyan pyrrolidines, a chemically significant class, have shown diverse medical relevance. Various researchers have reported the anti-diabetic potential of cyan pyrrolidine derivatives. The utilization of 3D QSAR aims to unravel the intricate three-dimensional structural attributes pivotal for their anti-diabetic activity. The obtained 3D QSAR model (characterized by a squared correlation coefficient, r^2, of 0.9945 and a cross-validated squared correlation coefficient, q^2, of 0.9866) attests to its statistical significance and predictive proficiency. The insights derived from this model shed light on the structural motifs driving the inhibitory potency of cyan pyrrolidines. Additionally, pharmacophore modeling has been employed to discern the structural prerequisites crucial for the biological efficacy of

these compounds. This study underscores the critical role of pharmacophore modeling and 3D QSAR analysis in elucidating the intricate structural attributes that underpin the efficacy of substituted cyan pyrrolidines as Type II anti-diabetic agents and DPP-IV inhibitors. The outcomes have potential implications for advancing the development of potent therapies in the realm of Type II diabetes treatment [11-15].

Type II Diabetes Mellitus (T2DM) is a persistent metabolic ailment characterized by three primary anomalies: insulin resistance, diminished insulin secretion, and excessive hepatic glucose production. However, existing treatments exhibit limitations in terms of safety, effectiveness, and tolerability. To address this, there is potential in Dipeptidyl Peptidase-IV (DPP-IV) inhibitors like saxagliptin, which operate through distinct mechanisms. This study delves into the creation, correlation of structure and activity, and modeling of pharmacophores for cyanopyrrolidine derivatives, aiming to establish them as potential DPP-IV inhibitors [16-20]. Saxagliptin belongs to the category of oral antidiabetic agents referred to as DPP-IV inhibitors or "incretin enhancers." The phase III trial initiative for saxagliptin encompassed investigations involving both standalone administration and concurrent use with other established antidiabetic medications such as metformin, sulphonylureas, and thiazolidinediones. Among the evolving classes of antidiabetic drugs for type 2 diabetes, DPP-IV inhibitors, including vildagliptin (Galvus®) and sitagliptin (Januvia®), are already endorsed and employed clinically. The appeal of these agents lies in their ability to sustainably lower HbA1c levels-a pivotal marker of blood glucose management-via an orally administered, well-tolerated approach, distinguishing them from many conventional oral antidiabetic drugs. The invention primarily revolves around DPP4 inhibitors, particularly in the context of a novel formulation involving cyano-pyrrolidine-based compounds. Saxagliptin, represented as (1S,3S,5S)-2-(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl)-2-azabicyclo[3.1.0]hexane-3-carbonitrile, falls within the scope of cyano-pyrrolidine-based DPP4 inhibitors. Its chemical structure is as follows: [Chemical formula representation] (Figure 1).

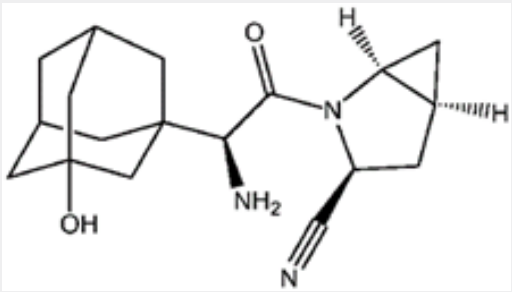

Figure 1.

Saxagliptin, in the form of its hydrochloride salt, is marketed under the trade name ONGLYZA® by Bristol-Myers Squibb for the treatment of type 2 diabetes mellitus. Each film-coated tablet of ONGLYZA for oral use contains either 2.79 mg saxagliptin hydrochloride (anhydrous) equivalent to 2.5 mg saxagliptin, or 5.58 mg saxagliptin hydrochloride (anhydrous) equivalent to 5 mg saxagliptin and the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. In addition, the film coating contains the following inactive ingredients: polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc, and iron oxides. Thermodynamic Degradation of Saxagliptin, cyclic amidine ("AMD") and oxamidine ("OXAMD") respectively. The hydrolysis of amidine to diketopiperazine occurs in the presence of water (Figure 2)[21-25].

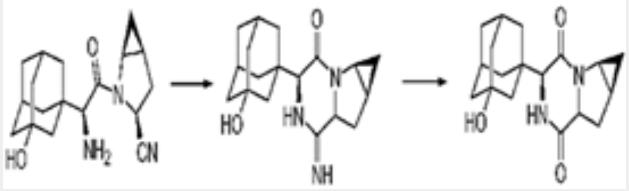

Figure 2.

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The intramolecular cyclization reaction leading to the formation of a cyclic amidine can occur in both the solid state and the solution state. Furthermore, this reaction can be exacerbated by utilizing processing conditions like wet granulation, roller compaction, or tableting. This chemical instability necessitates the provision of conditions and excipients that either minimize or prevent this undesired reaction during the manufacturing of saxagliptin formulations. The solid-state structures of (lS,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxy-l-adamantyl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile, referred to as Saxagliptin, can exist in the form of stable amorphous and crystalline solids. Crystalline solids exhibits long-range order, while amorphous solids lack this order, resembling a frozen liquid with solid-like rheological properties. When a compound like saxagliptin is transformed into an amorphous state but not fully dispersed within a polymer matrix, leading to amorphous clusters embedded in the polymer, it is termed a "glass suspension." This results in a glass suspension with two distinct glass transition temperatures, arising from the amorphous API and the polymer.

Discussion

The discussion section delves into the methodology, results, and implications of the study. It outlines the synthesis of saxagliptin, a DPP-IV inhibitor, using 3D QSAR and pharmacophore modeling to uncover structural features crucial for Type II anti-diabetic activity. A predictive model was created using a training set of molecules, with statistical analysis evaluating its forecasting accuracy. The study highlights molecular attributes impacting the inhibitory potency of cyanopyrrolidine derivatives, as identified through pharmacophore modeling for interaction with the DPP-IV receptor. Amorphous solids generally exhibit greater solubility compared to crystalline forms due to their lack of long-range order and higher surface area. To enhance the solubility of a crystalline solid, transforming the active pharmaceutical ingredient into an amorphous form is advantageous. When a crystalline material is heated to its melting point (Tm), it transitions from a solid to a liquid state, with reversible behavior upon cooling. Rapid cooling below Tm can prevent crystallization, resulting in a supercooled liquid. If this supercooled liquid is further cooled to its glass transition temperature (Tg), molecules kinetically solidify, forming a glass. While molecules in a supercooled liquid have higher mobility than in a glassy state, the latter still exhibits some mobility [26-30].

Due to this mobility, it is beneficial for the glass transition temperature of the active pharmaceutical ingredient to be significantly higher (e.g., at least 20°C, preferably 30°C, or even 40°C) than the actual storage conditions. Amorphous Saxagliptin, with a relatively low Tg of about 54°C, tends to recrystallize under storage conditions. Stabilizing the amorphous form by increasing its Tg is crucial to prevent recrystallization. This can be achieved by mixing the API with a second component, typically polymers that decrease the mobility of Saxagliptin molecules and thwart recrystallization. Two approaches can be used to prepare glass solutions via the spray drying technique: using Saxagliptin as a salt or as a free base in situ with an acid. This yields Saxagliptin dispersed within a polymer-formed matrix [31-40]. The intramolecular cyclization process that leads to the formation of a cyclic amidine can take place in both the solid and solution states. Moreover, this reaction can be intensified by employing various processing conditions such as wet granulation, roller compaction, or tableting. This chemical instability necessitates the establishment of conditions and additives that can either reduce or prevent this undesirable reaction during the manufacturing of saxagliptin formulations. The solid-state structures of Saxagliptin, specifically (lS,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxy-l-adamantyl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile, can exist in the form of both stable amorphous and crystalline solids. Crystalline solids exhibit a well-ordered structure over long distances, whereas amorphous solids lack this order, resembling a frozen liquid with solid-like rheological properties [41-45].

When a compound like saxagliptin transitions into an amorphous state but isn't fully dispersed within a polymer matrix, resulting in amorphous clusters embedded in the polymer, it is referred to as a "glass suspension." This leads to a glass suspension that possesses two distinct glass transition temperatures, stemming from the amorphous active pharmaceutical ingredient (API) and the polymer. The discussion section delves into the study's methodology, outcomes, and implications. It outlines the synthesis of saxagliptin, a DPP-IV inhibitor, using 3D QSAR and pharmacophore modeling to identify critical structural features for Type II anti-diabetic activity. A predictive model was developed using a training set of molecules, and its forecasting accuracy was assessed through statistical analysis. The research underscores the molecular attributes that influence the inhibitory potency of cyanopyrrolidine derivatives, as identified by pharmacophore modeling for interaction with the DPP-IV receptor. Amorphous solids generally exhibit higher solubility compared to crystalline forms due to their lack of long-range order and greater surface area. Converting a crystalline solid into an amorphous form can enhance its solubility. When a crystalline substance is heated to its melting point (Tm), it transforms from a solid to a liquid state and can revert upon cooling. Swift cooling below Tm can prevent crystallization, yielding a supercooled liquid. If this supercooled liquid is further cooled to its glass transition temperature (Tg), molecules solidify kinetically, forming a glass. Although molecules in a supercooled liquid have higher mobility compared to those in a glassy state, the latter still maintains some level of mobility [46-50].

Because of this inherent mobility, it's advantageous for the glass transition temperature of the active pharmaceutical ingredient to be substantially higher (e.g., at least 20°C, preferably 30°C, or even 40°C) than the actual storage conditions. Amorphous Saxagliptin, with a relatively low Tg of approximately 54°C, tends to revert to a crystalline state under storage conditions. Elevating the Tg of the amorphous form is essential to prevent such

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recrystallization. This can be achieved by blending the API with a secondary component, usually polymers that reduce the mobility of Saxagliptin molecules and hinder recrystallization. The spray drying technique can be employed in two ways to create glass solutions: utilizing Saxagliptin as a salt or as a free base in situ with an acid. This results in Saxagliptin being dispersed within a polymer-formed matrix. Critical Quality Attributes (CQAs) of the drug substance were defined, and strategies to control their impact on product quality were presented. Through risk assessments of the manufacturing process, Critical Process Parameters (CPP) and Key Process Parameters (KPP) were identified. Uni- and multivariate experiments were conducted to define the design space within the studied ranges. Acceptable ranges for all process parameters were established to ensure consistent attainment of defined CQAs. A five-batch campaign within the defined design space at the commercial manufacturing site validated the approach. In essence, the Quality by Design (QBD) approach to saxagliptin drug substance manufacturing yielded enhanced process knowledge and a manufacturing design space that consistently produces high-quality drug substances. The process is considered to be well under control [51-65].

Process Description

Stage 1

The reaction involves (1S, 3S, 5S)-2-(2-azabicyclo-[3.1.0] hexane-3-carboxamide methane sulfonic acid reacting with (2S)-2-{[(benzyloxy)carbonyl]amino}-2-(3-hydroxyadamantan-1-yl)acetic acid in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 1-hydroxybenzotriazole hydrate, and diisopropylethylamine. This yields Benzyl-N-[(1S)-2-[(1S,3S,5S)-3-carbamoyl-2-azabicyclo[3.1.0]hexan-2-yl]-1-(3-hydroxyadamantan-1-yl)-2-oxoethyl]carbamate (Stage-I) [66-70].

Stage 2

Benzyl-N-[(1S)-2-[(1S,3S,5S)-3-carbamoyl-2-azabicyclo[3.1.0]hexan-2-yl]-1-(3-hydroxyadamantan-1-yl)-2-oxoethyl]carbamate from Stage-I reacts with trifluoroacetic anhydride in the presence of ethyl nicotinate, leading to the pure Benzyl-N-[(1S)-2-[(1S,3S,5S)-3-cyano-2-azabicyclo[3.1.0] hexan-2-yl]-1-(3-hydroxyadamantan-1-yl)-2-oxoethyl)carbamate (Stage-II) [71-75].

Stage 3

In his step, Benzyl-N-[(1S)-2-[(1S,3S,5S)-3-cyano-2-azabicyclo[3.1.0]hexan-2-yl]-1-(3-hydroxyadamantan-1-yl)-2-oxoethyl)carbamate (Stage-II) reacts with hydrogen gas in the presence of palladium catalyst and is treated with HCl, resulting in saxagliptin HCl dihydrate tech material [76-78].

Stage 4

The product from Stage-III (Saxagliptin HCl dihydrate tech) is purified and dried to obtain pure saxagliptin HCl dihydrate product [79].

3D QSAR and Pharmacophore Modeling of Substituted Cyanopyrrolidines as Potential Type II Anti-Diabetic Agents. In the realm of medicinal chemistry, 3D QSAR and pharmacophore modeling have been employed to explore the promising potential of substituted cyan pyrrolidines as Type II anti-diabetic agents, particularly as Dipeptidyl Peptidase-IV (DPP-IV) inhibitors. These cyanopyrrolidines, possessing diverse medical functions, have garnered attention for their significant therapeutic applications. Several studies have been conducted to investigate their viability as Type II anti-diabetic agents. The application of 3D QSAR techniques aimed to unveil the intricate three-dimensional structural elements pivotal for eliciting Type II anti-diabetic activity. The outcomes of the 3D QSAR analysis, characterized by a squared correlation coefficient (r^2) of 0.9945 and a cross-validated squared correlation coefficient (q^2) of 0.9866, underscore the statistical significance and exceptional predictive capacity of the model. These findings yield critical insights into the structural attributes governing the inhibitory potential of cyanopyrrolidines.

Additionally, pharmacophore modeling was harnessed to discern the essential structural features contributing to the biological efficacy of cyanopyrrolidines. The knowledge garnered from this investigation holds paramount importance for shaping the development of potent Type II anti-diabetic agents, particularly as DPP-IV inhibitors. Type II diabetes, a prominent metabolic disorder with global prevalence, underscores the significance of this research. This ailment stems from impaired insulin effects on the liver and skeletal muscles, coupled with diminished insulin secretion. Glucagon-like peptide-1 (GLP-1) emerges as an insulinotropic hormone with anti-diabetic potential, marked by glucose-dependent insulin stimulation and glucagon secretion inhibition. However, the rapid inactivation of GLP-1 by Dipeptidyl Peptidase-IV (DPP-IV) curtails its clinical utility. To address this, orally active DPP-IV inhibitors have been pursued to extend GLP-1 activity, resulting in reduced blood glucose levels.

Previous studies involving GLP-1 analogs and DPP-IV inhibitors have shown promise in improving cardiovascular disease outcomes associated with diabetes. However, challenges such as side effects and potency limitations persist. This underscores the potential of computer-aided drug design, as exemplified by quantitative structure-activity relationship (QSAR) studies and pharmacophore modeling. These methodologies shed light on the structural attributes underpinning biological activity. In the current study, a series of cyanopyrrolidine derivatives were subjected to QSAR studies and pharmacophore modeling using VLife-MDS 4.3 software. Computational analyses were executed on standard hardware and software configurations. IV inhibitory activities compounds with reported DPP-IV inhibitory activities, was utilized for model development [80-82].

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Ligand preparation, molecular alignment, and descriptor generation were integral to the QSAR analysis. A meticulous selection process led to the identification of a robust QSAR model, marked by high correlation coefficients and statistically significant F and p values. Noteworthy descriptors like E-550, S-1165, and E-1204 emerged, revealing steric and electrostatic interactions crucial for anti-diabetic activity. Further, pharmacophore modeling delineated key interaction features between ligands and receptors, offering a blueprint for rational drug design. In conclusion, this study's integration of 3D QSAR and pharmacophore modeling techniques presents a holistic approach to designing effective Type II anti-diabetic agents. The insights gained from these analyses hold promise for guiding future drug development endeavors, yielding compounds with enhanced potency and improved pharmacological profiles. Ultimately, this work contributes to the pool of knowledge driving the discovery of novel DPP-IV inhibitors with potential therapeutic applications in diabetes management (Figure 3-7 and Table 1,2).

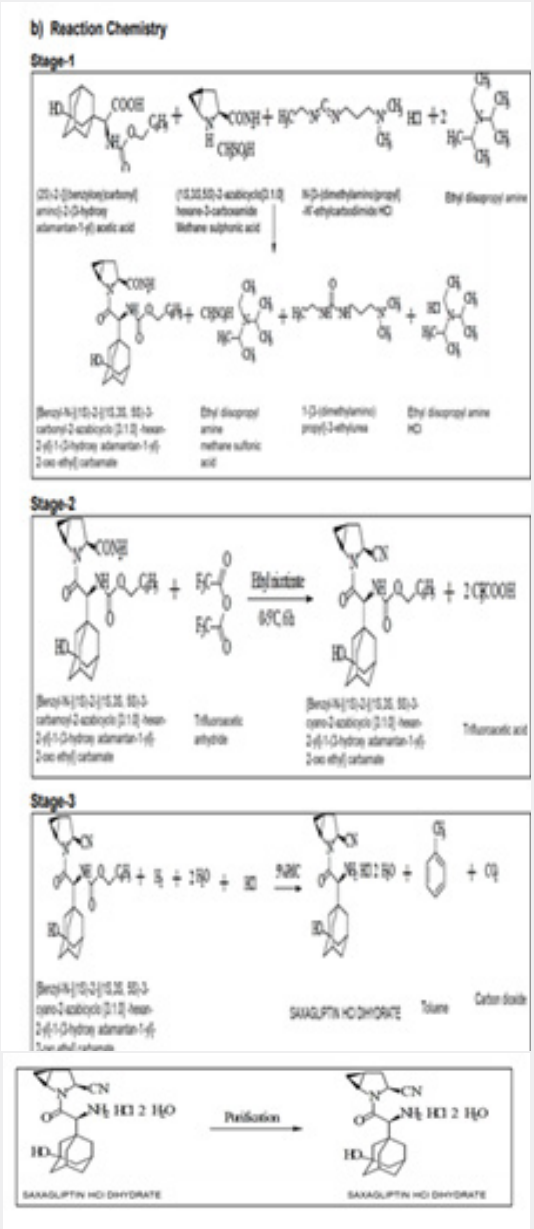

Figure 3: Reaction chemistry.

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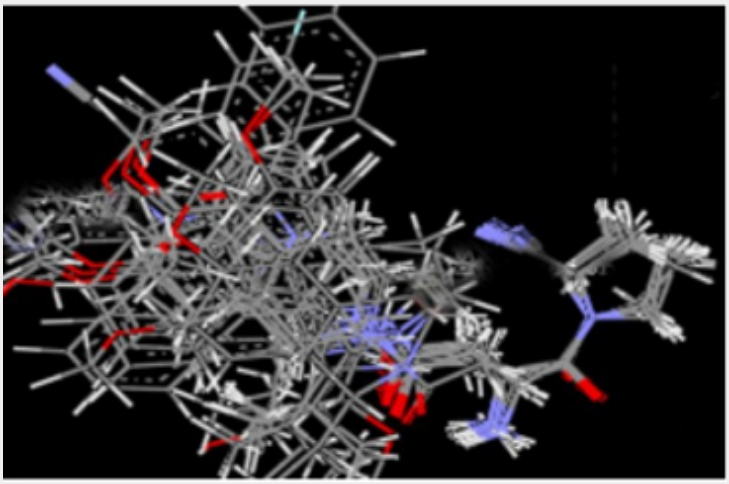

Figure 5: Showing alignment of molecules.

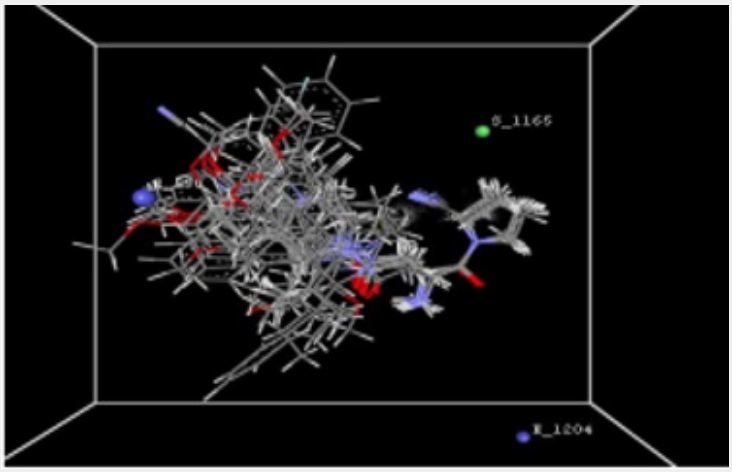

Figure 6: Field point of selected QSAR model.

Table 1: Presenting the molecules used in QSAR study.

Coin pound	R	Ri	OPP-IVICit(n!)
83	H	H	99
8b	6.7-(mtcJ)	H	63
8c	6.7-(OMc)	-(Cfb):OH	45
8d	6.7-(mic)	isopropyl!	47
St	6.7-(mk)i	Bet1zyl	97
8(	6.7-(mk)i	ltrl·B111)'1	73
8g	6--0 1<	tert·Bllt)'I	72
8h	7-0 1c	ttn·Bllt)'I	195
93	H	-CH(4-FC'..Ji5)l	211
9b	H	Nicolinoai1tik	87

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9c	H	Bet120yl	123
!Oa	H	H	238
!Ob	H	Bet1zyl	252
IOc	H	Ethyl	140
!Od	H	lsopropyl	212
!Oc	H	ttrt·Bllt)'I	251
Ila	3,4-0Mc	H	116
lib	H	CH_2O k	182
lie	H	lsopropyl	.>05

Table 2: Derivatives under study with observed and predicted activity.

Sr. No	Compound code	Observed activity	Predicted activity
1	8a	2	0.89
2	8b	1.8	1.2
3	8c	1.65	1.86
4	8d	1.67	0.69
5	8e	1.99	1.02
6	8f	1.86	1.66
7	8g	1.86	1.61
8	8h	2.29	0.59
9	9a	2.36	0.25
10	9b	1.94	1.59
11	9c	2.09	2
12	10a	2.38	1.87
13	10b	2.4	1.9
14	10c	2.15	1.57
15	10d	2.33	0.23
16	10e	2.4	1.25
17	11a	2.06	2.09
18	11b	2.26	1.52
19	11c	2.48	1.76

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