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Diamino Acid-Tetrazole Derivatives: Antihypertensive and Antimicrobial Investigation.

Sanket Parshuram Zanjad [1,2], Yashwant Bhaskar Pandit [3], Dattatraya Mahadu Chaudhari [4], Shivaji Sandu Pandit [1,2,4]*

Address: [1]Department of Chemistry and Research Center, Padmashri Vikhe Patil College of Arts, Science, and Commerce, Pravaranagar, Ahmednagar, Maharashtra, India;

[2]Savitribai Phule Pune University (formerly University of Pune), Ganeshkhind, Pune, Maharashtra, India, 411007,

[3]Department of Chemistry, Ben-Gurion University of the Negev, Beer-Sheva 8410501, Israel;

[4]Department of Chemistry, School of Basic and Applied Sciences, MGMU University, Chhatrapati Sambhajinagar, Maharashtra, India; And

[5]Pravara Gramin Shikshan Sanstha Art's, Commerce and Science College, Satral, Rahuri, Ahmednagar, Maharashtra, India.

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KEYWORDS

Diamino acid-functionalized tetrazole, Anti-hypertensive activity, In vivo study; biological activity.

ABSTRACT:

Background: Recent research for new antihypertensive drugs has been intensively attempted because of the high rate of morbidity and several side effects that are associated with first-line medications among hypertensive patients.

Objective: The current study investigates the antihypertensive and antibacterial effects of newly synthesized diamino acid-functionalized biphenyl tetrazole derivatives.

Result: Among the synthesized tetrazole derivatives, six selected compounds were investigated for antihypertension activity. In vivo experiments were conducted on male albino Wistar rats against the standard drug, telmisartan. Compounds Biphenyl Tetrazole Isonipecotic L-Alanine Isonipecotic–OH (BPT-Inp-Ala-Inp-OH), Biphenyl Tetrazole Isonipecotic L-Phenylalanine Isonipecotic–OH (BPT-Inp-Phe-Inp-OH), and Biphenyl Tetrazole Isonipecotic L-Leucine Isonipecotic–OH (BPT-Inp-Leu-Inp-OH) were found to have excellent activity. Whereas, compound Biphenyl Tetrazole Isonipecotic Glycine Isonipecotic–OH (BPT-Inp-Gly-Inp-OH) showed moderate Antihypertensive activity, and the remaining compounds, Biphenyl Tetrazole Isonipecotic L-Tyrosine Isonipecotic–OH (BPT-Inp-Tyr-Inp-OH), Biphenyl Tetrazole Isonipecotic L-Valine Isonipecotic–OH (BPT-Inp-Val-Inp-OH), exhibit less activity.

Significance: We observed that antihypertensive and antimicrobial activity investigations are correlated with electrical and structural properties of the compounds.

Conclusion: This study will contribute to the understanding of the correlation between activity and structural assessment of the compound.

INTRODUCTION

Tetrazole derivatives are known active pharmaceutical ingredients (APIs), essential synthetic scaffolds in medicinal chemistry that have a purely synthetic origin. Tetrazole is in the class of aromatic heterocycles with an unsaturated five-membered ring, with one carbon and four nitrogen atoms. The highest number of nitrogen consequences most stabilized compound compared with pentazoles. [1] Tetrazole has pyridine-like double bonds and exists in two tautomeric forms. The molecular formula of tetrazole is CN_4H_2 and has an acidic nature because of the presence of four nitrogen atoms. 5-substituted 1H-tetrazole is commonly used in medicinal chemistry as a carboxylic acid as its bio-isosteric replacement. [2]

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Although both functional groups differ in structure, but display similar biological activity because of minutely different physicochemical properties. [3] Tetrazole chemistry offers a wide range of applications in medicine, biochemistry, and agriculture. [4] They functionalize important parts as ligands in coordination chemistry [6], as explosives in material science [7] and photography [8], and serve as bioisosteres for cis-amide and carboxylic acids in medicinal chemistry [9]. They are adaptable pharmacophores in medicinal chemistry because of the multiple nitrogen atoms present in their structure. Tetrazole ring-containing drugs show significant activity and importance in drug categories like antibacterial [10], antifungal [11], antiviral [12] [13], analgesic [14] [15], anti-inflammatory [16] [17], anticonvulsants [18], anti-allergic [19], antiulcer [20], and antineoplastic [21].

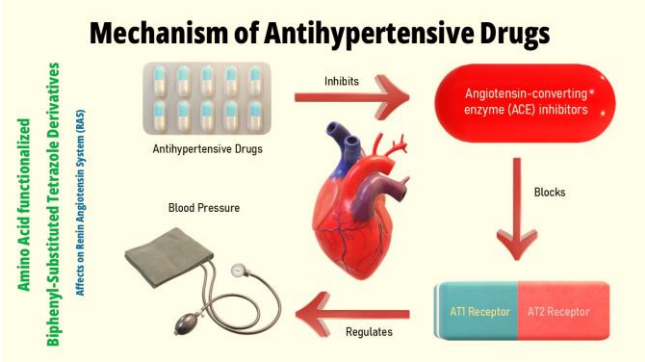

Fig. 1. Mechanism of antihypertensive drugs.

The basic distinction of blood pressure is conditional on the stage where pressure is exerted by the arterial walls upon the contraction of the heart or relaxation of the heart. Systolic blood pressure is measured when the heart contracts, while diastolic blood pressure is measured when the heart relaxes. A ratio is a distinctive way to represent blood pressure. Biphenyl-substituted Tetrazole received more attention because of its application in the synthesis of antihypertensive drugs, which are used to treat high blood pressure. [22] Moreover, tetrazole has been applied in the treatment of cancer [23] and AIDS [24]. Tetrazole derivatives actively support plant growth regulators, herbicides, and fungicides in crop protection in the agricultural domain. [6] [25] Tetrazole acts as an intermediate in organic synthesis for some complex heterocyclic compounds through various rearrangement reactions. [26] An enormous number of medicinally important compounds containing the tetrazole moiety have been approved by the US FDA. [27] The WHO estimates that around 1.13 billion people are suffering from hypertension, with only one in five achieving optimal blood pressure control. Nearly half of the US population, 108 million people, are diagnosed with hypertension, and 81 million are receiving antihypertensive treatment. [28] Hypertension can be caused by a variety of factors, including a poor diet, excessive salt and low potassium intake, obesity, alcohol use, and minimal physical activity. [29]

The available tetrazole analogs for the treatment of hypertension such as *Losartan*, *Telmisartan*, *Valsartan*, *Irbesartan*, *Candesartan*, and *Olmesartan*. These drugs played a vital role in inhibiting the angiotensin-converting enzyme. Rennin secretion in the kidney's juxtaglomerular apparatus indicates rennin-angiotensin activation, and it concludes in an octapeptide, angiotensin II (AII) generation, which interacts at targeted receptors present in various tissues. [30] The rennin angiotensin system (RAS) generates octapeptide angiotensin II (Ang II), which plays an important role in the pathological process of hypertension. Octapeptide angiotensin II (Ang II) is an effective vasoconstrictor. Either by inhibiting the angiotensin-converting enzyme (ACE), rennin, or by blocking the Ang II receptors, several researchers were encouraged to focus on the development of drugs that prevent the effects of Ang II. In wide distribution, mainly two kinds of receptors have been distinguished: the AT1 receptor, which is mainly responsible for these effects, and the functional role of the AT2 receptor is unclear. [31] [32] AII's most significant impacts are blood pressure regulation through vasoconstriction, which increases vascular resistance; Volemia regulation via stimulated release of vasopressin and aldosterone, which induces saline retention, and adrenocorticotropic hormone regulation. (ACTH). The effectiveness of angiotensin-converting enzyme (ACE) inhibitors as antihypertensive drugs therefore endorses the concept that lowering all levels by inhibiting one of the RAS enzymes or directly blocking the AII receptors is a good way to treat hypertension. [33]. They block AT1 and AT2 receptors, which are located in the kidney, heart, vascular smooth muscle cells, the brain, and adrenal glands. The Rennin Angiotensin System (RAS) is a powerful regulator of blood pressure. [34] The rennin-angiotensin system (RAS) has a vital role in maintaining electrolyte/ fluid balance in normal and hypertensive subjects and regulates

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cardiovascular homeostasis. These drugs block the Rennin-Angiotensin System (RAS, enzyme), which is secreted in the kidneys. [35]

MATERIALS AND METHODS

Different compounds were developed via a synthetic route for novel heterocyclic tetrazole di-peptide organic compounds, mainly focused on diamino acid functionalized biphenyl tetrazole derivatives. This procedure is performed in multiple stages, improving known methods of preparation that have been performed in our laboratory. We have developed the following diamino biphenyl tetrazole isonipecotic acid amine (BPT-Inp-X-OH) compounds. The following compounds were developed based on amino acid–(**1**) Biphenyl Tetrazole Isonipecotic Glycine Isonipecotic–OH (BPT-Inp-Gly-Inp-OH) (**2**) Biphenyl Tetrazole Isonipecotic L-Alanine Isonipecotic–OH (BPT-Inp-Ala-Inp-OH), (**3**) Biphenyl Tetrazole Isonipecotic L-Tyrosine Isonipecotic–OH (BPT-Inp-Tyr-Inp-OH), (**4**) Biphenyl Tetrazole Isonipecotic L-Phenylalanine Isonipecotic–OH (BPT-Inp-Phe-Inp-OH), (**5**) Biphenyl Tetrazole Isonipecotic L-Valine Isonipecotic–OH (BPT-Inp-Val-Inp-OH), and (**6**) Biphenyl Tetrazole Isonipecotic L-Leucine Isonipecotic–OH (BPT-Inp-Leu-Inp-OH). We tested them with standard *Telmisartan* on male albino Wistar rats for antihypertensive activity.

We applied the renovascular hypertension model that had been used with a mercury manometer to generate a physiograph operating a blood pressure transducer and strain gage coupler. Eight groups consisting male albino Wistar rats were created. Rats weighing 130 - 180 g were supplied by the Institutional Animal House and used for testing at Vivo Bio Tech Limited, Hyderabad (CPCSEA No: 1317/PO/RcBiBt/S/37/CPCSEA). The acute renal hypertension blood pressure measurement model was used for evaluation. Standard chemicals were used for the testing, which comprise Sodium chloride 0.9%, Heparin 1000 I.U./ml Solution, Adrenalin -10 µg/100ml, Noradrenalin -10 µg/100ml, Acetylcholine -10 µg/100ml, Telmisartan (STD)- 5 mg/ml, Anesthetic agent: ketamine HCI + xylazine.

The procedure followed was calibrating and standardization the physiograph and transducer with the help of a mercury manometer. [36] The level of mercury in the left arm of the manometer was adjusted to 90-100 mm of Hg (normal blood pressure); this was done in steps of 10 mm at a time, and the physiograph so obtained was used as a calibration graph for further calculation. One arm of the transducer syringe, containing 1000 I.U. heparin solution, was attached to prevent coagulation of blood. Male albino rats weighing about 130-180 g were taken for the study. The animal was anesthetized by intraperitoneal injection of a mixture of ketamine hydrochloride and xylazine. After induction of anesthesia, the left renal artery was blocked by the use of an artery clamp for 45 minutes. Clamping of the left renal artery was done to raise the systolic pressure. The trachea was cannulated to provide artificial respiration to the animals during surgery. Then, the jugular vein was cannulated, and a 0.5 ml dose of normal saline was given to the animal via the jugular vein. This standard protocol was followed for all the tests and compounds while operating on the animal. The carotid artery was cannulated and attached to a pressure transducer. This pressure transducer was previously calibrated with the help of a mercury manometer, and a calibration pressure curve was generated. After attaching the carotid cannula, the renal artery clamp was removed. This caused a sharp increase in blood pressure because of the activation of the rennin-angiotensin system and a rise in the plasma rennin level. A standard solution of *Telmisartan* (STD) at a dose of 5 mg/kg body weight was administered via the jugular vein, and after giving the drug dose, waited until blood pressure returned to the baseline level. The standard tests with compounds were administered one by one in the juggler's vein. They showed their response, i.e., decrease in blood pressure, on the obtained physiograph. Change in blood produced by the 12 compounds was compared against that of *Telmisartan*, and three responses of each sample for obtaining mean blood pressure were plotted and shown in Figure 3 and tabled in Table 1 of Results. [36]

RESULTS

Synthesized compound tested for biological activity. The antihypertensive activity was tested using the renovascular hypertension model at Aster Analytics Research Institute. Figure 2 pictures the several stages involved in testing with male, albino Wistar rats.

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Fig. 2. Pictures from experimentation *in vivo* testing on male albino Wistar rats.

Table 1 describes the results for synthesized compounds against the standard drug below.

Table 1. Antihypertensive activity testing

Sr. No.	Compound	Mean Arterial Blood Pressure (mm-Hg)	Mean Reduction in Systolic Blood Pressure (mm-Hg)
1.	Control	136	-
2.	STD (*Telmisartan*)	96.23	42.77±2.37
3.	BPT-Inp-Gly-Inp-OH	101.49	27.39±3.48
4.	BPT-Inp-Ala-Inp-OH	99.68	33.67±4.28
5.	BPT-Inp-Tyr-Inp-OH	108.17	26.19±6.23
6.	BPT-Inp-Phe-Inp-OH	104.28	34.74±7.29
7.	BPT-Inp-Val-Inp-OH	112.96	25.38±4.09
8.	BPT-Inp-Leu-Inp-OH	102.56	35.58±4.67

The compounds synthesized were confirmed employing FT-IR, 1H-NMR, and 13C-NMR. Amid all the synthesized Diamino Tetrazole derivatives, six compounds were selected and tested to evaluate their antihypertension activity against the standard drug Telmisartan. Compounds Biphenyl Tetrazole Isonipecotic L-Alanine Isonipecotic–OH (BPT-Inp-Ala-Inp-OH), Biphenyl Tetrazole Isonipecotic L-Phenylalanine Isonipecotic–OH (BPT-Inp-Phe-Inp-OH), and Biphenyl Tetrazole Isonipecotic L-Leucine Isonipecotic–OH (BPT-Inp-Leu-Inp-OH) were found to have excellent activity. Whereas, compound Biphenyl Tetrazole Isonipecotic Glycine Isonipecotic–OH (BPT-Inp-Gly-Inp-OH) showed moderate Antihypertensive activity, and the remaining compounds, Biphenyl Tetrazole Isonipecotic L-Tyrosine Isonipecotic–OH (BPT-Inp-Tyr-Inp-OH), Biphenyl Tetrazole Isonipecotic L-Valine Isonipecotic–OH (BPT-Inp-Val-Inp-OH), exhibit less activity.

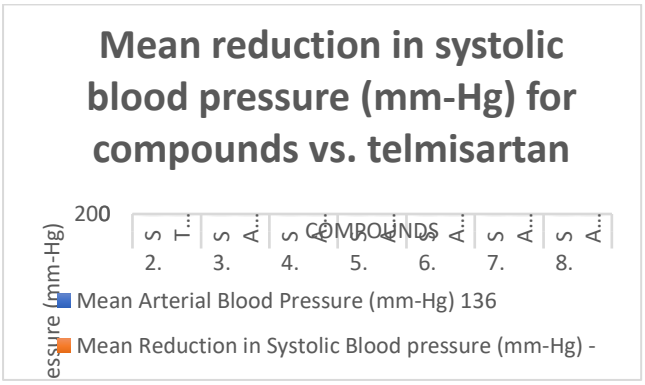

Fig. 3. Mean reduction in systolic blood pressure (mm Hg), synthesized compounds vs. STD.

DISCUSSION

We would extend this result to the reasoning of activity with structural aids. Figure 4 represents the structures of compounds 1-6 synthesized and tested for antihypertensive activity. Most of the discovered AT1 receptor antagonists are distinguished by the presence of a biphenyl fragment harboring an acidic moiety in their structure, as well as the pendant heterocyclic system (valsartan lacks the heterocyclic component) linked to the 4-position of the methyl, phenyl hydroxy groups. A significant effort has been made to develop rennin inhibitors, although orally active compounds have only recently been reported. [37-38]

A significant amount of research was performed on AII antagonists. Controlling RAS is the most direct way that can have the added advantage of minimizing the side effects observed with ACE inhibitors. [31] Researchers from DuPont discovered *Losartan*, the first orally active AT1 selective non-peptide AII antagonist, initiated by Takeda in 1995 as Cozaar, marketed for the treatment of hypertension.

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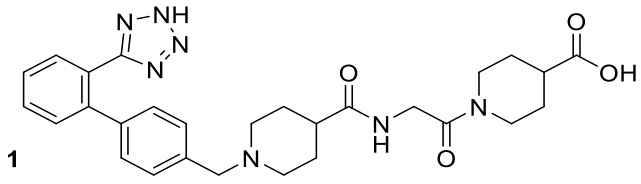
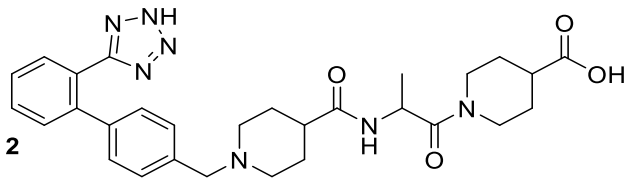
[39] In the *Losartan*, activity increases with a substitute at the 6th position of the nucleus, whereas it decreases with a small substituent at the 5-5-position. [39-40] Tetrazole and its typical derivative compounds are reported as AT1 receptor antagonists and exhibit non-competitive antagonism. [41] The amino group attaches to the carboxylic group and provides excellent electronic interactions, leading to antihypertensive activity and biological activity. [31] [42] The excellent activity of compounds 2, 4, and 6 refers to the two adjacent carboxyl groups near the phenyl, methyl group, and the nitrogen atom. An increase in electronic charge, balanced space, and structure results in controlled interactions, implying the highest activity. Compound 1 showed moderate activity; this might be a lack of charge balance because of the absence of carboxyl and phenyl groups compared to other structures. Compounds 3 and 5, because of the bulky phenyl structure and propyl group, which might be responsible for less interaction with RAS. [39-42]



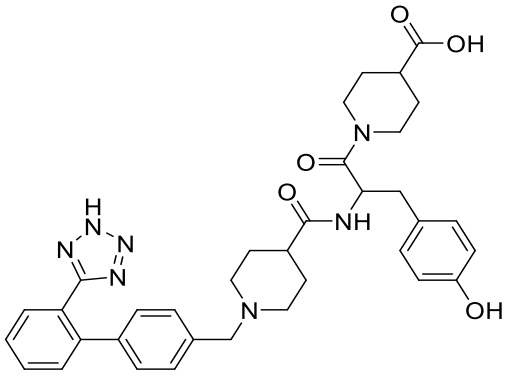
1

1-((1-((2'-(2*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)piperidine-4-carbonyl)glycyl)piperidine-4-carboxylic acid



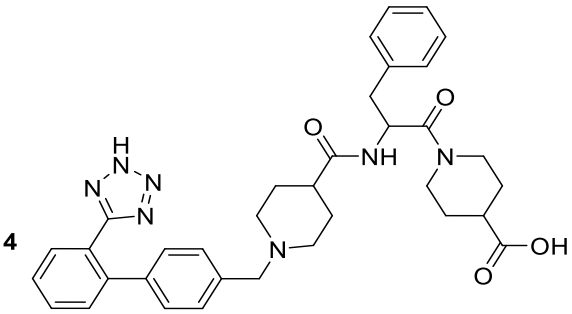
2

1-((1-((2'-(2*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)piperidine-4-carbonyl)alanyl)piperidine-4-carboxylic acid



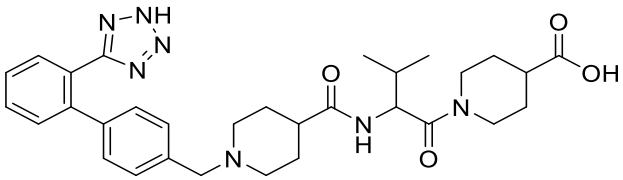
3

1-((1-((2'-(2*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)piperidine-4-carbonyl)tyrosyl)piperidine-4-carboxylic acid



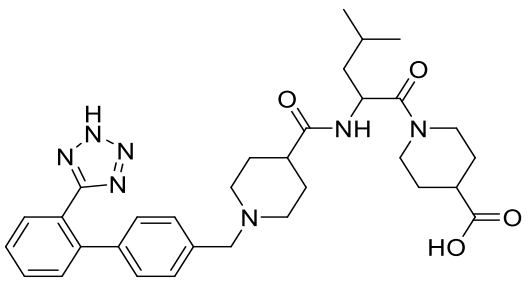
4

1-((1-((2'-(2*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)piperidine-4-carbonyl)phenylalanyl)piperidine-4-carboxylic acid



5

1-((1-((2'-(2*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)piperidine-4-carbonyl)valyl)piperidine-4-carboxylic acid



6

1-((1-((2'-(2*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)piperidine-4-carbonyl)leucyl)piperidine-4-carboxylic acid

Fig. 4. Structural representations of compounds 1-6.

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We have also tested the antimicrobial activity of the compound's Antimicrobial activity testing of compounds C-1, C-2, C-3, and C-4 was performed using a well diffusion method. Two test organisms, Escherichia coli and Staphylococcus aureus, were grown in nutrient broth for 14 to 18 h at 37 °C to get the culture in the log phase. These cultures were then adjusted with the optical density of 0.08-0.1 as per McFarland standards (0.5) [43], and 100µl of such bacterial suspension was spread on sterile Muller and Hinton agar medium. For a good diffusion technique, wells were bored with a sterile borer having an 8 mm diameter. Test compounds C-1, C-2, C-3, and C-4 were diluted to 100µg/ml, 500µg/ml, and 800 µg/ml concentrations. These concentrations were added to wells in aliquots of 100 µl. After this, the plates were incubated at 37 °C for 24 h and observed for the zone of inhibition. Tetracycline, penicillin, streptomycin, and gentamycin were selected as standard drugs.

Antimicrobial activity testing revealed that, after incubation at 37 °C for 24 h, the plate containing compounds C-1, C-2, C-3, and C-4 could not display a zone of inhibition against Escherichia coli and Staphylococcus aureus, indicating that the compounds C-1, C-2, C-3, and C-4 do not harbor antimicrobial activity. This result implies that the nitrogen present in the structure is a key point for the biologically active is absent in interaction, or the electron density is more on the carboxylic oxygen, which again an assist to the theory for antihypertensive activity.

Fig. 5. Antimicrobial activity

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CONCLUSION

Among the synthesized compounds, six diamino acids functionalized tetrazole derivatives were studied. The antihypertensive activity was studied with a standard drug. Three synthesized compounds were found to have excellent results toward antihypertensive activity, with one moderate and two low results for the synthesized compounds. The discussion on antihypertensive drug mechanisms is to elucidate the mechanism behind the synthesized diamino functionalized tetrazole derivative. We correlate the activity results of compounds to their structure and their electronic activity. This will help to understand the impact of structure on biological tests, such as antibacterial tests. The extensive studies include individual structural impacts.

Abbreviations

API: Active Pharmaceutical Drug Intermediates; SSNRI: Selective Serotonin And Nor Epinephrine Reuptake Inhibitors; RAS: Rennin-Angiotensin System; ABDD: Analogue-Based Drug Discovery; RAS: Rennin-Angiotensin System

Supporting Information

Supporting Information File 1: data and certificate of activity testing.

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Disclosure statement

The authors report that there are no competing interests to declare.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics of Experimentation

All procedures were done under the standard operating procedures and the guidelines provided by the Committee for the Control and Supervision of Experiments on Animals (CCSEA) as published in The Gazette of India, December 15, 1998, and biological evaluation of medical devices- Part 2: Animal welfare requirements. The study has been approved by the Institutional Animal Ethics Committee of Invitox R&D Institute. All animal studies were conducted under the guidelines of the Institutional Animal House of Vivo Bio Tech Limited, Hyderabad (CPCSEA No: 1317/PO/RcBiBt/S/37/CPCSEA).

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