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DESIGN, SYNTHESIS, AND MOLECULAR DOCKING OF BIPYRIDINE-BASED LIGANDS AS DUAL MODULATORS OF TGFB1 AND ITGB6

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ABSTRACT

Cancer remains a leading global health concern, with increasing incidence and mortality rates attributed to the limited availability of selective and effective anticancer therapies. Pyrimidine-based compounds and bipyridine derivatives have shown a wide range of pharmacological activities, including anticancer potential. In this study, we report the synthesis of 5'-Methoxy-[3,3'-bipyridine]-6-carboxamide via a Suzuki coupling reaction between 3-bromo-5-methoxypyridine and (6-carbamoylpyridin-3-yl) boronic acid using Pd $(PPh_3)_2Cl_2$ as a catalyst and K_2CO_3 as the base. The synthesized compound was characterized using NMR, FT-IR, HRMS, and chromatographic techniques. Ligands derived from this structure were evaluated through molecular docking studies against cancer-associated protein targets TGFβ1 (PDB ID: 1KLC) and ITGβ6 (PDB ID: 4UM8). Docking results revealed favorable binding energies, with SM showing stronger affinity towards ITGβ6 (–7.1 kcal/mol) and SM exhibiting better interaction with TGFβ1 (–6.1 kcal/mol). Detailed interaction analysis indicated key hydrogen bonding and hydrophobic interactions that contribute to the stability of the ligand-protein complexes. Drug-likeness and ADMET predictions further supported the potential of these compounds as therapeutic candidates. The findings provide a promising scaffold for the development of dual-target modulators of TGFβ1 and ITGβ6 pathways, pending further biological and pharmacological validation.

KEYWORDS: pyrimidine derivative, synthesis, anti-cancer, molecular docking.

INTRODUCTION

According to the WHO, 18 million people are diagnosed with cancer, and more than 9 million individuals lost their lives to the disease in 2018. These figures continue to rise as a result of the dearth of anticancer treatments that are both efficient and selective. Pyrimidine-based compounds have a wide range of pharmacological activities, including anti-inflammatory[1], antibacterial[2,3], anti-HIV[2], antidiabetic[4] and anticancer.[5,6,7] Antibacterial (sulfadiazine, trimethoprim), antiviral (trifluridine, idoxuridine), antimalarial (sulfadoxine), anti-HIV (Retrovir (zidovudine), stavudine), anti-tuberculosis (viomycin), and anticancer (5-fluorouracil) medications are the most well-known medications derived from pyrimidine analogs. Additionally, the findings indicate that compounds' anticancer activity is enhanced when a [(dialkylamino)alkyl] amino or (hydroxyalkyl)amino side chain is added.[8,9,10,11]

Bipyridines and their derivatives are widely employed as fundamental components in a variety of applications, including physiologically active compounds, ligands for transition-metal catalysis, photosensitizers, viologens, and supramolecular structures.[12-22] Many synthetic methods for the preparation of bipyridines have been devised, but they suffer from low conversion rates and harsh reaction conditions; hence, new methods are now under development. Problems can arise from the product's high coordination with the metal core, which reduces catalytic activity. The current study focuses on metal-catalyzed cross-coupling reactions (including Suzuki, Negishi, and Stille coupling), metal-catalyzed homocoupling reactions (Ullmann and Wurtz coupling), electrochemical methods, and other novel techniques for the synthesis of 5'-Methoxy-[3,3'-bipyridine]-6-carboxamide.[12]

Background: The Suzuki cross-coupling reaction

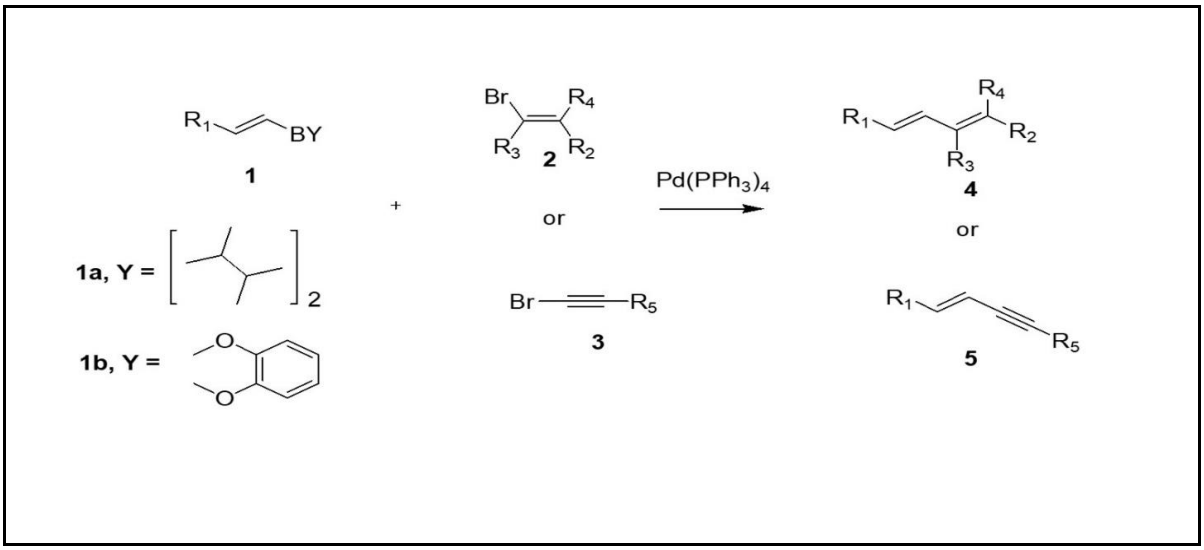
Reactions in which new carbon-carbon bonds are created are vital steps in organic synthesis. Many significant products (drugs, materials, polymers, optical devices, etc.) require the use of such reactions at some stage of their construction. During the past 50 years, transition-

metal mediated cross-coupling reactions have revolutionized this area of organic synthesis. They have become an important class of carbon-carbon bond forming reactions that have been modified and optimized over the years to give reliable, efficient results often using mild protocols. A few examples of the more well-known and utilized of these include the Heck,[23-27] Kumada,[28,29] Stille,[30-32] and Suzuki[33-45] coupling reactions. Prior to the discovery of these, the Ullmann reaction[46-48]– in which aryl halides are coupled in the presence of finely divided copper – was generally a routine method. Although its use in present times has somewhat dwindled, it is still of value and is still called upon on occasion. The scope of this reaction, however, is restricted by a number of inherent limitations. As the reaction usually requires elevated temperatures (in the region of 130 – 200°C) conditions as harsh as these automatically rule out the use of more thermally sensitive substrates. Also, stoichiometric or quasi stoichiometric quantities of copper are required resulting in large amounts of metal waste, which is costly in both economic and environmental terms. Lastly, when the Ullmann reaction is applied to the synthesis of symmetrical biaryl products, respectable results are usually achieved, but when unsymmetrical couplings are attempted between two unactivated aryl halides, three biaryl products are produced in approximately equal amounts. So, in light of these drawbacks, the need arose for an alternative, more selective cross-coupling protocol. Given its widespread popularity and extensive utilisation in both academic and industrial settings, it can be argued that these needs have been best fulfilled by the Suzuki coupling reaction.[19] Exponential numbers of papers have been published on the Suzuki reaction since its discovery, and it has often become the method of choice for carbon-carbon bond construction in many synthetic strategies.

The coupling of heteroaryl groups is in dispensable in today's synthesis of medicines and advanced materials.[46] The Suzuki–Miyaura coupling reaction is one of the most powerful methods to construct carbon bonds among the palladium-catalyzed arylations, and has been widely used for the formation of a biaryl structure in organic synthesis. In this coupling reaction between aryl halides and organoboron reagents there are a variety of advantages in the use of the latter due to their non-toxicity, tolerance toward functional groups, air- and moisture-stable properties and easy synthesis. During the last few decades, numerous efficient catalytic systems have been developed to expand the scope of relatively inert electrophilic substrates such as aryl bromide as coupling partners.[25]

Early Suzuki cross-coupling reactions

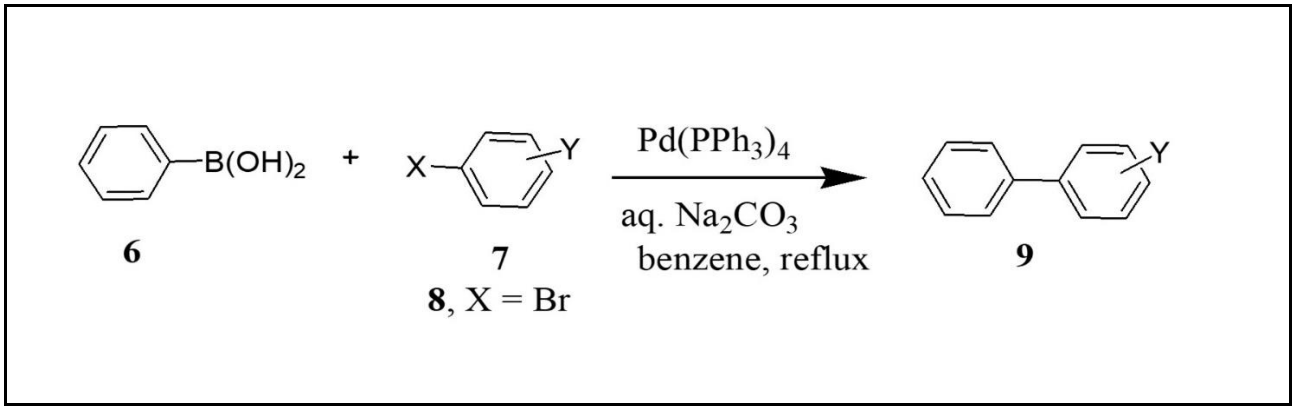
The first successful cross-coupling protocol employed by Suzuki and coworkers in 1979[47] coupled alkenyl boranes[48] together with alkenyl halides[49] or alkynyl halides[50] in the presence of a palladium catalyst and base to give conjugated dienes[40] or enzymes.



Scheme 1. First Suzuki cross-coupling reaction of (E)-1-alkenylboranes with 1alkenyl or 1-alkynyl bromides.

Despite being initially performed with alkenyl and alkynyl reagents, its scope was rapidly extended to include the coupling of carbons in aryl [51] alkyl [52] and heteroaryl group under a wide variety of conditions.

The first method towards the preparation of biaryls 10 was reported by Suzuki and Miyaura in 1981.[40] and used the conditions shown below.



Scheme 2.

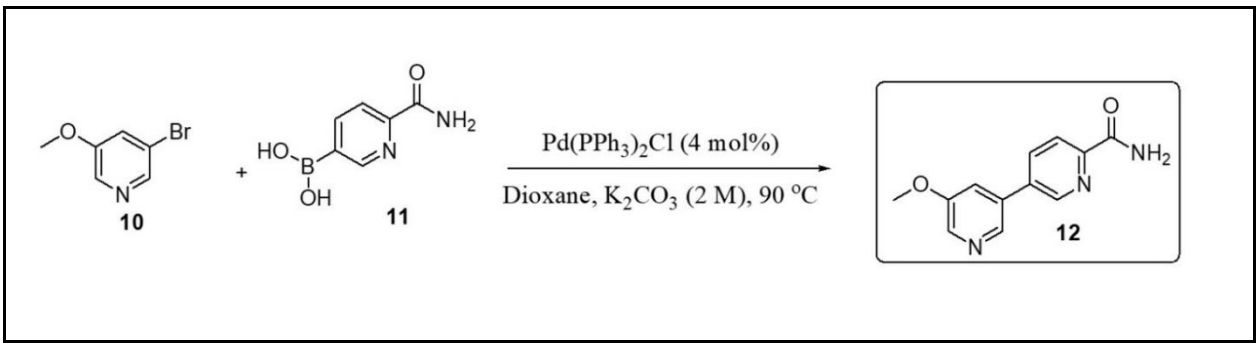
First Suzuki cross-coupling reaction towards biaryl products.

The reaction was carried out under homogeneous conditions, using aqueous Na_2CO_3 base. Good yields were also obtained under heterogeneous conditions. A wide range of standard bases were subsequently tested and used in the Suzuki reaction, namely K_2CO_3,[43] Cs_2CO_3, Tl_2CO_3 and K_3PO_4[49] and all gave the desired coupled products in high yields. Other alternative bases have also been tested, with good results achieved for more sterically challenging biaryl cross couplings with use of NaOH, $Ba(OH)_2$, to give just a few examples. Use of milder conditions such as those employing CsF, KF and Bu4NF have enabled the synthesis of biaryls containing base-sensitive functional groups.

METHODS

Synthesis of Synthesis of 5'-Methoxy-[3,3'-bipyridine]-6-carboxamide (12)

We Synthesis of 5'-Methoxy-[3,3'-bipyridine]-6-carboxamide (**12**) was started from commercially available 3-bromo-5-methoxypyridine (**10)** and 6-carbamoylpyridin-3-yl) boronic acid (**11**). For the exploration of substituents at the 3-position of the pyridine ring (Scheme 1), Suzuki coupling[22] of 3-bromo-5-methoxypyridine (**10)** was treated with 6-carbamoylpyridin-3-yl) boronic acid (**11**) using Pd $(PPh_3)_2Cl$ and Na_2CO_3, under reflux to obtained **12** as the sole product.



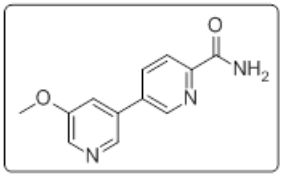
Scheme 3. 5'-Methoxy-[3,3'-bipyridine]-6-carboxamide (12).

Supporting information

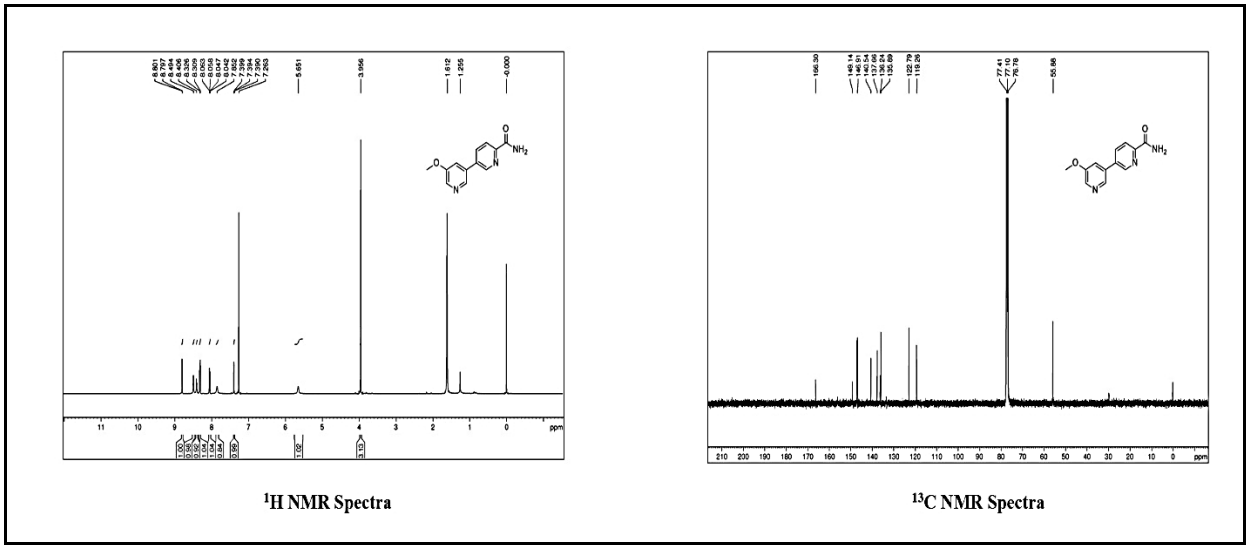
Synthesis of Synthesis of 5'-Methoxy-[3,3'-bipyridine]-6-carboxamide(12)

All reactions were carried out under nitrogen, unless otherwise specified. All required chemicals were procured from Aldrich or local manufacturers and used as purchased without further purification, unless noted (All carboxaldehydes were distilled prior to use). Melting points were determined using a hot stage apparatus and were uncorrected. ^1H and ^{13}C NMR spectra were recorded using 5 mm tubes on a 400 and 500 MHz NMR spectrometer [field strengths: 400/100 or 500/125 MHz respectively] in $CDCl_3$ solution (unless specified otherwise) with shifts referenced to tetramethyl silane (TMS, $\delta = 0$) for ^1H NMR spectra and chloroform-d middle peak of the triplet ($\delta = 77.10$ ppm) for ^{13}C NMR spectra. All *J* values are in Hz. Infrared spectra were recorded using ATR technique on a FT-IR spectrophotometer. Mass spectra were recorded using HRMS (ESI-TOF analyser) equipment. Thin-layer chromatography was performed on silica/alumina plates and components were visualized by observation under iodine/UV light at 254 nm. Column chromatography was performed on silica gel (100-200 mesh), for column elution process Hexane-EtOAc mixture was used as the eluent unless otherwise stated.

5'-Methoxy-[3,3'-bipyridine]-6-carboxamide



Yield: 59% (96 mg); white solid; mp:141-143 ^{o}C; TLC (EtOAc :Hexane), 60:40 (v/v): R_f = 0.26;^{1}H NMR (500 MHz, $CDCl_3$): δ 8.80 (d, *J* = 2.0 Hz, 1H), 8.49 (s, 1H), 8.41 (s, 1H), 8.32 (d, *J* = 8.5 Hz,1H), 8.05 (dd, *J* = 8.0, 2.5 Hz, 1H), 7.86 (brs, 1H), 7.40 (t, *J* = 2.5 Hz, 1H), 5.68 (brs, 1H), 3.96 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.3, 156.0, 149.1, 146.9, 140.5, 137.7, 136.2, 135.9, 133.4, 122.8, 119.3, 55.9; IR (neat): 3397, 3158, 2026, 2005, 1975, 1663, 1585, 1416, 1245, 1220, 1098, 1034, 772 cm^{-1}; HRMS (m/z): $[M+H]^{+}$calcd. for $C_{12}H_{11}N_3O_2$+H, 230.2424; found, 230.2426.



^{1}H NMR Spectra

^{13}C NMR Spectra

Ligand Preparation

The derived ligands were sketched in ChemDraw Pro 8.0 (Fig 1) and then converted into PDB format using Open Babel software. Energy minimization of the ligands was carried out converted them to pdbqt format by using PyRx Virtual Screening software.

Protein Receptor Preparation

The 3D structure of TGFβ, ITGβ6 with the PDB IDs: 1KLC, 4UM8 respectively were retrieved from the Protein Data Bank. All the ions, water molecules, and ligands were removed from the protein molecule using BIOVIA Discovery Studio software.[44,45] Proteins 1KLC, 4UM8 were loaded onto PyRx. Water molecules were removed and polar hydrogens were added, followed by addition of Kollman charges and converted the proteins to pdbqt format. After preparation of the proteins, receptors were subjected to molecular docking studies by using AutoDockVina - PyRx software.[46]

Prediction of Drug Likeness Activity

To check the pharmacological significance of the selected ligands, the drug likeness properties such as absorption, distribution, metabolism, excretion, and toxicity of the selected ligands were determined by using the SwissADME web tool.

RESULTS AND DISCUSSION

Starting with commercially available 3-bromo-5-methoxypyridine (**10**) and 6-carbamoylpyridin-3-yl) boronic acid (**11**) we synthesized 5'-Methoxy-[3,3'-bipyridine]-6-carboxamide (**12**). Suzuki coupling22 of 3-bromo-5-methoxypyridine (**10**) was performed with 6-carbamoylpyridin-3-yl) boronic acid (**11**) using Pd (PPh3)2Cl and K_2CO_3 under reflux to get 5'-Methoxy-[3,3'-bipyridine]-6-carboxamide (**12**) as the only product in order to explore substituents at the 3-position of the pyridine ring (Scheme 3).

Ligand protein analysis

To understand the possible interaction between the proteins TGFβ(1KLC), ITGβ6(4UM8) with ligand SM2, molecular docking was performed. The binding of the SM to TGFβ and ITGβ6 2D respectively were represented in 2D using Discovery studio and 3D representing in ribbon form and visualized using and PyMol in Fig 2 and 3. The binding energy of the protein ITGβ6 (4UM8) and the SM was found to be -7.0 kcal/mol respectively, whereas the binding energy of TGFβ1(1KLC) and ligand SM was found to be -6.1 kcal/mol respectively. whereas SM interacts with ITGB6 van der waals, hydrogen bonds, carbon-hydrogen bonds and alkyl bonds. SM interacts with Phe-159 Ala-96 by conventional hydrogen bond (Fig. 3). whereas SM interaction with TGFβ1 depicted conventional hydrogen bond formation with Arg18, Cys7, Ser10 and carbon-hydrogen bond with Phe8.

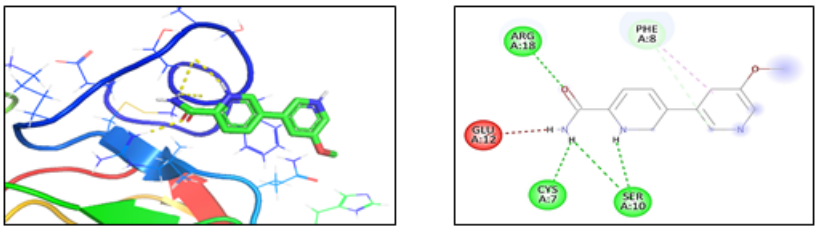


Figure 2: 3D and 2D representation of TGFβ_SM complex.

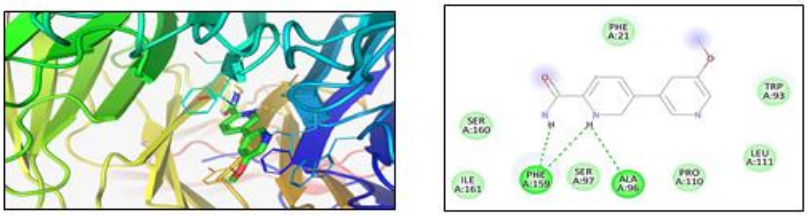


Figure 3: 3D and 2D representation of ITGβ6_SM complex.

Table 1: Molecular docking.

S.no	Ligand	Receptor	Binding Affinity kcal/mol	No. Hydrogen Bonds	Interacting Residues
1	SM	TGFβ	-6.1	4	Arg18, Cys7, Ser10, Phe8
2	SM	ITGβ6	-7.1	3	Ser160, Ile161, Phe159, Ser97, Ala96, Pro110, Leu111, Trp93, Phe21

The compound displayed favourable binding energies to the target proteins, with binding energies of -6.1 kcal/mol for SM with TFGFβ, binding energies of -7.1 kcal/mol for SM with ITGβ6. The synergic effect of hydrogen and hydrophobic interactions is evident in the binding affinity of the target protein with the docked ligands.

Interaction Analysis with ITGβ6, SM exhibits a more diverse interaction profile with van der Waals forces, hydrogen bonds, carbon-hydrogen, and alkyl bonds, suggesting a potentially more flexible or multi-point interaction. The conventional hydrogen bond with Phe-159 and Ala-96 in SM suggests a specific and potentially strong interaction with the active/binding site. SM in shows multiple hydrogen bonds (Arg18, Cys7, Ser10) and a carbon-hydrogen bond with Phe8, suggesting more electrostatic interactions which could compensate for slightly higher flexibility or lesser shape complementarity, reflected in a moderately stronger binding energy (–6.1 kcal/mol).

CONCLUSION

In this study, we successfully synthesized 5'-Methoxy-[3,3'-bipyridine]-6-carboxamide (**12**) through a Suzuki coupling reaction between 3-bromo-5-methoxypyridine (**10**) and (6-carbamoylpyridin-3-yl) boronic acid (**11**) using Pd $(PPh_3)_2Cl_2$ as the catalyst and K_2CO_3 as the base under reflux conditions. This reaction yielded the desired compound (**12**), which was further explored for its binding potential through molecular docking studies. The interaction profile highlights the synergistic role of hydrogen bonding and hydrophobic interactions in stabilizing these protein-ligand complexes.

Docking analysis revealed that both synthesized compounds (SM) demonstrated favourable binding energies with the target proteins TGFβ1 (1KLC) and ITGβ6 (4UM8). Overall, these findings suggest that compound SM may be a more selective and stronger binder for ITGβ6, while compound SM may be more balanced with slightly better affinity for TGFβ1. These ligands offer promising scaffolds for further structural optimization and biological evaluation as dual modulators of TGFβ1 and ITGβ6-associated pathways. However, experimental validation including biological assays and molecular dynamics simulations is essential to confirm the predicted interactions and assess stability, selectivity, and efficacy in physiological conditions.

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