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Synthesis, Characterization and Evaluation of their Antimicrobial Activity of Substituted 3-(4-((1-Phenyl-1H-1,2,3-Triazol-4-yl) Methoxy) Phenyl) Propanenitrile

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ABSTRACT: *We have developed a variety of novel phenyl propanenitrile conjugated triazole compounds* ***(7a–l)*** *and evaluated their anti-microbial activity (Anti-bacterial, anti-fungal activity). The synthesised compounds* ***7b, 7c, 7e, 7h*** *and* ***7i*** *have exhibited promising ani-microbial activity among all other analogues. Further, we disclosed the finding that 1,2,3-triazoles bearing a substituent like* ***(7b)*** *2-chlorophenyl,* ***(7c)*** *4-chlorophenyl,* ***(7e)*** *4-methylphenyl,* ***(7h)*** *4-Nitrophenyl and* ***(7i)*** *4-cynophenyl on triazole moiety might be the reason for the significant inhibitory activity. Moreover, 4-cynophenyl substituted compound* ***(7i)*** *showed better activity compared to Streptomycin.*

KEYWORDS: *Anti-bacterial, anti-fungal activity, triazole, inhibitory activity, Bacillus Subtilis, Streptomycin.*

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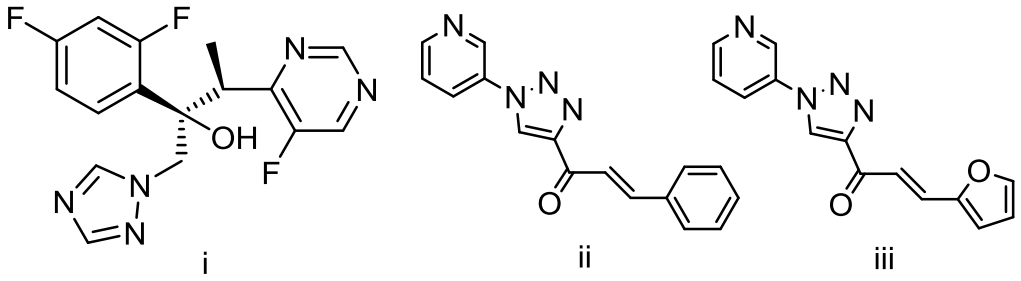
I. INTRODUCTION:

Harmful strains of bacteria proliferate on or within the body, leading to bacterial infections, which are mostly caused by Gram-positive and Gram-negative organisms. The worldwide health system is already under a great deal of strain from bacterial diseases contracted in hospitals and communities. One of the main issues with antibacterial therapy is the emergence of bacterial resistance to current medications, which calls for ongoing research into novel antibacterial drug classes.[1] Severe infections brought on by Gram-positive bacteria that are resistant to drugs are especially concerning since they have high fatality rates, particularly in hospital settings. The specific microorganisms accountable are vancomycin-resistant Enterococcus faecalis (VRE), methicillin-resistant Staphylococcus aureus (MRSA) [2-4], and penicillin-resistant Streptococcus pneumoniae, [5-6] The wide range of synthetic strategies that have been developed in order to get access to this scaffold has helped to high light the significant role that it plays in the field of organic chemistry [7].

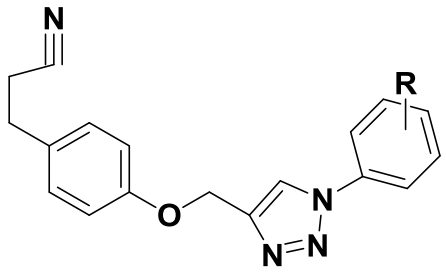
Triazoles are a class of chemical compounds that contain a five-membered ring composed of three nitrogen atoms and two carbon atoms. They find applications in various fields, including medicinal chemistry, agriculture, and materials science. The biological and chemical activities of triazoles largely depend on their specific structure and substituents. Copper-catalyzed alkyne-azide click reactions are the foundation of triazole synthesis.[8] Processes for making 1,4- (catalyzed by copper(I)[9] or 1,5-disubstituted (catalyzed by ruthenium (II) [10] Azide-alkyne mixtures Under benign conditions and with high regioselectivity, 1,2,3-triazoles provide a trustworthy way to assemble 1,2,3-triazoles with different substituents. Numerous biological screens conducted in 2018 [11–14] have demonstrated the anticancer, [15–17], antimicrobial, (i-iii) [18–21], anti-infective, [23–24], and antioxidant [25-27] properties of the 1,2,3-triazole-bearing hybrids under investigation. It was also believed that triazole-linked derivatives, which were frequently used in peptides that simulated a trans-amide bond despite their negative effects on the activity of native peptides,[29]. had an impact on the biology of adenosine diphosphate ribosylation [28].

A hybrid molecule behaves as two or more separate pharmacophores because it has two or more structural domains, each of which has a different biological function and dual activity [30, 31]. In comparison with the parent medications, hybrid molecules have the ability to lower toxicity, eliminate drug cross resistance, widen the biological range, and improve efficacy [32, 33]. For example, TD-1792 and Ro 23-9424 are examples of hybrid molecules that have been the subject of clinical studies for the treatment of a variety of disorders in the last three decades [34, 35]. This suggests that hybrid molecules are crucial to the creation of novel medications. It stands to reason that hybridizing 1,2,3-triazole with other antibacterial pharmacophores might yield novel compounds with exceptional efficacy against both drug-sensitive and drug-resistant microorganisms.



Voriconazole-antifungal

anti-bacterial activity compounds



7 (a-l)

R=a=H,
R=b=o-Cl,
R=c=p-Cl,
R=d=m-$COCH_3$,
R=e=p-CH_3,
R=f=o-OH,
R=g=p-OH,
R=h=p-NO_2,
R=i=p-CN,
R=j=p-Br,
R=k=o-OCH_3,
R=l=m-F

Some of the existed compounds showed potential in vitro anti-bacterial activity and synthesised compounds.

Developing new antimicrobial agents presents numerous challenges due to the complex nature of microbial life, their ability to evolve rapidly, and economic factors. To keep ahead of microbial adaptability and create strategies for creating potent antimicrobial agents while lowering the possibility of resistance development, we must continuously innovate. Developing strong antimicrobial activity is a difficult task that calls for a mix of innovative science, teamwork, and tactical planning. Triazoles [36] have drawn a lot of attention in the process of developing flow methods because they have uses in several industrial sectors. [1, 2, 3]-Triazoles are often put together by [3 + 2] dipolar cycloaddition processes, which are so efficient and atom-efficient that they are known as "click reactions."

II. RESULT AND DISCUSSION:

In our approach to a Cu(I) catalyzed alkyne azide cycloaddition (CuAAC) sequence to access substituted [1,2,3] triazoles **7(a-l)**, the model substrates chosen to work with are shown in **Scheme-4.** The 3-(4-Hydroxy-phenyl)-propanenitrile conjugate 1,2,3-triazole derivatives were synthesized from commercially available moieties. The present invention relates to preparation of 3-(4-Hydroxy-phenyl)-propanenitrile (3). In particular, the preparation method comprises of following steps: (I) Friedel-Crafts reaction of phenol (**1)** and acrylonitrile (**2**) materials under the effect of aluminum trichloride to obtain p-hydroxy phenyl propanenitrile crude product, and purified. The inventive method obtains 3-(4-Hydroxy-phenyl)-propanenitrile (3) with purity of more than 98%, and yield of more than 85%. A 4-Prop-2-ynyloxy-propanenitrile **(3)** and product confirmed by TLC which is spot appeared at slight non polar region in 30% pet ether, n-hexane medium**.** After that 3-(4-Hydroxy-phenyl)-propanenitrile **(3)** reaction with Propgyl bromide **(4)** in potassium carbonate, in DMF at 4-5hrs, to obtained 3-(4-Prop-2-yn-1-yloxy-phenyl)-propanenitrile **(5)**, product confirmed by TLC, now 3-(4-Prop-2-yn-1-yloxy-phenyl)-propanenitrile **(5)** reaction with different substituted aryl azides **(6 a-l)** at the end of the alkyne group is used to synthesize the compounds Substituted 3-(4-((1-phenyl-1H-1,2,3-triazol-4-yl) methoxy) phenyl) propanenitrile **(7a-l).** high yields of the products (80–85%) were obtained.

Every single structure of the recently created compounds was characterized using information from infrared spectroscopy (IR), 13C NMR, ESI-MS, and 1H NMR. The proton of the description molecule (7a-l) (dissolved in CDCl3 and DMSO) showed a singlet appearance at 8.18–9.50 ppm, which is characteristic of the triazole proton, and a singlet appearance at 5.00–5.80 ppm, which is indicative of the oxygen–attached methylene proton (O–CH2). In the 13C NMR spectra, the carbon of the triazole ring was detected at a frequency of 120 to 125 ppm. The oxygen-attached methylene carbon (O-CH2) was measured at 0.0 to 60 ppm the

oxygen-attached methylene carbon ($O–CH_2$) was observed, and all of the other protons and carbons resonated in the expected region and IR and Mass spectral values are observed their expected integral values.

III. ANTI-MICROBIAL ACTIVITY:

Antibacterial Activity of Compounds 7(a-l):

All the newly synthesized compounds **7(a-l)** were assayed for their antibacterial activity against three representative Gram-positive bacteria *viz*. *Bacillus Subtilis* (MTCC 441), *Bacillus Sphaericus* (MTCC 11) and *Staphylococcus Aureus* (MTCC 96), and three Gram-negative bacteria *viz*. *Pseudomonas Aeruginosa* (MTCC 741), *Klobsinella Aerogenes* (MTCC 39) and *Chromobacterium Violaceum* (MTCC 2656) by disc diffusion method. For the antibacterial assay standard inoculums ($1\text{-}2\times10^7$ c.f.u/mL 0.5 Mc Farland standards) were introduced on to the surface of sterile agar plates, and a sterile glass spreader was used for even distribution of the inoculums. The discs measuring 6.26 mm in diameter were prepared from Whatman no.1 filter paper and sterilized by dry heat at 140 °C for 1 h. The sterile discs previously soaked in a known concentration of the test compounds were placed in nutrient agar medium. The plates were inverted and incubated for 24 h at 37 °C. The mean inhibition zones were measured and compared with the standard drug Streptomycin and the results are presented in **Table 1**.

ANTIBACTERIAL ACTIVITY OF COMPOUNDS 7(a-l)

Compound	Mean Zone Inhibition (MZI) in 100 µg/mL					
	B. Subtilis	**B. Sphaericus**	**S. Aureus**	**P. aeruginosa**	**K. aerogenes**	**C. violaceum**
7a	26	25	22	24	22	20
7b	**30**	**28**	**30**	**25**	**25**	**26**
7c	**29**	**27**	**30**	**25**	**25**	**27**
7d	20	18	16	18	20	16
7e	**29**	**26**	**30**	**25**	**25**	**26**
7f	14	18	22	20	18	20
7g	16	20	18	20	22	18
7h	**30**	**27**	**30**	**25**	**25**	**27**
7i	**31**	**29**	**32**	**28**	**28**	**30**
7j	22	20	18	20	18	20
7k	20	18	22	24	20	24
7l	16	18	19	17	19	20
Streptomycin	**30**	**28**	**31**	**26**	**26**	**28**

The Compounds **7b**, **7c, 7e**, **7h,** and **7i**,exhibited potent good antibactirial activity compared to standard drug at the tested concentrations.The presence of **(7b)** 2-chlorophenyl, **(7c)** 4-chlorophenyl, **(7e)** 4-methylphenyl, **(7h)** 4-Nitrophenyl and **(7i)** 4-cynophenyl on triazole moiety might be the reason for the significant inhibitory activity.

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ANTIFUNGAL ACTIVITY OF COMPONDS 7(a-l)

Compound	Mean zone inhibition (MZI)[a] in 100 µg/mL			
	C.albicans	**A.fumigatus**	**T.rubrum**	**T.mentagrophytes**
7a	16	18	20	21
7b	**24**	**28**	**26**	**25**
7c	**24**	**27**	**24**	**26**

7d	22	24	23	24
7e	**25**	**26**	**25**	**25**
7f	16	18	22	20
7g	18	26	20	20
7h	**25**	**28**	**26**	**25**
7i	**26**	**28**	**28**	**26**
7j	20	18	19	20
7k	19	20	16	18
7l	20	18	17	20
Amphotericin B	**25**	**28**	**26**	**26**
Amphotericin B (100 µg/disc) was used as positive reference and compounds 7(a-l) (100 µg/disc).				

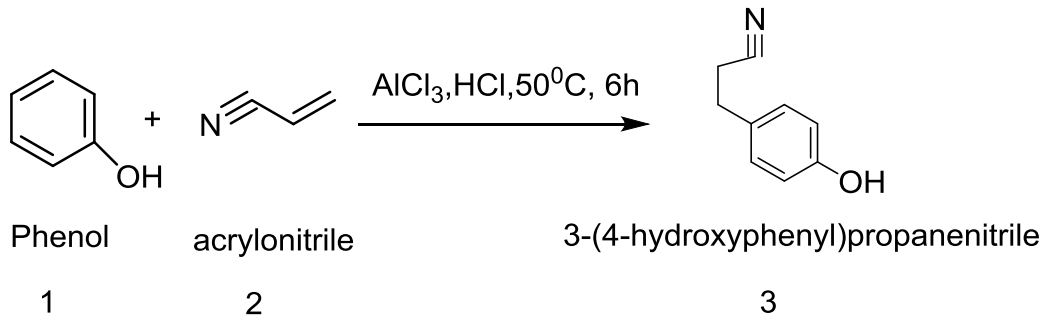
The Compounds **7b**, **7c, 7e**, **7h,** and **7i,**exhibited potent good antibactirial activity compared to standard drug at the tested concentrations.The presence of **(7b)** 2-chlorophenyl, **(7c)** 4-chlorophenyl, **(7e)** 4-methylphenyl, **(7h)** 4-Nitrophenyl and **(7i)** 4-cynophenyl on triazole moiety might be the reason for the significant inhibitory activity.

IV. EXPERIMETAL SECTION:

We used all of the chemical compounds that we bought from BLD, TCI, and Merck, including the organic reagents and solvents, without doing any further purification procedures. Instrument Bruker Advance II 500 MHz spectrometers running at 500 and 125 MHz helped get 13C NMR and 1H NMR spectra in CDCl3. Parts per million (ppm) is the unit of measurement for chemical shift values. The spin multiplicities are represented by the following notations: singlet (s), doublet (d), doublet of doublet (dd), triplet (t), multiples (m), and coupling constant values are shown in hertz (Hz). The mass and infrared spectra were recorded using the QSTAR XL GCMS and the Shimadzu FT-IR-8400s mass spectrometer, respectively. Melting points in an open glass capillary tube were measured using a DbkProg melting point device, and the findings were given without correction.

Synthesis of 3-(4-hydroxyphenyl) propanenitrile (3):

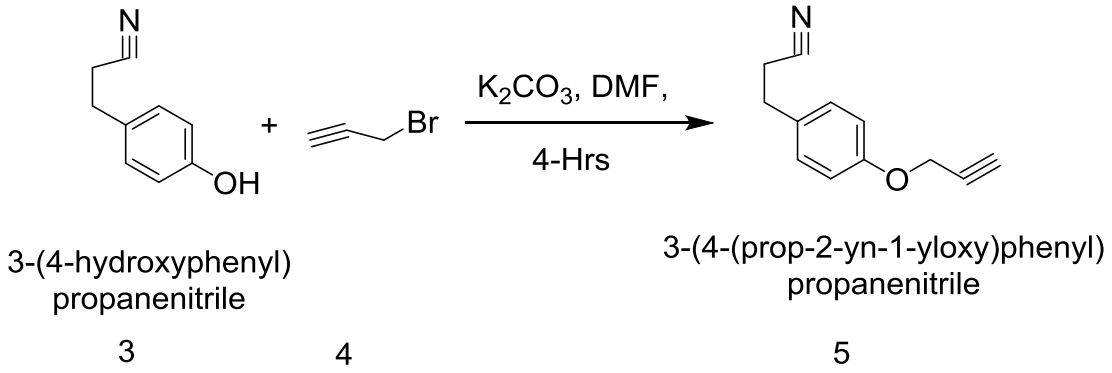
The present invention relates to preparation of 3-(4-hydroxyphenyl) propanenitrile (3). In particular, the preparation method comprises of following steps: (I) Friedel-Crafts reaction of phenol (1) and acrylonitrile (2) materials under the effect of aluminum trichloride to obtain 3-(4-hydroxyphenyl) propanenitrile crude product, and finally, the compound was purified by column chromatography using 20% EtOAc/ hexane solvent mixture as an eluent. The inventive method obtains 3-(4-hydroxyphenyl) propanenitrile (3) with purity of more than 98%, and yield 90%. (MP:118-120 ^{0}C) IR Data IR: υ_{max} cm^{-1}(KBr) 3403.87, 3102.08, 2995.42, 2302.14, 1421.56, 1256.46, 768.34, 668.27 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.02 (s, 1H), 7.25 (d, J=6.68 Hz, 2H), 7.16 (d, J=7.08 Hz, 2H), 2.96 (t, 2H), 1.85 (t, 2H). ^{13}C NMR(DMSO) 158.25, 146.26, 132.35, 128.46, 78.59, 35.75, 17.31. ESI-MS: *m/z* 147 [M+H] $^+$; HRMS: cacld. For C_9H_9NO.



Scheme-1

Synthesis of 3-(4-(prop-2-yn-1-yloxy) phenyl) propanenitrile (5):

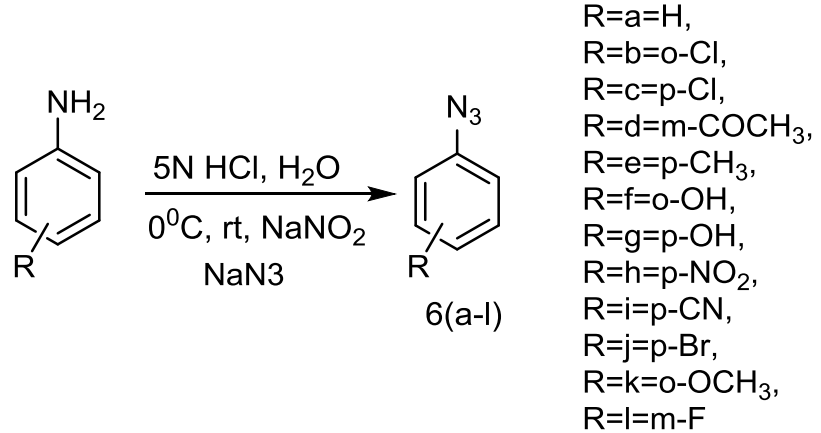
In order to synthesize the compound **3-(4-(prop-2-yn-1-yloxy) phenyl) propanenitrile (5)**, the starting material commercially available compound of **3-(4-hydroxyphenyl) propanenitrile (3),** which was treated with propargyl bromide **(4)** in the presence of dry dimethyl formamide (Dry DMF) and dry potassium carbonate at room temperature for 4 to 5 hours. The Compound **3-(4-(prop-2-yn-1-yloxy) phenyl) propanenitrile (5)** were identified by TLC in 30% Pet ether: Ethyl Acetate (EtOAc), spot was observed at slight non polar region compare to starting material. finally, the compound was purified by column chromatography using 12% EtOAc/ hexane solvent mixture as an eluent. yield 85%. (MP: 126-128^{0}C). IR Data IR: υ_{max} cm^{-1}(KBr) 3109.21, 2996.51, 2301.14, 1402.26, 1252.24, 762.56, 662.42. cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, J=6.91 Hz, 2H), 6.98 (d, J=7.01 Hz, 2H), 2.24 (s,1H), 2.08 (s, 2H), 1.34 (t, 2H), 1.24 (t, 2H). ^{13}C NMR(DMSO) 156.25, 148.26, 142.76, 136.35, 128.46, 78.59,76.85, 68.45, 36.75, 16.31. ESI-MS: *m/z* 185 $[M+H]^+$; HRMS: cacld. For $C_{12}H_{11}NO$.



Scheme-2

Synthesis of substituted azido benzene (6.1a-l):

The aromatic substituted azido benzene **(6.1 a-l)** was made by adding 5N hydrochloric acid (HCl) solution to a mixture of corresponding amines (6 a-l) in CH_2Cl_2 at 0°C, then gradually adding sodium nitrite solution ($NaNO_2$) while shaking at zero degrees Celsius for half an hour. After adding NaN_3 at zero degrees Celsius, the mixture was agitated for two hours at the ambient temperature. After that, it was left alone to let the organic and aqueous layers separate. To get the needed aryl azides **(6.1 a-l)**, the organic layer was washed with $NaHCO_3$, then brine, and the solvent was evaporated in a vacuum. In the next step, these azides are used without any further purification.

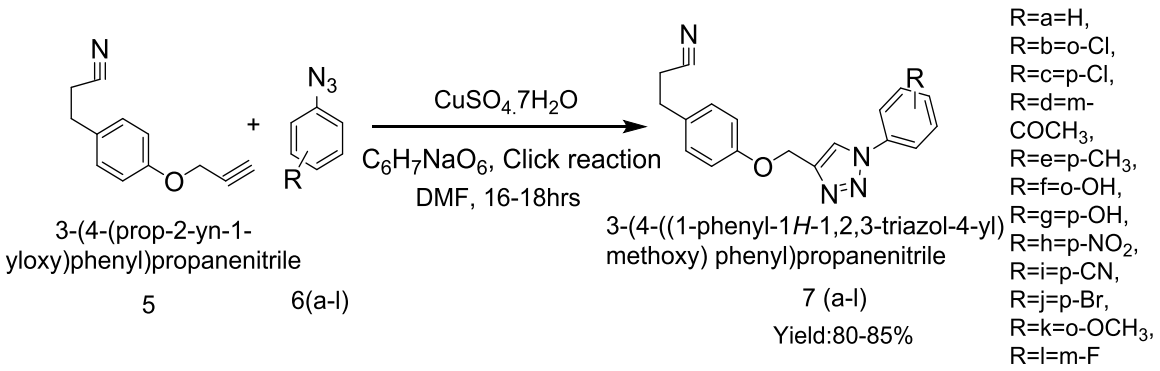


Scheme-3

Synthesis of Substituted 3-(4-((1-phenyl-1H-1,2,3-triazol-4-yl) methoxy) phenyl) propanenitrile (7a-l):

Reaction in between 3-(4-(prop-2-yn-1-yloxy) phenyl) propanenitrile **(5)** and substituted azido benzene **(6a-l)** on treatment with $CuSO_4.7H_2O$ and $C_6H_7NaO_6$ (Sodium Ascorbate) in dry DMF at ambient temperature, were converted to corresponding products Substituted 3-(4-((1-phenyl-1H-1,2,3-triazol-4-yl) methoxy) phenyl) propanenitrile **(7a-l)**, finally, the compound was purified by column chromatography using 22% EtOAc/ hexane solvent mixture as an eluent. 80-85% Yields were obtained.). IR Data IR: υ_{max} cm^{-1}(KBr) 3149.03, 3105.39,

2225.11, 1660.99, 1501.54, 1394.49, 1075.05, 689.78, cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.87 (s,1H), 7.93-7.91(d,1H), 7.12-7.63(m,9H), 5.24 (s,1H), 3.96 (d,1H), 2.15(d,1H). ^{13}C NMR (DMSO) 162.30, 141.43, 136.05, 131.34, 127.00, 124.07, 122.16, 61.98, 30.74, 17.31. ESI-MS: *m/z* 304 $[M+H]^+$; HRMS: cacld. For $C_{18}H_{16}N_4O$.



Scheme-4

V. CONCLUSION

In conclusion, we have synthesized a variety of novel derivatives of Substituted 3-(4-((1-phenyl-1H-1,2,3-triazol-4-yl) methoxy) phenyl) propanenitrile **(7a-l)** and characterized by IR, ^{13}C NMR, ESI-MS, and 1H NMR and also evaluation of their anti-microbial activity (Anti-bacterial, anti-fungal activity). Some of the compounds exhibits promising activity and the presence of **(7b)** 2-chlorophenyl, **(7c)** 4-chlorophenyl, **(7e)** 4-methylphenyl, **(7h)** 4-Nitrophenyl and **(7i)** 4-cynophenyl on triazole moiety might be the reason for the significant inhibitory activity.

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