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Suzuki-Miyaura Coupling of Quinazolines Containing an Unprotected NH_2 group: Synthesis and Biological Testing of Quinazoline Derivatives

Yadagiri Pulipati[1,2], Venkateshwarlu Gurram[1], S. Vijaya Laxmi[2], Yennam Satyanarayana[1], Karan Singh[3], Vinod Kumar[3], Somesh Sharma[1], Narender Pottabathini[1], Vijaya Bhaskara Reddy Iska[1]

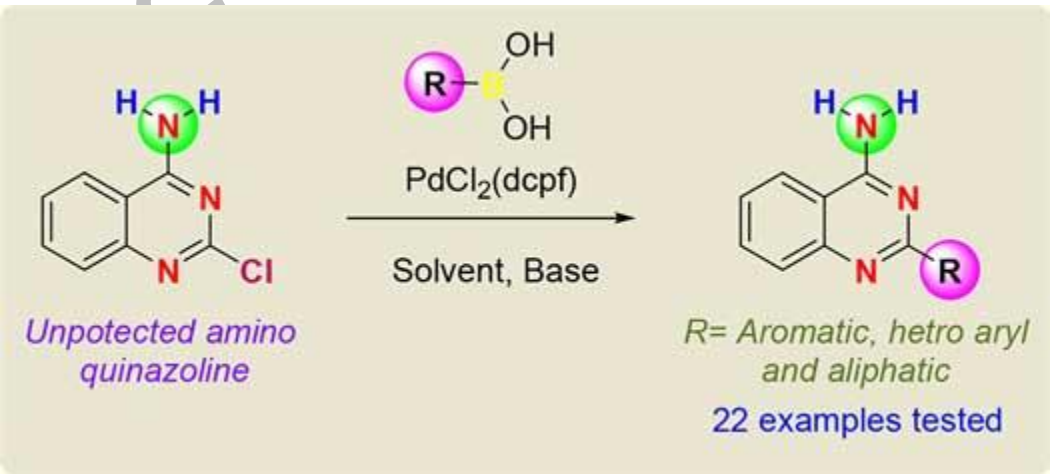
[1]Medicinal Chemistry Division, GVK Biosciences Pvt. Ltd, Hyderabad, India, [2]KL University, Guntur, Andhra Pradesh, India, [3]Akal College of Engineering and Technology, Eternal Univeristy, Himachal Pradesh, India

Corresponding Author: Vijaya Bhaskara Reddy Iska, Medicinal Chemistry Division, GVK Biosciences Pvt. Ltd, Plot 28A, IDA Nacharam, Hyderabad, India. Email: vijayabhaskara.iska@gvkbio.com

Abstract

A robust approach to 4-amino quinazoline bi-aryl compounds was developed via Suzuki–Miyaura coupling reaction of quinazoline containing an unprotected NH_2 group and arylboronic acids. $Pd(dcpf)Cl_2$ was found to be an efficient catalyst for the reaction. All the compounds were evaluated for antimicrobial activity against Gram-positive and Gram-negative bacteria and fungi. One of the compounds, **3l**, found to be more active against *C.albicans* than the standard Miconazole.

Graphical Abstract



INTRODUCTION

Quinazoline derivatives have proven to be an important class of heterocyclic compounds found in biologically and pharmacologically active compounds, natural compounds and functional materials[1,2]. Among various quinazoline derivatives 4-amino quinazolines drew less attention in finding their applications. There are only a limited number of literature reports on biological activity of 4-amino-2-arylquinazoline derivatives. However, from the known set of 4-amino quinazolines, it has been found that these molecules are useful as fungicides[3,4] and as anti-inflammatory[5,6], anti-cancer[7,8], anti-microbial[9,10] and anti-hypertensive agents[11].

Despite the interest in pharmacological activity of 4-amino-2-aryl quinazolines almost no general synthetic method has been reported. All the literature reports to synthesize 4-amino-2-arylquinazolines follow classical methods[12-15] involving ring construction approach. Thus there is a need to improve the synthesis of these compounds using modern synthetic methodologies.

Synthesis of quinazolines and finding their biological applications has been an active area of research in our group. We developed different C-C and C-N bond forming methods to construct quinazoline derivatives with therapeutic activity[16,17,18]. Direct synthesis of substituted aryl compounds containing an unprotected NH_2 group *via* palladium- and nickel-catalysed cross-coupling strategy has been developed by different research groups during the past two decades[19,20]. In this article we report a robust Suzuki-Miyaura coupling procedure to obtain a variety of 2-aryl quinazolines with unprotected

NH_2 group at 2-position of quinazoline by reacting 4-amino-2-chloro quinazolne with aryl boronic acids. In 2005, Itoh et al, reported[21] synthesis of hetero-biaryl compounds containing an unprotected NH_2 group via Suzuki-Miyaura reaction. To demonstrate the applicability of their catalytic system 6,7-dimethoxy-3-phenylnaphthalen-1-amine was synthesized as the only example of such kind. Apart from this one single report and to the best of our knowledge, there is no other literature evidence to synthesize 2-aryl-4-amino quinazolines following a direct catalytic method.

RESULTS AND DISCUSSION

Chemistry

In search of a suitable synthetic approach towards C-2 arylation of 4-aminoquinazoline, we were interested in finding an optimised Suzuki coupling reaction conditions. Itoh et. al, reported hetero-biaryl synthesis *via* Suzuki-Miyaura reaction. They found that $Pd(OAc)_2$/D-*t*-BPF catalyst is an applicable method for the cross-coupling of NH_2-unprotected hetero-aryl chlorides with phenylboronic acid[21]. We took the same catalyst system as a bench mark reference to develop Suzuki-Miyaura cross-coupling of 4-amino-2-chloro quinazoline with different boronic acids. When we applied Itoh et. al, conditions to react 2-chloro-6,7-dimethoxyquinazolin-4-amine (**1**) with phenyl boronic acid, we observed complete conversion of starting material to provide the corresponding product in 85% yield. However, under the same conditions, **1** reacted with naphthyl boronic acid and thienylboronic acid only with 45% and 51% conversions respectively (Table 1). Hence, optimisation of a suitable catalytic system, which can be applicable to couple 4-amino-2-chloro quinazoline with a variety of boronic acids is required.

The effects of the catalyst, base, solvent, and temperature on the cross-coupling reaction of 4-amino-2-chloro quinazoline with phenyl boronic acid are summarised in Table 2. Initially a quick survey of catalysts: $Pd(PPh_3)_4$, $Pd_2(dba)_3$/S-Phos, $Pd(OAc)_2$/CyJhon-Phos, Pd-118, $Pd(dcpf)Cl_2$ and $Pd(amphos)_2Cl_2$ revealed that the reaction is very sensitive and the reactivity varies significantly from each catalyst. To understand the sensitivity of the reaction to water, the same reaction was performed under aqueous and non-aqueous conditions. $Pd(PPh_3)_4$ provided the product **5** with moderate yield (49%, entry 1) under non-aqueous conditions and with poor yield (19%, entry 2) under aqueous conditions. Hence all the subsequent reactions were performed only under non-aqueous conditions. $Pd_2(dba)_3$/S-Phos, $Pd(OAc)_2$/Cyjhon-Phos, Pd-118, $Pd(dcpf)Cl_2$, and $Pd(amphos)_2Cl_2$ provided product **2** with moderate yields 40%, 22%, 18%, 70% and 13% respectively (entries 3 – 7). From these initial results we chose $Pd(dcpf)Cl_2$ to study further due to its easy handling.

Next, we examined the role of base (Table 3) by keeping 10 mol% $Pd(dcpf)Cl_2$ loading. 3 equiv of K_3PO_4 provided 82% product (Entry 1). Whereas 3 equiv each of K_2CO_3 and Cs_2CO_3 provided 59% and 70% product respectively (Entries 2 and 3). Thus, by keeping the base (K_3PO_4), solvent (1,4-dioxane), temperature (100 °C) and reaction time (16 h) fixed, we decided to optimise the catalyst loading. 1 mol% $Pd(dcpf)Cl_2$ provided 22% product with 52% of starting material remain unreacted (Entry 4). Upon increasing the catalyst load to 4 mol%, 6 mol% and 8 mol% the yields improved to 64%, 74% and 92% respectively (Entries 5, 6, 7). Increase of catalyst load more than 8 mol% found to hav**e**

no impact on the conversion as well as on the reaction rate. Thus, keeping the catalyst load to 8 mol%, we changed the solvents to DME (Entry-8), THF (Entry-9) and THP (Entry-10). However, the reaction seems to work better in 1,4-dioxane solvent.

After optimising the best reaction conditions for Suzuki coupling of 4-amino-2-chloro quinazoline and phenyl boronic acid, we were interested to test the applicability of the reaction conditions by coupling with different boronic acids (Table 4). 6,7-Dimethoxy-4-amino-2-chloro quinazoline is coupled with variety of aryl boronic acids including bi-phenyl, naphthyl, tolyl boronic acids to get the Suzuki products in 50% to 82% yields (Entries 1-4). Substituents including methoxy, nitrile, ester, nitro, trimethyl silyl, trifluoro methyl shows no effect on the reaction while being stable under these conditions (Entries 5-11). However, hetero aryl boronic acids provided mixed results. Indole, dibenzofuran, thiophene and furan boronic acids provided **3n, 3o, 3c,** and **3p** in good to excellent yields 62%, 57%, 82% and 70% respectively (Entries 12-15), whereas pyridine and pyrimidine boronic acids found not to couple with **1** under this condition (Entries 16-19). Alkyl boronic acids *aka* isobutyl and cyclohexyl boronic acids did not react with **1** to provide **3v** and **3w** under this catalytic condition (Entries 21-22). However, methyl boronic acid reacted with **1** to provide **3q** with excellent yield (Entry 23).

Biology

The MIC is the lowest concentration of an antimicrobial, which inhibits microbial growth and is a routine assay to determine antimicrobial property of test compounds by a comparison with known antimicrobial agents. In this study, the antibacterial activity of all

the test compounds (**3a-w**) is measured against various Gram-positive and Gram-negative bacteria and against fungi. The best antibacterial activity was shown by compound **3d** (Two fold and four fold less compound was required for inhibition of *B. cereus* over **3b** and **3l**, respectively). *Y. enterocolitica* inhibition was observed at same concentration of test compounds. Antifungal activity was best reported in case of test compound **3l** (Two fold and four fold lead compound was required for inhibition of *C. albicans* over **3b** and **3d**, respectively). The antifungal property of test compounds **3l** (MIC = 31.25) and **3b** (MIC = 62.5) found to be better than standard antifungal agent 'Miconazole' (MIC = >78.1). Antibacterial activity (MIC) of standard antibiotic 'Ampicillin' was better than all test compounds and might need further modifications to make them more efficient antibacterial agent. Results are shown in Table 5.

CONCLUSIONS

In summary we have developed a convenient Suzuki condition with 8 mol% $Pd(dcpf)Cl_2$. This catalyst performs the Suzuki coupling of a variety of boronic acids and quinazoline with unprotected amino group. The conditions previously reported for similar Suzuki coupling are not suitable for many aryl and hetero aryl boronic acids. Our modified, robust, and simple protocol exhibits a broad substrate scope.

EXPERIMENTAL SECTION

Key starting materials and solvents were obtained from commercial sources and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded on either BRUKER 400 MHz or on VARIAN 300 MHz. NMR measurements were carried out in $CDCl_3$ or

DMSO-d_6 as NMR solvents. All chemical shifts were reported in parts per million (∂) with reference to the signal of $Si(CH_3)_4$. High resolution mass spectrometry was performed at the Mass Spectrometry Laboratory at GVK Biosciences Pvt Ltd.

General Procedure For Suzuki-Miyaura Coupling

Procedure For 2-Phenylquinazolin-4-Amine (5)

2-Chloroquinazolin-4-amine (4) (100 mg, 1.0 eq and 0.558 mmol), phenyl boronic acid (150 mol%), and K_3PO_4 (300 mol%) in anhydrous 1,4-dioxane (4 mL) were added in a dry screw-capped vial that was equipped with a stirring bar. The vial was flushed with argon gas for a few minutes and [$PdCl_2$(dcpf)] (0.08 eq, 8 mol%) was added. The vial was sealed with a teflon-lined cap and the mixture was heated at 100 °C with stirring for 16h. The mixture was cooled; filter through celite pad, the solvent was evaporated under reduced pressure and dried under high vacuum. Resulted crude compd was dissolved in ethyl acetate, washed with water, brine solution and dried over anhydrous Na_2SO_4. The organic layer was concentrated under reduced pressure. The crude product, which was loaded into a silica column packed in CH_2Cl_2. Sequential elution with pet-ether, followed by 2-5% MeOH in CH_2Cl_2, afforded **5** as off-white solid (Yield: 113 mg, 92%). R_f: (5% MeOH in CH_2Cl_2) = 0.20; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.50 (d, J = 8.1 Hz, 2H), 7.96 (d, J = 8.4 Hz, 1H), 7.79–7.73 (m, 2H), 7.49–7.44 (m, 4H), 5.66 (s, 2H), ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.4, 160.9, 151.1, 138.6, 133.2, 130.1, 129.0, 128.4, 125.7, 121.5, 113.1, HRMS (ESI): *m/z* calcd for $C_{14}H_{12}N_3$ $[M + H]^+$ 222.1026; found 222.1025.

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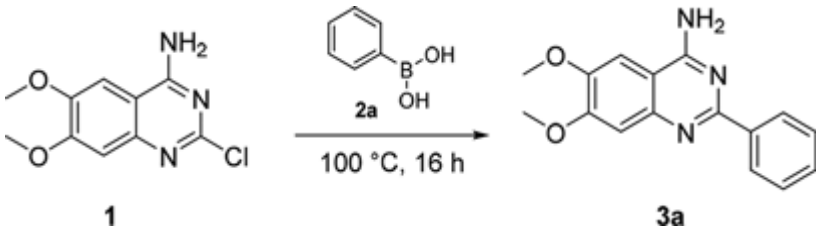
Table 1: Coupling of NH_2-unprotected aminochloropyrimidines with phenylboronic acid



1 3a

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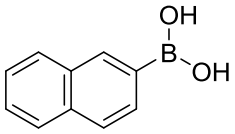
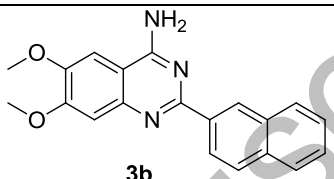
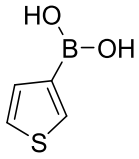
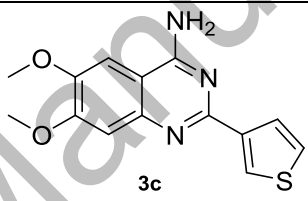
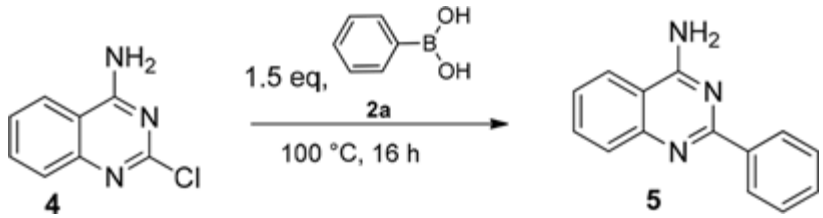
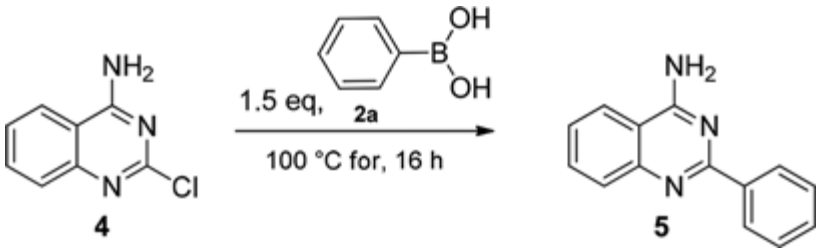
1	 2b	 3b	45%
2	 2c	 3c	51%

Table 2: Suitable Pd-catalyst screening for coupling of NH_2-unprotected aminochloropyrimidines with phenylboronic acid



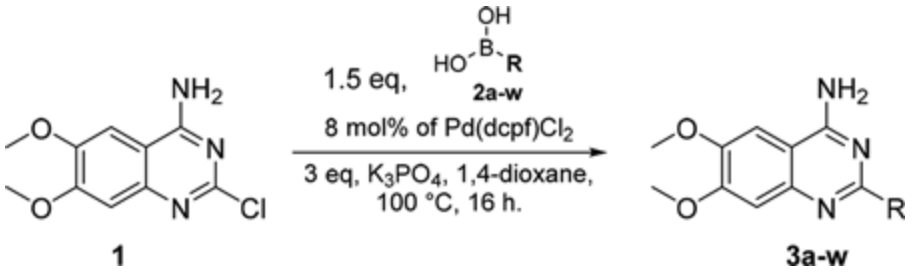
Entry	Catalyst	Ligand	Base (3 equiv)	Solvent	Yield
1	5 mol% $Pd(PPh_3)_4$	--	K_3PO_4	toluene	49%
2	5 mol% $Pd(PPh_3)_4$	--	2 *M* K_3PO_4	toluene	19%
3	5 mol% $Pd_2(dba)_3$	10 mol% S-Phos	K_3PO_4	1,4-dioxane	40%
4	5 mol% $Pd(OAc)_2$	10 mol% of Cyjhon-Phos	K_3PO_4	1,4-dioxane	22%
5	5 mol% Pd-118	--	Na_2CO_3	1,4-dioxane	18%
6	5 mol% $Pd(dcpf)Cl_2$	--	K_3PO_4	1,4-dioxane	70%
7	10 mol% $Pd(AMPHOS)_2Cl_2$	--	2*M* Na_2CO_3	toluene	13%

Table 3: Optimisation of Pd-catalyst condition for coupling of NH_2-unprotected aminochloropyrimidines with phenylboronic acid



Entry	Catalyst	Base (3 equiv)	Solvent	Yield
1	10 mol% $Pd(dcpf)Cl_2$	K_3PO_4	1,4-dioxane	82%
2	10 mol% $Pd(dcpf)Cl_2$	K_2CO_3	1,4-dioxane	59%
3	10 mol% $Pd(dcpf)Cl_2$	Cs_2CO_3	1,4-dioxane	70%
4	1 mol% $Pd(dcpf)Cl_2$	K_3PO_4	1,4-dioxane	22%
5	4 mol% $Pd(dcpf)Cl_2$	K_3PO_4	1,4-dioxane	64%
6	6 mol% $Pd(dcpf)Cl_2$	K_3PO_4	1,4-dioxane	74%
7	8 mol% $Pd(dcpf)Cl_2$	K_3PO_4	1,4-dioxane	92%
8	8 mol% $Pd(dcpf)Cl_2$	K_3PO_4	DME	78%
9	8 mol% $Pd(dcpf)Cl_2$	K_3PO_4	THF	66%
10	8 mol% $Pd(dcpf)Cl_2$	K_3PO_4	THP	86%

Table 4: Application of Pd-catalysis condition for coupling of NH_2-unprotected aminochloropyrimidines with phenylboronic acid



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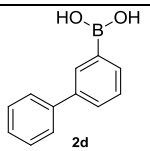
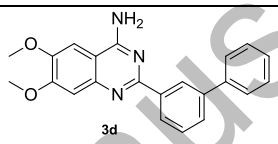
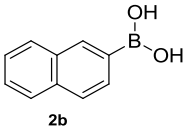
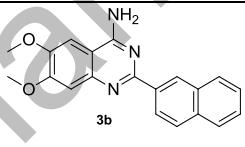
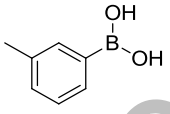
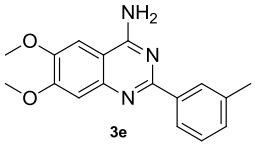
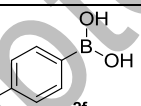
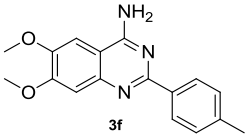
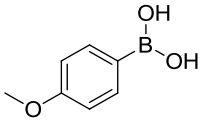
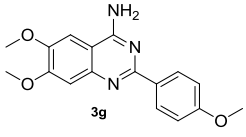
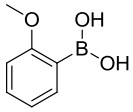
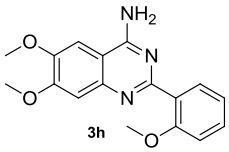
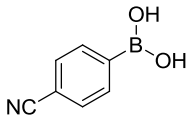
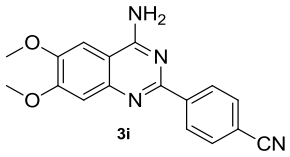
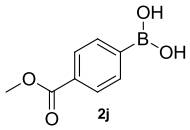
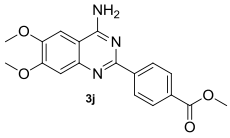
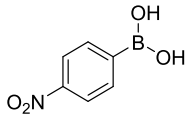
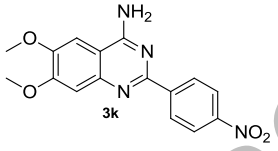
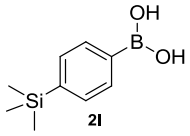
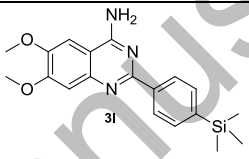
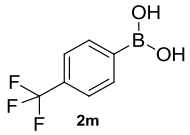
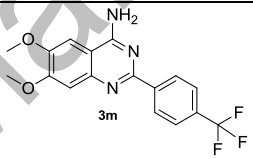
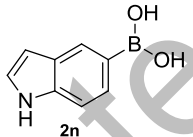
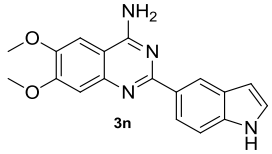
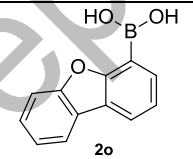
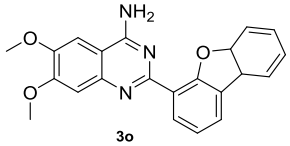
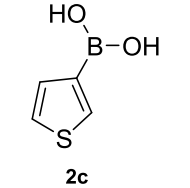
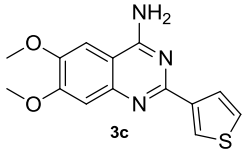
1			70%
2			70%
3			50%
4			82%
5			96%
6			73%

7	 2i	 3i	45%
8	 2j	 3j	62%
9	 2k	 3k	95%
10	 2l	 3l	54%
11	 2m	 3m	79%
12	 2n	 3n	62%
13	 2o	 3o	57%
14	 2c	 3c	82%

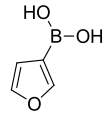
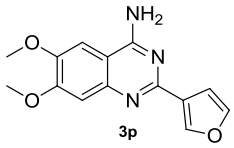
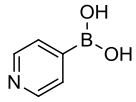
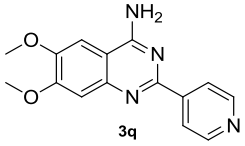
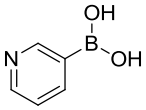
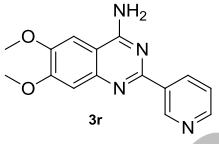
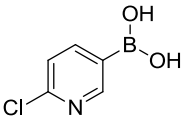
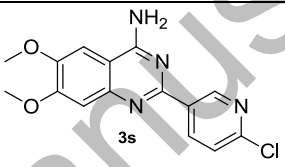
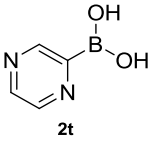
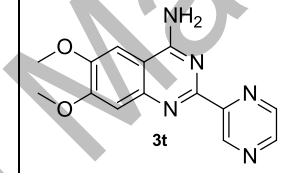
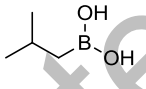
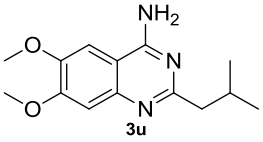
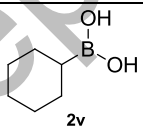
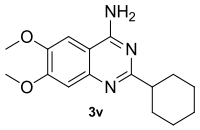
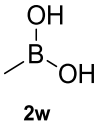
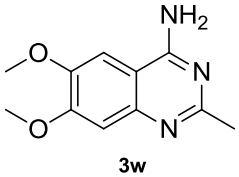
15	 2p	 3p	70%
16	 2q	 3q	NA
17	 2r	 3r	NA
18	 2s	 3s	NA
19	 2t	 3t	NA
20	 2u	 3u	NA
21	 2v	 3v	NA
22	 2w	 3w	85%

Table 5: Antibacterial nature of **3b**, **3d** and **3l**

Compound Code/Name	Concentration (µg/mL)			
	B. cereus	*E. coli*	*Y. enterocolitica*	*C. albicans*
3l	>500	>125	>125	>31.25
3b	>250	>250	>125	>62.5
3d	>125	>125	>125	>125
Miconazole	-	-	-	>78.1
Ampicillin	>39	>78.1	>39	-