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Application of Suzuki-Miyaura and Buchwald-Hartwig Cross-coupling Reactions to the Preparation of Substituted 1,2,4-Benzotriazine 1-Oxides Related to the Antitumor Agent Tirapazamine

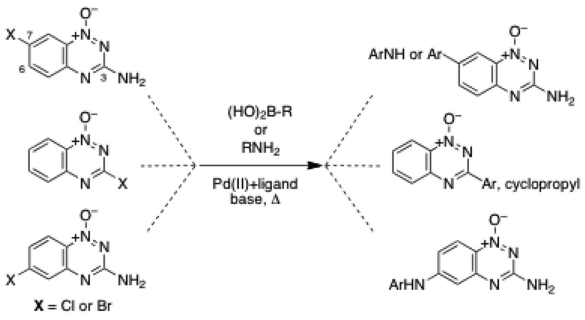
Ujjal Sarkar[#§], **Roman Hillebrand**[#§], **Kevin M. Johnson**[§], **Andrea H. Cummings**[§], **Ngoc Linh Phung**[§], **Anuruddha Rajapakse**[§], **Haiying Zhou**[§], **Jordan R. Willis**[§], **Charles, L. Barnes**[§], and **Kent S. Gates**[§,‡,*]

[§]University of Missouri, Department of Chemistry, 125 Chemistry Building, Columbia, MO 65211

[‡]University of Missouri, Department of Biochemistry, 125 Chemistry Building, Columbia, MO 65211

[#] These authors contributed equally to this work.

Abstract



Many 1,2,4-benzotriazine 1,4-dioxides display the ability to selectively kill the oxygen-poor cells found in solid tumors. As a result, there is a desire for synthetic routes that afford access to substituted 1,2,4-benzotriazine 1-oxides that can be used as direct precursors in the synthesis of 1,2,4-benzotriazine 1,4-dioxides. Here we describe the use of Suzuki-Miyaura and Buchwald-Hartwig cross-coupling reactions for the construction of various 1,2,4-benzotriazine 1-oxide analogs bearing substituents at the 3-, 6-, and 7-positions.

* gatesk@missouri.edu.

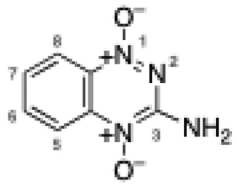
Additional Supporting Information may be found in the online version of this article

Supplementary data

Supplementary data (descriptions of experimental procedures and characterization of all compounds, 50 pages) related to this article can be found at http://dx.doi.org/10.1016/j.tet. The crystal structure shown in Figure 1 can be accessed from the Cambridge Crystallographic Data Centre deposition number CCDC 718512.

INTRODUCTION

Tirapazamine (**1**) and many other 1,2,4-benzotriazine 1,4-dioxides are selectively toxic to the oxygen poor (hypoxic) cells found within solid tumors.[1-3] These compounds undergo intracellular enzymatic one-electron reduction to yield a radical that undergoes relatively harmless back-oxidation to starting material in normally-oxygenated cells. On the other hand, under hypoxic conditions, the neutral radical intermediate decomposes to release a highly oxidizing secondary radical that causes cytotoxic DNA damage.[1-16] Promising preclinical results led to the examination of tirapazamine in a large number of clinical trials, but thus far, the results of these studies have not earned FDA approval for the drug.[17] As a result, there have been substantial efforts to prepare tirapazamine analogues with improved efficacy.[18-27] Accordingly, there is a continuing need for the development of synthetic routes that afford access to tirapazamine analogs.



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A variety of methods have been developed for the synthesis of tirapazamine and related analogs. Tirapazamine can be prepared by the reaction of benzofuroxan with sodium cyanamide.[28] Alternatively, condensation of 2-nitroaniline with cyanamide yields 1,2,4-benzotriazine 1-oxide (**2**, Scheme 1) which can be oxidized to tirapazamine using H_2O_2/HOAc, mCPBA, or HOF-CH_3CN.[14,29-31] The reaction of 1-fluoro-2-nitrobenzene or 1,2-dinitrobenzene with guanidine base provides another route to **2**.[32] Condensation of various 2-nitroaniline derivatives with cyanamide provides access to a large number of tirapazamine derivatives bearing substituents on the benzo ring.[18,20,26,33] Analogues of **2** bearing sulfur or alkoxy substitutents (rather than NH_2) at the 3-position have been prepared by diazotization and hydrolysis of **2** to afford the 3-hydroxy-1,2,4-benzotriazine 1-oxide analog, followed by reaction with phosphorus oxyhalide to give the 3-chloro- or 3-bromo-1,2,4-benzotriazine 1-oxide (**3a** and **b**), and finally treatment with an appropriate oxygen or sulfur nucleophile.[34] Similarly, a variety of tirapazamine analogues bearing alkyl and aryl groups on the 3-amino substituent have been prepared by nucleophilic aromatic substitution involving attack of amines on **3a**, followed by oxidation to give the di-*N*-oxides.[35,36] Photochemical methods also may enable preparation of 3-(arylamino)-1,2,4-benzotriazine 1,4-dioxide derivatives from 3-acetamido-1,2,4-benzotriazine 1,4-dioxide.[37]

There is interest in 3-alkyl- and 3-aryl-1,2,4-benzotriazine 1,4-dioxides because these compounds display hypoxia-selective DNA-cleaving properties and cytotoxicities that are comparable to tirapazamine.[8,38] In addition, these analogues may possess superior pharmacokinetic properties.[19,20] The analogs, 3-methyl- and 3-phenyl-1,2,4-benzotriazine oxide, have been prepared by BF_3-catalyzed cyclization of formazan precursors[39] or PtO_2-catalyzed cyclization of the 2-nitrophenylhydrazone of pyruvic acid,[40] followed by *N*-oxidation using H_2O_2/TFAA.[38]

Palladium-catalyzed cross-coupling reactions such as the Suzuki-Miyaura, Buchwald-Hartwig, and Stille reactions are powerful synthetic methods that may enable the synthesis of many diverse tirapazamine analogs.[41,42] Along these lines, the palladium-mediated Stille coupling reactions have been employed for the preparation of 3-alkyl, aryl, vinyl and allyl 1,2,4-benzotriazine 1-oxides from **3a**.[25,33] In addition, there is a single report in which the Suzuki-Miyaura reaction was used to prepare 3-aryl-1,2,4-benzotriazine 1,4-dioxides from 3-halo-1,2,4-benzotriazine 1-oxide precursors.[25] The results described herein expand the use of the Suzuki-Miyaura reaction and provide the first uses of the Buchwald-Hartwig reaction for the preparation of 1,2,4-benzotriazine 1-oxide analogs related to the antitumor agent tirapazamine.

RESULTS AND DISCUSSION

Six halogenated 1,2,4-benzotriazine 1-oxides were prepared for use in palladium-catalyzed coupling reactions. Compounds **3** were prepared via reaction of **2** with sodium nitrite in aqueous sulfuric acid, followed by treatment with the appropriate phosphorus oxyhalide (Scheme 2).[33,34] Analogs **4** bearing halogens on the benzo-ring were prepared by a well-established route involving condensation of cyanamide with the appropriately substituted 2-nitroaniline.[14,29,30]

The halogen derivatives **3** were employed as substrates in Suzuki coupling reactions with aryl and cyclopropyl boronic acids (Table 1). In these reactions, compound **3**, the boronic acid (1.2 equiv), and the ligand tricyclohexylphosphine or 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (PCy_3 or SPhos, 10 mol%)[43] were mixed with $Pd(OAc)_2$ (5 mol%) in a mixture of toluene or toluene-water (3:1 v/v) containing potassium phosphate or cesium carbonate and heated in a sealed tube at 110 °C for 24 h. Reactions of the chlorinated substrate **3a** with cyclopropylboronic acid and 4-cyanophenylboronic acid proceeded in reasonable yields to give the coupling products **5** and **9**, respectively.[44,45] Use of the brominated derivative **3b** did not substantially alter the yields in these cases. Reactions of **3a** with 4-bromophenylboronic acid and 4-nitrophenylboronic acid gave very low and modest yields of the products **6** and **7**, respectively (Table 1). In these cases, use of the brominated substrate **3b** improved the yields of the desired coupling products **6** and **7**. This was not unexpected because aryl bromides typically are better substrates than the analogous chlorides in Suzuki coupling reactions.[41,42] The reaction between quinolin-2-ylboronic acid and **3a** or **3b** employing the PCy_3 ligand proceeded in very low yields even with the brominated substrate **3b**, but use of the electron-rich SPhos ligand[46] afforded improved yields of the coupling product **8** (Table 1). Use of the SPhos ligand did not improve the yield of **6** obtained from the coupling of **3b** with 4-bromophenylboronic acid using the PCy_3 ligand (Table 1). The aryl bromide residue in **6** could be a useful handle for further elaboration via palladium-catalyzed reactions. Reaction of 4-(*N*-Boc-amino)phenylboronic acid with **3b** using the SPhos ligand afforded a reasonable yield of the coupling product **10**.

Column chromatography of the reaction between **3a** and cyclopropylboronic acid with PCy_3 as ligand for palladium, produced a fraction that, upon slow evaporation, gave a low yield (~ 1%) of pale yellow crystals that were characterized by X-ray diffraction. Interestingly, the material proved to be a dinuclear triazine-bridged palladium complex resulting from

oxidative addition of **3a** to the palladium catalyst. The C1-carbon and N2-nitrogen atoms of two benzotriazine 1-oxides and the two palladium centers form a six-membered ring in a boat conformation in which the nitrogens are *trans* to the phosphine ligands and carbons are *trans* to the chlorides (Figure 1). The Pd-Pd interatomic distance is 3.1709(4) Å. This structure is structurally analogous to that of a product previously obtained from the addition of $Pd(PPh_3)_4$ to 2-bromopyridine.[47,48]

The success of Suzuki coupling reactions employing **3** led us to extend this reaction to the aryl halides **4a** and **4b**. In these reactions, **4a** or **4b**, the boronic acid (1.2 equiv), and the ligand (PCy_3 or SPhos, 10 mol%) were combined with $Pd(OAc)_2$ (5 mol%) in a mixture of toluene or toluene-water (3:1 v/v) containing potassium phosphate or cesium carbonate and heated in a sealed tube at 110 °C for 24 h. These reactions afforded reasonable yields (up to 72%) of the products **11**-**14** (Table 2). Analogous reactions refluxed under nitrogen gas gave yields that were substantially lower than those obtained by heating in sealed tubes.

As part of these studies, we examined whether the boronic acid components of these reactions was stable in the presence of the *N*-oxide starting materials. We were motivated to examine this issue because Zhu et al. previously showed that alkyl- and aryl-*N*-oxides have the potential to convert boronic acids and boronic acid pinacol esters to the corresponding alcohols.[49] Under our reaction conditions, however, we did not observe significant decomposition of 4-(*N*-Boc-amino)phenylboronic acid or cyclopropylboronic acid when these materials were heated at 110 °C for three days in toluene/water (3:1) with **3a**, **3b**, **4**, or **4b** (2 equiv, in the absence of palladium catalyst).

We next examined whether the Buchwald-Hartwig reaction could be applied the construction of substituted 1,2,4-benzotriazine 1-oxides.[50] In these reactions, **4a** or **c,** the ligand 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (X-Phos, 10 mol%), $Pd(OAc)_2$ (5 mol%), K_3PO_4, and the desired amine (1.2 equiv) were dissolved in a solvent mixture composed of *t*-BuOH/water (3:1 v/v), placed in a sealed tube, and stirred for 24 h or subjected to microwave irradiation for 45 min (300 W, 60 PSI). Reactions of aniline or 6-aminoquinoline with **4a** or **4c** gave good yields of the coupling products **15**-**18** using either conventional or microwave heating (Table 3). Microwave heating has been used successfully in other palladium-mediated reactions[51] and, in this case, allowed the use of shorter reaction times. Diphenylamine gave no product under these reaction conditions, presumably due to steric crowding. These palladium-catalyzed C-N bond forming reactions offer a useful alternative to the previously described nucleophilic aromatic substitution reactions involving the reaction of amines with 6- and 7-fluoro derivatives of tirapazamine that give low yields in some cases.[12,18]

CONCLUSION

In summary, we examined the utility of palladium-mediated reactions for the synthesis of 1,2,4-benzotriazine derivatives related to the antitumor agent tirapazamine. Our work expands the use Suzuki-Miyaura-type reactions for the construction of 3-aryl-1,2,4-benzotriazines and presents the first use of Suzuki-Miyaura and Buchwald-Hartwig reactions for the functionalization of the 6- and 7-positions of the 1,2,4-benzotriazine ring system.

Given the large number of commercially available aryl boronic acids and arylamines, our results should enable the preparation of many structurally diverse tirapazamine analogs. Nitrogen-rich heterocycles sometimes present challenges in palladium-catalyzed coupling reactions[52,53] perhaps because of their propensity to coordinate the palladium catalyst. Indeed, we isolated and crystallographically characterized a dinuclear triazine-bridged palladium complex resulting from oxidative addition of **3a** to the palladium catalyst. Nonetheless, the yields of the coupling products obtained here are of practical utility in the short, 3-4 step synthetic routes used to prepare the 1,2,4-benzotriazine 1,4-dioxide antitumor agents.

EXPERIMENTAL

Representative Procedure for the Synthesis of 6- and 7-Halo-1,2,4-benzotriazine 1-Oxides: 6-Chloro-1,2,4-benzotriazine 1-oxide (4c)

The compound 4-chloro-2-nitroaniline (3.02 g, 36 mmol) and cyanamide (6.20 g, 72 mmol) were mixed, melted by heating at 100 °C, and then cooled to room temperature. Concentrated HCl (30 mL) was added dropwise and the resulting mixture heated to 100 °C and stirred for 2 h (Caution: exotherm). The red-orange solution was then cooled to room temperature and NaOH (30 mL of a 16 M solution in water) was added over 15 min with stirring. The reaction mixture was heated to 100 °C for 3.5 h and then cooled to room temperature. Water (25 mL) was added and the resulting solid collected by filtration and washed with a solution of ethyl acetate-hexane (3:1) to give **6** in 38% yieild. In cases where purification was required, column chromatography on silica gel eluted with a gradient of 5%→20% methanol in CH_2Cl_2. ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 8.12 (d, J = 2 Hz, 1H), 7.77 (dd, J = 9 Hz, J = 2 Hz, 1H), 7.54 (d, J = 9 Hz, 1H), 7.47 (s, 2H); ^{13}C-NMR (DMSO-d_6, 300 MHz): δ 160.4, 147.7, 136.1, 130.0, 128.3, 128.0, 119.0. HRMS (ESI, [M+H$^+$]) *m/z* calcd for $C_{10}H_{10}N_3O$ 197.0230, found 197.0228.

Representative Procedure for Coupling of 3-Halo-1,2,4-benzotriazine 1-Oxides with Boronic Acids: 3-Cyclopropyl-1,2,4-benzotriazine 1-Oxide (9)

The compound 3-chloro-1,2,4-benzotriazine 1-oxide[33,34] (**3a**, 60 mg, 0.33 mmol), cyclopropyl boronic acid (1.2 equiv, 34 mg), potassium phosphate (203 mg), PCy_3 (10 mol %), and $Pd(OAc)_2$ (5 mol%) were placed in a nitrogen-purged flask, dissolved in a mixture of toluene (2 mL) and water (100 μL), and refluxed for 24 h. The reaction was cooled to room temperature, water was added (5 mL), the mixture extracted with dichloromethane, the combined organic extracts dried over Na_2SO_4, and rotary evaporated. Column chromatography on silica gel eluted with a gradient of 5→25% ethyl acetate in hexane gave **9** as a pale yellow solid in 47% yield. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.41 (1H, d, 8.7 Hz), 7.89-7.87 (2H, m), 7.62 (ddd, J = 9 Hz, 6 Hz, 2 Hz, 1H), 2.31 (tt, J = 8 Hz, J = 4 Hz, 1H), 1.36-1.31 (2H, m), 1.22-1.16 (2H, m); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 167.7, 146.9, 134.7, 133.5, 128.4, 127.6, 119.4, 16.0, 10.42; HRMS (ESI) m/z calc for $C_{10}H_{10}N_3O$ (M+H$^+$) 188.0824, found 188.0823.

Representative Procedure for Coupling of 6- and 7-Halo-1,2,4-benzotriazine 1-Oxides with Arylamines: 7-Aminophenyl-1,2,4-benzotriazine 1-Oxide (15)

The compound 7-chloro-1,2,4-benzotriazine 1-oxide (80 mg, 0.4 mmol), $Pd(OAc)_2$ (5 mol %, 0.02 mmol, 4.6 mg), XPhos (10 mol%, 0.04 mmol), K_3PO_4 (3 equiv, 1.2 mmol, 254 mg) and aniline (75 mg, 0.8 mmol, 2 equiv) were placed in a sealed tube equipped with a stir bar and suspended in a solvent mixture composed of *t*-butanol:water (20 mL, 9:1). The mixture was stirred while heated at 110 °C for 24 h. The mixture was evaporated to dryness, taken up in methanol or tetrahydrofuran, filtered through celite, slurried with silica gel, evaporated, and the resulting powder dry-loaded on top of a silica gel column. Elution with a gradient of 0→50% ethyl acetate in hexane gave **15** as a red solid in 78% yield. ^{1}H-NMR (500 MHz, DMSO-d_6) δ 6.94 (s, 2 H) 7.00 (t, J=7 Hz, 1 H) 7.21 (d, J=8 Hz, 2 H) 7.36 (t, J=9 Hz, 2 H) 7.50 (d, J=9 Hz, 1 H) 7.58 (d, J=9 Hz, 2 H) 7.63 (s, 1 H) 8.77 (s, 1 H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ 159.3, 144.6, 142.1, 141.9,130.6 129.8, 129.5, 127.4, 122.1, 118.9, 98.4; HRMS(ESI) m/z calc for $C_{13}H_{11}N_3O$ 254.1036, found 254.1046.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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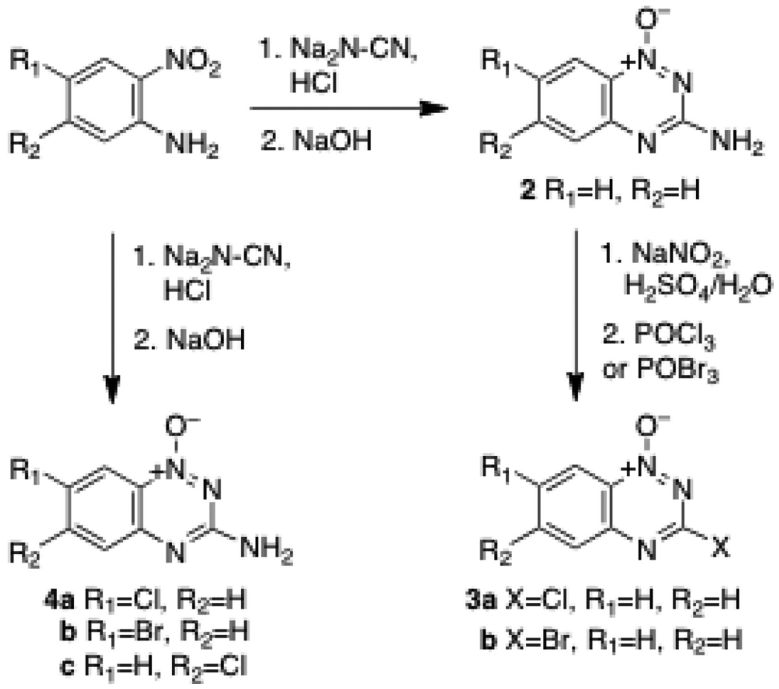


Scheme 1.

Synthesis of Halogenated Tirapazamine Derivatives for Use in Pd-Mediated Coupling Reactions.

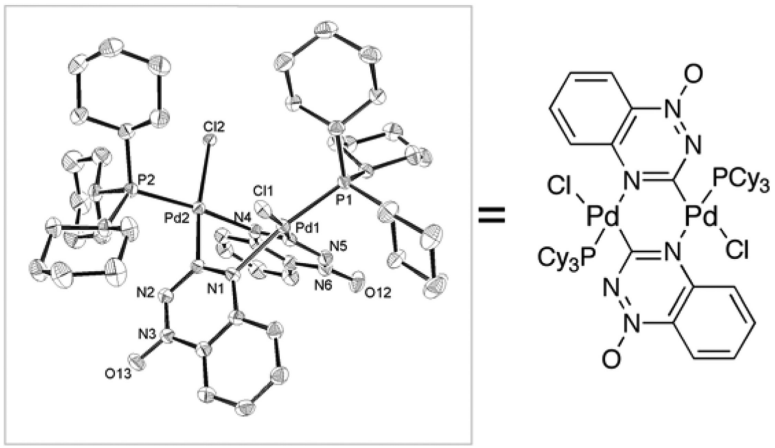
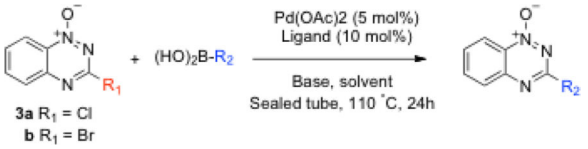


Fig. 1.

Crystal Structure of a Complex Resulting from Oxidative Addition of **3a** to Palladium.

Table 1

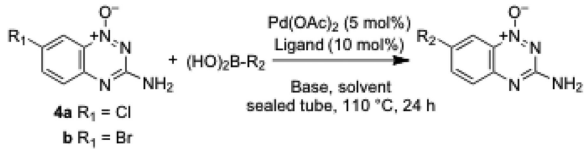
Preparation of 3-Aryl and 3-Cyclopropyl Derivatives of 1,2,4-Benzotriazine 1-Oxide.



Aryl halide	R_2, product	Yield [%]	Ligand	Base	Solvent
3a	4-cyanophenyl, **5**	66	SPhos	Cs_2CO_3	Toluene
3b		74	SPhos	Cs_2CO_3	Toluene
3a	4-bromophenyl, **6**	trace	PCy3	K_3PO_4	MeCN/Water
3b		57	PCy3	K_3PO_4	MeCN/Water
3a	4-nitrophenyl, **7**	42	SPhos	Cs_2CO_3	Toluene
3b		65	SPhos	Cs_2CO_3	Toluene
3a	quinolin-2-yl, **8**	29	SPhos	K_3PO_4	Toluene/Water
3b		40	SPhos	K_3PO_4	Toluene/Water
3a	cyclopropyl, **9**	76	SPhos	Cs_2CO_3	Toluene
3b		80	SPhos	Cs_2CO_3	Toluene
3b	4-***N***-Boc-aminophenyl, **10**	61	SPhos	K_3PO_4	Toluene/Water

Table 2

Preparation of 7-Aryl Derivatives of Tirapazamine.

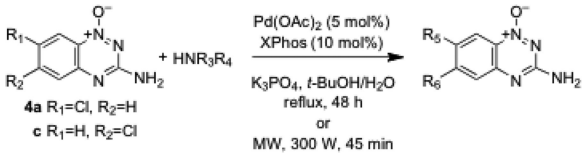


4a R_1 = Cl
b R_1 = Br

Aryl halide	R_2, product	Yield [%]	Ligand	Base	Solvent
4a	4-methoxyphenyl, **11**	46	SPhos	Cs_2CO_3	Toluene
4b		72	SPhos	Cs_2CO_3	Toluene
4b	4-aminophenyl, **12**	30	PCy_3	K_3PO_4	Toluene/Water
4b	4-cyanophenyl, **13**	60	SPhos	Cs_2CO_3	Toluene
4b	2-Naphtyl-6'-methoxy, **14**	27	PCy_3	K_3PO_4	Toluene/Water

Table 3

Preparation of 6- and 7-Aminoaryl Tirapazamine Derivatives.



4a R_1=Cl, R_2=H
c R_1=H, R_2=Cl

Aryl halide	Amine (R_3, R_4)	Product (R_5, R_6)	Yield [%] reflux	Yield [%] microwave
4c	R_3 = H, R_4 = Ph	R_5 = H, R_6 = NHPh, **15**	58	76
4a	R_3 = H, R_4 = Ph	R_5 = NHPh, R_6 = H, **16**	81	75
4c	R_3 = H, R_4 = quinoline	R_5 = H, R_6=6-aminoquinoline, **17**	73	61
4a	R_3 = H, R_4 = quinoline	R_5=6-aminoquinoline, R_6=H, **18**	70	45
4a	R_3 = Ph, R_4 = Ph	R_5 = NPh_2, R_6 = H	0	0
4c	R_3 = H, R_4 = Ph	R_5=H, R_6 = NPh_2	0	0