Synthesis and Antimalarial Activity of 7-Benzylamino-1-Isoquinolinamines

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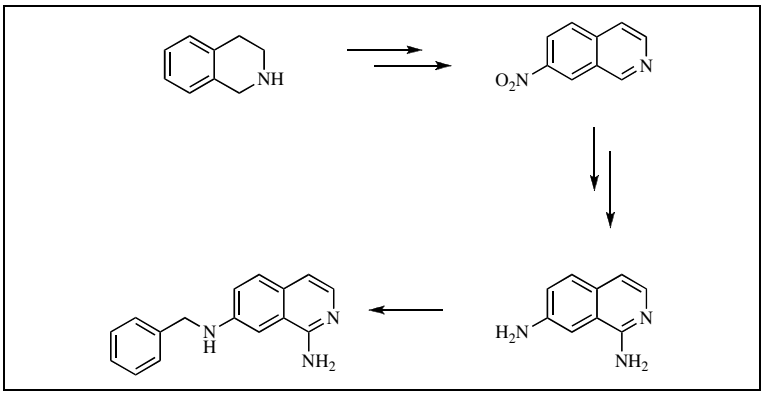

Computer modelling suggests that 7-benzylamino-1-isoquinolinamines should mediate antimalarial effects by a mechanism distinct from that employed by existing antimalarial drugs. A series of these compounds was prepared in seven synthetic steps, via reductive amination of 1,7-isoquinolinediamine. *In vitro* efficacy testing of the novel compounds against *Plasmodium falciparum* revealed them to be potent antimalarial agents.

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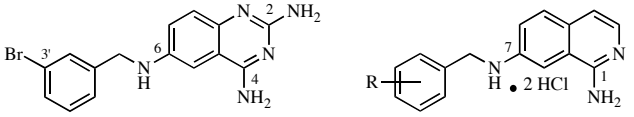
INTRODUCTION

Each year, more than 1 million people die from malaria. The organism responsible for most of these deaths, *Plasmodium falciparum*, has developed resistance to most available drugs [1]. Thus, there is an urgent need for novel and affordable therapeutics. The antimalarial activity of the chalcone class of compounds (1,3-diphenyl-2-propen-1-ones) is well established [2-10]. Several groups have studied the relationship between the structure of substituted 2-propen-1-ones and their antimalarial activity. Since the emerging relationship does not correlate with that between structure and the inhibition of any known antimalarial target, the mechanism by which the chalcones act appears to be distinct from the established mechanisms [7-9]. During our investigation of the relationship between 1,3-diaryl-2-propen-1-one structure and antimalarial activity [10], we generated a computer model of the structural and electronic features required in such compounds to maximize *in vitro* antimalarial activity [11]. When this pharmacophore was used to screen the collection of compounds at the Walter Reed Army Institute of Research, it was predicted that 6-(3'-bromobenzylamino)-2,4-quinazolinediamine (**1**) should also mediate antimalarial effects by this novel chalcone-mechanism. Such quinazolinetriamines are known to be potent antimalarials by their inhibition of dihydrofolate reductase [12], but are also known to be susceptible to the rapid development of drug resistance [13]. Using the pharmacophore and published data describing the structural requirements for the inhibition of dihydrofolate reductase [14-16], we sought to design compounds with minimal inhibition of dihydrofolate reductase, instead possessing antimalarial activity *via* the chalcone-mechanism.

7-Benzylamino-1-isoquinolinamines emerged as a class in which these goals were potentially met. It was anticipated that these compounds would be isolated as hydrogen chloride salts (**2a-e**). Though not described in detail, the synthesis of a potential precursor to these compounds, 1,7-isoquinolinediamine (**3**), has been outlined in the patent literature [17,18].



(**1**) (**2a-e**)

Figure 1

This study proposes a selective reductive amination of the 7-amino group of 1,7-isoquinolinediamine (**3**) to provide the target molecules [19]. Using benzaldehyde in this reaction, 7-benzylamino-1-isoquinolinamine (**2a**) would be the expected product. This paper describes the

synthesis of this, and several benzyl-substituted analogs (**2b-e**), along with their *in vitro* efficacy against a multi-drug resistant strain of *P. falciparum*.

RESULTS AND DISCUSSION

Scheme 1 outlines the synthetic route developed in our laboratory. As previously reported, commercially available 1,2,3,4-tetrahydroisoquinoline (**4**) underwent selective nitration at C7 upon treatment with potassium nitrate in aqueous sulfuric acid [20]. Though the protonated amine would direct the electrophile to C5 or C7, a peri hydrogen interaction at C5 ensures reaction proceeds exclusively at C7 [21]. Purification of the 1,2,3,4-tetrahydro-7-nitro-isoquinoline was achieved by recrystalization of the corresponding hydrogen chloride salt (**5**).

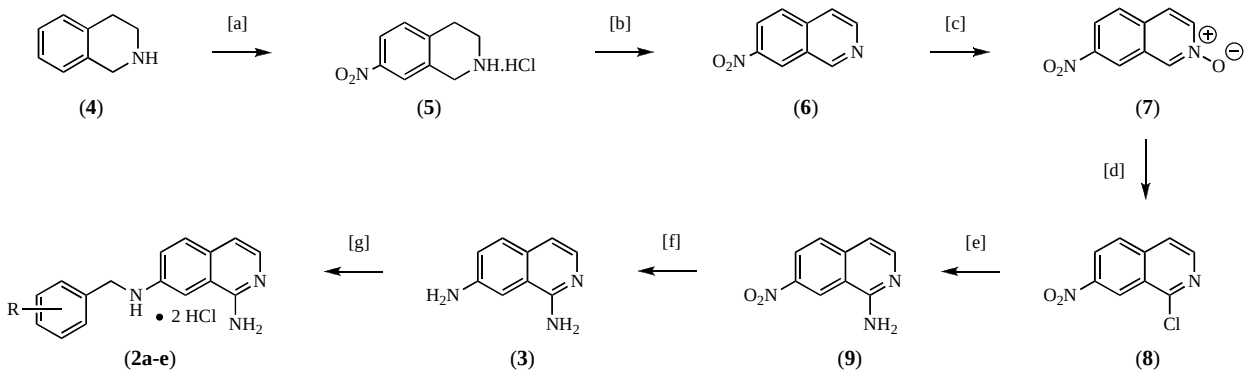
Oxidation of the heterocycle to provide 7-nitro-isoquinoline (**6**) was mediated by potassium nitro-sodisulfonate in aqueous sodium carbonate [17]. Purification was by extraction of the reaction mixture into chloroform. Depending upon the quality of the oxidizing agent used, in some cases this extraction was followed by alumina column chromatography. Attempts to purify the crude product by crystallization as described in the literature [22] were unsuccessful due to sparing compound solubility in a range of solvents. The high cost of the oxidant and the long reaction time required (7 days) led us to explore the other procedure known to mediate this reaction. Though reaction of the tetrahydro-isoquinoline (**5**) with iodine and potassium acetate did furnish 7-nitro-isoquinoline (**6**) [22], complete removal of the side-products from the reaction mixture by alumina column chromatography proved impossible.

Installation of the 1-amino group was carried out in three synthetic steps. Treatment of 7-nitro-isoquinoline (**6**) with *m*-chloroperbenzoic acid in acetone gave 7-nitro-isoquinoline-2-oxide (**7**) [18]. Subsequent reaction with *p*-toluenesulfonyl chloride gave 1-chloro-7-nitro-isoquinoline (**8**), which in turn was reacted with ethanolamine to provide 7-nitro-1-isoquinolinamine (**9**) [18]. This was purified by alumina column chromatography, and then hydrogenated to give 1,7-isoquinolinediamine (**3**) [17]. Full experimental details are provided for the steps from 1,2,3,4-tetrahydro-7-nitro-isoquinoline hydrogen chloride (**5**) since they are incomplete in the available literature [17,18].

The isoquinolinediamine (**3**) was dissolved in acetic acid and benzaldehyde added to generate an imine, which was then reduced using sodium cyanoborohydride. When the reaction was conducted using conditions described for a similar reaction (with 15 mole equivalents of benzaldehyde and 30 of sodium cyanoborohydride [19]) NMR analysis of the crude product suggested a small amount of dialkylation had occurred. When the quantity of reagent was decreased (to 2 mole equivalents of benzaldehyde and 3 of sodium cyanoborohydride) only the desired 7-benzylamino-1-isoquinolinamine was formed. Selective alkylation of the 7-amino over the 1-amino group would be expected upon electronic grounds. Preparation of the corresponding salt (**2a**) afforded material which was easily handled.

Four other 7-benzylamino-1-isoquinolinamine salts (**2b-e**), substituted on the benzyl group, were prepared similarly from the corresponding substituted benzaldehydes. For this initial series halogen substituents, at the 3- and 4- positions, were explored since such substituents are potency enhancing in the chalcone series [4]. The yield for the key reductive amination step in each case is shown in Table 1. All are isolated yields following alumina column chromatography, which was performed in such a way to maximize purity of isolated material, not yield. The yield of crude

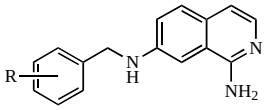
Scheme 1



[a] KNO_3, H_2SO_4, H_2O; HCl, EtOH. [b] $(KSO_3)_2NO$, Na_2CO_3, H_2O. [c] *m*-Chloroperbenzoic acid, acetone. [d] *p*-Toluenesulfonyl chloride, pyridine. [e] Ethanolamine. [f] H_2, Pd/C, MeOH. [g] R-C_6H_5CHO, acetic acid; $NaBH_3CN$, tetrahydrofuran; HCl, ethanol. R = H (**2a**), 3-Cl (**2b**), 4-Cl (**2c**), 3-Br (**2d**), 3,4-Cl_2 (**2e**).

Table 1

Physical, Analytical and Biological Data for Compounds **2a-e**



• 2 HCl • x H_2O

Cmpd.	R	Yield % [a]	Mp (°C) [b]	Molecular Formula	Analysis % Calcd./Found			Mass of MH^+ Calcd./Found	Inhibition of *P. falciparum* [d]
					C	H	N	[c]	(IC_{50} μM)
2a	H	86	160-165 dec.	$C_{16}H_{16}ClN_3$ • 2 HCl • 0.3 H_2O	58.65	5.41	12.83	250	0.49
					58.87	5.35	12.46	250	
2b	3-Cl	49	176-181 dec.	$C_{16}H_{15}Cl_2N_3$ • 2 HCl • 0.65 H_2O	52.17	4.73	11.41	284	0.21
					52.57	4.69	10.98	284	
2c	4-Cl	60	170-175 dec.	$C_{16}H_{15}Cl_2N_3$ • 2 HCl • 0.37 H_2O	52.89	4.64	11.56	284	0.14
					53.29	4.74	11.16	284	
2d	3-Br	22	207-215 dec.	$C_{16}H_{15}BrClN_3$ • 2 HCl • 0.8 H_2O	46.25	4.27	10.11	328	0.16
					46.61	4.35	9.73	328	
2e	3,4-Cl_2	49	200-205 dec.	$C_{16}H_{14}Cl_3N_3$ • 2 HCl • 0.9 H_2O	47.18	4.16	10.32	318	0.072
					46.95	3.78	10.12	318	
Chloroquine		-	-	-	-	-	-	-	0.071

[a] Of reductive amination step. [b] Precipitated from ethanolic hydrogen chloride solution. [c] Calcd. is molecular weight of MH^+ for the free base and Found is m/z for the molecular ion. [d] Inhibition of [^{3}H] hypoxanthine uptake by *P. falciparum* TM91C235.

product in each case was significantly higher (especially of **2b**, **d**, **e**).

All the analytical and spectroscopic data obtained (ir, nmr, ms) were in full agreement with the structures targeted (Table 1). Elemental analysis showed that the salts contain two equivalents of hydrogen chloride with a variable amount of water [23]. Attempts to completely dry the salts were unsuccessful: discoloration occurred even upon moderate heating. When this hydration is taken into account the elemental analyses for carbon, hydrogen and nitrogen for all analogs agree with the theoretical value to within 0.4% except that the nitrogen content of the 3-chloro analog (**2b**) agrees to 0.42%.

The *in vitro* antimalarial activity of the novel compounds was determined using a standard assay which measures the ability of the compound to inhibit the uptake of [^{3}H]-hypoxanthine by *P. falciparium* [4].

The parasite used for this test was a multi-drug resistant isolate from Southeast Asia, TM91C235. All five compounds were found to inhibit the parasite at submicromolar concentrations, the best possessing activity comparable to chloroquine (Table 1). The data suggest that both the 3- and the 4-halo substituent on the benzyl group contribute to this activity.

These compounds are potent enough to be considered for further development if the mechanism by which they act is found to be distinct from those employed by other antimalarial agents. Future studies will use the synthetic route described herein to prepare additional analogs. This will allow continued exploration of the structure-activity relationships for the 7-benzylamino-1-isoquinolinamines against malaria. The most potent compounds will be tested in an animal model of malaria. Determination of the mechanism by which they act will be crucial to assess their potential for development against drug-resistant malaria. Measurement of their activity against a panel of *P falciparum* strains resistant to standard antimalarial drugs will provide some information in this area.

EXPERIMENTAL

Reagents were obtained from Acros and Aldrich. Analytical TLC was performed using Basic Alumina Selectro Flexible-Backed TLC plates (Fisher). Liquid chromatography was performed using 50-200 μm activated neutral aluminum oxide (Fisher). Visualization of the developed chromatogram was by UV absorbance. Melting points were determined on an Electrothermal Mel-Temp melting point apparatus and are uncorrected. IR spectra were recorded on a Thermo Electron Corporation IR100 Spectrometer. ^{1}H NMR spectra were

recorded on a Jeol ECX 400 MHz spectrometer. Mass spectra were recorded on a Shimadzu QP-2010S GC/MS or an Agilent 1100/Waters Micromass ZQ LC/MS fitted with a Waters Xterra MS-C18 column, both operating in electrospray positive ion mode. Combustion analyses were performed by Atlantic Microlab, Inc. (Norcross, GA).

1,2,3,4-Tetrahydro-7-nitro-isoquinoline hydrogen chloride (5). Commercially available 1,2,3,4-tetrahydroisoquinoline (**4**) was reacted with potassium nitrate in sulfuric acid [20] to produce 1,2,3,4-tetrahydro-7-nitro-isoquinoline hydrogen chloride (**5**) as a white solid, mp 236-240° from methanol (lit. 214-216° [20]). *Anal.* Calcd. for $C_9H_{11}ClN_2O_2$: C, 50.36; H, 5.17; N, 13.05. Found: C, 50.44; H, 5.11; N, 13.10.

7-Nitro-isoquinoline (6). Compound (**5**) (2.16 g, 10 mmol) was added to a solution of potassium nitrosodisulfonate (30.1 g, 112 mmol) in 4% aqueous sodium carbonate solution (450 mL) [17]. The dark purple reaction mixture was allowed to stir for 7 d, and then extracted with chloroform (3 x 500 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (200 mL) and dried over anhydrous sodium sulfate. Following filtration, the solvent was removed by evaporation under reduced pressure. The residue was purified by alumina column chromatography (eluting with 10% v/v hexane in ethyl acetate) to give 7-nitro-isoquinoline (**6**) as an off-white solid (0.532 g, 30%), mp 168-169° (lit. 176-177° [22]); ir: 1625, 1581, 1516, 1328 cm^{-1}; ^1H nmr (deuteriochloroform): δ 9.48 (br, 1H, 1-H), 8.95 (br, 1H, 8-H), 8.75 (d, 1H, 3-H, J = 5.6 Hz), 8.48 (dd, 1H, 6-H, J = 2.4, 9.2 Hz), 8.00 (d, 1H, 5-H, J = 9.2 Hz), 7.79 ppm (d, 1H, 4-H, J = 5.6 Hz) [24]; ms: m/z 174 (M^+), 128, 116, 101, 75.

7-Nitro-1-isoquinolinamine (9). *m*-Chloroperoxy-benzoic acid (4.04 g of 70-75%, 16 mmol) was added to a solution of compound (**6**) (1.7 g, 9.8 mmol) in acetone (70 mL) [18]. The reaction was allowed to stir for 21 h, during which time a yellow solid formed. The solvent was then removed by evaporation under reduced pressure then the residual solid was dissolved in dichloromethane (300 mL). This solution was washed with 5% aqueous sodium hydroxide solution (300 mL), saturated aqueous sodium chloride solution (150 mL), and then dried over anhydrous magnesium sulfate. Following filtration, the solvent was removed by evaporation under reduced pressure to give 7-nitro-isoquinoline-2-oxide (**7**) as a bright yellow solid, which was used without further purification.

Pyridine (70 mL) was added to compound (**7**) followed by *p*-toluenesulfonyl chloride (2.24 g, 11.7 mmol) [18]. The resulting orange solution was stirred at room temperature for 2 h. The solvent was then removed by evaporation under reduced pressure yielding 1-chloro-7-nitro-isoquinoline (**8**) as a viscous brown oil, which was used without further purification.

Ethanolamine (150 mL) was added to compound (**8**) and the resulting dark solution was stirred at room temperature for 18 h [18]. The mixture was extracted with dichloromethane (2 x 600 mL). The combined organic layers were washed with water (2 x 500 mL) and saturated aqueous sodium chloride solution (100 mL) then dried over anhydrous magnesium sulfate. Following filtration, the solvent was then removed by evaporation under reduced pressure. The residue was purified by alumina column chromatography (eluting with 1% methanol in ethyl acetate) to give 7-nitro-1-isoquinolinamine (**9**) as an orange solid (280 mg, 15% yield from compound (**6**)), mp 225-233° dec.; ir: 3446, 3340, 3056, 1666, 1610, 1463 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.81 (d, 1H, 8-H, J = 1.6), 8.39 (dd, 1H, 6-H, J = 2.4, 9.2 Hz), 8.14 (d, 1H, 3-H, J = 5.6 Hz), 7.83 (d, 1H, 5-H, J = 9.2 Hz), 7.12 (d, 1H, 4-H, J = 5.6 Hz), 5.43 ppm (br, 2H, NH); ms: m/z 190 (MH^+).

1,7-Isoquinolinediamine (3). 10% Palladium on carbon (105 mg) suspended in methanol (3 mL) was added to a solution of compound (**9**) (260 mg, 1.38 mmol) in methanol (100 mL) [17]. The flask was evacuated, and then connected to a balloon containing hydrogen gas. After stirring vigorously for 15 h, the reaction mixture was filtered through Celite®. Removal of the solvent by evaporation under reduced pressure gave 1,7-isoquinolinediamine (**3**) as a pale yellow solid (254 mg, quantitative), mp 191-195° dec.; ir: 3548, 3486, 3389, 3281, 1663, 1595, 1550 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.75 (d, 1H, 3-H, J = 6.0 Hz), 7.54 (d, 1H, 5-H, J = 8.8 Hz), 7.07 (dd, 1H, 6-H, J = 2.4, 8.8 Hz), 6.95 (d, 1H, 4-H, J = 5.6 Hz), 6.91 (d, 1H, 8-H, J = 2.4), 4.91 (br, 2H, NH), 3.93 ppm (br, 2H, NH); ms: m/z 160 (MH^+).

General Procedure for the Reaction of Benzaldehydes with 1,7-isoquinolinediamine (3) [19]. Compound (**3**) was dissolved in acetic acid (1.65 mL), the requisite benzaldehyde was added, and the reaction was allowed to stir at room temperature for 30 min. Sodium cyanoborohydride (1.65 mL, 1 *M* THF solution) was added and the reaction stirred for 3 h. The mixture was poured into ice water, the pH adjusted to 11 by addition of 10% aqueous sodium hydroxide solution and then extracted into ethyl acetate (3 x 100 mL). Alumina column chromatography (eluting with 5% methanol in ethyl acetate) afforded the corresponding 7-benzylamino-1-isoquinolinamine. Following dissolution of this compound in ethanol, a saturated ethanolic solution of hydrogen chloride (4 mL) was added. After stirring for a few minutes the solvent was removed by evaporation under reduced pressure to give the corresponding hydrogen chloride salt (**2a-e**). Each salt was dried at 50°C under reduced pressure for 24 h.

7-Benzylamino-1-isoquinolinamine•2HCl•0.3H_2O (2a). The general procedure described above was carried out beginning with compound (**3**) (88 mg, 0.55 mmol) and using benzaldehyde (112 μL, 1.10 mmol) to afford 7-benzylamino-1-isoquinolinamine•2HCl•0.3H_2O (**2a**) as a yellow solid (135.3 mg, 86%), mp 160-165° dec.; ir: 3168, 2964, 2701, 2600, 2470, 1698, 1661, 1613, 1542 cm^{-1}; ^1H nmr (deuteriodimethylsufoxide): δ 8.70 (2H, br); 7.61 (1H, d, J = 8.4 Hz); 7.40-7.18 (7H, m); 7.21 (1H, m); 6.99 (1H, d, J = 7.2 Hz); 4.39 ppm (2H, s); ms: m/z 250 (MH^+). *Anal.* Calcd. for $C_{16}H_{16}ClN_3$•2HCl•0.3H_2O: C, 58.65; H, 5.41; N, 12.83. Found: C, 58.87; H, 5.35; N, 12.46.

7-(3'-Chlorobenzylamino)-1-isoquinolinamine•2HCl•0.65H_2O (2b). The general procedure described above was carried out beginning with compound (**3**) (86 mg, 0.54 mmol) and using 3-chlorobenzaldehyde (123 μL, 1.08 mmol) to afford 7-(3'-chlorobenzylamino)-1-isoquinolinamine•2HCl•0.65H_2O (**2b**) as a yellow solid (84.5 mg, 49%), mp 176-181° dec.; ir: 3404, 3165, 2704, 2597, 2463, 2366, 1695, 1613, 1549 cm^{-1}; ^1H nmr (deuteriodimethylsufoxide): δ 8.77 (2H, br); 7.62 (1H, d, J = 8.8 Hz); 7.47 (1H, s); 7.43-7.24 (6H, m); 6.99 (1H, d, J = 6.8 Hz); 4.39 ppm (2H, s); ms: m/z 286 (MH^+), 284 (MH^+). *Anal.* Calcd. for $C_{16}H_{15}Cl_2N_3$•2HCl•0.65 H_2O: C, 52.17; H, 4.73; N, 11.41. Found: C, 52.57; H, 4.69; N, 10.98.

7-(4'-Chlorobenzylamino)-1-isoquinolinamine•2HCl•0.37H_2O (2c). The general procedure described above was carried out beginning with compound (**3**) (71 mg, 0.45 mmol) and using 4-chlorobenzaldehyde (129 mg, 0.88 mol) to afford 7-(4'-chlorobenzylamino)-1-isoquinolinamine•2HCl•0.37H_2O (**2c**) as

a yellow solid (85.4 mg, 60%), mp 170-175° dec.; ir: 3362, 3178, 2958, 2699, 2604, 2469, 2365, 1698, 1662, 1543 cm^{-1}; ^1H nmr (deuteriodimethylsufoxide): δ 8.78 (2H, br); 7.68 (1H, d, J = 8.8 Hz); 7.50-7.38 (7H, m); 7.06 (1H, d, J = 6.8 Hz); 4.46 ppm (2H, s); ms: m/z 286 (MH^+), 284 (MH^+). *Anal.* Calcd. for $C_{16}H_{15}Cl_2N_3 \cdot 2HCl \cdot 0.37\ H_2O$: C, 52.89; H, 4.64; N, 11.56. Found: C, 53.29; H, 4.74; N, 11.16.

7-(3'-Bromobenzylamino)-1-isoquinolinamine•2HCl•0.8H_2O (2d). The general procedure described above was carried out beginning with compound (**3**) (88 mg, 0.55 mmol) and using 3-bromobenzaldehyde (123 μL, 1.05 mmol) to afford 7-(3'-bromobenzylamino)-1-isoquinolinamine•2HCl•0.8 H_2O (**2d**) as a yellow solid (44.5 mg, 22%), mp 207-215° dec.; ir: 3463, 3164, 2704, 2600, 2465, 1693, 1611, 1548 cm^{-1}; ^1H nmr (deuteriodimethylsufoxide): δ 8.75 (2H, br); 7.66-7.58 (2H, m); 7.42-7.22 (6H, m); 6.99 (1H, d, J = 6.8 Hz); 4.42 ppm (2H, s); ms: m/z 330 (MH^+), 328 (MH^+). *Anal.* Calcd. for $C_{16}H_{15}BrClN_3$•2HCl•0.8H_2O: C, 46.25; H, 4.27; N, 10.11. Found: C, 46.61; H, 4.35; N, 9.73.

7-(3',4'-Dichlorobenzylamino)-1-isoquinolinamine•2HCl •0.9H_2O (2e). The general procedure described above was carried out beginning with compound (**3**) (70 mg, 0.44 mmol) and using 3',4'-dichloro benzaldehyde (159.3 mg, 0.91 mmol) to afford 7-(3',4'-dichlorobenzylamino)-1-isoquinolinamine •2HCl•0.9H_2O (**2e**) as a yellow solid (78.7 mg, 49%), mp 200-205° dec.; ir: 3431, 2994, 2465, 1667, 1567 cm^{-1}; ^1H nmr (deuteriodimethylsufoxide): δ 8.66 (2H, br); 7.68-7.62 (2H, m); 7.56 (1H, d, J = 8.4 Hz); 7.35-7.25 (4H, m); 6.94 (1H, d, J = 6.8 Hz); 4.37 ppm (2H, s); ms: m/z 322 (MH^+), 320 (MH^+), 318 (MH^+). *Anal.* Calcd. for $C_{16}H_{14}Cl_3N_3$•2HCl•0.9 H_2O : C, 47.18; H, 4.16; N, 10.32. Found: C, 46.95; H, 3.78; N, 10.12.

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