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Synthesis and biological activity of anticoccidial agents: 2,3-diarylindoles

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ABSTRACT

Novel 2,3-diarylindoles bearing an amine substituent at the indole 5- and 6-positions have been synthesized and evaluated as anticoccidial agents in both in vitro and in vivo assays. Both subnanomolar in vitro activity and broad spectrum in vivo potency were detected for several compounds, particularly compound **27**.

Parasitic protozoa are responsible for a wide variety of infectious diseases in both humans and animals. Coccidiosis is a parasitic disease that is the major cause of morbidity and mortality in the poultry industry. It is a disease of the avian intestinal lining due to invasion by Apicomplexan protozoan parasites of the genus *Eimeria*,[1] where the most significant *Eimeria* species in poultry include *E. tenella*, *E. acervulina*, *E. mitis,* and *E. maxima*. Over 35 billion chickens are raised annually worldwide, and all major poultry operations use prophylactic anticoccidial agents. Nevertheless, resistance to current coccidiostats such as polyether ionophores has become widespread,[2] creating the need for new broad spectrum drugs with unprecedented mechanisms of action.

Recently, we have reported on novel anticoccidial agents with potent in vitro and in vivo activity against *Eimeria* parasites. It was found that the reduction of parasite growth by these compounds was due to the inhibition of parasite-specific cGMP-dependent protein kinase (PKG), a serine/threonine protein kinase.[3,4] In particular, we have found that various 2,3-diarylpyrroles[5–8], 2,3-diarylimidazo[1,2-*a*]pyridines[9–13], and 5,6-diarylimidazo[2,1-*b*][1,3]thiazoles[14] show exceptional potency as anticoccidial agents.

In this paper, we present the synthesis and biological activity of a series of 2,3-diarylindoles substituted at the 6-position with various amine sidechains, as we were curious how these compounds would compare with our analogous pyrroles, imidazopyridines, and imidazothiazoles. Within these three series, we found many of our active compounds possessed a 4-fluorophenyl ring, a pyrimidin-4-yl or pyridin-4-yl ring, and a piperidin-4-yl ring at strategic locations across the core heterocycle. We therefore decided to introduce such functionality across an indole template.

Scheme 1 depicts the synthesis of indoles bearing a 2-aminopyrimidin-4-yl or pyrimidin-4-yl ring at the indole 3-position. The synthesis of ketone **1** has been reported previously.[12] Palladium-catalyzed arylation[15] of the α-carbon of ketone **1** with 2,5-dibromonitrobenzene occurred regioselectively with displacement of the bromine ortho rather than meta to the nitro group, yielding α-aryl ketone **2**. Reductive cyclization with iron in acetic acid then rendered indole **3**. The indole nitrogen was subsequently protected to give *N*-tosylindole **4**. The methylsulfanyl group of **4** was then oxidized with *m*-CPBA to yield sulfone **5**, which itself was treated with ammonia to afford 2-aminopyrimidine **6**. Alternatively, the methylsulfanyl group of **4** was reduced with Raney nickel to give 2-H-pyrimidine **7**. Subsequent Negishi coupling[16] of aryl bromides **6** and **7** with 1-Boc-4-iodozincpiperidine[17] gave 6-(1-Boc-piperidin-4-yl)indoles **8** and **9**, respectively. Cleavage of the Boc protecting group followed using trifluoroacetic acid to give NH-piperidines **10** and **11**. Deprotection of the indole nitrogen yielded N–H indoles **12** and **13**, while alkylation by reductive amination with formaldehyde gave *N*-methylpiperi-

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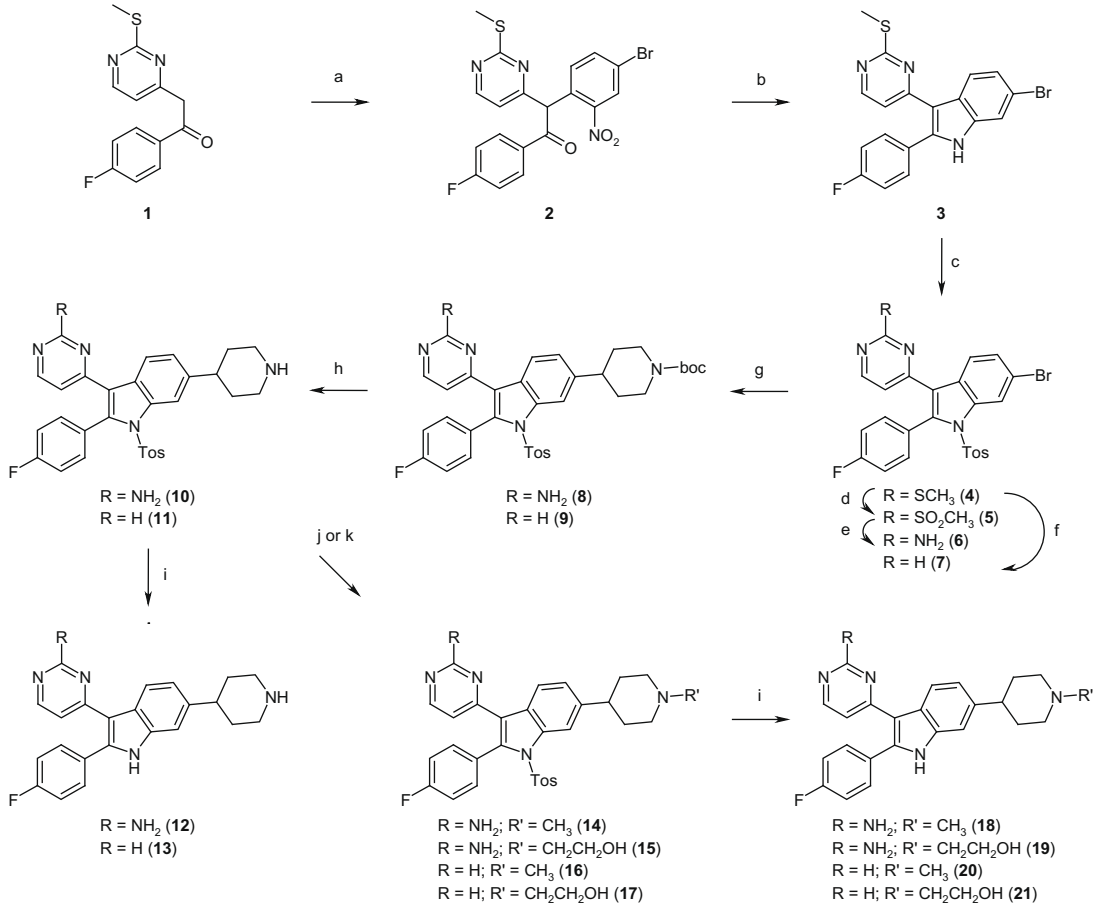
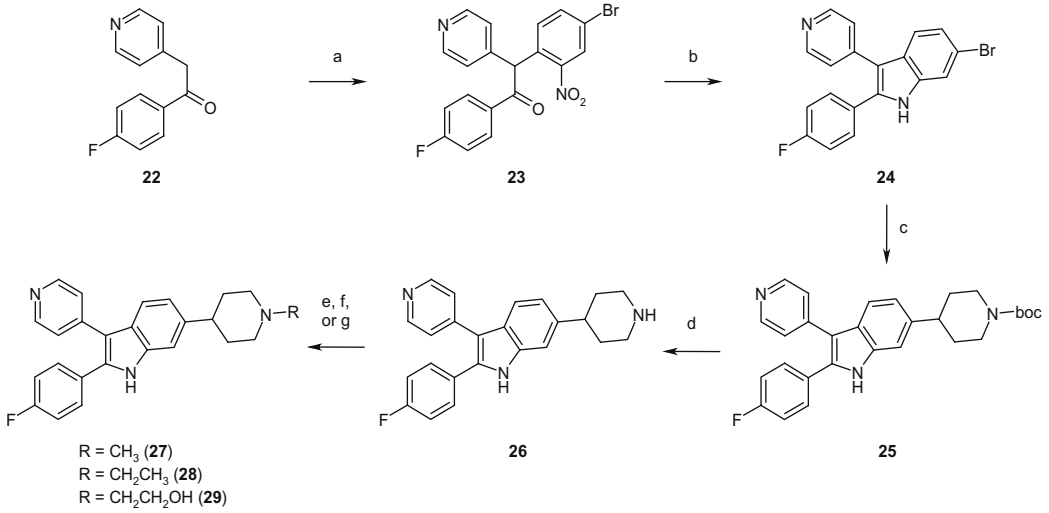


Scheme 1. Reagents and conditions: (a) 2,5-dibromonitrobenzene, $Pd(OAc)_2$, 2-(di-*tert*-butylphosphino)biphenyl, Cs_2CO_3, DMF, 70 °C; (b) Fe, AcOH, 15 °C–rt; (c) TosCl, NaH, THF; (d) *m*-CPBA, CH_2Cl_2; (e) NH_3, THF, 50 psi; (f) Raney Ni, EtOH, 80 °C; (g) 1-Boc-4-iodozincpiperidine, $PdCl_2(dppf)CH_2Cl_2$, CuI, DMA, 80 °C; (h) CF_3CO_2H, CH_2Cl_2; (i) K_2CO_3, MeOH, 65 °C; (j) $H_2C{=}O$, $NaBH_3CN$, MeOH, AcOH; (k) $BrCH_2CH_2OH$, K_2CO_3, DMF, 65 °C.

dines **14** and **16**, and alkylation with 2-bromoethanol under basic conditions gave *N*-(2-hydroxyethyl)piperidines **15** and **17**. *N*-Tosyl indoles **14–17** were ultimately deprotected to yield NH-indoles **18–21**.

We then prepared the analogous 3-(pyridin-4-yl)indoles, as shown in Scheme 2. The synthesis of ketone **22** has been reported previously.[5] Regioselective arylation of ketone **22** proceeded as in the pyrimidine series to yield α-aryl ketone **23**. At this point, we



Scheme 2. Reagents and conditions: (a) 2,5-dibromonitrobenzene, $Pd(OAc)_2$, 2-(di-*tert*-butylphosphino)biphenyl, Cs_2CO_3, DMF, 60 °C; (b) $TiCl_3$, NH_4OAc, 10:1 EtOH:EtOAc; (c) 1-Boc-4-iodozincpiperidine, $PdCl_2(dppf)CH_2Cl_2$, $Pd_2(dba)_3$, CuI, XANTPHOS, RuPHOS, CuSCN, NMP, DMA, 100 °C; (d) CF_3CO_2H, CH_2Cl_2; (e) $H_2C{=}O$, $NaBH_3CN$, MeOH, AcOH; (f) $H_3CC(=O)H$, $NaBH_3CN$, MeOH, AcOH; (g) glycolaldehyde, $NaBH_3CN$, MeOH, AcOH.