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Divergent synthesis of 2,6-diaryl-substituted 5,7,8-trimethyl-1,4-benzoxazines via microwave-promoted palladium-catalyzed Suzuki–Miyaura cross coupling and biological evaluation

Eftychia N. Koini [a,†], Nicolaos Avlonitis [a,b,†], Erica S. Martins-Duarte [c], Wanderley de Souza [c,d], Rossiane C. Vommaro [c], Theodora Calogeropoulou [a,*]

[a] Institute of Biology, Medicinal Chemistry and Biotechnology, National Hellenic Research Foundation, 48 Vassileos Constantinou Avenue, 11635 Athens, Greece
[b] Centre for Inflammation Research, The Queen's Medical Research Institute, MRC/University of Edinburgh, 47 Little France Crescent, EH16 4TJ Edinburgh, UK
[c] Laboratório de Ultraestrutura Celular Hertha Meyer, Instituto de Biofísica Carlos Chagas Filho, UFRJ, CCS, Bloco G, Av. Carlo, Chagas Filho, Cidade Universitária, Ilha do Fundão, 21941-902 Rio de Janeiro, RJ, Brazil
[d] Instituto Nacional de Metrologia, Qualidade e Tecnologia-Inmetro, Xerém, Duque de Caxias, Rio de Janeiro, RJ, Brazil

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ABSTRACT

An efficient palladium-catalyzed Suzuki–Miyaura cross-coupling protocol effected in a mixture of DME/water (2:1) enables the reaction of sterically hindered and electron rich 6-chloro or 6-bromo-1,4-benzoxazines(ones) with a variety of aryl, vinyl or alkylboronic acids. Coupling is effected with catalyst loading of 5 mol % using sealed-vessel microwave processing. The resulting compounds exhibit potent activity against *Toxoplasma gondii* tachyzoite proliferation.

1. Introduction

The 2*H*-1,4-benzoxazine-3-(4*H*)-one and 3,4-dihydro-2*H*-1,4-benzoxazine systems are considered as privileged scaffolds for the development of potential new drugs and have been extensively employed in the synthesis of a variety of biologically active compounds, such as herbicides, fungicides, K_{ATP} channel openers, cardiovascular, anti-diabetic, neuroprotective, anxiolytic agents and antidepressants.[1] Recently we reported that 5,7,8-trimethyl-1,4-benzoxazine aminoamide derivatives possess activity against reperfusion arrhythmias.[2] The 5,7,8-trimethyl-1,4-benzoxazine core can be considered as a classical bioisostere of the 5,7,8-trimethylbenzopyran nucleus of the well known chain breaking antioxidant, vitamin E. As part of an ongoing lead optimization project we sought a strategy that would enable rapid exploration of structure–activity relationships through the late-stage, divergent installation of different C-6 substituents in 5,7,8-trimethyl-1,4-benzoxazines and 2-aryl-5,7,8-trimethyl-1,4-benzoxazines.[3] We therefore investigated a straightforward route towards this end via Suzuki–Miyaura cross coupling reaction of the corresponding 6-halogen-substituted 5,7,8-trimethyl-1,4-benzoxazines/ones and a variety of boronic acids. The palladium catalyzed Suzuki–Miyaura reaction represents one of the most highly prized processes in synthetic chemistry and an extensively studied cross coupling reaction for carbon–carbon bond formation.[4] It has found wide applications in the synthesis of bioactive complex molecules because of its mild reaction conditions and its compatibility with a broad range of functional groups. Typically it involves reaction of an aryl or vinyl halide or triflate with an aryl, vinyl or alkyl boron compound to obtain biaryls, 1,3-dienes, alkyl/aryl-substituted alkenes and alkyl-substituted aromatics. Recent significant advancements in the area of phosphine catalyst ligand design and synthesis were contributed by Beller,[5] Buchwald,[6] Hartwig,[7] and others[8] while Fu[9] and co-workers extended the scope of the reaction to cross-coupling to alkyl electrophiles. The reaction involves the palladium catalyzed cross coupling of alkyl boranes to primary alkyl halides and tosylates in the presence of catalysts with bulky electron rich phosphane ligands.[10] During the last decade, advances in the organoboron nucleophilic counterpart have emerged and more

* Corresponding author. Tel.: +30 210 7273833; fax: +30 210 7273831; e-mail address: tcalog@eie.gr (T. Calogeropoulou).
† These authors contributed equally to this work.

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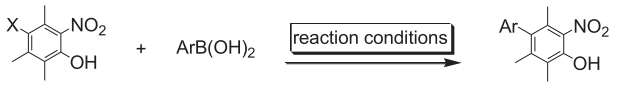
specifically the use of organotrifluoroborates developed by the groups of Genet[11] and Molander.[12] Recently, Kwong et al. reported on the palladium catalyzed Suzuki–Miyaura coupling of aryl mesylates to aryl-, heteroaryl-, alkenyl-, and alkyl-trifluoroborate salts[13] while, Molander and Beaumard reported the Suzuki-type cross coupling of aryl- and heteroaryl mesylates with potassium aminomethyltrifluoroborates and amidomethyltrifluoroborates.[14]

2. Results and discussion

In this work we examined the Suzuki–Miyaura coupling reaction of 6-halogen-substituted 5,7,8-trimethyl-1,4-benzoxazinones, 6-bromo-5,7,8-trimethyl-1,4-benzoxazines and of 4-halogen-substituted 3,5,6-trimethyl-2-nitrophenol, prepared using our previously described halogenation procedure.[15] 2-Nitrophenols have been widely used as the starting materials in the synthesis of 3,4-dihydro-2*H*-1,4-benzoxazines and 2*H*-1,4-benzoxazin-3-(4*H*)-ones[16] therefore, the biaryls obtained through the Suzuki–Miyaura cross coupling reactions could allow for increased structural diversity of the resulting heterocyclic derivatives. Alternatively, 1,4-benzoxazine derivatives are synthesized via cyclocondensation of aminophenols with dihalo derivatives[17] or with substituted halogeno acyl bromides followed by reduction of the resulting lactams, or by epoxide opening with *o*-halosulfonamides followed by cyclization[18] or by epoxide opening with aminophenols followed by cyclocondensation[19] or by domino aziridine ring opening with *o*-iodophenols followed by the copper catalyzed Goldberg coupling cyclization.[20] 3,4-Dihydro-3-oxo-2*H*-1,4-benzoxazine derivatives have been prepared from *o*-aminophenols by a one-pot microwave-assisted O-alkylation with substituted halogeno acyl bromides and spontaneous cyclization[21] or by microwave-assisted reductive N-arylmethylation followed by regioselective O-alkylation with 2-bromoalkanoates and spontaneous cyclization[22] or via an Ugi four component reaction followed by intramolecular O-alkylation.[23]

To achieve our goal we compared the effects of thermal versus microwave-assisted conditions for the Suzuki–Miyaura coupling reactions. Microwave enhanced synthesis has emerged as a powerful tool due to the high-speed construction of versatile chemical entities.[24] Several examples have been reported for its application for the palladium catalyzed Suzuki–Miyaura cross coupling reaction.[25] Previous synthetic efforts towards simple 6-aryl-2,4,4-trimethyl-1,4-dihydro-2*H*-benzo[*d*][1,3]oxazines involved thermal conditions for the Suzuki–Miyaura cross-coupling reaction.[26] Furthermore, the microwave assisted palladium-catalyzed intramolecular direct arylation of suitably *N*-substituted 1,4-benzoxazinones has been reported.[27] However, to the best of our knowledge, no reports on the synthesis of 6-aryl-1,4-benzoxazines/ones with the extremely sterically hindered 5,7,8-trimethyl-1,4-benzoxazine/one core, under microwave-assisted conditions have appeared in the literature. Initially we focused our efforts in finding the optimum conditions for the Suzuki–Miyaura coupling of 4-chloro- and 4-bromo-3,5,6-trimethyl-2-nitrophenol with neutral and electron rich aryl boronic acids (Table 1) using conventional heating. Our experimentation was focused in the use of a number of bases $Ba(OH)_2$, Cs_2CO_3, K_3PO_4, Na_2CO_3, solvents (THF, DMF), various reaction times and temperature, while $Pd(PPh_3)_4$ was used as catalyst. However, we were not able to detect any coupling product with 4-chloro-3,5,6-trimethyl-2-nitro phenol (**1a**) and phenyl or 2-methoxyphenyl boronic acid (Table 1, entries 1 and 2). Conversely, the more reactive 4-bromo-substituted analogue (**1b**) afforded the coupling products in isolated yields ranging between 54 and 82% (Table 1, entries 3–6). Fine tuning of the reaction parameters led to the use of controlled microwave irradiation using a closed vessel and we were gratified to obtain the desired biaryls from 4-chloro-3,5,6-trimethyl-2-nitro phenol (**1a**) in around 70% yield (Table 1, entries 1 and 2). It should be noted that compound **1a** is a sterically demanding substrate, while 2-methoxyphenyl boronic acid, an electron rich *ortho*-substituted aryl boronic acid, properties, which do not favour productive coupling between the two partners. As an example, reaction of mesitylboronic acid with iodobenzene requires heating at 80 °C and strong base ($Ba(OH)_2$) due to the steric hindrance during the transmetalation to the palladium (II) complex.[28] Furthermore, the conventional heating approach, suffers from long reaction times at an elevated temperature regime (2–20 h and 80–100 °C) and the necessity to employ double the quantity of palladium catalyst to obtain acceptable yields for these difficult substrates. Conversely, employing sealed-vessel microwave heating an improved protocol was obtained that allows performing the reaction in only 5 min at 160 °C using 5 mol % palladium catalyst, Na_2CO_3 as base and almost equimolar boronic acid stoichiometry. Finally, utilization of an aqueous solvent system (DME/water 2:1) renders the reaction more environmentally friendly. The yields of microwave-assisted Suzuki–Miyaura cross coupling of 4-bromo-3,5,6-trimethyl-2-nitrophenol (**1b**) and phenyl or 4-methoxyphenyl boronic acid were superior to conventional heating (Table 1, entries 3 and 6), while with 2-methoxyphenyl boronic acid was lower due to dehalogenation of the starting bromo-nitrophenol **1b** (Table 1, entry 4). Furthermore, in the case that 3-methoxyphenyl boronic acid was used as coupling partner the yield was slightly lower under microwave irradiation conditions (Table 1, entry 5).

Table 1
Suzuki–Miyaura cross coupling of 6-halo-3,5,6-trimethyl-2-nitrophenol and aryl boronic acids. Optimization studies



1a X = Cl
1b X = Br

2a Ar = C_6H_5
2b Ar = o-MeC_6H_5
2c Ar = m-$MeOC_6H_5$
2d Ar = p-$MeOC_6H_5$

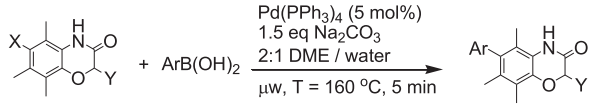
3a Ar = C_6H_5
3b Ar = o-$MeOC_6H_5$
3c Ar = m-$MeOC_6H_5$
3d Ar = p-$MeOC_6H_5$

Entry	Halo phenol	$ArB(OH)_2$	Product	Reaction conditions (% isolated yield[a])	
				Microwave irradiation	Normal heating
1	**1a**	**2a**	**3a**	A (71)	—
2	**1a**	**2b**	**3b**	A (77)	—
3	**1b**	**2a**	**3a**	B (90)	C (82)
4	**1b**	**2b**	**3b**	B (50)	C (55)
5	**1b**	**2c**	**3c**	B (51)	C (63) D (72)
6	**1b**	**2d**	**3d**	B (73)	D (54)

[a] Isolated yield after purification by flash chromatography (A) **1a** (1 equiv), $ArB(OH)_2$ (1.5 equiv), Na_2CO_3 (1.5 equiv), $Pd(PPh_3)_4$ (5 mol %), Toluene, μw, T=160 °C, t=5 min (B) **1b** (1 equiv), $ArB(OH)_2$ (1.5 equiv), Na_2CO_3 (1.5 equiv), $Pd(PPh_3)_4$ (5 mol %), 2:1 DME/H_2O, μw, T=160 °C, t=5 min (C) **1b** (1 equiv), $ArB(OH)_2$ (1.5 equiv), Cs_2CO_3 (1.5 equiv), $Pd(PPh_3)_4$ (10 mol %), DMF, T=100 °C, t=2 h (D) **1b** (1 equiv), $ArB(OH)_2$ (1.5 equiv), Cs_2CO_3 (1.5 equiv), $Pd(PPh_3)_4$ (10 mol %), THF, T=80 °C, t=20 h.

We then explored the Suzuki–Miyaura coupling reaction of 6-halo-5,7,8-trimethyl-1,4-benzoxazinones using our optimized microwave-assisted conditions. However, the yields of the cross coupling of 6-chloro- and 6-bromo-substituted analogues **4a** and **4b** with 2-methoxyphenyl boronic acid were low probably due to steric hindrance of the boronic acid counterpart (Table 2, entries 1,3). It is well-known that Suzuki–Miyaura coupling is sensitive to steric hindrance. In addition, electron-rich chloroarenes are more difficult substrates than electron-poor ones.[29] Cross coupling of 6-chloro substituted **4a** and 3-methoxyphenyl boronic acid was effected in low yield (Table 2, entry 2), which was markedly increased to 67% when the 6-bromo derivative **4b** was used (Table 2, entry 4) and was improved further to 86% when 4-methoxyphenyl boronic acid was employed as the nucleophilic partner and Cs_2CO_3 as base (Table 2, entry 5). Gratifyingly, Suzuki–Miyaura coupling reactions with 2-phenyl-6-bromo-5,7,8-trimethyl-1,4-benzoxazinone (**4c**)

Table 2
Microwave-promoted Suzuki–Miyaura cross coupling of 6-halo-3,5,6-trimethyl-1,4-benzoxazinones and aryl boronic acids



4a X = Cl, Y = H **2a-d**
4b X = Br, Y = H
4c X = Br, Y = C_6H_5

5a Ar = o-$MeOC_6H_5$, Y = H
5b Ar = m-$MeOC_6H_5$, Y = H
5c Ar = p-$MeOC_6H_5$, Y = H
5d Ar = C_6H_5, Y = C_6H_5
5e Ar = m-$MeOC_6H_5$, Y = C_6H_5
5f Ar = p-$MeOC_6H_5$, Y = C_6H_5

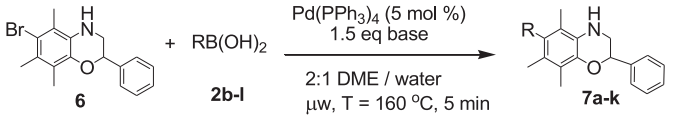
Entry	6-Halo-5,7,8-trimethyl-1,4-benzoxazinone	$ArB(OH)_2$	Product	Yield (%)[a]
1	**4a**	**2b**	**5a**	24
2	**4a**	**2c**	**5b**	18
3	**4b**	**2b**	**5a**	15
4	**4b**	**2c**	**5b**	67
5	**4b**	**2d**	**5c**	86[b]
6	**4c**	**2a**	**5d**	97
7	**4c**	**2c**	**5e**	85[b]
8	**4c**	**2d**	**5f**	91

[a] Isolated product after purification by flash chromatography.
[b] Cs_2CO_3 (1.5 equiv) was used as base instead of Na_2CO_3.

and phenyl or 3-methoxyphenyl or 4-methoxyphenyl boronic acid were effected in almost quantitative yields (Table 2, entries 6–8).

Capitalizing on the excellent results of the Suzuki–Miyaura cross coupling of 2-phenyl-6-bromo-5,7,8-trimethyl-1,4-benzoxazinone (**4c**) we applied our optimized conditions to the corresponding 1,4-benzoxazine derivative (**6**) and a variety of aryl- and heteroarylboronic acids to investigate further the synthetic scope of the reaction (Table 3).

Table 3
Microwave-promoted Suzuki–Miyaura cross coupling of 2-phenyl-6-bromo-5,7,8-trimethyl-1,4-benzoxazine with various boronic acids



6 **2b-l** **7a-k**

Entry	$RB(OH)_2$	Product	Yield (%)[a]
1	**2b** R=*o*-MeOPh	**7a**	47[b] 55[d]
2	**2c** R=*m*-MeOPh	**7b**	80[b]
3	**2d** R=*p*-MeOPh	**7c**	83[c]
4	**2e** R=(*E*)-styryl	**7d**	81[b]
5	**2f** R=4-vinylphenyl	**7e**	88[b]
6	**2g** R=2-furyl	**7f**	90[b]
7	**2h** R=2-thienyl	**7g**	85[b]
8	**2i** R=2-naphthyl	**7h**	84[b]
9	**2j** R=*p*-CF_3Ph	**7i**	85[b]
10	**2k** R=*p*-butylphenyl	**7j**	87[b]
11	**2l** R=butyl	**7k**	55[b]

[a] Isolated yield.
[b] Base: Na_2CO_3.
[c] Base: Cs_2CO_3.
[d] Base: $Ba(OH)_2$.

The reaction conditions remained general across electron deficient (Table 3, entry 9), electron rich (Table 3, entries 1, 2, 3, 5, 10) and neutral hindered (Table 3, entry 8) aryl boronic acids, an alkenylboronic acid (Table 3, entry 4), heteroarylboronic acids (Table 3, entries 6, 7) and even an alkylboronic acid, albeit in moderate yield (Table 3, entry 11). As previously observed in the case of compound **5a**, coupling with 2-methoxyphenyl boronic acid (**2b**) was effected in moderate yield due to steric hindrance (Table 3, entry 1). The byproduct of the reaction was the debrominated 1,4-benzoxazine analogue of **6**.

In the Suzuki–Miyaura cross coupling reaction the role of the base is to facilitate the slow transmetalation of the boronic acid. Usually, in the case of sterically hindered boronic acids, a mild base like Na_2CO_3 is preferable in order to avoid elimination of the boronic acid group. However, switching to the stronger base $Ba(OH)_2$ was necessary in order to increase the yield of the desired product **7a** (Table 3, entry 1). Accordingly, Cs_2CO_3 was employed as base when 4-methoxyphenyl boronic acid (**2d**) was employed as coupling partner to obtain analogue **7c** (Table 3, entry 3). It has been previously reported that the presence of nitrogen heterocyclic moieties, that are valuable structural motifs in medicinal chemistry, leads to low reactivity in coupling reactions due to the binding of the heteroatom of the substrate and product to the metal complex. Even though binding is reversible, the large excess of substrate can lead to a strong inhibitory effect.[30]

However, in our case the corresponding 6-bromo-1,4-benzoxazine derivative **6** exhibited good reactivity resulting to the corresponding 6-aryl or 6-heteroaryl derivatives in high to excellent yields thus, allowing the generation of a small compound library, which was further investigated for its biological activity against *Toxoplasma gondii* tachyzoites (Table 4). *T. gondii*, the causative agent of toxoplasmosis, is a ubiquitous opportunistic pathogen that infects individuals worldwide and a wide range of animals including all warm blooded animals.[31] It is a leading cause of severe congenital, neurologic and ocular disease in humans, exacerbated when immunodepression of the host takes place due to chemotherapy, radiotherapy and HIV infection. Throughout the world, new *T. gondii* infection during pregnancy can lead to devastating disease for the foetus and newborn infant, later impacting on the child's health and development and potentially on his/her later productivity.[32] Furthermore, *T. gondii* is designated as an NIAID Category B biowarfare (priority) pathogen, in large part due to its danger to both humans and livestock, its persistence in the environment, and the ease with which it disseminates. The treatment of choice for toxoplasmosis is the combined administration of pyrimethamine with either sulfadiazine or clindamycin. Since no vaccine for humans is available, and hypersensitivity and toxicity limit the use of the few available drugs safer and more effective medicines to treat toxoplasmosis are urgently needed. Compounds **7a**–**k** inhibited *T. gondii* tachyzoite proliferation showing IC_{50} values in the low micromolar range (0.86–4.5 μM, Table 4). The most active compounds were 6-(3-methoxyphenyl)-5,7,8-trimethyl-2-phenyl-3,4-dihydro-2*H*-1,4-benzoxazine (**7b**) and 6-(4-butylphenyl)-5,7,8-trimethyl-2-phenyl-3,4-dihydro-2*H*-1,4-benzoxazine (**7j**) with IC_{50}=1.21±0.04 μM and 0.86±0.4 μM, respectively, after 72 h.

3. Conclusions

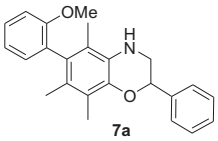
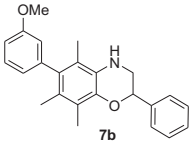
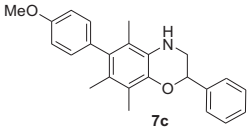
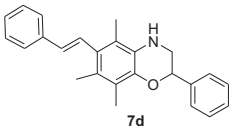
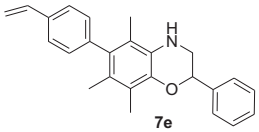
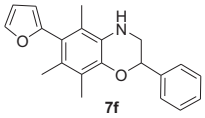
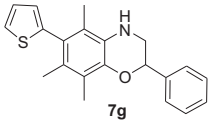
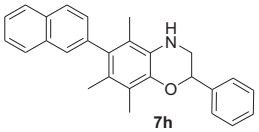
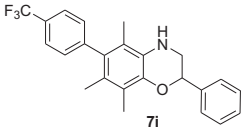
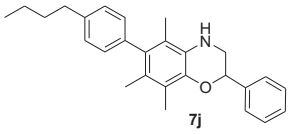
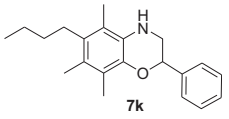
In summary, we have developed a convenient and efficient strategy for the synthesis of 6-substituted-5,7,8-trimethyl-1,4-benzoxazines(ones) via microwave-assisted Suzuki–Miyaura cross coupling with a variety of boronic acids. This approach allows for the rapid incorporation of aryl, heteroaryl and alkyl functionalities into this heterocyclic privileged scaffold. Furthermore, our results demonstrate that 2-phenyl-6-aryl-5,7,8-trimethyl-1,4-benzoxazines are very active against *T. gondii* tachyzoite proliferation in vitro and suggest further investigation of this class of molecules as potential agents against toxoplasmosis.

4. Experimental section

4.1. General remarks

^{1}H NMR spectra were recorded at 600 or 300 MHz, ^{13}C NMR spectra at 150.9 or 75.5 MHz and ^{19}F NMR spectra at 564.8 MHz. ^{1}H

Table 4
Growth inhibition of *T. gondii* tachyzoites RH strain by 6-substituted 2-phenyl-5,7,8-trimethyl-1,4-benzoxazines after 48 and 72 h of treatment

Compounds	IC_{50} (μM)	
	48 h	72 h
 **7a**	1.41±0.64[a,c]	2.65±0.53[a,c]
 **7b**	0.90±0.32[b]	1.21±0.04[a]
 **7c**	1.81±0.9[a]	2.13±0.86[a]
 **7d**	2.27± 0.80[a]	1.33±0.39[b]
 **7e**	2.07±0.83[a]	1.64±0.5[a]
 **7f**	1.64±0.40[b]	1.79±0.37[a]
 **7g**	2.07±0.47[a]	2.15±0.62[a]
 **7h**	3.00±0.96[a]	1.83±0.19[a]
 **7i**	1.60±0.29[a]	1.57±0.35[b]
 **7j**	1.69±0.79[a]	0.86±0.40[b]
 **7k**	4.5±0.67[b]	2.31±0.18[b]

Results were expressed as the mean±standard deviation of [a]three or [b]two different experiments. [c]The less polar rotamer was evaluated.

and ^{13}C NMR spectra are internally referenced to residual solvent signals ($CDCl_3$). ^{19}F NMR spectra are referenced to CCl_3F. Data for ^1H NMR are reported as follows: chemical shift (δ ppm), integration, multiplicity (s=singlet, d=doublet, dd=doublet of doublet, ddd=doublet of doublet of doublet, m=multiplet) and coupling constant. Data for ^{13}C NMR are reported in terms of chemical shift (δ ppm). Melting points (°C) are uncorrected. Reactions were performed in a microwave reactor CEM Discover LabMate. IR spectra were obtained on an ATR-IR spectrometer. Thin-layer chromatography (TLC) was performed on glass plates coated with silica gel (0.2 mm, 60 F254) and flash chromatography using silica gel (200–400 mesh).

4.2. Experimental procedures

*4.2.1. 6-Bromo-5,7,8-trimethyl-2-phenyl-2H-benzo[b][1,4] oxazin-3(4H)-one (**4c**).* To a solution of 5,7,8-trimethyl-2-phenyl-2*H*-1,4-benzoxazin-3(4*H*)-one (0.001 mol) in petroleum ether (10 mL) was added a mixture of CH_3COOH/H_2O_2 (30%)/HBr (48%) (6.50 mmol:6.50 mmol:2.50 mmol) and the reaction was stirred at room temperature for 1 h. After dilution with EtOAc (50 mL), the organic layer was separated, washed with $NaHCO_3$ (50 mL, satd aq), brine (50 mL), dried (Na_2SO_4) and the solvent evaporated in vacuo. Purification of the crude product by flash chromatography (10% acetone/petroleum ether 40–60 °C) gave *the title compound* **4c** (0.225 g, 65%) as a white solid, mp 210–212 °C (recrystallized from EtOAc); R_f (20% EtOAc/petroleum ether 40–60 °C/4:1) 0.35; ν_{max}(neat) 3212, 3140, 1681, 1578, 1228 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.88 (1H, s, NH), 7.41–7.33 (5H, m, Ph), 5.70 (1H, s, C*H*Ph), 2.35 (6H, s, 2*Me*), 2.27 (3H, s, *Me*); δ_C (75.5 MHz, $CDCl_3$) 166.4, 140.3, 135.1, 132.6, 129.0, 128.9, 126.8, 124.3, 123.2, 121.5, 121.4, 78.2, 20.6, 17.6, 13.3; MS (EI), *m/z* 347 (90, $[M+2]^+$), 345 (89, M^+), 118 (100); HRMS (ESI^+): MH^+, found 346.0444. $C_{17}H_{17}Br^{79}NO_2$ requires 346.0437.

*4.2.2. 6-Bromo-3,4-dihydro-5,7,8-trimethyl-2-phenyl-2H-benzo[b][1,4]oxazine (**6**).* To a solution of benzoxazinone **4c** (0.346 g, 0.001 mol) in anhydrous THF (2 mL) was added drop wise at 0 °C a solution of borane dimethyl sulfide complex (24.0 mmol, 2.28 mL). The resulting mixture was stirred at room temperature for 12 h and the reaction was quenched by the drop wise addition of water at 0 °C until gas evolution ceased. After dilution with EtOAc (50 mL), the organic layer was separated, washed with brine (50 mL), dried (Na_2SO_4) and the solvent evaporated in vacuo. Purification of the crude product by flash chromatography (3% acetone/hexane) afforded *the title compound* **6** (0.249 g, 75%) as a white solid, mp 122–124 °C (recrystallized from hexane/EtOAc); R_f (20% acetone/petroleum ether 40–60 °C) 0.40; ν_{max}(neat) 3413, 1601, 1383, 1124 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.44–7.35 (5H, m, Ph), 5.03 (1H, dd, *J* 8.7, 2.1 Hz, C*H*Ph), 3.61 (1H, dd, *J* 12.0, 2.1 Hz, CH_2CHPh), 3.31 (1H, dd, *J* 12.0, 8.7 Hz, CH_2CHPh), 2.37 (3H, s, *Me*), 2.30 (3H, s, *Me*), 2.25 (3H, s, *Me*); δ_C (75.5 MHz, $CDCl_3$) 141.9, 139.5, 129.4, 128.8, 128.3, 126.9, 126.3, 123.9, 120.7, 119.9, 75.6, 48.4, 20.2, 17.6, 13.0; MS (EI), *m/z* 333 (95, $[M+2]^+$), 331 (96, M^+), 242 (100), 240 (100); HRMS (FAB^+): M^+, found 331.0556. $C_{17}H_{18}Br^{79}NO$ requires 331.0572.

4.3. General procedure for the microwave assisted Suzuki–Miyaura cross coupling reaction, synthesis of compounds 3a–3d, 5a–5f, 7a–7k

To a thick-wall borosilicate glass vial (5 mL) were sequentially added the appropriate 4-halo-2,3,5-trimethyl-6-nitrophenol (**1a** or **1b**), or 6-halo-5,7,8-trimethyl-1,4-benzoxazinone (**4a** or **4b**), or 6-bromo-2-phenyl-5,7,8-trimethyl-1,4-benzoxazinone (**4c**) or 6-bromo-5,7,8-trimethyl-1,4-benzoxazine (**6**) (0.001 mol), $Pd(PPh_3)_4$

(5 mol %), aryl boronic acid (1.50 mmol), Na_2CO_3 (1.50 mmol) and a mixture of DME/H_2O (2:1, 1 mL). The mixture was degassed with argon, the reaction vial was sealed, was placed in a CEM Discover LabMate microwave reactor and was irradiated at 160 °C for 5 min. After cooling to room temperature, the mixture was diluted with dichloromethane, dried (Na_2SO_4) and the solvent evaporated in vacuo. Purification of the crude product by flash chromatography afforded *the title compounds* **3a**–**3d**, **5a**–**5f**, **7a**–**7k**.

*4.3.1. 2,3,6-Trimethyl-5-nitro[1.1′-biphenyl]-4-ol (**3a**).* Following the general procedure described above, using phenyl boronic acid (**2a**) and 4-chloro-2,3,5-trimethyl-6-nitrophenol (**1a**)[15] or 4-bromo-2,3,5-trimethyl-6-nitrophenol (**1b**)[15] *the title compound* **3a** was obtained (0.181 g, 71%) or (0.230 g, 90%), respectively, as a yellow solid after purification by flash chromatography (2% Et_2O/petroleum ether 40–60 °C). Mp 84 °C; R_f (5% Et_2O/petroleum ether 40–60 °C) 0.30; ν_{max}(neat) 3500–3300 (br), 1581, 1522, 1249 cm^{-1}; δ_H (300 MHz $CDCl_3$) 10.20 (1H, s, *OH*), 7.46–7.34 (3H, m, Ph), 7.08–7.06 (2H, m, Ph), 2.27 (3H, s, *Me*), 2.16 (3H, s, *Me*), 1.96 (3H, s, *Me*); δ_C (75.5 MHz $CDCl_3$) 151.3, 144.0, 140.2, 135.8, 134.6, 130.5, 129.6, 128.8, 127.3, 124.1, 19.3, 19.0, 12.3; MS (EI), *m*/*z*: 257 (100, M^+); HRMS (ESI^-): $[M-H]^-$, found 256.0975. $C_{15}H_{14}NO_3$ requires 256.0979.

*4.3.2. 2′-Methoxy-2,3,6-trimethyl-5-nitro[1.1′-biphenyl]-4-ol (**3b**).* Following the general procedure described above, using 2-methoxyphenyl boronic acid (**2b**) and 4-chloro-2,3,5-trimethyl-6-nitrophenol (**1a**) or 4-bromo-2,3,5-trimethyl-6-nitrophenol (**1b**) *the title compound* **3b** was obtained (0.220 g, 77%) or (0.143 g, 50%), respectively, as a yellow solid after purification by flash chromatography (1% Et_2O/1% CH_2Cl_2/petroleum ether 40–60 °C). Mp 135–137 °C; R_f (5% Et_2O/petroleum ether 40–60 °C) 0.25; ν_{max}(neat) 3400–3300 (br), 1581, 1522, 1341, 1249 cm^{-1}; δ_H (300 MHz $CDCl_3$) 10.29 (1H, s, *OH*), 7.41–7.35 (1H, m, Ph), 7.06–6.94 (3H, m, Ph), 3.74 (3H, s, O*Me*), 2.27 (3H, s, *Me*), 2.16 (3H, s, *Me*), 1.95 (3H, s, *Me*); δ_C (75.5 MHz $CDCl_3$) 156.7, 151.5, 144.7, 134.6, 132.1, 131.4, 131.1, 129.1, 128.5, 123.9, 121.0, 110.9, 55.5, 18.9, 18.5, 12.4; MS (EI), *m*/*z*: 287 (100, M^+); HRMS (ESI^-): $[M-H]^-$, found 286.1079, $C_{16}H_{16}NO_4$ required 286.1085; HRMS (ESI^+): $[M+Na]^+$ found 310.1054. $C_{16}H_{17}NNaO_4$ requires 310.1050.

*4.3.3. 3′-Methoxy-2,3,6-trimethyl-5-nitro[1.1′-biphenyl]-4-ol (**3c**).* Following the general procedure described above using 4-bromo-2,3,5-trimethyl-6-nitrophenol (**1b**) and 3-methoxyphenyl boronic acid (**2c**) *the title compound* **3c** was obtained (0.146 g, 51%) as a yellow solid after purification by flash chromatography (2% Et_2O/1% CH_2Cl_2/petroleum ether 40–60 °C). R_f (5% Et_2O/petroleum ether 40–60 °C) 0.32; ν_{max}(neat) 3500–3250 (br), 1576, 1519, 1223, 1182 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 10.19 (1H, s, *OH*), 7.37–7.32 (1H, m, Ph), 6.93–6.89 (1H, m, Ph), 6.66–6.60 (2H, m, Ph), 3.82 (3H, s, O*Me*), 2.26 (3H, s, *Me*), 2.17 (3H, s, *Me*), 1.97 (3H, s, *Me*); δ_C (75.5 MHz, $CDCl_3$) 159.9, 151.3, 143.9, 141.6, 135.6, 130.4, 129.8, 124.1, 121.9, 119.6, 115.2, 112.6, 55.2, 19.2, 18.9, 12.3; MS (EI), *m*/*z*: 287 (100, M^+); HRMS (ESI^-): $[M-H]^-$, found 286.1079. $C_{16}H_{16}NO_4$ requires 286.1085.

*4.3.4. 4′-Methoxy-2,3,6-trimethyl-5-nitro[1.1′-biphenyl]-4-ol (**3d**).*[3] Following the general procedure described above using 4-bromo-2,3,5-trimethyl-6-nitrophenol (**1b**) and 4-methoxyphenyl boronic acid (**2d**) *the title compound* **3d** was obtained (0.209 g, 73%) as a yellow solid after purification by flash chromatography (2% Et_2O/1% CH_2Cl_2/petroleum ether 40–60 °C); R_f (5% Et_2O/petroleum ether 40–60 °C) 0.30; δ_H (300 MHz, $CDCl_3$) 10.16 (1H, s, *OH*), 6.97 (4H, s, Ph), 3.86 (3H, s, O*Me*), 2.26 (3H, s, *Me*), 2.17 (3H, s, *Me*), 1.97 (3H, s, *Me*); δ_C (75.5 MHz $CDCl_3$) 158.6, 151.1, 144.4, 135.4, 134.6, 132.3, 130.8, 130.5, 123.9, 114.1, 55.2, 19.2, 18.9, 12.3; MS (EI), *m*/*z*: 287 (100, M^+); HRMS (ESI^-): $[M-H]^-$, found 286.1077. $C_{16}H_{16}NO_4$ requires 286.1085.

*4.3.5. 6-(2-Methoxyphenyl)-5,7,8-trimethyl-2H-1,4-benzoxazin-3(4H)-one (**5a**).* Following the general procedure described above using 2-methoxyphenyl boronic acid (**2b**) and 6-chloro-5,7,8-trimethyl-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one (**4a**)[3] or 6-bromo-5,7,8-trimethyl-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one (**4b**),[15] *the title compound* **5a** was obtained (0.071 g, 24%) or (0.046 g, 15%), respectively, as a white solid after purification by flash chromatography (20% EtOAc/petroleum ether 40–60 °C). Mp 209–211 °C (recrystallized from EtOAc); R_f (25% EtOAc/petroleum ether 40–60 °C) 0.24; ν_{max}(neat) 3215, 3144, 1682, 1461, 1405, 1239 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.34 (1H, s, *NH*), 7.38–7.32 (1H, m, Ph), 7.01–6.94 (3H, m, Ph), 4.59 (2H, s, O*CH*$_2$), 3.75 (3H, s, O*Me*), 2.19 (3H, s, *Me*), 1.89 (6H, s, 2*Me*); δ_C (75.5 MHz, $CDCl_3$) 166.2, 156.8, 141.1, 132.5, 131.3, 131.2, 129.3, 128.6, 122.5, 122.2, 120.7, 119.9, 110.8, 67.1, 55.5, 17.0, 13.8, 12.1; MS (EI), *m*/*z* 297 (100, M^+); HRMS (FAB^+) $[M]^+$, found 297.1361. $C_{18}H_{19}NO_3$ requires 297.1365.

*4.3.6. 6-(3-Methoxyphenyl)-5,7,8-trimethyl-2H-1,4-benzoxazin-3(4H)-one (**5b**).* Following the general procedure described above using 3-methoxyphenyl boronic acid (**2c**) and **4a** or **4b**, *the title compound* **5b** was obtained (0.054 g, 18%) or (0.199 g, 67%), respectively, as a white solid after purification by flash chromatography (15% EtOAc/petroleum ether 40–60 °C), mp 231–232 °C (recrystallized from EtOAc); R_f (25% EtOAc/petroleum ether 40–60 °C) 0.31; ν_{max}(neat) 3205, 3144, 1679, 1587, 1463, 1407, 1240 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.26 (1H, s, *NH*), 7.35–7.30 (1H, m, Ph), 6.90–6.87 (1H, m, Ph), 6.68–6.62 (2H, m, Ph), 4.59 (2H, s, O*CH*$_2$), 3.81 (3H, s, O*Me*), 2.19 (3H, s, *Me*), 1.91 (6H, s, 2*Me*); δ_C (75.5 MHz, $CDCl_3$) 165.9, 159.6, 142.4, 141.1, 136.2, 130.8, 129.5, 122.6, 122.1, 122.0, 119.1, 115.2, 112.2, 67.2, 55.2, 17.3, 13.9, 11.9; MS (EI), *m*/*z* 297 (100, M^+); HRMS (FAB^+): $[M]^+$, found 297.1394. $C_{18}H_{19}NO_3$ requires 297.1365.

*4.3.7. 6-(4-Methoxyphenyl)-5,7,8-trimethyl-2H-1,4-benzoxazin-3(4H)-one (**5c**).*[3] Following the general procedure described above using 4-methoxyphenyl boronic acid (**2d**), **4b**, and Cs_2CO_3 (1.50 mmol) *the title compound* **5c** was obtained (0.256 g, 86%) as a white solid after purification by flash chromatography (15% EtOAc/petroleum ether 40–60 °C), mp 211–213 °C (recrystallized from EtOAc); R_f (25% EtOAc/petroleum ether 40–60 °C) 0.29; δ_H (300 MHz, $CDCl_3$) 8.34 (1H, s, N*H*), 6.94 (4H, ABq, $\Delta\delta_{AB}$=0.04, J_{AB}=9.0 Hz), 4.59 (2H, s, O*CH*$_2$), 3.85 (3H, s, O*Me*), 2.19 (3H, s, *Me*), 1.90 (6H, s, 2*Me*); δ_C (75.5 MHz, $CDCl_3$) 165.7, 158.4, 140.9, 136.0, 133.2, 131.4, 130.6, 122.6, 122.1, 119.3, 113.8, 67.2, 55.2, 17.4, 13.9, 12.0; MS (EI), *m*/*z* 297 (100, M^+); HRMS (FAB^+): $[M]^+$, found 297.1352. $C_{18}H_{19}NO_3$ requires 297.1365.

*4.3.8. 5,7,8-Trimethyl-2,6-diphenyl-2H-1,4-benzoxazin-3(4H)-one (**5d**).* Following the general procedure described above using phenyl boronic acid (**2a**) and **4c** *the title compound* **5d** was obtained (0.333 g, 97%) as a white sticky solid after purification by flash chromatography (10% EtOAc/cyclohexane); R_f (20% EtOAc/cyclohexane) 0.38; ν_{max}(neat) 3210, 3144, 1680, 1460, 1406, 1235 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.23 (1H, s, N*H*), 7.50–7.33 (8H, m, Ph), 7.08–7.03 (2H, m, Ph), 5.72 (1H, s, C*H*Ph), 2.25 (3H, s, *Me*), 1.88 (3H, s, *Me*), 1.86 (3H, s, *Me*); δ_C (75.5 MHz, $CDCl_3$) 165.7, 141.0, 140.0, 136.3, 135.3, 130.9, 129.6, 128.7, 128.6, 128.4, 126.8, 126.7, 122.7, 121.8, 118.8, 78.2, 17.4, 14.0, 12.1; HRMS (ESI^+): $[M+H]^+$, found 344.1649. $C_{23}H_{22}NO_2$ requires 344.1645.

*4.3.9. 6-(3-Methoxyphenyl)-5,7,8-trimethyl-2-phenyl-2H-1,4-benzoxazin-3(4H)-one (**5e**).* Following the general procedure described above using 3-methoxyphenyl boronic acid (**2c**), **4c**, and

Cs_2CO_3 (1.50 mmol), *the title compound* **5e** was obtained (0.317 g, 85%) as a white solid after purification by flash chromatography (15% EtOAc/petroleum ether 40–60 °C), mp 156–159 °C (recrystallized from petroleum ether 40–60 °C–EtOAc); R_f (30% EtOAc/petroleum ether 40–60 °C) 0.47; ν_{max}(neat) 3207, 3144, 1679, 1462, 1408, 1237 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.32 (1H, s, N*H*), 7.50–7.30 (6H, m, Ph), 6.89–6.87 (1H, m, Ph), 6.68–6.61 (2H, m, Ph), 5.72 (1H, s, C*H*Ph), 3.81 (3H, s, O*Me*), 2.26 (3H, s, *Me*), 1.91 (3H, s, *Me*), 1.89 (3H, s, *Me*); δ_C (75.5 MHz, $CDCl_3$) 165.9, 159.6, 142.5, 140.0, 136.1, 135.3, 130.8, 129.4, 128.5, 126.7, 122.6, 122.1, 121.9, 119.0, 115.1, 112.3, 112.1, 78.1, 55.2, 17.3, 14.0, 12.1; MS (EI), *m*/*z* 373 (100, M^+); HRMS (ESI^+): $[M+H]^+$, found 374.1753. $C_{24}H_{24}NO_3$ requires 374.1751.

*4.3.10. 6-(4-Methoxyphenyl)-5,7,8-trimethyl-2-phenyl-2H-1,4-benzoxazin-3(4H)-one (**5f**).* Following the general procedure described above using 4-methoxyphenyl boronic acid (**2d**) and **4c**, *the title compound* **5e** was obtained (0.340 g, 91%) as a white solid after purification by flash chromatography (15% EtOAc/petroleum ether 40–60 °C), mp 207–209 °C (recrystallized from petroleum ether 40–60 °C–EtOAc 7:3); R_f (30% EtOAc/petroleum ether 40–60 °C) 0.47; ν_{max}(neat) 3201, 3139, 1675, 1464, 1395, 1243 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.41 (1H, s, N*H*), 7.49–7.47 (2H, m, Ph), 7.39–7.30 (3H, m, Ph), 7.00–6.91 (4H, m, Ph), 5.72 (1H, s, C*H*Ph), 3.84 (3H, s, O*Me*), 2.24 (3H, s, *Me*), 1.89 (3H, s, *Me*), 1.88 (3H, s, *Me*); δ_C (75.5 MHz, $CDCl_3$) 166.0, 158.3, 139.9, 136.0, 135.4, 133.3, 131.3, 130.6, 128.6, 128.5, 126.7, 122.5, 121.8, 119.5, 113.7, 78.1, 55.2, 17.4, 14.1, 12.2; MS (EI), *m*/*z* 373 (100, M^+); HRMS (FAB^+): $[M]^+$, found 373.1669. $C_{24}H_{23}NO_3$ requires 373.1678.

*4.3.11. 3,4-Dihydro-6-(2-methoxyphenyl)-5,7,8-trimethyl-2-phenyl-2H-benzo[b][1,4]-oxazine (**7a**).* Following the general procedure described above using 2-methoxyphenyl boronic acid (**2b**), benzoxazine **6**, and Na_2CO_3 (1.50 mmol) or $Ba(OH)_2$ (1.50 mmol) *the title compound* **7a** was obtained (as a mixture of rotamers) (0.169 g, 47%) or (0.198 g, 55%), respectively, after purification by flash chromatography (5% EtOAc/hexane).

Less polar: sticky solid; R_f (10% EtOAc/petroleum ether 40–60 °C) 0.32; ν_{max}(neat) 3370, 1578, 1495, 1279, 1237, 1109 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.50–7.32 (6H, m, Ph), 7.07–6.98 (3H, m, Ph), 5.14 (1H, dd, *J* 9.1, 2.3 Hz, C*H*Ph), 3.77 (3H, s, O*Me*), 3.61 (1H, dd, *J* 11.8, 2.3 Hz, CH_2CHPh), 3.40–3.33 (1H, m, CH_2CHPh), 2.24 (3H, s, *Me*), 1.91 (3H, s, *Me*), 1.83 (3H, s, *Me*); δ_C (75.5 MHz $CDCl_3$) 157.1, 141.9, 139.9, 131.7, 130.5, 130.4, 128.5, 128.1, 128.0, 127.9, 126.1, 125.8, 122.1, 120.5, 119.6, 110.7, 75.6, 55.5, 48.4, 16.8, 14.1, 12.0; MS (EI), *m*/*z* 359 (100, M^+); HRMS (FAB^+): $[M]^+$, found 359.1879. $C_{24}H_{25}NO_2$ requires 359.1885.

More polar: sticky solid; R_f (10% EtOAc/petroleum ether 40–60 °C) 0.25; ν_{max}(neat) 3403, 1460, 1338, 1238, 1109 cm^{-1}; δ_H (300 MHz $CDCl_3$) 7.51–7.30 (6H, m, Ph), 7.04–6.97 (3H, m, Ph), 5.13 (1H, dd, *J* 9.0, 2.3 Hz, C*H*Ph), 3.76 (3H, s, O*Me*), 3.63 (1H, dd, *J* 11.8, 2.3 Hz, CH_2CHPh), 3.34 (1H, dd, *J* 11.8, 9.0 Hz, CH_2CHPh), 2.22 (3H, s, *Me*), 1.89 (3H, s, *Me*), 1.81 (3H, s, *Me*); δ_C (75.5 MHz, $CDCl_3$) 157.1, 141.9, 139.8, 131.8, 130.6, 130.5, 128.5, 128.1, 127.9, 127.8, 126.1, 125.9, 122.1, 120.4, 119.8, 110.7, 75.3, 55.5, 48.4, 16.8, 14.1, 12.0; MS (EI), *m*/*z* 359 (M^+, 100); MS (EI), *m*/*z* 359 (100, M^+); HRMS (ESI^+): $[M]^+$, found 359.1883. $C_{24}H_{25}NO_2$ requires 359.1880; $[M+H]^+$, found 360.1947. $C_{24}H_{26}NO_2$ requires 360.1958.

*4.3.12. 3,4-Dihydro-6-(3-methoxyphenyl)-5,7,8-trimethyl-2-phenyl-2H-benzo[b][1,4]-oxazine (**7b**).* Following the general procedure described above using 3-methoxyphenyl boronic acid (**2c**) and benzoxazine **6** *the title compound* **7b** was obtained (0.288 g, 80%) as a white gummy solid after purification by flash chromatography (10% EtOAc/hexane); R_f (10% EtOAc/petroleum ether 40–60 °C) 0.35; ν_{max}(neat) 3412, 1597, 1578, 1465, 1340, 1230, 1102 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 7.50–7.29 (6H, m, Ph), 6.87 (1H, ddd, *J* 8.2, 2.6, 1.0 Hz, Ph), 6.76–6.70 (2H, m, Ph), 5.13 (1H, dd, *J* 8.9, 2.3 Hz, C*H*Ph), 3.83 (3H, s, O*Me*), 3.65 (1H, dd, *J* 11.8, 2.3 Hz, CH_2CHPh) 3.38 (1H, dd, *J* 11.8, 8.9 Hz, CH_2CHPh), 2.26 (3H, s, *Me*), 1.95 (3H, s, *Me*), 1.87 (3H, s, *Me*); δ_C (75.5 MHz, $CDCl_3$) 159.5, 143.6, 141.7, 139.7, 134.5, 129.1, 128.5, 128.0, 126.1, 125.3, 122.5, 122.4, 122.2, 119.0, 115.4, 111.9, 75.5, 55.2, 48.4, 17.0, 14.3, 11.9; MS (EI), *m*/*z* 359 (100, M^+); HRMS (FAB^+): $[M]^+$, found 359.1887. $C_{24}H_{25}NO_2$ requires 359.1885.

*4.3.13. 3,4-Dihydro-6-(4-methoxyphenyl)-5,7,8-trimethyl-2-phenyl-2H-benzo[b][1,4]-oxazine (**7c**).* Following the general procedure described above using 4-methoxyphenyl boronic acid (**2d**), benzoxazine **6**, and Cs_2CO_3 (1.50 mmol) *the title compound* **7c** was obtained (0.298 g, 83%) as a white solid after purification by flash chromatography (5% acetone/hexane), mp 175–176 °C; R_f (10% EtOAc/petroleum ether 40–60 °C) 0.26; ν_{max}(neat) 3412, 1596, 1514, 1468, 1337, 1277, 1235, 1028 cm^{-1}; δ_H (600 MHz $CDCl_3$) 7.47 (2H, d, *J* 7.5 Hz, Ph), 7.42 (2H, d, *J* 7.5 Hz, Ph), 7.37–7.34 (1H, m, Ph), 7.05 (2H, dd, *J* 7.5, 0.7 Hz, Ph), 6.95 (2H, d, *J* 7.5 Hz, Ph), 5.11 (1H, d, *J* 8.2 Hz, C*H*Ph), 3.85 (3H, s, O*Me*), 3.62 (1H, d, *J* 11.6 Hz, CH_2CHPh), 3.37–3.33 (1H, m, CH_2CHPh), 2.22 (3H, s, *Me*), 1.91 (3H, s, *Me*), 1.83 (3H, s, *Me*); δ_C (75.5 MHz, $CDCl_3$) 158.0, 141.6, 139.7, 134.4, 134.2, 131.0, 130.9, 128.5, 128.0, 126.1, 125.8, 122.1, 119.5, 113.5, 75.5, 55.2, 48.4, 17.1, 14.4, 11.9; MS (EI), *m*/*z* 359 (100, M^+); HRMS (ESI^+): $[M+Na]^+$, found 382.1785. $C_{24}H_{25}NNaO_2$ requires 382.1778.

*4.3.14. (E)-3,4-Dihydro-5,7,8-trimethyl-2-phenyl-6-styryl-2H-benzo[b][1,4]oxazine (**7d**).* Following the general procedure described above using *trans*-2-phenylvinylboronic acid (**2e**) and benzoxazine **6** *the title compound* **7d** was obtained (0.288 g, 81%) as a yellow solid after purification by flash chromatography (20% EtOAc/hexane), mp 132–135 °C; R_f (10% EtOAc/petroleum ether 40–60 °C) 0.33; ν_{max}(neat) 3387, 1595, 1468, 1448, 1379, 1339, 1108 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 7.52–7.35 (9H, m, Ph), 7.28–7.25 (1H, m, Ph), 7.14 (1H, d, *J* 16.5 Hz, C*H*=), 6.45 (1H, d, *J* 16.5 Hz, C*H*=), 5.10 (1H, d, *J* 8.7, C*H*Ph), 3.63 (1H, d, *J* 11.8 Hz, CH_2CHPh), 3.35–3.23 (1H, m, CH_2CHPh), 2.24 (3H, s, *Me*), 2.23 (3H, s, *Me*), 2.18 (3H, s, *Me*); δ_C (75.5 MHz, $CDCl_3$) 141.7, 139.6, 137.7, 134.0, 130.1, 128.6, 128.5, 128.4, 128.3, 128.0, 127.3, 126.2, 126.1, 125.6, 122.4, 119.0, 75.5, 48.3, 16.8, 14.2, 11.9; MS (EI), *m*/*z*: 355 (100, M^+); HRMS (ESI^+): $[M]^+$, found 355.1935. $C_{25}H_{25}NO$ requires 355.1931; $[M+H]^+$, found 356.2007. $C_{25}H_{26}NO$ requires 356.2009.

*4.3.15. 3,4-Dihydro-5,7,8-trimethyl-2-phenyl-6-(4-vinylphenyl)-2H-benzo[b][1,4]oxazine (**7e**).* Following the general procedure described above using 4-vinylphenylboronic acid (**2f**) and benzoxazine **6** *the title compound* **7e** was obtained (0.313 g, 88%) as a yellow solid after purification by flash chromatography (20% EtOAc/hexane), mp 179–182 °C; R_f (10% EtOAc/petroleum ether 40–60 °C) 0.38; ν_{max}(neat) 3406, 1628, 1595, 1467, 1337, 1276, 1101 cm^{-1}; δ_H (600 MHz $CDCl_3$) 7.49–7.42 (6H, m, Ph), 7.38–7.36 (1H, m, Ph), 7.12 (2H, d, *J* 7.2 Hz, Ph), 6.79 (1H, dd, *J* 17.6, 10.9 Hz, C*H*=CH_2), 5.81 (1H, d, *J* 17.6 Hz, CH=CH_2), 5.27 (1H, d, *J* 10.9 Hz, CH=CH_2), 5.13 (1H, d, *J* 8.9 Hz, C*H*Ph), 3.64 (1H, d, *J*=11.8 Hz, CH_2CHPh), 3.38–3.35 (1H, m, CH_2CHPh), 2.24 (3H, s, *Me*), 1.93 (3H, s, *Me*), 1.84 (3H, s, *Me*); δ_C (75.5 MHz, $CDCl_3$) 141.9, 141.7, 139.7, 136.7, 135.5, 134.3, 130.2, 128.5, 128.1, 128.0, 126.1, 126.0, 125.3, 122.2, 119.0, 113.3, 75.5, 48.4, 17.1, 14.4, 11.9; MS (EI), *m*/*z*: 355 (100, M^+); HRMS (FAB^+): $[M]^+$, found 355.1920. $C_{25}H_{25}NO$ requires 355.1936.

*4.3.16. 6-(Furan-2-yl)-3,4-dihydro-5,7,8-trimethyl-2-phenyl-2H-benzo[b][1,4]oxazine (**7f**).* Following the general procedure described above using 2-furanboronic acid (**2g**) and benzoxazine **6** *the title compound* **7f** was obtained (0.288 g, 90%) as an oil after purification by flash chromatography (5% EtOAc/hexane); R_f (10% EtOAc/petroleum ether 40–60 °C) 0.40; ν_{max}(neat) 3379, 1598, 1468, 1331, 1273, 1118, 1103 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 7.46 (1H, m,

furyl), 7.42–7.36 (4H, m, Ph), 7.32–7.30 (1H, m, Ph), 6.43 (1H, dd, *J* 2.7, 1.9 Hz, furyl), 6.17 (1H, d, *J* 2.7 Hz, furyl), 5.06 (1H, dd, *J* 8.8, 1.9 Hz, C*H*Ph), 3.58 (1H, dd, *J*=11.7, 1.9 Hz, CH_2CHPh), 3.29 (1H, dd, *J*=11.7, 8.8 Hz, CH_2CHPh), 2.17 (3H, s, *Me*), 1.97 (3H, s, *Me*), 1.89 (3H, s, *Me*); δ_C (75.5 MHz, $CDCl_3$) 153.5, 143.1, 141.3, 139.5, 128.5, 128.3, 128.15, 128.07, 126.1, 123.8, 122.4, 121.7, 110.3, 109.1, 75.6, 48.1, 16.8, 14.1, 11.9; MS (EI), *m*/*z*: 320 (100, M^+); HRMS (ESI^+): $[M+H]^+$, found 320.1658. $C_{21}H_{22}NO_2$ requires 320.1645.

*4.3.17. 3,4-Dihydro-5,7,8-trimethyl-2-phenyl-6-(thiophen-2-yl)-2H-benzo[b][1,4]oxazine (**7g**).* Following the general procedure described above using 2-thienylboronic acid (**2h**) and benzoxazine **6** *the title compound* **7g** was obtained (0.285 g, 85%) as an oil after purification by flash chromatography (5% EtOAc/hexane); R_f (10% EtOAc/petroleum ether 40–60 °C) 0.44; ν_{max}(neat) 3385, 1595, 1496, 1421, 1343, 1114 cm^{-1}; δ_H (600 MHz $CDCl_3$) 7.47–7.40 (4H, m, Ph), 7.36–7.33 (2H, m, Ph and thienyl), 7.08 (1H, dd, *J* 5.1, 3.4 Hz, thienyl), 6.79 (1H, dd, *J* 3.4, 1.1 Hz, thienyl), 5.11 (1H, dd, *J* 8.9, 2.1 Hz, C*H*Ph), 3.62 (1H, dd, *J* 11.9, 2.1 Hz, CH_2CHPh), 3.32 (1H, dd, *J* 11.9, 8.9 Hz, CH_2CHPh), 2.21 (3H, s, *Me*), 2.00 (3H, s, *Me*), 1.91 (3H, s, *Me*); δ_C (75.5 MHz, $CDCl_3$) 143.1, 142.6, 139.5, 128.5, 128.3, 128.1, 127.7, 126.9, 126.8, 126.2, 126.1, 125.1, 122.3, 121.4, 75.6, 48.2, 17.1, 14.4, 11.9; MS (EI), *m*/*z*: 335 (100, M^+); HRMS (ESI^+): $[M+H]^+$, found 336.1420. $C_{21}H_{22}NOS$ requires 336.1417.

*4.3.18. 3,4-Dihydro-5,7,8-trimethyl-6-(naphthalen-2-yl)-2-phenyl-2H-benzo[I][1,4]oxazine (**7h**).* Following the general procedure described above using 2-naphthaleneboronic acid (**2i**) and benzoxazine **6** *the title compound* **7h** was obtained (0.319 g, 84%) as a white solid after purification by flash chromatography (10% EtOAc/hexane), mp 172–175 °C; R_f (10% EtOAc/petroleum ether 40–60 °C) 0.38; ν_{max}(neat) 3404, 1597, 1473, 1339, 1277, 1115, 1099 cm^{-1}; δ_H (600 MHz $CDCl_3$) 7.90–7.82 (3H, m, Ph), 7.61 (1H, s, Ph), 7.51–7.48 (4H, m, Ph), 7.45–7.42 (2H, m, Ph), 7.38–7.36 (1H, m, Ph), 7.31–7.29 (1H, m, Ph), 5.16–5.13 (1H, m, C*H*Ph), 3.65 (1H, dd, *J* 11.8, 2.2 Hz, CH_2CHPh), 3.38 (1H, dd, *J* 11.8, 9.3 Hz, CH_2CHPh), 2.25 (3H, s, *Me*), 1.92 (3H, s, *Me*), 1.84 (3H, s, *Me*); δ_C (75.5 MHz, $CDCl_3$) 141.8, 139.8, 139.7, 134.5, 133.5, 132.1, 128.8, 128.7, 128.6, 128.5, 128.4, 128.1, 127.9, 127.7, 127.6, 126.1, 126.0, 125.6, 122.3, 119.2, 75.6, 48.4, 17.2, 14.5, 12.0; MS (EI), *m*/*z*: 379 (100, M^+); HRMS (ESI^+): $[M+H]^+$, found 380.2010. $C_{27}H_{26}NO$ requires 380.2009.

*4.3.19. 6-(4-(Trifluoromethyl)phenyl)-3,4-dihydro-5,7,8-trimethyl-2-phenyl-2H-benzo[b][1,4]oxazine (**7i**).* Following the general procedure described above using 4-(trifluoromethyl)phenylboronic acid (**2j**) and benzoxazine **6** *the title compound* **7i** was obtained (0.338 g, 85%) as a white solid after purification by flash chromatography (5% EtOAc/hexane), mp 213–214 °C; R_f (10% EtOAc/petroleum ether 40–60 °C) 0.40; ν_{max}(neat) 3439, 1614, 1320, 1103 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 7.67 (2H, d, *J* 7.7 Hz, Ph), 7.48–7.42 (4H, m, Ph), 7.38–7.35 (1H, m, Ph), 7.27 (2H, d, *J* 7.7 Hz, Ph), 5.12 (1H, dd, *J* 8.8, 1.5 Hz, C*H*Ph), 3.64 (1H, dd, *J*=11.9, 1.5 Hz, CH_2CHPh), 3.36 (1H, dd, *J* 11.9, 8.8 Hz, *J* CH_2CHPh), 2.23 (3H, s, *Me*), 1.87 (3H, s, *Me*), 1.79 (3H, s, *Me*); δ_C (150 MHz, $CDCl_3$) 146.2, 142.0, 139.5, 133.2, 130.4, 128.6 (q, *J* 32.3 Hz), 128.5, 128.3, 128.1, 126.1, 125.2 (d, *J* 3.62 Hz), 124.8, 124.4 (q, *J* 272.9 Hz), 122.5, 118.6, 75.6, 48.3, 17.1, 14.3, 11.9; δ_F (564.8 MHz, $CDCl_3$) −62.3; MS (EI), *m*/*z*: 397 (100, M^+); HRMS (ESI^+): $[M+H]^+$, found 398.1726. $C_{24}H_{23}F_3NO$ requires 398.1726.

*4.3.20. 6-(4-Butylphenyl)-3,4-dihydro-5,7,8-trimethyl-2-phenyl-2H-benzo[b][1,4]oxazine (**7j**).* Following the general procedure described above using 4-butylphenylboronic acid (**2k**) and benzoxazine **6** *the title compound* **7j** was obtained (0.335 g, 87%) as an oil after purification by flash chromatography (3% EtOAc/hexane); R_f (10% EtOAc/petroleum ether 40–60 °C) 0.49; ν_{max}(neat) 3393, 1465, 1450, 1339, 1276, 1102 cm^{-1}; δ_H (600 MHz $CDCl_3$) 7.48–7.47 (2H, m, Ph), 7.43–7.40 (2H, m, Ph), 7.36–7.34 (1H, m, Ph), 7.20 (2H, d, *J* 7.7 Hz, Ph), 7.04–7.02 (2H, m, Ph), 5.12 (1H, dd, *J* 9.0, 2.0 Hz, C*H*Ph), 3.62 (1H, dd, *J* 11.8, 2.0 Hz, CH_2CHPh), 3.35 (1H, dd, *J* 11.8, 9.0 Hz, CH_2CHPh), 2.66 (2H, t, *J* 7.8 Hz, PhCH_2CH_2CH_2CH_3), 2.23 (3H, s, *Me*), 1.90 (3H, s, *Me*), 1.82 (3H, s, *Me*), 1.69–1.63 (2H, m, PhCH_2CH_2CH_2CH_3), 1.43–1.37 (2H, m, PhCH_2CH_2CH_2CH_3), 0.96 (3H, t, *J* 7.4 Hz, PhCH_2CH_2CH_2CH_3), δ_C (75.5 MHz, $CDCl_3$) 141.6, 140.7, 139.8, 139.3, 134.7, 129.8, 129.7, 128.5, 128.1, 127.9, 126.1, 125.5, 122.1, 119.2, 75.5, 48.4, 35.4, 33.7, 22.5, 17.1, 14.4, 14.0, 11.9; MS(EI), *m*/*z*: 385 (100, M^+); HRMS (ESI^+): $[M+H]^+$, found 386.2496. $C_{27}H_{32}NO$ requires 386.2478.

*4.3.21. 6-Butyl-3,4-dihydro-5,7,8-trimethyl-2-phenyl-2H-benzo[b][1,4]oxazine (**7k**).* Following the general procedure described above using butylboronic acid (**2l**) and benzoxazine **6** *the title compound* **7k** was obtained (0.170 g, 55%) as an oil after purification by flash chromatography (5% EtOAc/hexane); R_f (10% EtOAc/petroleum ether 40–60 °C) 0.40; ν_{max}(neat) 3390, 1499, 1259, 1104 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 7.45–7.39 (4H, m, Ph), 7.35–7.33 (1H, m, Ph), 5.04 (1H, dd, *J* 9.0, 1.9 Hz, C*H*Ph), 3.59 (1H, dd, *J* 11.9, 1.9 Hz, CH_2CHPh), 3.55 (1H, bs, 1H, N*H*), 3.29 (1H, dd, *J* 11.9, 9.0 Hz, CH_2CHPh), 2.63–2.61 (2H, m, PhCH_2CH_2CH_2CH_3), 2.20 (6H, s, *Me*), 2.11 (3H, s, *Me*), 1.47–1.42 (4H, m, PhCH_2CH_2CH_2CH_3), 0.98 (3H, t, *J* 7.0 Hz, PhCH_2CH_2CH_2CH_3); δ_C (75.5 MHz, $CDCl_3$) 140.7, 139.9, 131.6, 128.4, 128.3, 127.9, 126.1, 125.3, 122.3, 119.0, 75.4, 48.6, 32.5, 29.7, 23.2, 15.3, 14.0, 12.6, 12.0; MS(EI), *m*/*z*: 309 (100, M^+); HRMS (ESI^+): $[M+H]^+$, found 310.2171. $C_{21}H_{28}NO$ requires 310.2165.

4.4. Biology, antiproliferative assays

The antiproliferative activity of compounds **7a**–**k** was evaluated utilizing tachyzoites of m2m3 strain expressing the yellow fluorescent protein.[33] Parasites of m2m3 strain were maintained in LLC-MK_2 (kidney, Rhesus monkey, *Macaca mulata*—ATCC CCL7, Rockville, MD/USA) cultures and freshly egressed parasites were collected and used for experiments. Approximately 1×10^6 LLC-MK_2 cells placed in a black with clear flat bottom 96- plate (Nalge Nunc International, New York, USA) were infected with 1×10^6 parasites resuspended in RPMI medium 1640 without phenol red (Gibco®, Invitrogen™, USA) and supplemented with 2% of foetal bovine serum. The compounds were added after 6 h of infection and the antiproliferative effect was evaluated for 48 h and 72 h of treatment. Plate fluorescence was read from the bottom in SpectraMax Me[2] Molecular Devices equipment. Excitation and emission wavelengths were 510 and 540 nm, respectively. All experiments were performed together with untreated infected cultures (positive control) and non-infected cultures (negative control-blank). For IC_{50} (concentration for 50% growth inhibition) calculations, the percentage of growth inhibition was plotted as a function of the drug concentration by fitting the values to the non-linear curve analysis where f=min+(max−min)/(1+(x/EC_{50})^{Hillslope}). The regression analyses were performed by using Sigma Plot 8.0 software (Systat Software Inc, Chicago, IL, USA).

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Supplementary data

Copies of ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra and HPLC chromatograms. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2012.10.009. These data includes MOL files and InChiKeys of the most important compounds described in this article.

References and notes

1. (a) Largeron, M.; Dupuy, H.; Fleury, M. B. *Tetrahedron* **1995**, *51*, 4953–4968; (b) Achari, B.; Mandal, S. B.; Dutta, P. K.; Chowdhurry, C. *Synlett* **2004**, 2449–2467; (c) Cecchetti, V.; Tabarrini, O.; Sabatini, S. *Curr. Top. Med. Chem.* **2006**, *6*, 1049–1068; (d) Rybczynski, P. J.; Zeck, R. E.; Dudash, J.; Combs, D. W.; Burris, T. P.; Yang, M.; Osborne, M. C.; Chen, X.; Demarest, K. T. *J. Med. Chem.* **2004**, *47*, 196–209.
2. Koini, E. N.; Papazafiri, P.; Vassilopoulos, A.; Koufaki, M.; Horváth, Z.; Koncz, I.; Virág, L.; Papp, G. J.; Varró, A.; Calogeropoulou, T. *J. Med. Chem.* **2009**, *52*, 2328–2340.
3. Filippou, P. S.; Koini, E. N.; Calogeropoulou, T.; Kalliakmani, P.; Panagiotidis, C. A.; Kyriakidis, D. A. *Bioorg. Med. Chem.* **2011**, *19*, 5061–5070.
4. For recent reviews, see: (a) Suzuki, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 6722–6737; (b) Alonso, I. P.; Beletskaya, F.; Yus, M. *Tetrahedron* **2008**, *64*, 3047–3101.
5. (a) Pews-Davtyan, A.; Tillack, A.; Ortinau, S.; Rolfs, A.; Beller, M. *Org. Biomol. Chem.* **2008**, *6*, 992–997; (b) Neumann, H.; Brennführer, A.; Beller, M. *Chem.—Eur. J.* **2008**, *14*, 3645–3652.
6. (a) Biscoe, M. R.; Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 6686–6687; (b) Bhayana, B.; Fors, B. P.; Buchwald, S. L. *Org. Lett.* **2009**, *11*, 3954–3957.
7. (a) Carrow, B. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 2116–2119; (b) Huang, D. S.; DeLuca, R. J.; Hartwig, J. F. *Org. Synth.* **2011**, *88*, 4–13.
8. (a) Fu, X.-L.; Wu, L.-L.; Fu, H.-Y.; Chen, H.; Li, R.-X. *Eur. J. Org. Chem.* **2009**, 2051–2054; (b) Dai, W.-M.; Li, Y.; Zhang, Y.; Yue, C.; Wu, J. *Chem.—Eur. J.* **2008**, *14*, 5538–5554; (c) So, C. M.; Yeung, C. C.; Lau, C. P.; Kwong, F. Y. *J. Org. Chem.* **2008**, *73*, 7803–7806.
9. Hills, I. D.; Netherton, M. R.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 5749–5752.
10. For a review, see: (a) Frisch, A. C.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 674–688.
11. Darses, S.; Genet, J. P. *Chem. Rev.* **2008**, *108*, 288–325.
12. (a) Cho, Y. A.; Kim, D. S.; Ahn, H. R.; Canturk, B.; Molander, G. A.; Ham, J. *Org. Lett.* **2009**, *11*, 4330–4333; (b) Molander, G. A.; Febo-Ayala, W.; Jean-Gerard, L. *Org. Lett.* **2009**, *11*, 3830–3833 For recent reviews on the coupling reactions with R-BF_3K salts, see: (c) Molander, G. A.; Canturk, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 9240–9261; (d) Molander, G. A.; Ellis, N. O. *Acc. Chem. Res.* **2007**, *40*, 275–286.
13. Chow, W. K.; So, C. M.; Lau, C. P.; Kwong, F. Y. *J. Org. Chem.* **2010**, *75*, 5109–5112.
14. Molander, G. A.; Beaumard, F. *Org. Lett.* **2011**, *13*, 1242–1245.
15. Koini, E. N.; Avlonitis, N.; Calogeropoulou, T. *Synlett* **2011**, 1537–1542.
16. Ilās, J.; Anderluh, P.; Dolenc, M. S.; Kikelj, D. *Tetrahedron* **2005**, *61*, 7325–7446.
17. Kuroita, T.; Sakamori, M.; Kawakita, T. *Chem. Pharm. Bull.* **1996**, *44*, 756–764.
18. Albanese, D.; Landini, D.; Lupi, V.; Penso, M. *Ind. Eng. Chem. Res.* **2003**, *42*, 680–686.
19. Brown, D. W.; Ninan, A.; Sainsbury, M. *Synthesis* **1997**, 895–898.
20. Rao, R. K.; Naidu, A. B.; Sekar, G. *Org. Lett.* **2009**, *11*, 1923–1926.
21. Dai, W.-M.; Wang, X.; Ma, C. *Tetrahedron* **2005**, *61*, 6879–6885.
22. Feng, G.; Wu, J.; Dai, W.-M. *Tetrahedron* **2006**, *62*, 4635–4642.
23. Xing, X.; Wu, J.; Feng, G.; Dai, W.-M. *Tetrahedron* **2006**, *62*, 6774–6781.
24. (a) Caddick, S.; Fitzmaurice, R. *Tetrahedron* **2009**, *65*, 3325–3355; (b) Kappe, C. O.; Dallinger, D. *Mol. Diversity* **2009**, *13*, 71–193.
25. For recent reviews (a) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890–931; (b) Mehta, V. P.; Van der Eycken, E. V. *Chem. Soc. Rev.* **2011**, *40*, 4925–4936.
26. Zhang, P.; Terefenko, E. A.; Fensome, A.; Zhang, Z.; Zhu, Y.; Cohen, J.; Winneker, R.; Wrobela, J.; Yardleya, J. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 787–790.
27. Wu, J.; Nie, L.; Luo, J.; Dai, W.-M. *Synlett* **2007**, 2728–2732.
28. Watanabe, T.; Miyaura, N.; Suzuki, A. *Synlett* **1992**, 207–210.
29. (a) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685–4696; (b) Navarro, O.; Marion, N.; Mei, J. G.; Nolan, S. P. *Chem.—Eur. J.* **2006**, *12*, 5142–5148.
30. Slagt, V. F.; de Vries, A. H. M.; de Vries, J. G.; Kellogg, R. M. *Org. Process Res. Dev.* **2010**, *14*, 30–47.
31. (a) Lehmann, T.; Marcet, P. L.; Graham, D. H.; Dahl, E. R.; Dubey, J. P. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 11423–11428; (b) Boothroyd, J. C. *Int. J. Parasitol.* **2009**, *39*, 935–946.
32. (a) Sullivan, W. J., Jr.; Jeffers, V. *FEMS Microbiol. Rev.* **2012**, *36*, 713–733; (b) Ibebuike, K.; Mantanga, L.; Emereole, O.; Ndolo, P.; Kajee, A.; Gopal, R.; Pather, S. *Neurol. Sci.* **2012**, http://dx.doi.org/10.1007/s10072-012-0960-x12
33. Gubbels, M.-J.; Li, C.; Striepen, B. *Antimicrob. Agents Chemother.* **2003**, *47*, 309–316.