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N-Aryl Heterocycles via Coupling Reactions with Arylboronic Acids

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Abstract: Compounds having a partial 2-pyridone structure or 3-pyridazinones can be selectively *N*-arylated with phenylboronic acids according to the procedure described by Chan and Lam. This procedure leads to *N*5-arylated imidazo[4,5-c]pyridin-4-ones, precursors of potent factor Xa inhibitors. In addition, the synthesis of *N*-aryl substituted pyrrole- and indole-2-carboxylic acid esters is described. In the indole series this procedure offers a flexible entry in the synthesis of different 1,3-diaryl-2-carboxyindoles.

Keywords: *arylation, coupling reactions, indoles, pyridazinones, pyridones, pyrroles*

INTRODUCTION

In recent years the 2-pyridone system has attracted our attention due to its variety of biological activities towards several diseases. The imidazo[4,5-c]pyridin-4-one heterocycle[1] has become a prominent feature in the class of angiotensin II receptor antagonists and the benzofuro[3,2-b]pyridin-2-one[2] is a representative of the class of endothelin receptor antagonists. All of theses derivatives are *N*-alkyl-2-pyridones. The *N*-alkylation of ambident heterocyclic 6-membered rings possessing a tautomeric or mesomeric structure such as 2(1*H*)-pyridones is often inefficient and lacks regiocontrol.[3]

One of our strategies in the field of blood coagulation factor Xa inhibitors focused on the preparation of *N*-aryl pyridin-2-ones. Therefore a general method for the direct *N*-arylation of amides was needed. However, the arylation of NH substrates which are deactivated by an adjacent group such as carbonyl is less developed. The original work of Goldberg[4] heating anilides and aryl halides at high temperature in the presence of potassium carbonate and cuprous iodide has received little attention.[5] Recently, López-Alvarado described the arylation of carbostyrils with catalytic cupric acetate/*p*-tolyllead triacetate.[6] However, this is restricted to *p*-tolyllead and requires elevated temperatures. More recently, Chan and Lam reported on the efficient *N*-arylation of a wide range of NH substrates including poorly nucleophilic substrates such as arylamides by reaction with a boronic acid in the presence of cupric acetate and either triethylamine or pyridine at room temperature.[7]

To our knowledge the application of this mild arylation reaction to a pyridone ring system has not been reported and we were interested in exploring the generality of this procedure. For this investigation, the reaction conditions were the same as those described by Chan and Lam,[7] but with simultaneous use of both tertiary amine bases, triethylamine and pyridine.

A distinct emphasis of our work in the field of factor Xa antagonists concentrated on indole and pyrrole heterocycles. Despite the obvious utility of the coupling reaction forming a wide range of *N*-arylated heteroarenes, pyrroles and indoles exhibited virtually no reactivity towards arylation.[7b] We anticipated that NH substrates which are substituted in *ortho* position by an acceptor such as carbonyl could activate the nitrogen in this reaction. Therefore, in the pyrrole and indole series we focused on easily available 2-carboxylic acid esters. This approach should lead to *N*-aryl substituted pyrrole- and indole-2-carboxylic acid esters.

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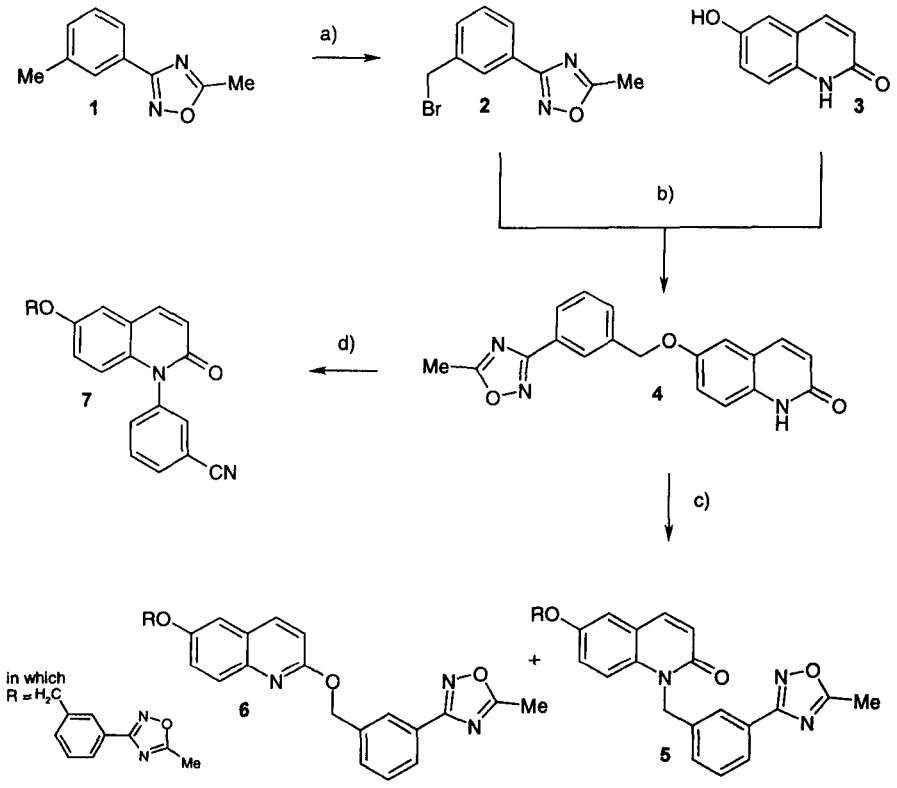
In this paper the *N*-arylation of 2-pyridones, 3-pyridazinones, 2-carboxyindoles and 2-carboxypyrroles with different arylboronic acids is described.

RESULTS AND DISCUSSION

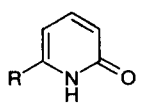
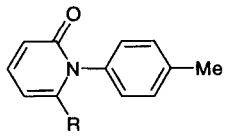
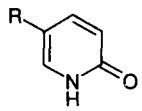
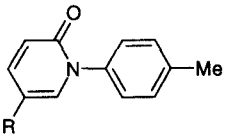
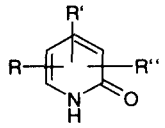
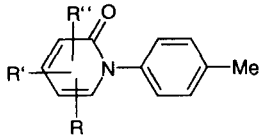
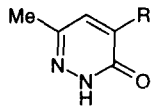
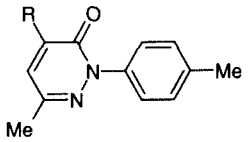
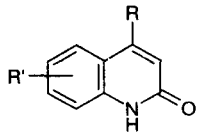
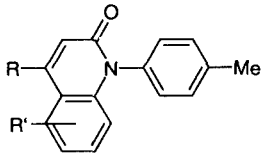
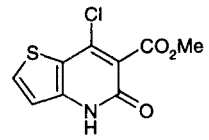
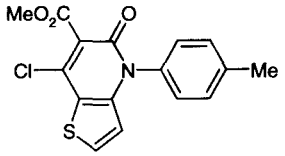
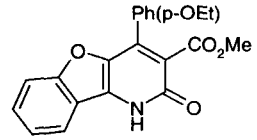
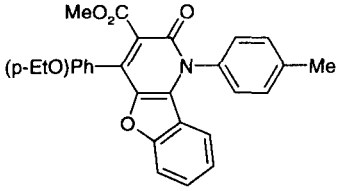
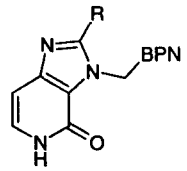
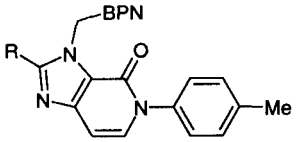
At the outset of our studies we compared the alkylation of carbostyril derivative **4** and the benzyl bromide **2** with the arylation of **4** and 3-cyanophenylboronic acid (Scheme 1). The *O*-alkylated quinolinone **4** was obtained by the bromination with *N*-bromosuccinimide of *m*-tolyl-oxadiazole **1**[8,9] to **2**, followed by the treatment of **2** with 6-hydroxyquinolinone **3**.[10] The alkylation of **4** gave rise to a mixture of *N*- and *O*-alkylated products **5** and **6** (< 2:1) in moderate yield. In contrast, the arylation of **4** led exclusively to the *N*-arylated product **7** in good yield.



Scheme 1: Reagents: (a) NBS, CCl_4, hv, reflux, (b) KO*t*Bu, DMF, +10°C to room temperature, (c) 3-(3-bromomethylphenyl)-5-methyl-[1,2,4]oxadiazole **2**, KO*t*Bu, DMF, room temperature, (27% **5** and 14% **6**), (d) 3-cyanophenylboronic acid, anhydrous $Cu(OAc)_2$, pyridine, $N(Et)_3$, molecular sieve 4Å, CH_2Cl_2, room temperature (76% **7**).

This result encouraged us to study the scope of this *N*-arylation reaction by choosing different available 2-pyridones and 3-pyridazinones. Table 1 shows the cupric acetate mediated coupling of NH substrates with 4-methylphenylboronic acid under standard conditions used by Chan and Lam. A number of structurally and elec-

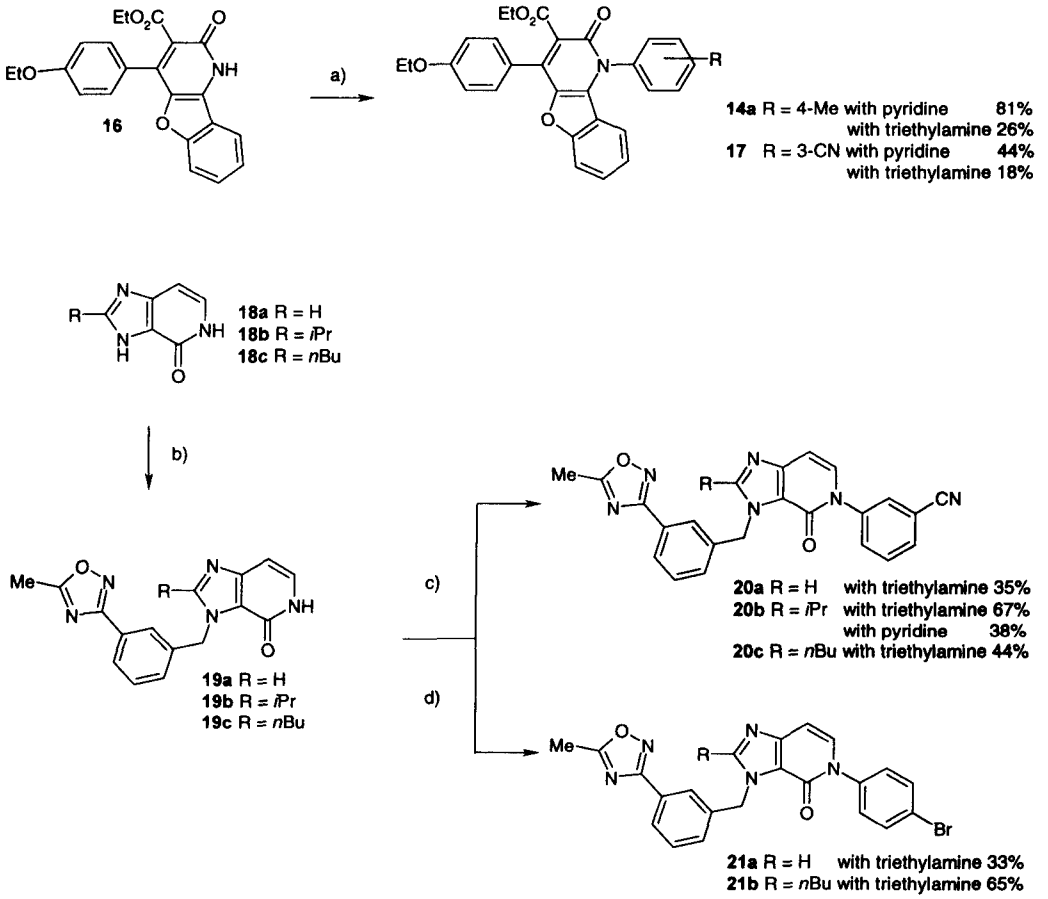
Table 1: *N*-arylation of various 2-pyridones and 3-pyridazinones with 4-methylphenylboronic acid

	Substrate	Product	Yield (%)
8			**8a** R = H (38) **8b** R = Me (0)
9			**9a** R = NO_2 (38) **9b** R = Cl (58)
10			**10a** R = 3-CN, R' = 6-*n*Bu, R''= H (0) **10b** R = 4-Me, R' = 5-NO_2, R'' = H (30) **10c** R,R' = 3,5-Cl, R'' = H (19) **10d** R,R' = 5,6-Me, R'' = 3-CN (4) **10e** R, R ' = H, R'' = 3-OMe (33) **10f** R =3-CN, R'= 5-(4-pyridyl),R''= H (10)
11			**11a** R = H (33) **11b** R = Me (19)
12			**12a** R = Me, R' = 7-Me (21) **12b** R = H, R' = 6-OAc (25)
13			**13a** (29)
14			**14a** (54)
15			**15a** R = cyclopropyl (30) **15b** R = *n*-Pn (30)

BPN = biphenylyl-2-carbonitrile. 2.0 eq. boronic acid, 2.0 eq. anhydrous $Cu(OAc)_2$, 2.0 eq. $N(Et)_3$, 2.0 eq. pyridine, molecular sieve 4Å, CH_2Cl_2, room temperature, 48h.

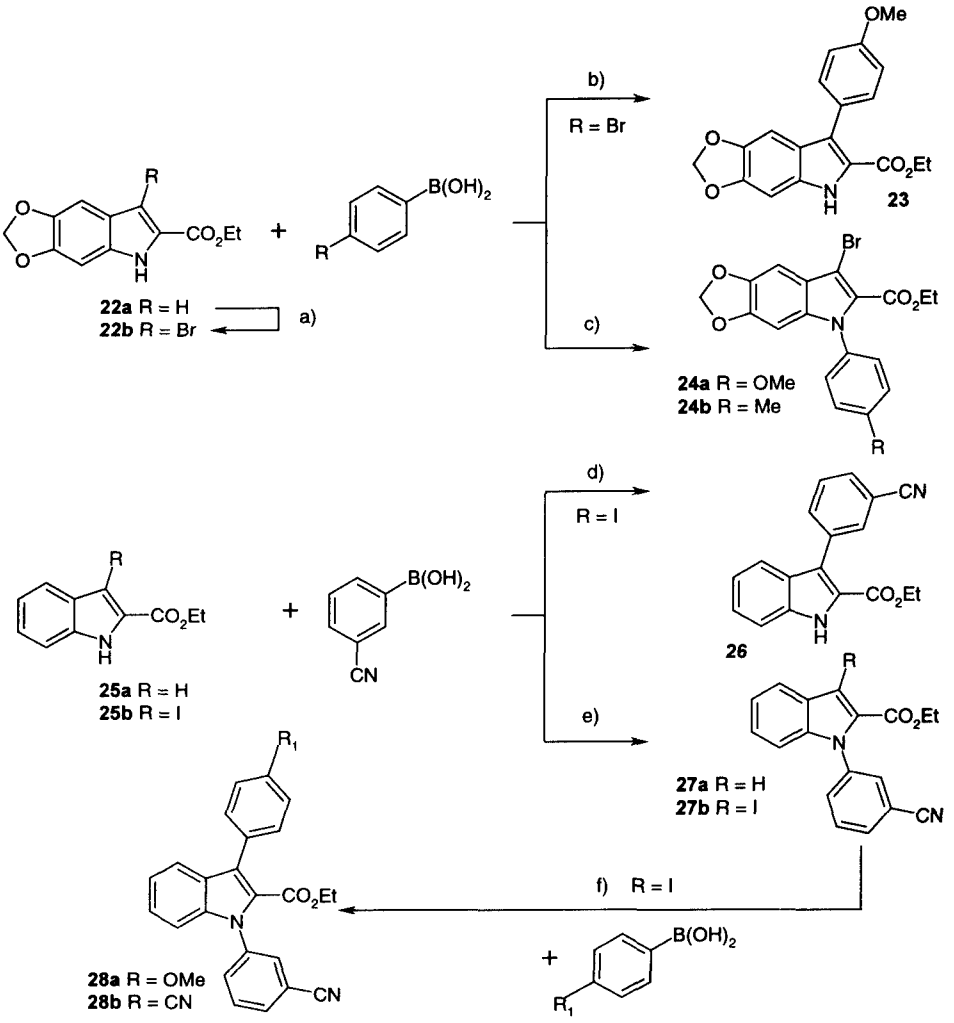
tronically diverse substrates were evaluated. This boronic acid underwent coupling with a variety of pyridones (**8-10** and **12-15**) and some pyridazinones (**11**), albeit in moderate yield. The results with nitro- and chloropyridones **9** or methoxypyridone **10e** indicate that there is no obvious trend for either electron poor or electron rich substrates in their reactivity with the boronic acid. The most reactive substrate in this series was benzofuro[3,2-b]pyridone **14** which gave the corresponding *N*-aryl product **14a** in good yield. The low yield of **10d** and the absence of reaction with 6-alkylpyridones to **8b** and **10a** may be attributed to steric congestion at the reaction center. Although these heterocycles are capable of forming tautomeric heteroarene structures no traces of *O*-arylation products were found.[11]

These preliminary results caused us to try to improve the yields in the benzofuro[3,2-b]pyridone and imidazo[4,5-c]pyridone series because of their functions as core structures in the field of factor Xa inhibitors. It is known from the literature that the choice of the base has a significant bearing on the outcome of this reaction.[7] Therefore, we changed from the mixture of the two tertiary bases to pure triethylamine or pyridine (Scheme 2).



Scheme 2: Reagents: 3.0 eq. 4-methylphenylboronic acid (for **14**), 3.0 eq. 3-cyanophenylboronic acid (for **17**, **20a**, **20b** and **20c**) or 3.0 eq. 4-bromophenylboronic acid (for **21a** and **21b**); (a), (c) and (d) 2.0 eq. anhydrous $Cu(OAc)_2$, 4.0 eq. base, CH_2Cl_2, molecular sieve 4Å, room temperature, 48h, (b) 3-(3-bromomethylphenyl)-5-methyl-[1,2,4]oxadiazole **2**, KO*t*Bu, DMF, room temperature.

The *p*-tolylation of compound **16** with pyridine as the base led to derivative **14a** with improved yields in comparison to triethylamine (Scheme 2) or the mixture (Table 1, substrate **14**). The result with 3-cyanophenylboronic acid is similar, although the yields are diminished (compound **17**). In the case of benzofuro[3,2-b]-pyridone, pyridine seems to be the preferred base. However, in the imidazo[4,5-c]pyridone series the outcome is quite the opposite (Scheme 2). The starting materials **19a-c** were obtained from alkylation of the *N*-3 unsubstituted imidazo[4,5-c]pyridones **18a-c**[1a, 12] with benzyl bromide **2**. Pyridone **19b** was first arylated at *N*-5 with 3-cyanoboronic acid and triethylamine as the base to give cyano derivative **20b** (a precursor of a potent factor Xa inhibitor) in good yield whereas pyridine afforded **20b** only in minor amount.



Scheme 3. Reagents: a) NBS, THF, room temperature, b), d) and f) 1.0 eq. boronic acid, Na_2CO_3, 10mol% Pd(II)Cl_2dppf, $MeO(CH_2)_2OMe$, reflux (74% **23**, 90% **26**, 59% **28a** and 85% **28b**); c) and e) 3.0 eq. boronic acid, 2.0 eq. anhydrous $Cu(OAc)_2$, 4.0 eq. pyridine, molecular sieve 2 Å, CH_2Cl_2, room temperature (50% **24a** and 26% **24b**), (21% **27a** and 31% **27b**).

For synthetic reasons conversion of **19a** and **19c** to the targeted compounds **20a** and **20c** proceeded with triethylamine as the base. In both cases the corresponding *N*-5 benzonitriles **20a** and **20c** were only produced in moderate yields. As a further extension in our factor Xa inhibitor program **19a** and **19c** were arylated with 4-bromophenylboronic acid to give both derivatives **21a** and **21b** in varying yields.

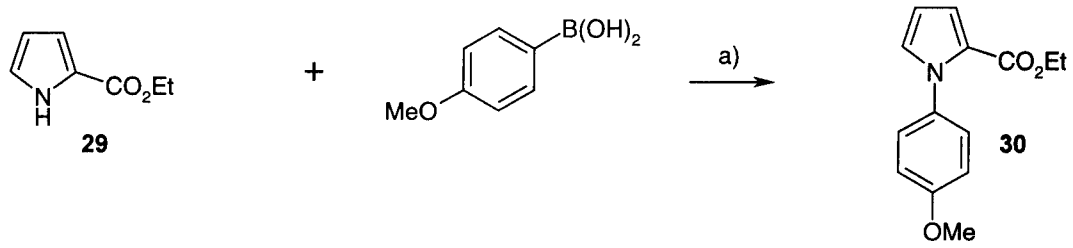
For the synthesis of endothelin antagonists 3-substituted indole-2-carboxylic acid esters such as compound **22b** were needed (Scheme 3).[3] This compound was synthesized by bromination of indole ester **22a**[13] and *N*-bromosuccinimide in tetrahydrofuran and could easily be coupled under Suzuki type reaction conditions with 4-methoxyphenylboronic acid to give 3-aryl derivative **23** in good yield. In contrast, when the reaction conditions described by Chan and Lam employing cupric acetate as the catalyst were used the *N*-arylated product **24a**[7b,14] was observed. In the same manner, the *p*-tolylboronic acid afforded the corresponding compound **24b** in diminished yield.

For the synthesis of certain factor Xa antagonists compound **27a** was required. Treatment of substrate **25a** (R = H) with 3-cyanophenylboronic acid led to the corresponding *N*-arylation product **27a** only in moderate yield. However, starting from **25b** (R = I)[15] the corresponding iodo compound **27b** was obtained in better yield under the same reaction conditions. These preliminary results indicate that both the halogen at C-3 and the carboxylic function at C-2 contributed to the positive outcome of this arylation process. The Suzuki type reaction of the same substrate **25b** led exclusively to 3-aryl compound **26** in good yield.

It is obvious, that the combination of the sequential reaction of an arylboronic acid either with copper or palladium as the catalyst would generate a 2-carboxyindole with a 1,3-diaryl substitution pattern. To support this assumption, 3-iodoindole **27b** was converted to the corresponding 1,3-diaryl compounds **28a** and **28b** under palladium catalysis in good to excellent yield.

This synthetic route, as outlined in Scheme 3 [b)-f)], allows the introduction of a variety of aryl substituents at *N*-1 and C-3, respectively. Therefore, these findings offer an alternative and more flexible approach compared to the synthesis of 1,3-diaryl-2-carboxyindoles reported by Bunker *et al.*[16]

To further support our conjecture that the nitrogen in such heterocycles is activated by carbonyl groups, ethyl pyrrole-2-carboxylate **29** was *N*-arylated with 4-methoxyphenylboronic acid and gave the pyrrole ester **30** in good yield (Scheme 5).



Scheme 4. Reagents: a) 3.0 eq. boronic acid, 2.0 eq. anhydrous $Cu(OAc)_2$, 4.0 eq. pyridine, molecular sieve 2 Å, CH_2Cl_2, room temperature (50% **30**).

CONCLUSION

In conclusion, it has been shown that a variety of 2-pyridones and some 3-pyridazinones can be *N*-arylated by reacting different boronic acids with NH substrates under Chan-Lam conditions. Using this approach *N*5-aryl imidazo[4,5-c]pyridone derivatives can be obtained. These compounds can be precursors of potent factor Xa inhibitors.

We have also extended the methodology of Chan and Lam to the synthesis of pyrrole- and indole-2-carboxylic acid esters. In the indole series this procedure offers a flexible entry in the synthesis of different 1,3-diaryl-2-carboxyindoles.

The results of these investigations in the design of factor Xa antagonists will be reported in due course.

EXPERIMENTAL

General: Melting points were determined with a HWS Labortechnik SGV 500 Plus melting point apparatus and are uncorrected. IR, NMR and mass spectra are in agreement with the structures cited and were recorded on a Bruker 85 IFS 48 IR spectrophotometer, a Bruker AC 200, WM 250 or AM 500 (TMS as internal standard), and a Micromass (Manchester, England) VG 70-70E (electron-impact: ei) or 70-250SE (fast atom bombardement: fab) at 70eV, respectively. High-resolution mass spectra were recorded on a Autospec M from Micromass. Thin layer chromatography (TLC) was carried out on precoated silica gel 60 F_{254} plates with a layer thickness of 0.25 mm from Merck KGaA (Darmstadt, Germany). Visualization was performed with UV and I_2. Yields were not optimized. The preparative chromatography was performed on Merck KGaA silica gel 60 (230-400 mesh) and all solvents were of Merck extra-pure grade. 1-(4-Methylphenyl)-1,2-dihydropyridin-2-one **8a** is described in the literature.[17]

3-[3-Bromomethyl)-phenyl]-5-methyl-1,2,4-oxadiazole (2): A mixture of 823 g (4.3 mol) 5-methyl-3-(*m*-tolyl)-1,2,4-oxadiazole **1** and 765 g (4.3 mol) *N*-bromosuccinimde in 10.0 l of refluxing carbon tetrachloride was irradiated 2 h with a 100 W tungsten light bulb. After filtration and evaporation of the solvent the crude material was dissolved in about 1 l of ethanol. The precipitated solid was filtered off, washed with 0.5 l ethanol and dried under high vacuum to yield 570 g (52.4 %) crude product **2**, which was directly used in alkylation reactions: mp 64-65 °C. MS (ei): m/z = 251 (M^+, 10%), 173 (100%). ^{1}H NMR (DMSO-d_6) δ 8.10 (t, *J* = 1.7 Hz, 1H), 7.93 (tt, *J* = 7.6, *J* = 1.6 and *J* = 1.5 Hz, 1H), 7.66 (tt, *J* = 7.6, *J* = 1.6 and *J* = 1,5 Hz, 1H), 7.58 (d, *J* = 7.6, 1H), 4.81 (s, 2H), 2.67 (s, 3H). HRMS calcd for $C_{10}H_9BrN_2O$ (M^+) m/e 251.9898, found m/e 251.9881.

6-[3-(5-Methyl-1,2,4-oxadiazol-3-yl)-benzyloxy]-1,2-dihydroquinolin-2-one (4): The mixture of 1.0 g (6.2 mmol) 6-hydroxyquinoline **3** in 30 ml dimethylformamide was treated with 0.84 g (7.5 mmol) potassium *tert*-butoxide and 2.0 g (7.5 mmol) benzyl bromide **2** at +10 °C. The reaction mixture was allowed to stir at room temperature for 2 h. It was diluted with water and extracted with ethyl acetate. After drying over sodium sulfate, the solvent was evaporated to yield an oil which was purified by flash chromatography on silica gel with ethyl acetate to provide 0.5 g (24.5 %) of **4**: mp 208-209 °C. IR (KBr) 1677 cm^{-1}. MS (ei): m/z = 333 (M^+, 26%), 173 (100%). ^{1}H NMR (DMSO-d_6) δ 11.6 (sbr, 1H), 8.09 (t, *J* = 1.6 Hz, 1H), 7.95 (tt, *J* = 7.6, *J* = 1.6 and *J* = 1.5 Hz, 1H), 7.81 (d, *J* = 9.6 Hz, 1H), 7.67 (tt, *J* = 7.8, *J* = 1.6 and *J* = 1.5 Hz, 1H), 7.60 (d, *J* = 7.6 Hz, 1H), 7.32 (t, *J* = 1.6 Hz, 1H), 7.26 (d, *J* = 1.6 Hz, 2H), 6.47 (d, *J* = 9.6 Hz, 1H), 5.23 (s, 2H), 2.66 (s, 3H). HRMS calcd for $C_{19}H_{15}N_3O_3$ (M^+) m/e 333.1113, found m/e 333.1115.

1-[3-(5-Methyl-1,2,4-oxadiazol-3-yl)-benzyl]-6-[3-(5-methyl-1,2,4-oxadiazol-3-yl)-benzyloxy]-1,2-dihydro-quinolin-2-one (5) and **2,6-Bis-[3-(5-methyl-1,2,4-oxadiazol-3-yl)-benzyloxy]-quinoline (6):** These compounds were prepared from 250 mg (0.75 mmol) **4** according to the synthesis of compound **4** and provided 0.1 g (27%) of **5** and 0.05 g (14%) of **6**.

5: mp 174-175 °C. IR (KBr) 1664 cm^{-1}. MS (ei): m/z = 505 (M^+, 32%), 173 (100%). ^{1}H NMR (DMSO-d_6) δ 8.08 (s, 1H), 7.96 (d, *J* = 4.4 Hz, 1H), 7.94 (d, *J* = 3.7 Hz, 1H), 7.86 (d, *J* = 7.8 Hz, 1H), 7.82 (s, 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.58 (t, *J* = 7.7 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 1H), 7.45 (d, *J* = 2.9 Hz, 1H), 7.41 (d, *J* = 7.9 Hz, 1H), 7.37 (d, *J* = 9.3 Hz, 1H), 7.25 (dd, *J* = 9.3 and *J* = 2.9 Hz, 1H), 6.76 (d, *J* = 9.4 Hz, 1H), 5.60 (sbr, 2H), 5.24 (s, 2H), 2.65 (s, 3H), 2.63 (s, 3H). HRMS calcd for $C_{29}H_{23}N_5O_4$ (M^+) m/e 505.1750, found m/e 505.1752.

6: mp 145-147 °C. MS (ei): m/z = 505 (M^+, 15%), 173 (100%). ^{1}H NMR (DMSO-d_6) δ 8.18 (d, *J* = 8.9 Hz, 1H), 8.14 (d, *J* = 6.2 Hz, 2H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 9.0 Hz, 1H), 7.71 (d, *J* = 6.3 Hz, 1H), 7.61 (t, *J* = 7.7 Hz, 1H), 7.63 (t, *J* = 7.7 Hz, 1H), 7.48 (d, *J* = 2.9 Hz, 1H), 7.44 (dd, *J* = 9.0 and *J* = 2.9 Hz, 2H), 7.09 (d, *J* = 8.8 Hz, 1H), 5.66 (s, 2H), 5.31 (s, 2H), 2.67 (s, 3H), 2.66 (s, 3H). HRMS calcd for $C_{29}H_{23}N_5O_4$ (M^+) m/e 505.1750, found m/e 505.1750.

3-{6-[3-(5-Methyl-1,2,4-oxadiazol-3-yl)-benzyloxy]-2-oxo-2*H*-quinolin-1-yl}-benzonitrile (7): A mixture of 200mg (0.6 mmol) **4**, 177 mg (1.2 mmol) 3-cyanophenylboronic acid, 220 mg (1.2 mmol) anhydrous cupric acetate, 800 mg activated 4 Å molecular sieves, 0.1 ml (1.2 mmol) pyridine and 0.17 ml (1.2 mmol)

triethylamine in 14 ml dichloromethane was treated at room temperature for 18 h. The reaction mixture was filtered through Celite, washed with dichloromethane and was purified by flash chromatography on silica gel with ethyl acetate to provide 196 mg (76%) of 7: mp 75-76 °C. IR (KBr) 2230, 1662 cm^{-1}. MS (ei): m/z = 434 (M^+, 30%), 173 (100%). ^1H NMR (DMSO-d_6) δ 8.09 (t, J = 1.6 Hz, 1H), 8.02 (tt, J = 6.2, J = 1.6 and J =1.5 Hz, 1H), 7.98-7.92 (m, 3H), 7.82 (t, J = 7.7 Hz, 1H), 7.74 - 7.64 (m, 2H), 7.60 (d, J = 7.6 Hz, 1H), 7.49 (d, J = 2.9 Hz, 1H), 7.17 (dd, J = 9.2 and J = 2.9 Hz, 1H), 6.69 (d, J = 9.6 Hz, 1H), 6.49 (d, J = 9.6 Hz, 1H), 5.26 (s, 2H), 2.66 (s, 3H). HRMS calcd for $C_{26}H_{18}N_4O_3$ (M^+) m/e 434.1379, found m/e 434.1373.

General procedure for coupling reactions of pyridones 8-10, pyridazinones 11, quinolinones 12, thieno[3,2-b]pyridine 13, benzofuro[3,2-b]pyridine 14, and imidazo[4,5-c]pyridones 15 with 4-methylphenylboronic acid: A mixture of the substrate (**8-15**) (7.6 mmol), 4-methylphenylboronic acid (2.067 g, 15.2 mmol), anhydrous cupric acetate (1.706 g, 15.2 mmol), activated 4 Å molecular sieves (2.0 g), pyridine (1.227 ml, 15.2 mmol) and triethylamine (2.107 ml, 15.2 mmol), in dichloromethane (50 ml) was treated at room temperature for 48 h. The reaction mixture was filtered through Celite, washed with dichloromethane and purified by flash chromatography on silica gel with ethyl acetate to provide the corresponding *N*-(4-methylphenyl) heterocycles **8a**[17], **9a**, **9b**, **10b-f**, **11a**, **11b**, **12a**, **12b**, **13a**, **14a**, **15a** and **15b** as shown below.

1-(4-Methylphenyl)-5-nitro-1,2-dihydropyridin-2-one (9a): This compound was prepared from 5-nitro-1,2-dihydropyridin-2-one by the method described above with a yield of 38%: mp 165-166 °C. IR (KBr) 1679 cm^{-1}. MS (ei): m/z = 230 (M^+, 100%). ^1H NMR (DMSO-d_6) δ 8.85 (d, J = 3.1 Hz, 1H), 8.21 (dd, J = 10.1 and J = 3.1 Hz, 1H), 7.40 (d, J = 8.6 Hz, 2H), 7.34 (d, J = 8.6 Hz, 2H), 6.58 (d, J = 10.1 Hz, 1H), 2.39 (s, 3H). HRMS calcd for $C_{12}H_{10}N_2O_3$ (M^+) m/e 230.0691, found m/e 230.0689.

5-Chloro-1-(4-methylphenyl)-1,2-dihydropyridin-2-one (9b): This compound was prepared from 5-chloro-1,2-dihydropyridin-2-one by the method described above with a yield of 58%: mp 95-96 °C. IR (KBr) 1668 cm^{-1}. MS (ei): m/z = 219 (M^+, 100%). ^1H NMR (DMSO-d_6) δ 7.84 (d, J = 2.9 Hz, 1H), 7.54 (dd, J = 9.8 and J = 2.9 Hz, 1H), 7.30 (s, 4H), 6.50 (d, J = 9.8 Hz, 1H), 2.36 (s, 3H). HRMS calcd for $C_{12}H_{10}ClNO$ (M^+) m/e 219.0451, found m/e 219.0449.

4-Methyl-3-nitro-1-(4-methylphenyl)-1,2-dihydropyridin-2-one (10b): This compound was prepared from 4-methyl-3-nitro-1,2-dihydropyridin-2-one by the method described above with a yield of 30%: mp 167-168 °C. IR (KBr) 1670 cm^{-1}. MS (ei): m/z = 244 (M^+, 100%). ^1H NMR (DMSO-d_6) δ 8.78 (s, 1H), 7.38 (d, J = 8.9 Hz, 2H), 7.34 (d, J = 8.9 Hz, 2H), 6.50 (d, J = 1.1 Hz, 1H), 2.49 (s, 3H), 2.39 (s, 3H). HRMS calcd for $C_{13}H_{12}N_2O_3$ (M^+) m/e 244.0848, found m/e 244.0850.

3,5-Dichloro-1-(4-methylphenyl)-1,2-dihydropyridin-2-one (10c): This compound was prepared from 3,5-dichloro-1,2-dihydropyridin-2-one by the method described above with a yield of 19%: mp 138-139 °C. IR (KBr) 1672 cm^{-1}. MS (ei): m/z = 253 (M^+, 100%). ^1H NMR (DMSO-d_6) δ 8.02 (d, J = 2.7 Hz, 1H), 7.93 (d, J = 2.7 Hz, 1H), 7.32 (s, 4H), 2.37 (s, 3H). HRMS calcd for $C_{12}H_9Cl_2NO$ (M^+) m/e 253.0061, found m/e 253.0052.

5,6-Dimethyl-1-(4-methylphenyl)-2-oxo-1,2-dihydropyridin-3-carbonitrile (10d): This compound was prepared from 5,6-dimethyl-2-oxo-1,2-dihydropyridin-3-carbonitrile by the method described above with a yield of 4%: mp 114-115 °C. IR (KBr) 2219, 1664 cm^{-1}. MS (ei): m/z = 238 (M^+, 100%). ^1H NMR (DMSO-d_6) δ 8.09 (s, 1H), 7.35 (d, J = 8.3 Hz, 2H), 7.14 (d, J = 8.3 Hz, 2H), 2,39 (s, 3H), 2.10 (s, 3H), 1.94 (s, 3H). HRMS calcd for $C_{15}H_{14}N_2O$ (M^+) m/e 238.1106, found m/e 238.1103.

3-Methoxy-1-(4-methylphenyl)-1,2-dihydropyridin-2-one (10e): This compound was prepared from 3-methoxy-1,2-dihydropyridin-2-one by the method described above with a yield of 33%: mp 142-144 °C. IR (KBr) 1658 cm^{-1}. MS (ei): m/z = 215 (M^+, 100%). ^1H NMR (DMSO-d_6) δ 7.30 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H), 7.14 (dd, J = 7.1 and J = 1.7 Hz, 1H), 6.86 (dd, J = 7.4 and J= 1.7 Hz, 1H), 6.21 (t, J = 7.2 Hz, 1H), 3.73 (s, 3H), 2.36 (s, 3H). HRMS calcd for $C_{13}H_{13}NO_2$ (M^+) m/e 215.0946, found m/e 215.0944.

1-(4-Methylphenyl)-2-oxo-5-(4-pyridyl)-1,2-dihydropyridin-3-carbonitrile (10f): This compound was prepared from 2-oxo-5-(4-pyridyl)-1,2-dihydropyridin-3-carbonitrile by the method described above with a yield of 10%: mp 286-287 °C. IR (KBr) 2226, 1668 cm^{-1}. MS (ei): m/z = 287 (M^+, 100%). ^1H NMR (DMSO-d_6) δ 8.83 (d, J = 2.8 Hz, 2H), 8.60 (d, J = 2.8 Hz, 2H), 7.75 (d, J = 5.8 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H), 7.36 (d, J = 8.4 Hz, 2H), 2.40 (s, 3H). HRMS calcd for $C_{18}H_{13}N_3O$ (M^+) m/e 287.1059, found m/e 287.1058.

6-Methyl-2-(4-methylphenyl)-2,3-dihydropyridazin-3-one (11a): This compound was prepared from 6-methyl-2,3-dihydropyridazin-3-one by the method described above with a yield of 33%: mp 68-69 °C. IR (KBr) 1676 cm^{-1}. MS (ei): m/z = 200 (M^+, 100%). ^1H NMR (DMSO-d_6) δ 7.41 (d, J = 9.5 Hz, 1H), 7.39 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 6.97 (d, J = 9.5 Hz, 1H), 2.36 (s, 3H), 2.30 (s, 3H). HRMS calcd for $C_{12}H_{12}N_2O$ (M^+) m/e 200.0950, found m/e 200.0948.

4,6-Dimethyl-2-(4-methylphenyl)-2,3-dihydropyridazin-3-one (11b): This compound was prepared from 4,6-dimethyl-2,3-dihydropyridazin-3-one by the method described above with a yield of 19%: mp 115-117 °C. IR (KBr) 1662 cm^{-1}. MS (ei): m/z = 214 (M^+, 100%). ^1H NMR (DMSO-d_6) δ 7.39 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 1.3 Hz, 1H), 7.26 (d, J = 8.4 Hz, 2H), 2.35 (s, 3H), 2.25 (s, 3H), 2.10 (d, J = 1.3 Hz, 3H). HRMS calcd for $C_{13}H_{14}N_2O$ (M^+) m/e 214.1106, found m/e 214.1102.

4,7-Dimethyl-1-(4-methylphenyl)-1,2-dihydroquinolin-2-one (12a): This compound was prepared from 4,7-dimethyl-1,2-dihydroquinolin-2-one by the method described above with a yield of 21%: mp 143-144 °C. IR (KBr) 1654 cm^{-1}. MS (ei): m/z = 263 (M^+, 100%). ^1H NMR (DMSO-d_6) δ 7.71 (d, J = 6.0 Hz, 1H), 7.40 (d, J = 8.3 Hz, 2H), 7.13 (d, J = 8.3 Hz, 2H), 6.50 (d, J = 1.1 Hz, 1H), 6.35 (s, 1H), 2.47 (d, J = 1.1 Hz, 3H), 2.43 (s, 3H), 2.22 (s, 3H). HRMS calcd for $C_{18}H_{17}NO$ (M^+) m/e 263.1310, found m/e 263.1305.

[1-(4-Methylphenyl)-2-oxo-1,2-dihydroquinolin-6-yl]-acetate (12b): This compound was prepared from [2-oxo-1,2-dihydroquinolin-6-yl]-acetate by the method described above with a yield of 25%: mp 225-226 °C. IR (KBr) 1760, 1657 cm^{-1}. MS (ei): m/z = 293 (M^+, 42%), 251 (100%). ^1H NMR (DMSO-d_6) δ 8.00 (d, J = 9.6 Hz, 1H), 7.57 (d, J = 2.7 Hz, 1H), 7.42 (d, J = 8.3 Hz, 2H), 7.20 (d, J = 8.3 Hz, 2H), 7.19 (d, J = 2.7 Hz, 1H), 6.71 (d, J = 9.6 Hz, 1H), 6.55 (d, J = 9.1 Hz, 1H), 2.43 (s, 3H), 2.29 (s, 3H). HRMS calcd for $C_{18}H_{15}NO_3$ (M^+) m/e 293.1052, found m/e 293.1052.

7-Chloro-4-(4-methylphenyl)-5-oxo-4,5-dihydrothieno[3,2-b]pyridin-6-carboxylic acid ethyl ester (13a): This compound was prepared from 7-chloro-5-oxo-4,5-dihydrothieno[3,2-b]pyridin-6-carboxylic acid ethyl ester by the method described above with a yield of 29%: mp 155-156 °C. IR (KBr) 1740, 1640 cm^{-1}. MS (ei): m/z = 333 (M^+, 100%). ^1H NMR ($CDCl_3$) δ 7.55 (d, J = 5.4 Hz, 1H), 7.34 (d, J = 7.9 Hz, 2H), 7.20 (d, J = 7.9 Hz, 2H), 6.51 (d, J = 5.4 Hz, 1H), 3.96 (s, 3H), 2.44 (s, 3H). HRMS calcd for $C_{16}H_{12}NO_3SCl$ (M^+) m/e 333.0226, found m/e 333.0227.

4-(4-Ethoxyphenyl)-1-(4-methylphenyl)-2-oxo-1,2-dihydrobenzofuro[3,2-b]pyridin-3-carboxylic acid ethyl ester (14a): This compound was prepared from 4-(4-ethoxyphenyl)-2-oxo-1,2-dihydrobenzofuro[3,2-b]-pyridin-3-carboxylic acid ethyl ester by the method described above with a yield of 54%: mp 255-256 °C. IR (KBr) 1729, 1638 cm^{-1}. MS (ei): m/z = 467 (M^+, 100%). ^1H NMR ($CDCl_3$) δ 7.65 (d, J = 8.8 Hz, 2H), 7.46 (t, J = 8.4 Hz, 1H), 7.43 – 7.33 (m, 5H), 7.07 – 6.99 (m, 3H), 6.36 (d, J = 8.0 Hz, 1H), 4.23 (q, J = 7.1 Hz, 2H), 4.13 (q, J = 7.0 Hz, 2H), 2.52 (s, 3H), 1.47 (t, J = 7.0 Hz, 3H), 1.17 (t, J = 7.1 Hz, 3H). HRMS calcd for $C_{29}H_{25}NO_5$ (M^+) m/e 467.1733, found m/e 467.1723.

4'-[2-Cyclopropyl-5-(4-methylphenyl)-4-oxo-4,5-dihydro-3*H*-imidazo[4,5-c]pyridyl-3-methyl]-biphenyl-2-carbonitrile (15a): This compound was prepared from 4'-[2-cyclopropyl-4-oxo-4,5-dihydro-3*H*-imidazo[4,5-c]pyridyl-3-methyl]-biphenyl-2-carbonitrile by the method described above with a yield of 30%: mp 233-234 °C. IR (KBr) 2222, 1664 cm^{-1}. MS (ei): m/z = 456 (M^+, 85%), 264 (100%). ^1H NMR (DMSO-d_6) δ 7.93 (d, J = 7.7 Hz, 1H), 7.76 (dd, J = 7.7 and J = 1.5 Hz, 1H), 7.68 (s, 2H), 7.65 (s, 2H), 7.40 (d, J = 8.3 Hz, 1H), 7.33 (d, J

= 7.3 Hz, 1H), 7.30 (s, 2H), 7.15 (s, 2H), 7.11 (s, 2H), 5.89 (s, 2H), 2.53 – 2.52 (m, 1H), 1.10 – 1.00 (m, 4H). HRMS calcd for $C_{30}H_{24}N_4O$ (M^+) m/e 456.1950, found m/e 456.1952.

4'-[5-(4-Methylphenyl)-4-oxo-2-pentyl-4,5-dihydro-3*H*-imidazo[4,5-c]pyridyl-3-methyl]-biphenyl-2-carbonitrile (15b): This compound was prepared from 4'-[4-oxo-2-pentyl-4,5-dihydro-3*H*-imidazo[4,5-c]pyridyl-3-methyl]-biphenyl-2-carbonitrile by the method described above with a yield of 30%: mp 63-65 °C. IR (KBr) 2222, 1664 cm^{-1}. MS (ei): m/z = 486 (M^+, 40%), 192 (100%). ^1H NMR (DMSO-d_6) δ 7.94 (dd, *J* = 7.7 and *J* = 1.7 Hz, 1H), 7.77 (dd, *J* = 7.7 and *J* = 1.4 Hz, 1H), 7.59 (d, *J* = 7.6 Hz, 2H), 7.55 (d, *J* = 7.6 Hz, 2H), 7.37 (d, *J* = 7.3 Hz, 1H), 7.31 – 7.29 (m, 2H), 7.31 (s, 4H), 6.70 (d, *J* = 7.3 Hz, 1H), 5.85 (s, 2H), 2.76 (t, *J* = 7.6 Hz, 2H), 2.37 (S, 3H), 1.70 – 1.58 (m, *J* = 7.3 Hz, 2H), 1.29 – 1.19 (m, 4H), 0.80 (t, *J* = 7.1 Hz, 3H). HRMS calcd for $C_{32}H_{30}N_4O$ (M^+) m/e 486.2420, found m/e 486.2418.

1-(3-Cyanophenyl)-4-(4-ethoxyphenyl)-2-oxo-1,2-dihydrobenzofuro[3,2-b]pyridin-3-carboxylic acid ethyl ester (17): This compound was prepared from 4-(4-ethoxyphenyl)-2-oxo-1,2-dihydrobenzofuro[3,2-b]-pyridin-3-carboxylic acid, ethyl ester with 3-cyanophenylboronic acid and pyridine as the base by the method described above with a yield of 44%: mp 211-212 °C. IR (KBr) 2238, 1728, 1648 cm^{-1}. MS (ei): m/z = 478 (M^+, 100%). ^1H NMR ($CDCl_3$) δ 7.93 (tt, *J* = 6.7 and *J* = 2.1 Hz, 1H), 7.87 (t, *J* = 2.1 Hz, 1H), 7.82 – 7.76 (m, 2H), 7.66 (d, *J* = 8.8 Hz, 2H), 7.54 (d, *J* = 8.4 Hz, 1H), 7.45 – 7.41 (m, *J* = 7.3 and *J* = 1.2 Hz, 1H), 7.09 (t, *J* = 7.8 Hz, 1H), 7.06 (d, *J* = 8.8 Hz, 2H), 6.31 (d, *J* = 8.1 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 4.14 (q, *J* = 7.0 Hz, 2H), 1.48 (t, *J* = 7.0 Hz, 3H), 1.17 (t, *J* = 7.1 Hz, 3H). HRMS calcd for $C_{29}H_{22}N_2O_5$ (M^+) m/e 478.1529, found m/e 478.1525.

3-[3-(5-Methyl-1,2,4-oxadiazol-3-yl)-benzyl]-4,5-dihydro-3*H*-imidazo[4,5-c]pyridin-4-one (19a): The solution of 1.0 g (7.4 mmol) **18a** in 25 ml dimethylformamide was treated with 1.125 g (8.14 mmol) finely ground potassium carbonate and 2.06 g (8.14 mmol) **2**. The reaction mixture was allowed to stir at room temperature overnight. It was diluted with water and extracted with ethyl acetate. After drying over sodium sulfate, the solvent was evaporated to yield a yellow oil with was purified by flash chromatography on silica gel with ethyl acetate to provide 0.43 g (19%) of monomer **18a**: mp 211-212 °C. IR (KBr) 1653 cm^{-1}. MS (ei): m/z = 307 (M^+, 92%), 249 (100%). ^1H NMR (DMSO-d_6) δ 11.35 (sbr, 1H), 8.46 (s, 1H), 8.05 (s, 1H), 8.00 – 7.94 (m, 1H), 7.04 – 7.55 (m, 2H), 7.16 (dd, *J* = 7.1 and *J* = 5.8 Hz, 1H), 6.63 (d, *J* = 7.1 Hz, 1H), 5.81 (s, 2H), 2.71 (s, 3H). HRMS calcd for $C_{16}H_{13}N_5O_2$ (M^+) m/e 307.1069, found m/e 307.1069.

2-Isopropyl-3-[3-(5-methyl-1,2,4-oxadiazol-3-yl)-benzyl]-4,5-dihydro-3*H*-imidazo[4,5-c]pyridin-4-one (19b): This compound was prepared from **18b** and **2** by the method described above with a yield of 32%: mp 192-193 °C. IR (KBr) 1651 cm^{-1}. MS (fab): m/z = 350 (M^++H, 100%). ^1H NMR (DMSO-d_6) δ 11.27 (dbr, *J* = 5.3 Hz, 1H), 7.89 (d, *J* = 7.8 Hz, 1H), 7.78 (s, 1H), 7.53 (t, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 7.8 Hz, 1H), 7.10 (t, *J* = 6.5 Hz, 1H), 6.56 (d, *J* = 7.0 Hz, 1H), 5.90 (s, 2H), 3.19 – 3.13 (m, *J* = 6.7 Hz, 1H), 2.64 (s, 3H), 1.14 (d, *J* = 6.7 Hz, 6H). HRMS calcd for $C_{19}H_{19}N_5O_2$ (M^+) m/e 349.1539, found m/e 349.1543.

2-Butyl-3-[3-(5-methyl-1,2,4-oxadiazol-3-yl)-benzyl]-4,5-dihydro-3*H*-imidazo[4,5-c]pyridin-4-one (19c): This compound was prepared from **18c** and **2** by the method described above with a yield of 38%: mp 137-138 °C. IR (KBr) 1669 cm^{-1}. MS (ei): m/z = 363 (M^+, 65%), 148 (100%). ^1H NMR (DMSO-d_6) δ 11.28 (sbr, 1H), 7.90 (d, *J* = 7.8 Hz, 1H), 7.80 (s, 1H), 7.53 (t, *J* = 7.8 Hz, 1H), 7.36 (d, *J* = 7.8 Hz, 1H), 7.10 (d, *J* = 7.0 Hz, 1H), 6.55 (d, *J* = 7.0 Hz, 1H), 5.86 (s, 2H), 2.70 (t, *J* = 7.5 Hz, 2H), 2.64 (s, 3H), 1.60 – 1.53 (m, *J* = 7.4 Hz, 2H), 1.30 – 1.22 (m, *J* = 7.5 Hz, 2H), 0.78 (t, *J* = 7.4 Hz, 3H). HRMS calcd for $C_{20}H_{21}N_5O_2$ (M^+) m/e 363.1695, found m/e 363.1693.

3-{3-[3-(5-Methyl-1,2,4-oxadiazol-3-yl)-benzyl]-4-oxo-4,5-dihydro-3*H*-imidazo[4,5-c]pyrid-5-yl}-benzonitrile (20a): This compound was prepared from **19a** with 3-cyanophenylboronic acid and triethylamine as the base by the method described for **7** with a yield of 67%: mp 209-210 °C. IR (KBr) 2226, 1668 cm^{-1}. MS (ei): m/z = 408 (M^+, 18%), 166 (100%). ^1H NMR (DMSO-d_6) δ 8.02 (t, *J* = 1.7 Hz, 1H), 7.91 (t, *J* = 7.5 Hz, 2H), 7.86 – 7.80 (m, 2H), 7.71 (t, *J* = 7.8 Hz, 1H), 7.57 – 7.49 (m, 2H), 7.34 (d, *J* = 7.8 Hz, 1H), 6.78 (d, *J* = 7.3 Hz,

1H), 5.89 (s, 2H), 3.29 – 3.16 (m, J = 6.6 Hz, 1H), 2.65 (s, 3H), 1.19 (d, J = 6.7 Hz, 6H). HRMS calcd for $C_{23}H_{16}N_6O_2$ (M^+) m/e 408.1335, found m/e 408.1338.

3-{2-Isopropyl-3-[3-(5-methyl-1,2,4-oxadiazol-3-yl)-benzyl]-4-oxo-4,5-dihydro-3*H*-imidazo[4,5-c]pyrid-5-yl}-benzonitrile (20b): This compound was prepared from **19b** with 3-cyanophenylboronic acid and triethylamine as the base by the method described for **7** with a yield of 35%: mp 168-170 °C. IR (KBr) 2240, 1672 cm^{-1}. MS (ei): m/z = 450 (M^+, 38%), 277 (100%). ^1H NMR (DMSO-d_6/+ TFA) δ 8.14 (s, 1H), 8.03-7.94 (m, 4H), 7.87-7.73 (m, 3H), 7.65 (d, J = 7.6 Hz, 1H), 7.56 (t, J = 7.6 Hz, 1H), 7.00 (s, 1H), 5.90 (s, 2H), 2.66 (s, 3H). HRMS calcd for $C_{26}H_{22}N_6O_2$ (M^+) m/e 450.1804, found m/e 450.1802.

3-{2-Butyl-3-[3-(5-methyl-1,2,4-oxadiazol-3-yl)-benzyl]-4-oxo-4,5-dihydro-3*H*-imidazo[4,5-c]pyrid-5-yl}-benzonitrile (20c): This compound was prepared from **19c** with 3-cyanophenylboronic acid and triethylamine as the base by the method described for **7** with a yield of 44%: mp 151-152 °C. IR (KBr) 2234, 1672 cm^{-1}. MS (fab): m/z = 465 (M^++H, 95%), 91 (100%). ^1H NMR (DMSO-d_6) δ 8.03 (t, J = 1.8 Hz, 1H), 7.96 – 7.81 (m, 4H), 7.74 (d, J = 7.8 Hz, 1H), 7.68 – 7.47 (m, 2H), 7.36 (d, J = 7.9 Hz, 1H), 6.77 (d, J = 7.3 Hz, 1H), 5.86 (s, 2H), 2.77 (t, J = 7.4 Hz, 2H), 2.65 (s, 3H), 1.70 – 1.53 (m, J = 7.3 Hz, 2H), 1.40 – 1.20 (m, J = 7.7 Hz, 2H), 0.80 (t, J = 7.3 Hz, 3H). HRMS calcd for $C_{27}H_{24}N_6O_2$ (M^+) m/e 464.1961, found m/e 464.1962.

5-(4-Bromophenyl)-3-[3-(5-methyl-1,2,4-oxadiazol-3-yl)-benzyl]-4,5-dihydro-3*H*-imidazo[4,5-c]pyridin-4-one (21a): This compound was prepared from **19a** with 4-bromophenylboronic acid and triethylamine as the base by the method described for **7** with a yield of 33%: mp 107-108 °C. IR (KBr) 1668 cm^{-1}. MS (ei): m/z = 461 (M^+, 62%), 463 (60%), 404 (100%), 406 (99%). ^1H NMR (DMSO-d_6) δ 8.50 (s, 1H), 7.99 (s, 1H), 7.94 – 7.87 (m, 1H), 7.71 (d, J = 8.7 Hz, 2H), 7.54 (d, J = 1.2 Hz, 1H), 7.53 (d, J = 2.3 Hz, 1H), 7.41 (d, J = 8.7 Hz, 2H), 7.39 (d, J = 1.2 Hz, 1H), 6.74 (d, J = 7.3 Hz, 1H), 5.75 (s, 2H), 2.65 (s, 3H). HRMS calcd for $C_{22}H_{16}N_5O_2Br$ (M^+) m/e 461.0487, found m/e 461.0486.

5-(4-Bromophenyl)-2-butyl-3-[3-(5-methyl-1,2,4-oxadiazol-3-yl)-benzyl]-4,5-dihydro-3*H*-imidazo[4,5-c]-pyridin-4-one (21b): This compound was prepared from **19c** with 4-bromophenylboronic acid and triethylamine as the base by the method described for **7** with a yield of 65%: mp 175-176 °C. IR (KBr) 1670 cm^{-1}. MS (ei): m/z = 517 (M^+, 55%), 519 (57%), 173 (100%). ^1H NMR (DMSO-d_6) δ 7.91 (d, J = 7.8 Hz, 1H), 7.89 (s, 1H), 7.72 (d, J = 8.6 Hz, 2H), 7.55 (d, j = 7.5 Hz, 1H), 7.53 (d, J = 7.2 Hz, 1H), 7.44 (d, J = 8.6 Hz, 2H), 7.34 (d, J = 7.8 Hz, 1H), 6.87 (d, J = 7.2 Hz, 1H), 5.92 (s, 2H), 2.91 (t, J = 7.2 Hz, 2H), 2.65 (s, 3H), 1.59 – 1.52 (m, J = 7.2 Hz, 2H), 1.30 – 1.22 (m, J = 7.2 Hz, 2H), 0.75 (t, J = 7.2 Hz, 3H). HRMS calcd for $C_{26}H_{24}N_5O_2$ (M^+) m/e 517.1113, found m/e 517.1110.

7-Bromo-5*H*-1,3-dioxolo[4,5-f]indole-6-carboxylic acid ethyl ester (22b): 1.87 g (0.008 mol) **22a** was dissolved in 30 ml tetrahydrofuran, the solution was treated with 1.42 g (0.008 mol) *N*-bromosuccinimide and the mixture stirred at room temperature for 15 min. . The resultant light brown solution was treated with 100 ml water and allowed to stand to precipitate. The solid was collected by filtration, washed with THF and dried under high vacuum to give 1.9 g (75%) of **22b**: mp 182-183 °C. IR (KBr) 1681 cm^{-1}. MS (ei): m/z = 313, (66%), 311 (M^+, 71%), 267 (99%), 265 (100%). ^1H NMR (DMSO-d_6) δ 11.99 (sbr, 1H), 6.90 (s, 1H), 6.88 (s, 1H), 6.04 (s, 2H), 4.34 (q, J = 7.1 Hz, 2H), 1.35 (t, J = 7.1 Hz, 3H). HRMS calcd for $C_{12}H_{10}NO_4Br$ (M^+) m/e 310.9793, found m/e 310.9798.

7-(4-Methoxyphenyl)-5*H*-1,3-dioxolo[4,5-f]indole-6-carboxylic acid ethyl ester (23): A solution of 0.5 g (0.002 mol) **22b** in 20 ml dimethoxyethane was treated with 4.0 ml 2 N sodium carbonate, 0.365 g (0.002 mol) 4-methoxyphenylboronic acid and 10.0 mg [1,1'-bis-(diphenylphosphino)ferrocenedichloropalladium (II)]. The mixture was stirred at 84°C overnight, cooled to room temperature, quenched with water and extracted with ethyl acetate. The organic extract was dried on sodium sulfate, concentrated in vacuo, and chromatographed on silica gel with ethyl acetate/petrol ether (80:20) to give 0.4 g (74 %) of **23**: mp 168-169 °C. IR (KBr) 3309, 1653 cm^{-1}. MS (ei): m/z = 339 (M^+, 75%), 293 (100%). ^1H NMR (DMSO-d_6) δ 11.62 (sbr, 1H), 7.38 (d, J = 8.8

Hz, 2H), 6.99 (d, J = 8.8 Hz, 2H), 6.92 (s, 1H), 6.80 (s, 1H), 5.99 (s, 2H), 4.18 (q, J = 7.1 Hz, 2H), 3.81 (s, 3H), 1.19 (t, J = 7.1 Hz, 3H). HRMS calcd for $C_{19}H_{17}NO$ (M^+) m/e 339.1107, found m/e 339.1110.

7-Bromo-5-(4-methylphenyl)- 5*H*-1,3-dioxolo[4,5-f]indole-6-carboxylic acid ethyl ester (24a): This compound was prepared from **22b** with 4-methylphenylboronic acid and pyridine as the base by the method described for **7** with a yield of 26%: mp 126-128 °C. IR (KBr) 1703 cm^{-1}. MS (ei): m/z = 401 (M^+, 100%), 403 (98%). ^1H NMR (DMSO-d_6) δ 7.26 (d, J = 8.9 Hz, 2H), 7.06 (d, J = 8.9 Hz, 2H), 6.99 (s, 1H), 6.44 (s, 1H), 6.05 (s, 2H), 4.09 (q, J = 7.1 Hz, 2H), 3.84 (s, 3H), 1.04 (t, J = 7.1 Hz, 3H). HRMS calcd for $C_{19}H_{16}NO_4Br$ (M^+) m/e 401.0263, found m/e 401.0264.

7-Bromo-5-(3-methoxyphenyl)-5*H*-1,3-dioxolo[4,5-f]indole-6-carboxylic acid ethyl ester (24b): This compound was prepared from **22b** with 4-methoxyphenylboronic acid and pyridine as the base by the method described for **7** with a yield of 50%: mp 152-153 °C. IR (KBr) 1703 cm^{-1}. MS (ei): m/z = 417 (M^+, 97%), 419 (100%). ^1H NMR (DMSO-d_6) δ 7.34 (d, J = 8.3 Hz, 2H), 7.22 (d, J = 8.3 Hz, 2H), 7.01 (s, 1H), 6.48 (s, 1H), 6.06 (s, 2H), 4.07 (q, J = 7.1 Hz, 2H), 2.41 (s, 3H), 1.02 (t, J = 7.1 Hz, 3H). HRMS calcd for $C_{19}H_{16}NO_5Br$ (M^+) m/e 417.0211, found m/e 417.0209.

3-(3-Cyanophenyl)-indole-2-carboxylic acid ethyl ester (26): This compound was prepared from **25b** with 3-cyanophenylboronic acid by the method described for **23** to give **26** with a yield of 90%: mp 133-134 °C. IR (KBr) 2227, 1684 cm^{-1}. MS (fab): m/z = 291 (M^++H, 100%). ^1H NMR (DMSO-d_6) δ 7.95 (t, J = 1.7 Hz, 1H), 7.87 – 7.80 (m, 2H), 7.65 (t, J = 7.6 Hz, 1H), 7.54 (d, J = 8.3 Hz, 1H), 7.50 (d, J = 8.3 Hz, 1H), 7.38 – 7.30 (m, J = 7.1 and J = 1.2 Hz, 1H), 7.16 – 7.09 (m, J = 7.1 and J = 1.2 Hz, 1H), 4.24 (q, J = 7.1 Hz, 2H), 1.20 (t, J = 7.1 Hz, 1H). HRMS calcd for $C_{18}H_{14}N_2O_2$ (M^+) m/e 290.1055, found m/e 290.1055.

1-(3-Cyanophenyl)-indole-2-carboxylic acid ethyl ester (27a): This compound was prepared from **25a** with 3-cyanophenylboronic acid and pyridine as the base by the method described for **7** with a yield of 21%: mp 101-102 °C. IR (KBr) 2231, 1688 cm^{-1}. MS (ei): m/z = 290 (M^+, 100%). ^1H NMR (DMSO-d_6) δ 8.04 – 7.95 (m, 2H), 7.83 – 7.74 (m, 3H), 7.52 (d, J = 0.7 Hz, 1H), 7.39 – 7.18 (m, J = 6.8 and J = 1.5 Hz, 2H), 7.10 (dd, J = 8.1 and J = 0.7 Hz, 1H), 4.16 (q, J = 7.1 Hz, 2H), 1.15 (t, J = 7.1 Hz, 3H). HRMS calcd for $C_{18}H_{14}N_2O_2$ (M^+) m/e 290.1055, found m/e 290.1056.

1-(3-Cyanophenyl)-3-iodoindole-2-carboxylic acid ethyl ester (27b): This compound was prepared from **25b** with 3-cyanophenylboronic acid and pyridine as the base by the method described for **7** with a yield of 31%: mp 213-214 °C. IR (KBr) 2232, 1700 cm^{-1}. MS (ei): m/z = 416 (M^+, 100%). ^1H NMR (DMSO-d_6) δ 8.05 – 7.96 (m, 2H), 7.79 – 7.74 (m, 2H), 7.57 (dd, J = 6.6 and J = 1.2 Hz, 1H), 7.45 – 7.28 (m, 2H), 7.07 (dd, J = 6.0 and J = 1.2 Hz, 1H), 4.15 (q, J = 7.1 Hz, 2H), 1.06 (t, J = 7.1 Hz, 3H). HRMS calcd for $C_{18}H_{13}IN_2O_2$ (M^+) m/e 416.0022, found m/e 416.0020.

1-(3-Cyanophenyl)-3-(4-methoxyphenyl)-indole-2-carboxylic acid ethyl ester (28a): This compound was prepared from **27b** with 4-methoxyphenylboronic acid by the method described for **23** to give **28a** with a yield of 59%: mp 115-118 °C. IR (KBr) 2231, 1706 cm^{-1}. MS (ei): m/z = 396 (M^+, 100%). ^1H NMR (DMSO-d_6) δ 8.06 (t, J = 2.0 Hz, 1H), 7.99 (tt, J = 2.0 and J = 6.8 Hz, 1H), 7.84-7.73 (m, 2H), 7.58 (d, J = 8.0 Hz, 1H), 7.46 (d, J = 8.8 Hz, 2H), 7.40-7.23 (m, 1H), 7.27-7.14 (m, 2H), 7.06 (d, J = 8.8 Hz, 2H), 3.97 (q, J = 7.1 Hz, 2H), 3.84 (s, 3H), 0.85 (t, J = 7.1 Hz, 3H). HRMS calcd for $C_{25}H_{20}N_2O_3$ (M^+) m/e 396.1474, found m/e 396.1477.

1-(3-Cyanophenyl)-3-(4-cyanophenyl)-indole-2-carboxylic acid ethyl ester (28b): This compound was prepared from **27b** with 4-cyanophenylboronic acid by the method described for **23** to give **28b** with a yield of 85%: mp 152-153 °C. IR (KBr) 2225, 1699 cm^{-1}. MS (ei): m/z = 391 (M^+, 100%). ^1H NMR (DMSO-d_6) δ 8.09 (t, J = 1.7 Hz, 1H), 8.02 (tt, J = 7.1 and J = 1.7 Hz, 1H), 7.96 (d, J = 8.4 Hz, 2H), 7.88-7.78 (m, 1H), 7.74 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 8.0 Hz, 1H), 7.41 (dtd, J = 7.1, J = 1.3 and J = 1.3 Hz, 1H), 7.28 (dtd, J = 7.0, J =

1.1 and J = 1.0 Hz, 1H), 7.18 (d, J = 8.3 Hz, 1H), 3.98 (q, J = 7.1 Hz, 2H), 0.84 (t, J = 7.1 Hz, 3H). HRMS calcd for $C_{25}H_{17}N_3O_2$ (M^+) m/e 391.1321, found m/e 391.1314.

1-(4-Methoxyphenyl)-pyrrole-2-carboxylic acid ethyl ester (30): This compound was prepared from **29** with 4-methoxyphenylboronic acid and pyridine as the base by the method described for **7** with a yield of 50%: mp 48-50 °C. IR (KBr) 1707 cm^{-1}. MS (ei): m/z = 245 (M^+, 100%). ^1H NMR (DMSO-d_6) δ 7.24 (d, J = 8.9 Hz, 2H), 7.13 (dd, J = 4.5 and J = 2.3 Hz, 1H), 6.99 (dd, J = 4.6 and J = 2.3 Hz, 1H), 6.96 (d, J = 8.9 Hz, 2H), 6.27 (dd, J = 3.9 and J = 2.6 Hz, 1H), 4.06 (q, J = 7.1 Hz, 2H), 3.80 (s, 3H), 1.13 (t, J = 7.1 Hz, 3H). HRMS calcd for $C_{14}H_{15}NO_3$ (M^+) m/e 245.1052, found m/e 245.1056.

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