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Discovery of novel modulators of metabotropic glutamate receptor subtype-5

Bowei Wang,[a,*] Jean-Michel Vernier,[a] Sara Rao,[b] Janice Chung,[b] Jeffery J. Anderson,[b] Jesse D. Brodkin,[b] Xiaohui Jiang,[a] Michael F. Gardner,[a] Xiaoqing Yang[a] and Benito Munoz[a,*]

[a]*Department of Chemistry, Merck Research Laboratories, MRLSDB2, 3535 General Atomics Court, San Diego, CA 92121, USA*
[b]*Department of Neuropharmacology, Merck Research Laboratories, MRLSDB1, 3535 General Atomics Court, San Diego, CA 92121, USA*

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Abstract—A series of potent and selective mGluR5 antagonists were synthesized and evaluated in vitro and in vivo. It was found that a pyridyl functionality is a potential replacement for acetonitrile in the lead structure, with 2-pyridyl being most favored. Additionally, the benzoxazole moiety could also be replaced by other heterobicyclic rings such as imidazothiazole.

1. Introduction

Glutamate is the major excitatory neurotransmitter in the mammalian nervous system, which binds to neurons and thereby activates cell surface receptors. Such surface receptors are characterized as either ionotropic or metabotropic glutamate receptors (mGluRs). mGluRs are G protein-coupled receptors that activate intracellular secondary messenger systems when bound by glutamate. Activation of mGluRs results in a variety of cellular responses. In particular, mGluR1 and mGluR5 activate phospholipase C, which is followed by mobilization of intracellular calcium. Modulation of mGluR5 represents a potential approach for the treatment of diseases that affect the nervous system.[1] For example, recent reports have implicated the involvement of mGluR5 in nociceptive processes and have shown that modulation of mGluR5 by mGluR5-selective compounds is useful in the treatment of various pain states, including acute, persistent and chronic pain,[2] inflammatory pain[3] and neuropathic pain.[4]

Further evidence supports the use of mGluR5 modulators for the treatment of psychiatric and neurological disorders. For example, mGluR5-selective compounds, such as 2-methyl-6-(phenylethynyl)-pyridine, MPEP (**1**), are effective in animal models of mood disorders, including anxiety and depression.[5] Gene expression data from humans indicate that mGluR5 modulation may be useful for the treatment of schizophrenia.[6] Additional studies have also shown the potential utility of mGluR5-modulatory compounds for the treatment of movement disorders such as Parkinson's disease.[7] Other research supports a role for mGluR5 modulation in the treatment of cognitive dysfunction,[8] epilepsy[9] and neuroprotection.[10] Finally, studies with mGluR5 knockout mice and **1** also suggest that modulation of these receptors may be useful in the treatment of drug addiction, drug abuse and drug withdrawal.[11]

As part of our ongoing drug discovery efforts[5] the novel mGluR5 antagonist [4-(1,3-benzoxazol-2-yl)2-chlorophenyl]-acetonitrile (**2**) was identified by high throughput screening. Preliminary SAR around this structure led to replacement of the chloro functional group with methoxy, as in **7**, an analogue that is twice as potent as **2** in vitro. Methoxy was therefore incorporated into the core structure during subsequent SAR investigation. Herein, we report on the optimization of this lead into a novel series of potent and selective mGluR5 antagonists with in vitro activity that are suitable for further evaluation of in vivo efficacy in rat (Fig. 1).

* Corresponding authors. Tel.: +1-858-202-5272; fax: +1-858-202-5752; e-mail: bowei_wang@merck.com

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2. Chemistry

The benzoxazole analogues were made either through a stepwise amide-coupling reaction followed by dehydration reaction or a one-pot reaction. The stepwise procedure, as shown in Scheme 1, entails conversion of 3-methoxy-4-methylbenzoic acid to its corresponding acyl chloride followed by coupling with 2-aminophenol to give compound **4**. PTSA catalyzed-dehydration of compound **4** gave benzoxazole **5**. NBS bromination of compound **5** and subsequent substitution of the benzyl bromide by sodium cyanide gave compound **7**.

Alternatively, a one-pot procedure was utilized to prepare compounds (**11a**, **11b**, **11c**) as shown in Scheme 2. Treatment of 4-hydroxy-3-methoxybenzoic acid with 2-aminophenol in the presence of trimethylsilylpolyphosphate gave benzoxazole **9**.[12] Conversion of the phenol group in **9** to its triflate followed by palladium-catalyzed coupling reactions with 2-pyridylzinc bromide, 3-pyridylboronic acid or 4-pyridylboronic acid to give compound **11a**, or **11b**, or **11c**, respectively.

The imidazole-fused analogues (**16a, 16b, 16c**) were prepared as outlined in Scheme 3. Conversion of 4-acetyl-2-methoxyphenol to its corresponding triflate followed by palladium-catalyzed coupling reaction with 2-pyridylzinc bromide gave compound **14**. Bromination of **14** and subsequent cyclization reaction with either 2-aminothiazole, 2-amino-2-thiazoline, or 2-aminopyridine gave compounds **16a**, or **16b,** or **16c**, respectively.

3. Results and discussion

Aryl benzoxazoles **2** and **7** were discovered to be potent mGluR5 antagonists with IC_{50} values of 6 and 3 nM, respectively (Table 1). However, these compounds were not suitable for in vivo studies because of poor solubility and poor pharmacokinetic properties in rat. For example, **2** has low oral bioavailability ($F = 0.7\%$) and a short half-life ($T_{1/2} = 0.6$ h) in rat. Based on in vitro human and rat liver microsomes metabolism studies, the major metabolic pathway is proposed to be as follows: the acetonitrile methylene undergoes metabolic oxidation to release cyanide and afford the aldehyde **18**, subsequent oxidation then yeilds the corresponding carboxylic acid **19** (Scheme 4) which was observed and identified by LC/MS/MS.

Consequently, our efforts were directed at optimization of **2** and **7** with an emphasis on improving solubility, oral bioavailability and half-life. In an attempt to improve the metabolic stability, replacement for the labile acetonitrile group were sought. Pyridyl groups were chosen for initial studies because they may increase

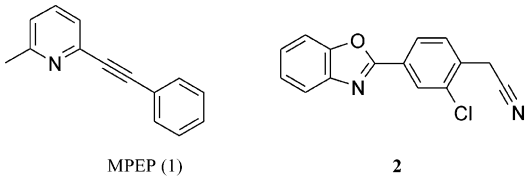
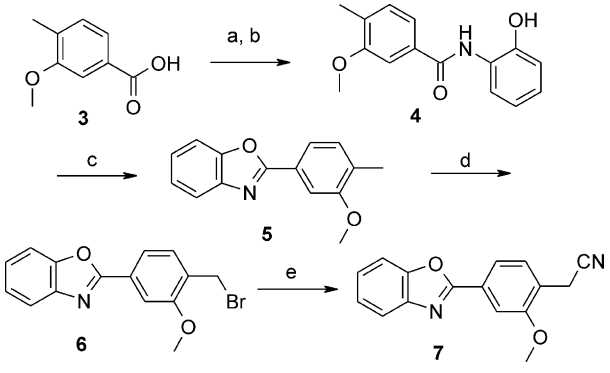
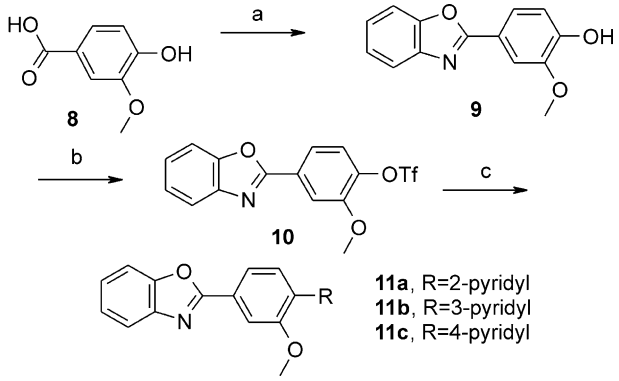


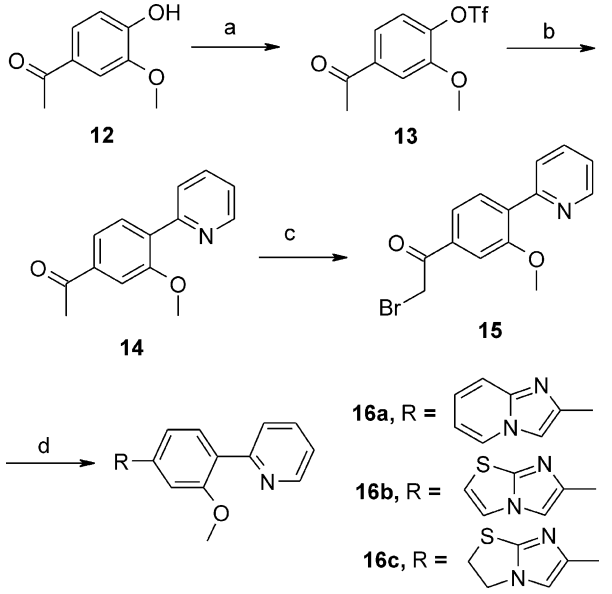
Figure 1. mGluR5 antagonists.



Scheme 1. Reagents: (a) $SOCl_2$; (b) 2-aminophenol, diisopropylethylamine, THF; (c) *p*-TsOH, toluene; (d) NBS, benzoyl peroxide, CCl_4; (e) NaCN, DMF.



Scheme 2. Reagents: (a) 2-aminophenol, trimethylsilylpolysphate; (b) Cs_2CO_3, *N*-phenyltrifluoromethanesulfonimide, DMF; (c) **11a**: 2-tri-*n*-butylstannylpyridine, $Pd(PPh_3)_4$, DMF; **11b**: 3-pyridylboronic acid, $Pd(PPh_3)_4$, K_2CO_3, *n*-Bu_4NBr, DMF/H_2O; **11c**: 4-pyridylboronic acid, $Pd(PPh_3)4$, K_2CO_3, *n*-Bu_4NBr, DMF/H_2O.

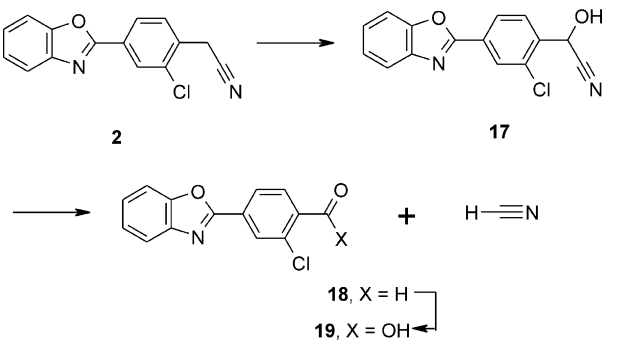


Scheme 3. Reagents: (a) Cs_2CO_3, *N*-phenyltrifluoromethane-sulfonimide, DMF; (b) 2-pyridyl zinc bromide, $Pd(PPh_3)_4$, THF; (c) Br_2, AcOH/HBr; (d) **16a**: 2-aminopyridine, EtOH; **16b**: 2-aminothiazole, EtOH; **16c**: 2-amino-2-thazoline, EtOH.

Table 1. In vitro data for mGlu5 receptor antagonists

Compd	mGlu5 Ca^{2+} flux IC_{50} (nM)[a]	K_i (nM)[b]
2	6	30
7	3	3
11a	41	159
11b	416	254
11c	IA[c]	IA[c]
16a	22	91
16b	23	94
16c	325	IA[c]

[a] Ca^{2+} flux assay using glutamate (10 μM) as agonist. Concentration-response curves were performed using 12 concentrations, performed in duplicate wells in two or more separate experiments.[5]
[b] Displacement by test compounds of [^{3}H]-3-methoxy-PEPy bound to rat cortical membranes.[13]
[c] IA denotes inactive at 2 μM concentration.



Scheme 4. Proposed major metabolite in rat PK study.

the solubility. Introduction of a 2-pyridyl group led to compound **11a** (Table 1) and this represents a significant improvement over **2**, with regard to the PK profile: $F = 100\%$ and $T_{1/2} = 1.5$ h. Further studies showed that this compound, however, has poor receptor occupancy (RO)[14] about 33% (IP). In addition, there were no observed in vivo effects in the Fear Potentiated startle (FPS)[15] rat model of anxiety, consistent with poor RO.

Interestingly the 3- and 4-pyridyl analogues (**11b** and **11c**, Table 1) were much less active than the 2-pyridyl compound **11a**. Further SAR studies showed that imidazopyridine, as in **16a** ($IC_{50} = 22$ nM) (Table 1), is an acceptable isostere for the benzoxazole moiety. Unfortunately, **16a** had a poor rat PK profile, and was not efficacious in the FPS rat model, again consistent with the low RO (Table 2). However the imidazothiazole derivative **16b**, which is equipotent with **16a** (Table 1), showed good bioavailability (91%), half-life (2.6 h) and acceptable RO (52%) (Table 2). Interestingly, compound **16c**, which has a saturated thiazole ring, is 10-fold less potent than the parent Compound **16a** (Table 1). Compounds **11a** and **16b** have been tested in a panel of animal models most notably in the FPS rat models. Although the compounds were potent against the receptor, brain penetrant, they did not show any efficacy. This is likely due to the poor receptor occupancy for the compounds. Efforts are currently being directed towards improving the RO for the series as well as potency.

Table 2. Rat pharmacokinetic and RO data for mGluR5 antagonists

Compd	F%[a]	$T_{1/2}$ (iv)[a]	Cl (mL/min/kg)[a]	RO (%)[b]	Brain levels (μM)[b]
2	0.7	0.6	74	NRO[c]	BLQ[d]
11a	100	1.5	70	33	3.1
16a	73	0.77	6	27	2.9
16b	91	2.6	7	52	6.8

[a] Dosed at 2 mg/kg iv and 10 mg/kg po.
[b] Dosed at 10 mg/kg ip.
[c] NRO denotes no receptor occupancy.
[d] BLQ denotes below low limit of quantitation (<20 nM).

4. Conclusion

In summary, a series of potent, bioavailable mGluR5 antagonists have been identified. Based on the in vitro and in vivo data generated to date, compounds **11a** and **16b** are being evaluated in a panel of further investigation in animal models of pain, anxiety and drug dependence.

5. Experimental

5.1. *N*-(2-Hydroxyphenyl)-3-methoxy-4-methylbenzamide (4)

3-Methoxy-4-methylbenzoic acid (**3**) (1.2 g, 7.2 mmol) and thionyl chloride (10 mL) was heated to reflux under Argon for 2 h. The cooled reaction mixture was concentrated in vacuo, and the resulting brown oil was dissolved in THF (15 mL) and slowly added to a cooled mixture of 2-aminophenol (780 mg, 7.1 mmol), diisopropylethylamine (1.5 mL, 8.6 mmol) and THF (20 mL) at 0 °C. The resulting reaction mixture was allowed to warm to rt, after 1 h the reaction mixture was concentrated in vacuo, and the resulting brown oil was purified by flash chromatography on silica gel, using 1:4 EtOAc/hexane, to afford compound **4** as a yellow solid (1.9 g, 100% yield). MS (ESI) 258 $(M+H)^+$.

5.2. 2-(3-Methoxy-4-methylphenyl)-1,3-benzoxazole (5)

A solution of **4** (1.5 g, 5.8 mmol) and *p*-toluenesulfonic acid monohydrate (7.6 g, 40 mmol) in toluene (30 mL) was refluxed overnight. The mixture was cooled to rt, filtered, washed with warm chloroform. The filtrate was concentrated in vacuo. The resulting brown oil was purified by flash chromatography on silica gel, using 1:4 EtOAc:hexane, to afford compound **5** as a colorless solid (690 mg, 50% yield). MS (ESI) 240 $(M+H)^+$.

5.3. 2-[4-(Bromomethyl)-3-methoxyphenyl]-1,3-benzoxazole (6)

A solution of compound **5** (1.0 g, 4.1 mmol), benzoyl peroxide (66 mg, 0.3 mmol) and *N*-bromosuccinimide (970 mg, 5.4 mmol) in carbon tetrachloride (18 mL) was heated to reflux conditions under argon and placed under a UV light for 1 h. The reaction mixture was cooled to rt, filtered, washed with dichoromethane. After concentrating the filtrate in vacuo, the resulting

colorless solid was purified by flash chromatography, using a gradient elution of 1:4 EtOAc/hexane to EtOAc, to afford compound **6** as a colorless solid (1.3 g, 100% yield). MS (ESI) 319 $(M+H)^+$.

5.4. 2-[4-(1,3-Benzoxazol-2-yl)-2-methoxyphenyl]acetonitrile (7)

A solution of **6** (318 mg, 1 mmol) in DMF (7.5 mL) and deionzed water (2.5 mL) was treated with sodium cyanide (150 mg, 3.0 mmol) at rt under argon for 3 h. DMF (10 mL) was added to help dissolve the solids, and the reaction mixture was stirred overnight at rt. Workup was done by washing reaction with satd brine (3×30 mL), extraction with EtOAc. The combined organic extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. Flash chromatography of resulting orange solid on silica gel, using a gradient elution of 1:9 EtOAc/hexane to 1:3 EtOAc/hexane, afforded the desired product **7** as a yellow solid (264 mg, 100% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.86–7.36 (m, 7H), 3.99 (s, 3H), 3.74 (s, 2H), 2.59−1.91 (m, 8H). MS (ESI) 265 $(M+H)^+$.

5.5. 4-(1,3-Benzoxazol-2-yl)-2-methoxyphenol (9)

3-Hydroperoxy-4-hydroxybenzoic acid (**8**) (25 g, 149 mmol) and 2-amino phenol (16.2 g, 149 mmol) were combined in a round bottom flask. Trimethylsilyl polyphosphate (80 mL) was added neat. The mixture was heated at 180 °C for 30 min. The mixture was poured over ice and allowed to stir overnight. The suspension was filtered to afford compound **9** as a pale green solid (31.4 g, 100% yield). MS (ESI) 242 $(M^+H)^+$.

5.6. 4-(1,3-Benzoxazol-2-yl)-2-methoxyphenyl trifluoromethanesulfonate (10)

A solution of **9** (7.1 g, 29.4 mmol) in anhydrous DMF (100 mL) was treated with Cs_2CO_3 (9.6 g, 29.4 mmol) and *N*-phenyl trifluoromethanesulfonimide (10.5 g, 29.4 mmol) at rt. After 30 min the reaction mixture was quenched with sat. $NaHCO_3$ (50 mL) and the product was extracted with EtOAc (500 mL). The EtOAc solution was washed with sat. brine (3×100 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was chromatographed on silica gel, using 1:4 EtOAc/hexane, to afford compound **10** as a colorless oil (10.8 g, 100% yield). MS (ESI) 374 $(M^+H)^+$.

5.7. 2-(3-Methoxy-4-pyridin-2-ylphenyl)-1,3-benzoxazole hydrochloride salt (11a)

A solution of **10** (11.7 g, 31.3 mmol) in anhydrous DMF (150 mL) was degassed via argon for 10 min. Then 2-tri-*n*-butylstannylpyridine (11.5 g, 31.3 mmol) and $Pd(Ph_3P)_4$ (3.6 g, 3.1 mmol) were added at rt. The resulting mixture was then heated at 100 °C for 1 h under Argon, cooled to rt and filtered through a pad of Celite. The filtrate was concentrated in vacuo after purification by flash chromatography on silica gel, using 1:3 EtOAc/hexane, to afford the desired compound as an off-colorless solid which was then dissolved in diethyl ether (200 mL) and precipitated as the hydrochloride salt upon treatment with 1 M HCl in diethyl ether (20 mL). The resulting colorless solid was then treated with EtOAc (1 L) and heated at refluxing. The reaction clear solution was cooled to rt, and the solid was collected by filtration to yield a colorless solid as the desired compound **11a** (3.3 g, 32% yield) (mp 215 °C) ^{1}H NMR (CD_3OD, 300MHz) δ 8.88 (m, 1H), 8.69 (m, 1H), 8.41 (d, 1H), 8.09 (m, 3H), 7.91 (d, 1H), 7.82 (m, 1H), 7.45 (m, 1H), 7.48 (m, 2H), 4.10 (s, 3H). MS (ESI) 303 $(M+H)^+$.

5.8. 2-(3-Methoxy-4-pyridin-3-ylphenyl)-1,3-benzoxazole (11b)

A solution of **10** (148 mg, 0.4 mmol) in 6mL of 2:1 DMF:H_2O (5 mL) was degassed via argon for 10 min. K_2CO_3 (137 mg, 0.99 mmol), $Pd(Ph_3P)_4$ (23 mg, 0.02 mmol), *n*-Bu_4NBr (128 g, 0.40 mmol) and 3-pyridylboronic acid (73 mg, 0.60 mmol) were added at rt. The resulting mixture was then heated at 75 °C for 1 h under argon. The reaction mixture was cooled to rt and filtered through a pad of Celite. The filtrate was concentrated in vacuo and purified by flash chromatography on silica gel, using 1:3 EtOAc/hexane, to afford compound **11b** as a yellow solid (35 mg, 29% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.83 (d, 1H), 8.60 (dd, 1H), 7.92 (m, 3H), 7.81 (m, 1H), 7.62 (m, 1H), 7.48 (d, 1H), 7.39 (m, 3H), 3.98 (s, 3H). MS (ESI) 303 $(M+H)^+$.

5.9. 2-(3-Methoxy-4-pyridin-3-ylphenyl)-1,3-benzoxazole (11c)

See **11b**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.68 (m, 2H), 7.95 (dd, 1H), 7.90 (m, 1H), 7.81 (m, 1H), 7.62 (m, 1H), 7.52 (m, 3H), 7.41 (m, 2H), 4.00 (s, 3H). MS (ESI) 303 (M^++H).

5.10. 4-Acetyl-2-methoxyphenyl trifluoromethanesulfonate acetovanillone (13)

Acetovanillone **12** (10 g, 0.06 mol), *N*-phenyltrifluoromethanesulfonimide (21.5 g, 0.06 mol) and Cs_2CO_3 (19.5 g, 0.06 mol) were dissolved in acetonitrile (90 mL) and DMF (10 mL). The resulting solution was then stirred at rt for 12 h, diluted with diethyl ether (100 mL) and was washed successively with satd Na_2CO_3 (100 mL) and sat. brine (100 mL). The organic layer was dried ($MgSO_4$), concentrated and purified by flash column chromatography on silica gel, using a gradient elution of 1:9 EtOAc/hexane to 3:7 EtOAc/hexane, to afford compound **13** as a colorless oil (17.9 g, 100% yield). MS (ESI) 299 $(M+H)^+$.

5.11. 1-(3-Methoxy-4-pyridin-2-ylphenyl)ethanone (14)

A solution of **13** (5.8 g, 19.5 mmol) in THF (100 mL) was degassed by bubbling Argon through the solution for 15 min, then treated with 2-pyridyl zinc bromide (3 mL of 0.5 M in THF, 19.5 mmol) and $Pd(PPh_3)_4$ (1.1 g, 0.97 mmol). The resulting reaction mixture was degassed for further 5 min and heated to reflux for 12 h under

Argon. The reaction mixture was cooled to rt and filtered through a pad of Celite. The filtrate was concentrated in vacuo, purified by flash chromatography on silica gel, using a gradient elution of 1:9 EtOAc/hexane to 2:3 EtOAc/hexane, to afford compound **14** as a white solid (4 g, 90.5% yield). MS (ESI) 228 $(M+H)^+$.

5.12. 2-Bromo-1-(3-methoxy-4-pyridin-2-ylphenyl)ethanone (15)

A solution of **14** (400 mg, 1.7 mmol) in benzene (6 mL) and 30% HBr/Acetic acid (6 mL) was cooled to 0 °C and was treated with a solution of bromine (0.086 mL, 1.67 mmol) in benzene (1 mL) over 1 h via syringe pump. The reaction was stirred for an additional 30 min, then poured into an iced solution of satd $NaHCO_3$ (100 mL), and the product was extracted into EtOAc (3×50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to afford compound **15** as a brownish oil (470 mg, 87.2% yield). MS (ESI) 307 $(M+H)^+$.

5.13. 2-(3-Methoxy-4-pyridin-2-ylphenyl)imidazo[1,2-*a*]-pyridine (16a)

Compound **15** (520 mg, 1.7 mmol) and 2-aminopyridine (160 mg, 1.7 mmol) in ethanol (10 mL) was heated to reflux for 12 h, then concentrated. The residue was dissolved in EtOAc (25 mL), washed with a solution of satd $NaHCO_3$ (25 mL), dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography on silica gel, using EtOAc to MeOH/EtOAc (1:19), to afford compound **16a** as a yellow solid (160 mg, 31.3% yield). ^1H NMR ($CDCl_3$, 300 MHz) δ 8.72 (d, 1H), 8.13 (d, 1H), 7.75 (s, 1H), 7.91 (d, 1H), 7.87 (d, 1H), 7.75 (s, 1H), 7.70 (dd, 1H), 7.66 (d, 1H), 7.57 (dd, 1H), 7.20 (m, 2H), 6.79 (dd, 1H), 4.00 (s, 3H) ppm. MS (ESI) 302 $(M)^+$.

5.14. 6-(3-Methoxy-4-pyridin-2-ylphenyl)imidazo[2,1-*b*]-[1,3]thiazole (16b)

See **16a**. 24.7%. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.73 (m, 1H), 7.92 (d, 1H), 7.89 (d, 1H), 7.86 (s, 1H), 7.73 (dt, 1H), 7.64 (s, 1H), 7.48 (s, 1H), 7.46 (d, 1H), 7.22 (m, 1H), 6.87 (d, 1H), 4.04 (s, 3H) ppm. MS (ESI) 308 $(M)^+$.

5.14.1. 6-(3-methoxy-4-pyridin-2-ylphenyl)-2,3-dihydroimidazo[2,1-*b*][1,3]thiazole (16c). See **16a**. 30% yield. ^1H NMR (CD_3OD, 300 MHz) δ 8.86 (d, 1H), 8.67 (t, 1H), 8.35 (d, 1H), 8.17 (s, 1H), 8.04 (m, 1H), 7.84 (m, 1H), 7.62 (s, 1H), 7.54 (m, 1H), 4.60 (m, 2H), 4.26 (m, 2H), 4.07 (s, 3H) ppm. MS (ESI) 310 $(M)^+$.

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