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3*N*-Methylbiphenylsulfonylurea and -Carbamate Substituted Imidazo[4,5-*b*]pyridines. Potent Antagonists of the ANG II AT_1 Receptors

Holger Heitsch,* Reinhard H. A. Becker, Heinz-Werner Kleemann and Adalbert Wagner
Hoechst AG, HMR TA Cardiovascular Agents, D-65926 Frankfurt/Main, Germany

Abstract—The synthesis and the SAR study of imidazo[4,5-*b*]pyridine biphenyl sulfonylureas and -carbamates as highly potent AT_1-selective ANG II receptor antagonists are described. Several members of this new class of antagonists efficiently inhibited the ANG II-induced pressor response in pithed rats after iv and intraduodenal (id) administration. © 1997 Elsevier Science Ltd.

Introduction

ACE-inhibition is a well established and eminently successful therapeutic strategy in the treatment of hypertension. Recently, the blockade of the AT_1 angiotensin II receptor subtype has also been identified as an alternative approach to interfere with the Renin Angiotensin Aldosterone System.[1]

The high efficacy both in vitro and in vivo of methylbiphenylsulfonylurea and -carbamate substituted imidazoles as potent, selective AT_1[2] or even balanced AT_1/AT_2[3] receptor antagonists has demonstrated that both the sulfonylurea and the sulfonylcarbamate function are powerful acidic surrogates of the tetrazole moiety found in most of the known antagonists.[4] Recently, Merck has delineated highly potent biphenyl-2′-tetrazoles[5] and biphenyl-2′-acylsulfonamide substituted imidazo-[4,5-*b*]pyridines.[6] We report here novel methylbiphenyl imidazo[4,5-*b*]pyridines with sulfonylurea and sulfonylcarbamate moieties as acidic groups, which possess high affinity to ANG II AT_1 receptors in vitro and in vivo.

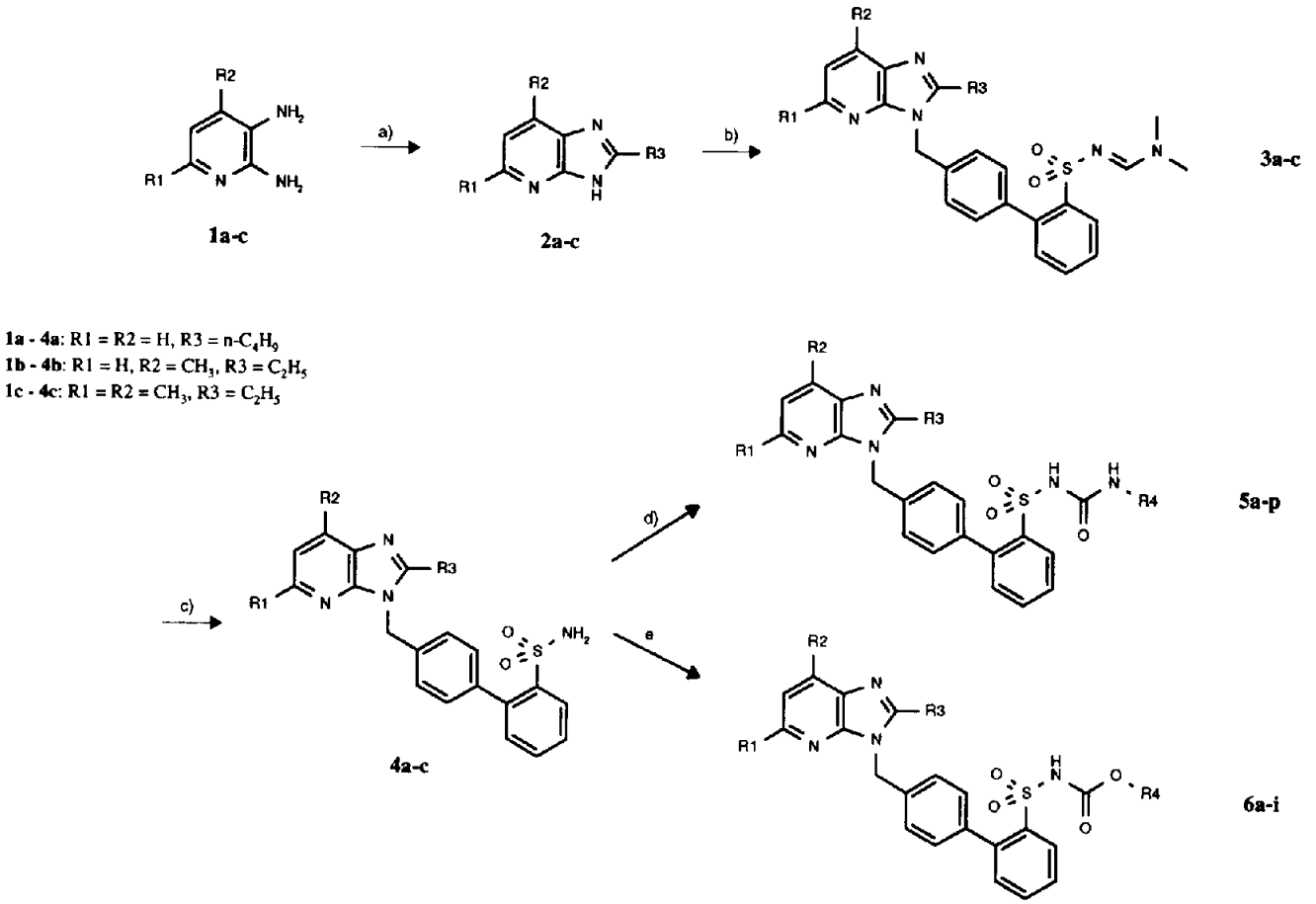
Results and Discussion

Syntheses

The synthesis of antagonists **5a–p** and **6a–i** listed in Tables 1 (ureas) and 2 (carbamates) follows the common convergent path via 3*N*-alkylation of the requisite imidazo[4,5-*b*]pyridines **2a–c** by 4′-bromomethyl-1,1′-biphenyl-2-[*N*-[(dimethylamino)-methylene]]-sulfonamide[2] as illustrated in Scheme 1. The desired imidazo[4,5-*b*]pyridines **2a–c** were obtained by condensation of the appropriate 2,3-diamino-pyridines **1a–c** with propionic or *n*-pentanoic acid in polyphosphoric acid.[5] Subsequent acid-catalysed deprotection of the amidines **3a–c** gave the corresponding sulfonamides **4a–c**, which were converted into the final antagonists **5a–p** and **6a–i** by application of a variety of methods depending on the targeted molecule and the nature of the reagents.[2] Thus, the ureas **5a–p** were derived from **4a–c** either by condensation with the requisite isocyanate, treatment of the corresponding ethyl sulfonylcarbamate intermediate with amines or by reaction with 2,2,2-trichloroacetamide derivatives. The carbamates **6a–i** resulted from **4a–c** either via reaction with the appropriate chloroformates, treatment with dimethyldicarbonate or condensation with phosgene and alcohols. The yields for each methodology are outlined in Tables 1 and 2.

Alternatively, the imidazo[4,5-*b*]pyridine **2c** was obtained by nitration of 2-amino-5-bromo-4,6-dimethylpyridine **8a** derived from bromination of **7** followed by isolation of the 10:1 favoured 5-bromo isomer (Scheme 2). The overall yield of this path was superior to those via immediate nitration of **7** without blockade of position 5, which yielded the 3/5-nitro isomers in a 1:1-ratio.[7] Subsequent catalytic hydrogenation of **9** by ammonium formate provided the desired diamine **1c** by simultaneous reduction of the nitro group and dehalogenation. This intermediate was then converted to imidazo[4,5-*b*]pyridine moiety **2c** as described above (Scheme 1).

In Scheme 3, an optional straight-forward access to 3*N*-substituted imidazo[4,5-*b*]pyridines is shown, which avoids the $N_1/N_3/N_4$-regioisomer formation arising from the alkylation step in the above-mentioned convergent approach (N_3/N_1 1:1 for **2a** using NaH, 7:1 for **2b** and 10:1 for **2c** using K_2CO_3). In this path the 2-amino group of **10** was first acylated and the obtained amide **11** was then alkylated with 4′-bromomethyl-1,1′-biphenyl-2-[*N*-[(dimethylamino)-methylene]-sulfonamide. Subsequent hydrogenation of **12** by ammonium formate in



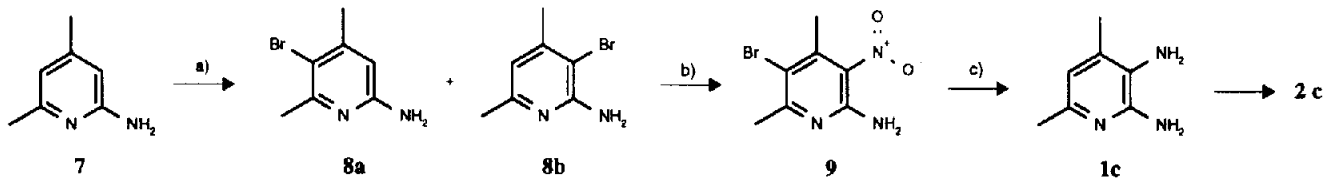
Scheme 1. (a) R^3CO_2H, PPA, 100 °C, 5 h, 62% (**2a**), 79% (**2b**), 69% (**2c**); (b) 4'-$BrCH_2$-1,1'-C_6H_4-C_6H_4-2-SO_2-$NCHN(CH_3)_2$, Cs_2CO_3, DMF, 24 h, rt, 45% (**3a**), 76% (**3b**), 85% (**3c**); (c) conc HCl, EtOH, reflux, 2 h, 48% (**4a**), 90% (**4b**), 72% (**4c**); (d) **Method 1**: R^4NCO, K_2CO_3, acetone, reflux, 3 h; **Method 2**: 1. $ClCO_2C_2H_5$, K_2CO_3, DME, reflux, 6 h; 2. H_2NR^4, toluene, reflux, 8 h; **Method 3**: 1. R^4NH_2, $ClCOCCl_3$, NEt_3, dioxane, 2 h, rt; 2. Cs_2CO_3, DMF, 80 °C, 1 h; (e) **Method 1**: $ClCO_2R^4$, K_2CO_3, DME, reflux, 6 h; **Method 2**: $O(CH_3OCO)_2$, K_2CO_3, DMAP, $(CH_3OC_2H_4)_2O$, reflux, 2 h; **Method 3**: 1. HOR^4, $COCl_2$, toluene, 2 h, rt; 2. pyridine, 20 h, rt.

refluxing ethanol finally gave the desired imidazo[4,5-*b*]pyridine derivative **3b** via reduction of the nitro group and dehydration/cyclization in a one-step procedure. The following steps towards **5c–h** and **6b–d** were performed analogously to the procedures described in Scheme 1.

In vitro and in vivo activity

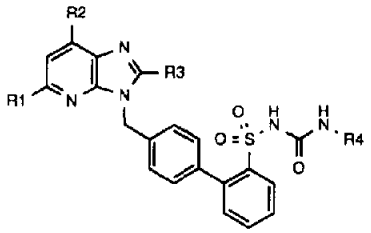
The in vitro potencies of the synthesized sulfonylureas and -carbamates in this series regarding their ability to displace [^{125}I]ANG II from AT_1 receptors in rat liver membrane preparations are listed in Tables 1 and 2, respectively. Selected compounds were further evaluated in vivo for their inhibition of the pressor response induced by exogenously administered ANG II in normotensive pithed rats after iv and intraduodenal (id) administration.

The in vitro affinity towards AT_1 receptors of all tested ureas was in the nanomolar or subnanomolar range. The influence of the chosen substituents on both the imidazo[4,5-*b*]pyridine and the biphenylsulfonylurea moiety on the activity was only moderate, which indicates that a large variety of residues are accepted at this site of the target receptor. The affinity of the parent sulfonylamides[8] was significantly lower than those of the unsubstituted sulfonylurea **5c**[9] and its alkylated homologous **5a,b,d–p**, which emphasizes the contribution of the urea substituents on the biphenyl moiety to the activity of the antagonists. The alteration



Scheme 2. (a) 1,3-Dibromo-5,5-dimethylhydantoine, CH_2Cl_2, −50 °C, 30 min, 92%, **8a**:**8b** = 10:1, separation by crystallization from ethyl acetate; (b) HNO_3/H_2SO_4, −10 °C — rt, 30 min, 95%; (c) $HCO_2^-NH_4^+$, Pd/C, MeOH, reflux, 4 h, 85%.

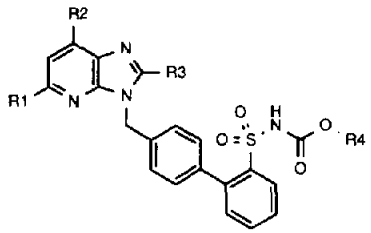
Table 1. Sulfonylureas



	R1	R2	R3	R4	Yield (%) (method)[a]	IC_{50}[b] (nM)	ED_{50} (μg/kg)[c] iv	id
5a	-H	-H	-n-C_4H_9	-$CH_2CH_2CH_3$	79 (2)	1.50	>100–<300	>1000
5b	-H	-H	-n-C_4H_9	-$CH(CH_3)_2$	64 (2)	5.50	ND[d]	ND[d]
5c	-H	-CH_3	-C_2H_5	-H	—[s]	12.00	ND[d]	ND[d]
5d	-H	-CH_3	-C_2H_5	-CH_3	63 (3)	1.80	>100–<300	ND[d]
5e	-H	-CH_3	-C_2H_5	-$CH_2CH_2CH_3$	71 (1)	0.52	<30	>100–<300
5f	-H	-CH_3	-C_2H_5	-$CH_2CH{=}CH_2$	94 (1)	0.43	15*	14*
5g	-H	-CH_3	-C_2H_5	—CH_2— 	52 (3)	0.59	>10–<30	ND[d]
5h	-H	-CH_3	-C_2H_5	-CH_2Ph	65 (1)	0.38	>10–<30	ND[d]
5i	-CH_3	-CH_3	-C_2H_5	-CH_3	53 (3)	2.20	>10–<30	<100
5j	-CH_3	-CH_3	-C_2H_5	-CH_2CH_3	58 (1)	1.70	>10–<30	<100
5k	-CH_3	-CH_3	-C_2H_5	-$CH_2CH_2CH_3$	61 (1)	1.20	>10–<30	<100
5l	-CH_3	-CH_3	-C_2H_5	-$CH_2CH{=}CH_2$	53 (1)	0.10	<10	≥30
5m	-CH_3	-CH_3	-C_2H_5	—CH_2— 	58 (3)	1.00	14*	12*
5n	-CH_3	-CH_3	-C_2H_5	-CH_2CH_2Ph	82 (2)	1.50	ND[d]	ND[d]
5o	-CH_3	-CH_3	-C_2H_5		73 (2)	5.90	>10–<30	>300
5p	-CH_3	-CH_3	-C_2H_5	-$CH_2CH_2OCH_2CH_2OH$	56 (2)	2.80	>1–<3	≈30

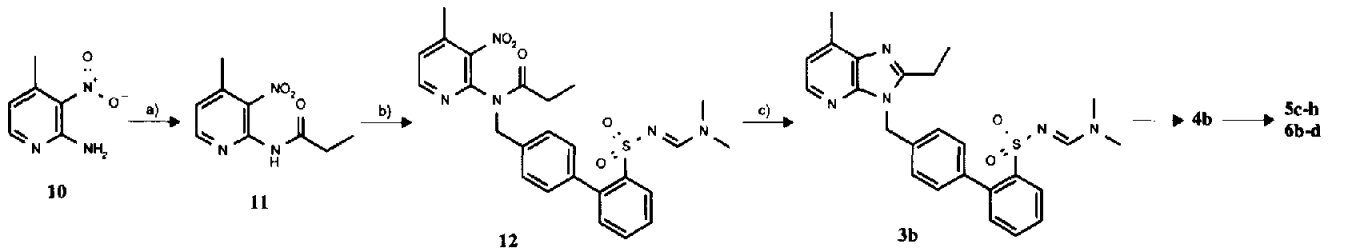
[a]Methods according to Scheme 1, step (d).
[b]IC_{50} for inhibition of specific binding of [^{125}I]ANG II to rat liver AT$_1$ membrane preparations (n = 13).
[c]ED_{50} for inhibition of pressor response induced by injection of 30 ng ANG II to pithed rats; iv after 10 min, id after 60 min; tested dose range: 1, 3, 10, 30, 100, 300 μg/kg iv and 10, 30, 100, 300, 1000 μg/kg id with two (or six*) rats per dose.
[d]Not determined.

Table 2. Sulfonylcarbamates



	R1	R2	R3	R4	Yield (%) (method)[a]	IC_{50}[b] (nM)	ED_{50} (μg/kg)[b] iv	id
6a	-H	-H	-n-C_4H_9	-CH_2CH_3	54 (1)	1.50	ND[b]	ND[b]
6b	-H	-CH_3	-C_2H_5	-CH_2CH_3	74 (1)	0.50	>10–<30	≈100
6c	-H	-CH_3	-C_2H_5	-$CH_2CH_2CH_3$	40 (1)	0.55	ND[b]	ND[b]
6d	-H	-CH_3	-C_2H_5	-CH_2Ph	83 (1)	1.00	ND[b]	ND[b]
6e	-CH_3	-CH_3	-C_2H_5	-CH_3	38 (2)	3.80	7*	19*
6f	-CH_3	-CH_3	-C_2H_5	-CH_2CH_3	28 (1)	0.62	<30	<100
6g	-CH_3	-CH_3	-C_2H_5	-$CH_2CH_2CH_3$	41 (1)	0.92	<30	<30
6h	-CH_3	-CH_3	-C_2H_5	—CH_2— 	35 (3)	1.40	>30–<100	≈30
6i	-CH_3	-CH_3	-C_2H_5	-CH_2Ph	42 (1)	2.10	>30–<100	<100

[a]Methods according to Scheme 1, step (e).
[b]See Table 1 for an explanation of tabulated data.



Scheme 3. (a) C_2H_5COCl, pyridine, DMF, reflux, 8 h, 76%; (b) 4′-BrCH$_2$-1,1′-C_6H_4-C_6H_4-2-$SO_2NCHN(CH_3)_2$, K_2CO_3, DMF, rt, 24 h, 69%; (c) HCO_2^- NH_4^+, Pd/C, EtOH, reflux, 6 h, 72%.

in activity is probably due to the different pK_a values of the less acidic NH function of the sulfonamides and those of **5c** and its substituted derivatives. This phenomenon has already been revealed in the corresponding imidazole series,[2] likewise the enhancement in receptor affinity of the sulfonylureas with an increase in the lipophilicity of the substituent on the urea nitrogen from hydrogen, methyl, ethyl, propyl to benzyl and allyl. Consequently, the allyl-substituted urea **5l** was the most active antagonist synthesized in this series exhibiting an IC_{50} value of 0.1 nM.

The in vivo activity of the prepared ureas increases slightly with the number of methyl groups on the imidazo[4,5-*b*]pyridine moiety with methyl groups in 5- and 7-position as the optimal substitution pattern. The iv and also the id efficacy of most of the antagonists with ED_{50} values between 10 and 30 µg/kg for iv and below 100 µg/kg for id administration was barely affected by the selected substituents on the urea nitrogen. Maximum in vivo potency with balanced inhibitory activity on iv and id administration was found for the allyl and for the cyclopropylmethyl-substituted ureas **5f** and **5m** with ED_{50} values of 15 and 14 µg/kg for **5f** and 14 and 12 µg/kg for **5m**, respectively.

Conclusion

In summary, new highly potent, nontetrazolyl AT_1 ANG II receptor antagonists were synthesized in which imidazo[4,5-*b*]pyridines were substituted with 3*N*-methylbiphenyl-2-sulfonylureas and -carbamates as powerful bioisosteres for the biphenyl moiety present in losartan. Besides their nano- and subnanomolar binding affinity to the AT_1 receptor subtype, which is only moderately affected by the respective substituents, selected compounds of this series exhibit an excellent in vivo potency when tested in normotensive pithed rats. In this animal model several compounds of this series, like **5f**, **5m** or **6e**, are significantly more potent than losartan[10] and their corresponding 4-thiomethyl imidazole homologues described recently.[2] The cyclopropylmethyl substituted 5,7-dimethyl-2-ethyl imidazo[4,5-*b*]pyridine biphenylsulfonylurea **5m** as the representative member of this series with an ED_{50} of 14 µg/kg on iv and 12 µg/kg on id administration and is one of the most active ANG II antagonists in vivo known to date.

Experimental

General

Solvents and other reagents were used without further purification unless otherwise stated. Column chromatography was carried out on E. Merck silica gel 60 (0.04–0.063 mm). The NMR spectra were recorded on a Bruker AM 270. Chemical shifts are reported as δ values from an internal tetramethylsilane standard. DCI mass spectra were measured on a Kratos MS 80 RFA using isobutane as reagent gas. Positive FAB mass spectra were obtained on a Kratos MS 902 in a 3-nitrobenzylic alcohol matrix using xenon as the target gas.

*The compounds **5a–p** and **6a–i** were synthesized according to Scheme 1. Illustrative synthetic procedures are given for the sulfonylurea **5m** and for the sulfonylcarbamate **6e** as representative examples of both series.*

5,7-Dimethyl-2-ethyl-imidazo[4,5-*b*]pyridine (2c).[5] To a solution of 2,3-diamino-4,6-dimethylpyridine **1c** (29.0 g, 0.21 mol) and polyphosphoric acid (340 mL) was added propionic acid (18.8 g, 0.25 mol) at 100 °C. The reaction mixture was stirred at 100 °C for 5 h. After cooling to 0 °C aqueous ammonia was added and the mixture was extracted with EtOAc. The combined organic layers were dried, the solvent was evaporated, and the remaining residue purified by chromatography using EtOAc:methanol (20:1) as eluent to provide **2c** (25.6 g, 69%) as a pale-yellow solid; mp 143 °C. ^{1}H NMR ($CDCl_3$) δ 1.44 (t, J = 7.0 Hz, 3H), 2.62 (s, 3H), 2.66 (s, 3H), 3.04 (q, 2H), 6.92 (s, 1H). MS (DCI) *m/z* 176 (M + H^+).

5,7-Dimethyl-3-[[2′-[(dimethylamino)-methylene]-aminosulfonyl][1,1′-biphenyl-4-yl]-methyl]-2-ethyl-imidazo[4,5-*b*]pyridine (3c). A mixture of **2c** (25.3 g, 0.14 mol), Cs_2CO_3 (45.6 g, 0.14 mol) and 4′-bromomethyl-1,1′-biphenyl-2-[*N*-(dimethylamino)-methylene]-sulfonamide[2] (53.3 g, 0.14 mol) in dry DMF (300 mL) was stirred at ambient temperature for 24 h. After removal of DMF, the residue was suspended in EtOAc, washed with water and brine, and concentrated. Recrystallization from EtOAc afforded **3c** (57.1 g, 85%); mp 193 °C. ^{1}H NMR ($CDCl_3$) δ 1.38 (t, J = 7.0 Hz, 3H), 2.54 (s, 3H), 2.65 (s, 3H), 2.68 (s, 3H), 2.71 (s, 3H), 2.85 (q, 2H), 5.50 (s, 2H), 6.90–7.50 (m, 9H), 8.28 (m, 1H). MS (FAB) *m/z* 476 (M + H^+).

3-[[2′-Aminosulfonyl][1,1′-biphenyl-4-yl]-methyl]-5,7-dimethyl-2-ethyl-imidazo[4,5-*b*]pyridine (4c). A mixture of

3c (5.0 g, 10.5 mmol), ethanol (40 mL), and concentrated HCl (10 mL) was refluxed for 2 h. After cooling, the solution was adjusted to pH 5 by using 2 N NaOH. Filtration of the resulting precipitates gave 3.2 g (72%) of **4c** as a yellow solid; mp 178 °C. ^{1}H NMR ($CDCl_3$) δ 1.36 (t, J = 8.0 Hz, 3H), 2.56 (s, 3H), 2.63 (s, 3H), 2.85 (q, 2H), 4.36 (br s, 2H), 5.53 (s, 2H), 6.90 (s, 1H), 7.20–7.60 (m, 7H), 8.14 (m, 1H). MS (FAB) m/z 421 (M + H$^+$).

3-[[2′-Cyclopropylmethylaminocarbonylamino-sulfonyl]-[1,1′-biphenyl-4-yl]-methyl]-5,7-dimethyl-2-ethyl-imidazo-[4,5-*b*]pyridine (5m). A mixture of **4c** (1.3 g, 3.1 mmol) and Cs_2CO_3 (2.0 g, 6.2 mmol) in dry DMF (60 mL) was heated to 80 °C under an argon atmosphere. At this temperature, 2,2,2-trichloro-*N*-cyclopropylmethylacetamide (0.7 g, 3.1 mmol; prepared from cyclopropylamine and trichloroacetyl chloride) was added, and stirring was continued for 1 h. The precipitate was removed by filtration and the filtrate diluted with EtOAc. The obtained solution was washed with diluted HCl, water and brine, dried, and concentrated under vacuum. Purification by chromatography using EtOAc:methanol (20:1) provided **5m** (0.9 g, 58%) as a white solid; mp 186–188 °C. ^{1}H NMR ($CDCl_3$) δ 0.10 (m, 2H), 0.38 (m, 2H), 0.75 (m, 1H), 1.35 (t, J = 8.0 Hz, 3H), 2.56 (s, 3H), 2.64 (s, 3H), 2.88 (m, 4H), 5.52 (s, 2H), 6.90 (s, 1H), 7.20–7.62 (m, 7H), 8.12 (m, 1H). MS (DCI) m/z 518 (M + H$^+$).

5,7-Dimethyl-2-ethyl-3-[[2′-methoxycarbonyl-aminosulfonyl][1,1′-biphenyl-4-yl]-methyl]-imidazo[4,5-*b*]pyridine (6e). To a mixture of **4c** (500.0 mg, 1.2 mmol), K_2CO_3 (330.0 mg, 2.4 mmol) and 4-dimethylaminopyridine (100 mg) in dry dimethoxyethane (70 mL) was added dimethyl dicarbonate (161.0 mg, 1.2 mmol) under an argon atmosphere. The mixture was refluxed for 2 h. After being cooled, the mixture was filtered and the filtrate diluted with water. The solution was adjusted to pH 5 with 2 N HCl, and extracted with EtOAc. The combined organic layers were washed with water and brine, dried, and concentrated. Chromatographic purification (EtOAc:heptane, 2:1) afforded 220.0 mg (38%) of **6e** as a white solid; mp 168–172 °C. ^{1}H NMR ($CDCl_3$) δ 1.38 (t, J = 7.5 Hz, 3H), 2.60 (s, 3H), 2.64 (s, 3H), 2.86 (q, 2H), 3.57 (s, 3H), 5.50 (s, 2H), 6.90 (s, 1H), 7.24 (m, 5H), 7.60 (m, 2H), 8.24 (m, 1H). MS (FAB) m/z 479 (M + H$^+$).

2-Ethylamido-4-methyl-3-nitropyridine (11). A solution of 2-amino-4-methyl-3-nitropyridine **10** (10.0 g, 65.3 mmol), propionic acid chloride (81.4 mL, 88.6 mmol) and dry pyridine (10.7 mL, 130.6 mmol) in dimethoxyethane (250 mL) was refluxed for 8 h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in water. After extraction with CH_2Cl_2, the combined organic layers were washed with brine, dried and evaporated. Chromatography using EtOAc:heptane (2:3) as eluent provided 10.4 g (76%) of **11** as a pale-yellow solid; mp 155 °C. ^{1}H NMR ($CDCl_3$) δ 1.05 (t, J = 7.5 Hz, 3H), 2.45 (s, 3H), 2.58 (q, 2H), 7.40 (m, 2H), 8.60 (m, 2H). MS (DCI) m/z 210 (M + H$^+$).

2-[[2′-[(Dimethylamino)methylene]-aminosulfonyl]-[1,1′-biphenyl-4-yl]methyl]-propionylamino-4-methyl-3-nitro-pyridine (12). A mixture of **11** (3.6 g, 17.3 mmol), 4′-bromomethyl-1,1′-biphenyl-2-[*N*-[(dimethylamino)-methylene]]-sulfonamide[2] (6.6 g, 17.3 mmol) and K_2CO_3 (2.4 g, 17.3 mmol) in dry DMF was stirred at rt for 24 h. The solvent was evaporated and the residue dissolved in CH_2Cl_2. The solution was washed with water, dried, and concentrated in vacuo. Purification by chromatography with EtOAc:heptan (9:1) as eluent yielded **12** (6.1 g, 69%) as a white foam. ^{1}H NMR ($CDCl_3$) δ 1.12 (t, J = 8.0 Hz, 3H), 2.15 (br m, 2H), 2.46 (s, 3H), 2.75 (s, 3H), 2.78 (s, 3H), 5.20 (s, 2H), 7.15–7.5 (m, 10H), 8.27 (m, 1H). MS (DCI) m/z 510 (M + H$^+$).

3-[[2′-[(Dimethylamino)methylene]-aminosulfonyl]-[1,1′-biphenyl-4-yl]methyl]-2-ethyl-7-methyl-imidazo-[4,5-*b*]pyridine (3b). A mixture of **12** (1.9 g, 3.80 mmol), ammonium formate (2.4 g, 38.0 mmol) and palladium (10%) on charcoal (30.0 mg) in ethanol (50 mL) was refluxed for 6 h. The catalyst was removed by filtration and the filtrate was evaporated to dryness. The obtained residue was taken up in CH_2Cl_2, the solution washed with water and brine, dried and evaporated. Chromatography using EtOAc as eluent afforded **3b** (1.30 g, 72%) as a pale-yellow solid; mp 160–162 °C. ^{1}H NMR ($CDCl_3$) δ 1.30 (t, J = 7.5 Hz, 3H), 2.72 (s, 3H), 2.78 (s, 3H), 3.03 (s, 3H), 3.10 (q, 2H), 5.56 (s, 2H), 7.05–7.5 (m, 11H), 8.24 (m, 2H). MS (FAB) m/z 462 (M + H$^+$).

2-Amino-5-bromo-4,6-dimethylpyridine (8a). 2-Amino-4,6-dimethylpyridine (50.0 g, 0.41 mol) was dissolved in CH_2Cl_2 (400 mL) and the solution cooled to −50 °C. At this temperature, 1,3-dibromo-5,5-dimethylhydantoine (58.5 g, 0.41 mol) was added and stirring continued at −50 °C for 30 min. After saturated aqueous Na_2CO_3-solution (400 mL) was added, the mixture was allowed to warm to room temperature. The organic layer separated, dried and evaporated. The residue was recrystallized from EtOAc to give 75.4 g (92%) of **8a** as a pale-brown solid; mp 108–110 °C. ^{1}H NMR ($CDCl_3$) δ 2.26 (s, 3H), 2.50 (s, 3H), 4.32 (br s, 2H), 6.25 (s, 1H). MS (DCI) m/z 201 (M + H$^+$).

2-Amino-5-bromo-4,6-dimethyl-3-nitropyridine (9). Into concentrated sulfuric acid (15 mL) **8a** (7.3 g, 36.5 mmol) was slowly introduced ($T \leq 50$ °C). After being cooled to −10 °C, a mixture of concentrated nitric acid (6.0 mL) and sulfuric acid (4.0 mL) was added. Stirring was continued for 30 min while the reaction mixture was allowed to warm at room temperature. The mixture was poured into water and the pH adjusted to 7 by using concentrated NH_4OH (22%). The resulting precipitate was collected by filtration, washed with water and dried under vacuum to provide 8.5 g (95 %) of **9** as a yellow solid; mp 160–162 °C. ^{1}H NMR ($CDCl_3$) δ 2.56 (s, 3H), 2.58 (s, 3H), 5.86 (br s, 2H). MS (DCI) m/z 246 (M + H$^+$).

2,3-Diamino-4,6-dimethylpyridine (1c).[5] To a suspension of **9** (8.2 g, 33.0 mmol) and ammonium formate (15.8 g, 0.25 mol) in methanol (70 mL) was added palladium (10%) on charcoal (850 mg). The mixture was refluxed for 4 h. After filtration the mixture was concentrated under vacuum and the residue was taken up in EtOAc. The solution was washed with a saturated aqueous solution of Na_2CO_3, brine and dried over $MgSO_4$, and then concentrated to yield 3.8 g of **1c** (85 %) as a white solid; mp 160–162 °C. ^1H NMR ($CDCl_3$) δ 2.13 (s, 3H), 2.30 (s, 3H), 3.10 (br s, 2H), 4.15 (br s, 3H), 6.38 (s, 1H). MS (DCI) *m/z* 138 ($M + H^+$).

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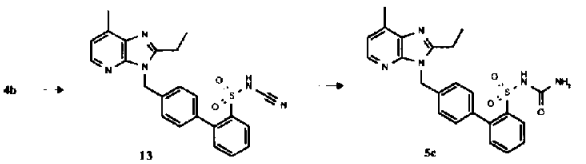
8. For example: IC_{50} (AT_1) = 79 nM for 3*N*-[[2′-(amino-sulfonyl)-(1,1′-biphenyl)-4-yl]-methyl]-5,7-dimethyl-2-ethyl-imidazo[4,5-*b*]pyridine.

9. Synthesized via the sulfonamidonitrile **13** obtained by treatment of **4b** with cyanogen bromine/K_2CO_3 in CH_3CN at reflux for 8 h followed by saponification with sulfuric acid at −10 °C (85% and 54% yield, respectively):



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