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Effects of the Pyridine 3-Substituent on Regioselectivity in the Nucleophilic Aromatic Substitution Reaction of 3-Substituted 2,6-Dichloropyridines with 1-Methylpiperazine Studied by a Chemical Design Strategy

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A chemical design strategy has been used to select 3-substituted 2,6-dichloropyridines for the nucleophilic aromatic substitution reaction with 1-methylpiperazine. The aim was to study the dependency of the regioselectivity in these reactions on the character of the pyridine 3-substituent expressed by their lipophilicity (PI), size (MR), and inductive effect (σ_p). Interestingly, the regioselectivity did not correlate with any of these parameters, but in a statistically significant manner with the Verloop steric parameter B1, as indicated by the p value of 0.006 ($R^2 = 0.45$). This implies that bulky 3-substituents close to the pyridine ring induce regioselectivity towards the 6-position. Useful in practical synthesis is the different regioselectivity obtained with a carboxylic acid 3-substituent and precursors or derivatives thereof. Thus, in acetonitrile as solvent, 3-carboxylate and 3-amide substituents were preferred to obtain the 2-isomer (9:1 ratio of the 6-isomer), whereas the 3-cyano and 3-trifluoromethyl substitutents were preferred to obtain the 6-isomer (9:1 ratio of the 2-isomer). Analysis of the regioselectivity R_{sel} for the pyridine 2-position in the reaction of 2,6-dichloro-3-(methoxycarbonyl)-pyridine with 1-methylpiperazine in 21 different solvents showed that R_{sel} could be predicted by the Kamlet–Taft equation: $R_{sel} = 1.28990 + 0.03992\alpha - 0.59417\beta - 0.46169\pi^*$ ($R^2 = 0.95$, $p = 1.9 \times 10^{-10}$). R_{sel} is thus mainly correlated with the ability of the solvent to function as a hydrogen-bond acceptor, as expressed by the solvatochromic β parameter. Thus, the 16:1 regioselectivity for the 2-isomer in DCM ($\beta = 0.10$) could be switched to a 2:1 selectivity for the 6-isomer in DMSO ($\beta = 0.76$).

Introduction

Understanding the underlying factors that govern reaction selectivity in organic synthesis is key to controlling reaction outcome. This enables improvements to reaction efficiency by minimizing side-reactions. One type of selectivity in organic reactions is regioselectivity. In a regioselective reaction, one direction of bond making or breaking occurs preferentially over all other possible directions.[1]

In 3-substituted 2,6-dichloropyridines, which are useful starting materials in organic synthesis,[2] the two carbon atoms neighboring the pyridine nitrogen atom are electrophilic. 2,6-Dichloropyridine derivatives that are monosubstituted at the 3-position are nonsymmetric and can thus form two different products when treated with a nucleophile (Nu) in a nucleophilic aromatic substitution (S_NAr) reaction (Scheme 1).

Of particular relevance for this study are reactions that employ amines as the nucleophile. The regioselectivity outcome of this S_NAr reaction has been reported in the literature for different combinations of 3-substituted 2,6-dichloropyridine, amine nucleophiles, and reaction conditions. However, no systematic approach to study how the regioselectivity in this reaction depends on the 3-substituent has previously been reported. Examples of reactions that are selective at the 2-position include the treatment of 2,6-dibromo-3-(trifluoroacetylamino)pyridine with benzylamine in the presence of 0.1 equiv. of CuI and 0.2 equiv. of L-proline in DMSO, which solely gave the 2-regioisomer.[3] Likewise, the 2-isomers were isolated as the sole products from the reaction of ammonia with 2,6-dichloro-3-(hydroxymethyl)pyridine[4,5] (in EtOH) and 2,6-dichloronicotinic acid[6,7] (in water); however, no further analysis of regioselectivity outcomes was provided. Also, the treatment of 2,6-dichloronicotinamides with amines has been reported to selectively give the 2-isomer, as exemplified by the reaction of phenethylamine with 2,6-dichloro-*N*-(2-phenoxyethyl)nicotinamide in THF.[8] The reactions of 2,6-dichloro-3-nitropyridine with ammonia in *i*PrOH,[9,10] methylamine in EtOH,[11] allylamine in DCM,[12] diethylamine in MeCN,[13] iBuNH$_2$, tBuCH$_2$NH$_2$, or iPrSO$_2$NH$_2$ in

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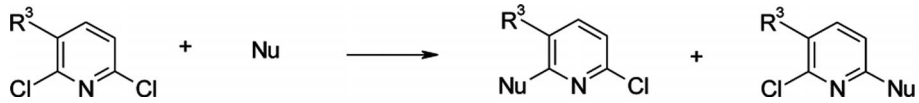


Scheme 1. Reaction of a 3-substituted 2,6-dichloropyridine with a nucleophile.

EtOH,[14] 4-(ethoxycarbonyl)-1-piperazine in $CHCl_3$,[15] or *N*-(*tert*-butoxycarbonyl)aniline in DMF[16] gave primarily or solely the 2-isomer. Hirokawa et al.[17] reported that the reaction of methyl 2,6-dichloronicotinate with methylamine gave moderate selectivity for the 2-isomer (49:12 in THF at 5 °C), whereas the reaction with benzylamine increased the selectivity for the 2-isomer (86:14 in THF at –20 °C).

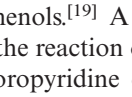
With 2,6-dichloro-3-(trifluoromethyl)pyridine, the regioselectivity was biased towards the 6-isomer; thus, treatment with methylamine in EtOH gave the 2- and 6-isomers in a 1:4 ratio, whereas treatment with the sterically more demanding dibenzylamine in *N*-methyl-2-pyrrolidone gave solely the 6-isomer.[18] DABCO reacted selectively at the 6-position of methyl 2,6-dichloronicotinate in [D_7]DMF or THF to form a reactive intermediate that was subsequently treated with phenols.[19] A number of other reports[20–22] have described the reaction of N-nucleophiles with 3-substituted 2,6-dichloropyridine derivatives without mentioning the regiochemical outcome.

Given the differences in nucleophiles and reaction conditions, including solvents, it was difficult to draw general conclusions from these literature reports about the factors that control the regioselectivity.

In this paper, the factors that govern the regioselectivity in the S_NAr reactions of 3-substituted 2,6-dichloropyridines with 1-methylpiperazine have been studied by a chemical design strategy. To make this type of comparative study it was necessary to apply the general assumption for S_NAr reactions,[23] that is, that the rate-determining step in all reactions is the initial attack of the nucleophile at the 2- or 6-position of the electrophile. Three parameters that express different aspects of the character of the pyridine 3-substituent (R^3) were varied systematically: lipophilicity (PI), size (MR = molar refraction), and inductive effect (σ_p).[24] Although the size and inductive effects are usual in this context, it was decided also to include the lipophilicity as a way to represent and study the effect of the polar character of the 3-substituent. Values for the molar refraction (MR) were available for more relevant substituents than were, for example, Taft's steric constants (E_s)[25] or Charton's steric constants (ν),[26] and MR was thus used as the size/steric parameter of the 3-substituent. Although MR values do not distinguish between substituents that have steric bulk close to or remote from the pyridine ring, the substituents selected are comparatively small and for these reasons MR was considered a reasonable size parameter for this study. The inductive effect is represented by the σ_p parameter. Although σ_p does not take into consideration the resonance effects, which are possible for some 3-substituents, these were assumed to be similar for reactions at the 2- (*ortho* to the 3-substituent) and 6-positions (*para* to the 3-substituent).

Each value of PI, MR, and σ_p were categorized as low (L), medium (M), or high (H). This gave a three-letter code to each starting material, for example, LLH. The starting materials **1**–**8** (Table 1) included the eight possible combinations of the extreme (either low or high) values of the three variables. Seven other starting materials **9**–**14** included at least one medium value, and secondary amine **15** was included to facilitate comparison with primary amine **1** and tertiary amine **4**. The 15 starting materials were selected with consideration given to synthetic feasibility and the chemical stability of the starting materials.

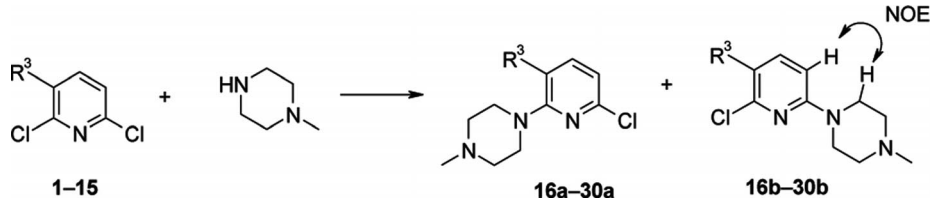
Table 1. Chemical design of the starting materials with variation of lipophilicity (PI), size (MR), and inductive effect (σ_p).

	 R^3 =	PI	MR	σ_p	Letter code[a]
1	NH_2	–1.23	5.4	–0.66	LLL
2	CH_3	0.56	5.67	–0.17	HLL
3	*p*-$(H_3C)_2NC_6H_4$	2.06	39.9	–0.56	HHL
4	morpholino	–0.77	24.6	–0.50	LHL
5	CN	–0.57	6.3	0.66	LLH
6	CF_3	0.88	5.0	0.54	HLH
7	COOPh	1.46	30.2	0.44	HHH
8	$SO_2N(CH_3)_2$	–0.78	21.9	0.65	LHH
9	$COOCH_3$	–0.01	12.9	0.45	MMH
10	OCH_2CH_3	0.38	12.5	–0.24	MML
11	COO^-	–4.36	6.0	0	LLM
12	$CONH_2$	–1.49	9.8	0.36	LMH
13	Br	0.86	8.9	0.23	HMH
14	SCH_2CH_3	1.06	18.1	0.03	HHM
15	NHPh	1.37	30.0	–0.56	HHL

[a] The letter code represents the combination PI, MR, and σ_p, with each value being L = low, M = medium, or H = high.

Reactions of the starting materials **1**–**15** (Scheme 2) with 1-methylpiperazine (MP) produced the 2-MP regioisomers **16a**–**30a** and the 6-MP regioisomers **16b**–**30b**, such that compound **1** gave **16a** and **16b**, compound **2** gave **17a** and **17b** etc.

The regioselectivity R_{sel} was determined by ^1H NMR spectroscopy as the ratio between the integral of the two aromatic pyridine hydrogen atoms in the 2-isomer and the total integral of the four aromatic pyridine hydrogen atoms in the 2- and 6-isomers. Thus, R_{sel} = 0.5 signifies a reaction with no regioselectivity. To determine R_{sel} reliably, it was important that no byproducts were formed in the reactions. In particular, in reactions of some of the reactive starting materials it was difficult to completely avoid the formation of the 2,6-bis-MP addition product. This could form from either the 2-MP- or 6-MP-monosubstituted product; however, the reaction of 1-methylpiperazine with either of these compounds might have different rate constants. Thus, to ensure that R_{sel} was determined correctly, reaction condi-



Scheme 2. Reactions of 3-substituted 2,6-dichloropyridines **1**–**15** with 1-methylpiperazine (MP) to give 2-MP-pyridines **16a**–**30a** and 6-MP-pyridines **16b**–**30b**.

tions were chosen such that the formation of the 2,6-bis-MP addition product was kept below 4% of the total product. In general, the pyridine hydrogen atoms in the ^{1}H NMR spectra of the reaction mixtures appeared as two sets of signals (three if starting material remained), as confirmed by ^{1}H COSY. In most cases, both regioisomers could be isolated by chromatography and characterized. Only in the 6-MP regioisomers (Scheme 2) could the NOE between the pyridine 5-hydrogen and hydrogen atoms in MP be observed, and this was used as a diagnostic tool to identify the 6-MP regioisomers.

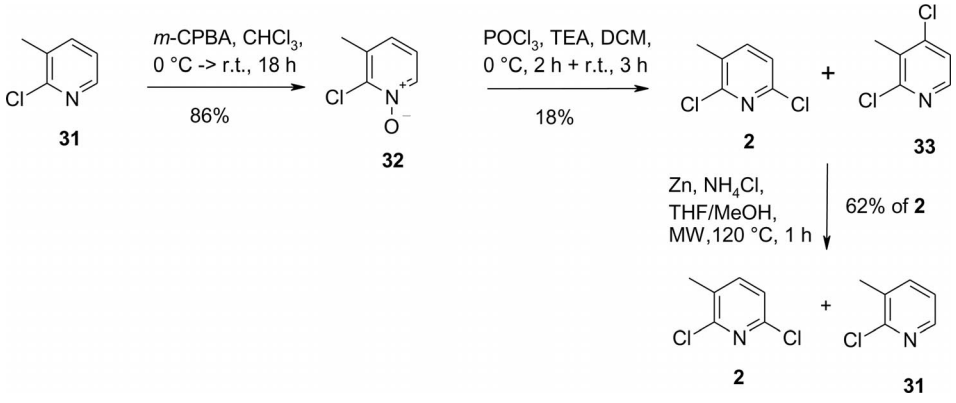
The spectra of the pure regioisomers were compared with the spectra of the reaction mixtures, and thus R_{sel} could be determined. In some cases, regioisomers were formed in very uneven ratios, and only one regioisomer could be isolated. In these cases, LC–MS of the reaction mixtures was used to establish that a pair of isomers with identical masses had formed (and not one isomer and one byproduct), and the ^{1}H NMR spectrum of the minor product was determined from the ^{1}H NMR spectrum of the product mixture.

The two 3-carboxy regioisomers formed from the reaction of 3-carboxy-2,6-dichloropyridine (**11**) with 1-methylpiperazine could not be separated by chromatography. Instead, reference samples for these two products were obtained by hydrolysis of the separated 3-methoxycarbonyl regioisomers obtained from the reaction of **9** with 1-methylpiperazine.

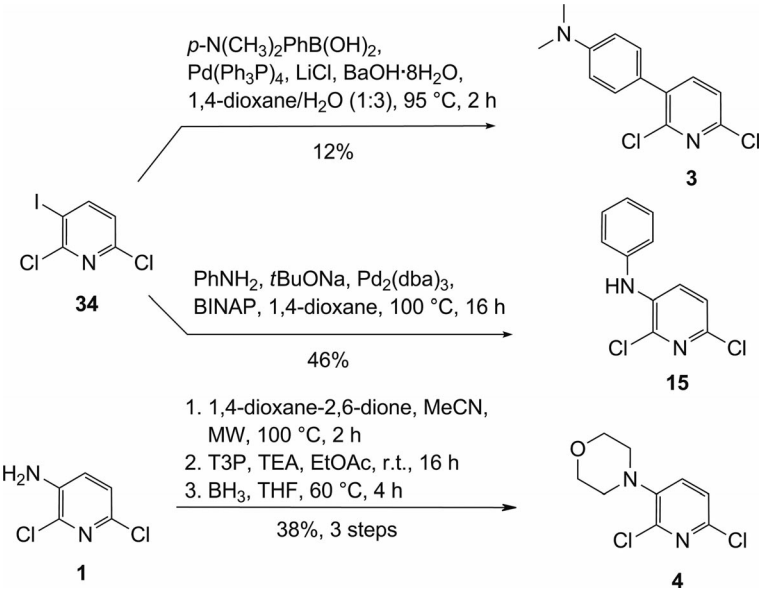
We hypothesized that a hydrogen-bond-accepting 3-substituent could form hydrogen bonds with 1-methylpiperazine and thus direct the addition of 1-methylpiperazine to the 2-position. The bias for the formation of a hydrogen bond to 1-methylpiperazine would depend on the type of solvent, because a hydrogen-bond-accepting solvent could compete with the 3-substituent for hydrogen bonding to 1-methylpiperazine. In the starting materials **1**–**15**, a number of the 3-substituents were hydrogen-bonding acceptors. For example, the 3-methoxycarbonyl substituent in compound **9** has this ability. To study any such effect of the solvent, compound **9** was treated with 1-methylpiperazine in 21 different and separate solvents. These were selected based on differences in, for example, polarity, hydrogen-bond-donating and -accepting ability, molecular dipolar momentum μ, and relative static permittivity (dielectric constant) ε.

Results and Discussion

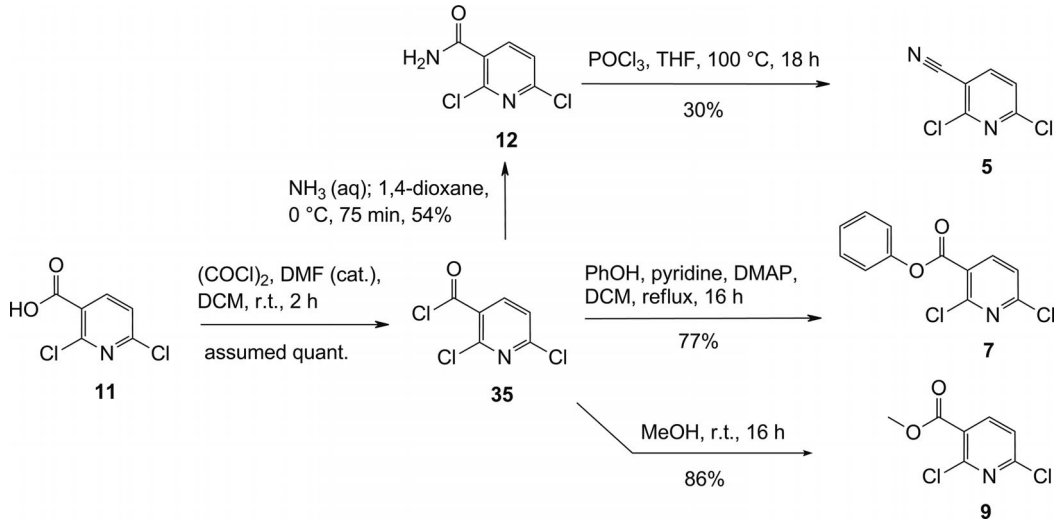
Oxidation of 2-chloro-3-methylpyridine (**31**; Scheme 3) to *N*-oxide **32** followed by chlorination provided a 6:1 mixture of 3-methyl-2,6-dichloropyridine (**2**) and byproduct 2,4-dichloro-3-methylpyridine (**33**); however, separation of the products by chromatography was not possible.[27] Treatment of the mixture with Zn selectively reduced the 4-chlorine atom of byproduct **33** to give **31**, and compound **2** could be separated from **31** by chromatography.



Scheme 3. Synthesis of an inseparable mixture of 2,6- and 2,4-dichloro-3-methylpyridine isomers **2** and **33** followed by selective reduction of 4-Cl of byproduct **33**.



Scheme 4. Derivatization of 3-iodo compound **34** to provide **3** and **13** and conversion of the 3-amino compound **1** to provide **4**.



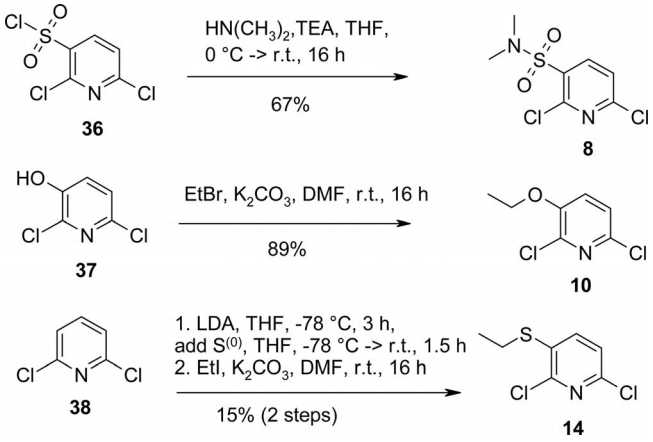
Scheme 5. Derivatization of 2,6-dichloronicotinic acid (**11**) to give primary amide **12**, nitrile **5**, phenyl ester **7**, and methyl ester **9**.

3-Iodo-2,6-dichloropyridine (**34**; Scheme 4) was employed in Suzuki[28] and Buchwald–Hartwig[29] reactions to produce **3** and **15**, respectively. 2,6-Dichloro-3-morpholinopyridine (**4**) was synthesized by a three-step procedure from **1**.

The conversion of 2,6-dichloronicotinic acid (**11**; Scheme 5) into acyl chloride **35**[30] followed by treatment with aqueous ammonia produced primary amide **12**. Subsequent dehydration provided 2,6-dichloronicotinonitrile (**5**). Reaction of **35** with phenol or methanol gave esters **7** and **9**,[31] respectively.

Compounds **8**, **10**, and **14** were prepared as outlined in Scheme 6. *N*,*N*-Dimethylsulfonamide **8** was prepared by treatment of commercial sulfonyl chloride **36** with dimethylamine. 3-Hydroxy compound **37**, prepared by the method of Voisin et al.,[32] was *O*-ethylated with ethyl bromide to provide compound **10**. Deprotonation of 2,6-dichloropyridine (**38**) with LDA[33] followed by reaction with elemental sulfur gave a mixture of thiols that was ethylated swiftly to avoid disulfide formation and provided **14**.

The results of the reactions, in relation to the regioselectivity, of the starting materials **1**–**15** with 1-methylpiperazine are shown in Table 2. Single variable data analysis of this set of data did not reveal any significant correlations (as defined by the statistical standard of the p value < 0.05) between the regioselectivity R_{sel} and each of the parameters PI, MR, and σ_p used in the chemical design strategy, as shown in Figure 1. Despite the paucity of observations ($N = 15$), an attempt was made to combine the different descriptors (PI, MR, and σ_p) in a multiple linear regression model as a way to predict R_{sel} and explain its variance in more detail. Here, all the possible combinations up to two



Scheme 6. Synthesis of sulfonamide **8**, ethyl ether **10**, and ethyl thioether **14**.

molecular descriptors were evaluated by using least-squares fitting to R_{sel}. Unfortunately, no linear combination of descriptors yielded a significant correlation with the regioselectivity R_{sel}.

Table 2. Verloop steric parameters B1 for the 3-substituents and regioselectivity R_{sel} for the 2-isomer in the reaction of 3-substituted 2,6-dichloropyridines with 1-methylpiperazine.

	3-Substituent	B1	2-isomer	6-isomer	Reaction conditions[a] (a) R_{sel}	(b) R_{sel}	(c) R_{sel}
1	NH_2	1.65	**16a**	**16b**	–	0.96	–
2	CH_3	1.7	**17a**	**17b**	0.52	0.26	–
3	p-$(H_3C)_2NC_6H_4$	1.65	**18a**	**18b**	–	0.17	–
4	morpholino	1.76	**19a**	**19b**	–	0.43	–
5	CN	1.7	**20a**	**20b**	0.11		0.15
6	CF_3	2.1	**21a**	**21b**	0.09		0.02
7	COOPh	2.03	**22a**	**22b**	0.67		0.40
8	$SO_2N(CH_3)_2$	1.95	**23a**	**23b**	0.37		0.20
9	$COOCH_3$	1.74	**24a**	**24b**	0.75		0.56
10	OCH_2CH_3	1.42	**25a**	**25b**	–	0.96	–
11	COO^-	1.7	**26a**	**26b**	0.95	0.93	–
12	$CONH_2$	1.7	**27a**	**27b**	0.91	0.94	–
13	Br	1.82	**28a**	**28b**	0.75	0.66	–
14	SCH_2CH_3	1.85	**29a**	**29b**	0.42	0.26	–
15	NHPh	1.85	**30a**	**30b**	–	0.71	–

[a] Reaction conditions (a)–(c): (a) 0.1 M in MeCN, 1.0 equiv. of 1-methylpiperazine, 3.0 equiv. of DIPEA, stirring at room temp. or heating in a microwave oven; (b) 0.1 M in neat 1-methylpiperazine (54 equiv.), heating in a microwave oven; (c) 0.1 M in neat 1-methylpiperazine (54 equiv.), 0 °C, 20–30 s, then quench with excess HCOOH.

However, further investigations employing a variety of 2D- and 3D-based descriptors[34] highlighted the fact that the regioselectivity R_{sel} is correlated with the Verloop steric parameter B1 (R^2 = 0.45).[35] Because B1 describes the smallest width of the 3-substituent, as measured perpendicular to the axis of the bond between the first atom of the substituent and the parent molecule, this implies that 3-substituents with steric bulk in proximity to the pyridine ring would steer regioselectivity towards the 6-position. Interestingly, this effect was not captured by other steric descriptors normally employed, such as Taft's or Charton's steric constants. The regioselectivity is thus governed by a steric factor, and no statistically significant effects from the lipophilicity or the inductive effect of the 3-substituent was identified by this chemical design strategy with the present set of compounds.

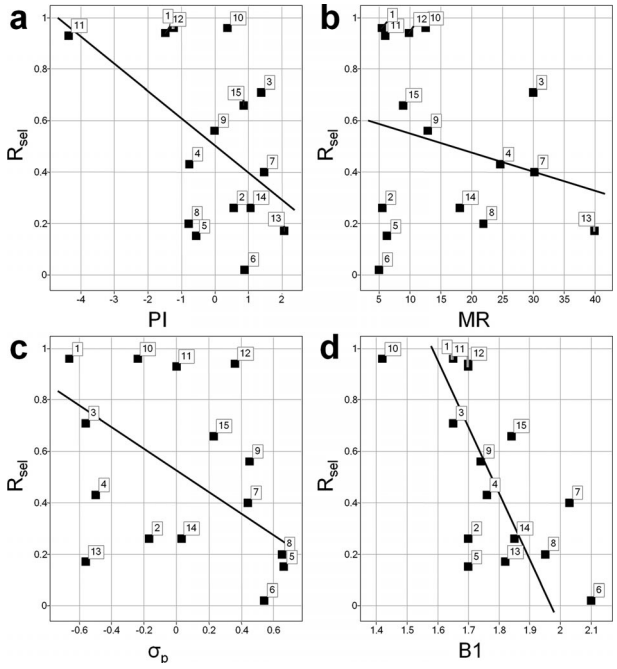


Figure 1. Relationship between the regioselectivity R_{sel} for the 2-position and selected parameters describing (a) lipophilicity (PI, R^2 = 0.24, p = 0.06), (b) size (MR, R^2 = 0.06, p = 0.37), and (c) inductive effect (σ_p, R^2 = 0.13, p = 0.18), and (d) steric bulk in proximity to the pyridine 3-substituent (Verloop parameter B1, R^2 = 0.45, p = 0.006). Labels indicate compound numbers of the starting materials.

Group and pairwise comparisons led to some interesting observations that could be useful in the planning of synthetic strategies. Particularly interesting in synthesis would be a carboxylic acid or derivative thereof as substituent at the pyridine 3-position due to their possible interconversion and synthetic versatility. Thus, to obtain the 2-isomer (9:1 ratio with the 6-isomer), 3-carboxylate (**11**) and 3-amide (**12**) substituents were preferred, whereas to obtain the 6-isomer (9:1 ratio with the 2-isomer) the 3-cyano (**5**) and 3-trifluoromethyl (**6**) substituents were preferred. To obtain high regioselectivity, these substituents were preferred to 3-methyl (**2**), 3-phenoxycarbonyl (**7**), and 3-methoxycarbonyl (**9**) substituents, of which the 3-methoxycarbonyl gave the highest (3:1) selectivity for the 2-isomer. The 3-amino (**1**) substituent gave a high (R_{sel} = 0.96) selectivity for the 2-isomer; however, to avoid prolonged heating at high temperatures, an electron-withdrawing 3-substituent is usually preferred in synthesis. With substituted 3-amines the selectivity for the 2-position decreased significantly, as observed with 3-phenylamino (**15**, R_{sel} = 0.71) and 3-morpholino (**4**, R_{sel} = 0.43). Although this comparison indicates a steric

Table 3.[37] Solvent effect on the regioselectivity R_{sel} for the 2-position in the reaction of methyl 2,6-dichloronicotinate (**9**) with 1-methylpiperazine.[a]

	Solvent	R_{sel}	Unreacted **9** [%][b]	Reaction time [h]	β	α	π^*	B.p. [°C]	DN
S1	DMSO	0.34	0	20	0.76	0	1	189	29.8
S2	DMF	0.47	0	20	0.69	0	0.88	153	26.6
S3	MeCN	0.74	< 1	20	0.40	0.19	0.75	81	14.1
S4	acetone	0.72	< 1	20	0.43	0.08	0.71	56	17.0
S5	*N*-methylpyrrolidone	0.40	< 1	20	0.77	0	0.92	203	27.3
S6	1,2-DCE	0.91	< 1	20	0	0	0.81	84	0
S7	CH_3NO_2	0.82	1	20	0.06	0.22	0.85	101	2.7
S8	DCM	0.93	6	20	0.10	0.13	0.82	40	1.0
S9	THF	0.78	21	20	0.55	0	0.58	66	20.0
S10	$O=P(OEt)_3$	0.44	14	4	0.77	0	0.72	215	26.0
S11	*N*-methylimidazole	0.32	5	4	0.82	0	–	198	–
S12	triethylamine	0.82	0	20	0.71	0	0.14	89	61.0
S13	pyridine	0.57	3	20	0.64	0	0.87	115	33.1
S14	DMA	0.39	5	4	0.76	0	0.88	165	27.8
S15	*N*-methylformamide	0.48	7	4	0.80	0.62	0.90	199	27.0
S16	EtOAc	0.81	11	20	0.45	0	0.55	77	17.1
S17	1,4-dioxane	0.80	5	20	0.37	0	0.55	101	14.3
S18	tetramethylurea	0.43	5	4	0.80	0	0.83	177	29.6
S19	1,2-DME	0.73	10	20	0.41	0	0.53	84	20.0
S20	toluene	0.94	30	20	0.11	0	0.54	111	1
S21	MeOH	0.62	13	20	0.66	0.98	0.60	65	30.0

[a] Reaction conditions: 0.1 M solution of **9**, 1.0 equiv. of 1-methylpiperazine, and 3.0 equiv. of DIPEA, room temp., 4 or 20 h. [b] Determined as percentage of the total ^{1}H NMR intensity of **9**, 2-isomer **24a**, and 6-isomer **24b** in the aromatic region.

effect of the 3-substituent, the Verloop B1 values would suggest the steric effect of 3-phenylamino (B1 = 1.85) to be higher than that of 3-morpholino (B1 = 1.76). The high selectivity for the 2-isomer (R_{sel} = 0.96) of the 3-ethoxy compound (**10**) compared with the moderate selectivity for the 6-isomer (R_{sel} = 0.26) of the analogous 3-ethylthio compound (**14**) is in line with their values of B1 (1.42 for ethoxy vs. 1.85 for ethylthio).

For a given starting material, it appears that the regioselectivity for the pyridine 2-position was slightly higher in acetonitrile than in 1-methylpiperazine [Table 2, compare conditions (a) with (b) or (c)] as the reaction medium. Consequently, it was decided to investigate whether this apparent solvent effect could be utilized to increase the regioselectivity for either the 2- or 6-isomer. 3-Methoxycarbonyl compound **9**, which had shown only a moderate 3:1 selectivity for the 2-isomer when allowed to react in acetonitrile, was selected for this study. Thus, **9** was treated with 1-methylpiperazine in 21 different solvents; the results are listed in Table 3.[36]

Data analysis based on the parameters in Table 3 showed that the regioselectivity R_{sel} is linearly correlated with the solvatochromic parameter β (R^2 = 0.75, $p = 4.6 \times 10^{-7}$; see Figure 2).[38] R_{sel} is also linearly correlated with the boiling point b.p. (R^2 = 0.72) and Gutmann's donor number DN (R^2 = 0.68); however, both b.p. and DN are cross-correlated with β (R^2 = 0.46 and R^2 = 0.68, respectively). A combination of α, β, and π^* in a linear free-energy relationship, as originally described by Kamlet and Taft,[37c] yielded accurate predictions of R_{sel} (RMSE = 0.047, R^2 = 0.95, $p = 1.9 \times 10^{-10}$), in line with the added mathematical complexity, as summarized in Figure 3.

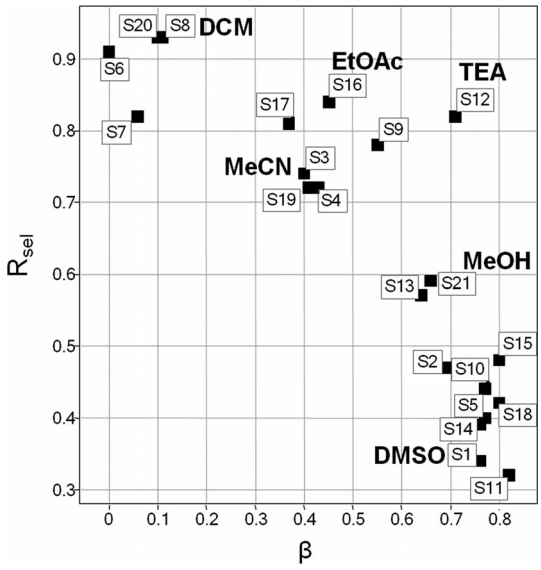


Figure 2. Regioselectivity R_{sel} for the pyridine 2-position as a function of the solvatochromic β parameter in the reaction of methyl 2,6-dichloronicotinate (**9**) with 1-methylpiperazine in 21 different solvents (S1–S21). Labels indicate solvent numbers. Selected solvents frequently used in synthesis are highlighted.

For the planning of syntheses it is noteworthy that the regioselectivity could be controlled by choosing a solvent with a high or low β parameter. Thus, the highest selectivity (16:1) for the 2-isomer (R_{sel} = 0.93–0.94) was obtained in solvents such as 1,2-DCE and DCM with low β parameters. By the same reasoning, the highest selectivity (2:1) for the 6-isomer (R_{sel} = 0.32–0.34) was obtained in solvents such

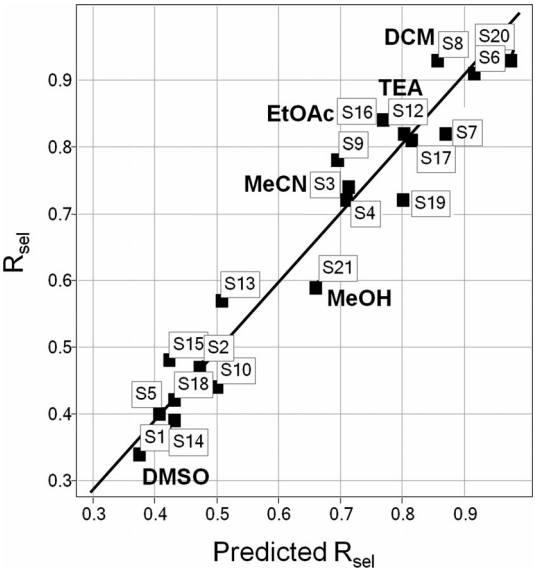


Figure 3. Prediction of the regioselectivity R_{sel} for the pyridine 2-position based on the Kamlet–Taft equation: $R_{sel} = 1.28990 + 0.03992\alpha - 0.59417\beta - 0.46169\pi^*$ ($R^2 = 0.95$, $p = 1.9 \times 10^{-10}$).

as *N*-methylimidazole and DMSO with high β parameters. On this basis it seems that selectivity for nucleophilic attack at the 2-position is most easily attained.[39] It is notable that common solvents frequently employed in synthesis, such as MeCN, EtOAc, acetone, and ethers (1,4-dioxane, 1,2-DME, THF) gave only moderate regioselectivity.

The β parameter is a measure of a solvent's hydrogen-bond acceptor basicity, and solvents that are the weakest hydrogen-bond acceptors have the lowest β values. The regioselectivity for the 2-position in solvents with a low β parameter, that is, solvents that are weak hydrogen-bond acceptors (like DCM), can be tentatively explained by the formation of a hydrogen bond between the 3-methoxycarbonyl substituent on pyridine and the hydrogen atom of the secondary amine of 1-methylpiperazine. This could guide the nucleophile to reaction at the 2-position. A similar effect would be less effective in solvents with a high β parameter, that is, solvents that are strong hydrogen-bond acceptors (like DMSO), in which hydrogen bonds between the hydrogen atom of the secondary amine of 1-methylpiperazine and the solvent could compete with a hydrogen bond to the 3-methoxycarbonyl substituent.

Conclusions

A chemical design strategy has been used to study the effect of the 3-substituent on the regioselectivity in the reactions of 3-substituted 2,6-dichloropyridines with 1-methylpiperazine. Interestingly, the regioselectivity in this reaction is not correlated with the lipophilicity (PI), size (MR), or inductive effect (σ_p) of the 3-substituent, but is correlated in a statistically significant manner with the Verloop steric parameter B1, as indicated by the *p* value (0.006) for their relationship ($R^2 = 0.45$). This implies that 3-substituents that are bulky close to the pyridine ring directed the reaction towards the 6-position.

Particularly useful in synthesis is the different regioselectivity observed when the 3-substituent was carboxylic acid or its precursors/derivatives, because these substituents are interconvertible. Thus, to obtain the 2-isomer (9:1 ratio with the 6-isomer), the 3-carboxylate and 3-amide substituents would be preferred, whereas to obtain the 6-isomer (9:1 ratio with the 2-isomer) the 3-cyano and 3-trifluoromethyl substituents would be preferred. To gain a high regioselectivity, these substituents would be preferred to 3-methyl, 3-methoxycarbonyl, and 3-phenoxycarbonyl substituents.

The effect of solvent on the regioselectivity was also studied in the reaction of methyl 2,6-dichloronicotinate with 1-methylpiperazine. It was found that the regioselectivity is correlated with the ability of the solvent to function as a hydrogen-bond acceptor, as expressed by the solvatochromic β parameter. Thus, the modest 3:1 regioselectivity for the 2-isomer in acetonitrile ($\beta = 0.40$) could be increased to 16:1 in DCM ($\beta = 0.10$) and switched to a selectivity of 2:1 for the 6-isomer in DMSO ($\beta = 0.76$) as the reaction medium.

Experimental Section

General Methods: Commercial materials were used as provided by the commercial supplier without further purification. Reaction glassware was oven-dried and purged with anhydrous nitrogen prior to use. All reactions were performed under dry nitrogen. Heating was performed in sealed vials in a microwave reactor (Biotage Initiator, single node heating), and the reaction temperature was measured inside the vial. Solutions were concentrated in vacuo with a rotary evaporator at temperatures < 50 °C. ^{1}H NMR spectra were recorded at 400, 500, or 600 MHz and ^{13}C NMR spectra at 101, 126, and 151 MHz with Varian UNITY plus 400, 500, and 600 spectrometers. TMS was used as internal standard for spectra recorded in $CDCl_3$. Sodium 3-(trimethylsilyl)tetradeuteriopropionate was used as the internal standard for spectra recorded in D_2O. Otherwise, the NMR solvent was used as internal standard. Isolute phase separators from Biotage were used for extractions. Analytical TLC was performed on silica gel 60 F_{254} (Merck KGaA, Darmstadt). Flash column chromatography was performed on silica gel Merck grade 9385, 60 Å, from Sigma–Aldrich. Oasis solid-phase extraction resins from Waters were used. Preparative reversed-phase HPLC was performed at either acidic or basic pH. HPLC at acidic pH was performed with a Kromasil C8 column (10 μm; 250 × 20 mm, i.d.) or a Kromasil C8 column (10 μm, 250 × 50 mm i.d.) using linear gradients by increasing the ratio between mixtures of CH_3CN in $H_2O/CH_3CN/HCOOH$ (95:5:0.2) or $H_2O/CH_3CN/CH_3COOH$ (95:5:0.2). HPLC at basic pH was carried out with XBridge C18 columns (10 μm, 250 × 19 mm i.d. or 10 μm, 250 × 50 mm i.d.) using linear gradients by increasing the ratio between CH_3CN and a mixture of $H_2O/CH_3CN/NH_3$ (95:5:0.2). HRMS was determined using an Agilent 6530 Accurate Mass Q-TOF LC/MS spectrometer equipped with a Waters Acquity UPLC BEH C18 column (2.1 mm × 50 mm, 1.7 μm particles) at 50 °C with a gradient of 4–95% MeCN in aqueous 40 mM NH_3/6 mM $(NH_4)_2CO_3$ at pH = 10 over 6 min with a flow of 0.8 mL/min. UV detection was carried out at 210 nm and mass detection in the positive ionization mode (ESI^+). Alternatively, HRMS was determined by GC–MS using an Agilent 6890N capillary gas chro-

matograph (15 m OB5-column, 0.25 mm i.d. × 0.25 μm film) coupled to a GCT (Waters) mass spectrometer with electron-impact ionization (70 eV) and lock mass [tris(trifluoromethyl)-*s*-triazine] for internal mass calibration.

2,6-Dichloro-3-methylpyridine (2): 2-Chloro-3-methylpyridine (**31**; 1.02 g, 8.00 mmol) was dissolved in chloroform (11.4 mL), and *m*-CPBA (3.94 g, 16.0 mmol) was added at 0 °C. The reaction mixture was stirred at room temp. for 18 h. Sodium pyrosulfite (4.56 g, 24.0 mmol) was added at 0 °C, and the mixture was stirred at room temp. for 15 min. A saturated aq. solution of $NaHCO_3$ was added carefully (gas evolution) and the mixture extracted with DCM. The combined organic phases were washed with a saturated aq. solution of Na_2CO_3, and the combined aq. phases were extracted with DCM. The combined organic phases were dried (Na_2SO_4) and concentrated. Yield: 0.991 g (86%) of 2-chloro-3-methylpyridine 1-oxide (**32**). ^1H and ^{13}C NMR spectroscopic data were found to match those cited in the literature.[40] Purity analysis: 99%. HRMS: calcd. for C_6H_7ClNO 144.0216; found 144.0217. Compound **32** (0.991 g, 6.90 mmol) and TEA (1.44 mL, 10.35 mmol) were dissolved in DCM (6.30 mL), and $POCl_3$ (0.965 mL, 10.35 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 2 h and then at room temp. for 3 h. Water (3 mL) and NaOH (6 M, 2.76 mL, 16.57 mmol) were added at 0 °C. The organic phase was separated, and the aq. phase was extracted with DCM. The combined organic phases were concentrated. The crude material was purified by flash chromatography (5–40% EtOAc in heptane). Yield: 0.201 g (18%). The product was formed as a mixture of 2,6-dichloro-3-methylpyridine (**2**) and 2,4-dichloro-3-methylpyridine (**33**) in a 6:1 ratio (by ^1H NMR). The 6:1 mixture of **2** and **33** (145 mg, 0.89 mmol) in THF/MeOH (1:1, 6 mL) was added to Zn powder (0.117 g, 1.79 mmol) in a microwave vial. A saturated aq. solution of NH_4Cl (3 mL) was added, and the reaction mixture was stirred at room temp. for 45 min and then heated in a microwave oven at 120 °C for 1 h. The material was extracted with DCM (3 × 8 mL), and the combined organic fractions were concentrated. The crude material was purified by flash chromatography (EtOAc/heptane gradient). Yield: 74 mg (62%, considering a purity of 83% of the starting material). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.52 (d, J = 7.85 Hz, 1 H), 7.18 (d, J = 7.85 Hz, 1 H), 2.36 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 150.4, 147.5, 141.5, 131.3, 122.9, 18.9 ppm. Purity analysis: > 99%. GC–HRMS (EI): calcd. for $C_6H_5Cl_2N$ $[M]^{+\cdot}$ 160.9799; found 160.9799.

4-(2,6-Dichloropyridin-3-yl)-*N*,*N*-dimethylaniline (3): 2,6-Dichloro-3-iodopyridine (**34**; 1.51 g, 5.50 mmol) was dissolved in water/dioxane (1:3, 45 mL). [4-(Dimethylamino)phenyl]boronic acid (910 mg, 5.50 mmol), LiCl (350 mg, 8.25 mmol), $Ba(OH)_2{\cdot}8H_2O$ (0.80 mL, 5.50 mmol), and $[Pd(Ph_3P)_4]$ (640 mg, 0.55 mmol) were added, and the reaction mixture was stirred at 95 °C for 2 h. The mixture was quenched with 10% $NaCO_3$ and extracted with DCM. The organic phase was washed with brine and water, dried with Na_2SO_4, and concentrated. The crude product was purified by reversed-phase preparative HPLC. Yield after freeze drying: 180 mg (12%) as a light-brown solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.61 (d, J = 7.99 Hz, 1 H), 7.35–7.30 (m, 2 H), 7.28 (d, J = 7.99 Hz, 1 H), 6.79–6.74 (m, 2 H), 3.01 (s, 6 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 150.4, 148.5, 147.5, 141.5, 135.9, 130.1, 123.5, 123.0, 111.8, 40.3 ppm. Purity analysis: 92%. HRMS: calcd. for $C_{13}H_{13}Cl_2N_2$ $[M + H]^+$ 267.0450; found 267.0458.

4-(2,6-Dichloropyridin-3-yl)morpholine (4): A mixture of 3-amino-2,6-dichloropyridine (**1**; 815 mg, 5.0 mmol) and 1,4-dioxane-2,6-dione (677 mg, 5.25 mmol) in MeCN (12.5 mL) was heated in a microwave oven at 100 °C for 2 h. Phosphate buffer (0.2 M, pH = 7, 30 mL) was added, and the mixture was washed with DCM (3 × 20 mL). The organic phases were discarded, and the aq. phase was acidified with HCl (1 M, 6 mL) and extracted with DCM (3 × 20 mL) and EtOAc (3 × 20 mL). The combined organic phases were dried (Na_2SO_4) and concentrated to give 2-{2-[(2,6-dichloropyridin-3-yl)amino]-2-oxoethoxy}acetic acid. Yield: 780 mg (56%). ^1H NMR (400 MHz, $CDCl_3$): δ = 9.09 (s, 1 H), 8.74 (d, J = 8.5 Hz, 1 H), 8.54 (br. s, 1 H), 7.29 (d, J = 8.5 Hz, 1 H), 4.34 (s, 2 H), 4.28 (s, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.7, 168.2, 144.0, 138.9, 131.4, 130.2, 123.7, 70.8, 68.1 ppm. Purity analysis: 99%. HRMS: calcd. for $C_9H_9Cl_2N_2O_4$ $[M + H]^+$ 278.9939; found 278.9940. 2-{2-[(2,6-Dichloropyridin-3-yl)amino]-2-oxoethoxy}acetic acid (698 mg, 2.50 mmol) was dissolved in EtOAc (20.6 mL), and TEA (1.4 mL, 10.0 mmol) was added. 1-Propanephosphonic acid cyclic anhydride (T3P; 3.0 mL, 5.0 mmol, 50% in EtOAc) was added at 0 °C. After 30 min, the reaction mixture was stirred at room temp. for 16 h, and the mixture was washed with water (3 × 20 mL), dried (Na_2SO_4), and concentrated to give 4-(2,6-dichloropyridin-3-yl)morpholine-3,5-dione. Yield: 507 mg (78%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.54 (d, J = 8.2 Hz, 1 H), 7.40 (d, J = 8.2 Hz, 1 H), 4.53 (s, 4 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.8, 151.0, 149.1, 141.2, 126.5, 124.0, 67.9 ppm. Purity analysis: 98%. HRMS: calcd. for $C_9H_7Cl_2N_2O_3$ $[M + H]^+$ 260.9834; found 260.9829. 4-(2,6-Dichloropyridin-3-yl)morpholine-3,5-dione (104 mg, 0.40 mmol) was dissolved in THF (0.80 mL) in a microwave vial, and borane–THF (1 M, 1.2 mL, 1.20 mmol) was added. The vial was sealed, and the reaction mixture was heated at 60 °C for 4 h. The mixture was quenched with water (5 mL), and the aq. phase was extracted with DCM (3 × 5 mL). The combined organic phases were concentrated, and the crude product was purified by flash chromatography on silica gel (gradient: 8–50% EtOAc in heptane) to yield compound **4**. Yield: 81 mg (87%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.29 (d, J = 8.30 Hz, 1 H), 7.22 (d, J = 8.30 Hz, 1 H), 3.86 (m, 4 H), 3.04 (m, 4 H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 144.82, 144.75, 142.7, 130.4, 123.4, 66.8, 51.1 ppm. Purity analysis: 99%. HRMS: calcd. for $C_9H_{11}Cl_2N_2O$ $[M + H]^+$ 233.0248; found 233.0252.

2,6-Dichloronicotinonitrile (5): 2,6-Dichloronicotinamide (**12**; 460 mg, 2.41 mmol) was dissolved in THF (10 mL). $POCl_3$ (0.449 mL, 4.82 mmol) was added, and the reaction mixture was heated at 100 °C for 18 h. The mixture was concentrated and redissolved in DCM. The solution was washed with $NaHCO_3$ (10% aq. solution), water, and brine, dried (Na_2SO_4), and concentrated. The crude product was purified by reversed-phase preparative HPLC. Yield after freeze drying: 125 mg (30%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, J = 8.10 Hz, 1 H), 7.43 (d, J = 8.12 Hz, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.3, 152.2, 144.0, 123.2, 113.7, 109.3 ppm. Purity analysis: 99.6%. HRMS: calcd. for $C_6HCl_2N_2$ $[M - H]^-$ 170.9522; found 170.952.

Phenyl 2,6-Dichloronicotinate (7): 2,6-Dichloronicotinic acid (**11**; 2.016 g, 10.5 mmol) was dissolved in DCM (25 mL). $(COCl)_2$ (1.19 mL, 12.60 mmol) and DMF (0.081 mL, 1.05 mmol) were added, and the reaction mixture was stirred at room temp. for 2 h. The mixture was concentrated and co-concentrated twice with DCM. PhOH (0.934 mL, 10.50 mmol), pyridine (1.274 mL, 15.75 mmol), and DMAP (0.128 g, 1.05 mmol) were dissolved in DCM (5 mL) and stirred at room temp. for 3 min. The crude acyl chloride dissolved in DCM (20 mL) was added to this solution at room temp. The reaction mixture was heated at reflux for 16 h and then cooled to room temp. Water (20 mL) was added, and the organic phase was separated, washed with water and brine, filtered, and concentrated. The crude product was purified by reversed-

phase preparative HPLC. Yield after freeze drying: 2.161 g (77%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.32 (d, J = 8.15 Hz, 1 H), 7.41 (d, J = 8.39 Hz, 1 H), 7.47–7.38 (m, 2 H), 7.32–7.25 (m, 1 H), 7.24–7.19 (m, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 162.0, 153.5, 150.2, 142.9, 129.6, 126.5, 124.6, 123.0, 121.3 ppm. Purity analysis: 99.9%. HRMS: calcd. for $C_{12}H_8Cl_2NO_2$ $[M + H]^+$ 267.9927; found 267.9934.

2,6-Dichloro-*N*,*N*-dimethylpyridine-3-sulfonamide (8): 2,6-Dichloropyridine-3-sulfonyl chloride (**36**; 493 mg, 2.00 mmol) and TEA (0.335 mL, 2.40 mmol) were dissolved in THF (20 mL) and the solution was cooled to 0 °C. $HN(CH_3)_2$ (0.078 mL, 2.40 mmol) was added, and the reaction mixture was stirred at room temp. for 16 h. The mixture was filtered and the filtrate washed with a saturated aq. solution of NH_4Cl, brine, and water, dried (Na_2SO_4), and concentrated. Yield: 343 mg (67%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.25 (d, J = 8.17 Hz, 1 H), 7.39 (d, J = 8.18 Hz, 1 H), 2.87 (s, 6 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 153.4, 147.9, 143.2, 132.9, 123.3, 37.6 ppm. Purity analysis: 98.3%. HRMS: calcd. for $C_7H_9Cl_2N_2O_2S$ $[M + H]^+$ 254.9756; found 254.9766.

Methyl 2,6-Dichloronicotinate (9): 2,6-Dichloronicotinic acid (**11**; 5.76 g, 30.0 mmol) was dissolved in DCM (80 mL). $(COCl)_2$ (3.15 mL, 36.0 mmol) and then DMF (0.232 mL, 3.00 mmol) were added at room temp. The reaction mixture was stirred at room temp. for 2 h. MeOH (36.4 mL, 900 mmol) was added, and stirring at room temp. was continued for 16 h. The mixture was concentrated, and the crude material was purified by flash chromatography (5–40% EtOAc in heptane). Yield: 5.34 g (86%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20 (d, J = 8.10 Hz, 1 H), 7.42 (d, J = 8.10 Hz, 1 H), 3.97 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 163.5, 152.5, 149.3, 142.3, 124.8, 122.7, 52.7 ppm. Purity analysis: 99.9%. HRMS: calcd. for $C_7H_6Cl_2NO_2$ $[M + H]^+$ 205.977; found 205.9769.

2,6-Dichloro-3-ethoxypyridine (10): 2,6-Dichloropyridin-3-ol (**37**; 120 mg, 0.73 mmol) was dissolved in DMF (5 mL). K_2CO_3 (152 mg, 1.10 mmol) and EtBr (0.164 mL, 2.20 mmol) were added, and the reaction mixture was stirred at room temp. for 16 h. Water (5 mL) was added, and the organic phase was separated, washed with water and brine, concentrated, and co-concentrated twice with DCM. Yield: 141 mg (89%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 (d, J = 8.45 Hz, 1 H), 7.18 (d, J = 8.47 Hz, 1 H), 4.11 (q, J = 6.99 Hz, 2 H), 1.49 (t, J = 6.99 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 150.5, 139.8, 139.6, 123.3, 122.8, 65.5, 14.5 ppm. Purity analysis: > 99%. HRMS: calcd. for $C_7H_8Cl_2NO$ $[M + H]^+$ 191.9977; found 191.9977.

2,6-Dichloronicotinamide (12): 2,6-Dichloronicotinoyl chloride (**35**; 4.21 g, 20.0 mmol) was dissolved in 1,4-dioxane (8.0 mL) and added to NH_4OH (100 mL, ca. 25% aq. solution) at 0 °C. The reaction mixture was stirred at 0 °C for 75 min and then vacuum-filtered. The solids were washed with water. Yield: 2.054 g (54%). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.06 (br. s, 1 H), 7.97 (d, J = 7.97 Hz, 1 H), 7.83 (br. s, 1 H), 7.63 (d, J = 7.96 Hz, 1 H) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 166.1, 149.1, 145.8, 141.1, 132.7, 123.7 ppm. Purity analysis: > 99%. HRMS: calcd. for $C_6H_5Cl_2N_2O$ $[M + H]^+$ 190.9773; found 190.9771.

2,6-Dichloro-3-(ethylthio)pyridine (14): Diisopropylamine (1.069 mL, 7.50 mmol) was dissolved in THF (5 mL) and cooled to –40 °C. *n*BuLi (3.00 mL, 7.50 mmol) was added dropwise, and the reaction mixture was stirred at –40 °C for 20 min. Then the mixture was cooled to –80 °C, and 2,6-dichloropyridine (**38**; 1.110 g, 7.5 mmol) in THF (3.5 mL) was added dropwise. The reaction mixture was stirred at this temperature for 1 h. Sulfur (0.240 g, 7.50 mmol) was then added in three portions. The mixture was warmed up and allowed to react at room temp. for 1.5 h. The reaction was quenched by the slow addition of water (10 mL). The mixture was cooled to 0 °C, and the aq. layer was acidified to pH = 4 by the dropwise addition of 6 M HCl. The mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. This gave 1.419 g of a crude intermediate that contained the 3- and 4-SH isomers in a 1:1 ratio and some disulfides as well. NOTE: This crude intermediate dimerized completely at room temp. within 24 h and should be used directly in the next step. A solution of the intermediate (0.979 g, 5.44 mmol) in DMF (17.6 mL) at 0 °C was treated with K_2CO_3 (1.127 g, 8.16 mmol) and EtI (0.526 mL, 6.52 mmol), and the reaction mixture was stirred at room temp. for 16 h. Water (10 mL) was added, and the mixture was extracted with DCM. The organic phase was concentrated. The residue was difficult to purify, but was carried out by preparative HPLC on a Kromasil C8 column (10 μm 250 × 50 mm i.d.). Gradient: 42–52% MeCN in H_2O/MeCN/HCO_2H (95:5:0.2). Yield: 0.160 g (15% over two steps). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.49 (d, J = 8.20 Hz, 1 H), 7.23 (d, J = 8.20 Hz, 1 H), 2.96 (q, J = 7.40 Hz, 2 H), 1.38 (t, J = 7.40 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 147.5, 145.7, 137.2, 133.6, 123.0, 26.3, 13.3 ppm. Purity analysis: 96%. HRMS: calcd. for $C_7H_8Cl_2NS$ $[M + H]^+$ 207.9749; found 207.9740.

2,6-Dichloro-*N*-phenylpyridin-3-amine (15): 2,6-Dichloro-3-iodopyridine (**34**; 274 mg, 1.0 mmol), aniline (0.48 mL, 5.0 mmol), and sodium *tert*-butoxide (144 mg, 1.50 mmol) were mixed. A solution of BINAP (47 mg, 0.08 mmol) and $[Pd_2(dba)_3]$ (23 mg, 0.03 mmol) in 1,4-dioxane (10 mL) was added, and the reaction mixture was heated at 100 °C for 16 h. The mixture was concentrated, dissolved in DCM, and filtered through silica. The solution was washed with $NaHCO_3$ (5% aq. solution), brine, and water, dried with Na_2SO_4, and concentrated. The crude product was purified by reversed-phase preparative HPLC. Yield after freeze-drying: 0.110 g (46%) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 (d, J = 8.54 Hz, 1 H), 7.40–7.32 (m, 2 H), 7.16–7.10 (m, 3 H), 7.08 (d, J = 8.48 Hz, 1 H), 6.10 (s, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 139.7, 138.2, 137.0, 136.5, 129.8, 124.3, 123.8, 123.4, 121.3 ppm. Purity analysis: 97%. HRMS: calcd. for $C_{11}H_9Cl_2N_2$ $[M + H]^+$ 239.0137; found 239.0144.

6-Chloro-2-(4-methylpiperazin-1-yl)pyridin-3-amine (16a): Compound **1** (33 mg, 0.20 mmol) was dissolved in 1-methylpiperazine (1.2 mL, 10.78 mmol). The reaction mixture was heated at 170 °C for 3 h. The mixture was concentrated, and the compound was purified by preparative HPLC. The relevant fractions were pooled and concentrated. A 1 M NaOH solution was added, and the substance was extracted with DCM. The organic phase was concentrated. Yield: 5 mg (11%). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.89 (d, J = 8.06 Hz, 1 H), 6.81 (d, J = 8.06 Hz, 1 H), 3.70 (br. s, 2 H), 3.16 (br. s, 4 H), 2.56 (br. s, 4 H), 2.34 (s, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 150.4, 137.6, 133.9, 124.3, 118.6, 55.3, 48.2, 46.27, 46.23 ppm. Purity analysis: 98%. HRMS: calcd. for $C_{10}H_{16}ClN_4$ $[M + 1]^+$ 227.1058; found 227.1053.

1-(6-Chloro-3-methylpyridin-2-yl)-4-methylpiperazine (17a): Prepared according to the procedure used for the synthesis of **16a** from **2** (24 mg, 0.15 mmol) and 1-methylpiperazine (0.89 mL, 8.00 mmol) with heating at 150 °C for 1 h. Yield: 5 mg (15%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.31 (d, J = 8.32 Hz, 1 H), 6.81 (d, J = 8.32 Hz, 1 H), 3.22 (m, 4 H), 2.56 (m, 4 H), 2.35 (s, 3 H), 2.23 (s, 3 H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 161.2, 146.3, 141.7, 122.3, 116.9, 55.2, 49.1, 46.2, 18.1 ppm. Purity analysis: 98%. HRMS: calcd. for $C_{11}H_{17}ClN_3$ $[M + H]^+$ 226.1106; found 226.1095.

1-(6-Chloro-5-methylpyridin-2-yl)-4-methylpiperazine (17b): From the batch of **17a** was isolated the regioisomer **17b**. Relevant fractions were pooled and concentrated. A 1 M NaOH solution was added, and the substance was extracted with DCM. Yield: 10 mg (30%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.32 (d, J = 7.68 Hz, 1 H), 6.47 (d, J = 7.67 Hz, 1 H), 3.51 (m, 4 H), 2.51 (m, 4 H), 2.35 (s, 3 H), 2.23 (s, 3 H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 157.7, 149.0, 140.9, 119.8, 105.2, 54.8, 46.2, 45.3, 18.3 ppm. Purity analysis: 98%. HRMS: calcd. for $C_{11}H_{17}ClN_3$ [M + H]$^+$ 226.1106; found 226.1105.

4-[2-Chloro-6-(4-methylpiperazin-1-yl)pyridin-3-yl]-*N*,*N*-dimethylaniline (18a): Prepared according to the procedure used for the synthesis of **16a** from **3** (27 mg, 0.10 mmol) and 1-methylpiperazine (0.60 mL, 5.40 mmol) with heating at 170 °C for 50 min. Yield: 10 mg (30%). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.46 (d, J = 8.40 Hz, 1 H), 7.31 (d, J = 8.60 Hz, 2 H), 6.76 (d, J = 8.72 Hz, 2 H), 6.58 (d, J = 8.40 Hz, 1 H), 3.59 (m, 4 H), 2.99 (s, 6 H), 2.53 (m, 4 H), 2.36 (s, 3 H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 157.4, 149.7, 147.3, 141.1, 130.1, 126.0, 125.3, 111.9, 105.2, 54.7, 46.1, 44.9, 40.5 ppm. Purity analysis: 83%. HRMS: calcd. for $C_{18}H_{24}ClN_4$ [M + 1]$^+$ 331.1684; found 331.1683.

4-[6-Chloro-2-(4-methylpiperazin-1-yl)pyridin-3-yl]morpholine (19a): Prepared according to the procedure used for the synthesis of **16a** from **4** (35 mg, 0.15 mmol) and 1-methylpiperazine (0.900 mL, 5.4 mmol) with heating at 160 °C for 1 h. Yield: 12 mg (27%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.04 (d, J = 8.08 Hz, 1 H), 6.79 (d, J = 8.08 Hz, 1 H), 3.83 (m, 4 H), 3.55 (br. m, 4 H), 3.03 (m, 4 H), 2.52 (br. m, 4 H), 2.34 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 153.3, 141.6, 136.3, 127.5, 116.0, 67.0, 55.2, 49.0, 46.6, 46.2 ppm. Purity analysis: 95%. HRMS: calcd. for $C_{14}H_{22}ClN_4O$ [M + 1]$^+$ 297.1482; found 297.1477.

4-[2-Chloro-6-(4-methylpiperazin-1-yl)pyridin-3-yl]morpholine (19b): From the batch of **19a** was isolated the regioisomer **19b**. Relevant fractions were pooled and concentrated. A 1 M NaOH solution was added, and the substance was extracted with DCM. Yield: 8 mg (17%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26 (d, J = 8.65 Hz, 1 H), 6.52 (d, J = 8.65 Hz, 1 H), 3.84 (m, 4 H), 3.48 (m, 4 H), 2.93 (m, 4 H), 2.50 (m, 4 H), 2.33 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.3, 144.5, 135.7, 131.1, 105.5, 67.2, 54.7, 51.9, 46.2, 45.4 ppm. Purity analysis: 99%. HRMS: calcd. for $C_{14}H_{22}ClN_4O$ [M + 1]$^+$ 297.1482; found 297.1492.

2-Chloro-6-(4-methylpiperazin-1-yl)nicotinonitrile (20b): Prepared according to the procedure used for the synthesis of **16a** from **5** (0.017 g, 0.10 mmol) and 1-methylpiperazine (0.011 mL, 0.10 mmol) with heating at 120 °C for 20 min. Yield: 6 mg (25%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.58 (d, J = 8.86 Hz, 1 H), 6.49 (d, J = 8.88 Hz, 1 H), 3.70 (m, 4 H), 2.49 (m, 4 H), 2.34 (s, 3 H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 158.7, 152.4, 142.3, 116.7, 103.9, 95.7, 54.5, 46.1, 44.6 ppm. Purity analysis: 99.1%. HRMS: calcd. for $C_{11}H_{14}ClN_4$ [M + 1]$^+$ 237.0902; found 237.0907.

1-[6-Chloro-5-(trifluoromethyl)pyridin-2-yl]-4-methylpiperazine (21b): Compound **6** (0.022 g, 0.10 mmol) was dissolved in MeCN (1 mL) and 1-methylpiperazine (0.011 mL, 0.10 mmol) and DIPEA (0.052 mL, 0.30 mmol) were added. The reaction mixture was heated at 120 °C for 20 min. The reaction mixture was concentrated, and the crude product was purified by preparative HPLC. Relevant fractions were pooled and concentrated. A 1 M NaOH solution was added, and the substance was extracted with DCM. Yield: 7 mg (25%) as a yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.66 (d, J = 8.79 Hz, 1 H), 6.48 (d, J = 8.79 Hz, 1 H) 3.66 (m, 4 H), 2.49 (m, 4 H), 2.34 (s, 3 H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 159.2, 147.6, 137.5 (q, $J_{C\text{-}C\text{-}C\text{-}F}$ = 4.5 Hz), 123.3 (q, $J_{C\text{-}F}$ = 268.5 Hz), 112.2 (q, $J_{C\text{-}C\text{-}F}$ = 33 Hz), 103.1, 54.6, 46.1, 44.6 ppm. Purity analysis: 98.1%. HRMS: calcd. for $C_{11}H_{14}ClF_3N_3$ [M + 1]$^+$ 280.0823; found 280.0834.

Phenyl 2-Chloro-6-(4-methylpiperazin-1-yl)nicotinate (22b): Compound **7** (54 mg, 0.20 mmol) was dissolved in MeCN (2.0 mL), and DIPEA (0.105 mL, 0.60 mmol) and 1-methylpiperazine (0.022 mL, 0.20 mmol) were added. The reaction mixture was stirred at room temp. for 24 h. The reaction mixture was concentrated and the compound purified by preparative HPLC. A 10% solution of Na_2CO_3 was added, and the substance was extracted with DCM. Yield: 33 mg (42%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22 (d, J = 8.90 Hz, 1 H), 7.44–7.38 (m, 2 H), 7.28–7.22 (m, 1 H), 7.22–7.17 (m, 2 H), 6.54 (d, J = 8.90 Hz, 1 H), 3.76 (m, 4 H), 2.56 (m, 4 H), 2.38 (s, 3 H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 162.9, 159.0, 151.4, 150.8, 142.6, 129.4, 125.8, 121.8, 111.5, 103.5, 54.6, 46.1, 44.6 ppm. Purity: 97%. HRMS: calcd. for $C_{17}H_{19}ClN_3O_2$ [M + 1]$^+$ 332.1160; found 332.1173.

6-Chloro-*N*,*N*-dimethyl-2-(4-methylpiperazin-1-yl)pyridine-3-sulfonamide (23a): Compound **8** (51 mg, 0.20 mmol) was dissolved in MeCN (2.0 mL), and DIPEA (0.105 mL, 0.60 mmol) and 1-methylpiperazine (0.022 mL, 0.20 mmol) were added. The reaction mixture was stirred at room temp. for 24 h. The reaction mixture was concentrated, and the compound was purified by preparative HPLC. Relevant fractions were pooled and concentrated. A 1 M NaOH solution was added, and the substance was extracted with DCM. Yield: 7 mg (11%). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.01 (d, J = 8.15 Hz, 1 H), 6.97 (d, J = 8.19 Hz, 1 H), 3.47 (m, 4 H), 2.77 (s, 6 H), 2.56 (m, 4 H), 2.34 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.0, 152.4, 143.1, 122.3, 116.9, 54.8, 51.5, 46.1, 38.1 ppm. Purity analysis: 96.7%. HRMS: calcd. for $C_{12}H_{20}ClN_4O_2S$ [M + 1]$^+$ 319.099; found 319.1004.

2-Chloro-*N*,*N*-dimethyl-6-(4-methylpiperazin-1-yl)pyridine-3-sulfonamide (23b): From the batch of **23a** was isolated the regioisomer. Relevant fractions were pooled and concentrated. A 1 M NaOH solution was added, and the substance was extracted with DCM. Yield: 15 mg (24%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.02 (d, J = 8.89 Hz, 1 H), 6.50 (d, J = 8.96 Hz, 1 H), 3.69 (m, 4 H), 2.87 (s, 6 H), 2.49 (m, 4 H), 2.35 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.0, 147.8, 142.4, 119.2, 103.2, 54.5, 46.1, 44.6, 37.5 ppm. Purity analysis: 97.1%. Contained 1.4% of the isomer. HRMS: calcd. for $C_{12}H_{20}ClN_4O_2S$ [M + 1]$^+$ 319.0990; found 319.1000.

Methyl 6-Chloro-2-(4-methylpiperazin-1-yl)nicotinate (24a): Compound **9** (0.206 g, 1.0 mmol) was dissolved in pyridine (9.36 mL), and 1-methylpiperazine (0.111 mL, 1.0 mmol) and DIPEA (0.524 mL, 3.0 mmol) were added. The reaction mixture was stirred at room temp. for 3.5 h. The reaction mixture was concentrated, and the crude material purified by preparative HPLC. Relevant fractions were pooled and concentrated. A 10% aq. solution of Na_2CO_3 (3 mL) was added, and the material was extracted with DCM (3 × 3 mL). Yield: 110 mg (41%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.91 (d, J = 7.98 Hz, 1 H), 6.68 (d, J = 7.99 Hz, 1 H), 3.86 (s, 3 H), 3.48 (m, 4 H), 2.50 (m, 4 H), 2.33 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.0, 158.6, 151.9, 143.4, 113.1, 110.9, 54.9, 52.2, 48.9, 46.1 ppm. Purity analysis: > 99%. HRMS: calcd. for $C_{12}H_{17}ClN_3O_2$ [M + 1]$^+$ 270.1009; found 270.1008.

Methyl 2-Chloro-6-(4-methylpiperazin-1-yl)nicotinate (24b): From the batch of **24a** was isolated the regioisomer **24b**. Relevant fractions were pooled and concentrated. A 10% solution of Na_2CO_3 (3 mL) was added, and the substance was extracted with DCM (3 × 3 mL). Yield: 78 mg (29%) as a yellow oil. ^{1}H NMR

(500 MHz, $CDCl_3$): δ = 8.03 (d, J = 8.79 Hz, 1 H), 6.48 (d, J = 8.75 Hz, 1 H), 3.87 (s, 3 H), 3.68 (m, 4 H), 2.48 (m, 4 H), 2.34 (s, 3 H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 164.9, 158.9, 150.4, 142.2, 112.4, 103.5, 54.6, 52.0, 46.1, 44.5 ppm. Purity analysis: > 99%. HRMS: calcd. for $C_{12}H_{17}ClN_3O_2$ $[M + 1]^+$ 270.1009; found 270.0995.

1-(6-Chloro-3-ethoxypyridin-2-yl)-4-methylpiperazine (25a): Prepared according to the procedure used for the synthesis of **16a** from **10** (19 mg, 0.10 mmol) and 1-methylpiperazine (0.6 mL, 5.4 mmol) with heating at 170 °C for 1 h. Yield: 12 mg (47%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.95 (d, J = 8.17 Hz, 1 H), 6.73 (d, J = 8.11 Hz, 1 H), 4.01 (q, J = 6.95 Hz, 2 H), 3.51 (m, 4 H), 2.54 (m, 4 H), 2.34 (s, 3 H), 1.44 (t, J = 6.89 Hz, 3 H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 151.3, 144.5, 139.2, 121.6, 115.1, 64.5, 55.0, 47.7, 46.2, 14.8 ppm. Purity analysis: 96.5%. HRMS: calcd. for $C_{12}H_{19}ClN_3O$ $[M + 1]^+$ 256.1211; found 256.122.

6-Chloro-2-(4-methylpiperazin-1-yl)nicotinic Acid (26a):[41] Compound **24a** (13 mg, 0.05 mmol) was dissolved in MeOH (0.25 mL), and $LiOH·H_2O$ (21 mg, 0.50 mmol) was added. The reaction mixture was heated in a microwave oven at 80 °C for 20 min. The crude product was purified by solid-phase extraction (Oasis MCX, 500 mg) and eluted with 5% NH_4OH. Yield: 7 mg (55%). ^{1}H NMR [600 MHz, 18% DCl in D_2O, $(CH_3)_3Si(CD_2)_2COONa$]: δ = 8.32 (d, J = 8.23 Hz, 1 H), 7.28 (d, J = 8.20 Hz, 1 H), 3.99 (app. d, J = 14.55 Hz, 2 H), 3.72 (app. d, J = 12.59 Hz, 2 H), 3.57 (app. t, J = 12.56 Hz, 2 H), 3.40 (app. t, J = 12.46 Hz, 2 H), 3.04 (s, 3 H) ppm. Purity analysis: 96%. HRMS: calcd. for $C_{11}H_{15}ClN_3O_2$ $[M + 1]^+$ 256.0853; found 256.0852.

2-Chloro-6-(4-methylpiperazin-1-yl)nicotinic Acid (26b): Prepared from **24b** (10 mg, 0.04 mmol) by the procedure of **26a**. Yield: 9 mg (95%). ^{1}H NMR [500 MHz, 18% DCl in D_2O, $(CH_3)_3Si(CD_2)_2CO$-ONa]: δ = 8.08 (d, J = 8.82 Hz, 1 H), 6.83 (d, J = 8.82 Hz, 1 H), 4.52 (app. d, J = 14.88 Hz, 2 H), 3.65 (app. d, J = 12.41 Hz, 2 H), 3.39 (app. t, J = 13.51 Hz, 2 H), 3.19 (app. t, J = 12.47 Hz, 2 H), 2.97 (s, 3 H) ppm. Purity analysis: 95%. HRMS: calcd. for $C_{11}H_{15}ClN_3O_2$ $[M + 1]^+$ 256.0853; found 256.0859.

6-Chloro-2-(4-methylpiperazin-1-yl)nicotinamide (27a): A mixture of compound **12** (57 mg, 0.30 mmol), 1-methylpiperazine (0.033 mL, 0.30 mmol), and DIPEA (0.16 mL, 0.90 mmol) in MeCN (2.8 mL) was heated at 80 °C for 30 min. The mixture was concentrated and purified by preparative HPLC. Relevant fractions were pooled and concentrated. A 10% solution of Na_2CO_3 was added, and the substance was extracted with DCM. Yield: 31 mg (41%) as a colorless oil. ^{1}H NMR (400 MHz, MeOD): δ = 7.84 (d, J = 7.88 Hz, 1 H), 6.93 (d, J = 7.88 Hz, 1 H), 4.89 (s, 2 H), 3.45 (m, 4 H), 2.61 (m, 4 H), 2.37 (s, 3 H) ppm. ^{13}C NMR (101 MHz, MeOD): δ = 172.3, 159.8, 151.9, 142.9, 119.8, 116.4, 55.9, 50.1, 46.4 ppm. Purity analysis: > 99%. HRMS: calcd. for $C_{11}H_{16}ClN_4O$ $[M + 1]^+$ 255.1013; found 255.1008.

1-(3-Bromo-6-chloropyridin-2-yl)-4-methylpiperazine (28a): Prepared from **13** (0.091 g, 0.40 mmol) by the procedure used for the synthesis of **27a** with heating at 140 °C for 1 h. Yield: 0.035 g (30%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.67 (d, J = 8.02 Hz, 1 H), 6.75 (d, J = 8.02 Hz, 1 H), 3.42 (m, 4 H), 2.57 (m, 4 H), 2.35 (s, 3 H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 158.9, 147.8, 144.4, 117.7, 109.3, 54.8, 49.1, 46.2 ppm. Purity analysis: > 99%. HRMS: calcd. for $C_{10}H_{14}BrClN_3$ $[M + H]^+$ 290.0060; found 290.0056.

1-(5-Bromo-6-chloropyridin-2-yl)-4-methylpiperazine (28b): From the batch of **28a** was isolated the regioisomer. Relevant fractions were pooled and concentrated. A 10% solution of Na_2CO_3 was added, and the substance was extracted with DCM. Yield: 9 mg (8%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.58 (d, J = 8.76 Hz, 1 H), 6.41 (d, J = 8.79 Hz, 1 H), 3.54 (m, 4 H), 2.48 (m, 4 H), 2.33 (s, 3 H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 157.5, 148.1, 142.8, 106.3, 104.9, 54.6, 46.2, 44.9 ppm. Purity analysis: > 99%. HRMS: calcd. for $C_{10}H_{14}BrClN_3$ $[M + H]^+$ 290.0060; found 290.0064.

1-[6-Chloro-3-(ethylthio)pyridin-2-yl]-4-methylpiperazine (29a): Compound **14** (21 mg, 0.10 mmol) was dissolved in 1-methylpiperazine (0.60 mL, 5.40 mmol) in a microwave vial. The reaction mixture was heated in a microwave oven at 80 °C for 2 min, and the compound was purified by preparative HPLC. Relevant fractions were pooled and concentrated. A 10% solution of Na_2CO_3 was added, and the substance was extracted with DCM. Yield: 2 mg (8%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.40 (d, J = 7.97 Hz, 1 H), 6.85 (d, J = 7.94 Hz, 1 H), 3.40 (m, 4 H), 2.90 (q, J = 7.35 Hz, 2 H), 2.57 (m, 4 H), 2.35 (s, 3 H), 1.30 (t, J = 7.35 Hz, 3 H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 159.5, 145.9, 139.2, 122.5, 117.1, 55.0, 48.9, 46.2, 26.5, 13.8 ppm. Purity analysis: 92%. HRMS: calcd. for $C_{12}H_{19}ClN_3S$ $[M + H]^+$ 272.0983; found 272.0977.

1-[6-Chloro-5-(ethylthio)pyridin-2-yl]-4-methylpiperazine (29b): From the batch of **29a** was isolated the regioisomer. Relevant fractions were pooled and concentrated. A 1 M NaOH solution was added and the substance was extracted with DCM. Yield: 2 mg (8%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56 (d, J = 8.55 Hz, 1 H), 6.48 (d, J = 8.57 Hz, 1 H), 3.57 (m, 4 H), 2.82 (q, J = 7.35 Hz, 3 H) 2.51 (m, 4 H), 2.35 (s, 3 H), 1.23 (t, J = 7.35 Hz, 3 H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 157.8, 152.2, 144.4, 116.6, 105.2, 54.6, 46.1, 44.8, 28.9, 14.4 ppm. Purity analysis: 96.5%. HRMS: calcd. for $C_{12}H_{19}ClN_3S$ $[M + H]^+$ 272.0983; found 272.0978.

6-Chloro-2-(4-methylpiperazin-1-yl)-*N*-phenylpyridin-3-amine (30a): Prepared according to the procedure used for the synthesis of **16a** from **15** (24 mg, 0.10 mmol) and 1-methylpiperazine (0.60 mL, 5.4 mmol) with heating at 160 °C for 1 h. Yield: 12 mg (40%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.45 (d, J = 8.20 Hz, 1 H), 7.36–7.28 (m, 2 H), 7.08–6.97 (m, 3 H), 6.86 (d, J = 8.20 Hz, 1 H), 5.80 (s, 1 H), 3.22 (m, 4 H), 2.57 (m, 4 H), 2.36 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 152.5, 141.6, 139.3, 130.9, 129.6, 124.3, 122.0, 118.6, 118.4, 55.2, 48.6, 46.1 ppm. Purity analysis: 98.7%. HRMS: calcd. for $C_{16}H_{20}ClN_4$ $[M + 1]^+$ 303.1371; found 303.1383.

2-Chloro-6-(4-methylpiperazin-1-yl)-*N*-phenylpyridin-3-amine (30b): From the batch of **30a** was isolated the regioisomer. Relevant fractions were pooled and concentrated. A 1 M NaOH solution was added, and the substance was extracted with DCM. Yield: 10 mg (33%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (d, J = 8.63 Hz, 1 H), 7.26–7.21 (m, 2 H), 6.93–6.87 (m, 3 H), 6.55 (d, J = 8.60 Hz, 1 H), 5.55 (s, 1 H), 3.51 (m, 4 H), 2.53 (m, 4 H), 2.36 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.5, 143.7, 140.1, 131.6, 129.4, 126.4, 120.7, 116.5, 106.1, 54.7, 46.2, 45.6 ppm. Purity analysis: > 99%. HRMS: calcd. for $C_{16}H_{20}ClN_4$ $[M + 1]^+$ 303.1371; found 303.1379.

2,6-Dichloronicotinoyl Chloride (35): 2,6-Dichloronicotinic acid (**11**; 3.84 g, 20 mmol) was added to toluene (8 mL) to form a slurry, and then DMF (0.077 mL, 1.00 mmol) was added. The slurry was cooled to 0 °C, and $SOCl_2$ (4.38 mL, 60.00 mmol) was added. The reaction mixture was stirred at 0 °C for 10 min, at room temperature for 10 min, and then heated to reflux for 2 h. The mixture was concentrated and co-concentrated twice with toluene and used in due course.

2,6-Dichloropyridin-3-ol (37): Prepared according to the procedure by Voisin et al.[32] ^{1}H and ^{13}C NMR spectra are in agreement with literature values. Purity analysis: 98%. HRMS: calcd. for $C_5H_4Cl_2NO$ $[M + H]^+$ 163.9664; found 163.9667.

Compounds **16b**, **18b**, **20a**, **21a**, **22a**, **25b**, and **27b** were not isolated, because the regioselectivities of the reactions were biased towards the other isomers; thus, their ^{1}H NMR spectroscopic data were determined from the reaction mixtures.

Supporting Information (see footnote on the first page of this article): Table of ^{1}H NMR chemical shifts and coupling constants for pyridine hydrogen atoms in the starting materials **1**–**15** and the products **16a**–**30a** (2-isomers) and **16b**–**30b** (6-isomers), copies of the ^{1}H and ^{13}C NMR spectra for all isolated new compounds.

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