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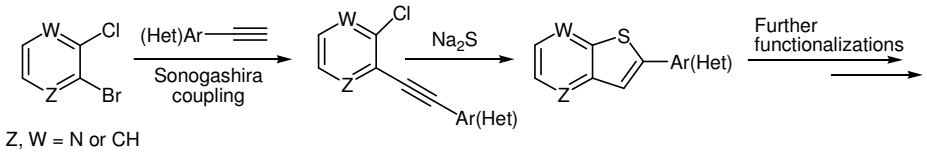

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Synthesis of 2-(hetero)arylthieno[2,3-*b*] or [3,2-*b*]pyridines from 2,3-dihalopyridines, (hetero)arylalkynes and Na_2S. Further functionalizations

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ABSTRACT

A simple and efficient three-step methodology is described for the first time for the synthesis of 2-(hetero)arylthieno[2,3-*b*] or [3,2-*b*]pyridines. The first step is a Sonogashira coupling from 3-bromo-2-chloropyridine or 2-bromo-3-chloropyridine with several (hetero)arylalkynes to obtain the corresponding 2- or 3-chloro(hetero)arylethynylpyridines. These were cyclized by treatment with Na_2S affording the expected 2-(hetero)arylthienopyridines. As an improvement, these reactions were also performed in one-pot, without the isolation of the Sonogashira product, giving the thienopyridines in similar or better yields, reducing significantly the reaction time after the addition of Na_2S. Further functionalizations were achieved in the thienopyridine system either by bromination in the thiophene ring or chlorination in the pyridine ring *via* a *N*-oxide intermediate, allowing metal-catalyzed coupling reactions and/or nucleophilic substitutions. The functionalization of some substituents is also possible and as an example a 1,3-diarylurea was obtained from the reaction of an aniline derivative with an arylisocyanate.

1. Introduction

Pyridine derivatives have attracted considerable interest because of their great practical usefulness due to their various biological activities. Among them, fused analogues are often much more biologically active. More particularly, thienopyridines have been shown to exhibit a large variety of biological activities.[1] Nowadays the chemistry of the [2,3-*b*]-isomers is better known in comparison with the [3,2-*b*]-isomers. The diversity of biological activities gave an impulse to the development of convenient synthetic routes for the synthesis of the thieno[3,2-*b*]pyridine system. Most of the methods for the synthesis of thieno[3,2-*b*]pyridines are based on the use of readily accessible 3-aminothiophenes or their *N*-derivatives[2] and only few synthesis have already been described starting from the pyridine ring.[3] For example, Fort *et al.* have reported a three-step process allowing the construction of the thiophene ring. The key step was the almost regioselective lithiation–bromination of the 3-methylthiopyridine induced by the BuLi-LiDMAE superbase (DMAE: 2-(dimethylamino)ethanol) followed by a Sonogashira coupling and a halogenocyclization to give the corresponding 2-substituted (Ph or TMS) 3-halothieno[3,2-*b*]pyridines.[3d]

In the last few years our group has been interested in the synthesis of thieno[3,2-*b*]pyridine derivatives. We have reported a one-pot two-step synthesis of the methyl 3-amino-6-bromothieno[3,2-*b*]pyridine-2-carboxylate from 5-bromo-3-nitropicolinonitrile and methyl thioglycolate in DMF/KOH(aq).[4] This product was obtained in excellent yield and it was further functionalized by C-C (Suzuki, Sonogashira)[5a,b] or C-N (Buchwald-Hartwig)[5c] couplings, to give new derivatives exhibiting inhibitory growth activity in human tumor cell lines.[5]

Herein, we describe a new and general method for the synthesis of thieno[2,3-*b*] and [3,2-*b*]pyridines bearing a (hetero)aryl substituent in the 2-position, from 2- or 3-chloro(hetero)arylethynylpyridines obtained by Sonogashira coupling of 2,3-dihalopyridines with (hetero)arylalkynes, followed by treatment with sodium sulfide (Na_2S) as depicted in Scheme 1.

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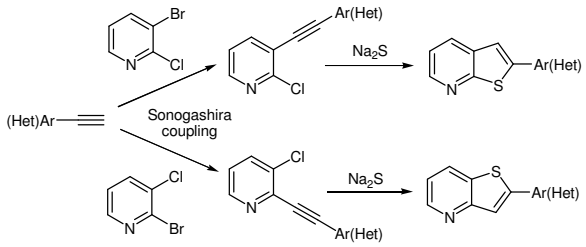
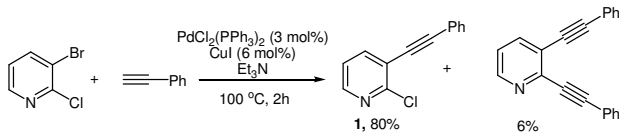


Scheme 1. Strategy for the synthesis of 2-(hetero)arylthieno[2,3-*b*] and [3,2-*b*]pyridines.

2. Results and discussion

Optimization experiments were first carried out on the Sonogashira reaction[6] of the 3-bromo-2-chloropyridine with phenylacetylene using $PdCl_2(PPh_3)_2$ as the catalyst, CuI as the co-catalyst. The best conditions were the ones presented in Scheme 2, using Et_3N as the base and the solvent, with only a slight excess of phenylacetylene (1.1 equiv.), as it is well known that an important side reaction, namely the Glaser-type oxidative dimerization of the alkyne, usually occurs in the presence of Cu(I).[7]



Scheme 2. Sonogashira coupling of 3-bromo-2-chloropyridine with phenylacetylene.

The isolation of the 2,3-bis(phenylethynyl)pyridine as a minor product has been observed and its formation increases with the reaction time.

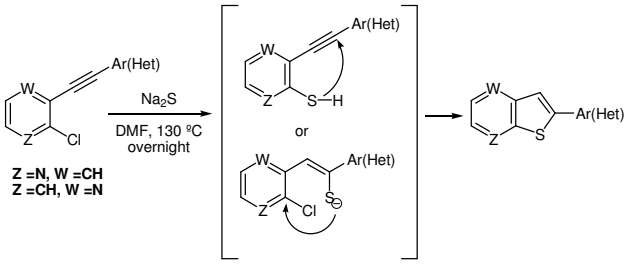
Using these conditions various 2-chloro-3-ethynylpyridines were synthesized in moderate to good yields (Table 1, products **1**-**13**). The reaction time being quite low, the moderate yields that were obtained with some aryl and heteroarylalkynes were mostly related to the dimerization of the alkyne, and not to the formation of the di(hetero)arylethynylpyridine, as it occurred when phenylacetylene was used (Scheme 2).

The synthesis of the corresponding 3-chloro-2-ethynylpyridines was also performed, using the same conditions (Table 1, products **14**-**26**). As expected, the yields were much higher when 2-bromo-3-chloropyridine was used as the starting material, due to the better activation of the bromine in the 2-position for the Sonogashira coupling. Thus, all the expected 3-chloro-2-(hetero)arylethynylpyridines were synthesized in very good to excellent yields from either electron-rich or electron-poor (hetero)arylalkynes (from 70% to 93%).

The synthesis of annulated thiophene rings from *ortho*-haloalkynyl antraquinones, benzenes, naphthalenes, and pyrazoles to give antrathiophenediones,[8a] benzo[*b*]thiophenes,[8b,c] naphthodithiophenes,[8d,e] and thieno[2,3-*c*]pyrazoles,[8f] respectively, has already been described using Na_2S.

In the present work the reaction of the Sonogashira coupling products **1**-**26** with Na_2S overnight, gave the thieno[2,3-*b*]pyridines **27**-**39** and the thieno[3,2-*b*]pyridines **40**-**52** in good to excellent yields (Table 1). This methodology was applied by us for the first time to the synthesis of thienopyridine derivatives.

A plausible mechanism is a nucleophilic attack (S_NAr) of the hydrosulfide ion on the *ortho*-chloroalkynylpyridine followed by an intramolecular addition on the triple bond but on the other hand an addition of the hydrosulfide ion to the triple bond may occur, followed by a S_NAr/cyclization (Scheme 3).



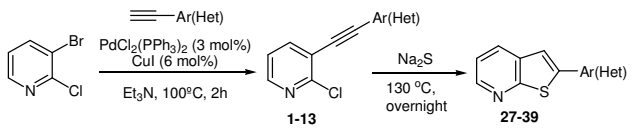
Scheme 3. Plausible mechanisms for the synthesis of 2-(hetero)arylthieno[2,3-*b*] or [3,2-*b*]pyridines from the *ortho*-choroalkynylpyridines

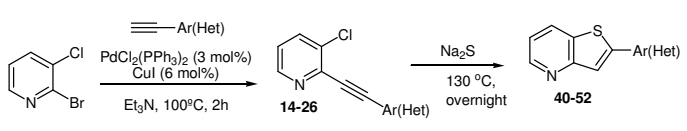
Unexpected results were obtained for the cyclization of the *ortho*-methoxylated Sonogashira coupling products **7** and **20**: instead of the expected 2-(2-methoxyphenyl)thienopyridines, the cyclization with Na_2S gave the corresponding hydroxylated thienopyridines **33** and **46** in good to high yields (Table 1), maybe due to the spatial proximity of the sulfide anion intermediate with the methoxy group.

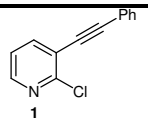
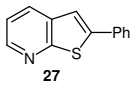
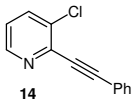
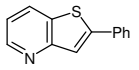
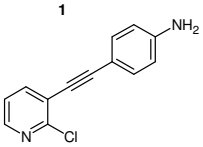
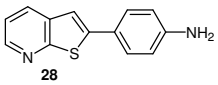
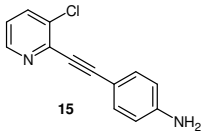
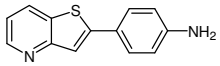
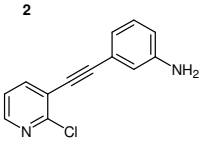
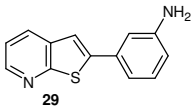
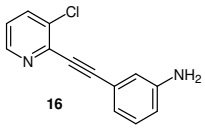
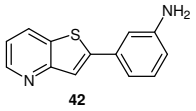
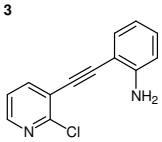
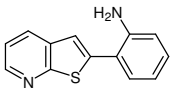
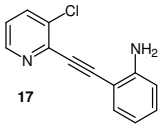
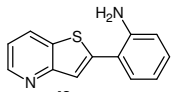
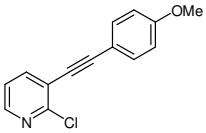
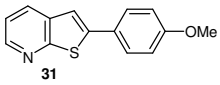
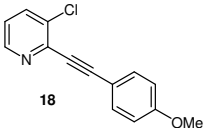
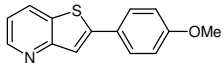
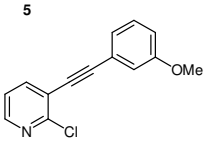
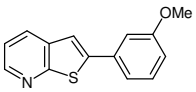
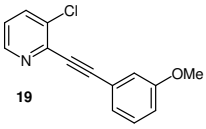
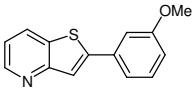
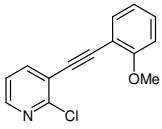
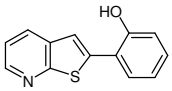
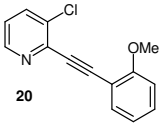
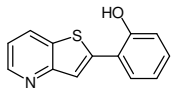
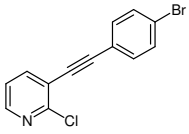
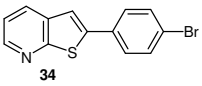
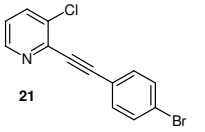
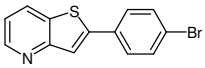
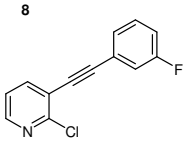
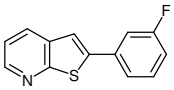
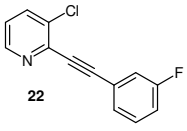
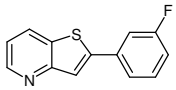
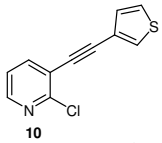
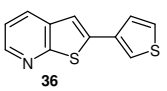
We have also used this methodology through a one-pot procedure. Thus, after coupling the 2,3-dihalopyridines with (hetero)arylalkynes at 100 °C for 2h, Na_2S was added to the reaction mixture without the isolation of the Sonogashira coupling product and the solution was allowed to stir at 130 ºC for a further 2h. Some examples were performed using these conditions and the thienopyridines **27**, **28**, **30**-**32**, **36**-**41**, **43**-**45** and **49**-**52** were obtained in good to excellent yields (Table 2). The expected thienopyridines were purified by recrystallization or dry flash chromatography. The yields obtained under this one-pot procedure were at least as good and often higher than those obtained when the reactions were performed with isolation of the Sonogashira coupling product.

After adding Na_2S, the reaction was much faster when performed in one-pot, as only 2h of heating were required for the reaction to reach completion. This is agreement with Müller *et al.*[9] that for the synthesis of several annulated 4*H*-thiopyran-4-ones by one-pot microwave-assisted reaction, from *ortho*-chloro or fluoro(hetero)aroylchlorides, alkynes and Na_2S, postulated that the cyclizing step is assisted by Pd and/or Cu.

Table 1. Synthesis of 2-(hetero)arylthienopyridines





Ethynylpyridines	Yields	Thieno[2,3-*b*]pyridines	Yields	Ethynylpyridines	Yields	Thieno[3,2-*b*]pyridines	Yields
 **1**	80%	 **27**	90%	 **14**	88%	 **40**	80%
 **2**	40%	 **28**	91%	 **15**	70%	 **41**	85%
 **3**	55%	 **29**	96%	 **16**	83%	 **42**	86%
 **4**	50%	 **30**	82%	 **17**	89%	 **43**	94%
 **5**	65%	 **31**	91%	 **18**	90%	 **44**	97%
 **6**	74%	 **32**	91%	 **19**	92%	 **45**	95%
 **7**	64%	 **33**	86%	 **20**	90%	 **46**	64%
 **8**	40%	 **34**	71%	 **21**	85%	 **47**	94%
 **9**	70%	 **35**	87%	 **22**	60%	 **48**	85%
 **10**	70%	 **36**	82%	**23**	70%	**49**	80%
11	60%	**37**	70%	**24**	87%	**50**	70%

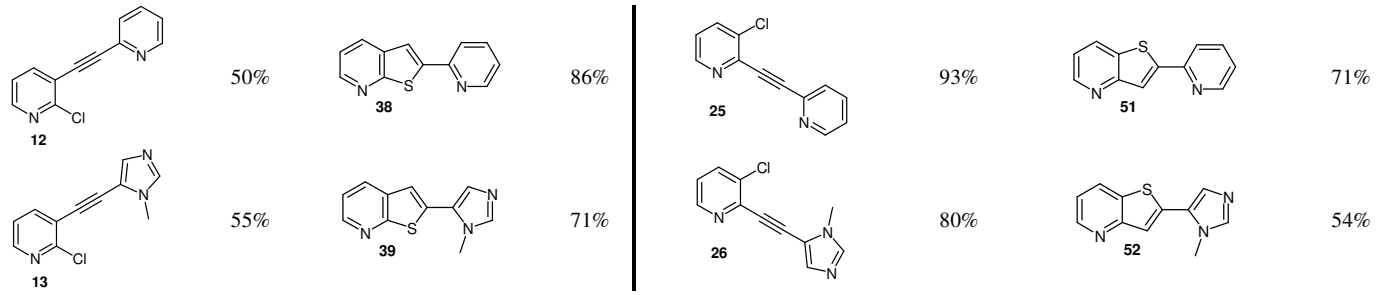
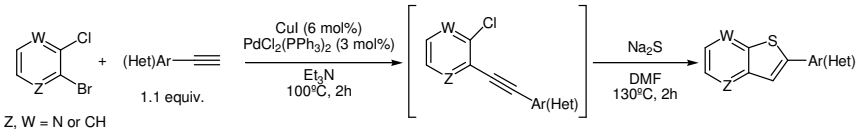


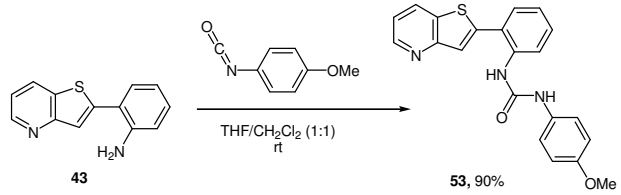
Table 2. Synthesis of 2-(hetero)arylthienopyridines in one-pot



Thieno[2,3-*b*]pyridines	Yields		Thieno[3,2-*b*]pyridines	Yields	
	One-pot fashion	Two-pot fashion[a]		One-pot fashion	Two-pot fashion[a]
27	85%	72%	**40**	94%	71%
28	40%	36%	**41**	65%	60%
30	45%	41%	**43**	80%	84%
31	74%	59%	**44**	86%	87%
32	62%	67%	**45**	84%	87%
36	60%	57%	**49**	73%	56%
37	70%	42%	**50**	77%	61%
38	66%	68%	**51**	78%	66%
39	66%	39%	**52**	69%	43%

[a] global yields calculated for the synthesis in two-pot of thienopyridines

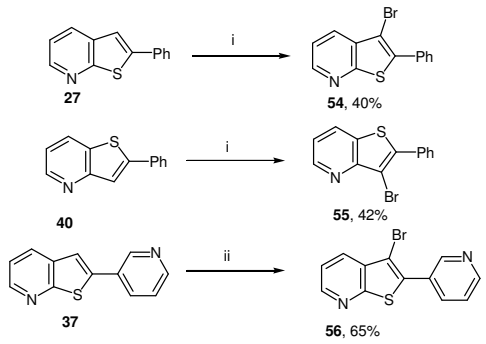
To valorize this work, some of the thienopyridines obtained were further functionalized. Our group is interested in the synthesis of di(hetero)arylureas from thienopyridine derivatives bearing an amine moiety. Indeed, it has been well established that urea derivatives have got a significant place in modern medicinal chemistry as they have been reported in the literature as anticancer agents,[10] anticonvulsant[11] and $CXCR_3$ antagonist.[12] 1,3-Diarylurea derivatives, and particularly in the thienopyridine series, were also reported as cell growth factor receptor tyrosine kinase inhibitors, as anticancer and/or antiangiogenic compounds.[1f,13] The reaction of 2-(thieno[3,2-*b*]pyridin-2-yl)aniline **43** with 4-methoxyphenylisocyanate was performed at room temperature and successfully provided the expected 1-(4-methoxyphenyl)-3-[2-(thieno[3,2-*b*]pyridin-2-yl)phenyl]urea **53** in excellent yield (Scheme 4).



Scheme 4. Synthesis of the new 1,3-diarylurea **53** from thieno[3,2-*b*]pyridine **43** and 4-methoxyphenylisocyanate.

The halogenation of some thienopyridines was also performed. The presence of a bromine or a chlorine atom will allow further functionalizations by metal-catalyzed coupling reactions (C-C, C-N and C-O) or nucleophilic substitution, leading to the synthesis of new thienopyridine derivatives.

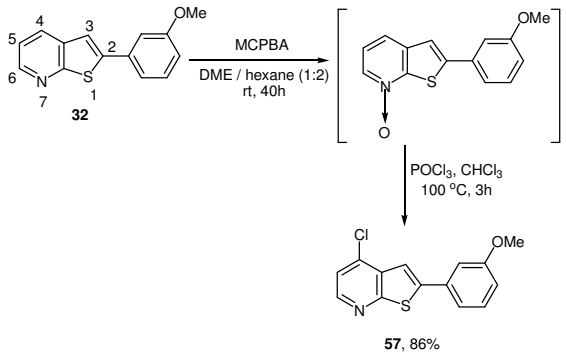
The bromination in the 3-position of the 2-phenylthienopyridines **27** and **40** was done using Br_2 in dry ether at 0 ºC, affording the corresponding 3-bromo-2-phenylthienopyridines **54** and **55** in moderate yields (Scheme 5). With 2-(pyridin-3-yl)thieno[2,3-*b*]pyridine **37**, the expected 3-bromo derivative **56** was obtained in a good yield (65%) using dry CH_2Cl_2 as the solvent due to the low solubility of the starting material.



Scheme 5. i: Br_2 (1.1 equiv.), dry Et_2O, 0ºC, 30-60 min. ii: dry CH_2Cl_2 used as the solvent.

Compound **55** was already obtained by Fort *et al.*[3d] in a total yield of 32% in a three-step methodology starting from 3-methylthiopyridine (that has to be previously synthesized by reacting 3-bromopyridine with *t*BuLi and dimethylsulfur). However this methodology implies the use of delicate reaction conditions (the use of *n*BuLi and *t*BuLi requires to work in extremely dry conditions, under argon, and at temperatures as low as -90ºC), and the reactions were not completely regioselective. In our case, product **55** was synthesized from the commercially available 2-bromo-3-chloropyridine also in three steps in a better total yield (40% through the one-pot procedure for compound **40**), using simple and regioselective reactions.

Chlorination in the 4-position of the thieno[2,3-*b*]pyridine **32** was also performed, following a procedure *via* the preparation of the *N*-oxide using 3-chloroperoxybenzoic acid (MCPBA).[14] After evaporation of the solvents the solid obtained was treated with $POCl_3$ using $CHCl_3$ as the solvent[15] to afford the 4-chlorothieno[2,3-*b*]pyridine **57** in high yield (Scheme 6). This will allow the functionalization of the pyridine ring of the system which is also important for the synthesis of biologically active compounds.



Scheme 6. Chlorination in the 4-position of thieno[2,3-*b*]pyridine **32**.

3. Conclusion

We have developed a general and efficient methodology for the synthesis of 2-(hetero)arylthieno[2,3-*b*] or [3,2-*b*]pyridines from 2,3-dihalopyridines, (hetero)arylalkynes and Na_2S, that works also in a one-pot procedure, reducing significantly the time of the last steps. The compounds obtained were submitted to further functionalizations. A 1,3-diarylurea was prepared as an example of functionalization of thienopyridines bearing an aniline with an arylisocyanate. The corresponding 3-bromo-2-(hetero)arylthienopyridines were successfully obtained after bromination with bromine. An example of chlorination in the pyridine ring was also presented with the synthesis of the 4-chloro-2-(3-methoxyphenyl)thieno[2,3-*b*]pyridine, *via* the corresponding *N*-oxide followed by the reaction with $POCl_3$. These thienopyridines may be used as precursors to synthesize biologically active compounds.

4. Experimental section

4.1. **General methods:** Melting points (°C) were determined in a Stuart SMP3 and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance III at 400 and 100.6 MHz or on a Varian Unity Plus at 300 and 75.4 MHz, respectively. Heteronuclear correlations ^1H-^{13}C, HMQC or HSQC and HMBC were performed to attribute some signals. Elemental analyses were determined on a LECO CHNS 932 elemental analyzer. MS-EI, MS-ESI and HRMS on the M^+ or on the $[M^+H]$ data were recorded by the mass spectrometry service of the University of Vigo, Spain.

Column chromatography was performed on Macherey-Nagel silica gel 230-400 mesh or on silica-gel. Preparative layer chromatography (PLC) was performed on Macherey–Nagel 20 x 20 cm^2 silica plates, layer 2 mm SIL G-200 UV_{254}. Petroleum ether refers to the boiling range 40-60 °C. Ether refers to diethyl ether. The increase of polarity in solvent gradient was made from neat petroleum ether to mixtures of ether/petroleum ether, increasing 10% of ether each time until the isolation of the products, unless stated otherwise. The most polar products were isolated using neat ether, mixtures of ether/ethyl acetate or neat ethyl acetate.

4.2. **General experimental conditions for the Sonogashira reactions:**

In a dry Schlenk tube, the dihalopyridine, CuI (6 mol%) and $PdCl_2(PPh_3)_2$ (3 mol%) were added in Et_3N (2 ml per mmol of pyridine). After stirring for 10 minutes, the (hetero)arylacetylene (1.0 or 1.1 equiv.) was added, and the solution was heated to 100 °C in a silicone bath for 2h. The reactions were monitored by TLC, following the disappearance of the starting materials. After completion, the mixture was allowed to cool to room temperature. Then ethyl acetate and water were added and the organic phase was separated, dried ($MgSO_4$) and filtered. Removal of the solvent under reduced pressure gave either oils which were submitted to column chromatography or pure products corresponding to the expected (hetero)arylethynyl)pyridines.

*4.2.1. 2-Chloro-3-(phenylethynyl)pyridine (**1**) and 2,3-bis(phenylethynyl)pyridine*

From 3-bromo-2-chloropyridine (192 mg, 1.00 mmol) and phenylacetylene (1.1 equiv.) and after purification by column chromatography using a solvent gradient from neat petroleum ether to 10% ether/petroleum ether, compound **1** was obtained as an yellow solid (170 mg, 80%). Recrystallization from ether/petroleum ether gave yellow crystals, m.p. 57-59 ºC. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.23-7.26 (dd, *J* = 7.6 and 4.8 Hz, 1H, 5-H), 7.38-7.40 (m, 3H, Ar-H), 7.58-7.60 (m, 2H, Ar-H), 7.86 (dd, *J* = 7.6 and 2.0 Hz, 1H, 4-H), 8.35 (dd, *J* = 4.8 and 2.0 Hz, 1H, 6-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ =

83.20 (C), 95.82 (C), 119.60 (3-C), 120.85 (5-CH), 121.21 (C), 127.46 (2 × CH), 128.15 (4´-CH), 130.75 (2 × CH), 140.17 (4-CH), 147.15 (6-CH), 151.30 (2-C) ppm. MS-EI: m/z (%) 215 (M^+ ^{37}Cl, 25) 213 (M^+ ^{35}Cl, 25). HRMS: Calcd for $C_{13}H_8{}^{35}ClN$ [M^+] 213.0345. Found 213.0346. Calcd for $C_{13}H_8{}^{37}ClN$ [M^+] 215.0316. Found 215.0322.

In another fraction of the column chromatography eluted with 20% ether/petroleum ether, 2,3-bis(2-phenylethynyl)pyridine was isolated as a brownish oil (17.0 mg, 6 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26 (dd, *J* = 8.0 and 5.2 Hz, 1H, 5-H), 7.36-7.39 (m, 6H), 7.58-7.61 (m, 2H), 7.64-7.66 (m, 2H), 7.87 (dd, *J* = 8.0 and 1.6 Hz, 1H, 4-H), 8.57 (dd, *J* = 5.2 and 1.6 Hz, 1H, 6-H,) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): 85.84 (C), 87.73 (C), 93.64 (C), 96.17 (C), 122.03 (5-CH), 122.29 (C), 122.64 (C),123.08 (C), 128.41 (2 × CH), 128.48 (2 × CH), 128.95 (CH), 129.18 (CH), 131.69 (2 × CH), 132.16 (2 × CH), 138.96 (4-CH), 144.90 (C), 148.57 (6-CH) ppm. MS-EI: m/z (%) 279 (M^+, 100). HRMS: Calcd for $C_{21}H_{13}N$ [M^+] 279.1048. Found 279.1049.

*4.2.2. 4-[(2-Chloropyridin-3-yl)ethynyl]aniline (**2**)*

From 3-bromo-2-chloropyridine (144 mg, 0.750 mmol) and 4-ethynylaniline (1.1 equiv.) and after purification by column chromatography using a solvent gradient from 40% ether/petroleum ether to 50% ether/petroleum ether, compound **2** was obtained as a yellow pale solid (68.0 mg, 40%). Recrystallization from ether/petroleum ether gave pale yellow crystals, m.p. 111-113 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.96 (br s, 2H, NH_2), 6.65 (d, *J* = 8.4 Hz, 2H, 3 and 5-H), 7.21 (dd, *J* = 7.6 and 4.8 Hz, 1H, 5'-H), 7.39 (d, *J* = 8.4 Hz, 2H, 2 and 6-H), 7.81 (dd, *J* = 7.6 and 2.0 Hz, 1H, 4'-H), 8.29 (br d, 1H, 6'-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 82.52 (C), 98.03 (C), 111.39 (C), 114.69 (3 and 5-CH), 121.25 (C), 121.81 (5´-CH), 132.67 (C), 133.22 (2 and 6-CH), 140.72 (4'-CH), 147.42 (6´-CH), 151.93 (C) ppm. MS-EI: m/z (%) 230 (M^+ ^{37}Cl, 25), 228 (M^+ ^{35}Cl, 100). HRMS: Calcd for $C_{13}H_9{}^{35}ClN_2$ [M^+] 228.0454. Found 228.0452. Calcd for $C_{13}H_9{}^{37}ClN_2$ [M^+] 228.0425. Found 228.0435.

*4.2.3. 3-[(2-Chloropyridin-3-yl)ethyny]aniline (**3**)*

From 3-bromo-2-chloropyridine (150 mg, 0.770 mmol) and 3-ethynylaniline (1.1 equiv.) and after purification by column chromatography using a solvent gradient from 35% ether/petroleum ether to 50% ether/petroleum ether, compound **3** was obtained as a yellow oil (95.2 mg, 55%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.65 (br s, 2H, NH_2), 6.70-6.73 (m, 1H, 6-H), 6.88-6.92 (m, 1H, 2-H), 6.92-6.99 (m, 1H, 4-H), 7.16 (apparent t, *J* = 8.0 Hz, 1H, 5-H), 7.23 (dd, *J* = 8.0 and 4.8 Hz, 1H, 5'-H), 7.84 (dd, *J* = 8.0 and 1.6 Hz, 1H, 4'-H), 8.33 (dd, *J* = 4.8 and 1.6 Hz, 1H, 6'-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 83.57 (C), 97.17 (C), 116.15 (6-CH), 117.78 (2-CH), 120.69 (C), 121.83 (5´-CH), 122.11 (4-CH), 122.83 (C), 129.39 (5-CH), 141.14 (4'-CH), 146.35 (C), 148.03 (6´-CH), 152.27 (C) ppm. MS-EI: m/z (%) 230 (M^+ ^{37}Cl, 27), 228 (M^+ ^{35}Cl, 100). HRMS: Calcd for $C_{13}H_9{}^{35}ClN_2$ [M^+] 228.0454. Found 228.0449. Calcd for $C_{13}H_9{}^{37}ClN_2$ [M^+] 230.0425. Found 230.0430.

*4.2.4. 2-[(2-Chloropyridin-3-yl)ethynyl]aniline (**4**)*

From 3-bromo-2-chloropyridine (192 mg, 1.00 mmol) and 2-ethynylaniline (1.1 equiv.) and after purification by column chromatography using a solvent gradient from 50% ether/petroleum ether to 60% ether/petroleum ether, compound **4** was obtained as a brown solid (116 mg, 50%). Recrystallization from ether/petroleum ether gave pale brown crystals, m.p. 97-98 ºC. ^{1}H NMR (400MHz, $CDCl_3$): δ = 4.35 (br s, 2H, NH_2), 6.71-6.77 (m, 2H), 7.17-7.22 (m, 1H), 7.25 (dd, *J* = 7.6 and 4.8 Hz, 1H, 5'-H), 7.39 (dd, *J* = 7.6 and 1.2 Hz, 1H, 5-H), 7.86 (dd, *J* = 7.6 and 1.8 Hz, 1H, 4'-H), 8.33 (br d,1H, 6'-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 89.67 (C), 94.13 (C), 106.60 (C), 114.53 (CH), 117.94 (CH), 120.69 (C), 121.99 (5´-CH), 130.69 (CH), 132.08 (5-CH), 140.64 (4'-CH), 147.87 (6´-CH), 148.44 (C), 151.58 (C) ppm. MS-EI: m/z (%) 230 (M^+ ^{37}Cl, 27), 228 (M^+ ^{35}Cl, 100). HRMS: Calcd for $C_{13}H_9{}^{35}ClN_2$ [M^+] 228.0454. Found 228.0450. Calcd for $C_{13}H_9{}^{37}ClN_2$ [M^+] 230.0425. Found 230.0429.

*4.2.5. 2-Chloro-3-[(4-methoxyphenyl)ethynyl]pyridine(**5**)*

From 3-bromo-2-chloropyridine (150 mg, 0.780 mmol) and 1-ethynyl-4-methoxybenzene (1.0 equiv) and after purification by column chromatography using a solvent gradient from 25% ether/petroleum ether to 30% ether/petroleum ether, compound **5** was obtained a yellow solid (120.0 mg, 65%) m. p. 59-60 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.85 (s, 3H, OMe), 6.91 (d, *J* = 8.8 Hz, 2H, 3' and 5'-H), 7.24 (dd, *J* = 8.0 and 4.8 Hz, 1H, 5-H), 7.52 (d, *J* = 8.8 Hz, 2H, 2' and 6'-H), 7.84 (dd, *J* = 8.0 and 1.6 Hz, 1H, 4-H), 8.32 (dd, *J* = 4.8 and 1.6 Hz, 1H, 6-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 55.33 (OMe), 83.05 (C), 97.25 (C), 114.13 (3' and 5'-CH), 114.22 (C), 121.05 (C), 121.88 (5-CH), 133.32 (2' and 6'-CH), 141.05 (4-CH), 147.57 (6-CH), 151.94 (C), 160.34 (C) ppm. MS-EI: m/z (%) 245 (M^+ ^{37}Cl, 28), 243 (M^+ ^{35}Cl, 100). HRMS: Calcd for $C_{14}H_{10}{}^{35}ClNO$ [M^+] 243.0451. Found 243.0450. Calcd for Calcd for $C_{14}H_{10}{}^{37}ClNO$ [M^+] 245.0421. Found 245.0427.

*4.2.6. 2-Chloro-3-[(3-methoxyphenyl)ethynyl]pyridine(**6**)*

From 3-bromo-2-chloropyridine (150 mg, 0.780 mmol) and 1-ethynyl-3-methoxybenzene (1.0 equiv) and after purification by column chromatography using a solvent gradient from 25% ether/petroleum ether to 30% ether/petroleum ether, compound **6** was obtained as a colorless oil (140 mg, 74%) ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.84 (s, 3H, OMe), 6.94-6.97 (m, 1H, 4'-H), 7.09-7.11 (m, 1H, 2'-H), 7.17-7.20 (m, 1H, 6'-H), 7.24 (dd, *J* = 8.0 and 4.8 Hz, 1H, 5-H), 7.27-7.31 (m, 1H, 5'-H), 7.86 (dd, *J* = 8.0 and 1.6 Hz, 1H, 4-H), 8.34 (dd, *J* = 4.8 and 1.6 Hz, 1H, 6-H) ppm. ^{13}C NMR (100.6MHz, $CDCl_3$): δ = 55.32 (OMe), 83.96 (C), 96.73 (C), 115.74 (4'-CH), 116.48 (2'-CH), 120.53 (C), 121.84 (5-CH), 123.76 (C), 124.31 (6'-CH), 129.54 (5'-CH), 141.20 (4-CH), 148.18 (6-CH), 152.30 (C), 159.38 (C) ppm. MS-EI: m/z (%) 245 (M^+ ^{37}Cl, 29), 243 (M^+ ^{35}Cl, 100). HRMS: Calcd for $C_{14}H_{10}{}^{35}ClNO$ [M^+] 243.0451. Found 243.0443. Calcd for $C_{14}H_{10}{}^{37}ClNO$ [M^+] 245.0421. Found 245.0430.

*4.2.7. 2-Chloro-3-[(2-methoxyphenyl)ethynyl]pyridine(**7**)*

From 3-bromo-2-chloropyridine (150 mg, 0.780 mmol) and 1-ethynyl-2-methoxybenzene (1.0 equiv) and after purification by column chromatography using a solvent gradient from 25% ether/petroleum ether to 30% ether/petroleum ether, compound **7** was obtained as a colorless oil (118 mg, 64%) ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.93 (s, 3H, OMe), 6.92-6.99 (m, 2H), 7.23 (dd, *J* = 8.0 and 4.8 Hz, 1H, 5-H), 7.34-7.39 (m, 1H), 7.54 (dd, *J* = 8.0 and 2.0 Hz, 1H, 6'-H), 7.89 (dd, *J* = 8.0 and 1.6 Hz, 1H, 4-H), 8.32 (dd, *J* = 4.8 and 1.6 Hz, 1H, 6-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 55.88 (OMe), 88.10 (C), 93.52 (C), 110.83 (CH), 111.48 (C), 120.54 (CH), 120.92 (C), 121.76 (5-CH), 130.70 (6'-CH), 133.67 (4-CH), 141.16

(C), 147.94 (6-CH), 152.20 (C), 160.25 (C) ppm. MS-EI: m/z (%) 245 (M^{+} ^{37}Cl, 41), 243 (M^{+} ^{35}Cl, 100). HRMS: Calcd for $C_{14}H_{10}{}^{35}ClNO$ [M^{+}] 243.0451. Found 243.0450. Calcd for $C_{14}H_{10}{}^{37}ClNO$ [M^{+}] 245.0421. Found 245.0415.

*4.2.8. 3-[(4-Bromophenyl)ethynyl]-2-chloropyridine (**8**)*

From 3-bromo-2-chloropyridine (150 mg, 0.770 mmol) and 1-bromo-4-ethynylbenzene (1.0 equiv) and after purification by column chromatography using a solvent gradient from 25% ether/petroleum ether to 30% ether/petroleum ether, compound **8** was obtained a yellow solid (90 mg, 40%), m. p. 99-100 ºC. ^{1}H NMR (400 MHz, acetone-d_6): δ = 7.49-7.51 (m, 1H, 5-H), 7.67 (d, *J* = 8.8 Hz, 2H, 2' and 6'-H), 7.69 (d, *J* = 8.8 Hz, 2H, 3' and 5'-H), 8.09-8.12 (m, 1H, 4-H), 8.44-8.46 (m, 1H, 6-H) ppm. ^{13}C NMR (100.6 MHz, acetone-d_6): δ = 90.57 (C), 96.54 (C), 120.58 (C), 122.17 (C), 123.56 (5-CH), 124.06 (C), 132.85 (2' and 6'-CH), 134.17 (3' and 5'-CH), 142.57 (4-CH), 149.87 (6-CH), 152.39(C) ppm. MS-ESI: m/z (%) 296 (M^{+} ^{81}Br^{37}Cl+H, 25), 294 (M^{+} ^{81}Br^{35}Cl or ^{79}Br^{37}Cl +H, 100), 292 (M^{+}^{79}Br^{35}Cl+H, 81). HRMS: Calcd for $C_{13}H_7{}^{79}Br^{35}ClN$ [M^{+}+H] 291.9529. Found 291.9524. Calcd for $C_{13}H_7{}^{81}Br^{35}ClN$ [M^{+}+H] 293.9502. Found 293.9502. Calcd for $C_{13}H_7{}^{79}Br^{37}ClN$ [M^{+}+H] 293.9499. Found 293.9502. Calcd for $C_{13}H_7{}^{81}Br^{37}ClN$ [M^{+}+H] 295.9479. Found 295.9478.

*4.2.9. 2-Chloro-3-[(3-fluorophenyl)ethynyl]pyridine (**9**)*

From 3-bromo-2-chloropyridine (100 mg, 0.530 mmol) and 1-ethynyl-3-fluorobenzene (1.0 equiv) and after purification by column chromatography using a solvent gradient from 25% ether/petroleum ether to 30% ether/petroleum ether, compound **9** was obtained as a colourless oil (80.0 mg, 70 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.08-7.13 (m, 1H), 7.24-7.28 (m, 2H), 7.35-7.37 (m, 2H), 7.87 (dd, *J* = 8.0 and 1.6 Hz, 1H, 4-H), 8.37 (dd, *J* = 4.8 and 1.6 Hz, 1H, 6-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 84.93 (C), 95.34 (d, *J* = 4.0 Hz, C), 116.53 (d, *J* = 21.1 Hz, CH), 118.51 (d, *J* = 23.1 Hz, CH), 120.17 (C), 121.88 (5-CH), 124.00 (d, *J* = 10.1 Hz, 1'-C), 127.66 (d, *J* = 3.0 Hz, 6'- CH), 130.10 (d, *J* = 9.1 Hz, 5'-CH), 141.29 (4-CH), 148.48 (6-CH), 152.37 (C), 162.35 (d, *J* = 247.5 Hz, CF) ppm. MS-EI: m/z (%) 233 (M^{+} ^{37}Cl, 36), 231 (M^{+} ^{35}Cl, 100). HRMS: Calcd for $C_{13}H_7{}^{35}ClFN$ [M^{+}] 231.0251. Found 231.0259. Calcd for $C_{13}H_7{}^{37}ClFN$ [M^{+}] 233.0222. Found 233.0230.

*4.2.10. 2-Chloro-3-[(thiophen-3-yl)ethynyl]pyridine (**10**)*

From 3-bromo-2-chloropyridine (150 mg, 0.770 mmol) and 3-ethynylthiophene (1.1 equiv) and after purification by column chromatography using 30% ether/petroleum ether, compound **10** was obtained as a colorless oil (117 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23-7.25 (m, 2H), 7.33-7.35 (m, 1H), 7.62-7.65 (m, 1H), 7.85 (dd, *J* = 8.0 and 2.0 Hz, 1H, 4-H), 8.34 (dd, *J* = 4.8 and 2.0 Hz, 1H, 6-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 83.77 (C), 92.05 (C), 120.61 (C), 121.29 (C), 121.84 (CH), 125.72 (CH), 129.72 (CH), 129.95 (CH), 141.14 (4-CH), 148.05 (6-CH), 152.12 (C) ppm. MS-ESI: m/z (%) 222 (M^{+} ^{37}Cl+H, 40), 220 (M^{+} ^{35}Cl+H, 100) HRMS: Calcd for $C_{11}H_7ClNS$ [M^{+} ^{35}Cl] 219.9988. Found 219.9993. Calcd for $C_{11}H_7ClNS$ [M^{+} ^{37}Cl] 221.9958. Found 221.9952.

*4.2.11. 2-Chloro-3-(pyridin-3-ylethynyl)pyridine (**11**)*

From 3-bromo-2-chloropyridine (192 mg, 1.00 mmol) and 3-ethynylpyridine (1.1 equiv.) and after purification by column chromatography using a solvent gradient from 40% ether/petroleum ether to 50% ether/petroleum ether, compound **11** was obtained as a white-off solid (130 mg, 60%). Recrystallization from ether/petroleum ether gave off-white crystals, m.p. 64-66 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24-7.27 (dd, *J* = 7.6 and 4.8 Hz, 1H, 5-H), 7.31-7.34 (m, 1H), 7.85-7.88 (m, 2H), 8.37 (dd, *J* = 4.8 and 1.6 Hz, 1H, 6-H), 8.60 (dd, *J* = 5.2 and 1.6 Hz, 1H, 6'-H), 8.81 (br s, 1H, 2'-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): 87.33 (C), 93.10 (C), 119.51 (C), 119.85 (C), 121.89 (5-CH), 123.16 (CH), 138.68 (CH), 141.30 (CH), 148.72 (6-CH), 149.21 (6'-CH), 152.11 (2'-CH), 152.33 (C) ppm. Anal. Calcd for $C_{12}H_7ClN_2$ (214.65): C, 67.15; H, 3.29; N, 13.05. Found: C, 66.99; H, 3.42; N, 12.76.

*4.2.12. 2-Chloro-3-(pyridin-2-ylethynyl)pyridine (**12**)*

From 3-bromo-2-chloropyridine (150.0 mg, 0.770 mmol) and 2-ethynylpyridine (1.0 equiv) and after purification by column chromatography using a solvent gradient from 35% ether/petroleum ether to 40% ether/petroleum ether, compound **12** was obtained as a colorless oil (83.0 mg, 50%) ^{1}H NMR (400 MHz, acetone-d_6): δ = 7.46-7.49 (m, 1H), 7.53 (dd, *J* = 8.0 and 4.8 Hz, 1H, 5-H), 7.70-7.73 (m, 1H), 7.89-7.93 (m, 1H), 8.16 (dd, *J* = 8.0 and 2.0 Hz, 1H, 4-H), 8.48 (dd, *J* = 4.8 and 2.0 Hz, 1H, 6-H) 8.68-8.70 (m, 1H, 3'-H) ppm. ^{13}C NMR (100.6 MHz, acetone-d_6): δ = 83.62 (C), 96.44 (C), 120.19 (C), 123.57 (5-CH), 124.72 (CH), 128.48 (CH), 137.39 (CH), 143.03 (4-CH), 143.28 (C), 150.24 (6-CH), 151.23 (6'-CH) 152.62 (C) ppm. MS-EI: m/z (%) 216 (M^{+} ^{37}Cl, 29), 214 (M^{+} ^{35}Cl, 100). HRMS: Calcd for $C_{12}H_7{}^{35}ClN_2$ [M^{+}] 214.0298. Found 214.0297. Calcd for $C_{12}H_7{}^{37}ClN_2$ [M^{+}] 216.0268. Found 216.0274.

*4.2.13. 2-Chloro-3-[(1-methyl-1H-imidazol-5-yl)ethynyl]pyridine (**13**)*

From 3-bromo-2-chloropyridine (192 mg, 1.00 mmol) and 5-ethynyl-1-methyl-1*H*-imidazole (1.1 equiv.) and after purification by column chromatography using neat ethyl acetate as the solvent, compound **13** was obtained as an off-white solid (116 mg, 55%). Recrystallization from ether/petroleum ether gave yellow crystals, m.p. 120-122 ºC. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.74 (s, 3H, NMe), 7.42 (br s, 1H), 7.50 (dd, *J* = 7.8 and 4.8 Hz, 1H, 5-H), 7.86 (br s, 1H), 8.17 (dd, *J* = 7.8 and 2.0 Hz, 1H, 4-H), 8.42 (dd, *J* = 4.8 and 2.0 Hz, 1H, 6-H) ppm. ^{13}C NMR (75.4 MHz, DMSO-d_6): δ = 30.65 (NMe), 85.38 (C), 91.09 (C), 118.98 (C), 123.06 (5-CH), 135.63 (C), 141.46 (4-CH), 149.01 (6-CH), 150.11 (C) ppm. MS-ESI: m/z (%) 220 (M^{+} ^{37}Cl+H, 37), 218 (M^{+} ^{35}Cl+H, 100). HRMS: Calcd for $C_{11}H_9{}^{35}ClN_3$ [M^{+}+H] 218.0480. Found 218.0472. Calcd for $C_{11}H_9{}^{37}ClN_3$ [M^{+}+H] 220.0455. Found 220.0451.

*4.2.14. 3-Chloro-2-(phenylethynyl)pyridine (**14**)*

From 2-bromo-3-chloropyridine (96.0 mg, 0.500 mmol) and phenylacetylene (1.1 equiv.) and after purification by column chromatography using a solvent gradient from neat petroleum ether to 20% ether/petroleum ether, compound **14** was obtained as a yellow solid (94.0 mg, 88%). Recrystallization from ether/petroleum ether gave yellow crystals, m.p. 48-50 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22 (dd, *J* = 8.0 and 4.8 Hz, 1H, 5-H), 7.37-7.41 (m, 3H, 3´, 4´and 5´-H), 7.64-7.67 (m, 2H, 2´and 6´-H), 7.77 (dd, *J* = 8.0 and 1.6 Hz, 1H, 4-H), 8.52 (br d, 1H, 6-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 85.78 (C), 94.83 (C), 121.91 (C), 123.36 (5-CH), 128.41 (3´and 5´-CH),

129.37 (4´-CH), 132.20 (2´and 6´-CH), 134.14 (C), 136.72 (4-CH), 142.04 (C), 147.70 (6-CH) ppm. Anal. Calcd for $C_{13}H_8ClN$ (213.66): C, 73.08; H, 3.77; N, 6.56. Found: C, 72.77; H, 3.80; N, 6.59.

*4.2.15. 4-[(3-Chloropyridin-2-yl)ethynyl]aniline (**15**)*

From 2-bromo-3-chloropyridine (96.0 mg, 0.500 mmol) and 4-ethynylaniline (1.1 equiv.) and after purification by column chromatography using a solvent gradient from 50% ether/petroleum ether to 70% ether/petroleum ether, compound **15** was obtained as an orange solid (80.0 mg, 70%). Recrystallization from ether/petroleum ether gave yellow crystals, m.p. 161-163 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.92 (br s, 2H, NH_2), 6.65 (d, *J* = 8.4 Hz, 2H, 2- and 6-H), 7.15 (dd, *J* = 8.2 and 4.6 Hz, 1H, 5'-H), 7.45 (d, *J* = 8.4 Hz, 2H, 3- and 5-H), 7.73 (dd, *J* = 8.2 and 1.4 Hz, 1H, 4'-H), 8.48 (dd, *J* = 4.6 and 1.4 Hz, 1H, 6'-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 84.47 (C), 96.29 (C), 111.00 (C), 114.59 (2 and 6-CH), 122.63 (5´-CH), 133.50 (C), 133.78 (3 and 5-CH), 136.50 (4´-CH), 142.66 (C), 147.64 (6´-CH), 147.68 (C) ppm. MS-EI: m/z (%) 230 (M^+ ^{37}Cl, 30), 228 (M^+ ^{35}Cl, 100). HRMS: Calcd for $C_{13}H_9{}^{35}ClN_2$ [M^+] 228.0454. Found 228.0462. Calcd for $C_{13}H_9{}^{37}ClN_2$ [M^+] 230.0425. Found 230.0434.

*4.2.16. 3-[(3-Chloropyridin-2-yl)ethynyl]aniline (**16**)*

From 2-bromo-3-chloropyridine (96.0 mg, 0.500 mmol) and 3-ethynylaniline (1.1 equiv.) and after purification by column chromatography using a solvent gradient from 50% ether/petroleum ether to 70% ether/petroleum ether, compound **16** was obtained as a beige solid (95.0 mg, 83%). Recrystallization from ether/petroleum ether gave beige crystals, m.p. 109-111 ºC. ^{1}H NMR (400MHz, $CDCl_3$): δ = 3.16 (br s, 2H, NH_2), 6.72 (br d, 1H), 6.96 (br s, 1H, 2-H), 7.05 (br d, 1H), 7.14-7.22 (m, 2H, 5'-H and ArH), 7.75 (dd, *J* = 8.2 and 1.4 Hz, 1H, 4'-H), 8.51 (br d, 1H, 6'-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 85.26 (C), 95.12 (C), 116.43 (CH), 118.28 (2-CH), 122.56 (C), 122.69 (CH), 123.27 (5´-CH), 129.34 (CH), 134.13 (C), 136.64 (4´-CH), 142.16 (C), 146.21 (C), 147.72 (6´-CH) ppm. MS-EI: m/z (%) = 230 (M^+ ^{37}Cl, 30), 228 (M^+ ^{35}Cl, 100). HRMS: Calcd for $C_{13}H_9{}^{35}ClN_2$ [M^+] 228.0454. Found 228.0457 [M^+]. Calcd for $C_{13}H_9{}^{37}ClN_2$ [M^+] 230.0425. Found 230.0434.

*4.2.17. 2-[(3-Chloropyridin-2-yl)ethynyl]aniline (**17**)*

From 2-bromo-3-chloropyridine (120 mg, 0.624 mmol) and 2-ethynylaniline (80.0 mg, 0.687 mmol) and after purification by column chromatography using a solvent gradient from 50% ether/petroleum ether to 70% ether/petroleum ether, compound **17** was obtained as a yellow solid (126 mg, 89%). Recrystallization from ether/petroleum ether gave beige crystals, m.p. 111-112 ºC. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.53 (br s, 2H, NH_2), 6.57-6.61 (m, 1H, 4-H), 6.77-6.80 (m, 1H, 6-H), 7.15-7.19 (m, 1H, 5-H), 7.28-7.32 (m, 1H, 3-H), 7.42 (dd, *J* = 8.0 and 4.8 Hz, 1H, 5'-H), 8.05 (dd, *J* = 8.0 and 1.6 Hz, 1H, 4'-H), 8.55 (dd, *J* = 4.8 and 1.6 Hz, 1H, 6'-H) . ^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 91.03 (C), 91.95 (C), 103.79 (C), 114.17 (6-CH), 116.17 (4-CH), 124.18 (5´-CH), 131.11 (5-CH), 132.03 (3-CH), 132.33 (C), 137.00 (4'-CH), 140.99 (C), 148.38 (6´-CH), 150.27 (C). MS-EI: m/z (%) 230 (M^+ ^{37}Cl, 27), 228 (M^+ ^{35}Cl, 100). HRMS: Calcd for $C_{13}H_9{}^{35}ClN_2$ [M^+] 228.0454. Found 228.0465 [M^+]. Calcd for $C_{13}H_9{}^{37}ClN_2$ [M^+] 230.0425. Found 230.0436.

*4.2.18. 3-Chloro-2-[(4-methoxyphenyl)ethyny]pyridine (**18**)*

From 2-bromo-3-chloropyridine (100 mg, 0.530 mmol) and 1-ethynyl-4-methoxybenzene (1.0 equiv), compound **18** was obtained a yellow solid (114.0 mg, 90%). Recrystallization from ether/petroleum ether gave beige crystals, m.p. 64-65ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.83 (s, 3H, OMe), 6.90 (d, *J* = 8.8 Hz, 2H, 3' and 5'-H), 7.21-7.22 (m, 1H, 5-H), 7.59 (d, *J* = 8.8 Hz, 2H, 2' and 6'-H), 8.73-8.77 (m, 1H, 4-H), 8.50-8.54 (m, 1H, 6-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 55.29 (OMe), 84.87 (C), 95.56 (C), 113.85 (C), 114.08 (3' and 5'-CH), 123.04 (5-CH), 133.81 (2' and 6'-CH), 133.97 (C), 136.68 (4-CH), 142.23 (C), 147.47 (6-CH), 160.53 (C) ppm. MS-EI: m/z (%) 245 (M^+ ^{37}Cl, 29), 243 (M^+ ^{35}Cl, 100). HRMS: Calcd for $C_{14}H_{10}{}^{35}ClNO$ [M^+] 243.0451. Found 243.0449. Calcd for $C_{14}H_{10}{}^{37}ClNO$ [M^+] 245.0421. Found 245.0427.

*4.2.19. 3-Chloro-2-[(3-methoxyphenyl)ethynyl]pyridine (**19**)*

From 2-bromo-3-chloropyridine (100 mg, 0.530 mmol) and 1-ethynyl-3-methoxybenzene (1.0 equiv.) compound **19** was obtained as oil (120.0 mg, 92%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.79 (s, 3H, OMe), 6.91-6.94 (m, 1H), 7.14-7.25 (m, 4H), 7.71 (dd, *J* = 8.2 and 1.2 Hz, 1H, 4-H), 8.50 (dd, *J* = 4.8 and 1.2 Hz, 1H, 6-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 55.20 (OMe), 85.44 (C), 94.83 (C), 116.04 (CH), 116.64 (CH), 122.68 (C), 123.34 (CH), 124.50 (CH), 129.37 (CH), 134.03 (C), 136.60 (4-CH), 141.79 (C), 147.76 (6-CH), 159.19 (C) ppm. MS-EI: m/z (%) 245 (M^+ ^{37}Cl, 31), 243 (M^+ ^{35}Cl, 100). HRMS: Calcd for $C_{14}H_{10}{}^{35}ClNO$ [M^+] 243.0451. Found 243.0454. Calcd for $C_{14}H_{10}{}^{37}ClNO$ [M^+] 245.0421. Found 245.0428.

*4.2.20. 3-Chloro-2-[(2-methoxyphenyl)ethynyl]pyridine (**20**)*

From 2-bromo-3-chloropyridine (100 mg, 0.530 mmol) and 1-ethynyl-2-methoxybenzene (1.0 equiv), compound **20** was obtained as oil (118.0 mg, 90%) ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.89 (s, 3H, OMe), 6.88-6.95 (m, 2H), 7.17 (dd, *J* = 8.4 and 4.8 Hz, 1H, 5-H), 7.31-7.36 (m, 1H), 7.56-7.58 (m, 1H), 7.70-7.73 (m, 1H), 7.50 (dd, *J* = 4.8 and 1.6 Hz, 1H, 6-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 55.77 (OMe), 89.60 (C), 91.80 (C), 110.72 (CH), 111.03 (C), 120.35 (CH), 123.12 (5-CH), 130.91 (CH), 133.88 (C), 133.94 (CH), 136.62 (CH), 142.11 (C), 147.59 (6-CH), 160.59 (C) ppm. MS-EI: m/z (%) 245 (M^+ ^{37}Cl, 40), 243 (M^+ ^{35}Cl, 100). HRMS: Calcd for $C_{14}H_{10}{}^{35}ClNO$ [M^+] 243.0451. Found 243.0459. Calcd for $C_{14}H_{10}{}^{37}ClNO$ [M^+] 245.0421. Found 245.0429.

*4.2.21. 2-[(4-Bromophenyl)ethynyl]-3-chloropyridine (**21**)*

From 2-bromo-3-chloropyridine (150 mg, 0.770 mmol) and 1-bromo-4-ethynylbenzene (1.0 equiv) and after purification by column chromatography using a solvent gradient from 25% ether/petroleum ether to 30% ether/petroleum ether, compound **21** was obtained a brown solid (192 mg, 85 %), m. p. 71-72ºC. ^{1}H NMR (400 MHz, acetone-d_6): δ = 7.47 (dd, *J* = 8.2 and 4.4 Hz, 1H, 5-H), 7.65 (d, *J* = 8.4 Hz, 2H, 2' and 6'-H), 7.70 (d, *J* = 8.4 Hz, 2H, 3' and 5'-H), 8.00 (dd, *J* = 8.2 and 1.6 Hz, 1H, 4-H), 8.60 (dd, *J* = 4.8 and 1.6 Hz, 1H, 6-H) ppm. ^{13}C NMR (100.6 MHz, acetone-d_6): δ = 87.83 (C), 93.21 (C), 121.85 (C), 124.31 (C), 125.29 (5-CH), 132.87 (3' and 5'-CH), 134.43 (2' and 6'-CH), 134.57 (C), 137.70 (4-CH), 142.07 (C),

149.16 (6-CH) ppm. Anal. Calcd for $C_{13}H_7BrClN$ (292.56): C, 53.37; H, 2.41; N, 4.79. Found: C, 53.04; H, 2.62; N, 4.74.

*4.2.22. 3-Chloro-2-[(3-fluorophenyl)ethynyl]pyridine (**22**)*

From 2-bromo-3-chloropyridine (60.0 mg, 0.300 mmol) and 1-ethynyl-3-fluorobenzene (1.0 equiv) and after purification by column chromatography using a solvent gradient from 25% ether/petroleum ether to 30% ether/petroleum ether, compound **22** was obtained as an oil (40.0 mg, 60 %). ^{1}H NMR (400MHz, $CDCl_3$): δ = 7.08-7.14 (m, 1H), 7.24 (dd, *J* = 8.0 and 4.8 Hz, 1H, 5-H), 7.31-7.38 (m, 2H), 7.42-7.44 (m, 1H), 7.77 (dd, *J* = 8.0 and 1.6 Hz, 1H, 4-H), 8.53 (dd, *J* = 4.8 and 1.6 Hz, 1H, 6-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 86.38 (C), 93.19 (d, *J* = 3.0 Hz, C), 116.82 (d, *J* = 21.1 Hz, CH), 118.89 (d, *J* = 23.0 Hz, CH), 123.66 (5-CH), 128.09 (d, *J* = 3.0 Hz, 6'-CH), 130.04 (d, *J* = 6.0 Hz, 5'-CH), 130.13 (d, *J* = 6.0 Hz, C) 134.33 (C), 136.80 (4-CH), 141.60 (C), 147.76 (6-CH), 162.29 (d, *J* = 247.5 Hz, CF) ppm. MS-EI: m/z (%) 233 (M^+ ^{37}Cl, 33), 231 (M^+ ^{35}Cl, 100). HRMS: Calcd for $C_{13}H_7ClFN$ [M^+ ^{35}Cl] 231.0251. Found 231.0243. Calcd for $C_{13}H_7ClFN$ [M^+ ^{37}Cl] 233.0222. Found 233.0223.

*4.2.23. 3-Chloro-2-[(thiophen-3-yl)ethynyl]pyridine (**23**)*

From 2-bromo-3-chloropyridine (150 mg, 0,770 mmol) and 3-ethynylthiophene (1.1 equiv) and after purification by column chromatography using 30% ether/petroleum ether, compound **23** was obtained as an oil (130.7 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 (dd, *J* = 8.2 and 4.8 Hz, 1H, 5-H) 7.28-7.35 (m, 1H,), 7.32-7.34 (m, 1H), 7.69-7.74 (m, 1H), 7.78 (dd, *J* = 8.2 and 1.6 Hz, 1H, 4-H), 8.52 (dd, *J* = 4.8 and 1.6 Hz, 1H, 6-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 85.13 (C), 90.86 (C), 120.91 (C), 123.31 (5-CH), 125.65 (CH), 130.01 (CH), 131.13 (CH), 134.02 (C), 137.11 (4-CH), 141.70 (C), 147.29 (6-CH) ppm. MS-ESI: m/z (%) 222 [M^+ ^{37}Cl+H, 40], 220 [M^+ ^{35}Cl+H, 100]. HRMS: Calcd for $C_{11}H_7{}^{35}ClNS$ [M^+] 219.9982, found 219.9982. Calcd for $C_{11}H_7{}^{37}ClNS$ [M^+] 221.9958, found 221.9953.

*4.2.24. 3-Chloro-2-(pyridin-3-ylethynyl)pyridine (**24**)*

From 2-bromo-3-chloropyridine (96.0 mg, 0.500 mmol) and 3-ethynylpyridine (1.1 equiv.) and after purification by column chromatography using a solvent gradient from 50% ether/petroleum ether to 70% ether/petroleum ether, compound **24** was obtained as an off-white solid (93.0 mg, 87%). Recrystallization from ether/petroleum ether gave off-white crystals, m.p. 58-60 ºC. ^{1}H NMR (400MHz, $CDCl_3$): δ = 7.23 (dd, *J* = 8.2 and 4.6 Hz, 1H, 5-H), 7.29-7.33 (m, 1H, 5'-H), 7.76 (dd, *J* = 8.2 and 1.2 Hz, 1H, 4-H), 7.89-7.92 (m, 1H, 4'-H), 8.51 (dd, *J* = 4.6 and 1.2 Hz, 1H, 6-H), 8.59 (dd, *J* = 5.0 and 1.6 Hz, 1H, 6'-H), 8.85 (br s, 1H, 2'-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 88.75 (C), 90.75 (C), 119.17 (C), 123.07 (5'-CH), 123.84 (5-CH), 134.26 (C), 136.75 (4-CH), 139.00 (4'-CH), 141.36 (C), 147.86 (6-CH), 149.40 (6'-CH), 152.52 (2'-CH) ppm. Anal. Calcd for $C_{12}H_7ClN_2$ (214.65): C, 67.15; H, 3.29; N, 13.05. Found: C, 66.85; H,3.46; N, 12.74.

*4.2.25. 3-Chloro-2-(pyridin-2-ylethynyl)pyridine (**25**)*

From 2-bromo-3-chloropyridine (96.0 mg, 0.500 mmol) and 2-ethynylpyridine (1.1 equiv.) and after purification by column chromatography using a solvent gradient from 50% ether/petroleum ether to 100% ether, compound **25** was obtained as an off-white solid (100 mg, 93%). Recrystallization from ether/petroleum ether gave yellow crystals, m.p. 57-59 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25 (dd, *J* = 8.0 and 4.8 Hz, 1H, 5-H), 7.29-7.31 (m, 1H), 7.64 (br d, 1H), 7.69-7.73 (m, 1H), 7.75-7.77 (m, 1H), 8.52 (br d, 1H, H), 8.67 (br s, 1H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 84.40 (C), 92.80 (C), 123.58 (CH), 123.96 (5-CH), 127.93 (CH), 134.67 (C), 136.15 (CH), 136.73 (4-CH), 141.29 (C), 142.31 (C), 147.84 (CH), 150.24 (CH) ppm. MS-EI: m/z (%) 216 (M^+ ^{37}Cl, 34), 214 (M^+ ^{35}Cl, 100), 179 (M^+-35, 60). HRMS: Calcd for $C_{12}H_7{}^{35}ClN_2$ [M^+] 214.0298, found 214.0301. Calcd for $C_{12}H_7{}^{37}ClN_2$ [M^+] 216.0268, found 216.0277.

*4.2.26. 3-Chloro-2-[2-(1-methyl-1H-imidazol-5-yl)ethynyl]pyridine (**26**)*

From 2-bromo-3-chloropyridine (96.0 mg, 0.500 mmol) and 5-ethynyl-1-methyl-1*H*-imidazole (1.1 equiv.) and after purification by column chromatography using neat ethyl acetate, compound **26** was obtained as a yellow solid (86.0 mg, 80%). Recrystallization from ether/petroleum ether gave yellow crystals, m.p. 149-151 ºC. ^{1}H NMR (400 MHz,DMSO-d_6): δ = 3.78 (s, 3H, NMe), 7.47 (dd, *J* = 8.2 and 4.6 Hz, 1H, 5-H), 7.64 (br s, 1H), 8.07 (dd, *J* = 8.2 and 1.4 Hz, 1H, 4-H), 8.11 (br s, 1H), 8.56 (dd, *J* = 4.6 and 1.4 Hz, 1H, 6-H) ppm. ^{13}C NMR (100.6MHz, DMSO-d_6): δ = 32.40 (NMe), 81.97 (C), 93.16 (C), 114.89 (C), 124.83 (5-CH), 132.59 (C), 134.38 (CH), 137.23 (4-CH), 140.18 (C), 140.53 (CH), 148.57 (6-CH) ppm. MS-ESI: m/z (%) 220 (M^+ ^{37}Cl+ H, 37), 218 (M^+ ^{35}Cl+H, 100). HRMS: Calcd for $C_{11}H_9{}^{35}ClN_3$ [M^++H] 218.0479. Found 218.0475. Calcd for $C_{11}H_9{}^{37}ClN_3$ [M^++H] 220.0455. Found 220.0437.

4.3. **General conditions for the synthesis of thienopyridines:**

Two-pots: A suspension of the (hetero)arylethynylpyridines with Na_2S (4.0 equiv.) in DMF was stirred in an oil bath at 130 ºC overnight. Then the mixture was diluted with H_2O and extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to dryness under reduced pressure, affording the expected thienopyridines as solids.

One-pot: the Sonogashira reaction was performed according to 4.2. After completion, Na_2S (4.0 equiv.) in DMF was added and the mixture was heated at 130ºC during 2h. After workup (described in 4.3) the crude product was purified by recrystallization or dry flash chromatography.

*4.3.1. 2-Phenylthieno[2,3-b]pyridine (**27**)*

From compound **1** (91.0 mg, 0.426 mmol), compound **27** was obtained as an orange solid (81.0 mg, 90%). Recrystallization from ether/petroleum ether gave orange crystals, m.p. 88-90 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (dd, *J* = 8.0 and 4.8 Hz 1H, 5-H), 7.36-7.41 (m, 1H), 7.44-7.48 (m, 3H), 7.73 (m, 2H), 8.02 (dd, *J* = 8.0 and 1.6 Hz, 1H, 4-H), 8.53 (br d, 1H, 6-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 116.62 (CH), 119.79 (5-CH), 126.56 (2×CH), 128.80 (CH), 129.03 (2×CH), 130.66 (4-CH), 133.81 (C), 134.24 (C), 144.55 (C), 146.24 (6-CH), 161.46 (C) ppm. MS-EI: m/z (%) = 211 (M^+, 100). HRMS: Calcd for $C_{13}H_9NS$ [M^+] 211.0456. Found 211.0458.

In one-pot, from 3-bromo-2-chloropyridine (70.0 mg, 0.364 mmol) and phenylacetylene (1.1 equiv.) and after purification by dry flash chromatography using a solvent gradient from

neat petroleum ether to 10% ether/petroleum ether, compound **27** was obtained as an orange solid (65.0 mg, 85%).

*4.3.2. 4-(Thieno[2,3-b]pyridin-2-yl)aniline (**28**)*

From compound **2** (50.0 mg, 0.220 mmol), compound **28** was obtained as a yellow oil (45.0 mg, 91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.65 (br s, 2H, NH_2), 6.60 (d, *J* = 8.4 Hz, 2H, 2 and 6-H), 6.97 (dd, *J* = 8.0 and 4.8 Hz, 1H, 5'-H), 7.03 (s, 1H, 3'-H), 7.23 (d, *J* = 8.4 Hz, 2H, 3 and 5-H), 7.68 (dd, *J* = 8.0 and 1.6 Hz, 1H, 4'-H), 8.12 (dd, *J* = 4.8 and 1.6 Hz, 1H, 6'-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 113.82 (3'-CH), 116.12 (2 and 6-CH), 119.09 (5'-CH), 124.30 (C), 126.78 (3 and 5-CH), 129.45 (4'-CH), 133.81 (C), 143.88 (C), 144.16 (C), 144.73 (6'-CH), 159.97 (C) ppm. MS-EI: m/z (%) 226 (M^+, 100). HRMS: Calcd. for $C_{13}H_{10}N_2S$ [M^+] 226.0565. Found 226.0567.

In one-pot, from 3-bromo-2-chloropyridine (65.0 mg, 0.338 mmol) and 4-ethynylaniline (1.1 equiv.) and after purification by dry flash chromatography using a solvent gradient from 40% ether/petroleum ether to 60% ether/petroleum ether, compound **25** was obtained as a beige solid (31.0 mg, 40%).

*4.3.3. 3-(Thieno[2,3-b]pyridin-2-yl)aniline (**29**)*

From compound **3** (50.0 mg, 0.220 mmol), compound **29** was obtained as a yellow solid (45.0 mg, 96%), m.p. 145-146 ºC. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.47 (br s, 2H, NH_2), 6.61-6.64 (br d, 1H, 6-H), 6.96-6.98 (m, 2H, 2 and 4-H), 7.11-7.15 (m, 1H, 5-H), 7.41 (dd, *J* = 8.0 and 4.8 Hz, 1H, 5'-H), 7.67 (s, 1H, 3'-H), 8.20 (dd, *J* = 8.0 and 1.6 Hz,1H, 4'-H), 8.50 (dd, *J* = 4.8 and 1.6 Hz, 1H, 6'-H) ppm. ^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 111.49 (2-CH), 113.88 (4-CH), 114.87 (6-CH), 116.90 (3'-CH), 120.30 (5'-CH), 129.77 (5-CH), 131.18 (4'-CH), 133.59 (C), 133.97 (C), 143.96 (C), 146.32 (6'-CH), 149.02 (C), 160.15 (C) ppm. MS-EI: m/z (%) 226 (M^+, 100). HRMS: Calcd. for $C_{13}H_{10}N_2S$ [M^+] 226.0565. Found 226.0567.

*4.3.4. 2-(Thieno[2,3-b]pyridin-2-yl)aniline (**30**)*

From compound **4** (100 mg, 0.430 mmol), compound **30** was obtained as a brownish oil (80.0 mg, 82%). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.53 (br s, 2H, NH_2), 6.66 (dt, *J* = 7.6 and 1.2 Hz, 1H, 4-H), 6.84 (dd, *J* = 7.6 and 1.2 Hz, 1H, 6-H), 7.11 (dt, *J* = 7.6 and 1.2 Hz, 1H, 5-H), 7.26 (dd, *J* = 7.6 and 1.2 Hz, 1H, 3-H), 7.41 (dd, *J* = 8.2 and 4.8 Hz, 1H, 5'-H), 7.54 (s, 1H, 3'-H), 8.19 (dd, *J* = 8.2 and 1.6 Hz, 1H, 4'-H), 8.51 (dd, *J* = 4.8 and 1.6 Hz, 1H, 6'-H) ppm. ^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 116.10 (6-CH), 116.74 (4-CH), 117.41 (C), 119.76 (3'-CH), 120.05 (5'-CH), 129.62 (5-CH), 130.36 (3-CH), 131.01 (4'-CH), 133.76 (C), 141.51 (C), 146.00 (C), 146.08 (6'-CH), 160.40 (C) ppm. MS-EI: m/z (%) 226 (M^+, 100). HRMS: Calcd. for $C_{13}H_{10}N_2S$ [M^+] 226.0565. Found 226.0566.

In one-pot, from 3-bromo-2-chloropyridine (65.0 mg, 0.338 mmol) and 2-ethynylaniline (1.1 equiv.) and after purification by dry flash chromatography using a solvent gradient from 40% ether/petroleum ether to 60% ether/petroleum ether, compound **27** was obtained as a beige solid (35.0 mg, 45%).

*4.3.5. 2-(4-Methoxyphenyl)thieno[2,3-b]pyridine (**31**)*

From compound **5** (62.0 mg, 0.250 mmol), compound **31** was obtained as a yellow solid, (55.0 mg, 91%), m.p. 119-120 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.86 (s, 3H, OMe), 6.97 (d, *J* = 8.8 Hz, 2H, 3' and 5'-H), 7.28 (dd, *J* = 8.0 and 4.8 Hz, 1H, 5-H), 7.34 (s, 1H, 3-H), 7.66 (d, *J* = 8.8 Hz, 2H, 2' and 6'-H), 7.99 (dd, *J* = 8.0 and 2.0 Hz, 1H, 4-H), 8.49 (br d, 1H, 6-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 55.39 (OMe), 114.46 (3' and 5'-CH), 115.26 (3-CH), 119.76 (5-CH), 126.47 (C), 127.86 (2' and 6'-CH), 130.41 (4-CH), 134.60 (C), 144.59 (C), 145.60 (6-CH), 160.24 (C), 161.04 (C) ppm. MS-EI: m/z (%) 241 (M^+, 100). HRMS: Calcd. for $C_{14}H_{11}NOS$ [M^+] 241.0561. Found 241.0561.

In one-pot, from 3-bromo-2-chloropyridine (65.0 mg, 0.338 mmol) and 4-ethynylanisole (1.1 equiv.) and after recrystallization from ether/petroleum ether, compound **31** was obtained as a yellow solid (60.0 mg, 74%).

*4.3.6. 2-(3-Methoxyphenyl)thieno[2,3-b]pyridine (**32**)*

From compound **6** (102 mg, 0.420 mmol), compound **32** was obtained as a yellow solid (92.0 mg, 91%), m.p. 85-86 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.90 (s, 3H, OMe), 6.91-6.95 (m, 1H), 7.24-7.39 (m, 4H), 7.46 (s, 1H, 3-H), 8.03 (dd, *J* = 8.0 and 1.6 Hz, 1H, 4-H), 8.53 (dd, *J* = 4.8 and 1.6 Hz, 1H, 6-H) ppm ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 55.36 (OMe), 112.20 (CH), 114.31 (CH), 116.83 (3-CH), 119.12 (CH), 119.81 (CH), 130.08 (CH), 130.87 (4-CH), 134.26 (C), 135.06 (C), 144.51 (C), 146.05 (6-CH), 160.00 (C), 161.15 (C) ppm. MS-EI: m/z (%) 241 (M^+, 100). HRMS: Calcd. for $C_{14}H_{11}NOS$ [M^+] 241.0561. Found 241.0563.

In one-pot, from 3-bromo-2-chloropyridine (65.0 mg, 0.338 mmol) and 3-ethynylanisole (1.1 equiv.) and after recrystallization from ether/petroleum ether, compound **32** was obtained as a yellow solid (50.0 mg, 62%).

*4.3.7. 2-(Thieno[2,3-b]pyridin-2-yl)phenol (**33**)*

From compound **7** (58.0 mg, 0.240 mmol), compound **33** was obtained as a yellow solid, (60.0 mg, 86 %), m.p. 191-192 ºC. ^{1}H NMR (400 MHz, acetone-d_6): δ = 6.99-7.04 (m, 1H, 5-H), 7.11-7.13 (m, 1H, 3-H), 7.26-7.30 (m, 1H, 4-H), 7.40 (dd, *J* = 8.0 and 4.8 Hz, 1H, 5'-H), 7.75-7.78 (m, 1H, 6-H), 7.94 (s, 1H, 3'-H), 8.20 (dd, *J* = 8.0 and 1.6 Hz, 1H, 4'-H), 8.53 (dd, *J* = 4.8 and 1.6 Hz, 1H, 6'-H), 9.42 (br s, 1H, OH) ppm. ^{13}C NMR (100.6 MHz, acetone-d_6): δ = 117.46 (3-CH), 120.57 (3'-CH), 120.60 (5'-CH), 121.05 (5-CH), 121.49 (C), 129.91 (6-CH), 130.59 (4-CH), 131.38 (4'-CH), 134.53 (C), 141.41 (C), 146.95 (6'-CH), 155.38 (C), 162.27 (C) ppm. MS-EI: m/z (%) = 227 (M^+, 100). HRMS: Calcd. for $C_{13}H_9NOS$ [M^+] 227.0405. Found 227.0405.

*4.3.8. 2-(4-Bromophenyl)thieno[2,3-b]pyridine (**34**)*

From compound **8** (50.0 mg, 0.170 mmol), compound **34** was obtained as a yellow solid (35.0 mg, 71 %) m.p.104-105 ºC. ^{1}H NMR (400 MHz, acetone-d_6): δ = 7.46 (dd, *J* = 8.0 and 4.8 Hz, 1H, 5-H), 7.72 (d, *J* = 8.8 Hz, 2H, 2' and 6'-H), 7.82 (d, *J* = 8.8 Hz, 2H, 3' and 5'-H), 7.84 (s, 1H, 3-H), 8. 25 (dd, *J* = 8.0 and 1.6 Hz, 1H, 4-H), 8.57 (dd, *J* = 4.8 and 1.6 Hz, 1H, 6-H) ppm. ^{13}C NMR (100.6 MHz, acetone-d_6): δ = 119.10 (3-CH), 121.21 (6-CH), 123.25(C), 129.01 (3' and 5'-CH), 130.09 (C), 132.10 (4-CH), 133.15 (2' and 6'-CH), 135.13 (C), 143.15 (C), 147.73 (6-CH), 162.07(C) ppm. MS-EI: m/z (%) 291 (M^+ ^{81}Br, 100), 289 (M^+ ^{79}Br, 100). HRMS: Calcd for

$C_{13}H_8{}^{79}BrNS$ [M^+] 288.9561. Found 288.9565. Calcd for $C_{13}H_8{}^{81}BrNS$ [M^+] 290.9540. Found 290.9551.

*4.3.9. 2-(3-Fluorophenyl)thieno[2,3-b]pyridine (**35**)*

From compound **9** (60.0 mg, 0.280 mmol), compound **35** was obtained as a yellow solid (50.0 mg, 87%), m.p.78-79 ºC. ^{1}H NMR (400 MHz, acetone-d_6): δ = 7.21-7.26 (m, 1H), 7.46 (dd, *J* = 8.2 and 4.4 Hz, 1H, 5-H), 7.56-7.70 (m, 3H), 7.87 (s, 1H, 3-H), 8.25 (dd, *J* = 8.2 and 1.6 Hz, 1H, 4-H), 8.56 (dd, *J* = 4.4 and 1.6 Hz, 1H, 6-H) ppm. ^{13}C NMR (100.6 MHz, acetone-d_6): δ = 113.73 (d, *J* = 24.1 Hz, CH), 116.38 (d, *J* = 22.1 Hz, CH), 119.55 (3-CH), 121.21 (5-CH), 123.32 (d, *J* = 3.0 Hz, 6'-CH), 132.07 (d, *J* = 9.1 Hz, 5'-CH), 132.18 (4-CH), 134.97 (C), 136.99 (d, *J* = 8.0 Hz, 1'-C), 142.95 (C), 147.87 (6-CH), 162.13 (C), 164.06 (d, *J* = 244.5 Hz, CF) ppm. MS-EI: m/z (%) 229 (M^+, 100). HRMS: Calcd. for $C_{13}H_8FNS$ [M^+] 229.0361. Found 229.0365.

*4.3.10. 2-(Thiophen-3-yl)thieno[2,3-b]pyridine (**36**)*

From compound **10** (80.0 mg, 0.370 mmol), compound **36** was obtained as a yellow solid (66.0 mg, 82%), m.p. 109-110 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 (dd, *J* = 8.0 and 4.8 Hz, 1H, 5-H), 7.33 (s, 1H, 3-H), 7.41-7.44 (m, 2H), 7.55-7.59 (m, 1H), 8.01 (dd, *J* = 8.0 and 1.6 Hz, 1H, 4-H), 8.50 (br d, 1H, 6-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 116.38 (3-CH), 119.85 (5-CH), 122.32 (CH), 125.77 (CH), 126.92 (CH), 130.85 (4-CH), 134.33 (C), 135.16 (C), 139.51 (C), 145.59 (6-CH), 160.48 (C) ppm. MS-EI: m/z (%) 217 (M^+, 100). HRMS: Calcd. for $C_{11}H_7NS_2$ [M^+] 217.0020. Found 227.0023.

In one-pot, from 3-bromo-2-chloropyridine (65.0 mg, 0.338 mmol) and 3-ethynylthiophene (1.1 equiv.) and after purification by dry flash chromatography using a solvent gradient from neat petroleum ether to 20% ether/petroleum ether, compound **36** was obtained as a yellow solid (44.0 mg, 60%).

*4.3.11. 2-(Pyridin-3-yl)thieno[2,3-b]pyridine (**37**)*

From compound **11** (101 mg, 0.471 mmol), compound **37** was obtained as a brown solid (70.0 mg, 70%). Recrystallization from ether/petroleum ether gave brown crystals, m.p. 86-88 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 (dd, *J* = 8.0 and 4.8 Hz, 1H, 5-H), 7.40-7.44 (m, 1H, 5'-H), 7.54 (s, 1H, 3-H), 8.00-8.03 (m, 1H), 8.06 (dd, *J* = 8.0 and 1.6 Hz, 1H, 4-H), 8.56 (dd, *J* = 4.8 and 1.6 Hz, 1H, 6-H), 8.61 (br dd, 1H, 6'-H), 9.01 (br d, 1H, 2'-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 118.27 (3-CH), 120.09 (5-CH), 123.98 (6'-CH), 130.24 (C), 131.13 (4-CH), 133.81 (C), 134.29 (4'-CH), 140.21 (C), 146.72 (2'-CH), 146.96 (6-CH), 148.86 (6'-CH), 161.61 (C) ppm. MS-EI: m/z (%) 212 (M^+, 100). HRMS: Calcd. for $C_{12}H_8N_2S$ [M^+] 212.0408. Found 212.0407.

In one-pot, from 3-bromo-2-chloropyridine (80.0 mg, 0.416 mmol) and 3-ethynylpyridine (1.1 equiv.) and after purification by dry flash chromatography using neat ether as the solvent, compound **37** was obtained as an off-white solid (62.0 mg, 70%).

*4.3.12. 2-(Pyridin-2-yl)thieno[2,3-b]pyridine (**38**)*

From compound **12** (60.0 mg, 0.280 mmol), compound **38** was obtained as a colourless oil (50.0 mg, 86%). ^{1}H NMR (400 MHz, acetone-d_6): δ = 7.39-7.41 (m, 1H), 7.44 (dd, *J* = 8.0 and 4.8 Hz, 1H, 5-H), 7.92-7.97 (m, 1H), 8.08 (s, 1H, 3-H), 8.10-8.13 (m, 1H), 8.26 (dd, *J* = 8.0 and 1.6 Hz, 1H, 4-H), 8.58 (dd, *J* = 4.8 and 1.6 Hz, 1H, 6-H), 8.65-8.67 (m, 1H) ppm. ^{13}C NMR (100.6 MHz, acetone-d_6): δ = 119.81 (3-CH), 120.34 (CH), 120.90 (5-CH), 121.09 (C), 124.25 (CH), 132.36 (4-CH), 134.92 (C), 137.86 (CH), 146.00 (C), 148.06 (6-CH), 150.56 (CH), 163.05(C) ppm. MS-EI: m/z (%) 212 (M^+, 100). HRMS: Calcd. for $C_{12}H_8N_2S$ [M^+] 212.0408. Found 212.0406.

In one-pot, from 3-bromo-2-chloropyridine (65.0 mg, 0.338 mmol) and 2-ethynylpyridine (1.1 equiv.) and after purification by dry flash chromatography using neat ether as the solvent, compound **38** was obtained as an off-white solid (47.0 mg, 66%).

*4.3.13. 2-(1-Methyl-1H-imidazol-5-yl)thieno[2,3-b]pyridine (**39**)*

From compound **13** (100 mg, 0.466 mmol), compound **39** was obtained as an off-white solid (70.0 mg, 71%). Recrystallization from ether/petroleum ether gave off-white crystals, m.p. 78-80 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.85 (s, 3H, NMe), 7.24 (s, 1H, 3-H), 7.32 (dd, *J* = 8.0 and 4.8 Hz, 1H, 5-H), 7.35 (br s, 1H), 7.66 (br s, 1H), 8.03 (dd, *J* = 8.0 and 1.6 Hz, 1H, 4-H), 8.54 (dd, *J* = 4.8 and 1.6 Hz, 1H, 6-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 33.19 (NMe), 119.14 (3-CH), 119.96 (5-CH), 126.74 (C), 130.18 (CH), 130.74 (4-CH), 131.29 (C), 133.27 (C), 140.21 (CH), 146.71 (6-CH), 161.45 (C) ppm. MS-EI: m/z (%) 215 (M^+, 100). HRMS: Calcd. for $C_{11}H_9N_3S$ [M^+] 215.0517. Found 215.0518.

In one-pot, from 3-bromo-2-chloropyridine (65.0 mg, 0.338 mmol) and 5-ethynyl-1-methyl-1*H*-imidazole (1.1 equiv.) and after recrystallization from ether/petroleum ether, compound **39** was obtained as an off-white solid (47.0 mg, 66%).

*4.3.14. 2-Phenylthieno[3,2-b]pyridine (**40**)*

From compound **14** (80.0 mg, 0.374 mmol), compound **40** was obtained as an orange solid (63.0 mg, 80%). Recrystallization from ether/petroleum ether gave orange crystals, m.p. 115-117 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22 (dd, *J* = 8.2 and 4.4 Hz, 1H, 6-H), 7.38-7.49 (m, 3H), 7.75-7.77 (m, 3H), 8.13 (m, 1H, 7-H), 8.67 (dd, *J* = 4.4 and 1.6 Hz, 1H, 5-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 118.60 (6-CH), 120.50 (3-CH), 126.48 (2×CH), 129.07 (2×CH), 129.10 (CH), 130.01 (7-CH), 133.38 (C), 133.63 (C), 147.46 (5-CH), 148.32 (C), 156.86 (C) ppm. MS-EI: m/z (%) 211 (M^+, 100). HRMS: Calcd for $C_{13}H_9NS$ [M^+] 211.0456. Found 211.0459.

In one-pot, from 2-bromo-3-chloropyridine (70.0 mg, 0.364 mmol) and phenylacetylene (1.1 equiv.) and after recrystallization from ether/petroleum ether, compound **40** was obtained as an orange solid (72.0 mg, 94%).

*4.3.15. 4-(Thieno[3,2-b]pyridin-2-yl)aniline (**41**)*

From compound **15** (134.0 mg, 0.586 mmol), compound **41** was obtained as a brown solid (113 mg, 85%). Recrystallization from ether/petroleum ether gave brown crystals, m.p. 142-144 ºC. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.59 (br s, 2H, NH_2), 6.64 (d, *J* = 8.4 Hz, 2H, 2 and 6-H), 7.22 (dd, *J* = 8.2 and 4.8 Hz, 1H, 6'-H), 7.52 (d, *J* = 8.4 Hz, 2H, 3 and 5-H), 7.63 (s, 1H, 3'-H), 8.29-8.33 (m, 1H, 7'-H), 8.53 (dd, *J* = 4.8 and 1.6 Hz, 1H, 5'-H) ppm. ^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 113.89 (2 and 6-CH), 116.29 (3'-CH), 118.04 (6'-CH), 118.51 (C), 120.19 (C), 127.24 (3 and 5-CH), 130.10 (7'-CH), 147.10 (5'-CH), 149.13 (C), 150.28 (C), 157.18 (C)

ppm. MS-EI: m/z (%) 226 (M^+, 100). HRMS: Calcd. for $C_{13}H_{10}N_2S$ [M^+] 226.0565. Found 226.0568.

In one-pot, from 2-bromo-3-chloropyridine (96.0 mg, 0.500 mmol) and 4-ethynylaniline (1.1 equiv.) and after purification by dry flash chromatography using neat ether, compound **41** was obtained as a brown solid (74.0 mg, 65%).

*4.3.16. 3-(Thieno[3,2-b]pyridin-2-yl)aniline (**42**)*

From compound **16** (67.0 mg, 0.293 mmol), compound **42** was obtained as a yellow solid (57.0 mg, 86%), m.p. 145-146 ºC. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.31 (br s, 2H, NH_2), 6.62-6.64 (m, 1H, 6-H), 6.99-7.01 (m, 2H, 2 and 4-H), 7.11-7.15 (m, 1H, 5-H), 7.31 (dd, *J* = 8.0 and 4.4 Hz, 1H, 6'-H), 7.78 (s, 1H, 3'-H), 8.41 (dd, *J* = 8.0 and 1.2 Hz, 1H, 7'-H), 8.61 (dd, *J* = 4.4 and 1.2 Hz, 1H, 5'-H) ppm. ^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 111.10 (CH), 113.70 (CH), 114.95 (6-CH), 118.87 (6'-CH), 119.56 (3'-CH), 129.77 (5-CH), 130.55 (7'-CH), 132.30 (C), 133.44 (C), 147.45 (5'-CH), 148.60 (C), 149.36 (C), 156.44 (C) ppm. MS-EI: m/z (%) 226 (M^+, 100). HRMS: Calcd. for $C_{13}H_{10}N_2S$ [M^+] 226.0565. Found 226.0564.

*4.3.17. 2-(Thieno[3,2-b]pyridin-2-yl)aniline (**43**)*

From compound **17** (50.0 mg, 0.220 mmol), compound **43** was obtained as an brown oil (47 mg, 94 %). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.35 (br s, 2H, NH_2), 6.65-6.69 (m, 1H, 4-H), 6.83-6-86 (m, 1H, 6-H), 7.10-7.15 (m, 1H, 5-H), 7.27-7.30 (m, 1H, 3-H), 7.33 (dd, *J* = 8.2 and 4.8 Hz, 1H, 6'-H), 7.65 (s, 1H, 3'-H), 8.42 (dd, *J* = 8.2 and 1.6 Hz, 1H, 7'-H), 8.63 (dd, *J* = 4.8 and 1.6 Hz, 1H, 5'-H) ppm. ^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 116.20 (6-CH), 116.78 (4-CH), 117.41 (C), 118.70 (6'-CH), 122.14 (3'-CH), 129.84 (5-CH), 130.09 (3-CH), 130.24 (7'-CH), 132.41 (C), 146.00 (C), 146.09 (C), 147.21 (5'-CH), 156.42 (C) ppm. MS-EI: m/z (%) 226 (M^+, 100). HRMS: Calcd. for $C_{13}H_{10}N_2S$ [M^+] 226.0565. Found 226.0563.

In one-pot, from 2-bromo-3-chloropyridine (65.0 mg, 0.338 mmol) and 2-ethynylaniline (1.1 equiv.) and after purification by dry flash chromatography using neat ether as the solvent, compound **43** was obtained as a beige solid (62.0 mg, 80%).

*4.3.18. 2-(4-Methoxyphenyl)thieno[3,2-b]pyridine (**44**)*

From compound **18** (94.0 mg, 0.380 mmol) compound **44** was obtained as a yellow solid (90.0 mg, 97%). Recrystallization from ether/petroleum ether gave yellow crystals, m.p. 106-107 ºC. ^{1}H NMR (400 MHz, acetone-d_6): δ = 3.91 (s, 3H, OMe), 7.10 (d, *J* = 8.8 Hz, 2H, 3' and 5'-H), 7.31 (dd, *J* = 8.2 and 4.8 Hz, 1H, 6-H), 7.77 (s, 1H, 3-H), 7.83 (d, *J* = 8.8 Hz, 2H, 2' and 6'-H), 8.34 (dd, *J* = 8.2 and 1.2 Hz, 1H, 7-H), 8.65 (dd, *J* = 4.8 and 1.2 Hz, 1H, 5-H) ppm. ^{13}C NMR (100.6 MHz, acetone-d_6): δ = 55.76 (OMe), 115.44 (3' and 5'-CH), 119.44 (6-CH), 120.05 (3-CH), 123.99 (C), 127.01 (C), 128.51 (2' and 6'-CH), 130.73 (7-CH), 148.32 (5-CH), 148.78 (C), 158.24 (C), 161.63 (C) ppm. MS-EI: m/z (%) 241 (M^+, 100). HRMS: Calcd. for $C_{14}H_{11}NOS$ [M^+] 241.0561. Found 241.0563.

In one-pot, from 2-bromo-3-chloropyridine (65.0 mg, 0.338 mmol) and 4-ethynylanisole (1.1 equiv.) and after recrystallization from ether/petroleum ether, compound **44** was obtained as a beige solid (70.0 mg, 86%).

*4.3.19. 2-(3-Methoxyphenyl)thieno[3,2-b]pyridine (**45**)*

From compound **19** (119 mg, 0.480 mmol) compound **45** was obtained as a yellow solid (110 mg, 95%). Recrystallization from ether/petroleum ether gave yellow crystals, m.p. 85-86 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.89 (s, 3H, OMe), 6.94-6.97 (m, 1H), 7.25 (dd, *J* = 8.0 and 4.8 Hz, 1H, 6-H), 7.27-7.28 (m, 1H), 7.35-7.38 (m, 2H), 7.80 (s, 1H, 3-H), 8.15-8.17 (m, 1H, 7-H), 8.65-8.67 (m, 1H, 5-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 55.57 (OMe), 112.18 (CH), 114.70 (CH), 118.64 (6-CH), 119.07 (CH), 120.23 (3-CH), 130.15 (CH), 130.55 (7-CH), 133.64 (C), 134.76 (C), 146.81 (5-CH), 148.82 (C), 156.08 (C), 160.03 (C) ppm. MS-EI: m/z (%) 241 (M^+, 100). HRMS: Calcd. for $C_{14}H_{11}NOS$ [M^+] 241.0561. Found 241.0560.

In one-pot, from 2-bromo-3-chloropyridine (96.0 mg, 0.500 mmol) and 3-ethynylanisole (1.1 equiv.) and after recrystallization from ether/petroleum ether, compound **45** was obtained as a beige solid (101 mg, 84%).

*4.3.20. 2-(Thieno[3,2-b]pyridin-2-yl)phenol (**46**)*

From compound **20** (121 mg, 0.490 mmol) compound **46** was obtained as a white solid which was washed with $CHCl_3$ (70.0 mg, 64%), m.p. 136-137 ºC. ^{1}H NMR (400 MHz, acetone-d_6): δ = 7.01-7.05 (m, 1H, 4-H), 7.13-7.16 (m, 1H, 6-H), 7.28-7.35 (m, 2H, 6' and 5-H), 7.81-7.83 (m, 1H, 3-H), 8.12 (m, 1H, 3'-H), 8.35-8.38 (m, 1H, 7'-H), 8.68 (br s, 1H, 5'-H), 9.63 (br s, 1H, OH) ppm. ^{13}C NMR (100.6 MHz, acetone-d_6): δ = 117.53 (6-CH), 119.37 (6'-CH), 121.04 (4-CH), 121.24 (C), 123.51 (3'-CH), 129.67 (3-CH), 130.58 (7'-CH), 130.92 (5-CH), 133.97 (C), 145.57 (C), 147.96 (5'-CH), 155.49 (C), 157.48 (C) ppm. MS-EI: m/z (%) 227 (M^+, 100). HRMS: Calcd. for $C_{13}H_9NOS$ [M^+] 227.0405. Found 227.0405.

*4.3.21. 2-(4-Bromophenyl)thieno[3,2-b]pyridine (**47**)*

From compound **21** (50.0 mg, 0.170 mmol), compound **47** was obtained as a yellow solid (45.0 mg, 94 %), m.p. 104-105 ºC. ^{1}H NMR (400 MHz, acetone-d_6): δ = 7.35 (dd, *J* = 8.0 and 4.4 Hz, 1H, 6-H), 7.54 (d, *J* = 8.8 Hz, 2H, 2' and 6'-H), 7.90 (d, *J* = 8.8 Hz, 2H, 3' and 5'-H), 7.99 (s, 1H, 3-H), 8.39 (dd, *J* = 8.0 and 1.2 Hz, 1H, 7-H), 8.69 (br d, 1H, 5-H) ppm. ^{13}C NMR (100.6 MHz, acetone-d_6): δ = 119.83 (6-CH), 121.53 (3-CH), 127.12 (3' and 5'-CH), 130.05 (C), 130.08 (2' and 6'-CH), 130.94 (7-CH), 133.94 (C), 134.47 (C), 148.51 (5-CH), 148.69 (C), 157.94 (C) ppm. MS-EI: m/z (%) 291 (M^+ ^{81}Br, 100), 289 (M^+ ^{79}Br, 100). HRMS: Calcd for $C_{13}H_8{}^{79}BrNS$ [M^+] 288.9561. Found 288.9565. Calcd for $C_{13}H_8{}^{81}BrNS$ [M^+] 290.9540. Found 290.9549.

*4.3.22. 2-(3-Fluorophenyl)thieno[3,2-b]pyridine (**48**)*

From compound **22** (30.0 mg, 0.130 mmol), compound **48** was obtained as a yellow solid (25.0 mg, 85%), m.p. 122-123 ºC. ^{1}H NMR (400 MHz, acetone-d_6): δ = 7.25-7.28 (m, 1H), 7.32 (dd, *J* = 8.2 and 4.8 Hz, 1H, 6-H), 7.56-7.62 (m, 1H), 7.68-7.74 (m, 2H), 8.00 (s, 1H, 3-H), 8.42 (dd, *J* = 8.2 and 1.6 Hz, 1H, 7-H), 8.71 (dd, *J* = 4.8 and 1.6 Hz, 1H, 5-H) ppm. ^{13}C NMR (100.6 MHz, acetone-d_6): δ = 113.79 (d, *J* = 23.1 Hz, CH), 116.64 (d, *J* = 21.1 Hz, CH), 120.18 (6-CH), 122.73 (3-

CH), 123.18 (d, *J* = 3.0 Hz, 6'-CH), 131.08 (7-CH), 132.08 (d, *J* = 8.0 Hz, 5'-CH), 134.12 (C), 137.83 (d, *J* = 8.0 Hz, 1'-C) 143.32 (C), 148.75 (5-CH), 157.71 (C), 164.06 (d, *J* = 224.5 Hz, C-F). MS-EI: m/z (%) 229 (M^+, 100). HRMS: Calcd. for $C_{13}H_8FNS$ [M^+] 229.0361. Found 229.0362.

4.3.23. 2-(Thiophen-3-yl)thieno[3,2-b]pyridine ***(49)***

From compound **23** (50.0 mg, 0. 230 mmol), compound **49** was obtained as a yellow solid (40.0 mg, 80%), m.p. 98-99 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25-7.29 (m, 1H), 7.42-7.46 (m, 2H), 7.63-7.64 (m, 1H), 7.69 (s, 1H, 3-H), 8.15 (br d, 1H, 7-H), 8.66 (br s, 1H, 5-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 118.55 (CH), 119.46 (3-CH), 122.74 (CH), 125.97 (CH), 127.09 (CH), 130.82 (7-CH), 133.48 (C), 134.91 (C), 143.96 (C), 146.26 (5-CH), 155.64 (C) ppm. MS-EI: m/z (%) 217 (M^+, 100). HRMS: Calcd. for $C_{11}H_7NS_2$ [M^+] 217.0020. Found 217.0021.

In one-pot, from 2-bromo-3-chloropyridine (65.0 mg, 0.338 mmol) and 3-ethynylthiophene (1.1 equiv.) and after purification by dry flash chromatography using a solvent gradient from neat petroleum ether to 20% ether/petroleum ether, compound **49** was obtained as a beige solid (54.0 mg, 73%).

4.3.24. 2-(Pyridin-3-yl)thieno[3,2-b]pyridine ***(50)***

From compound **24** (60.0 mg, 0.279 mmol), compound **50** was obtained as an orange solid (41.0 mg, 70%). Recrystallization from ether/petroleum ether gave orange crystals, m.p. 153-154 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26 (dd, *J* = 8.2 and 4.6 Hz, 1H, 6-H), 7.39 (dd, *J* = 8.0 and 4.8 Hz, 1H, 5'-H), 7.83 (s, 1H, 3-H), 8.01-8.02 (m, 1H, 4'-H), 8.16-8.19 (dd, *J* = 8.2 and 1.2Hz, 1H, 7-H), 8.62 (br d, 1H, 6'-H), 8.68 (dd, *J* = 4.6 and 1.2 Hz, 1H, 5-H), 9.00 (br s, 1H, 2'-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 119.08 (6-CH), 121.51 (3-CH), 123.80 (5'-CH), 129.63 (C), 130.50 (7-CH), 133.63 (4'-CH), 133.73 (C), 144.61 (C), 147.29 (CH), 147.35 (CH), 149.91 (6'-CH), 156.00 (C) ppm. MS-EI: m/z (%) 212 (M^+, 100). HRMS: Calcd. for $C_{12}H_8N_2S$ [M^+] 212.0408. Found 212.0414.

In one-pot, from 2-bromo-3-chloropyridine (65.0 mg, 0.338 mmol) and 3-ethynylpyridine (1.1 equiv.) and after recrystallization from ether/petroleum ether, compound **50** was obtained as a beige solid (55.0 mg, 77%).

4.3.25. 2-(Pyridin-2-yl)thieno[3,2-b]pyridine ***(51)***

From compound **25** (100 mg, 0.466 mmol), compound **51** was obtained as an orange solid (70.0 mg, 71%). Recrystallization from ether/petroleum ether gave orange crystals, m.p. 153-155 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28-7.31 (m, 2H), 7.77-7.81 (m, 1H), 7.89-7.91 (m, 1H), 8.06 (s, 1H, 3-H), 8.24 (br d, 1H), 8.65-8.68 (m, 2H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 119.19 (CH), 119.96 (CH), 120.98 (3-CH), 123.59 (CH), 131.21 (CH), 135.13 (C), 136.87 (CH), 146.62 (CH), 149.75 (CH), 149.89 (C), 151.49 (C), 155.64 (C) ppm. Anal. Calcd for $C_{12}H_8N_2S$ (212.27): C, 67.90; H, 3.80; N, 13.20; S, 15.11. Found: C, 67.66; H, 4.01; N, 12.93; S, 14.89.

In one-pot, from 2-bromo-3-chloropyridine (65.0 mg, 0.338 mmol) and 2-ethynylpyridine (1.1 equiv.) and after recrystallization from ether/petroleum ether, compound **51** was obtained as a beige solid (56.0 mg, 78%).

4.3.26. 2-(1-Methyl-1H-imidazol-5-yl)thieno[3,2-b]pyridine ***(52)***

From compound **26** (75.0 mg, 0.450 mmol), compound **52** was obtained as an off-white solid (40.0 mg, 54%). Recrystallization from ether/petroleum ether gave off-white crystals, m.p. 110-112 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.86 (s, 3H, NMe), 7.24 (dd, *J* = 8.2 and 4.6 Hz, 1H, 6-H), 7.39 (br s, 1H), 7.52 (s, 1H, 3-H), 7.65 (br s, 1H), 8.23 (dd, *J* = 8.2 and 1.4 Hz, 1H, 7-H), 8.54 (dd, *J* = 4.6 and 1.4 Hz, 1H, 5-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 33.25 (NMe), 118.92 (6-CH), 121.76 (3-CH), 126.51 (C), 129.83 (7-CH), 130.41 (CH), 132.99 (C), 135.29 (C), 140.61 (CH), 147.60 (5-CH), 156.23 (C) ppm. MS-EI: m/z (%) 215 (M^+, 100). HRMS: Calcd. for $C_{11}H_9N_3S$ [M^+] 215.0517. Found 215.0519.

In one-pot, from 2-bromo-3-chloropyridine (96.0 mg, 0.500 mmol) and 5-ethynyl-1-methyl-1*H*-imidazole (1.1 equiv.) and after recrystallization from ether/petroleum ether, compound **52** was obtained as an off-white solid (74.0 mg, 69%).

4.4. **Synthesis of 1-(4-methoxyphenyl)-3-[2-(thieno[3,2-*b*]pyridin-2-yl)phenyl]urea (53):**

Thienopyridine **43** (30.0 mg, 0.120 mmol) and 4-methoxyphenylisocyanate (1 equiv.) were left stirring in 6 mL THF:CH_2Cl_2 (1:1) at room temperature for 16 h. A precipitate did not come out after this time and hexane (3-5 mL) was added to the mixture and the precipitate formed was filtered under vacuum. Compound **53** was obtained as a yellow solid (20.0 mg, 90%), m.p. 199-200 ºC. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.69 (s, 3H, OMe), 6.83 (d, *J* = 8.8 Hz, 2H, 3' and 5'-H), 7.16-7.21 (m, 1H), 7.31 (d, *J* = 8.8 Hz, 2H, 2' and 6'-H), 7.36-7.44 (m, 2H), 7.53-7.55 (m, 1H), 7.71 (s, 1H, 3'''-H), 7.92-7.95 (m, 1H), 8.02 (br s, 1H, NH), 8.47-8.50 (m, 1H), 8.67-8.68 (m, 1H, 5'''-H) 8.84 (br s, 1H, NH) ppm. ^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 55.12 (OMe), 113.97 (3' and 5'-CH), 119.11 (CH), 119.84 (2' and 6'-CH), 123.22 (CH), 123.43 (CH), 124.18 (3'''-CH), 125.01 (C), 129.49 (CH), 130.36 (CH), 130.58 (CH), 132.63 (C), 133.56 (C), 136.63 (C), 144.26 (C), 147.42 (5'''-CH), 152.76 (C), 154.44 (C), 155.91 (C) ppm. MS-ESI: m/z (%) 376 (M^+ +H, 100). HRMS: Calcd for $C_{21}H_{18}N_3O_2S$ [M^+] 376.1114. Found 376.1111.

4.5. General conditions for the bromination in position 3:

In a dry Schlenk tube, thienopyridines **27**, **37** or **40** were put in dry Et_2O or dry CH_2Cl_2. Then, Br_2 (1.1 equiv.) was added dropwise at 0 ºC and the solution was stirred at this temperature for 30 min to 1h. Then the mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The resulting crudes were submitted to column chromatography or PLC to give the expected 3-bromo-2-phenylpyridines.

4.5.1. 3-Bromo-2-phenylthieno[2,3-b]pyridine ***(54)***

From compound **27** (60.0 mg, 0.284 mmol), and after purification by PLC using neat Et_2O as eluent, compound **54** was obtained as a yellow solid (33.0 mg, 40%), m.p. 54-55 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.54 (m, 4H), 7.77-7.80 (m, 2H), 8.14 (dd, *J* = 8.0 and 1.6 Hz, 1H, 4-H), 8.62 (br

d, 1H, 6-H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 102.30 (C), 120.51 (CH), 128.73 (2×CH), 129.28 (CH), 129.64 (2×CH), 131.43 (4-CH), 132.38 (C), 133.64 (C), 139.23 (C), 147.06 (6-CH), 158.74 (C). MS-EI: m/z (%) 291 (M^+ ^{81}Br, 99), 289 (M^+ ^{79}Br, 100). HRMS: Calcd for $C_{13}H_8{}^{79}BrNS$ [M^+] 288.9561. Found 288.9555. Calcd for $C_{13}H_8{}^{81}BrNS$ [M^+] 290.9540. Found 290.9533.

*4.5.2. 3-Bromo-2-phenylthieno[3,2-b]pyridine (**55**)*

From compound **40** (69.0 mg, 0.328 mmol), and after purification by column chromatography using 40% ether/petroleum ether, compound **55** was obtained as an off-white solid (40.0 mg, 42%), m.p 109-111 °C (lit[3d] 110-112 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ =7.36-7.39 (br m, 1H, 6-H), 7.49-7.55 (m, 3H), 7.81-7.83 (m, 2H), 8.20 (br d, 1H, 7-H), 8.85 (br s, 1H, 5-H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 107.05 (C), 119.90 (6-CH), 128.79 (2×CH), 129.47 (2×CH), 129.51 (4'CH), 130.75 (7-CH), 132.57 (C), 133.18 (C), 142.77 (C), 147.90 (5-CH), 152.79 (C), 161.46 (C) ppm. MS-EI: m/z (%) = 211 (M^+, 100).

*4.5.3. 3-Bromo-2-pyridin-3-yl-thieno[2,3-b]pyridine (**56**)*

From compound **37** (30.0 mg, 0.142 mmol), and after purification by recrystallization with ether/petroleum ether, compound **56** was obtained as an ocre solid (27.0 mg, 65%), m.p. 201-203 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49 (dd, *J* = 8.0 and 4.8 Hz, 1H, 5-H), 7.64-7.69 (br m, 1H, 5'-H), 8.15 (dd, *J* = 8.0 and 1.6 Hz, 1H, 4-H), 8.30 (br d, 1H, 4'-H), 8.68 (dd, *J* = 4.8 and 1.6 Hz, 1H, 6-H), 8.79 (br s, 1H, 6'-H), 9.13 (br s, 1H, 2'-H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 120.95 (5-CH), 124.61 (5'-CH), 131.71 (4-CH), 131.93 (C), 132.96 (C), 139.40 (4'-CH), 142.74 (C), 147.03 (6'-CH), 147.25 (2'-CH), 148.53 (6-CH), 159.29 (C), 161.59 (C). MS-EI: m/z (%) 292 (M^{+81}Br, 100), 290 (M^{+79}Br, 93). HRMS: Calcd. for $C_{12}H_7{}^{79}BrN_2S$ [M^+] 289.9513. Found 289.9507. Calcd. for $C_{12}H_7{}^{81}BrN_2S$ [M^+] 291.9493. Found 291.9492.

4.6. Chlorination of the thieno[2,3-*b*]pyridine 32:

*4.6.1. 4-Chloro-2-(3-methoxyphenyl)thieno[2,3-b]pyridine (**57**)*

To compound **32** (60.0 mg, 0.250 mmol) in 6 mL DME/hexane (1:2), MCPBA (1.2 equiv.) was added portionwise at 0 °C and the mixture was left stirring for 40h at rt, following the reaction by tlc. After this time the solvents were evaporated and the resulting solid was put in $CHCl_3$ and $POCl_3$ (19.5 equiv) was added dropwise at 0 °C. After 3h the reaction was completed, ice H_2O and Na_2CO_3 sat. were added and the reaction was extracted with $CHCl_3$. The organic phases were collected, dried with MgSO4, filtered and evaporated to give a brown oil. This was submitted to PLC ether/petroleum ether 2:1 and compound **57** was obtained as a yellow solid (60.0 mg, 86%) m.p 95-96 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.90 (s, 3H, OMe), 7.35-7.45 (m, 3H), 7.58-7.61 (m, 1H), 7.62 (s, 1H, 3-H), 8.00-8.03 (m, 1H), 8.10-8.11 (m, 1H), 8.50 (br s, 1H, 6-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 55.45 (OMe), 114.96 (3-CH), 119.28 (CH), 120.26 (C), 128.27 (CH), 129.80 (CH), 130.23 (CH), 131.11 (C), 133.77 (CH), 134.67 (C), 138.65 (C), 160.00 (C), 145.86 (6-CH), 160.11 (3'-C) ppm. MS-EI: m/z (%) 277 (M^+ ^{37}Cl, 29), 275 (M^+ ^{35}Cl, 100). HRMS: Calcd for $C_{14}H_{10}{}^{35}ClNSO$ [M^+] 275.0172. Found 275.0165. Calcd for $C_{14}H_{10}{}^{37}ClNSO$ [M^+] 277.0142. Found 277.0139.

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