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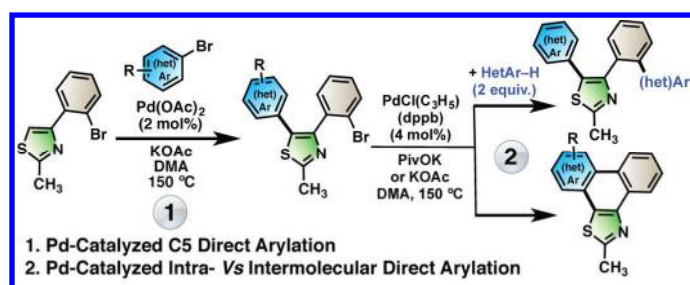
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Synthesis of Phenanthrothiazoles and 1,2-Di(heteroaryl)benzenes Through Successive Pd-Catalyzed Direct Arylations

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Abstract: Palladium-catalyzed direct arylation of 4-(2-bromophenyl)-2-methylthiazole proceeds in high efficiency at the thiazolyl C5 position using aryl bromides as aryl source.

This transformation provides a simple access to 4-(2-bromophenyl)-2-methyl-5-arylthiazoles, which could be further converted into phenanthrothiazoles *via* palladium-catalyzed intramolecular direct arylation. When the direct arylation of 4-(2-bromophenyl)-2-methyl-5-arylthiazoles is conducted in the presence of an external heteroarene such as thiazoles, thiophenes, or imidazo[1,2-a]pyridines, the intermolecular arylation of such external heteroarenes proceeds faster than the intramolecular reaction, allowing the formation of 1,2-di(heteroaryl)benzene derivatives.

Polyaromatic hydrocarbons are an important class of molecules that find applications in organic electronics and optoelectronics due to their unique π - π stacking features in solid states.¹ The incorporation of heteroatoms such as sulfur or nitrogen, in such polyaromatic hydrocarbon structures induces a positive switch of their chemical and/or physical properties. As examples, some thiophene-analogues of polyaromatic hydrocarbons found applications in solar cell systems,² as motifs in helicenes,³

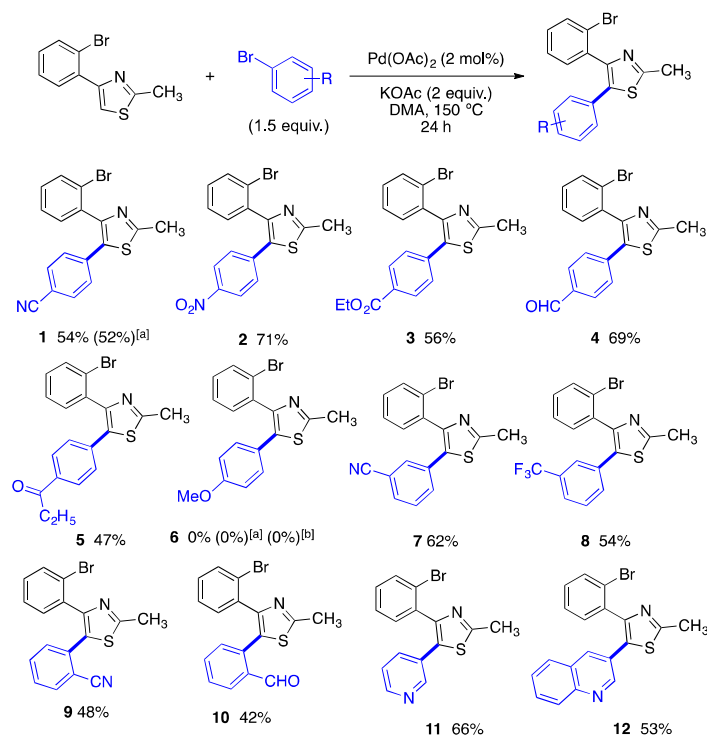
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3 and in nanographenes.⁴ Some nitrogen-containing polycyclic aromatic hydrocarbons displayed
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5 unprecedented luminescence properties and represent promising candidates for fabricating organic
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7 optoelectronic devices.⁵ On the other hand, the thiazole moiety is present in a number of important natural
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9 products with high pharmacological activities.⁶ The synthesis of phenanthroid-fused thiazoles is poorly
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11 developed, albeit some phenanthrothiazoles display interesting potential pharmacological activity.⁷ One
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13 of the major reason of the limited information concerning phenanthrothiazole derivatives probably arises
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15 from the scarce synthetic routes described in the literature. Therefore, the discovery of straightforward
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17 synthetic routes for access to phenanthrothiazoles remains an important challenge for both academic
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19 research groups and for chemical companies.
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23 Domínguez, Tellitu and co-worker reported the synthesis of phenanthrothiazoles through the oxidative
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25 cyclization of 4,5-diarylthiazole using a stoichiometric amount of phenyliodine(III)*bis*(trifluoroacetate)
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27 reagent.⁸ A few example of phenanthrothiazoles synthesis by pyrolysis of 1,2,4-triazine ring under hash
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29 reaction conditions (i.e. up to 350 °C) were also reported.⁹ However, with these two procedures, the
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31 substrate scope remains very limited due to both challenging access to starting materials and poor
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33 functional group tolerance. During the last decades, transition-metal catalyzed direct C–H bond
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35 functionalization has emerged as a powerful methodology for the formation of C–C bonds,¹⁰ including
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37 direct arylations,¹¹ C–heteroatom bonds,¹² using palladium catalysis,¹³ ruthenium,¹⁴ or other metals,¹⁵
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39 directed C–H bonds,¹⁶ oxidative couplings,¹⁷ and it was also apply to the straightforward synthesis and
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41 the easy modifications of organic molecules.¹⁸ In 2013, Nishihara and co-workers reported the synthesis
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43 of polyaromatic hydrocarbon such as triphenylenes through cross-coupling followed by annulation
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45 reaction of *ortho*-bromobenzylalcohols.¹⁹ A similar strategy was employed by Greaney and co-workers
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47 using 2-bromophenylboronic esters.²⁰ C–H bond arylation was recently transfer to the synthesis of
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49 polyaromatic hydrocarbons containing heteroatoms. As example, phenanthro[9,10-*b*]thiophene were
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51 synthesized by palladium-catalyzed oxidative intramolecular C–H bond arylation.²¹ In 2014, Bach and co-
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53 workers reported a novel synthetic route for the preparation of phenanthro[9,10-*c*]thiophenes involving C–
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55 H bond activation, Suzuki cross-coupling and photocyclization.²² Recently, we have reported the
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3 synthesis of thiophene-analogues of polyaromatic hydrocarbons in two operations from thiophenes, 2-
4 bromobenzenesulfonyl chlorides and aryl bromides.²³ The C3-desulfitative arylation of thiophenes
5 provides a straightforward access to 4-(2-bromophenyl)thiophene derivatives,²⁴ which could react with
6 activated aryl bromides in Pd-promoted two-fold C–H bond arylation to allow to the formation of
7 phenanthro[9,10-*b*]thiophenes. We employed a similar synthetic scheme for the elaboration of medium-
8 size heterocycles with a bridgehead nitrogen atom.²⁵ However, to the best of our knowledge, there is no
9 example of palladium-catalyzed successive C–H bond arylation reactions for the formation of
10 phenanthrothiazoles.

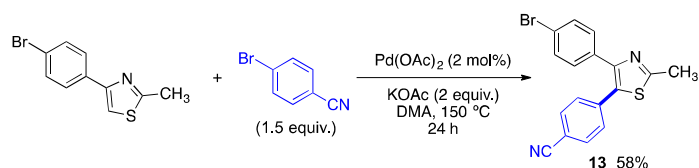
11
12 Our investigations started with the evaluation of the reactivity of commercially available 4-(2-
13 bromophenyl)-2-methylthiazole in the presence of 4-bromobenzonitrile under our previously optimized
14 reaction conditions for the synthesis of C5-arylated thiophenes^{23, 26} (*i.e.*, 2 mol% PdCl(C₃H₅)(dppb) as
15 catalyst in the presence of PivOK as base in DMA at 150 °C). Interestingly, the intermolecular palladium-
16 catalyzed direct arylation proceeded to give **1** in good yield, without the cleavage of the phenyl C–Br
17 bond. However, under these conditions, no formation of phenanthrothiazole **14**, which would result from
18 a palladium-catalyzed one-pot two-fold direct arylation was observed. This reactivity might be explained
19 by a slower oxidative addition rate to palladium(0) of a bromobenzene bearing a thiazole substituent than
20 a bromobenzene bearing a nitrile group. The use of Pd(OAc)₂ as catalyst instead of PdCl(C₃H₅)(dppb) and
21 KOAc as base provided **1** in a similar yield. Consequently, this phosphine-free catalytic system was
22 selected to evaluate the reactivity of 4-(2-bromophenyl)-2-methylthiazole with other aryl bromides. All
23 the aryl bromides that we selected displayed a similar reactivity, and only the C5-arylated thiazole
24 derivatives were obtained. Good yields in the desired 4-(2-bromophenyl)-2-methyl-5-arylthiazoles **2-5**
25 were obtained with bromobenzenes substituted at *para*-position by nitro-, ester-, formyl-, or propionyl-
26 substituents in the presence of 2 mol% of phosphine-free Pd(OAc)₂. A complex mixture was formed
27 when 4-bromonitrobenzene was used as the aryl source, even using PdCl(C₃H₅)(dppb) catalyst. We also
28 investigated the reactivity of 4-iodoanisole, but the desired product **6** was observed in only trace amount
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by GC/MS analysis of the crude mixture with other side-products. Among them a huge amount of 4-iodoanisole homocoupling prevents the isolation of **6** in a pure form. The *meta*-substituted electron-deficient aryl bromides, 3-bromobenzonitrile and 1-bromo-3-(trifluoromethyl)benzene, were also found to be suitable reactants, affording **7** and **8** in 62% and 54% yields, respectively. The reaction was found to be slightly sensitive to steric hindrance as the *ortho*-substituted electron-deficient aryl bromides 2-bromobenzonitrile and 2-bromobenzaldehyde delivered the desired 4-(2-bromophenyl)-2-methyl-5-arylthiazoles **9** and **10** in moderate yields of 42% and 48%, respectively. The *N*-containing heteroaryl bromides, 3-bromopyridine and 3-bromoquinoline, were also successfully employed as coupling partners to afford the C5 arylated thiazoles **11** and **12** in 66% and 53% yields, respectively. It is important to mention that, in all the examples mentioned above, the C–Br bond of 4-(2-bromophenyl)-2-methylthiazole remained untouched under these reaction conditions.



Scheme 1. Palladium-Catalyzed Direct Intermolecular C5-Arylation of 4-(2-bromophenyl)-2-methylthiazole. [a] PdCl(C₃H₅)(dppb) and PivOK were used instead of Pd(OAc)₂ and KOAc. [b] The reaction is performed with 4-iodoanisole instead of 4-bromoanisole and Ag₂CO₃ as base.

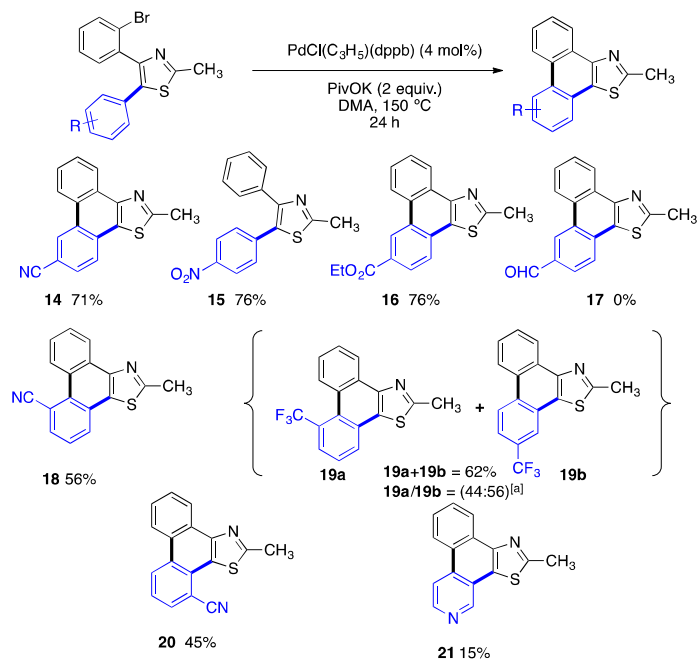
We also investigated the C–Br bond cleavage selectivity using 4-(4-bromophenyl)-2-methylthiazole (Scheme 2). In the presence of 4-bromobenzonitrile, under the optimized reaction conditions (i.e., 2 mol% Pd(OAc)₂, KOAc as base in DMA at 150 °C), we obtained the formation of the C5 arylated product **13** without cleavage of the 4-(4-bromophenyl)-2-methylthiazole C–Br bond. This result suggests that the selectivity of the oxidative addition to palladium(0) is due to electronic effects rather than to steric effects.



Scheme 2. Palladium-Catalyzed Direct Intermolecular C5-Arylation of 4-(4-bromophenyl)-2-methylthiazole.

In a second step, we investigated the reactivity of some of the 5-(2-bromophenyl)-2-methyl-4-arylthiazoles prepared in the Scheme 1 for intramolecular direct arylation (Scheme 3).²⁷ As expected, the compound **1** did not react in the presence of 4 mol% of Pd(OAc)₂ as catalyst associated to PivOK as base in DMA. But, we were pleased to find that **1** was cyclized into the desired phenanthrothiazole **14** using 4 mol% PdCl(C₃H₅)(dppb) as catalyst. The use of this palladium catalyst which contains a phosphine ligand, promote the oxidative addition of the 2-bromophenyl moiety. However, the use of a lower catalyst loading of 2 mol% resulted in a partial conversion of **1**. It is important to note that under these conditions, the reaction between 4-(2-bromophenyl)-2-methylthiazole and 4-bromobenzonitrile did not afford the product **12** resulting from a palladium-catalyzed one-pot two-fold direct arylation. Then, we evaluated, under these reaction conditions, the cyclization of few other 4-(2-bromophenyl)-2-methyl-5-arylthiazoles previously prepared. No cyclization occurred using more electron-deficient 4-(2-bromophenyl)-2-methyl-5-(4-nitrophenyl)thiazole (**2**), and only the product **15** resulting from a debromination reaction was isolated in 76% yield. This result might be explained by the formation of “palladium black” due to the presence of a nitro group in the reaction mixture. Such palladium species could catalyze the debromination reaction. On the contrary, the cyclization reaction was found to be operative when the C5 aryl group on thiazole is substituted at the *para* position by an ester group (product **3**) allowing the

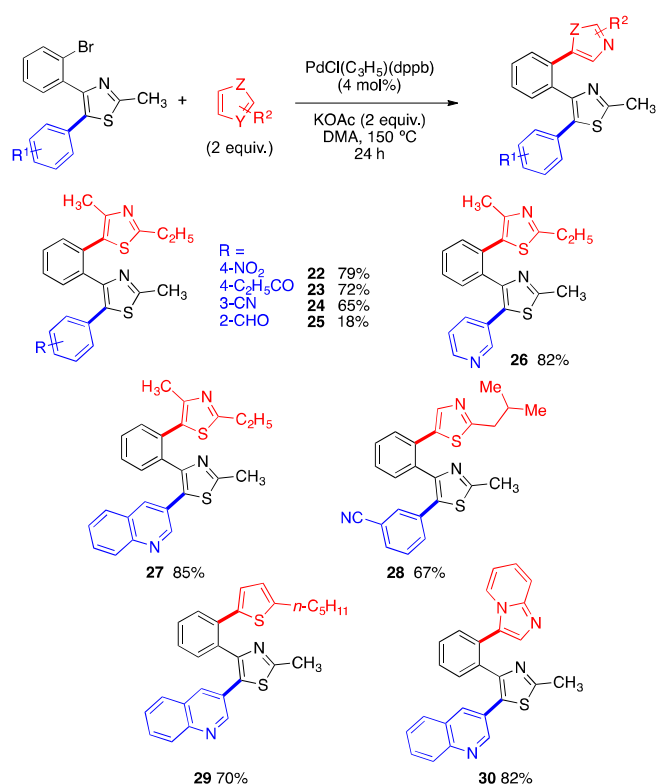
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3 synthesis of the desired phenanthrothiazole **16** in 76% yield. The intramolecular direct arylation does not
4 occur using 4-(4-(2-bromophenyl)-2-methylthiazol-5-yl)benzaldehyde (**4**), but only the degradation of **4**
5 was observed by GC-MS and NMR analysis, including its deformatylation. The cyclization of 3-(4-(2-
6 bromophenyl)-2-methylthiazol-5-yl)benzotrile (**7**), containing a *meta*-substituent on the benzotrile
7 unit, lead to the single regioisomer **18** in 56% yield. The cyclization occurred at the more sterically
8 hindered *ortho*-position of the cyano group. This regioselectivity is similar to our previous observations
9 for the cyclization of 4-(2-bromophenyl)thiophene in the presence of 3-bromobenzotrile.²³ This
10 regioselectivity might be explained by electronic factors, such as repulsing effect between sulfur atom and
11 CN group,²⁸ or a directing group effect of the cyano group. In contrast, the *meta*-substituted 4-(2-
12 bromophenyl)-2-methyl-5-(3-(trifluoromethyl)phenyl)thiazole (**8**) gave a mixture of the two
13 phenanthrothiazole regioisomers **19a** and **19b** in 44:56 ratio. The major product **19b** results from the
14 functionalization of the less sterically hindered C–H bond (at *para* position of the CF₃) and the minor
15 product **19a** arises from the cyclization at the *ortho*-position of the CF₃ substituent, which is the most
16 electron-deficient C–H bond. A cyano substituent at *ortho*-position of the C5-aryl group on thiazole
17 decreases the yield in cyclization product, as desired phenanthrothiazole **20** was isolated in only 45%
18 yield. Finally, the reactivity of the compound **11**, which bears a pyridine at the thiazolyl C5 position was
19 examined in cyclization reaction. Very few examples of or intramolecular palladium-catalyzed direct
20 arylations of substrates containing a pyridine motif have been reported.²⁹ Using the standard reaction
21 conditions, the cyclization reaction allowed the formation of the desired phenanthrothiazole derivative **21**
22 as a single regioisomer, resulting from the activation of the C4–H bond of the pyridine unit, but in a very
23 low yield.
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Scheme 3. Synthesis of Phenanthrothiazole Derivatives *via* Palladium-Catalyzed Direct Intramolecular Arylation of 5-(2-Bromophenyl)-2-methyl-4-arylthiazoles **1-3**, **8-9** and **11**. [a] ratio determined by NMR.

Next, we investigated the reactivity of some 4-(2-bromophenyl)-2-methyl-5-arylthiazoles prepared in the Scheme 1 in intermolecular direct arylation in the presence of heteroarenes (Scheme 4). Under the quite similar conditions than those employed for intramolecular direct arylation in the Scheme 2, namely, 4 mol% $\text{PdCl}(\text{C}_3\text{H}_5)(\text{dppb})$ associated to KOAc as base in DMA , we found that 4-(2-bromophenyl)-2-methyl-5-arylthiazole **2** in the presence of 1.5 equivalents of 2-ethyl-4-methylthiazole lead exclusively to the polyaromatic compound **22** in 79% yield, without formation of the phenanthrothiazole **14**. This result indicates that the palladium-catalyzed intermolecular arylation proceeds faster than the intramolecular reaction. It confirms that the thiazolyl C–H bond is more reactive than the C–H bond of the nitrobenzene in palladium-catalyzed direct arylation. Similar results were obtained with the other 4-(2-bromophenyl)-2-methyl-5-arylthiazoles **5**, **7** to furnish the products **23** and **24** in good yields. Starting from 2-(4-(2-bromophenyl)-2-methylthiazol-5-yl)benzaldehyde (**10**) and 2-ethyl-4-methylthiazole, the intermolecular direct arylation reaction proceeded in low yield without formation of intramolecular cyclizing product, but the presence of a huge amount of degradation product including one coming from a deformylation was observed. In contrast to the cyclization reaction, in which pyridine or quinoline substituents as C5

position of the thiazole decreased drastically their reactivity, such *N*-containing heteroaryls does not affect the yields for the formation of the derivatives **26** and **27**, which were obtained in 82% and 85% yields from the compounds **11** and **12**, respectively. Using 2-isobutylthiazole, the intermolecular reaction also proceeded faster than the cyclization reaction to afford the compound **28** in good yield. When *n*-pentylthiophene was used as heteroarene with **12**, again only the intermolecular reaction was observed to afford the C5-arylated thiophene **29** in 70% yield. Finally, using imidazo[1,2-*b*]pyridine, which is also a very reactive substrate in palladium-catalyzed C–H bond arylation, again only the intermolecular coupling was observed allowing the formation of **30** in 82% yield.



Scheme 4. Synthesis of 1,2-Dithiazolyarenes Derivatives *via* Palladium-Catalyzed Direct Intermolecular Arylation of 4-(2-Bromophenyl)-2-methyl-5-arylthiazoles **2**, **5**, **7**, and **10-12**.

In summary, we have discovered that in contrast to the reaction between 4-(2-bromophenyl)thiophene and electron-deficient aryl bromides, in which palladium-catalyzed one-pot cascade two-fold direct arylations to allow the synthesis of phenanthro[9,10-*b*]thiophenes, the reaction with 4-(2-bromophenyl)-2-methylthiazole stopped after the first direct arylation. This procedure tolerates a wide variety of

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3 substituents on the aryl bromide such as nitro, cyano, ester, ketone, formyl, trifluoromethyl and also
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5 pyridine derivatives. The cyclization occurred in a second step using PdCl(C₃H₅)(dppb) as catalyst. We
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7 also demonstrated that PdCl(C₃H₅)(dppb) catalyst preferentially promotes the intermolecular arylation
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9 between 4-(2-bromophenyl)-2-methyl-5-arylthiazoles and heteroarenes such as thiazoles, thiophenes, and
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11 imidazo[1,2-*a*]pyridines. These two steps procedures from commercially available starting materials
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13 represent an economically attractive, and straightforward route for the preparation of a wide range of
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15 phenanthro-fused thiazoles and polyaryl derivatives, which could inspire the preparation of structures with
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17 applications in electronic devices or potent pharmaceuticals.
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20 21 **EXPERIMENTAL SECTION**

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24 All reactions were carried out under argon atmosphere with standard Schlenk techniques. DMA was was
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26 not purified before use. ¹H NMR spectra were recorded on 400 MHz spectrometer. Chemical shifts (δ)
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28 were reported in parts per million relative to residual chloroform (7.26 ppm for ¹H; 77.0 ppm for ¹³C),
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30 constants were reported in Hertz. ¹H NMR assignment abbreviations were the following: singlet (s),
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32 doublet (d), triplet (t), quartet (q), doublet of doublets (dd), doublet of triplets (dt), and multiplet (m). ¹³C
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34 NMR spectra were recorded at 100 MHz on the same spectrometer and reported in ppm. All reagents
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36 were weighed and handled in air.
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40 **Preparation of the PdCl(C₃H₅)(dppb) catalyst:**³⁰ An oven-dried 40 mL Schlenk tube equipped with a
41
42 magnetic stirring bar under argon atmosphere, was charged with [Pd(C₃H₅)Cl]₂ (182 mg, 0.5 mmol) and
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44 dppb (426 mg, 1 mmol). 10 mL of anhydrous dichloromethane were added, then, the solution was stirred
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46 at room temperature for twenty minutes. The solvent was removed in vacuum. The powder was used
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48 without purification. (³¹P 381 MHz, CDCl₃) δ = 19.3 (s).
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52 **General Procedure A (Palladium-catalyzed direct intermolecular arylation):** To a 25 mL oven dried
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54 Schlenk tube 4-(2-bromophenyl)-2-methylthiazole (254 mg, 1 mmol), aryl bromides (1.5 mmol, 1.5
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56 equiv.), KOAc (196 mg, 2 mmol, 2 equiv.), DMA (4 mL) and Pd(OAc)₂ (4.5 mg, 0.02 mmol, 2 mol%)
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58 were successively added. The reaction mixture was evacuated by vacuum-argon cycles (5 times) and
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3 stirred at 150 °C (oil bath temperature) for 24 hours. After cooling the reaction at room temperature and
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5 concentration, the crude mixture was purified by flash chromatography to afford the desired arylated
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7 products.
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10 **General Procedure B (Palladium-catalyzed direct intramolecular arylation):** To a 25 mL oven dried
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12 Schlenk tube 5-(2-bromophenyl)-2-methyl-4-arylthiazole (0.5 mmol), PivOK (140 mg, 1 mmol, 2 equiv.),
13
14 DMA (4 mL) and PdCl(C₃H₅)(dppb) (12.2 mg, 0.02 mmol, 4 mol%) were successively added. The
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16 reaction mixture was evacuated by vacuum-argon cycles (5 times) and stirred at 150 °C (oil bath
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18 temperature) for 24 hours. After cooling the reaction at room temperature and concentration, the crude
19
20 mixture was purified by flash chromatography to afford the desired arylated products.
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24 **General Procedure C (Palladium-catalyzed direct intermolecular arylation):** To a 25 mL oven dried
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26 Schlenk tube 5-(2-bromophenyl)-2-methyl-4-arylthiazole (0.5 mmol), heteroarenes (1 mmol, 2 equiv.),
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28 KOAc (98 mg, 1 mmol, 2 equiv.) DMA (4 mL) and PdCl(C₃H₅)(dppb) (12.2 mg, 0.02 mmol, 4 mol%)
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30 were successively added. The reaction mixture was evacuated by vacuum-argon cycles (5 times) and
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32 stirred at 150 °C (oil bath temperature) for 24 hours. After cooling the reaction at room temperature and
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34 concentration, the crude mixture was purified by flash chromatography to afford the desired arylated
35
36 products.
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39 **4-(4-(2-Bromophenyl)-2-methylthiazol-5-yl)benzotrile (1):** Following the general procedure A using
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41 4-(2-bromophenyl)-2-methylthiazole (254 mg, 1 mmol) and 4-bromobenzotrile (273 mg, 1.5 mmol), the
42
43 residue was purified by flash chromatography on silica gel (pentane-EtOAc, 80-20) to afford the desired
44
45 compound **1** (192 mg, 54%) as yellow oil: ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.62 (d, *J* = 8.0 Hz, 1H),
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47 7.50 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 4.2 Hz, 2H), 7.28 – 7.24 (m, 3H), 2.79 (s, 3H). ¹³C NMR (75 MHz,
48
49 CDCl₃) δ (ppm) 165.2, 150.2, 136.4, 136.0, 133.3, 132.8, 132.4, 131.8, 130.4, 128.8, 127.7, 123.6, 118.5,
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51 111.2, 19.4. Elemental analysis: calcd (%) for C₁₇H₁₁BrN₂S (355.25): C 57.48, H 3.12; found: C 57.56, H
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53 3.01. MS (IE) = (M+1) 356 m/z.
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3 **4-(2-Bromophenyl)-2-methyl-5-(4-nitrophenyl)thiazole (2):** Following the general procedure A using
4 4-(2-bromophenyl)-2-methylthiazole (254 mg, 1 mmol) and 1-bromo-4-nitrobenzene (303 mg, 1.5 mmol),
5 the residue was purified by flash chromatography on silica gel (pentane-EtOAc, 80-20) to afford the
6 desired compound **2** (266 mg, 71%) as brown oil: ¹H NMR (400 MHz, CDCl₃) δ (ppm). 8.08 (d, *J* = 8.9
7 Hz, 2H), 7.63 (d, *J* = 7.9 Hz, 1H), 7.37 – 7.34 (m, 2H), 7.33 – 7.25 (m, 3H), 2.80 (s, 3H). ¹³C NMR (75
8 MHz, CDCl₃) δ (ppm) 165.5, 150.7, 146.8, 138.4, 135.9, 133.4, 132.4, 131.9, 130.5, 128.9, 127.8, 124.0,
9 123.6, 19.6. Elemental analysis: calcd (%) for C₁₆H₁₁BrN₂O₂S (375.24): C 51.21, H 2.95; found: C 51.38,
10 H 3.21. MS (IE) = (M+1) 376 m/z.
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21 **Ethyl 4-(4-(2-bromophenyl)-2-methylthiazol-5-yl)benzoate (3):** Following the general procedure A
22 using 4-(2-bromophenyl)-2-methylthiazole (254 mg, 1 mmol) and ethyl 4-bromobenzoate (344 mg, 1.5
23 mmol), the residue was purified by flash chromatography on silica gel (pentane-EtOAc, 80-20) to afford
24 the desired compound **3** (225 mg, 56%) as colorless oil: ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.89 (d, *J* =
25 8.4 Hz, 2H), 7.61 (d, *J* = 8.1 Hz, 1H), 7.39 – 7.29 (m, 2H), 7.27 – 7.18 (m, 3H), 4.34 (q, *J* = 7.1 Hz, 2H),
26 2.78 (s, 3H), 1.36 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ (ppm) 166.0, 164.4, 149.7, 136.4,
27 136.2, 133.8, 133.2, 131.9, 130.0, 129.8, 129.5, 128.2, 127.6, 123.8, 61.0, 19.4, 14.3. Elemental analysis:
28 calcd (%) for C₁₉H₁₆BrNO₂S (402.31): C 56.73, H 4.01; found: C 56.89, H 4.22. MS (IE) = (M+1) 403
29 m/z.
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41 **4-(4-(2-Bromophenyl)-2-methylthiazol-5-yl)benzaldehyde (4):** Following the general procedure A
42 using 4-(2-bromophenyl)-2-methylthiazole (254 mg, 1 mmol) and 4-bromobenzaldehyde (278 mg, 1.5
43 mmol), the residue was purified by flash chromatography on silica gel (pentane-EtOAc, 80-20) to afford
44 the desired compound **4** (247 mg, 69%) as yellow oil: ¹H NMR (400 MHz, CDCl₃) δ (ppm) 9.92 (s, 1H),
45 7.72 (d, *J* = 8.1 Hz, 2H), 7.61 (d, *J* = 7.9 Hz, 1H), 7.40 – 7.27 (m, 4H), 7.27 – 7.20 (m, 1H), 2.78 (s, 3H).
46 ¹³C NMR (75 MHz, CDCl₃) δ (ppm) 191.4, 165.0, 150.1, 137.8, 136.3, 135.2, 133.5, 133.3, 131.9, 130.2,
47 130.0, 128.8, 127.7, 123.7, 19.5. Elemental analysis: calcd (%) for C₁₇H₁₂BrNOS (358.25): C 57.00, H
48 3.38; found: C 56.87, H 3.59. MS (IE) = (M-1) 357 m/z.
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3 **1-(4-(4-(2-Bromophenyl)-2-methylthiazol-5-yl)phenyl)propan-1-one (5):** Following the general
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5 procedure **A** using 4-(2-bromophenyl)-2-methylthiazole (254 mg, 1 mmol) and 4-bromopropiophenone
6
7 (320 mg, 1.5 mmol), the residue was purified by flash chromatography on silica gel (pentane-EtOAc, 85-
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9 15) to afford the desired compound **5** (181 mg, 47%) as yellow oil: ¹H NMR (400 MHz, CDCl₃) δ (ppm)
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11 7.81 (d, *J* = 8.1 Hz, 2H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.42 – 7.29 (m, 2H), 7.28 – 7.19 (m, 3H), 2.93 (q, *J* =
12
13 7.1 Hz, 2H), 2.78 (s, 3H), 1.19 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ (ppm) 200.0, 164.5,
14
15 149.7, 136.5, 136.2, 135.7, 133.7, 133.2, 131.9, 130.1, 128.4, 128.3, 127.6, 123.8, 31.7, 19.4, 8.2.
16
17 Elemental analysis: calcd (%) for C₁₉H₁₆BrNOS (386.31): C 59.07, H 4.17; found: C 59.21, H 4.02. MS
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19 (IE) = (M+1) 387 m/z.
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23 **3-(4-(2-Bromophenyl)-2-methylthiazol-5-yl)benzotrile (7):** Following the general procedure **A** using
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25 4-(2-bromophenyl)-2-methylthiazole (254 mg, 1 mmol) and 3-bromobenzotrile (273 mg, 1.5 mmol), the
26
27 residue was purified by flash chromatography on silica gel (pentane-EtOAc, 80-20) to afford the desired
28
29 compound **7** (220 mg, 62%) as brown oil: ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.60 (d, *J* = 7.7 Hz, 1H),
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31 7.53 – 7.42 (m, 2H), 7.40 – 7.28 (m, 4H), 7.25 (d, *J* = 8.1 Hz, 1H), 2.77 (s, 3H). ¹³C NMR (75 MHz,
32
33 CDCl₃) δ (ppm) 164.7, 149.9, 135.8, 133.3, 133.2, 132.6, 132.2, 131.9, 131.7, 131.1, 130.4, 129.5, 127.7,
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35 123.6, 118.2, 112.9, 19.4. Elemental analysis: calcd (%) for C₁₇H₁₁BrN₂S (355.25): C 57.48, H 3.12;
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37 found: C 57.24, H 2.95. MS (IE) = (M-1) 354 m/z.
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41 **4-(2-Bromophenyl)-2-methyl-5-(3-(trifluoromethyl)phenyl)thiazole (8):** Following the general
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43 procedure **A** using 4-(2-bromophenyl)-2-methylthiazole (254 mg, 1 mmol) and 1-bromo-3-
44
45 (trifluoromethyl)benzene (338 mg, 1.5 mmol), the residue was purified by flash chromatography on silica
46
47 gel (pentane-EtOAc, 90-10) to afford the desired compound **8** (215 mg, 54%) as colorless oil: ¹H NMR
48
49 (400 MHz, CDCl₃) δ (ppm) 7.61 (d, *J* = 7.8 Hz, 1H), 7.49 – 7.44 (m, 1H), 7.43 (s, 1H), 7.37 – 7.29 (m,
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51 4H), 7.27 – 7.20 (m, 1H), 2.78 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ (ppm) 164.3, 149.7, 136.1, 133.2,
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53 133.1, 132.6, 131.9, 131.5, 130.9 (q, *J* = 32.1 Hz), 130.1, 129.1, 127.6, 125.2 (q, *J* = 3.9 Hz), 124.4 (q, *J* =
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3.7 Hz), 123.9 (q, $J = 272.7$ Hz), 123.8, 19.4. Elemental analysis: calcd (%) for $C_{17}H_{11}BrF_3NS$ (398.24): C 51.27, H 2.78; found: C 51.33, H 2.89. MS (IE) = (M+1) 399 m/z.

2-(4-(2-Bromophenyl)-2-methylthiazol-5-yl)benzonitrile (9): Following the general procedure A using 4-(2-bromophenyl)-2-methylthiazole (254 mg, 1 mmol) and 2-bromobenzonitrile (273 mg, 1.5 mmol), the residue was purified by flash chromatography on silica gel (pentane-EtOAc, 80-20) to afford the desired compound **9** (170 mg, 48%) as yellow oil: 1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.63 (dd, $J = 1.3, 7.5$ Hz, 1H), 7.50 (dd, $J = 1.0, 8.0$ Hz, 1H), 7.45 – 7.32 (m, 3H), 7.32 – 7.21 (m, 2H), 7.14 (td, $J = 1.8, 7.8$ Hz, 1H), 2.79 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 165.8, 151.8, 135.4, 135.3, 133.5, 133.0, 132.5, 132.4, 131.7, 130.0, 129.8, 128.6, 127.3, 123.6, 117.8, 113.2, 19.4. Elemental analysis: calcd (%) for $C_{17}H_{11}BrN_2S$ (355.25): C 57.48, H 3.12; found: C 57.21, H 3.32. MS (IE) = (M+1) 356 m/z.

2-(4-(2-Bromophenyl)-2-methylthiazol-5-yl)benzaldehyde (10): Following the general procedure A using 4-(2-bromophenyl)-2-methylthiazole (254 mg, 1 mmol) and 2-bromobenzaldehyde (278 mg, 1.5 mmol), the residue was purified by flash chromatography on silica gel (pentane-EtOAc, 80-20) to afford the desired compound **10** (150 mg, 42%) as yellow oil: 1H NMR (400 MHz, $CDCl_3$) δ (ppm) 10.04 (s, 1H), 7.84 (d, $J = 7.5$ Hz, 1H), 7.54 – 7.46 (m, 2H), 7.44 – 7.33 (m, 2H), 7.23 – 7.16 (m, 2H), 7.14 – 7.06 (m, 1H), 2.81 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 190.8, 165.7, 152.0, 134.9, 134.3, 134.3, 133.6, 133.2, 132.4, 132.4, 130.1, 129.8, 129.0, 127.9, 127.3, 123.6, 19.4. Elemental analysis: calcd (%) for $C_{17}H_{12}BrNOS$ (358.25): C 57.00, H 3.38; found: C 57.11, H 3.61. MS (IE) = (M-1) 357 m/z.

4-(2-Bromophenyl)-2-methyl-5-(pyridin-3-yl)thiazole (11): Following the general procedure A using 4-(2-bromophenyl)-2-methylthiazole (254 mg, 1 mmol) and 3-bromopyridine (237 mg, 1.5 mmol), the residue was purified by flash chromatography on silica gel (pentane-EtOAc, 70-30) to afford the desired compound **11** (218 mg, 66%) as brown oil: 1H NMR (400 MHz, $THF-d_8$) δ (ppm) 8.57 – 8.31 (m, 2H), 7.60 (d, $J = 7.7$ Hz, 1H), 7.46 (d, $J = 5.2$ Hz, 1H), 7.41 – 7.10 (m, 4H), 2.71 (s, 3H). ^{13}C NMR (75 MHz, $THF-d_8$) δ (ppm) 164.9, 151.0, 149.8, 149.6, 137.5, 136.1, 133.9, 133.1, 131.9, 130.9, 129.2, 128.3, 124.4,

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3 124.2, 19.2. Elemental analysis: calcd (%) for C₁₅H₁₁BrN₂S (331.23): C 54.39, H 3.35; found: C 54.67, H
4 3.19. MS (IE) = (M+1) 332 m/z.
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8 **4-(2-Bromophenyl)-2-methyl-5-(quinolin-3-yl)thiazole (12):** Following the general procedure **A** using
9 4-(2-bromophenyl)-2-methylthiazole (254 mg, 1 mmol) and 3-bromoquinoline (312 mg, 1.5 mmol), the
10 residue was purified by flash chromatography on silica gel (pentane-EtOAc, 70-30) to afford the desired
11 compound **12** (202 mg, 53%) as brown oil: ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.69 (d, *J* = 2.1 Hz, 1H),
12 8.01 (d, *J* = 8.8 Hz, 1H), 7.93 (d, *J* = 1.9 Hz, 1H), 7.65 (s, 2H), 7.59 (d, *J* = 8.1 Hz, 1H), 7.48 (t, *J* = 7.5
13 Hz, 1H), 7.38 (dd, *J* = 1.6, 7.6 Hz, 1H), 7.30 (td, *J* = 1.0, 7.1 Hz, 1H), 7.21 (td, *J* = 1.7, 7.8 Hz, 1H), 2.79
14 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ (ppm) 164.7, 150.1, 149.8, 147.0, 136.1, 134.7, 133.3, 132.0,
15 131.3, 130.3, 129.9, 129.2, 127.9, 127.7, 127.5, 127.2, 125.3, 123.8, 19.5. Elemental analysis: calcd (%)
16 for C₁₉H₁₃BrN₂S (381.29): C 59.85, H 3.44; found: C 60.13, H 3.58. MS (IE) = (M+1) 382 m/z.
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28 **4-(4-(4-Bromophenyl)-2-methylthiazol-5-yl)benzotrile (13):** Following the general procedure **A** using
29 4-(4-bromophenyl)-2-methylthiazole (254 mg, 1 mmol) and 4-bromobenzotrile (273 mg, 1.5 mmol), the
30 residue was purified by flash chromatography on silica gel (pentane-EtOAc, 80-20) to afford the desired
31 compound **13** (206 mg, 58%) as yellow oil: ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.58 (d, *J* = 8.3 Hz, 2H),
32 7.42 (d, *J* = 8.5 Hz, 2H), 7.38 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.5 Hz, 2H), 2.75 (s, 3H). ¹³C NMR (100
33 MHz, CDCl₃) δ (ppm) 165.6, 149.8, 136.8, 133.2, 132.6, 131.8, 130.7, 130.6, 130.0, 122.6, 118.4, 111.7,
34 19.3. Elemental analysis: calcd (%) for C₁₇H₁₁BrN₂S (355.25): C 57.48, H 3.12; found: C 57.21, H 2.89.
35 MS (IE) = (M+1) 356 m/z.
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46 **2-Methylphenanthro[9,10-*d*]thiazole-9-carbonitrile (14):** Following the general procedure **B** using 4-
47 (4-(2-bromophenyl)-2-methylthiazol-5-yl)benzotrile (**1**) (178 mg, 0.5 mmol), the residue was purified by
48 flash chromatography on silica gel (pentane-Et₂O, 85-15) to afford the desired compound **14** (97 mg,
49 71%) as a white solid (mp = 251-254 °C): ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.99 (s, 1H), 8.82 (d, *J* =
50 8.9 Hz, 1H), 8.62 (d, *J* = 7.7 Hz, 1H), 7.97 (d, *J* = 8.3 Hz, 1H), 7.83 – 7.73 (m, 3H), 2.99 (s, 3H). ¹³C
51 NMR (75 MHz, CDCl₃) δ (ppm) 167.7, 150.7, 129.8, 129.7, 129.0, 128.8, 128.7, 128.6, 128.5, 128.3,
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3 127.6, 126.7, 125.0, 123.0, 119.3, 109.5, 20.3. Elemental analysis: calcd (%) for C₁₇H₁₀N₂S (274.34): C
4 74.43, H 3.67; found: C 74.59, H 3.72. MS (IE) = (M) 274 m/z.
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8 **2-Methyl-5-(4-nitrophenyl)-4-phenylthiazole (15)** Following the general procedure **B** using 4-(2-
9 bromophenyl)-2-methyl-5-(4-nitrophenyl)thiazole (**2**) (188 mg, 0.5 mmol), the residue was purified by
10 flash chromatography on silica gel (pentane-Et₂O, 80-20) to afford the desired compound **15** (112 mg,
11 76%) as a yellow solid (mp = 133-136 °C): ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.14 (d, *J* = 8.9 Hz, 2H),
12 7.48-7.46 (m, 2H), 7.46 – 7.43 (m, 2H), 7.36 – 7.30 (m, 3H), 2.79 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ
13 (ppm) 165.6, 151.7, 147.0, 139.1, 134.2, 130.0, 129.8, 129.1, 128.7, 128.5, 124.0, 19.4. Elemental
14 analysis: calcd (%) for C₁₆H₁₂N₂O₂S (296.34): C 64.85, H 4.08; found: C 65.11, H 4.23. MS (IE) = (M)
15 296 m/z.
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26 **Ethyl 2-methylphenanthro[9,10-*d*]thiazole-9-carboxylate (16):** Following the general procedure **B**
27 using 4 ethyl 4-(4-(2-bromophenyl)-2-methylthiazol-5-yl)benzoate (**3**) (201 mg, 0.5 mmol), the residue
28 was purified by flash chromatography on silica gel (pentane-CH₂Cl₂, 40-60) to afford the desired
29 compound **16** (122 mg, 76%) as a yellow solid (mp = 175-178 °C): ¹H NMR (400 MHz, CDCl₃) δ (ppm)
30 9.40 (s, 1H), 8.86 – 8.66 (m, 2H), 8.21 (dd, *J* = 1.4, 8.3 Hz, 1H), 7.91 (d, *J* = 8.3 Hz, 1H), 7.81 – 7.63 (m,
31 2H), 4.50 (q, *J* = 7.1 Hz, 2H), 2.97 (s, 3H), 1.50 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ (ppm)
32 166.9, 166.6, 150.1, 130.2, 130.1, 129.8, 128.2, 128.1, 127.9, 127.8, 127.4, 127.2, 125.9, 125.8, 124.8,
33 123.3, 61.3, 20.2, 14.5. Elemental analysis: calcd (%) for C₁₉H₁₅NO₂S (321.39): C 71.01, H 4.70; found:
34 C 70.87, H 4.65. MS (IE) = (M+1) 322 m/z.
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46 **2-Methylphenanthro[9,10-*d*]thiazole-8-carbonitrile (18):** Following the general procedure **B** using 3-
47 (4-(2-bromophenyl)-2-methylthiazol-5-yl)benzotrile (**7**) (178 mg, 0.5 mmol), the residue was purified by
48 flash chromatography on silica gel (pentane-CH₂Cl₂, 20-80) to afford the desired compound **18** (77 mg,
49 56%) as a white solid (mp = 231-234 °C): ¹H NMR (400 MHz, CDCl₃) δ (ppm) 9.77 (d, *J* = 8.8 Hz, 1H),
50 8.85 (dd, *J* = 1.5, 7.9 Hz, 1H), 8.11 (dd, *J* = 1.3, 8.0 Hz, 1H), 8.03 (dd, *J* = 1.3, 7.4 Hz, 1H), 7.86 – 7.71
51 (m, 2H), 7.63 (t, *J* = 7.7 Hz, 1H), 2.96 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ (ppm) 166.7, 149.5, 135.5,
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3 131.0, 130.3, 128.9, 128.9, 128.4, 128.4, 128.0, 127.2, 126.3, 125.2, 124.9, 121.3, 108.4, 20.2. Elemental
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5 analysis: calcd (%) for C₁₇H₁₀N₂S (274.34): C 74.43, H 3.67; found: C 74.63, H 3.55. MS (IE) = (M) 274
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7 m/z.
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10 **2-Methyl-8-(trifluoromethyl)phenanthro[9,10-*d*]thiazole (19a)** and **2-Methyl-10-**
11 **(trifluoromethyl)phenanthro[9,10-*d*]thiazole (19b)**: Following the general procedure **B** using 3-(4-(2-
12 bromophenyl)-2-methylthiazol-5-yl)benzotrile (**8**) (199 mg, 0.5 mmol), the residue was purified by flash
13 chromatography on silica gel (pentane-CH₂Cl₂, 60-40) to afford the desired compound **19** (98 mg, 62%) as
14 a mixture of the two regioisomers in 44:56 ratio as a white solid (mp = 111-115 °C): ¹H NMR (400 MHz,
15 CDCl₃) δ (ppm) 8.80 (dd, *J* = 1.3, 8.0 Hz, 1H, **19b**), 8.78 – 8.71 (m, 2H, **19a+19b**), 8.67 (d, *J* = 8.7 Hz, 1H, **19b**),
16 8.57 (d, *J* = 8.0 Hz, 1H, **19b**), 8.06 (s, 1H, **19b**), 8.04 (d, *J* = 8.2 Hz, 1H, **19a**), 7.99 (d, *J* = 7.9 Hz, 1H, **19a**), 7.78 –
17 7.66 (m, 5H, **19a+19b**), 7.64 – 7.57 (m, 1H, **19a**), 2.93 (s, 3H, **19b**), 2.92 (s, 3H, **19a**). ¹³C NMR (75 MHz,
18 CDCl₃) δ (ppm). 166.3, 166.2, 149.4, 149.1, 130.7 (q, *J* = 2.1 Hz), 130.5 (q, *J* = 30.1 Hz), 130.0, 129.5, 129.1,
19 128.9, 128.9 (q, *J* = 32.1 Hz), 128.8, 128.7, 128.5, 128.4, 128.1, 127.9, 127.3, 127.1 (q, *J* = 8.2 Hz), 127.1, 126.6,
20 126.0, 125.9, 125.4 (q, *J* = 271.5 Hz), 124.8, 124.4, 124.2, 124.1 (q, *J* = 271.5 Hz), 123.3, 122.8 (q, *J* = 4.0 Hz),
21 122.1 (q, *J* = 4.0 Hz), 20.1, 20.1. Elemental analysis: calcd (%) for C₁₇H₁₀F₃NS (317.33): C 64.35, H 3.18;
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23 found: C 64.49, H 3.11. MS (IE) = (M) 317 m/z.
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38 **2-Methylphenanthro[9,10-*d*]thiazole-11-carbonitrile (20)**: Following the general procedure **B** using 2-
39 (4-(2-bromophenyl)-2-methylthiazol-5-yl)benzotrile (**9**) (178 mg, 0.5 mmol), the residue was purified by
40 flash chromatography on silica gel (pentane-CH₂Cl₂, 10-90) to afford the desired compound **20** (61 mg,
41 45%) as a yellow solid (mp = 150-153 °C): ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 9.24 (d, *J* = 8.3 Hz,
42 1H), 8.89 (d, *J* = 7.5 Hz, 1H), 8.71 (d, *J* = 7.5 Hz, 1H), 8.25 (d, *J* = 7.4 Hz, 1H), 7.91 – 7.73 (m, 3H), 2.96
43 (s, 3H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ (ppm) 168.8, 151.1, 135.4, 130.1, 129.3, 129.2, 129.1, 128.4,
44 127.8, 127.5, 127.4, 126.7, 124.9, 124.3, 119.9, 107.4, 19.9. Elemental analysis: calcd (%) for C₁₇H₁₀N₂S
45 (274.34): C 74.43, H 3.67; found: C 74.59, H 3.72. MS (IE) = (M) 274 m/z.
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2-Methylbenzo[f]thiazolo[4,5-*h*]isoquinoline (21): Following the general procedure **B** using 4-(2-Bromophenyl)-2-methyl-5-(pyridin-3-yl)thiazole (**11**) (166 mg, 0.5 mmol, 1 equiv.) the residue was purified by flash chromatography on silica gel (pentane-Et₂O, 50-50) to afford the desired compound **21** (19 mg, 15%) as a brown solid (mp = 45-50 °C): ¹H NMR (400 MHz, CDCl₃) δ (ppm) 9.34 (d, *J* = 8.0 Hz, 1H), 9.02 (d, *J* = 3.3 Hz, 1H), 8.80 (d, *J* = 7.9 Hz, 1H), 8.27 (d, *J* = 7.7 Hz, 1H), 7.89 – 7.75 (m, 2H), 7.58 (dd, *J* = 4.4, 8.1 Hz, 1H), 3.01 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ (ppm) 166.3, 148.3, 145.2, 133.0, 130.9, 130.8, 129.3, 129.0, 127.1, 125.1, 124.0, 122.2, 122.1, 118.6, 20.2. Elemental analysis: calcd (%) for C₁₅H₁₀N₂S (250.31): C 71.97, H 4.03; found: C 72.08, H 4.34. MS (IE) = (M) 250 m/z.

2-Ethyl-4-methyl-5-(2-(2-methyl-5-(4-nitrophenyl)thiazol-4-yl)phenyl)thiazole (22): Following the general procedure **C** using 4-(2-bromophenyl)-2-methyl-5-(4-nitrophenyl)thiazole (**2**) (188 mg, 0.5 mmol, 1 equiv.) and 2-ethyl-4-methylthiazole (127 mg, 1 mmol, 2 equiv.), the residue was purified by flash chromatography on silica gel (pentane-EtOAc, 50-50) to afford the desired compound **22** (172 mg, 79%) as a brown solid (mp = 99-102 °C): ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.98 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 7.5 Hz, 1H), 7.50 (t, *J* = 7.2 Hz, 1H), 7.44 (d, *J* = 7.4 Hz, 1H), 7.26-7.24 (m, 1H), 7.00 (d, *J* = 8.6 Hz, 2H), 2.87 – 2.69 (m, 2H), 2.77 (s, 3H), 1.74 (s, 3H), 1.24 (t, *J* = 7.5 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ (ppm) 165.9, 150.5, 147.9, 146.9, 138.6, 134.7, 132.0, 131.9, 131.3, 131.2, 129.2, 129.2, 129.1, 129.0, 128.9, 123.9, 26.8, 19.5, 15.2, 14.6. Elemental analysis: calcd (%) for C₂₂H₁₉N₃O₂S₂ (421.53): C 62.69, H 4.54; found: C 62.79, H 4.31. MS (IE) = (M) 421 m/z.

1-(4-(4-(2-(2-Ethyl-4-methylthiazol-5-yl)phenyl)-2-methylthiazol-5-yl)phenyl)propan-1-one (23): Following the general procedure **C** using 1-(4-(4-(2-bromophenyl)-2-methylthiazol-5-yl)phenyl)propan-1-one (**5**) (193 mg, 0.5 mmol, 1 equiv.) and 2-ethyl-4-methylthiazole (127 mg, 1 mmol, 2 equiv.), the residue was purified by flash chromatography on silica gel (pentane-EtOAc, 50-50) to afford the desired compound **23** (156 mg, 72%) as a brown solid (mp = 64-49 °C): ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.78 – 7.68 (m, 3H), 7.50 (t, *J* = 7.0 Hz, 1H), 7.43 (td, *J* = 1.3, 7.5 Hz, 1H), 7.26 (d, *J* = 7.6 Hz, 1H), 6.96 (d, *J* = 8.3 Hz, 2H), 2.95 (q, *J* = 7.2 Hz, 2H), 2.89 – 2.81 (m, 2H), 2.78 (s, 3H), 1.75 (s, 3H), 1.27 (d, *J* = 7.3

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3 Hz, 3H), 1.22 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ (ppm) 200.0, 164.8, 149.4, 147.7, 136.5,
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5 136.5, 136.3, 135.6, 135.2, 134.4, 133.3, 131.7, 131.2, 129.2, 128.6, 128.3, 128.2, 31.8, 26.6, 19.3, 15.1,
6
7 14.5, 8.2. Elemental analysis: calcd (%) for $\text{C}_{25}\text{H}_{24}\text{N}_2\text{OS}_2$ (432.60): C 69.41, H 5.59; found: C 69.49, H
8
9 5.21. MS (IE) = (M) 432 m/z.

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12 **3-(4-(2-(2-Ethyl-4-methylthiazol-5-yl)phenyl)-2-methylthiazol-5-yl)benzotrile (24):** Following the
13
14 general procedure C using 3-(4-(2-bromophenyl)-2-methylthiazol-5-yl)benzotrile (7) (178 mg, 0.5
15
16 mmol, 1 equiv.) and 2-ethyl-4-methylthiazole (127 mg, 1 mmol, 2 equiv.), the residue was purified by
17
18 flash chromatography on silica gel (pentane-EtOAc, 50-50) to afford the desired compound **24** (130 mg,
19
20 65%) as a brown solid (mp = 47-50 °C): ^1H NMR (400 MHz, CDCl_3) δ (ppm) 7.70 (dd, $J = 1.4, 7.6$ Hz,
21
22 1H), 7.46 (d, $J = 7.2, 16.6$ Hz, 3H), 7.30 – 7.19 (m, 2H), 7.10 (s, 1H), 7.05 (d, $J = 7.9$ Hz, 1H), 2.84 (q, $J =$
23
24 7.5 Hz, 2H), 2.76 (s, 3H), 1.74 (s, 3H), 1.28 (t, $J = 7.6$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ (ppm)
25
26 165.2, 149.7, 147.9, 134.5, 133.4, 132.5, 131.9, 131.7, 131.6, 131.4, 131.1, 131.0, 129.5, 129.2, 129.0,
27
28 128.9, 118.2, 112.9, 26.8, 19.5, 15.3, 14.5. Elemental analysis: calcd (%) for $\text{C}_{23}\text{H}_{19}\text{N}_3\text{S}_2$ (401.55): C
29
30 68.80, H 4.77; found: C 68.79, H 5.03. MS (IE) = (M) 401 m/z.

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34 **2-(4-(2-(2-Ethyl-4-methylthiazol-5-yl)phenyl)-2-methylthiazol-5-yl)benzaldehyde (25):** Following the
35
36 general procedure C using 2-(4-(2-bromophenyl)-2-methylthiazol-5-yl)benzaldehyde (10) (179 mg, 0.5
37
38 mmol, 1 equiv.) and 2-ethyl-4-methylthiazole (127 mg, 1 mmol, 2 equiv.), the residue was purified by
39
40 flash chromatography on silica gel (pentane-EtOAc, 50-50) to afford the desired compound **25** (37 mg,
41
42 18%) as yellow oil: ^1H NMR (400 MHz, CDCl_3) δ (ppm) ^1H NMR (400 MHz, CDCl_3) δ 9.64 (s, 1H), 7.75
43
44 (dd, $J = 3.4, 5.9$ Hz, 1H), 7.72 (d, $J = 7.8$ Hz, 1H), 7.46 (t, $J = 7.0$ Hz, 1H), 7.39 – 7.31 (m, 3H), 7.13 (d, J
45
46 = 7.7 Hz, 1H), 6.78 (dd, $J = 3.2, 5.7$ Hz, 1H), 2.86 (q, $J = 7.5$ Hz, 2H), 2.82 (s, 3H), 1.67 (s, 3H), 1.30 (t, J
47
48 = 7.6 Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ (ppm) 190.1, 166.2, 151.6, 135.8, 134.3, 133.8, 133.4,
49
50 133.3, 132.2, 131.8, 131.5, 131.2, 129.4, 129.1, 128.8, 128.7, 128.6, 127.8, 125.5, 26.6, 19.3, 15.2, 14.2.
51
52 Elemental analysis: calcd (%) for $\text{C}_{23}\text{H}_{20}\text{N}_2\text{OS}_2$ (404.54): C 68.29, H 4.98; found: C 68.12, H 5.21. MS
53
54 (IE) = (M) 404 m/z.

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3 **2-Ethyl-4-methyl-5-(2-(2-methyl-5-(pyridin-3-yl)thiazol-4-yl)phenyl)thiazole (26):** Following the
4 general procedure C using 4-(2-Bromophenyl)-2-methyl-5-(pyridin-3-yl)thiazole (**11**) (166 mg, 0.5 mmol,
5 1 equiv.) and 2-ethyl-4-methylthiazole (127 mg, 1 mmol, 2 equiv.), the residue was purified by flash
6 chromatography on silica gel (EtOAc, 100) to afford the desired compound **26** (155 mg, 82%) as brown
7 oil: ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) δ 8.40 (d, *J* = 3.8 Hz, 1H), 7.97 (s, 1H), 7.67 (d, *J* = 6.4 Hz,
8 1H), 7.59 – 7.40 (m, 2H), 7.30 (d, *J* = 7.2 Hz, 1H), 7.24 (d, *J* = 4.7 Hz, 1H), 7.20 – 7.14 (m, 1H), 2.76 (q,
9 *J* = 7.4 Hz, 2H), 2.72 (s, 3H), 1.64 (s, 3H), 1.18 (t, *J* = 7.5 Hz, 3H). ¹³C NMR (75 MHz, DMSO-*d*₆) δ
10 (ppm) 170.2, 165.2, 149.4, 148.8, 148.1, 147.8, 135.5, 134.9, 131.9, 131.7, 131.0, 130.7, 129.3, 129.0,
11 128.8, 128.0, 124.2, 26.3, 19.4, 15.4, 14.5. Elemental analysis: calcd (%) for C₂₁H₁₉N₃S₂ (377.52): C
12 66.81, H 5.07; found: C 67.06, H 4.85. MS (IE) = (M+1) 378 m/z.

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25 **2-Ethyl-4-methyl-5-(2-(2-methyl-5-(quinolin-3-yl)thiazol-4-yl)phenyl)thiazole (27):** Following the
26 general procedure C using 4-(2-bromophenyl)-2-methyl-5-(quinolin-3-yl)thiazole (**12**) (191 mg, 0.5
27 mmol, 1 equiv.) and 2-ethyl-4-methylthiazole (127 mg, 1 mmol, 2 equiv.), the residue was purified by
28 flash chromatography on silica gel (pentane-EtOAc, 40-60) to afford the desired compound **27** (182 mg,
29 85%) as brown oil: ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) δ 8.19 (d, *J* = 1.9 Hz, 1H), 7.93 (d, *J* = 8.4
30 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.78 – 7.72 (m, 3H), 7.63 – 7.53 (m, 2H), 7.48 (t, *J* = 7.3 Hz, 1H), 7.23
31 (d, *J* = 7.5 Hz, 1H), 2.76 (s, 3H), 2.59 (q, *J* = 7.5 Hz, 2H), 1.41 (s, 3H), 1.00 (t, *J* = 7.5 Hz, 3H). ¹³C NMR
32 (75 MHz, DMSO-*d*₆) δ (ppm) 170.2, 165.4, 149.5, 149.0, 147.6, 146.8, 134.9, 134.5, 132.1, 131.8, 130.9,
33 130.4, 129.3, 129.0, 128.9, 128.8, 128.5, 127.7, 125.2, 26.2, 19.5, 15.1, 14.0. Elemental analysis: calcd
34 (%) for C₂₅H₂₁N₃S₂ (427.58): C 70.23, H 4.95; found: C 70.29, H 5.12. MS (IE) = (M) 427 m/z.

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47 **3-(4-(2-(2-Isobutylthiazol-5-yl)phenyl)-2-methylthiazol-5-yl)benzotrile (28):** Following the general
48 procedure C using 3-(4-(2-bromophenyl)-2-methylthiazol-5-yl)benzotrile (**7**) (178 mg, 0.5 mmol, 1
49 equiv.) and 2-isobutylthiazole (141 mg, 1 mmol, 2 equiv.), the residue was purified by flash
50 chromatography on silica gel (pentane-EtOAc, 70-30) to afford the desired compound **28** (139 mg, 67%)
51 as brown oil: ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.51 (dd, *J* = 2.4, 5.1 Hz, 1H), 7.46 – 7.37 (m, 4H),
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3 7.21 (d, $J = 7.8$ Hz, 1H), 7.17 (d, $J = 5.4$ Hz, 1H), 7.10 (d, $J = 7.9$ Hz, 1H), 7.02 (s, 1H), 2.75 (s, 3H), 2.73
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5 (d, $J = 7.1$ Hz, 2H), 2.08 – 1.89 (m, 1H), 0.94 (d, $J = 6.6$ Hz, 6H). ^{13}C NMR (75 MHz, CDCl_3) δ (ppm)
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7 170.4, 165.1, 149.8, 139.9, 136.1, 133.2, 132.9, 132.4, 132.1, 131.6, 131.2, 131.0, 130.9, 130.3, 129.3,
8
9 129.3, 128.7, 118.1, 112.7, 42.1, 29.7, 22.2, 19.4. Elemental analysis: calcd (%) for $\text{C}_{24}\text{H}_{21}\text{N}_3\text{S}_2$ (415.57):
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11 C 69.37, H 5.09; found: C 69.44, H 5.21. MS (IE) = (M) 415 m/z.
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15 **2-Methyl-4-(2-(5-pentylthiophen-2-yl)phenyl)-5-(quinolin-3-yl)thiazole (29):** Following the general
16
17 procedure C using 4-(2-bromophenyl)-2-methyl-5-(quinolin-3-yl)thiazole (**12**) (191 mg, 0.5 mmol, 1
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19 equiv.) and 2-*n*-pentylthiophene (155 mg, 1 mmol, 2 equiv.), the residue was purified by flash
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21 chromatography on silica gel (pentane-EtOAc, 80-20) to afford the desired compound **29** (159 mg, 70%)
22
23 as yellow oil: ^1H NMR (400 MHz, CDCl_3) δ (ppm) ^1H NMR (400 MHz, CDCl_3) δ ^1H NMR (400 MHz,
24
25 CDCl_3) δ 8.47 (s, 1H), 7.99 (d, $J = 8.4$ Hz, 1H), 7.64 (dd, $J = 1.5, 6.8$ Hz, 1H), 7.60 (d, $J = 1.9$ Hz, 1H),
26
27 7.57 – 7.53 (m, 2H), 7.46 (t, $J = 7.5$ Hz, 1H), 7.39 – 7.32 (m, 3H), 6.36 (d, $J = 3.5$ Hz, 1H), 6.24 (d, $J =$
28
29 3.5 Hz, 1H), 2.81 (s, 3H), 2.55 (t, $J = 7.6$ Hz, 2H), 1.53 – 1.40 (m, 2H), 1.35 – 1.20 (m, 4H), 0.88 (t, $J =$
30
31 7.0 Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ (ppm) 164.6, 150.6, 149.9, 146.7, 139.6, 134.6, 134.5, 132.8,
32
33 131.2, 130.8, 130.0, 129.5, 129.1, 129.0, 127.7, 127.7, 127.5, 126.9, 125.5, 125.2, 123.8, 31.3, 31.2, 29.9,
34
35 22.4, 19.5, 14.0. Elemental analysis: calcd (%) for $\text{C}_{28}\text{H}_{26}\text{N}_2\text{S}_2$ (454.65): C 73.97, H 5.76; found: C 74.11,
36
37 H 5.69. HRMS (ESI) m/z: $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{28}\text{H}_{26}\text{N}_2\text{NaS}_2$ 477.14351; Found 477.1435.
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42 **4-(2-(Imidazo[1,2-*a*]pyridin-3-yl)phenyl)-2-methyl-5-(quinolin-3-yl)thiazole (30):** Following the
43
44 general procedure C using 4-(2-bromophenyl)-2-methyl-5-(quinolin-3-yl)thiazole (**12**) (191 mg, 0.5
45
46 mmol, 1 equiv.) and imidazo[1,2-*a*]pyridazine (118 mg, 1 mmol, 2 equiv.), the residue was purified by
47
48 flash chromatography on silica gel (CH_2Cl_2 -MeOH, 95-5) to afford the desired compound **30** (172 mg,
49
50 82%) as brown oil: ^1H NMR (400 MHz, CDCl_3) δ (ppm) 8.22 (d, $J = 2.2$ Hz, 1H), 7.89 (d, $J = 7.0$ Hz,
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52 1H), 7.76 (d, $J = 8.4$ Hz, 1H), 7.58 – 7.49 (m, 3H), 7.47 – 7.40 (m, 1H), 7.37 – 7.32 (m, 2H), 7.31 – 7.24
53
54 (m, 2H), 7.20 (d, $J = 8.8$ Hz, 1H), 7.12 (s, 1H), 6.54 (t, $J = 7.0, 7.7$ Hz, 1H), 5.91 (t, $J = 6.1, 7.4$ Hz, 1H),
55
56 2.74 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ (ppm) 165.3, 149.5, 149.0, 146.8, 144.7, 134.9, 134.1, 133.0,
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3 132.0, 130.3, 129.7, 129.5, 129.1, 129.1, 128.8, 127.8, 126.8, 126.8, 124.4, 123.5, 123.3, 121.8, 116.7,
4
5 111.3, 19.4. Elemental analysis: calcd (%) for C₂₆H₁₈N₄S (418.52): C 74.62, H 4.34; found: C 74.37, H
6
7 4.22. MS (IE) = (M) 418 m/z.
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10 ASSOCIATED CONTENT

11 The Supporting Information is available free of charge on the ACS Publications website. Characterization
12 data, ¹H and ¹³C NMR spectra for all new compounds.
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