RSC Medicinal Chemistry

ROYAL SOCIETY OF CHEMISTRY

RESEARCH ARTICLE

View Article Online
View Journal | View Issue

Cite this: *RSC Med. Chem.*, 2025, **16**, 179

Design, synthesis, and structure–activity relationship studies of 6*H*-benzo[*b*]indeno[1,2-*d*]thiophen-6-one derivatives as DYRK1A/CLK1/CLK4/haspin inhibitors†

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A series of sulfur-containing tetracycles was designed and evaluated for their ability to inhibit protein kinase DYRK1A, a target known to have several potential therapeutic applications including cancers, Down syndrome or Alzheimer's disease. Our medicinal chemistry strategy relied on the design of new compounds using ring contraction/isosteric replacement and constrained analogy of known DYRK1A inhibitors, thus resulting in their DYRK1A inhibitory activity enhancement. Whereas a good inhibitory effect of targeted DYRK1A protein was observed for 5-hydroxy compounds **4i–k** (IC_{50} = 35–116 nM) and the 5-methoxy derivative **4e** (IC_{50} = 52 nM), a fairly good selectivity towards its known DYRK1B off-target was observed for **4k**. In addition, the most active compound **4k**, having an ATP-competitive mechanism of action, proved to be also a potent inhibitor of CLK1/CLK4 (IC_{50} = 20 and 26 nM) and, to a lesser extent, of haspin (IC_{50} = 76 nM) kinases. *In silico* docking studies within the DYRK1A, CLK1/CLK4 and haspin ATP binding sites were carried out to understand the interactions of our tetracyclic derivatives **4** with these targets. Antiproliferative activities on U87/U373 glioblastoma cell lines of the most potent compound **4k** showed a moderate effect (IC_{50} values between 33 and 46 μM). Microsomal stabilities of the designed compounds **4a–m** were also investigated, showing great disparities, depending on benzo[*b*]thiophene ring 5-substitution.

Received 13th July 2024,
Accepted 6th September 2024

DOI: 10.1039/d4md00537f

rsc.li/medchem

Introduction

Since the approval of imatinib in 2001[1] and the clinical successes of this first rationally-designed kinase inhibitor (KI) for the treatment of chronic myelogenous leukemia[2] and gastrointestinal stromal tumors,[3] many KIs have been developed for the treatment of various cancers,[4] also addressing the problems of selectivity and resistance phenomena to KI treatments.[5] To date, more than 70 KIs have been clinically approved in the U.S.,[6] with different mechanisms of action, mainly targeting the ATP binding site (with few molecules acting as allosteric modulators). Currently, the main applications of KIs focus on oncology,[5] which remains one of the most challenging public health issues and a leading cause of death for the World population.[7]

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† Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra of synthesis intermediate alcohols **7a–m**, ketones **6a–m**, and final tetracyclic compounds **4a–m**, effect/dose curves for complementary kinase profiling, antiproliferative effects (U373 and U87 glioblastoma cells) for compound **4k** and molecular modelling data. See DOI: https://doi.org/10.1039/d4md00537f

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In this context, the search for new therapeutic/druggable protein kinase targets remains a tremendous area of research and KIs were also developed by industrial and academic research groups for potential applications not only in cancer but also in infectious diseases,[8–13] auto-immune pathologies such as multiple sclerosis,[14] Parkinson's[15,16] and Alzheimer's diseases.[17,18] More specifically, the dual-specificity tyrosine regulated kinase 1A (DYRK1A) has gained considerable attention due to its involvement in numerous diseases[19] such as diabetes,[20,21] viral infections[22,23] and central nervous disorders like Down syndrome and Alzheimer's disease.[24–26]

Many DYRK1A inhibitors, both from natural and synthetic origins, were developed,[27,28] such as harmine, INDY, its acetylated prodrug Pro-INDY or its methylated derivative **1** (also known as TG003), PST-001,[29] 7-azaindole DANDY-**5a**,[30] the tetracyclic derivative **2**[31] or leucettinibs, the most advanced and selective DYRK1A inhibitors reported to date.[32]

While being in some cases very active, some off-target cross-inhibition was sometimes observed for these molecules,[33,34] which stimulated the scientific community to develop new chemical entities with enhanced potency and selectivity.

Inspired by the structure of chromeno[3,4-*b*]indoles **3**[35] (Fig. 2), we planned on synthesizing the original 9-thia-indeno[1,2-*a*]inden-10-ones **4**, after chromene ring contraction to indenone and isoelectronic NH substitution by a sulfur atom. These original structures are also constrained analogs of the corresponding "open form", benzothiophenyl-acetophenones **5** (Fig. 2), known DYRK1A/CLK1 dual inhibitors, acting as pre-mRNA splicing modulators.[36,37]

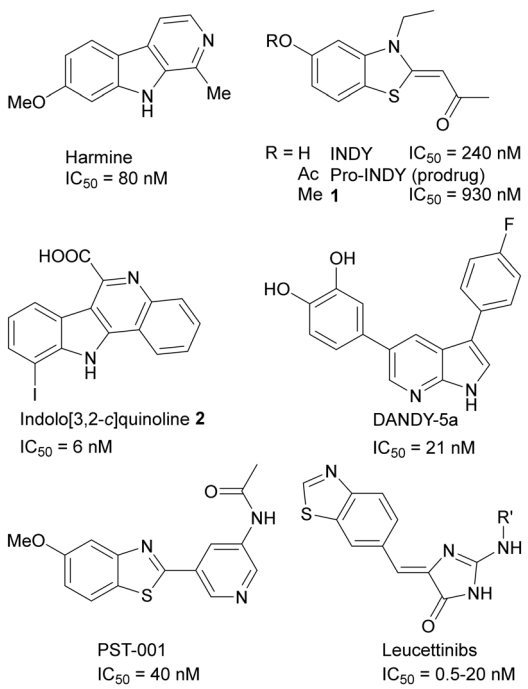


Fig. 1 Structures of some known DYRK1A inhibitors (IC_{50} for DYRK1A is indicated).

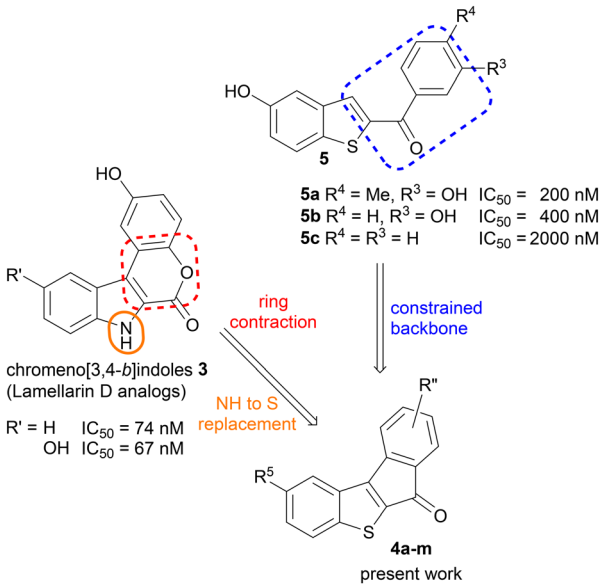


Fig. 2 Drug design strategy for the preparation of tetracycles **4** (IC_{50} for DYRK1A are indicated).

In the work described herein, we wish to report the synthesis and biological evaluations of a series of these new derivatives **4a–m**, initially designed to inhibit DYRK1A.

Results and discussion

Chemistry

The syntheses of the target products **4a–m** relied on a palladium-catalyzed annulation reaction of precursors **6a–m**. These substrates were prepared after oxidation of the corresponding alcohols **7a–m**, which were itself obtained using the addition of 2-benzothiophenyl lithium anions from **9a–c** onto methoxy *ortho*-iodobenzaldehydes **8a–e** (Fig. 3).

Functionalized benzo[*b*]thiophenes **9** were prepared by acidic cyclization of diethoxy acetals **10a**, **b**, obtained from corresponding *para*-thiophenols **11a**, **b**[38–41] (Scheme 1) and a

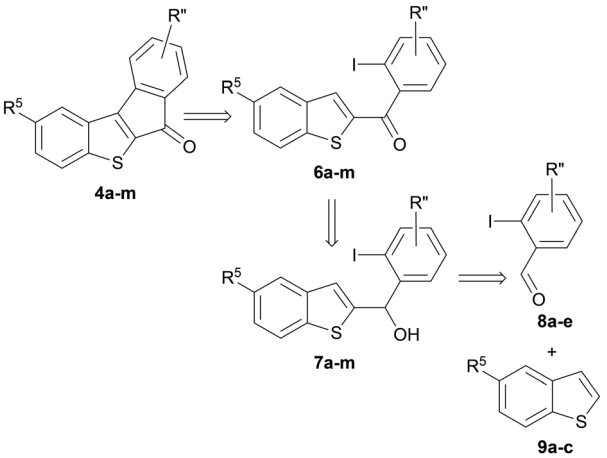
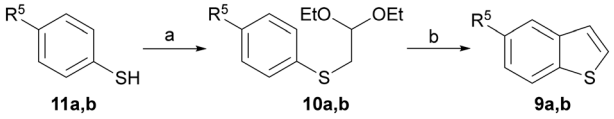


Fig. 3 Synthetic strategy for the preparation of tetracyclic targets **4**.

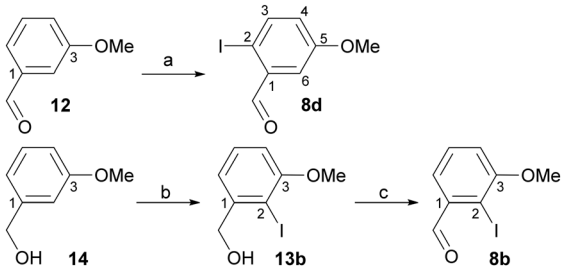


Scheme 1 Access to benzo[*b*]thiophenes **9**. Reagents and conditions: (a) bromoacetaldehyde diethyl acetal, K_2CO_3, acetone, rt, 18 h, 96% for **10a** (R^5 = OMe), 69% for **10b** (R^5 = F). (b) Polyphosphoric acid, chlorobenzene, 130 °C, 18 h, 85% for **9a** (R^5 = OMe), 60% for **9b** (R^5 = F).

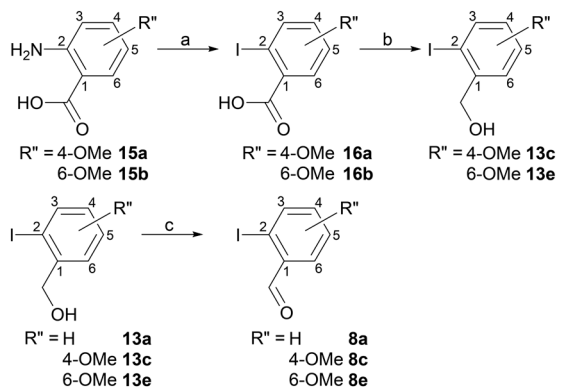
subsequent BBr_3-mediated demethylation on **9a**/silylation sequence for the preparation of silyl derivative **9c** (R^5 = OTBDMS).[42,43]

Ortho-Iodobenzaldehydes **8a–e** were prepared according to various protocols: electrophilic iodination of *meta*-methoxy anisaldehyde **12** into **8d**[44] or pyridinium dichromate PDC (Cornforth reagent) mediated oxidation of *ortho*-iodobenzyl alcohols **13a–c**, **e**[45] into **8a–c**, **e** (Schemes 2 and 3). Whereas aldehyde **8a** was obtained after PDC/silica oxidation of commercially available 2-iodobenzyl alcohol **13a** in 98% yield (Scheme 3), compound **8b** was obtained from 3-methoxy 2-iodobenzyl alcohol **13b**, first synthesized using a nucleophilic iodination (*n*-BuLi/I_2) on 3-methoxy benzyl alcohol **14** (Scheme 2).[46]

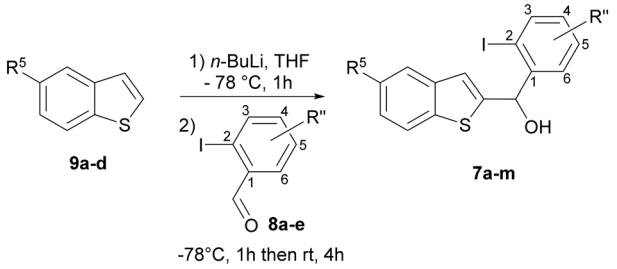
The other benzylic alcohols were prepared using a two steps sequence:[45] diazotation/diazonium iodination on 4-



Scheme 2 Access to *ortho*-iodobenzaldehydes **8b**,**d**. Reagents and conditions: (a) I_2/H_5IO_6, acetic acid/H_2SO_4, 70 °C, 16 h, 46%. (b) *n*-BuLi, I_2, Et_2O, 0 °C then rt, 2 h, 63%. (c) PDC, silica, CH_2Cl_2, rt, 6 h, 76%.



Scheme 3 Access to *ortho*-iodobenzaldehydes **8a**,**c**,**e**. Reagents and conditions: (a) $NaNO_2/HCl_{aq}$, KI, 0 °C then 90 °C, 1.5 h, quant. for **16a**, quant. for **16b**. (b) $BH_3{\cdot}Me_2S$, $B(OMe)_3$, THF, rt, 16 h, 65% for **13c**, 47% for **13e**. (c) PDC, silica, CH_2Cl_2, rt, 6 h, 98% for **8a**, 89% for **8c**, 61% for **8e**.



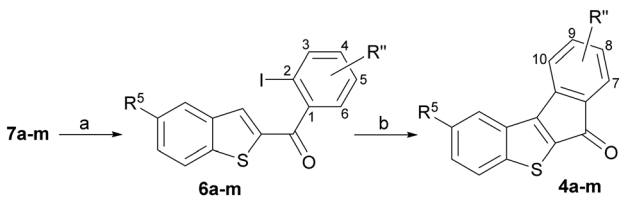
Benzo[*b*]thiophene	Aldehyde reagent		Product	Yield
R^5	R″	compound		%
H	3-OMe	**8b**	**7a**	75
H	4-OMe	**8c**	**7b**	74
H	5-OMe	**8d**	**7c**	68
H	6-OMe	**8e**	**7d**	38
OMe	H	**8a**	**7e**	88
OMe	3-OMe	**8b**	**7f**	60
OMe	4-OMe	**8c**	**7g**	82
OMe	5-OMe	**8d**	**7h**	91
OTBDMS	H	**8a**	**7i**	64
OTBDMS	4-OMe	**8c**	**7j**	91
OTBDMS	5-OMe	**8d**	**7k**	54
OTBDMS	6-OMe	**8e**	**7l**	20
F	5-OMe	**8d**	**7m**	51

Scheme 4 Synthesis of bis(het)arylcarbinols **7a–m**.

and 6-methoxy anthranilic acids **15a**, **b**, followed by reduction of the benzoic acid functions of **16a**, **b** into an alcohol using BH_3, yielding the iodo compounds **13c**, **e** (Scheme 3).

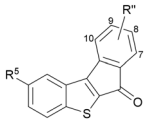
The two key partners were then engaged in the next step: the lithium anion was generated at position 2 of benzo[*b*]thiophene **9a–c**, after deprotonation using *n*-BuLi at low temperature, and was trapped by *ortho*-iodobenzaldehydes **8a–e** to give carbinols **7a–m** in 20–91% yield (Scheme 3). Yield disparities were indeed noticed: although good to very good yields for the preparation of most alcohols were observed, low yields were especially observed when using the *ortho*,*ortho*′-disubstituted aldehyde **8e**. Steric hindrance resulting from the presence of both iodo and methoxy groups on this electrophile may be responsible for the low 20% and 38% yields (Scheme 4).

The bis(het)arylcarbinols **7** were hereafter oxidized into the corresponding ketones **6** using stoichiometric amounts of manganese dioxide in 67–96% yield (Scheme 5 and Table 1). These substrates **6** then underwent a palladium-catalyzed



Scheme 5 Preparation of keto derivatives **6** and tetracyclic compounds **4**. Reagents and conditions: (a) MnO_2 6 eq., acetonitrile, rt, 6 h, 67–96%. (b) $Pd(OAc)_2$ 5 mol%, $Cy_3P{\cdot}HBF_4$ 10 mol%, K_2CO_3, DMF, 130 °C, 16 h, 51–87%.

Table 1 Primary screening of compounds **4a–m** on DYRK1A and DYRK1B



Entry				% inhibition[a,b] at 1 μM	IC_{50} for DYRK1A[a,b] in nM
1	**4a**	R^5 = H	R″ = 10-OMe	DYRK1A <5% DYRK1B <5%	nd
2	**4b**	R^5 = H	R″ = 9-OMe	DYRK1A <5% DYRK1B <5%	nd
3	**4c**	R^5 = H	R″ = 8-OMe	DYRK1A <5% DYRK1B <5%	nd
4	**4d**	R^5 = H	R″ = 7-OMe	DYRK1A 23% DYRK1B 7%	nd
5	**4e**	R^5 = OMe	R″ = H	DYRK1A 91% DYRK1B 68%	52
6	**4f**	R^5 = OMe	R″ = 10-OMe	DYRK1A 28% DYRK1B <5%	nd
7	**4g**	R^5 = OMe	R″ = 9-OMe	DYRK1A 25% DYRK1B <5%	nd
8	**4h**	R^5 = OMe	R″ = 8-OMe	DYRK1A <5% DYRK1B <5%	nd
9	**4i**	R^5 = OH	R″ = H	DYRK1A 98% DYRK1B 89%	105
10	**4j**	R^5 = OH	R″ = 9-OMe	DYRK1A 99% DYRK 1B 93%	116
11	**4k**	R^5 = OH	R″ = 8-OMe	DYRK1A 97% DYRK1B 78%	35
12	**4l**	R^5 = OH	R″ = 7-OMe	DYRK1A 93% DYRK1B 78%	54
13	**4m**	R^5 = F	R″ = 8-OMe	DYRK1A <5% DYRK1B <5%	nd

[a] Calculated after the measurement of residual kinase activity, using a functional, radiometric kinase assay. [b] Values are the mean of two experiments with SD ≤ 20%. nd: not determined.

annulation reaction,[47] thus leading to the desired tetracycles **4a–m** in good to very good yields (Scheme 5 and ESI† Table S2).

Inhibitory properties towards DYRK1A/DYRK1B and R^5/R″ structure–activity relationship studies

A primary screening of the tetracyclic derivatives **4a–m** inhibitory properties was first carried out on DYRK1A, together with its off-target DYRK1B, at a 1 μM concentration, using a radiometric assay with Woodtide substrate peptide.[48]

As shown above (Table 1), some interesting hits were identified, indicating a sharp structure–activity relationship depending on the molecular diversity brought by R^5 (H, OMe, OH and F) and R″ (H or OMe) substitution on the tetracyclic scaffold.

Low DYRK1A inhibitions were observed with compounds **4a–d**, without any substituent on R^5 of the benzo[*b*]thiophene ring (Table 1, entries 1–4).

On the other hand, compounds **4f** and **4g** bearing methoxy groups on R^5 displayed fairly low 25–32% inhibition at 1 μM (Table 1, entries 6 and 7), whereas no inhibition was detected for compound **4h** (Table 1, entry 8). Surprisingly, compound **4e** exhibited significant 91% DYRK1A inhibition at 1 μM, meaning that the introduction of a methoxy group at this position without any other substitution on the indenone ring could be useful to have a potent inhibitor (IC_{50} for DYRK1A = 52 nM, Table 1, entry 5). It should be noted that **4e** was the sole active derivative without a hydroxy group.

DYRK1A inhibitory activity for hydroxy compounds **4i–l** was higher than 90% at 1 μM (Table 1, entries 9–12) and these results encouraged us to determine their IC_{50}s. We were pleased to see that the potencies of compounds **4k** and **4l** against DYRK1A were quite high (IC_{50} = 35 and 54 nM, respectively) and, to a lesser extent, that the same tendency was observed for **4i** and **4j** (IC_{50} = 105 and 116 nM, respectively). These results demonstrated that higher potencies can be reached by introducing a hydroxyl group at R^5 position, in combination with a methoxy group at position 5 of the indenone moiety (Table 1, entry 11). The presence of a phenolic moiety on DYRK1A inhibitors was already reported in the literature[49,50] as for example INDY, DANDY-**5a** (Fig. 1), derivatives **3b** (R′ = OH) and **5** (Fig. 2).

A comparison of the "open form" **5c** activity (R^3 = R^4 = H, IC_{50} (DYRK1A) = 2000 nM, Fig. 2) with its rigidified analog **4i** (IC_{50} (DYRK1A) = 105 nM) showed that constraining the third cycle was a successful strategy to improve DYRK1A inhibition.

Finally, compound **4m** was synthesized to explore an isosteric replacement of the hydroxyl by a fluorine atom.[51–53]

However, **4m** displayed a complete lack of activity against DYRK1A (Table 1, entry 13).

For all the compounds **4a–m**, residual DYRK1B activity was determined at 1 μM concentration and, across the five most active compounds **4e**, **i–l** (IC_{50}s for DYRK1A ranged from 35 to 116 nM), a marked DYRK1B cross-inhibition was observed (68 to 93%, Table 1, entries 5, 9–12). However, the most potent derivative **4k** against DYRK1A was amongst the least active DYRK1B co-inhibitors of this series (78% inhibition at 1 μM, Table 1, entry 11).

ATP competition of **4k** was evaluated by measuring residual DYRK1A activity upon treatment with increasing concentrations of ATP, in the presence of a 50 nM concentration of **4k**. Inhibition decreases with increasing ATP concentration as shown in ESI† Fig. S1, clearly indicating an ATP-competitive mechanism of action, as described for other literature compounds (Fig. 1).

Kinase selectivity study

In order to evaluate the off-target activity of our lead compound **4k**, a complementary kinase profiling was then carried out at a 0.35 μM concentration (Table 2), *i.e.* 10-fold its IC_{50}. As significant disparities have been noted in the literature between fluorescence resonance energy transfer (FRET)-based and radiometric assays,[28] some of the kinase activities were quantified by both techniques, operated by ThermoScientific/Invitrogen and Eurofins/CEREP, respectively.

Using the FRET-based kinase assays (Z'-LYTE™/Adapta® activity assays or LanthaScreen europium kinase binding assay, see Table 2 footnotes), four hits with more than 50% inhibition were observed amongst the 21 selected kinases for our study: CLK4, DYRK1B, DYRK2 and haspin (Table 2).

Cross-inhibition for DYRK1A inhibitors was frequently observed with CLK1 and CLK4;[28] hence, the low inhibition of CLK1 by **4k** (16% inhibition at 0.35 μM, confirmed by its modest 1080 nM IC_{50} value) appeared suspicious, prompting us to evaluate the inhibition of this protein kinase, using a radiometric activity assay. This second technique allowed us to demonstrate that compound **4k** was in fact a potent CLK1 inhibitor, too, with a very low 20 nM IC_{50} value.

Our first hypothesis to tentatively explain this difference is that the 6*H*-benzo[*b*]indeno[1,2-*d*]thiophen-6-one scaffold displays intrinsic fluorescent properties that could interfere with the FRET measurements. Nonetheless, as no "warnings flags" indicating such an interference were detected during the "test compound interference" evaluation, we can assume that the marked difference could be attributed by different assay conditions (*e.g.* protein kinase and substrate concentrations), as previously outlined in the literature.[28]

For the three other impacted protein kinases (cross-validation was not realized for DYRK2, IC_{50} = 186 nM), results obtained by FRET techniques were corroborated by the radiometric activity assays.

The inhibitory effect of compound **4k** against DYRK1B was proved to be moderate, both determined with Z'-LYTE FRET activity assay (IC_{50} = 206 nM) and functional radiometric test (47% inhibition of kinase activity at 0.35 μM). Furthermore, compound **4k** is a moderate DYRK2 inhibitor but also a strong haspin inhibitor, as attested by both the FRET LanthaScreen Eu binding assay (IC_{50} = 28 nM) and the activity radiometric evaluation (IC_{50} = 76 nM). As expected, **4k** also strongly inhibits CLK4 in addition to CLK1, with low IC_{50} values of 14 nM (FRET-based binding assay) and 26 nM (functional radiometric test), respectively (Table 2).

Altogether, the selectivity profiling proved that compound **4k** was a mixed DYRK1A/CLK1/CLK4/haspin inhibitor, thus corroborating trends already observed with similar molecular architectures and these DYRK1A off-targets.[36,50,54,55] In contrast, none of the other challenging off-targets in the screening panel was significantly inhibited, suggesting a reasonable "group selectivity" for the identified targets.

Table 2 Kinase selectivity profiling of compound **4k** at 0.35 μM

Kinase	% inhibition/(IC_{50} [nM])	Kinase	% inhibition/(IC_{50} [nM])
CDK5/p25	8[a]	EGFR (ErbB1)	0[a]
CLK1	16[a] (1080[a]) 93[d] (20[d])	GSK3B (GSK3 beta)	2[a]
CLK2	34[a]	GSG2 (haspin)	95[b] (28[b]) 88[d] (76[d])
CLK3	7[a]	MLCK (MLCK2)	15[c]
CLK4	95[c] (14[c]) 91[d] (26[d])	HIPK1 (Myak)	0[a]
CSNK1D (CK1 delta)	2[a]	NTRK2 (TRKB)	0[a]
CSNK2A1 (CK2 alpha 1)	2[a]	PIM1	0[a]
STK17A (DRAK1)	42[c]	SRPK1	6[a]
DYRK1B	57[a] (206[a]) 47[d]	SRPK2	0[a]
DYRK2	66[c] (186[c])	STK33	8[c]
DYRK3	5[a]		

[a] Z'-LYTE kinase activity assay. [b] Adapta kinase activity assay. [c] LanthaScreen kinase binding assay. [d] Radiometric kinase assay.

On the other side, dual/multiple kinase inhibitors could emerge as interesting approaches to cure cancers,[56–58] and could involve DYRK/CLK protein kinases[59] such as CLK1,[60–63] CLK4[62–64] or the relatively underexplored but promising haspin kinase.[65]

Given that DYRK1A was previously identified as a promising target for a potential glioblastoma treatment,[49,66–69] we have chosen to evaluate some of our most potent compounds on these specific cell lines.

Antiproliferative effects on glioblastoma cells

The cellular effects of the most potent inhibitor **4k** were determined by measuring growth inhibition following treatment with this compound in comparison to the less active derivative **4i** and the reference compound harmine.[70] Dose–response curves allowed us to determine the IC_{50} on the two cell lines U373[67,68] and U87[68,70–73] (see ESI†), as DYRK1A proved to play a crucial role for cell proliferation and invasion of glioblastoma cells.[49,69,71,73]

These studies showed that compound **4i** (DYRK1A IC_{50} = 105 nM) had no significant effect on cell proliferation towards both glioblastoma cell lines U373 and U87 (Table 3, entry 1) whereas our most potent inhibitor **4k** (DYRK1A IC_{50} = 35 nM) exhibited a moderate anti-proliferative activity (Table 3, entry 2). Harmine also showed a moderate activity in both cell lines as well (Table 3, entry 3).

Harmine has a similar kinase selectivity profile as our compound **4k**, and their effects on U87 and U373 cell lines growth require further exploration to discern whether they are mainly caused by DYRK1A inhibition alone or by cross-inhibition of DYRK1A, CLK1, CLK4, and haspin.

Microsomal stability

In order to evaluate the potential druggability of this new family of DYRK/CLK/haspin inhibitors, we assessed their *in vitro* stability using rat liver microsomes (Table 4).

One can observe that 7- and 10-methoxy derivatives of 6*H*-benzo[*b*]indeno[1,2-*d*]thiophen-6-one scaffold are rapidly metabolized as shown with **4a**, **4d**, **4f** and **4l**. 2-Hydroxy substitutions (**4i–l**) showed poor stability with fast conversion in our assay system whereas their methoxy equivalents were less sensitive to microsomal degradation as for **4e**, **4g** and **4h**, except for **4d** and **4l**, bearing methoxy in 7- or 10-positions. Introduction of a 2-fluoro substituent (**4m**) did not improve stability against microsomal digestion. Interestingly, **4j** was rapidly degraded to 50% of its initial amount then plateaued for the rest of the assay, suggesting an inhibitory mechanism by **4j** (or its metabolite) against microsomes.

Table 3 Cell viability of compound **4i**, **k** and harmine on glioblastoma cells U373 and U87

Entry	Compound	U373[a]	U87[a]
1	**4i**	>100 μM	>100 μM
2	**4k**	32.8 ± 5.0 μM[b]	45.9 ± 3.8 μM[b]
3	Harmine	19.6 ± 4.7 μM[c]	16.0 ± 5.1 μM[c]

[a] IC_{50}: a sample's concentration which produces a 50% reduction in cell proliferation. [b] Mean of 6 independent experiments. [c] Mean of 4 independent experiments.

Table 4 Metabolic stability of **4a–m**, determined on rat liver microsomes

Entry	Compound	$t_{\frac{1}{2}}$ (min)	CL_{int} (μL min^{-1} mg^{-1})
1	**4a**	6.5 ± 0.5	355.5 ± 26.2
2	**4b**	33.7 ± 2.8	68.8 ± 5.7
3	**4c**	24.4 ± 0.8	94.8 ± 3.0
4	**4d**	<5.0	>500
5	**4e**	21.7 ± 1.1	106.5 ± 5.2
6	**4f**	<5.0	>500
7	**4g**	25.3 ± 3.0	92.4 ± 10.8
8	**4h**	18.9 ± 0.5	122.0 ± 2.9
9	**4i**	<5.0	>500
10	**4j**	—[a]	—[a]
11	**4k**	<5.0	>500
12	**4l**	<5.0	>500
13	**4m**	16.8 ± 1.2	93.9 ± 32.7

[a] Possible inhibition of microsomes – see text for more information.

Docking studies

To gain insights into the binding mode of the synthesized compounds, molecular docking was performed using one of the described X-ray structures of DYRK1A (PDB ID: 5AIK). Prior to docking, every ligands, cofactors and additional interacting proteins were removed from the structure, and preparation of the protein was done using Molecular Operating Environment (MOE).[74] Each tested ligand (**4a–m**) was prepared for docking using MOE. Docking was performed using HERMES-GOLD.[75]

The DYRK1A surfaces were generated and a superposition of the docking results for all the synthesized compounds **4a–m** was established (Fig. S2†). The comparison between all compounds showed significant positional homology, with the exception of compound **4b**, which was flipped compared to the others (Fig. S2 and S3†).

A comparative study of the interaction modes of the five best ligands was carried out (Fig. 4). From these results, four protein residues were identified as stabilizing the ligand–protein complex, namely: Ile165, Glu203, Glu239 and Leu241. These similarities are consistent with the observed biological activities of the prepared compounds. The interactions between the molecular tetracyclic scaffolds with Glu239 and Leu241 are the most preserved over all structures. The carbonyl group is engaged with Leu241 by a strong H-bond, and the sulfur atom connects with the Glu239 backbone oxygen through a sigma* interaction. Surprisingly, the usual observed H-bonding with Lys188[76,77] in DYRK1A was not observed with compounds **4a–m**. This could be explained by the tandem sulfur–carbonyl sigma* and carbonyl-Leu214-NH strong interactions. For some

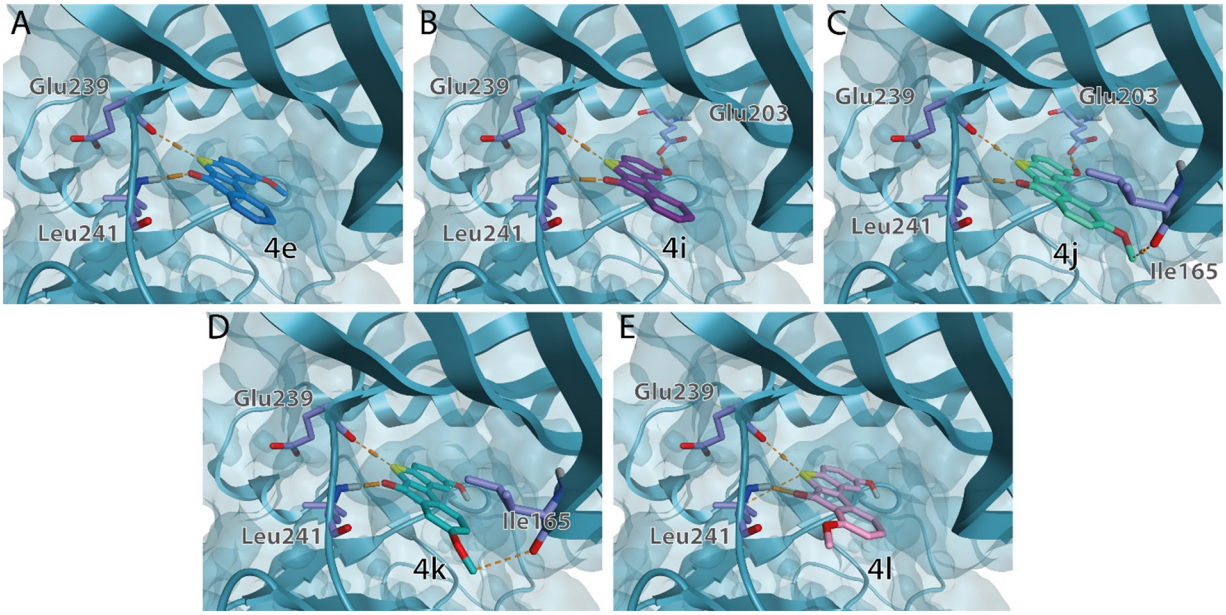


Fig. 4 Top docking poses obtained for the 5 most potent hits **4e**, **i**, **j**, **k**, **l**, (A, B, C, D and E respectively), obtained from the study with the X-ray structure of DYRK1A (PDB: 5AIK). Stabilizing interactions are highlighted in orange. Compounds **4a**–**m** representations are available in ESI† (Fig. S3).

of the structures bearing a hydroxyl group on the benzothiophene moiety, more interactions can be observed with Glu203 (**4i** and **4j**, Fig. 4B and C). Depending on the position of a methoxy group on the indenone ring, another weak interaction can occasionally be detected with Ile165, as observed with compounds **4j** and **4k** (Fig. 4C and D). Surprisingly, the most active compound **4k** did not show any interaction between the phenol group and Glu203.

Additionally, the best hit **4k** was overlaid with known ligands from the literature (harmine, INDY and compound **3a** (R′ = OH)) in order to better understand its position in the protein pocket (Fig. 5). The consistency on the heteroatoms'

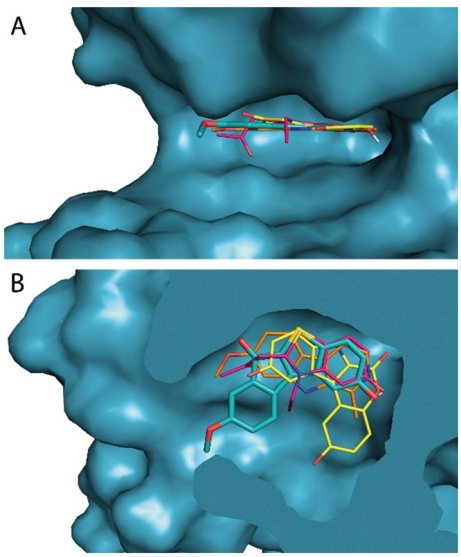


Fig. 5 Superposition of reference ligands described in the literature with compound **4k**. These images are generated from the docking of the molecules with the X-ray structure of DYRK1A (PDB: 5AIK), whose surface is represented in dark blue. Compound **4k** is depicted with thick sticks in turquoise, harmine in orange, INDY in magenta and compound **3a** (R′ = OH) in yellow (A: side view of the ATP cleft. B: Top view).

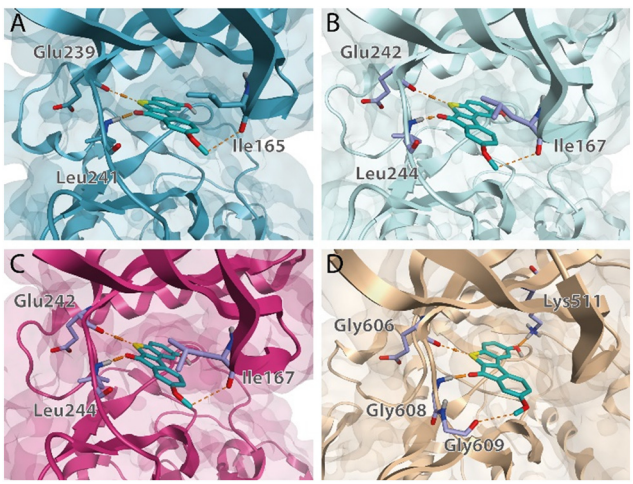


Fig. 6 Top docking poses of compound **4k** within the X-ray structures of DYRK1A (PDB: 5AIK) in dark blue (A), CLK1 (PDB: 6RAA) in cyan-grey (B), CLK4 (PDB: 6FYV) in magenta (C) and haspin (PDB: 3IQ7) in wheat (D). The kinases are shown as ribbon with their surfaces in transparency. The results showed marked homology in the stabilization of compound **4k** within the 4 proteins. Residues engaged in stabilizing interactions are highlighted in orange. Haspin kinase exhibits a slightly different binding system.

positions showed a similarity in the fitting mode in the protein pocket.

As mentioned above, the most potent compound **4k** showed crossed inhibition with three off-target kinases: CLK1, CLK4 and haspin. In order to evaluate similarities of the ligand/protein interactions, compound **4k** was docked within the four protein X-ray structures (Fig. 6). Some homologies in the binding mode were established. The H-bond interaction observed with Leu241 in DYRK1A (Fig. 6A) can also be shown with Leu244 in CLK1 (Fig. 6B) and CLK4 (Fig. 6C), and a similar H-bond is present with Gly608 in haspin (Fig. 6D). The sulfur atom sigma* interaction with Glu239 in DYRK1A can also be shown with Glu242 in CLK1 and CLK4, respectively, and with Glu606 for haspin. A similar weak interaction as Ile165 in DYRK1A can also be observed with Leu167 in CLK1 and CLK4. In haspin, two more interactions were identified: 1) a weak interaction of Gly609 with the methoxy group on the indanone side, 2) a H-bond between Lys511 and the hydroxyl group of **4k**. The latter could be explained by the smaller distance between Lys188 amino group and **4k** phenol moiety (Fig. 6D).

Conclusion

The goal of this study was to modulate the structure of known DYRK1A inhibitors with marked modifications, *i.e.* a ring contraction and an isosteric NH to S modification, thus leading to original 6*H*-benzo[*b*]indeno[1,2-*d*]thiophen-6-ones **4**.

Our pharmacomodulation study also aimed at exploring the molecular diversity on this scaffold: this was achieved by investigating the influence of grafting different moieties such as methoxy/hydroxy/fluorine substitution onto the benzothiophene ring and the presence of a methoxy group on different positions of the indanone part of tetracyclic derivatives **4a–m**.

First designed as a DYRK1A inhibitor, the most active compound **4k** of this series proved to be a potent multiple CLK1/CLK4/DYRK1A/haspin inhibitor, with interesting IC_{50} values (20/26/35/76 nM, respectively). Such a cross inhibition was already reported in the literature for DYRK1A inhibitors but was quite surprising, regarding the pronounced structural modifications, compared to the parent scaffolds.

The antiproliferative effects of the most active compound **4k** were also evaluated on two different glioblastoma cell lines. Surprisingly and given the broad inhibitory profile of this compound, the observed impact was only moderate.

The docking study of the entire set of molecules **4a–m** on DYRK1A crystal structure has provided a very interesting insight into the ligands–protein interactions of the most active derivatives **4e**, **i–l**, demonstrating key interactions between the benzo[*b*]thiophene ring sulfur atom and the indenone oxygen atom with residues Glu242 and Leu244 respectively. Comparison of docking poses of the most active DYRK1A inhibitor **4k** with CLK1, CLK4 and haspin showed similarities of protein ligand interactions for DYRK1A, CLK1 and CLK4 whereas interactions within the haspin ATP pocket relied on different residues.

Lastly, as a preliminary approach to evaluate the druggability of these tetracyclic derivatives, microsomal stability studies have shown the fast degradation of the most active compound **4k**, thus impeding its further development in its present form. To overcome this issue, a carbamate[78] prodrug of the phenol group[79,80] is currently under investigation to increase compound half-life, which could also be relevant for enhancing blood–brain barrier crossing[81] or compound targeting,[82–85] before considering further *in vivo* studies.

Experimental section

Chemistry – general

All moisture/air-sensitive reactions were carried out under a positive pressure of argon and with oven-dried glassware. Melting points were measured on a Büchi B-540 melting point apparatus and are uncorrected. Infra-red spectra (IR) were recorded on a Perkin Elmer Spectrum Two apparatus, equipped with an attenuated total reflectance sampling module: absorption bands are reported in cm^{-1}. Proton nuclear magnetic resonance (^1H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on Bruker DRX400 and AV500 Fourier transform spectrometers, using an internal deuterium lock, operating at 400 or 500 MHz. Chemical shifts are reported in parts per million (ppm) relative to internal standards (tetramethylsilane, $\delta_H = \delta_C = 0.00$; $CDCl_3$, $\delta_H = 7.26$ and $\delta_C = 77.16$; DMSO-d_6, $\delta_H = 2.50$ and $\delta_C = 39.52$; acetone-d_6, $\delta_H = 2.05$ and $\delta_C = 29.84$).[86] Data are presented as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet t = triplet, q = quadruplet, dd = doublet of doublet, m = multiplet, br = broad), coupling constant, integration. Atom numbering refers to benzo[*b*]thiophene or aromatic compounds nomenclature.

Agilent UHPLC/MS consists of a 1290 Infinity system with a binary pump, degasser, autosampler, thermostated column compartment, 1260 diode array detector and 6120 single quadrupole mass spectrometer. The entire system was controlled by Chemstation software (Agilent Technologies). The column was an Agilent Poroshell 120 SB-C18, 2.7 μm, 2.1 × 50 mm. The samples were analysed in the positive ion mode of the electro spray ionisation (ESI) source, whose conditions were as follow: gas temperature, 350 °C, drying gas at 12.0 l min^{-1}, nebulizer gas at 35 psig, V_{cap} at 3000 V, fragmentor at 60 V.

High-resolution mass spectra were recorded on a Bruker QTOF Impact II mass spectrometer (ESI mode).

Reactions were monitored with analytical thin layer chromatography (TLC), which was carried out using Merck commercial aluminium sheets coated (0.2 mm layer thickness) with Kieselgel 60 F_{254}, with visualization by ultraviolet and acidic anisaldehyde staining solution. Proportions of solvents used for TLC are by volume. Product purification by flash column chromatography was performed using Merck Kieselgel 60 Å (40–63 mm) or using pre-packed silica gel columns.

Proportions of solvents used for column chromatography are by volume. Tetrahydrofuran (THF), *N*,*N*-dimethylformamide (DMF), dimethylsulfoxide (DMSO) (Acroseal®, over molecular sieves) were purchased from Acros Organics. For extraction/purification, diethyl ether, dichloromethane (DCM), cyclohexane and ethyl acetate (AcOEt) were of reagent grade. All other chemical reagents were used as received. Commercial *n*-BuLi solutions in hexanes were titrated using *N*-benzylbenzamide.[87]

5-Methoxybenzo[*b*]thiophene **9a**,[38,39] 5-fluorobenzo[*b*]thiophene **9b**,[40,41] (benzo[*b*]thiophen-5-yloxy)-*tert*-butyl-dimethylsilane **9c**,[42,43] (2-iodo-3-methoxyphenyl)methanol **13b**,[46] (2-iodo-4-methoxyphenyl) methanol **13c**,[88] (2-iodo-6-methoxyphenyl) methanol **13e**[45] and 2-iodo-5-methoxybenzaldehyde **8d**[44] were prepared according to literature procedures.

Synthetic procedures

Preparation of aldehydes 8a–c,e[45]. The 2-iodobenzyl alcohol was dissolved in dichloromethane (0.2 M) with silica gel (1 g $mmol^{-1}$). The slurry was stirred at rt followed by the addition of PDC (2 equiv.). The reaction was stirred until the starting material was consumed by TLC typically 6 h. The crude was filtered through a silica gel pad, washing with ethyl acetate. The crude aldehyde was purified if required by flash column chromatography using ethyl acetate and cyclohexane.

*2-Iodobenzaldehyde **8a**.* Scale: 2-iodobenzylic alcohol **13a** (0.998 g, 4.27 mmol), silica (4.285 g), PDC (3.232 g, 8.60 mmol). Compound **8a** (0.973 g, 98%) was obtained as a pale yellow solid and was used without further purification.

Spectral data were identical to those reported in the literature.[89]

*2-Iodo-3-methoxybenzaldehyde **8b**.* Scale: (2-iodo-3-methoxyphenyl)methanol **13b** (1.423 g, 5.39 mmol), silica (5.400 g), PDC (4.063 g, 10.80 mmol). The residue was purified by flash chromatography (20% of EtOAc in cyclohexane) to afford compound **8b** as a white solid (1.070 g, 76%).

Spectral data were identical to those reported in the literature.[90]

*2-Iodo-4-methoxybenzaldehyde **8c**.* Scale: (2-iodo-4-methoxyphenyl) methanol **13c** (1.711 g, 6.48 mmol), silica (6.520 g), PDC (4.879 g, 12.97 mmol). The residue was purified by flash chromatography (20% of EtOAc in cyclohexane) to afford compound **8c** as a white solid (1.512 g, 89%).

Spectral data were identical to those reported in the literature.[91]

*2-Iodo-6-methoxybenzaldehyde **8e**.* Scale: (2-iodo-6-methoxyphenyl) methanol **13e** (1.240 g, 4.70 mmol), silica (4.200 g), PDC (3.136 g, 8.34 mmol). The residue was purified by flash chromatography (20% of EtOAc in cyclohexane) to afford compound **8e** as a white solid (0.750 g, 61%).

Spectral data were identical to those reported in the literature.[45]

General procedure A for the preparation of alcohols 7 using *n*-butyl lithium 2-deprotonation of benzo[*b*]thiophene 9 and subsequent electrophile addition of *ortho*-iodoaldehydes 8. To a solution of benzo[*b*]thiophene **9** (1.60 mmol) in THF (5 mL) under an argon atmosphere at – 78 °C was added dropwise *n*-BuLi 2.5 M in hexanes (0.72 mL, 1.80 mmol). The mixture was stirred at −78 °C for 1 h. A solution of 2-iodobenzaldehyde **8** (1.95 mmol) in THF (7 mL) was added then added dropwise. The stirring of the mixture was continued at – 78 °C for 1 h and at room temperature for 4 h. Subsequently, the mixture was quenched with brine (20 mL) and ethyl acetate (20 mL) was then added. After decantation, the aqueous layer was extracted with ethyl acetate (2 × 20 mL). The combined organic layers were washed with brine (3 × 20 mL) and dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a brown residue. The crude product was purified by flash chromatography (gradient of EtOAc in cyclohexane) to afford the desired alcohol **7**.

*Benzo[b]thiophen-2-yl(2-iodo-3-methoxy phenyl)methanol **7a**.* According to general procedure A, scale: benzo[*b*]thiophene (0.205 g, 1.53 mmol), *n*-BuLi 2.5 M in hexanes (0.72 mL, 1.80 mmol), 2-iodo-3-methoxybenzaldehyde (0.515 g, 1.96 mmol). The residue was purified by flash chromatography (0 to 30% of EtOAc in cyclohexane) to afford compound **7a** as a white solid (0.452 g, 75%), m.p. 48.0–49.2 °C. IR: 3532, 3357, 3057, 3002, 2962, 2936, 2835, 2329, 1699, 1585, 1566, 1463, 1425, 1365, 1333, 1262, 1184, 1155, 1105, 1088, 1068, 1009, 936, 893, 859, 834, 793, 767, 745, 725, 668, 657, 590, 553, 480. ^{1}H NMR (400 MHz, acetone-d_6) δ = 7.86–7.81 (m, 1H), 7.75–7.71 (m, 1H), 7.43–7.37 (m, 2H), 7.33–7.26 (m, 2H), 7.18 (s, 1H), 6.95 (dd, J = 7.1, 2.4 Hz, 1H), 6.45 (dd, J = 4.6, 1.1 Hz, 1H), 5.52 (d, J = 4.6 Hz, 1H), 3.90 (s, 3H). ^{13}C NMR (101 MHz, acetone-d_6) δ = 158.68(C), 149.82(C), 148.68(C), 140.61(C), 140.47(C), 130.34(CH), 124.97(CH), 124.90(CH), 124.32(CH), 123.05(CH), 122.15(CH), 121.17(CH), 111.16(CH), 90.97(C), 76.45(CH), 56.92(CH_3). LC/MS (retention time 4.21 min) m/z (ESI^+) 379.00 (MH^+–H_2O, 100%), 418.90 (MNa^+, 20.7%). HRMS (ESI^+): m/z calcd for $C_{16}H_{12}IOS^+$ [MH^+–H_2O]: 378.9648; found: 378.9648.

*Benzo[b]thiophen-2-yl(2-iodo-4-methoxy phenyl)methanol **7b**.* According to general procedure A, scale: benzo[*b*]thiophene (0.203 g, 1.51 mmol), *n*-BuLi 2.5 M in hexanes (0.72 mL, 1.80 mmol), 2-iodo-4-methoxybenzaldehyde (0.517 g, 1.97 mmol). The residue was purified by flash chromatography (0 to 30% of EtOAc in cyclohexane) to afford compound **7b** as a yellow oil (0.442 g, 74%). IR: 3376, 3055, 3002, 2959, 2936, 2894, 2834, 1702, 1594, 1562, 1484, 1457, 1436, 1395, 1363, 1305, 1282, 1228, 1179, 1154, 117, 1091, 1065, 1026, 1015, 938, 852, 343, 784, 745, 726, 708, 667, 591, 552, 529, 482. ^{1}H NMR (400 MHz, acetone-d_6) δ = 7.84 (ddt, J = 7.0, 1.6, 0.9 Hz, 1H), 7.77–7.71 (m, 1H), 7.63 (d, J = 8.8 Hz, 1H), 7.41 (d, J = 2.6 Hz, 1H), 7.34–7.26 (m, 2H), 7.17 (t, J = 1.0 Hz, 1H), 7.07 (dd, J = 8.7, 2.6 Hz, 1H), 6.25 (d, J = 4.5 Hz, 1H), 5.46 (d, J = 4.5 Hz, 1H), 3.82 (s, 3H). ^{13}C NMR (101 MHz, acetone-d_6) δ = 160.49(C), 150.40(C), 140.66(C), 140.58(C), 139.01(C), 129.47(CH), 125.03(CH), 124.92(CH), 124.75(CH), 124.36(CH), 123.08(CH), 121.93(CH), 115.60(CH), 98.40(C), 75.82(CH), 55.95(CH_3). LC/MS (retention time 4.38 min) m/z (ESI^+) 379.00 (MH^+–H_2O, 100%), 418.90 (MNa^+, 17.5%). HRMS (ESI^+): m/z calcd for $C_{16}H_{12}IOS^+$ [MH^+–H_2O]: 378.9648; found: 378.9644.

Benzo[b]thiophen-2-yl(2-iodo-5-methoxy phenyl)methanol ***7c***. According to general procedure A, scale: benzo[*b*]thiophene (0.205 g, 1.53 mmol), *n*-BuLi 2.5 M in hexanes (0.72 mL, 1.80 mmol), 2-iodo-4-methoxybenzaldehyde (0.511 g, 1.95 mmol). The residue was purified by flash chromatography (0 to 30% of EtOAc in cyclohexane) to afford compound **7c** as an orange oil (0.410 g, 68%). IR: 3443, 3073, 3049, 2959, 2931, 2850, 2831, 1590, 1564, 1458, 1437, 1411, 1397, 1281, 1271, 1224, 1156, 1115, 1052, 1024, 1001, 929, 881, 865, 836, 808, 791, 745, 726, 666, 633, 588, 556, 518, 457. ^{1}H NMR (400 MHz, acetone-d_6) δ = 7.85 (dd, J = 6.4, 2.1 Hz, 1H), 7.75 (dd, J = 8.8, 3.0 Hz, 2H), 7.39 (d, J = 3.1 Hz, 1H), 7.34–7.22 (m, 2H), 7.19 (s, 1H), 6.75 (dd, J = 8.7, 3.1 Hz, 1H), 6.23 (d, J = 4.5 Hz, 1H), 5.56 (d, J = 4.6 Hz, 1H), 3.81 (s, 3H). ^{13}C NMR (101 MHz, acetone-d_6) δ = 161.43(C), 149.44(C), 147.90(C), 140.70(C), 140.66(CH), 140.49(C), 125.06(CH), 125.03(CH), 124.44(CH), 123.10(CH), 122.40(CH), 116.69(CH), 114.78(CH), 86.42(C), 76.09(CH), 55.77(CH_3). LC/MS (retention time 4.38 min) m/z (ESI^+) 379.00 (MH^+–H_2O, 100%), 418.90 (MNa^+, 10.8%). HRMS (ESI^+): m/z calcd for $C_{16}H_{12}IOS^+$ [MH^+–H_2O]: 378.9648; found: 378.9645.

Benzo[b]thiophen-2-yl(2-iodo-6-methoxy phenyl)methanol ***7d***. According to general procedure A, scale: benzo[*b*]thiophene (0.137 g, 1.02 mmol), *n*-BuLi 2.5 M in hexanes (0.48 mL, 1.20 mmol), 2-iodo-6-methoxybenzaldehyde (0.340 g, 1.30 mmol). The residue was purified by flash chromatography (0 to 100% of MeOH in H_2O, using a reversed phase C18 column) to afford compound **7d** as a white solid (0.153 g, 38%), m.p. 109.8–110.7 °C. IR: 3529, 3095, 3059, 3043, 3013, 2970, 2940, 2922, 2853, 2839, 1582, 1566, 1458, 1432, 1404, 1324, 1296, 1262, 1231, 1194, 1176, 1154, 1140, 1098, 1083, 1011, 935, 889, 862, 845, 831, 788, 772, 744, 728, 706, 677, 657, 585, 556, 506, 462. ^{1}H NMR (400 MHz, acetone-d_6) δ 7.87–7.83 (m, 1H), 7.71 (dd, J = 6.7, 2.1 Hz, 1H), 7.57 (dd, J = 7.7, 1.2 Hz, 1H), 7.30 (ddd, J = 7.2, 5.2, 1.6 Hz, 2H), 7.13 (dd, J = 16.4, 7.6 Hz, 2H), 7.02 (s, 1H), 6.42–6.36 (m, 1H), 5.09 (d, J = 10.7 Hz, 1H), 3.82 (s, 3H). ^{13}C NMR (101 MHz, acetone-d_6) δ = 158.95(C), 150.19(C), 140.85(C), 140.54(C), 133.71(C), 133.09(CH), 131.67(CH), 124.97(CH), 124.69(CH), 124.15(CH), 123.00(CH), 120.59(CH), 113.39(CH), 99.89(C), 77.99(CH), 56.35(CH_3). LC/MS (retention time 4.52 min) m/z (ESI^+) 379.00 (MH^+–H_2O, 100%), 419.00 (MNa^+, 16.6%). HRMS (ESI^+): m/z calcd for $C_{16}H_{12}IOS^+$ [MH^+–H_2O]: 378.9648; found: 378.9643.

(2-Iodophenyl)(5-methoxy benzo[b]thiophen-2-yl)methanol ***7e***. According to general procedure A, scale: 5-methoxy benzo[*b*] thiophene (0.246 g, 1.50 mmol), *n*-BuLi 2.5 M in hexanes (0.72 mL, 1.80 mmol), 2-iodobenzaldehyde (0.454 g, 1.96 mmol). The residue was purified by flash chromatography (0 to 30% of EtOAc in cyclohexane) to afford compound **7e** as a yellow oil (0.523 g, 88%). IR: 3527, 3387, 3059, 2999, 2948, 2935, 2902, 2830, 1700, 1600, 1584, 1533, 1456, 1434, 1363, 1331, 1298, 1279, 1216, 1151, 1113, 1069, 1047, 1021, 1007, 943, 855, 832, 802, 746, 730, 718, 668, 649, 619, 597, 561, 537, 492. ^{1}H NMR (400 MHz, acetone-d_6) δ = 7.88 (dd, J = 7.9, 1.1 Hz, 1H), 7.79 (dd, J = 7.8, 1.7 Hz, 1H), 7.70 (d, J = 8.8 Hz, 1H), 7.51–7.45 (m, 1H), 7.27 (d, J = 2.5 Hz, 1H), 7.12 (s, 1H), 7.08 (td, J = 7.6, 1.7 Hz, 1H), 6.94 (dd, J = 8.8, 2.5 Hz, 1H), 6.30 (d, J = 4.3 Hz, 1H), 5.56 (d, J = 4.5 Hz, 1H), 3.81 (s, 3H). ^{13}C NMR (101 MHz, acetone-d_6) δ = 158.47(C), 150.75(C), 146.84(C), 141.52(C), 140.03(CH), 132.82(C), 130.44(CH), 129.47(CH), 129.00(CH), 123.68(CH), 122.22(CH), 115.12(CH), 106.53(CH), 98.37(C), 76.25(CH), 55.66(CH_3). LC/MS (retention time 4.28 min) m/z (ESI^+) 379.00 (MH^+–H_2O, 100%), 418.90 (MNa^+, 15.5%). HRMS (ESI^+): m/z calcd for $C_{16}H_{12}IOS^+$ [MH^+–H_2O]: 378.9648; found: 378.9646.

(2-Iodo-3-methoxyphenyl)(5-methoxy benzo[b]thiophen-2-yl) methanol ***7f***. According to general procedure A, scale: 5-methoxybenzo[*b*]thiophene (0.252 g, 1.53 mmol), *n*-BuLi 2.5 M in hexanes (0.72 mL, 1.80 mmol), 2-iodo-3-methoxybenzaldehyde (0.519 g, 1.98 mmol). The residue was purified by flash chromatography (0 to 30% of EtOAc in cyclohexane) to afford compound **7f** as a white solid (0.392 g, 60%), m.p. 133.0–135.4 °C. IR: 3566, 3530, 3068, 3000, 2970, 2934, 2905, 2834, 1584, 1598, 1564, 1526, 1455, 1428, 1357, 1332, 1284, 1276, 1264, 1246, 1211, 1173, 1116, 1068, 1010, 939, 859, 821, 794, 765, 725, 669, 679, 627, 583. ^{1}H NMR (400 MHz, acetone-d_6) δ = 7.69 (d, J = 8.8 Hz, 1H), 7.43–7.36 (m, 2H), 7.26 (d, J = 2.4 Hz, 1H), 7.09 (s, 1H), 6.97–6.90 (m, 2H), 6.42 (dd, J = 4.7, 1.1 Hz, 1H), 5.48 (d, J = 4.6 Hz, 1H), 3.90 (s, 3H), 3.81 (s, 3H). ^{13}C NMR (101 MHz, acetone-d_6) δ = 158.67(C), 158.50(C), 150.99(C), 148.75(C), 141.57(C), 132.83(C), 130.31(CH), 123.66(CH), 122.14(CH), 121.18(CH), 115.06(CH), 111.14(CH), 106.52(CH), 90.98(C), 76.50(CH), 56.93(CH_3), 55.68(CH_3). LC/MS (retention time 4.15 min) m/z (ESI^+) 409.00 (MH^+–H_2O, 100%), 449.00 (MNa^+, 30.0%). HRMS (ESI^+): m/z calcd for $C_{17}H_{14}IO_2S^+$ [MH^+–H_2O]: 408.9754; found: 408.9752.

(2-Iodo-4-methoxyphenyl)(5-methoxybenzo[b]thiophen-2-yl) methanol ***7g***. According to general procedure A, scale: 5-methoxybenzo[*b*]thiophene (0.210 g, 1.28 mmol), *n*-BuLi 2.5 M in hexanes (0.60 mL, 1.50 mmol), 2-iodo-4-methoxybenzaldehyde (0.428 g, 1.63 mmol). The residue was purified by flash chromatography (0 to 30% of EtOAc in cyclohexane) to afford compound **7g** as a yellow oil (0.447 g, 82%). IR: 3389, 3062, 3000, 2956, 2936, 2899, 2833, 1703, 1595, 1563, 1534, 1484, 1456, 1436, 1363, 1330, 1281, 1219, 1180, 1151, 1070, 1029, 943, 850, 803, 730, 718, 893, 657, 595, 563, 530. ^{1}H NMR (400 MHz, acetone-d_6) δ = 7.69 (d, J = 8.8 Hz, 1H), 7.62 (d, J = 8.7 Hz, 1H), 7.41 (d, J = 2.6 Hz, 1H), 7.27 (d, J = 2.5 Hz, 1H), 7.09–7.04 (m, 2H), 6.93 (dd, J = 8.8, 2.5 Hz, 1H), 6.22 (d, J = 4.4 Hz, 1H), 5.42 (d, J = 4.5 Hz, 1H), 3.82 (s, 3H), 3.82 (s, 3H). ^{13}C NMR (101 MHz, acetone-d_6) δ = 160.45(C), 158.55(C), 151.56(C), 141.66(C), 139.07(C), 132.85(C), 129.45(CH), 124.71(CH), 123.70(CH), 121.90(CH), 115.56(CH), 115.05(CH), 106.55(CH), 98.39(C), 75.85(CH), 55.94(CH_3), 55.69(CH_3). LC/MS (retention time 4.30 min) m/z (ESI^+) 409.00 (MH^+–H_2O, 100%), 449.00 (MNa^+, 23.4%). HRMS (ESI^+): m/z calcd for $C_{17}H_{14}IO_2S^+$ [MH^+–H_2O]: 408.9754; found: 408.9749.

(2-Iodo-5-methoxyphenyl)(5-methoxy benzo[b]thiophen-2-yl) methanol ***7h***. According to general procedure A, scale: 5-methoxybenzo[*b*]thiophene (0.247 g, 1.50 mmol), *n*-BuLi 2.5 M in hexanes (0.72 mL, 1.80 mmol), 2-iodo-5-methoxybenzaldehyde (0.510 g, 1.95 mmol). The residue was purified by flash chromatography (0 to 30% of EtOAc in cyclohexane) to afford

compound **7h** as a yellow oil (0.582 g, 91%). IR: 3428, 3062, 3001, 2973, 2935, 2910, 2883, 2832, 1599, 1584, 1564, 1532, 1456, 1447, 1406, 1370, 1331, 1294, 1278, 1263, 1240, 1204, 1150, 1137, 1111, 1069, 1045, 1019, 997, 943, 935, 924, 890, 859, 811, 802, 778, 756, 721, 697, 664, 631, 621, 590, 568, 521, 454. ^{1}H NMR (400 MHz, acetone-d_6) δ = 7.74 (d, J = 8.7 Hz, 1H), 7.70 (d, J = 8.8 Hz, 1H), 7.38 (d, J = 3.1 Hz, 1H), 7.28 (d, J = 2.5 Hz, 1H), 7.11 (s, 1H), 6.94 (dd, J = 8.8, 2.5 Hz, 1H), 6.74 (dd, J = 8.7, 3.1 Hz, 1H), 6.21 (d, J = 4.1 Hz, 1H), 5.53 (d, J = 4.6 Hz, 1H), 3.82 (s, 3H), 3.81 (s, 3H). ^{13}C NMR (101 MHz, acetone-d_6) δ = 161.42(C), 158.57(C), 150.61(C), 147.97(C), 141.58(C), 140.62(CH), 132.90(C), 123.72(CH), 122.38(CH), 116.66(CH), 115.21(CH), 114.77(CH), 106.60(CH), 86.43(C), 76.13(CH), 55.77 (CH_3), 55.69(CH_3). LC/MS (retention time 4.31 min) m/z (ESI^+) 409.00 (MH^+–H_2O, 100%), 449.00 (MNa^+, 32.4%), 450.10 (7.8), 451.00 (2.6). HRMS (ESI^+): m/z calcd for $C_{17}H_{14}IO_2S^+$ [MH^+–H_2O]: 408.9754; found: 408.9751.

(5-((Tert-Butyldimethylsilyl)oxy)benzo[b]thiophen-2-yl)(2-iodophenyl) methanol ***7i***. According to general procedure A, scale: (benzo[*b*] thiophen-5-yloxy)(*tert*-butyl)dimethylsilane (0.400 g, 1.51 mmol), *n*-BuLi 2.5 M in hexanes (0.72 mL, 1.80 mmol), 2-iodobenzaldehyde (0.452 g, 1.95 mmol). The residue was purified by flash chromatography (0 to 30% of EtOAc in cyclohexane) to afford compound **7i** as a yellow oil (0.481 g, 64%). IR: 3436, 3054, 2962, 2929, 2880, 2858, 1594, 1566, 1535, 1463, 1444, 1390, 1364, 1342, 1311, 1288, 1257, 1207, 1143, 1113, 1092, 1066, 1049, 1008, 959, 939, 870, 853, 835, 811, 784, 745, 730, 720, 701, 680, 676, 659, 637, 623, 605, 590, 560, 543, 485. ^{1}H NMR (400 MHz, acetone-d_6) δ = 7.88 (dd, J = 7.9, 1.1 Hz, 1H), 7.77 (dd, J = 7.8, 1.7 Hz, 1H), 7.70 (d, J = 8.6 Hz, 1H), 7.48 (td, J = 7.5, 1.0 Hz, 1H), 7.25 (d, J = 2.3 Hz, 1H), 7.11–7.07 (m, 2H), 6.90 (dd, J = 8.6, 2.4 Hz, 1H), 6.27 (d, J = 4.5 Hz, 1H), 5.53 (d, J = 4.5 Hz, 1H), 1.00 (s, 9H), 0.22 (s, 6H). ^{13}C NMR (101 MHz, acetone-d_6) δ = 153.96(C), 150.94(C), 146.92(C), 141.81(C), 140.10(CH), 133.83(C), 130.51(CH), 129.54(CH), 129.09(CH), 123.76(CH), 122.02(CH), 119.32(CH), 114.35(CH), 98.36(C), 76.32(CH), 26.07(CH_3), 18.79(C), −4.32(CH_3). LC/MS (retention time 5.89 min) m/z (ESI^+) 479.10 (MH^+–H_2O, 100%). HRMS (ESI^+): m/z calcd for $C_{21}H_{24}IOSSi^+$ [MH^+–H_2O]: 479.0356; found: 479.0347.

(5-((Tert-Butyldimethylsilyl)oxy)benzo[b]thiophen-2-yl)(2-iodo-4-methoxyphenyl)methanol ***7j***. According to general procedure A, scale: (benzo[*b*]thiophen-5-yloxy)(*tert*-butyl)dimethylsilane (0.322 g, 1.22 mmol), *n*-BuLi 2.5 M in hexanes (0.60 mL, 1.50 mmol), 2-iodo-4-methoxybenzaldehyde (0.421 g, 1.60 mmol). The residue was purified by flash chromatography (0 to 30% of EtOAc in cyclohexane) to afford compound **7j** as a yellow oil (0.581 g, 91%). IR: 3386, 2954, 2929, 2893, 2856, 1705, 1595, 1563, 1531, 1486, 1471, 1462, 1445, 1390, 1361, 1313, 1282, 1254, 1226, 1181, 1151, 1093, 1068, 1027, 1013, 967, 939, 855, 837, 800, 779, 737, 720, 674, 591, 563. ^{1}H NMR (400 MHz, acetone-d_6) δ = 7.69 (d, J = 8.6 Hz, 1H), 7.62 (d, J = 8.7 Hz, 1H), 7.41 (d, J = 2.6 Hz, 1H), 7.24 (d, J = 2.3 Hz, 1H), 7.09–7.04 (m, 2H), 6.89 (dd, J = 8.6, 2.4 Hz, 1H), 6.22 (d, J = 4.4 Hz, 1H), 5.41 (d, J = 4.5 Hz, 1H), 3.82 (s, 3H), 1.00 (s, 9H), 0.22 (s, 6H). ^{13}C NMR (101 MHz, acetone-d_6) δ = 160.47(C), 153.94(C), 151.68(C), 141.88(C), 139.05(C), 133.82(C), 129.48(CH), 124.71(CH), 123.74(CH), 121.68(CH), 119.22(CH), 115.60(CH), 114.31(CH), 98.39(C), 75.87(CH), 55.95(CH_3), 26.07(CH_3), 18.79 (C), −4.31 (CH_3). LC/MS (retention time 5.86 min) m/z (ESI^+) 509.10 (MH^+–H_2O, 100%). HRMS (ESI^+): m/z calcd for $C_{22}H_{26}IO_2SSi^+$ [MH^+–H_2O]: 509.0462; found: 509.0461.

(5-((Tert-Butyldimethylsilyl)oxy)benzo[b]thiophen-2-yl)(2-iodo-5-methoxyphenyl)methanol ***7k***. According to general procedure A, scale: (benzo[*b*]thiophen-5-yloxy)(*tert*-butyl)dimethylsilane (0.404 g, 1.52 mmol), *n*-BuLi 2.5 M in hexanes (0.72 mL, 1.80 mmol), 2-iodo-5-methoxybenzaldehyde (0.513 g, 1.95 mmol). The residue was purified by flash chromatography (0 to 30% of EtOAc in cyclohexane) to afford compound **7k** as a yellow oil (0.434 g, 54%). IR: 3418, 3054, 3002, 2954, 2928, 2884, 2856, 1704, 1595, 1567, 1532, 1463, 1445, 1414, 1362, 1312, 1287, 1255, 1226, 1148, 1114, 1068, 1047, 1034, 1003, 967, 939, 873, 837, 804, 780, 740, 720, 677, 635, 587, 521, 486. ^{1}H NMR (400 MHz, acetone-d_6) δ = 7.74 (d, J = 8.7 Hz, 1H), 7.70 (d, J = 8.6 Hz, 1H), 7.38 (d, J = 3.1 Hz, 1H), 7.25 (d, J = 2.3 Hz, 1H), 7.09 (s, 1H), 6.90 (dd, J = 8.6, 2.4 Hz, 1H), 6.74 (dd, J = 8.7, 3.2 Hz, 1H), 6.20 (dd, J = 4.6, 1.2 Hz, 1H), 5.52 (d, J = 4.6 Hz, 1H), 3.81 (s, 3H), 1.00 (s, 9H), 0.22 (s, 6H). ^{13}C NMR (101 MHz, acetone-d_6) δ = 161.42(C), 153.96(C), 150.70(C), 147.93(C), 141.80(C), 140.62(CH), 133.85(C), 123.77(CH), 122.15(CH), 119.35(CH), 116.66(CH), 114.79(CH), 114.37(CH), 86.42(C), 76.14(CH), 55.77(CH_3), 26.07(CH_3), 18.79 (C), −4.31 (CH_3). LC/MS (retention time 5.87 min) m/z (ESI^+) 509.10 (MH^+–H_2O, 100%), 549.10 (MNa^+, 6.3%). HRMS (ESI^+): m/z calcd for $C_{22}H_{26}IO_2SSi^+$ [MH^+–H_2O]: 509.0462; found: 509.0462.

(5-((Tert-Butyldimethylsilyl)oxy)benzo[b]thiophen-2-yl)(2-iodo-6-methoxyphenyl)methanol ***7l***. According to general procedure A, scale: (benzo[*b*]thiophen-5-yloxy)(*tert*-butyl)dimethylsilane (0.271 g, 1.03 mmol), *n*-BuLi 2.5 M in hexanes (0.45 mL, 1.13 mmol), 2-iodo-6-methoxybenzaldehyde (0.343 g, 1.31 mmol). The residue was purified by flash chromatography (0 to 100% of MeOH in H_2O, using a reversed phase C18 column) afford compound **7l** as a white solid (0.110 g, 20%), m.p. 124.6–125.6 °C. IR: 3533, 3097, 3054, 3008, 2958, 2917, 2852, 1595, 1567, 1535, 1445, 1432, 1408, 1362, 1326, 1310, 1290, 1256, 1219, 1176, 1153, 1139, 1099, 1082, 1068, 1012, 965, 938, 867, 832, 818, 787, 760, 735, 729, 713, 678, 659, 636, 613, 588, 563, 538, 512, 459. ^{1}H NMR (400 MHz, acetone-d_6) δ = 7.69 (d, J = 8.6 Hz, 1H), 7.57 (dd, J = 7.7, 1.3 Hz, 1H), 7.21 (d, J = 2.3 Hz, 1H), 7.15 (dd, J = 8.3, 1.2 Hz, 1H), 7.11 (d, J = 7.7 Hz, 1H), 6.92 (dd, J = 1.3, 0.6 Hz, 1H), 6.88 (dd, J = 8.6, 2.4 Hz, 1H), 6.34 (s, 1H), 5.05 (s, 1H), 3.83 (s, 3H), 1.00 (s, 9H), 0.22 (s, 6H). ^{13}C NMR (101 MHz, acetone-d_6) δ = 158.97(C), 153.92(C), 151.46(C), 142.17(C), 133.73(C), 133.71(C), 133.11(CH), 131.65(CH), 123.66(CH), 120.42(CH), 118.97(CH), 114.13(CH), 113.42(CH), 99.90(C), 78.11(CH), 56.38(CH_3), 26.08(CH_3), 18.79 (C), −4.30 (CH_3). LC/MS (retention time 6.03 min) m/z (ESI^+) 509.10 (MH^+–H_2O, 100%), 549.10 (MNa^+, 8.2%). HRMS (ESI^+): m/z calcd for $C_{22}H_{26}IO_2SSi^+$ [MH^+–H_2O]: 509.0462; found: 509.0456.

(5-Fluorobenzo[b]thiophen-2-yl)(2-iodo-5-methoxyphenyl)methanol ***7m***. According to general procedure A, scale: 5-fluoro benzo[*b*]

thiophene (0.229 g, 1.50 mmol), *n*-BuLi 2.5 M in hexanes (0.72 mL, 1.80 mmol), 2-iodo-5-methoxybenzaldehyde (0.511 g, 1.95 mmol). The residue was purified by flash chromatography (0 to 30% of EtOAc in cyclohexane) to afford compound **7m** as a yellow oil (0.317 g, 51%). IR: 3385, 3068, 3000, 2959, 2935, 2905, 2835, 1702, 1589, 1567, 1535, 1464, 1442, 1413, 1401, 1286, 1228, 1201, 1163, 1140, 1125, 1043, 1002, 954, 864, 798, 772, 746, 716, 687, 660, 628, 566, 521, 469. ^{1}H NMR (400 MHz, acetone-d_6) δ = 7.87 (dd, J = 8.8, 4.9 Hz, 1H), 7.75 (d, J = 8.7 Hz, 1H), 7.52 (dd, J = 9.8, 2.5 Hz, 1H), 7.37 (d, J = 3.1 Hz, 1H), 7.20 (s, 1H), 7.13 (td, J = 9.0, 2.6 Hz, 1H), 6.76 (dd, J = 8.7, 3.1 Hz, 1H), 6.25–6.21 (m, 1H), 5.63 (d, J = 4.6 Hz, 1H), 3.81 (s, 3H). ^{13}C NMR (101 MHz, acetone-d_6) δ = 161.65(C, d, J = 240.4 Hz), 161.46(C), 152.46(C), 147.74(C), 141.62(C, d, J = 10.1 Hz), 140.71(CH), 136.27(C), 124.65(CH, d, J = 9.1 Hz), 122.13(CH, d, J = 4.1 Hz), 116.78(CH), 114.79(CH), 113.51(CH, d, J = 25.3 Hz), 109.72(CH, d, J = 23.2 Hz), 86.37(C), 76.06(CH), 55.78(CH_3). ^{19}F NMR (376 MHz, acetone-d_6) δ = −120.45. LC/MS (retention time 4.45 min) m/z (ESI^{+}) 397.00 (MH^+–H_2O, 100%), 437.15 (MNa^+, 5.3%). HRMS (ESI^+): m/z calcd for $C_{16}H_{11}FIOS^+$ [MH^+–H_2O]: 396.9554; found: 396.9550.

General procedure B for the preparation of ketones 6 by an oxidation reaction of alcohols 7. To a solution of alcohol 7 (0.54 mmol) in ACN (12.5 mL) under an argon atmosphere at room temperature was added MnO_2 (0.142 g, 1.63 mmol) and, after a 2 h stirring at rt, a second portion of MnO_2 (0.142 g, 1.63 mmol) was added. After stirring for 4 h at room temperature, the reaction mixture was filtered over a pad of silica gel and washed with ACN (2 × 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (0 to 20% gradient of EtOAc in cyclohexane) to afford the desired ketone **6**.

*Benzo[b]thiophen-2-yl(2-iodo-3-methoxyphenyl)methanone **6a**.* According to general procedure B, scale: benzo[*b*]thiophen-2-yl(2-iodo-3-methoxyphenyl)methanol **7a** (0.229 g, 0.58 mmol) and MnO_2 (0.304 g, 3.50 mmol). The residue was purified by flash chromatography (0 to 20% of EtOAc in cyclohexane) to afford compound **6a** as a white solid (0.198 g, 87%), m.p. 121.1–122.3 °C. IR: 3059, 3011, 2943, 2921, 2842, 2328, 1640, 1592, 1562, 1511, 1464, 1417, 1333, 1308, 1262, 1248, 1202, 1184, 1143, 1099, 1049, 1012, 939, 915, 868, 841, 802, 776, 750, 732, 718, 709, 664, 601, 580, 547, 489, 483. ^{1}H NMR (400 MHz, acetone-d_6) δ = 8.06 (dq, J = 8.3, 0.9 Hz, 1H), 8.00 (dt, J = 8.0, 1.0 Hz, 1H), 7.69 (d, J = 0.8 Hz, 1H), 7.58–7.53 (m, 2H), 7.46 (ddd, J = 8.1, 7.1, 1.0 Hz, 1H), 7.18 (dd, J = 8.3, 1.3 Hz, 1H), 7.10 (dd, J = 7.5, 1.3 Hz, 1H), 3.98 (s, 3H). ^{13}C NMR (101 MHz, acetone-d_6) δ = 191.41(C), 159.32(C), 147.21(C), 143.89(C), 143.15(C), 140.13(C), 134.69(CH), 130.77(CH), 128.91(CH), 127.47(CH), 126.15(CH), 123.91(CH), 120.91(CH), 113.01(CH), 84.70(C), 57.09(CH_3). LC/MS (retention time 4.56 min) m/z (ESI^+) 395.00 (MH^+, 100%), 416.90 (MNa^+, 18.8%), 810.90 ($2MNa^+$, 21.9%). HRMS (ESI^+): m/z calcd for $C_{16}H_{12}IO_2S^+$ [MH^+]: 394.9597; found: 394.9596.

*Benzo[b]thiophen-2-yl(2-iodo-4-methoxyphenyl)methanone **6b**.* Following general procedure B, scale: benzo[*b*]thiophen-2-yl(2-iodo-4-methoxyphenyl)methanol **7b** (0.313 g, 0.79 mmol) and MnO_2 (0.418 g, 4.80 mmol). The residue was purified by flash chromatography (0 to 20% of EtOAc in cyclohexane) to afford compound **6b** as a colorless oil (0.272 g, 87%). IR: 3261, 3064, 3062, 3046, 2999, 2961, 2935, 2907, 2886, 2830, 2551, 1635, 1591, 1558, 1517, 1481, 1455, 1433, 1424, 1391, 1336, 1313, 1299, 1286, 1266, 1250, 1223, 1183, 1160, 1149, 1121, 1032, 1021, 952, 883, 871, 849, 815, 791, 760, 748, 726, 691, 660, 622, 572, 555, 522, 478. ^{1}H NMR (400 MHz, acetone-d_6) δ = 8.06 (dq, J = 8.2, 0.9 Hz, 1H), 8.01 (dt, J = 8.1, 1.1 Hz, 1H), 7.76 (d, J = 0.8 Hz, 1H), 7.59–7.54 (m, 3H), 7.47 (ddd, J = 8.1, 7.1, 1.1 Hz, 1H), 7.15 (dd, J = 8.5, 2.5 Hz, 1H), 3.93 (s, 3H). ^{13}C NMR (101 MHz, acetone-d_6) δ = 190.79(C), 162.19(C), 143.79(C), 143.76(C), 140.13(C), 136.82(C), 134.46(CH), 130.90(CH), 128.79(CH), 127.42(CH), 126.30(CH), 126.12(CH), 123.85(CH), 114.45(CH), 93.69(C), 56.24(CH_3). LC/MS (retention time 4.72 min) m/z (ESI^+) 395.00 (MH^+, 100%), 417.00 (MNa^+, 14.7%), 810.90 ($2MNa^+$, 26.7%). HRMS (ESI^+): m/z calcd for $C_{16}H_{12}IO_2S^+$ [MH^+]: 394.9597; found: 394.9595.

*Benzo[b]thiophen-2-yl(2-iodo-5-methoxyphenyl)methanone **6c**.* According to general procedure B, scale: benzo[*b*]thiophen-2-yl(2-iodo-5-methoxyphenyl)methanol **7c** (0.335 g, 0.84 mmol) and MnO_2 (0.441 g, 5.07 mmol). The residue was purified by flash chromatography (0 to 20% of EtOAc in cyclohexane) to afford compound **6c** as a yellow oil (0.302 g, 90%). IR: 3062, 3005, 2937, 2923, 2894, 2850, 2828, 2353, 2328, 1638, 1582, 1567, 1507, 1459, 1426, 1383, 1335, 1321, 1262, 1230, 1172, 1159, 1133, 1100, 1047, 1011, 951, 918, 861, 845, 807, 792, 761, 750, 721, 730, 663, 593, 576, 552, 470. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.07 (dd, J = 8.3, 0.9 Hz, 1H), 8.02 (d, J = 8.1 Hz, 1H), 7.87 (d, J = 8.8 Hz, 1H), 7.77 (d, J = 1.0 Hz, 1H), 7.58 (ddd, J = 8.2, 7.1, 1.2 Hz, 1H), 7.48 (ddd, J = 8.1, 7.1, 1.1 Hz, 1H), 7.18 (d, J = 3.1 Hz, 1H), 6.97 (dd, J = 8.8, 3.1 Hz, 1H), 3.88 (s, 3H). ^{13}C NMR (101 MHz, acetone-d_6) δ = 191.07(C), 160.75(C), 145.93(C), 143.96(C), 143.03(C), 141.35(C), 140.18(CH), 135.09(CH), 129.00(CH), 127.58(CH), 126.20(CH), 123.92(CH), 118.86(CH), 114.99(CH), 80.62(C), 56.12(CH_3). LC/MS (retention time 4.75 min) m/z (ESI^+) 395.00 (MH^+, 100%), 417.00 (MNa^+, 20.6%), 810.90 ($2MNa^+$, 26.3%). HRMS (ESI^+): m/z calcd for $C_{16}H_{12}IO_2S^+$ [MH^+]: 394.9597; found: 394.9594.

*Benzo[b]thiophen-2-yl(2-iodo-6-methoxyphenyl)methanone **6d**.* According to general procedure B, scale: benzo[*b*]thiophen-2-yl(2-iodo-6-methoxyphenyl)methanol **7d** (0.115 g, 0.29 mmol) and MnO_2 (0.300 g, 3.45 mmol). The residue was purified by flash chromatography (0 to 20% of EtOAc in cyclohexane) afford compound **6d** as a colorless oil (0.110 g, 96%). IR: 3288, 3080, 2964, 2937, 2835, 1927, 1646, 1580, 1562, 1512, 1456, 1425, 1360, 1331, 1281, 1258, 1180, 1159, 1147, 1112, 1060, 1022, 945, 910, 878, 840, 817, 777, 748, 721, 697, 671, 605, 581, 552, 530, 491, 477, 458. ^{1}H NMR (400 MHz, acetone-d_6) δ = 8.05 (dq, J = 8.2, 0.9 Hz, 1H), 8.00–7.97 (m, 1H), 7.72 (d, J = 0.8 Hz, 1H), 7.58–7.54 (m, 2H), 7.48–7.44 (m, 1H), 7.29–7.23 (m, 2H), 3.77 (s, 3H). ^{13}C NMR (101 MHz, acetone-d_6) δ = 190.13(C), 158.27(C), 143.77(C), 143.52(C), 140.20(C), 134.61(C), 133.34(CH), 132.96(CH), 131.85(CH),

128.76(CH), 127.36(CH), 126.10(CH), 123.94(CH), 112.35(CH), 93.12(C), 56.54(CH_3). LC/MS (retention time 4.56 min) *m*/*z* (ESI^+) 395.00 (MH^+, 100%), 416.90 (MNa^+, 11.5%), 810.90 ($2MNa^+$, 24.1%). HRMS (ESI^+): *m*/*z* calcd for $C_{16}H_{12}IO_2S^+$ [MH^+]: 394.9597; found: 394.9601.

(2-Iodophenyl)(5-methoxy benzo[b]thiophen-2-yl)methanone ***6e***. According to general procedure B, scale: (2-iodophenyl)(5-methoxybenzo[*b*]thiophen-2-yl)methanol **7e** (0.311 g, 0.79 mmol) and MnO_2 (0.420 g, 4.83 mmol). The residue was purified by flash chromatography (0 to 20% of EtOAc in cyclohexane) to afford compound **6e** as a yellow oil (0.256 g, 83%). IR: 3255, 3059, 2962, 2930, 2845, 2826, 2633, 1635, 1598, 1580, 1558, 1511, 1448, 1421, 1341, 1293, 1253, 1220, 1185, 1156, 1124, 1070, 1040, 1023, 943, 878, 854, 836, 809, 773, 745, 715, 681, 660, 636, 593, 555, 487. ^{1}H NMR (400 MHz, acetone-d_6) 8.04 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.93 (d, *J* = 8.9 Hz, 1H), 7.64–7.59 (m, 2H), 7.57 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.50 (d, *J* = 2.4 Hz, 1H), 7.39–7.33 (m, 1H), 7.21 (dd, *J* = 8.9, 2.6 Hz, 1H), 3.85 (s, 3H). ^{13}C NMR (101 MHz, acetone-d_6) δ = 191.30(C), 159.06(C), 145.11(C), 144.02(C), 141.23(C), 140.59(CH), 136.63(C), 134.60(CH), 132.42(CH), 129.11(CH), 128.99(CH), 124.61(CH), 120.10(CH), 108.19(CH), 92.49(C), 55.84(CH_3). LC/MS (retention time 4.63 min) *m*/*z* (ESI^+) 395.00 (MH^+, 100%), 416.90 (MNa^+, 16.1%), 810.90 ($2MNa^+$, 20.8%). HRMS (ESI^+): *m*/*z* calcd for $C_{16}H_{12}IO_2S^+$ [MH^+]: 394.9597; found: 394.9594.

(2-Iodo-3-methoxyphenyl)(5-methoxy benzo[b]thiophen-2-yl) methanone ***6f***. According to general procedure B, scale: (2-iodo-3-methoxyphenyl) (5-methoxybenzo[*b*]thiophen-2-yl) methanol **7f** (0.242 g, 0.57 mmol) and MnO_2 (0.299 g, 3.44 mmol). The residue was purified by flash chromatography (0 to 20% of EtOAc in cyclohexane) to afford compound **6f** as a yellow solid (0.172 g, 71%), m.p. 129.1–130.6 °C. IR: 3076, 3059, 3008, 2959, 2926, 2839, 2826, 2350, 1632, 1600, 1560, 1515, 1449, 1418, 1341, 1307, 1262, 1223, 1192, 1179, 1160, 1056, 1023, 912, 876, 834, 807, 784, 763, 747, 715, 663, 613, 495. ^{1}H NMR (400 MHz, acetone-d_6) δ = 7.92 (dt, *J* = 8.9, 0.6 Hz, 1H), 7.59 (d, *J* = 0.8 Hz, 1H), 7.55 (dd, *J* = 8.3, 7.5 Hz, 1H), 7.49 (d, *J* = 2.5 Hz, 1H), 7.22–7.16 (m, 2H), 7.08 (dd, *J* = 7.5, 1.3 Hz, 1H), 3.98 (s, 3H), 3.85 (s, 3H). ^{13}C NMR (101 MHz, acetone-d_6) δ = 191.30(C), 159.31(C), 159.06(C), 147.34(C), 144.05(C), 141.25(C), 136.58(C), 134.36(CH), 130.74(CH), 124.62(CH), 120.88(CH), 119.99(CH), 112.94(CH), 108.18(CH), 84.72(C), 57.09(CH_3), 55.83(CH_3). LC/MS (retention time 4.54 min) *m*/*z* (ESI^+) 425.00 (MH^+, 100%), 446.80 (MNa^+, 15.7%), 870.90 ($2MNa^+$, 24.7%). HRMS (ESI^+): *m*/*z* calcd for $C_{17}H_{14}IO_3S^+$ [MH^+]: 424.9703; found: 424.9704.

(2-Iodo-4-methoxyphenyl)(5-methoxy benzo[b]thiophen-2-yl) methanone ***6g***. According to general procedure B, scale: according to general procedure 2, scale: (2-iodo-4-methoxyphenyl)(5-methoxybenzo[*b*]thiophen-2-yl)methanol **7g** (0.286 g, 0.62 mmol) and MnO_2 (0.360, 4.14 mmol). The residue was purified by flash chromatography (0 to 20% of EtOAc in cyclohexane) to afford compound **6g** as a yellow oil (0.249 g, 95%). IR: 3074, 3002, 2959, 2935, 2834, 2777, 1710, 1638, 1586, 1556, 1510, 1485, 1451, 1437, 1421, 1386, 1342, 1296, 1284, 1217, 1180, 1157, 1121, 1070, 1019, 945, 868, 807, 764, 756, 715, 696, 676, 661, 621, 580, 572, 530, 486. ^{1}H NMR (400 MHz, acetone-d_6) δ = 7.92 (dt, *J* = 8.9, 0.7 Hz, 1H), 7.66 (d, *J* = 1.0 Hz, 1H), 7.57 (d, *J* = 2.6 Hz, 1H), 7.54 (d, *J* = 8.6 Hz, 1H), 7.51 (d, *J* = 2.6 Hz, 1H), 7.20 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.15 (dd, *J* = 8.6, 2.4 Hz, 1H), 3.93 (s, 3H), 3.86 (s, 3H). ^{13}C NMR (101 MHz, acetone-d_6) δ = 190.74(C), 162.16(C), 159.06(C), 144.67(C), 141.26(C), 136.99(C), 136.49(C), 134.15(CH), 130.82(CH), 126.23(CH), 124.59(CH), 119.87(CH), 114.45(CH), 108.17(CH), 93.66(C), 56.25(CH_3), 55.85(CH_3). LC/MS (retention time 4.70 min) *m*/*z* (ESI^+) 425.00 (MH^+, 100%), 447.00 (MNa^+, 17.3%), 870.90 ($2MNa^+$, 52.4%). HRMS (ESI^+): *m*/*z* calcd for $C_{17}H_{14}IO_3S^+$ [MH^+]: 424.9703; found: 424.9698.

(2-Iodo-5-methoxyphenyl)(5-methoxy benzo[b]thiophen-2-yl) methanone ***6h***. According to general procedure B, scale: according to general procedure 2, scale: (2-iodo-5-methoxyphenyl)(5-methoxybenzo[*b*]thiophen-2-yl)methanol **7h** (0.294 g, 0.69 mmol) and MnO_2 (0.367 g, 4.22 mmol). The residue was purified by flash chromatography (0 to 20% of EtOAc in cyclohexane) to afford compound **6h** as a yellow oil (0.233 g, 80%). IR: 3065, 3002, 2392, 2934, 2832, 1710, 1644, 1602, 1586, 1582, 1509, 1451, 1422, 1401, 1390, 1342, 1318, 1295, 1265, 1231, 1213, 1178, 1155, 1106, 1070, 1044, 1023, 1008, 946, 916, 888, 800, 765, 714, 698, 680, 657, 607, 566, 560, 530, 490, 456. ^{1}H NMR (400 MHz, acetone-d_6) δ 7.93 (d, *J* = 8.9 Hz, 1H), 7.87 (d, *J* = 8.8 Hz, 1H), 7.67 (d, *J* = 1.0 Hz, 1H), 7.51 (d, *J* = 2.4 Hz, 1H), 7.21 (dd, *J* = 8.9, 2.4 Hz, 1H), 7.16 (d, *J* = 3.1 Hz, 1H), 6.96 (dd, *J* = 8.8, 3.1 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H). ^{13}C NMR (101 MHz, acetone-d_6) δ = 190.97(C), 160.71(C), 159.08(C), 146.02(C), 143.89(C), 141.30(CH), 141.28(C), 136.65(C), 134.74(CH), 124.62(CH), 120.10(CH), 118.77(CH), 114.94(CH), 108.24(CH), 80.62(C), 56.12(CH_3), 55.85(CH_3). LC/MS (retention time 4.70 min) *m*/*z* (ESI^+) 425.00 (MH^+, 100%), 447.00 (MNa^+, 18.1%), 870.90 ($2MNa^+$, 33.5%). HRMS (ESI^+): *m*/*z* calcd for $C_{17}H_{14}IO_3S^+$ [MH^+]: 424.9703; found: 424.9699.

(5-((Tert-Butyldimethylsilyl)oxy)benzo[b]thiophen-2-yl)(2-iodophenyl) methanone ***6i***. According to general procedure B, scale: (5-((*tert*-butyldimethylsilyl)oxy)benzo[*b*]thiophen-2-yl)(2-iodophenyl)methanol **7i** (0.420 g, 0.85 mmol) and MnO_2 (0.443 g, 5.10 mmol). The residue was purified by flash chromatography (0 to 20% of EtOAc in cyclohexane) to afford compound **6i** as a yellow oil (0.358 g, 85%). IR: 3059, 2954, 2928, 2885, 2856, 1712, 1648, 1599, 1583, 1549, 1510, 1471, 1462, 1437, 1390, 1361, 1324, 1288, 1256, 1222, 1158, 1126, 1108, 1069, 1040, 1016, 968, 939, 878, 868, 838, 813, 780, 741, 716, 704, 673, 642, 632, 616, 592, 552, 529, 487. ^{1}H NMR (400 MHz, acetone-d_6) δ = 8.04 (ddd, *J* = 7.9, 1.1, 0.5 Hz, 1H), 7.94 (dt, *J* = 8.8, 0.7 Hz, 1H), 7.63 (d, *J* = 0.9 Hz, 1H), 7.61 (dd, *J* = 7.2, 1.1 Hz, 1H), 7.58–7.54 (m, 1H), 7.51 (d, *J* = 2.4 Hz, 1H), 7.35 (ddd, *J* = 8.1, 7.3, 2.0 Hz, 1H), 7.18 (dd, *J* = 8.7, 2.4 Hz, 1H), 1.00 (s, 9H), 0.24 (s, 6H). ^{13}C NMR (101 MHz, acetone-d_6) δ = 191.35(C), 154.65(C), 145.11(C), 144.20(C), 141.45(C), 140.61(CH), 137.34(C), 134.56(CH), 132.44(CH), 129.12(CH), 129.00(CH), 124.75(CH), 123.87(CH), 116.47(CH), 92.46(C), 26.01(CH_3), 18.78(C), −4.36 (CH_3). LC/MS (retention time 6.14 min) *m*/*z* (ESI^+) 495.10 (MH^+, 100%), 517.10 (MNa^+, 4.4%).

HRMS (ESI$^+$): *m*/*z* calcd for $C_{21}H_{24}IO_2SSi^+$ [MH$^+$]: 495.0306; found: 495.0302.

(5-((Tert-Butyldimethylsilyl)oxy)benzo[b]thiophen-2-yl)(2-iodo-4-methoxyphenyl)methanone ***6j***. According to general procedure B, scale: (5-((*tert*-butyldimethylsilyl)oxy)benzo[*b*]thiophen-2-yl)(2-iodo-4-methoxyphenyl)methanol **7j** (0.338 g, 0.64 mmol) and MnO_2 (0.336 g, 3.86 mmol). The residue was purified by flash chromatography (0 to 20% of EtOAc in cyclohexane) to afford compound **6j** as a yellow oil (0.225 g, 67%). IR: 3070, 3005, 2954, 2929, 2893, 2858, 1712, 1644, 1588, 1557, 1511, 1486, 1471, 1462, 1436, 1390, 1361, 1324, 1285, 1255, 1220, 1182, 1158, 1120, 1069, 1020, 968, 936, 880, 856, 838, 803, 780, 757, 740, 717, 696, 676, 625, 604, 590, 572, 529, 489. ^{1}H NMR (400 MHz, acetone-d_6) δ = 7.92 (d, J = 9.5 Hz, 1H), 7.66 (s, 1H), 7.57 (d, J = 2.4 Hz, 1H), 7.53 (d, J = 8.6 Hz, 1H), 7.50 (d, J = 2.4 Hz, 1H), 7.15 (ddd, J = 8.6, 7.7, 2.5 Hz, 2H), 3.92 (s, 3H), 1.01 (s, 9H), 0.25 (s, 6H). ^{13}C NMR (101 MHz, acetone-d_6) δ = 190.73(C), 162.13(C), 154.58(C), 144.80(C), 141.43(C), 137.19(C), 136.91(C), 134.07(CH), 130.80(CH), 126.24(CH), 124.68(CH), 123.63(CH), 116.37(CH), 114.41(CH), 93.64(C), 56.23(CH), 26.02(CH_3), 18.78(C), −4.35 (CH_3). LC/MS (retention time 6.16 min) *m*/*z* (ESI$^+$) 525.20 (MH$^+$, 100%), 527.20 (MNa$^+$, 1.9%). HRMS (ESI$^+$): *m*/*z* calcd for $C_{22}H_{26}IO_3SSi^+$ [MH$^+$]: 525.0411; found: 525.0413.

(5-((Tert-Butyldimethylsilyl)oxy)benzo[b]thiophen-2-yl)(2-iodo-5-methoxyphenyl)methanone ***6k***. According to general procedure B, scale: according to general procedure 2, scale: (5-((*tert*-butyldimethylsilyl)oxy)benzo[*b*]thiophen-2-yl)(2-iodo-5-methoxyphenyl)methanol **7k** (0.330 g, 0.63 mmol) and MnO_2 (0.326 g, 3.76 mmol). The residue was purified by flash chromatography (0 to 20% of EtOAc in cyclohexane) to afford compound **6k** as a yellow oil (0.292 g, 89%). IR: 3059, 3002, 2954, 2929, 2885, 2856, 1711, 1651, 1599, 1564, 1549, 1510, 1461, 1437, 1402, 1390, 1361, 1324, 1287, 1257, 1232, 1213, 1182, 1155, 1106, 1069, 1046, 1009, 968, 939, 917, 883, 838, 802, 780, 741, 716, 679, 637, 617, 587, 490. ^{1}H NMR (400 MHz, acetone-d_6) δ = 7.93 (d, J = 8.8 Hz, 1H), 7.86 (d, J = 8.8 Hz, 1H), 7.67 (d, J = 0.9 Hz, 1H), 7.52 (d, J = 2.3 Hz, 1H), 7.20–7.12 (m, 2H), 6.96 (dd, J = 8.7, 3.0 Hz, 1H), 3.88 (s, 3H), 1.01 (s, 9H), 0.25 (s, 6H). ^{13}C NMR (101 MHz, acetone-d_6) δ = 191.01(C), 160.73(C), 154.66(C), 146.02(C), 144.06(C), 141.50(C), 141.31(CH), 137.36(C), 134.70(CH), 124.75(CH), 123.87(CH), 118.77(CH), 116.51(CH), 114.95(CH), 80.60(C), 56.11(CH), 26.02(CH_3), 18.79(C), −4.36(CH_3). LC/MS (retention time 6.14 min) *m*/*z* (ESI$^+$) 525.20 (MH$^+$, 100%), 547.20 (MNa$^+$, 3.5%). HRMS (ESI$^+$): *m*/*z* calcd for $C_{22}H_{26}IO_3SSi^+$ [MH$^+$]: 525.0411; found: 525.0404.

(5-((Tert-Butyldimethylsilyl)oxy)benzo[b]thiophen-2-yl)(2-iodo-6-methoxyphenyl)methanone ***6l***. According to general procedure B, scale: (5-((*tert*-butyldimethylsilyl)oxy)benzo[*b*]thiophen-2-yl)(2-iodo-6-methoxyphenyl)methanol **7l** (0.084 g, 0.16 mmol) and MnO_2 (0.165 g, 1.90 mmol). The residue was purified by flash chromatography (0 to 20% of EtOAc in cyclohexane) to afford compound **6l** as a yellow solid (0.070 g, 83%), m.p. 124.8–125.5 °C. IR: 3535, 2953, 2928, 2856, 1660, 1585, 1566, 1513, 1456, 1428, 1325, 1288, 1257, 1221, 1159, 1114, 1064, 1025, 966, 938, 870, 838, 822, 776, 752, 742, 717, 674, 640, 613, 588, 562, 500, 465. ^{1}H NMR (400 MHz, acetone-d_6) δ = 7.92 (dt, J = 8.8, 0.7 Hz, 1H), 7.62 (d, J = 0.7 Hz, 1H), 7.55 (dd, J = 7.5, 1.3 Hz, 1H), 7.48 (d, J = 2.4 Hz, 1H), 7.31–7.23 (m, 2H), 7.19–7.14 (m, 1H), 3.77 (s, 3H), 1.01 (s, 9H), 0.24 (s, 6H). ^{13}C NMR (101 MHz, acetone-d_6) δ = 190.07(C), 158.28(C), 154.61(C), 144.57(C), 141.55(C), 137.16(C), 134.71(C), 132.94(CH), 132.92(CH), 131.85(CH), 124.77(CH), 123.61(CH), 116.36(CH), 112.34(CH), 93.13(C), 56.54(CH), 26.03(CH_3), 18.79(C), −4.35 (CH_3). LC/MS (retention time 5.99 min) *m*/*z* (ESI$^+$) 525.10 (MH$^+$, 100%), 547.00 (MNa$^+$, 11.3%). HRMS (ESI$^+$): *m*/*z* calcd for $C_{22}H_{26}IO_3SSi^+$ [MH$^+$]: 525.0411; found: 525.0406.

(5-Fluorobenzo[b]thiophen-2-yl)(2-iodo-5-methoxyphenyl)methanone ***6m***. According to general procedure B, scale: (5-fluoro benzo[*b*]thiophen-2-yl)(2-iodo-5-methoxyphenyl)methanol **7m** (0.206 g, 0.50 mmol) and MnO_2 (0.259 g, 2.97 mmol). The residue was purified by flash chromatography (0 to 20% of EtOAc in cyclohexane) to afford compound **6m** as a yellow oil (0.180 g, 88%). IR: 3089, 3073, 3000, 2935, 2845, 1647, 1585, 1570, 1515, 1461, 1437, 1437, 1389, 1330, 1319, 1289, 1268, 1234, 1204, 1186, 1149, 1138, 1105, 1069, 1036, 1008, 956, 881, 805, 769, 754, 724, 713, 673, 653, 600, 584, 488, 463. ^{1}H NMR (400 MHz, acetone-d_6) δ = 8.16–8.08 (m, 1H), 7.90–7.84 (m, 1H), 7.81–7.71 (m, 2H), 7.47–7.39 (m, 1H), 7.21–7.16 (m, 1H), 7.00–6.95 (m, 1H), 3.89–3.87 (m, 3H). ^{13}C NMR (101 MHz, acetone-d_6) δ = 190.99(C), 161.86(C, d, J = 240.4 Hz), 160.76(C), 145.67(C), 145.36 (C), 141.39(CH), 141.19(C, d, J = 9.1 Hz), 139.66(C), 134.47(CH, d, J = 5.1 Hz), 125.79(CH, J = 9.1 Hz), 118.95(CH), 117.89(CH, d, J = 26.3 Hz), 115.04(CH), 112.28(CH, d, J = 23.2 Hz), 80.54(C), 56.13(CH_3). ^{19}F NMR (376 MHz, acetone-d_6) δ = −118.54. LC/MS (retention time 4.78 min) *m*/*z* (ESI$^+$) 412.90 (MH$^+$, 100%), 434.90 (MNa$^+$, 30.0%), 844.00 (2MNa$^+$, 26.5%). HRMS (ESI$^+$): *m*/*z* calcd for $C_{16}H_{11}FIO_2S^+$ [MH$^+$]: 412.9503; found: 412.9494.

General procedure C for the palladium-catalysed cyclisation of iodoketone 6 into tetracyclic derivative 4. In a sealable tube was added iodoketone **6** (0.30 mmol) in DMF (4 mL) under an argon atmosphere. Then $Pd(OAc)_2$ (0.004 g, 0.018 mmol), $Cy_3P{\cdot}HBF_4$ (0.012 g, 0.03 mmol) and K_2CO_3 (0.084 g, 0.61 mmol) were added successively. After stirring for 15 min at room temperature, the tube was sealed and heated during 16 h at 130 °C. After cooling, the reaction mixture was filtered through a sintered-glass funnel. Water (10 mL) and DCM (10 mL) were added, the aqueous layer was separated and extracted with ethyl acetate (2 × 10 mL). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by flash chromatography (DCM or MeOH/DCM) to afford the desired product.

10-Methoxy-6H-benzo[b]indeno[1,2-d]thiophen-6-one ***4a***. According to general procedure C, scale: benzo[*b*]thiophen-2-yl(2-iodo-3-methoxyphenyl)methanone **6a** (0.124 g, 0.31 mmol), $Pd(OAc)_2$ (0.004 g, 0.018 mmol), $Cy_3P{\cdot}HBF_4$ (0.012 g, 0.03 mmol), K_2CO_3 (0.087 g, 0.63 mmol). The residue was purified by flash chromatography (DCM) to afford compound

4a as a red solid (0.068 g, 82%), m.p. 187.0–189.4 °C. IR: 3100, 3000, 2954, 2922, 2845, 1929, 1697, 1600, 1487, 1467, 1435, 1411, 1388, 1328, 1260, 1201, 1182, 1163, 1087, 1052, 985, 838, 828, 857, 801, 770, 762, 750, 731, 682, 628, 599, 551, 520, 498, 463. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 8.60–8.52 (m, 1H), 8.09–8.02 (m, 1H), 7.54–7.48 (m, 2H), 7.27 (dt, J = 5.1, 2.6 Hz, 2H), 7.09 (td, J = 4.6, 2.5 Hz, 1H), 4.02 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ = 186.14(C), 152.54(C), 151.44(C), 147.18(C), 137.44(C), 134.10(C), 131.65(C), 130.51(CH), 127.62(CH), 126.51(CH), 125.69(CH), 125.62(C), 124.32(CH), 120.00(CH), 116.57(CH), 55.81(CH_3). LC/MS (retention time 4.72 min) m/z (ESI^+) 267.10 (MH^+, 100%), 289.10 (MNa^+, 7.7%). HRMS (ESI^+): m/z calcd for $C_{16}H_{11}O_2S^+$ [MH^+]: 267.0474; found: 267.0465.

9-Methoxy-6H-benzo[b]indeno[1,2-d]thiophen-6-one **4b**. According to general procedure C, scale: benzo[*b*]thiophen-2-yl(2-iodo-4-methoxyphenyl)methanone **6b** (0.165 g, 0.42 mmol), $Pd(OAc)_2$ (0.005 g, 0.02 mmol), $Cy_3P{\cdot}HBF_4$ (0.016 g, 0.04 mmol), K_2CO_3 (0.116 g, 0.84 mmol). The residue was purified by flash chromatography (DCM) to afford compound **4b** as an orange solid (0.098 g, 88%), m.p. 201.8–203.3 °C. IR: 3054, 998, 2352, 1890, 1719, 1691, 1599, 1499, 1467, 1428, 1413, 1383, 1293, 1270, 1241, 1222, 1165, 1147, 1072, 1019, 965, 942, 865, 856, 828, 770, 761, 730, 706, 691, 648, 667, 621, 509, 491, 482. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 8.38–8.36 (m, 1H), 8.14–8.05 (m, 1H), 7.58–7.53 (m, 2H), 7.42 (d, J = 8.1 Hz, 1H), 7.33 (d, J = 2.2 Hz, 1H), 6.73 (dd, J = 8.1, 2.2 Hz, 1H), 3.92 (s, 3H). 13C NMR (126 MHz, DMSO-d_6) δ = 186.97(C), 164.55(C), 150.28(C), 146.75(C), 141.56(C), 137.55(C), 131.13(C), 128.35(C), 127.47(CH), 125.99(CH), 125.32(CH), 124.55(CH), 124.11(CH), 110.26(CH), 109.00(CH), 55.75(CH_3). LC/MS (retention time 4.61 min) m/z (ESI^+) 267.10 (MH^+, 100%), 289.10 (MNa^+, 4.2%), 555.10 ($2MNa^+$, 3.5%). HRMS (ESI^+): m/z calcd for $C_{16}H_{10}O_2S^+$ [MH^+]: 267.0474; found: 267.0475.

8-Methoxy-6H-benzo[b]indeno[1,2-d]thiophen-6-one **4c**. According to general procedure C, scale: benzo[*b*]thiophen-2-yl(2-iodo-5-methoxyphenyl)methanone **6c** (0.197 g, 0.50 mmol), $Pd(OAc)_2$ (0.006 g, 0.03 mmol), $Cy_3P{\cdot}HBF_4$ (0.018 g, 0.05 mmol), K_2CO_3 (0.140 g, 1.01 mmol). The residue was purified by flash chromatography (DCM) to afford compound **4c** as a red solid (0.117 g, 88%), m.p. 159.4–161.0 °C. IR: 3092, 3059, 3013, 2951, 2842, 2328, 1696, 1618, 1593, 1494, 1468, 1435, 1387, 1330, 1288, 1261, 1221, 1191, 1157, 1139, 1086, 1057, 1019, 944, 909, 892, 832, 817, 770, 742, 726, 710, 681, 631, 573, 542, 500. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 8.32–8.25 (m, 1H), 8.09 (ddd, J = 7.1, 3.9, 3.0 Hz, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.55 (qt, J = 9.4, 5.5, 4.7 Hz, 2H), 7.02 (d, J = 2.4 Hz, 1H), 6.92 (dd, J = 8.0, 2.5 Hz, 1H), 3.81 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ = 186.10(C), 160.06(C), 153.77(C), 147.62(C), 138.48(C), 134.27(C), 131.29(C), 131.15(C), 128.28(CH), 126.29(CH), 124.97(CH), 124.69(CH), 121.48(CH), 116.39(CH), 112.01(CH), 55.72(CH_3). LC/MS (retention time 4.68 min) m/z (ESI^+) 267.10 (MH^+, 100.0%), 289.0 (MNa^+, 8.7%), 555.20 ($2MNa^+$, 3.6%). HRMS (ESI^+): m/z calcd for $C_{16}H_{10}O_2S^+$ [MH^+]: 267.0474; found: 267.0465.

7-Methoxy-6H-benzo[b]indeno[1,2-d]thiophen-6-one **4d**. According to general procedure C, scale: benzo[*b*]thiophen-2-yl(2-iodo-6-methoxyphenyl)methanone **6d** (0.056 g, 0.14 mmol), $Pd(OAc)_2$ (0.002 g, 0.01 mmol), $Cy_3P{\cdot}HBF_4$ (0.005 g, 0.02 mmol), K_2CO_3 (0.040 g, 0.28 mmol). The residue was purified by flash chromatography (DCM) to afford compound **4d** as an orange solid (0.025 g, 67%), m.p. 178.6–183.7 °C. IR: 3372, 3263, 3067, 3002, 2978, 2923, 2847, 2839, 1662, 1690, 1597, 1501, 1478, 1460, 1435, 1415, 1386, 1279, 1246, 1200, 1165, 1138, 1069, 1049, 975, 881, 851, 825, 794, 783, 774, 758, 732, 702, 681, 647, 580, 503. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 8.32–8.28 (m, 1H), 8.15–8.10 (m, 1H), 7.58–7.51 (m, 2H), 7.49 (dd, J = 8.7, 7.1 Hz, 1H), 7.43–7.35 (m, 1H), 7.02 (d, J = 8.6 Hz, 1H), 3.88 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ = 184.56(C), 157.22(C), 150.16(C), 146.80(C), 141.14(C), 137.09(CH), 136.81(C), 131.53(C), 127.69(CH), 126.37(CH), 125.02(CH), 124.20(CH), 120.00(C), 114.88(CH), 113.76(CH), 55.75(CH_3). LC/MS (retention time 4.20 min) m/z (ESI^+) 267.10 (MH^+, 100%), 289.00 (MNa^+, 13.0%), 555.10 ($2MNa^+$, 51.1%). HRMS (ESI^+): m/z calcd for $C_{16}H_{11}O_2S^+$ [MH^+]: 267.0474; found: 267.0474.

2-Methoxy-6H-benzo[b]indeno[1,2-d]thiophen-6-one **4e**. According to general procedure C, scale: (2-iodophenyl)(5-methoxybenzo[*b*]thiophen-2-yl)methanone **6e** (0.213 g, 0.54 mmol), $Pd(OAc)_2$ (0.006 g, 0.03 mmol), $Cy_3P{\cdot}HBF_4$ (0.020 g, 0.05 mmol), K_2CO_3 (0.151 g, 1.09 mmol). The residue was purified by flash chromatography (DCM) to afford compound **4e** as an orange solid (0.119 g, 83%), m.p. 168.7–170.7 °C. IR: 3062, 3049, 3000, 2956, 2931, 2826, 1719, 1688, 1606, 1502, 1455, 1435, 1419, 1378, 1331, 1310, 1287, 1272, 1232, 1204, 1188, 1130, 1074, 1058, 1023, 973, 936, 877, 857, 824, 810, 766, 758, 721, 696, 653, 615, 566, 540, 482. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.97 (d, J = 9.0 Hz, 1H), 7.80 (dt, J = 7.3, 0.8 Hz, 1H), 7.62 (d, J = 2.5 Hz, 1H), 7.47 (td, J = 7.5, 1.1 Hz, 1H), 7.42 (dt, J = 7.2, 0.9 Hz, 1H), 7.25 (ddd, J = 8.0, 7.2, 0.9 Hz, 1H), 7.17 (dd, J = 9.0, 2.5 Hz, 1H), 3.92 (s, 3H). 13C NMR (126 MHz, DMSO-d_6) δ = 186.49(C), 158.45(C), 152.05(C), 140.11(C), 139.36(C), 136.92(C), 136.23(C), 134.37(CH), 132.44(C), 128.43(CH), 125.65(CH), 123.55(CH), 120.66(CH), 118.89(CH), 105.55(CH), 55.76(CH_3). LC/MS (retention time 4.63 min) m/z (ESI^+) 267.10 (MH^+, 100%), 289.20 (MNa^+, 5.2%), 555.20 ($2MNa^+$, 1.9%). HRMS (ESI^+): m/z calcd for $C_{16}H_{10}NaO_2S^+$ [MNa^+]: 289.0294; found: 289.0299.

2,10-Dimethoxy-6*H*-benzo[*b*]indeno[1,2-*d*]thiophen-6-one 4f. According to general procedure C, scale: (2-iodo-3-methoxyphenyl)(5-methoxybenzo[*b*]thiophen-2-yl)methanone **6f** (0.116 g, 0.27 mmol), $Pd(OAc)_2$ (0.003 g, 0.02 mmol), $Cy_3P{\cdot}HBF_4$ (0.010 g, 0.03 mmol), K_2CO_3 (0.076 g, 0.55 mmol). The residue was purified by flash chromatography (DCM) to afford compound **8** cycle as a red solid (0.070 g, 86%), m.p. 198.0–205.8 °C. IR: 3122, 2981, 2943, 2918, 2899, 2838, 1728, 1690, 1599, 1491, 1444, 1414, 1376, 1337, 1307, 1266, 1224, 1199, 1180, 1160, 1123, 1064, 1027, 973, 927, 851, 815, 799, 742, 679, 640, 569, 550, 485. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 8.07 (d, J = 2.6 Hz, 1H), 7.90 (d, J = 8.9 Hz, 1H), 7.31–7.23 (m, 2H), 7.14 (dd, J = 8.9, 2.6 Hz, 1H), 7.09 (q, J = 4.6, 4.0 Hz,

1H), 4.03 (s, 3H), 3.89 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ = 186.04(C), 157.65(C), 151.93(C), 151.21(C), 139.85(C), 137.40(C), 135.15(C), 132.76(C), 130.30(CH), 125.68(C), 124.88(CH), 119.86(CH), 118.26(CH), 116.56(CH), 107.63(CH), 55.91(CH_3), 54.94(CH_3). LC/MS (retention time 4.76 min) *m*/*z* (ESI^+) 297.10 (MH^+, 100%), 319.00 (MNa^+, 9.6%), 615.20 ($2MNa^+$, 15.5%). HRMS (ESI^+): *m*/*z* calcd for $C_{17}H_{13}O_3S^+$ [MH^+]: 297.0580; found: 297.0578.

2,9-Dimethoxy-6*H*-benzo[*b*]indeno[1,2-*d*]thiophen-6-one 4g. According to general procedure C, scale: (2-iodo-4-methoxyphenyl)(5-methoxybenzo[*b*]thiophen-2-yl)methanone **6g** (0.169 g, 0.40 mmol), $Pd(OAc)_2$ (0.005 g, 0.02 mmol), $Cy_3P{\cdot}HBF_4$ (0.015 g, 0.04 mmol), K_2CO_3 (0.114 g, 0.82 mmol). The residue was purified by flash chromatography (DCM) to afford compound **4g** as an orange solid (0.100 g, 84%), m.p. 194.2–196.0 °C. IR: 3106, 3070, 3019, 2983, 2926, 2902, 2861, 2826, 2358, 2326, 1694, 1595, 1500, 1452, 1439, 1409, 1369, 1341, 1312, 1282, 1237, 1204, 1169, 1147, 1122, 1084, 1061, 1018, 976, 913, 851, 822, 813, 807, 793, 760, 737, 700, 691, 664, 655, 632, 619, 565, 509, 484. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 7.93 (d, *J* = 9.0 Hz, 1H), 7.58 (d, *J* = 2.5 Hz, 1H), 7.35 (d, *J* = 8.1 Hz, 1H), 7.30 (d, *J* = 2.2 Hz, 1H), 7.13 (dd, *J* = 9.0, 2.5 Hz, 1H), 6.66 (dd, *J* = 8.1, 2.2 Hz, 1H), 3.90 (s, 3H), 3.87 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ = 184.70(C), 164.42(C), 158.23(C), 149.42(C), 141.39(C), 139.27(C), 138.62(C), 132.16(C), 128.34(C), 125.01(CH), 124.97(CH), 117.75(CH), 109.61(CH), 109.17(CH), 105.81(CH), 55.51(2 × CH_3). LC/MS (retention time 4.66 min) *m*/*z* (ESI^+) 297.10 (MH^+, 100%), 319.00 (MNa^+, 4.9%), 615.10 ($2MNa^+$, 11.9%). HRMS (ESI^+): *m*/*z* calcd for $C_{17}H_{13}O_3S^+$ [MH^+]: 297.0580; found: 297.0580.

2,8-Dimethoxy-6*H*-benzo[*b*]indeno[1,2-*d*]thiophen-6-one 4h. According to general procedure C, scale: (2-iodo-5-methoxyphenyl)(5-methoxybenzo[*b*]thiophen-2-yl)methanone **6h** (0.164 g, 0.39 mmol), $Pd(OAc)_2$ (0.004 g, 0.02 mmol), $Cy_3P{\cdot}HBF_4$ (0.014 g, 0.04 mmol), K_2CO_3 (0.108 g, 0.78 mmol). The residue was purified by flash chromatography (DCM) to afford compound **4h** as a brown solid (0.080 g, 70%), m.p. 192.4–193.9 °C. IR: 3383, 2975, 3956, 2935, 2877, 2850, 2826, 1885, 1720, 1700, 1606, 1502, 1487, 1469, 1458, 1445, 1432, 1416, 1375, 1328, 1310, 1278, 1269, 1234, 1200, 1132, 1073, 1057, 1020, 971, 884, 833, 822, 809, 787, 768, 761, 738, 657, 645, 583, 580, 541, 474. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 7.94 (d, *J* = 9.0 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.55 (d, *J* = 2.5 Hz, 1H), 7.15 (dd, *J* = 9.0, 2.5 Hz, 1H), 6.97 (d, *J* = 2.5 Hz, 1H), 6.88 (dd, *J* = 8.0, 2.5 Hz, 1H), 3.90 (s, 3H), 3.80 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ = 185.47(C), 159.73(C), 158.16(C), 152.54(C), 139.96(C), 138.18(C), 135.18(C), 131.96(C), 131.23(C), 125.04(CH), 120.91(CH), 118.25(CH), 116.37(CH), 111.40(CH), 105.90(CH), 55.47(CH_3), 55.38(CH_3). LC/MS (retention time 4.73 min) *m*/*z* (ESI^+) 297.10 (MH^+, 100%), 319.00 (MNa^+, 9.1%), 616.10 ($2MNa^+$, 13.7%). HRMS (ESI^+): *m*/*z* calcd for $C_{17}H_{13}O_3S^+$ [MH^+]: 297.0580; found: 297.0574.

*2-Hydroxy-6H-benzo[b]indeno[1,2-d]thiophen-6-one **4i**.* According to general procedure C, scale: (5-((*tert*-butyldimethylsilyl)oxy) benzo[*b*]thiophen-2-yl)(2-iodophenyl)methanone **6i** (0.235 g, 0.48 mmol), $Pd(OAc)_2$ (0.005 g, 0.02 mmol), $Cy_3P{\cdot}HBF_4$ (0.018 g, 0.05 mmol), K_2CO_3 (0.132 g, 0.96 mmol). The residue was purified by flash chromatography (DCM/MeOH: 99/1) to afford compound **4i** as a red solid (0.088 g, 74%), m.p. 265.4–270.8 °C. IR: 3372, 3321, 3054, 2921, 2847, 2328, 1720, 1680, 1607, 1504, 1455, 1424, 1402, 1364, 1328, 1279, 1237, 1201, 1141, 1130, 1075, 1056, 980, 883, 859, 848, 818, 802, 788, 759, 724, 694, 654, 614, 563, 543, 512. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 9.95 (s, 1H), 7.90 (d, *J* = 8.9 Hz, 1H), 7.57 (dt, *J* = 7.3, 0.8 Hz, 1H), 7.53 (d, *J* = 2.4 Hz, 1H), 7.48 (td, *J* = 7.5, 1.1 Hz, 1H), 7.43 (dt, *J* = 7.2, 0.9 Hz, 1H), 7.28–7.23 (m, 1H), 7.09 (dd, *J* = 8.9, 2.4 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ = 186.55(C), 156.48(C), 151.75(C), 139.55(C), 138.64(C), 136.74(C), 136.34(C), 134.50(CH), 132.72(C), 128.37(CH), 125.66(CH), 123.61(CH), 120.03(CH), 119.02(CH), 108.27(CH). LC/MS (retention time 3.71 min) *m*/*z* (ESI^+) 253.00 (MH^+, 100%), 275.00 (MNa^+, 14.2%), 527.00 ($2MNa^+$, 5.0%). HRMS (ESI^+): *m*/*z* calcd for $C_{15}H_9O_2S^+$ [MH^+]: 253.0318; found: 253.0325.

*2-Hydroxy-9-methoxy-6H-benzo[b]indeno[1,2-d]thiophen-6-one **4j**.* According to general procedure C, scale: (5-((*tert*-butyldimethylsilyl)oxy)benzo[*b*]thiophen-2-yl)(2-iodo-4-methoxyphenyl)methanone **6j** (0.141 g, 0.27 mmol), $Pd(OAc)_2$ (0.003 g, 0.02 mmol), $Cy_3P{\cdot}HBF_4$ (0.010 g, 0.03 mmol), K_2CO_3 (0.074 g, 0.54 mmol). The residue was purified by flash chromatography (DCM/MeOH: 99/1) to afford compound **4j** as a brown solid (0.060 g, 79%), m.p. 288.8–292.4 °C. IR: 3345, 3226, 3008, 2925, 2850, 2828, 1673, 1601, 1504, 1460, 1417, 1363, 1343, 1298, 1242, 1198, 1181, 1156, 1143, 1131, 1074, 1056, 1024, 982, 926, 846, 802, 765, 739, 699, 662, 624, 603, 567, 506, 487. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 9.89 (s, 1H), 7.88 (d, *J* = 8.9 Hz, 1H), 7.55 (d, *J* = 2.3 Hz, 1H), 7.37 (d, *J* = 8.1 Hz, 1H), 7.10 (d, *J* = 2.2 Hz, 1H), 7.07 (dd, *J* = 8.9, 2.4 Hz, 1H), 6.68 (dd, *J* = 8.1, 2.2 Hz, 1H), 3.89 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d$_6$) δ = 185.43(C), 164.59(C), 156.42(C), 149.58(C), 141.96(C), 138.55(C), 138.10(C), 132.70(C), 128.53(C), 125.62(CH), 125.54(CH), 118.57(CH), 110.15(CH), 108.68(CH), 108.23(CH), 55.96(CH_3). LC/MS (retention time 3.77 min) *m*/*z* (ESI^+) 283.00 (MH^+, 100%), 305.10 (MNa^+, 7.1%), 587.10 ($2MNa^+$, 17.2%). HRMS (ESI^+): *m*/*z* calcd for $C_{16}H_{11}O_3S^+$ [MH^+]: 283.0423; found: 283.0421.

*2-Hydroxy-8-methoxy-6H-benzo[b]indeno[1,2-d]thiophen-6-one **4k**.* According to general procedure C, scale: (5-((*tert*-butyldimethylsilyl)oxy)benzo[*b*]thiophen-2-yl)(2-iodo-5-methoxyphenyl)methanone **6k** (0.195 g, 0.37 mmol), $Pd(OAc)_2$ (0.004 g, 0.02 mmol), $Cy_3P{\cdot}HBF_4$ (0.014 g, 0.04 mmol), K_2CO_3 (0.103 g, 0.74 mmol). The residue was purified by flash chromatography (DCM/MeOH: 99/1) to afford compound **4k** as a dark brown solid (0.060 g, 57%), m.p. 224–229.7 °C. IR: 3319, 3002, 2962, 2397, 2921, 2853, 2834, 2350, 1906, 1700, 1674, 1621, 1600, 1498, 1471, 1462, 1421, 1363, 1338, 1260, 1242, 1222, 1198, 1189, 1140, 1056, 1029, 979, 926, 917, 880, 848, 823, 808, 796, 770, 741, 693, 657, 647, 625, 576, 512. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.92 (s, 1H), 7.87 (d, *J* = 8.9 Hz, 1H), 7.48 (d, *J* = 2.3 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.08 (dd, *J* = 8.9, 2.4 Hz, 1H), 7.00 (d, *J* = 2.5 Hz, 1H), 6.92 (dd, *J* = 8.1, 2.5 Hz, 1H), 3.80 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ = 186.12(C), 159.86(C), 156.35(C), 152.78(C), 138.77(C), 138.52(C), 135.12(C), 132.49(C), 131.51(C), 125.59(CH), 120.87(CH), 119.06(CH), 116.35(CH), 112.01(CH), 108.35(CH), 55.69(CH_3). LC/MS (retention time 3.86 min) *m*/*z* (ESI^+)

283.00 (MH^+, 100%), 305.00 (MNa^+, 10.3%). HRMS (ESI^+): *m/z* calcd for $C_{16}H_{11}O_3S^+$ [MH^+]: 283.0423; found: 283.0429.

2-Hydroxy-7-methoxy-6H-benzo[b]indeno[1,2-d]thiophen-6-one ***4l.*** According to general procedure C, scale: (5-((*tert*-butyldimethylsilyl) oxy)benzo[*b*]thiophen-2-yl)(2-iodo-6-methoxyphenyl)methanone **6l** (0.050 g, 0.10 mmol), $Pd(OAc)_2$ (0.001 g, 0.01 mmol), $Cy_3P{\cdot}HBF_4$ (0.004 g, 0.01 mmol), K_2CO_3 (0.026 g, 0.19 mmol). The residue was purified by flash chromatography (DCM/MeOH: 99/1) to afford compound **4l** as a brown solid (0.014 g, 51%), m.p. 264.7–269.9 °C. IR: 3369, 3324, 3097, 3065, 2924, 2853, 1739, 1683, 1600, 1508, 1468, 1424, 1361, 1341, 1288, 1254, 1231, 1177, 1160, 1135, 1077, 1053, 994, 930, 867, 855, 790, 782, 733, 692, 676, 652, 583, 528, 511. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 9.91 (s, 1H), 7.90 (dd, J = 8.9, 3.5 Hz, 1H), 7.51 (d, J = 2.2 Hz, 1H), 7.51–7.48 (m, 1H), 7.21 (d, J = 7.0 Hz, 1H), 7.08–7.05 (m, 1H), 7.03 (d, J = 8.7 Hz, 1H), 3.89 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ = 184.77(C), 157.38(C), 156.60(C), 149.37(C), 141.53(C), 138.01(C), 137.80(C), 137.27(CH), 133.03(C), 125.82(CH), 120.20(C), 118.54(CH), 114.82(CH), 113.37(CH), 108.17(CH), 55.90(CH_3). LC/MS (retention time 3.33 min) *m/z* (ESI^+) 283.10 (MH^+, 100%), 305.10 (MNa^+, 10.4%), 587.20 ($2MNa^+$, 47.4%). HRMS (ESI^+): *m/z* calcd for $C_{16}H_{11}O_3S^+$ [MH^+]: 283.0423; found: 283.0425.

2-Fluoro-8-methoxy-6H-benzo[b]indeno[1,2-d]thiophen-6-one ***4m.*** Following general procedure C, scale: (5-fluorobenzo[*b*] thiophen-2-yl)(2-iodo-5-methoxyphenyl)methanone **6m** (0.139 g, 0.34 mmol), $Pd(OAc)_2$ (0.004 g, 0.02 mmol), $Cy_3P{\cdot}HBF_4$ (0.013 g, 0.04 mmol), K_2CO_3 (0.097 g, 0.70 mmol). The residue was purified by flash chromatography (DCM) to afford compound **4m** as a purple solid (0.083 g, 87%), m.p. 196.6–198.7 °C. IR: 3092, 3032, 2994, 2956, 1703, 1618, 1599, 1499, 1468, 1438, 1418, 1371, 1333, 1288, 1260, 1225, 1181, 1143, 1120, 1056, 1016, 976, 922, 876, 854, 820, 797, 768, 740, 653, 640, 573, 504. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.16–8.07 (m, 2H), 7.74–7.67 (m, 1H), 7.42 (tdt, J = 9.1, 2.2, 1.0 Hz, 1H), 7.04 (dt, J = 2.9, 1.5 Hz, 1H), 6.94 (ddt, J = 8.0, 2.5, 1.2 Hz, 1H), 3.83 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ = 185.58(C), 160.83(C, J = 243.2 Hz), 159.93(C), 152.70(C, J = 5.0 Hz), 143.03(C), 137.89(C), 136.56(C), 131.78 (C, J = 10.1 Hz), 130.88(C), 126.38(CH, J = 8.8 Hz), 121.32(CH), 116.55(CH, J = 26.5 Hz), 116.54(CH), 111.78(CH), 109.52(CH, J = 22.7 Hz), 55.52(CH_3), ^{19}F NMR (471 MHz, DMSO-d_6) δ = −115.51 (td, J = 9.0, 4.7 Hz). LC/MS (retention time 4.77 min) *m/z* (ESI^+) 285.10 (MH^+, 100%), 307.10 (MNa^+, 24.3%), 591.10 ($2MNa^+$, 6.0%). HRMS (ESI^+): *m/z* calcd for $C_{16}H_9FO_2S^+$ [MH^+]: 285.0386; found: 285.0387.

Biological evaluations

DYRK1A/DYRK1B kinases inhibition assays. Human Dyrk1A was expressed and purified as described earlier.[48] Dyrk1B were purchased from Life Technologies.[50] Woodtide substrate peptide for Dyrk1A and Dyrk1B (KKISGRLSPIMTEQ) were custom synthesized at the Department of Medical Biochemistry and Molecular Biology, Saarland University, Homburg, Germany. Kinase inhibition assays for Dyrk1A and Dyrk1B were performed as described previously, in the presence of 15 mM ATP.[48] The calculated IC_{50} values are representative of at least two independent determinations and 3,3′-(2,4-thienediyl)dipyridine was used as the positive control.

The larger panel of kinases shown in Table 2 was screened by the SelectScreen Kinase Profiling Service, Thermo Fisher Scientific, Madison, USA and the Kinase Profiler service, Eurofins/CEREP Celle L'Evescault, France. For each kinase, ATP concentrations were set at ATP Km.

Cell viability of compounds – MTT protocol. Cell viability is evaluated through the MTT colorimetric assay. The MTT assay is based on protocol described by Mosmann.[92] The assay was optimized for cell line used in the experiment. U-87MG cells or U373MG cells (human malignant gliomas, respectively HTB14 and HTB17 ATCC) are plated at a density of 10 000 cells per well into 96 well culture plates. Cells are incubated overnight at 37 °C in 5% CO_2 in MEM (modified Eagle's medium) media supplemented with 10% FBS (fetal bovine serum). The following day, cells are treated in triplicated with the compounds (1–200 μM) in 1% DMSO or with vehicle control (1% DMSO). After 72 h, the cells are incubated with 20 μL of MTT at 5 mg mL^{-1} (Sigma Aldrich M2128) for 3 h at 37 °C. The medium is the removed and 100 μl of 0.1 N HCl in isopropanol is added in each well for 15 min. Absorbance is measured by a plate reader at 570 nm and the value measured at 690 nm was subtracted. Data are the mean ± SD of at least three independent experiments.

Microsomal stability assays. Protocol for metabolic stability was adapted from different published procedures.[93–95]

Compounds (10 μM) were preincubated with phosphate buffer (pH 7.4, 0.1 M) and rat liver microsomes (0.15 mg) for 10 min at 37 °C then NADPH (1 mM) was added to start the reaction. Final concentration of DMSO was 0.5% and total reaction volume was 500 μL. Aliquots (50 μL) were taken at desired timepoints (0, 5, 15, 30, 45, 60 min) and diluted with a solution of cold acetonitrile to stop the reaction (100 μL, containing 0.5 mg mL^{-1} BHT as internal standard). After centrifugation, supernatants were analyzed by gradient UHPLC-MS method using Agilent 1290 series (Agilent POROSHELL 120 SB-C18 column, 2.7 μm, 2.1 × 50 mm) with the following parameters: injection volume: 10 μl, flow rate: 0.5 mL min^{-1}, column temperature: 30 °C, solvents: A (0.1% HCO_2H in ACN) and B (0.1% HCO_2H in H_2O), t = 0–0.5 min, 10% A; t = 0.5–5.5 min, 10 → 90% A then t = 5.5–6 min, 90% A. Areas recorded at 254 nm were ratioed with internal standard peak area (BHT). Remaining compound was ratioed with t = 0 peak area and the natural logarithm of the remaining compound ratio was plotted against time. Linear fit of the curve allowed us to determine $t_{1/2}$ for tested compound and microsomal intrinsic clearance (CL_{int}, in μL min^{-1} mg^{-1} protein) was calculated using this equation as previously described:

$$CL_{int} = \frac{0.693 \times (\text{incubation volume})}{t_{1/2} \times (\text{mg microsomal protein})}$$

***In silico* docking studies.** Each protein (DYRK1A (PDB ID: 5AIK), CLK1 (PDB ID: 6RAA), CLK4 (PDB ID: 6FYV), haspin (PDB ID: 3IQ7)) has been setup and protonated (pH = 7) using MOE software (Molecular Operating Environment, 2022.2). The docking procedures were performed with GOLD software (version 2020.2.0) using the HERMES interface. GOLD scores have been optimized following variation of different parameters (solvated/unsolvated protein, co-crystallized structure origin, scoring and rescoring algorithms (Chemscore, Goldscore, PLP)).

The following parameters has showed the best correlations between biologics assays and fitness scoring: using protonated, unsolvated unminimized protein with a spherical site (10 Å radius) centered on the previously co-crystallized ligands, the GOLD template chemscore_kinase, Goldscore scoring and chemscore rescoring without using the "allow termination" option with a genetic algorithm (GA) search efficiency 100%.

Data were extracted as ".csv" extension and computed with excel.

Best and consistent results were extracted as "mol2" extension complexes and visualized with PyMOL (1.8.6.2) and MOE softwares to generate superposition, ligand interactions and images generation.

Data availability

The data used for the manuscript entitled "Design, synthesis, and structure–activity relationship studies of 6*H*-benzo[*b*] indeno[1,2-*d*]thiophen-6-one derivatives as DYRK1A/CLK1/CLK4/haspin inhibitors" will be included in a ESI† file, available online on *RSC Medicinal Chemistry* web site.

Author contributions

Conceptualization: TL and RB. Formal analysis: TL and ME. Funding acquisition: TL and FH. Investigation: AF, AA, FH, JR, MA, VD, CVD, AM, MS, AE, T-NP, AB. Methodology: TL, RB and ME. Project administration: TL. Resources: TL, MLB, RT. Supervision: TL. Validation: TL and AA. Visualization: TL, VD, JR and FH. Writing – original draft: TL, VD and FH. Writing – review & editing: FH, ME, AF and TL.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

AF and JR thank the Ministère de l'Enseignement Supérieur, de la Recherche et de l'innovation for PhD fellowships. CVD would like to thank the University of Science and Technology of Hanoi (USTH) for a PhD fellowship. FH thanks the Université Claude Bernard Lyon 1 (SENS 2022) and Agence Nationale de la Recherche (ANR-22-CE18-0004 – SINGE) for financial support. The Common Centre of Mass Spectrometry CCSM and Common Centre of NMR CCRMN of CNRS UMR 5246 research unit are gratefully acknowledged for the promptness and accuracy of their analyses.

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