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Synthesis, Skeletal Rearrangement, and Biological Activities of Spirooxindoles: Exploration of a Stepwise *C*-Piancatelli Rearrangement

Li Huang,[a] Xiaoyu Zhang,[a] Jing Li,[b] Ke Ding,[c] Xuehui Li,[a] Wenxu Zheng,*[b] and Biaolin Yin*[a]

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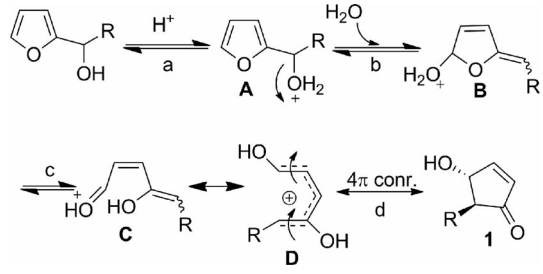
Based on our previous studies, the scope of the transformation of 2-furylcarbinols into spirofurooxindoles, and also the skeletal rearrangements of spiro[furo-oxindoles] and spiro-[thieno-oxindoles] were studied. The spiro[furo-oxindoles] thermally rearranged into spiro[pentenone-oxindoles] by a mechanism involving the conrotatory electrocyclization of the 4π-electron system. The free energy of the electrocyclization step was calculated to interpret the stereochemical outcomes. In contrast, the spiro[thieno-oxindoles] were rearranged under acidic conditions into thieno[2,3-*c*]quinolin-4-ones, involving an interesting dienone–phenol-like mechanism. The transformation of 2-furylcarbinols into spiro[pentenone-oxindoles] seems to be the first stepwise *C*-Piancatelli rearrangement. The spirooxindole products were biologically evaluated, and some of them showed promising cytotoxic activities against DU145 and LNCaP tumor cell lines.

Introduction

In 1976, Piancatelli et al. reported an acid-catalysed rearrangement (the so-called Piancatelli rearrangement) of suitable 2-furylcarbinols into 4-hydroxycyclopentenone derivatives.[1] The mechanism of this rearrangement has not been fully studied, but it is widely believed to proceed by a thermal conrotatory electrocyclization of the 4π-electron system.[2] The key steps include (Scheme 1): (a) protonation of the hydroxy group of α-furylcarbinols to form intermediate **A**; (b) nucleophilic attack at the other α position of the furan ring to form dienyl enol ether **B**; (c) ring-opening; and (d) thermal electrocyclization of the 4π-electron system **D** to form cyclopentenones **1**. Although the Piancatelli rearrangement has been used as a key step in the construction of a series of natural products and biologically active molecules such as the prostaglandins,[3] this reaction originally had limited synthetic applications, because it usually requires a stoichiometric amount of acid, and dilute aqueous reaction conditions. For the intensive exploitation of furan derivatives as green, renewable building blocks for organic synthesis,[4] it would be desirable to find new reaction conditions for the Piancatelli rearrangement. First, we envisioned that by studying the intramolecular Piancatelli rearrangement, we might be able to avoid the requirement of dilute reaction conditions with excessive water, so opening up a general route to spiro-heterocyclic compounds. Secondly, using carbon nucleophiles to trap oxacarbenium species **B** would be interesting for the construction of spiro *C*-skeletons (*C*-Piancatelli rearrangement). Thirdly, replacing the furan ring of α-furylcarbinols by a thiophene or other five-membered aromatic ring would lead to numerous new heterocyclic compounds.



Scheme 1. Proposed mechanism of the Piancatelli reaction. conr. = conrotatory.

Heterocyclic spirooxindoles **2** (Figure 1) have attracted much attention due to their significant biological activities.[5] A literature search revealed that their biological activities are usually associated with the structural features of their B rings. For example, compound **3,** with a pyrrolidine B-ring, is an inhibitor of the MDM2–p53 interaction.[6] Compound **4** has an isoxazolidine as its B-ring, and it shows potent cytotoxic effects against the A431 human epi-

[a] School of Chemistry and Chemical Engineering, South China University of Technology,
Guangzhou, Guangdong 510640, China
E-mail: blyin@scut.edu.cn
http://www.scut.edu.cn/ce/
[b] College of Science, South China Agricultural University,
Guangzhou, Guangdong 510640, China
E-mail: wzheng@scau.edu.cn
http://www.scau.edu.cn
[c] Guangzhou Institute of Biomedicine and Health, Chinese Academy of Sciences,
Guangzhou, Guangdong 510530, China

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dermoid carcinoma cell line.[7] In contrast, compounds **5** and **6** show significant inhibition of the growth of the MCF-7 human breast cancer cell line[8] and A549 lung adenocarcinoma cells,[9] respectively.

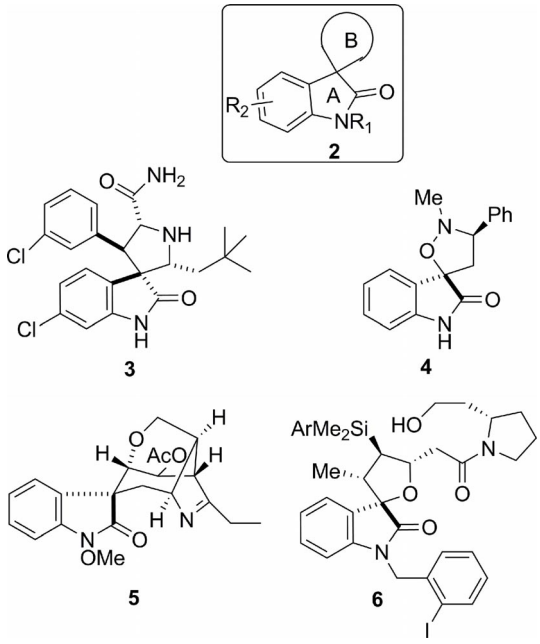


Figure 1. Biologically active spirooxindoles with various B-rings.

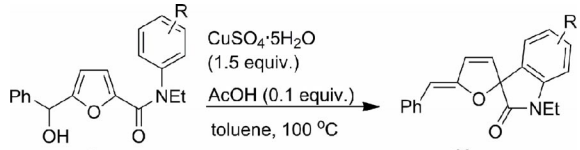
Accordingly, it would be desirable to develop methods that might lead to structural diversity in the B-ring of spirooxindoles **2**, starting from readily available materials.[10] Recently, we used the electron-rich *N*-aromatic ring of 2-furylcarbinol **8a** as an intramolecular nucleophile to trap the oxacarbenium in **9a**, which resulted in carbocyclization to give efficient access to spirofurooxindole **10a**.[11a] In addition, we also found that 2-thienylcarbinols **8b** were transformed into spirothienooxindoles **10b** in a similar fashion,[11b] and also that **10a** can undergo a skeletal rearrangement to provide spiropentenoneoxindoles **11a** by a 4π-electrocyclization mechanism.[11c] Through these studies, a library of new spirooxindoles with diverse B-rings with potent biological activities was established (Scheme 2). In this paper, we report the results of our studies of the scope of the stepwise *C*-Piancatelli rearrangement reaction, the mechanism of the transformation of **8** into **10**, the scope of the rearrangement of **10a** into **11a**, theoretical studies to support the mechanism, the rearrangement of **10b**, and the anti-tumor activities of the spirooxindole products.

Results and Discussion

1.1. The Reaction Scope of the Transformation of 8a into 10a

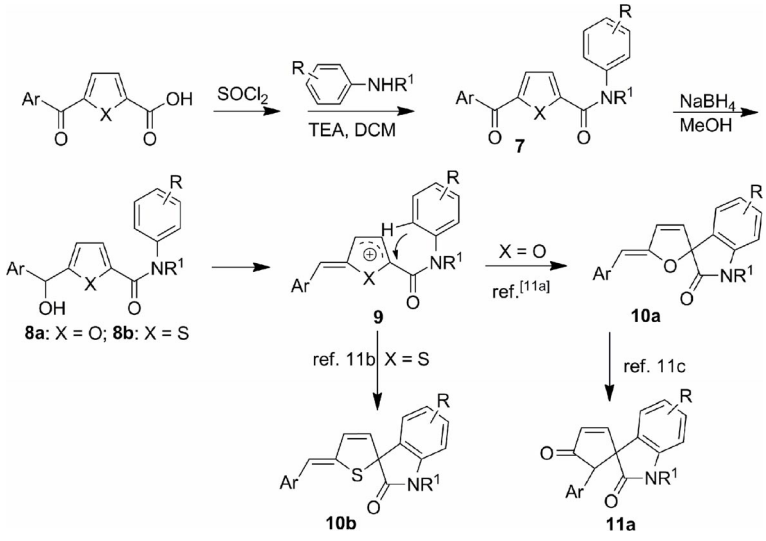
First, various 2-furylcarbinols **8a** with different R groups were tested to investigate the reaction scope under the optimized conditions previously reported [namely $CuSO_4·5H_2O$ (1.5 equiv.) and AcOH (0.1 equiv.) in toluene at 100 °C for 5 h]. The results are listed in Table 1. Similarly to other

Table 1. Scope of the reaction of **8a** with different R groups.[a,b]



Entry	8	R	10	Yield[c] [%]
1	**8a-1**	3,4,5-tri-MeO	**10a-1**	85
2	**8a-2**	3,5-di-MeO	**10a-2**	83
3	**8a-3**	3,4-di-MeO	**10a-3**	66
4	**8a-4**	3,5-di-Me	**10a-4**	46
5	**8a-5**	3-MeO	**10a-5**	57
6	**8a-6**	4-MeO	**10a-6**	n.d.
7	**8a-7**	H	**10a-7**	n.d.

[a] All reactions were performed on a 0.3 mmol scale. [b] Entries 1–7 have been presented in ref.[11a] [c] Isolated yield. n.d.: not detected.

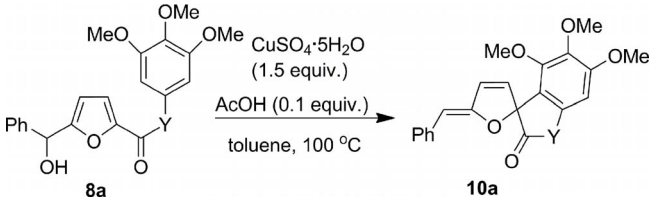


Scheme 2. Strategy for the synthesis of spirooxindoles.

Friedel–Crafts reactions, the electron density of the *N*-phenyl ring apparently influenced the yields. A higher electron density at the *ortho* positions of the phenyl ring bonded to the amino group generally led to higher yields (**8a-1** > **8a-2** > **8a-3** > **8a-4** > **8a-7**). The failure of the reactions of **8a-6** and **8a-7** may have resulted from the low electron density (Table 1, entries 6 and 7).

Next, different Y groups were screened (Table 2). When Y was NMe or NBn, the desired product (i.e., **10a-8** or **10a-9**, respectively) was obtained (Table 2, entries 8 and 9). The fact that **10a-9** was formed in a lower yield than **10a-8** or **10a-1** was possibly due to the steric hindrance of the Bn group being larger than that of Me or Et. Without *N*-protection (Y = NH; Table 2, entry 4) a complex reaction mixture was obtained. If Y was NCbz, $NEtCH_2$, or O, none of the desired product was isolated, but most of the starting material (i.e., **8a**) was recovered (Table 2, entries 5–7). These failures implied that a less strongly electron-withdrawing carbonyl group at the C-5 position of the furan ring would be beneficial to the stability of the carbocation and thus to the cyclization of **8a** into **10a**.

Table 2. Scope of the reaction of **8a** with different Y groups.[a]

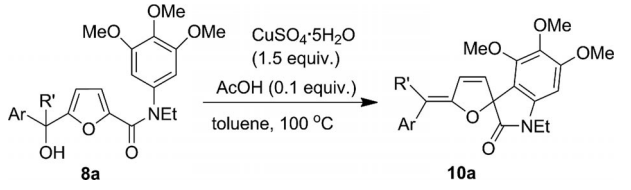


Entry	8	Y	10	Yield[b] [%]
1	**8a-1**	NEt	**10a-1**	85
2	**8a-8**	NMe	**10a-8**	88
3	**8a-9**	NBn	**10a-9**	50
4	**8a-10**	NH	**10a-10**	n.d.
5	**8a-11**	NCBz	**10a-11**	n.d.
6	**8a-12**	$NEtCH_2$	**10a-12**	n.d.
7	**8a-13**	O	**10a-13**	n.d.

[a] All reactions were performed on a 0.3 mmol scale. [b] Isolated yield. n.d.: not detected.

Finally, various Ar groups were also screened. As shown in Table 3, the electronic properties and resonance stabilization of the Ar groups apparently influenced the cyclization. Lower yields of the products were obtained when Ar was a phenyl group with one or more strongly electron-donating methoxy groups (Table 3, entries 2 and 3). It was inferred that more strongly electron-donating groups would result in a more reactive carbenium ion, thus leading to polymerization of the furan ring. In contrast, when Ar was substituted with a weakly electron-donating methyl group or an electron-withdrawing group, the products (i.e., **10a**) were produced in good to excellent yields (Table 3, entries 4–10). Interestingly, when Ar was a 1-naphthyl group (Table 3, entry 11), the products were formed as a mixture of two rotamers, possibly due to a lack of free rotation about the naphthyl–CH= linkage.[12] If Ar was an electron-rich 2-furyl group, a complex reaction mixture was obtained, and none of the desired product was observed (Table 3, entry 12). The cause of this failure might be the instability of the furan ring under the acidic conditions and low resonance stabilization of the furan ring. Similarly, when Ar was a 2-thienyl group, compound **10a-25** was formed in a very low yield, due to its resonance stabilization being lower than that of a phenyl ring (Table 3, entry 13). Negative results were obtained when R^1 was a vinyl group or an unstable phenylethynyl group (Table 3, entries 14 and 15). Due to their high resonance stabilizations, when both Ar and R′ were phenyl groups, the desired product (i.e., **10a-38**) was obtained in a fairly good yield (Table 3, entry 16).

Table 3. Scope of the reaction of **8a** with different Ar groups.[a,b]



Entry	8	Ar	10	Yield[c] [%]
1	**8a-1**	Ph	**10a-1**	85
2	**8a-14**	4-MeO–Ph	**10a-14**	33
3	**8a-15**	2,4-di-MeO–Ph	**10a-15**	trace
4	**8a-16**	2,6-di-Me–Ph	**10a-16**	75
5	**8a-17**	2-Me–Ph	**10a-17**	76
6	**8a-18**	4-Cl–Ph	**10a-18**	92
7	**8a-19**	2-Cl–Ph	**10a-19**	85
8	**8a-20**	2-F–Ph	**10a-20**	87
9	**8a-21**	2-Br–Ph	**10a-21**	80
10	**8a-22**	4-NO_2–Ph	**10a-22**	85
11	**8a-23**	1-naphthyl	**10a-23**	87[d] (5:1)
12	**8a-24**	2-furyl	**10a-24**	n.d.
13	**8a-25**	2-thienyl	**10a-25**	25
14	**8a-26**	CH_2=CH	**10a-26**	n.d.
15	**8a-27**	phenylthienyl	**10a-27**	n.d.
16[e]	**8a-28**	Ph	**10a-28**	87

[a] Unless otherwise noted, R′ = H. All reactions were performed on a 0.3 mmol scale. [b] Entries 1, 2, 7, 10, and 11 have been presented in ref.[11a] [c] Isolated yield. [d] Ratio in parentheses based on ^{1}H NMR spectroscopy. [e] R′ = Ph. n.d.: not detected.

1.2. Explorations into the Role of the Acid Cocatalyst for the Transformation of 8 into 10

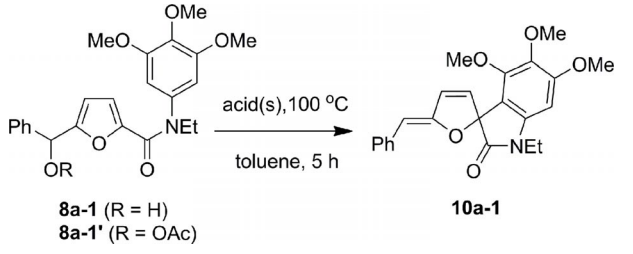
In principle, the transformation of **8a-1** into **10a-1** can be conceptually viewed as a special intramolecular Friedel–Crafts reaction using the oxocarbenium ion as the alkylating agent. Usually, harsh reaction conditions, including strong-acid catalysts, are required for this reaction.[13] However, a series of strong Lewis acids such as $TiCl_4$, $SnCl_4$, and $BF_3{\cdot}Et_2O$ were not suitable for the transformation of **8a-1** into **10a-1**, as they led to complex reaction mixtures. Weaker Brønsted or Lewis acids, i.e., CSA (camphorsulfonic acid), PTSA (*para*-toluenesulfonic acid), AcOH, $Yb(OTf)_3$, $AlCl_3$, and $ZnCl_2$ were also ineffective. To eluci-

date the role of the acid cocatalyst ($CuSO_4·5H_2O$/AcOH) and gain further insights into the mechanism, some control experiments were conducted. As shown in Table 4, when $CuSO_4·5H_2O$ (1.5 equiv.) was used as a promoter, **8a-1′** (derived from *O*-acetylation of **8a-1**) was hardly transformed into **10a-1** (Table 4, entry 1), which implied that the role of AcOH might not be to facilitate formation of the carbenium ion by transforming the hydroxy group into an acetoxy group, a better leaving group. The reaction did not take place in the presence of AcOH alone (Table 4, entry 2). More strongly acidic $Cu(OTf)_2$ led to a low yield of 42% of the product, and a complex reaction mixture (Table 4, entry 3). Lowering the amount of $Cu(OTf)_2$ to 0.5 equiv. resulted in a yield of 65% of the product, and a less complex reaction mixture (Table 4, entry 4). No reaction occurred with the more weakly acidic $Cu(OAc)_2$ (Table 4, entry 5). When CuX_2 (X = Cl, Br) were used, halogenation of the furan ring of **8a-1** and the α position of the enol ether segment of **10a-1** were observed (Table 4, entries 6–7). Notably, a combination of $CuSO_4·5H_2O$ with $Cu(OAc)_2$ gave a yield comparable with that obtained using $CuSO_4·5H_2O$/AcOH (Table 4, entry 8). Therefore, we concluded that firstly, a certain degree of acidity was crucial for this reaction. Under more weakly acidic conditions, the transformation did not proceed, while under very strongly acidic conditions, the starting material was prone to decomposition. Secondly, an organic copper salt was beneficial to this reaction, because a lipophilic counterion was required as a sort of phase-transfer catalyst. The role of AcOH is to produce the favourable $Cu(OAc)_2$. For the transformation of **8b** to **10b**,[11b] $CuSO_4·5H_2O$/TsOH was used as the acid cocatalyst. This combination would also produce a favourable organic copper salt, i.e., $Cu(OTs)_2$. Because the stability of a thiophene ring is higher than that of a furan ring, 0.5 equiv. of TsOH was required to guarantee the strongly acidic conditions.

1.3. Skeletal Rearrangement of Spirofurooxindoles 10a into Spiropentenoneoxindoles 11a

First, three spirofurooxindoles **10a** with different R groups were heated in DCE (1,2-dichloroethane) at 130 °C under metal-free conditions. As shown in Table 5, introduction of a methoxy group at the 3-position of the *N*-phenyl group significantly increased the diastereoselectivity of the reaction (Table 5, entry 1 > entry 3 < entry 2). The stereochemistry of the major isomer of the product was determined based on single-crystal X-ray diffraction analysis (*cis*-**16a-39**, see the Supporting Information, CCDC-958433). The substituents on the Ar rings of **10a** also influenced the reaction (Table 6). Introduction of an *ortho* substituent onto the Ar ring greatly improved the diastereoselectivity (Table 6, entries 4–6). Because of steric hindrance, introduction of two methyl groups at the 2- and 6-positions of the Ar rings resulted in no reaction under these conditions (Table 6, entry 7). Substrate **10a-28** also failed to undergo the rearrangement, due to the large steric hindrance of its Ar and R^2 groups (R^2 = Ar = Ph, Table 6, entry 8). Interestingly, the size of the R^1 group slightly influenced the diastereoselectivity (Table 7). A larger R^1 group generally led to a higher diastereoselectivity (Me < Et < Bn; **11a-8** < **11a-1** < **11a-9**).

Table 4. Some control experiments.[a]



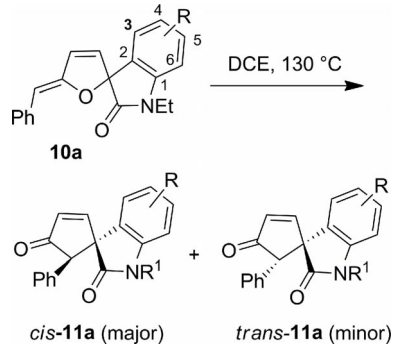
8a-1 (R = H)
8a-1' (R = OAc)

10a-1

Entry	Acid	Yield[b] [%]
1[c]	$CuSO_4·5H_2O$	20
2	AcOH	n.r.[d]
3	$Cu(OTf)_2$	56
4	$Cu(OTf)_2$[e]	42
5	$Cu(OAc)_2$	n.r.[d]
6	$CuBr_2$	trace
7	$CuCl_2$	trace
8	$Cu(OAc)_2$[f]/$CuSO_4·5H_2O$	82
9	$CuSO_4·5H_2O$	62
10	$CuSO_4·5H_2O$/AcOH[f]	85

[a] All reactions were carried out on a 0.3 mmol scale. Unless otherwised, the amount of the acid was 1.5 equiv. and **8a-1** was used as the substrate. [b] Isolated yield· [c] **8a-1′** was used as the substrate. [d] n.r.: no reaction. [e] 0.5 equiv. [f] 0.1 equiv.

Table 5. Synthesis of **11a** from **10a**.[a,b]



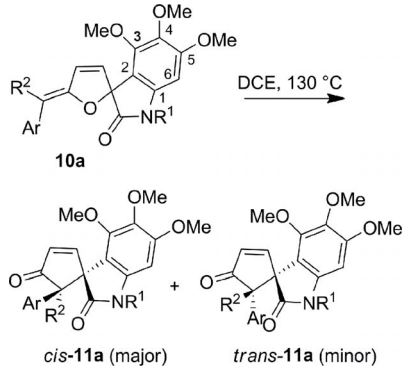
10a

cis-**11a** (major) *trans*-**11a** (minor)

Entry	**10a**	R	**11a** (Yield [%][c], *cis*/*trans*[d])
1	**10a-1**	3,4,5-tri-MeO	**11a-1** (94, 4:1)
2	**10a-2**	3,5-di-MeO	**11a-2** (91, 5:1)
3	**10a-3**	4,5-di-MeO	**11a-3** (89, 1.5:1)

[a] Unless otherwise noted, the reaction time was 12 h. [b] All reactions were performed on a 0.2 mmol scale. Entries 1–3 have been presented in ref.[11c] [c] Isolated yield. [d] Ratios are based on ^1H NMR spectroscopy.

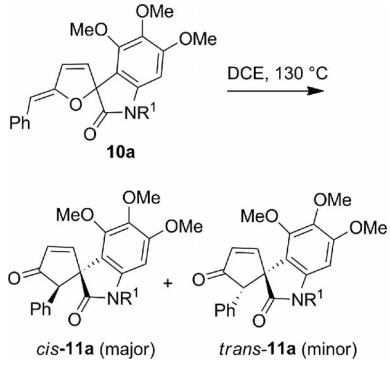
Table 6. Synthesis of **11a** from **10a**.[a][b]



Entry	10a	Ar	11a	Yield [%][c] (*cis*/*trans*[d])
1	**10a-1**	Ph	**11a-1**	94 (4:1)
2	**10a-18**	4-Cl–Ph	**11a-18**	93 (5.6:1)
3	**10a-22**	4-NO_2–Ph	**11a-22**	86 (1.8:1)
4	**10a-17**	2-Me–Ph	**11a-17**	94 (> 99:1)
5	**10a-19**	2-Cl–Ph	**11a-19**	92 (> 99:1)
6	**10a-20**	2-F–Ph	**11a-20**	87 (> 99:1)
7	**10a-29**	2,6-di-Me–Ph	**11a-29**	n.r.
8[e]	**10a-28**	Ph	**11a-28**	n.r.

[a] Unless otherwise noted, the reaction time was 12 h. [b] All reactions were performed on a 0.2 mmol scale. [c] Isolated yield. [d] Ratios are based on ^{1}H NMR spectroscopy.

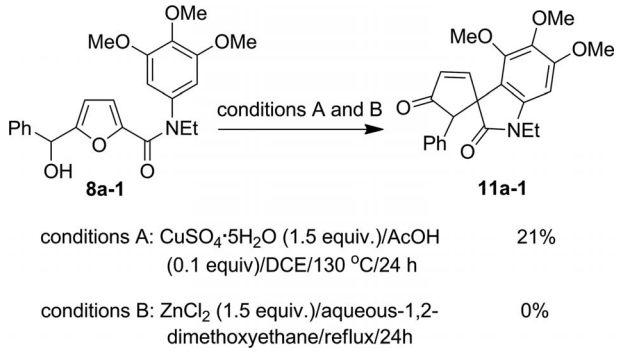
Table 7. Synthesis of **11a** from **10a**.[a,b]



Entry	10a (R^1)	11a (Yield [%][c], *cis*/*trans*[d])
1	**10a-8** (Me)	**11a-8** (92, 2.2:1)
2	**10a-1** (Et)	**11a-1** (94, 4:1)
3	**10a-9** (Bn)	**11a-9** (85, 5.5:1)

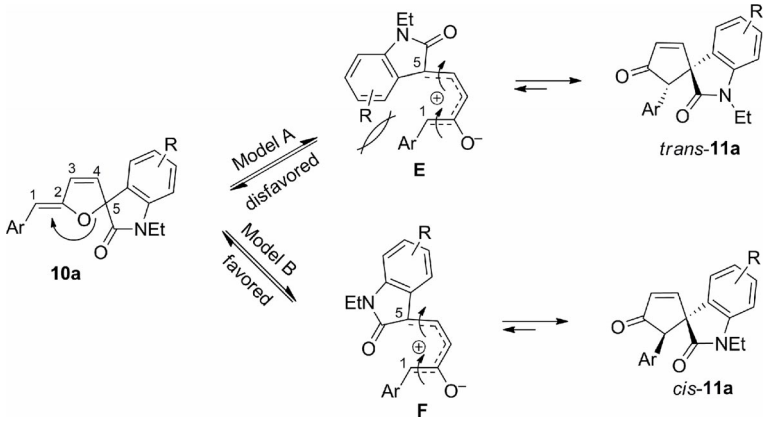
[a] Unless otherwise noted, the reaction time was 12 h. [b] All reactions were performed at a 0.2 mmol scale. [c] Isolated yield. [d] Ratios are based on ^{1}H NMR spectroscopy.

We previously reported that the furandiols exclusively underwent dehydration–spiroacetalization to give spiroacetal enol ethers when treated with acid in an aprotic aromatic solvent such as toluene. In contrast, if they were treated with an acid in a protic solvent, the furandiols underwent *O*-Piancatelli rearrangement to produce cyclopentenones.[14] To achieve the *C*-Piancatelli rearrangement, we treated **8a-1** with $CuSO_4{\cdot}5H_2O$ (1.5 equiv.) and AcOH (0.1 equiv.) in the aprotic solvent DCE at 130 °C for 24 h. *C*-Piancatelli rearrangement product **11a-1** was formed in only 21% isolated yield, accompanied by many other by-products. Even though the yield was low, the *C*-Piancatelli rearrangement had been achieved for the first time. We also found that **11a-1** was prone to decompose under the acidic reaction conditions, and this was possibly the reason for the low yield of **11a-1** from **8a-1**. When **8a-1** was treated with $ZnCl_2$ (1.5 equiv.) in aqueous 1,2-dimethoxyethane, hydrolysis of the amide group was observed, and none of the desired product (i.e., **11a-1**) was isolated (Scheme 3).



Scheme 3. Transformation of **8a-1** into **11a-1**.

Stereochemical models A and B were presented to rationalize the stereoselectivities observed. We proposed that intermediate **F** of model B, which leads to *cis*-**8**, was favoured, due to the steric hindrance between the aryl and carbonyl groups being lower than that between the aryl group and the *N*-phenyl ring (Scheme 4). To provide additional support for the stereochemical models, the free energy was calculated for the reaction. Molecular geometries of the intermediates, transition states, and products [**10a-30** (Ar = 1-Np, R = 3,5-di-MeO, R^1 = Et)] were optimized at the Becke3LYP/6-31+G* level of DFT theory.[15–17] The solvation effects of DCE (experimentally used) were simulated using the integral equation formulation of the polarized continuum model (PCM).[18] As the DFT functions poorly describe dispersion effects, dispersion correction for the free energies was estimated using the DFT-D3 program developed by Grimme and co-workers.[19] Frequency analysis was used to confirm whether the energy of the molecule is a local minimum (with no imaginary frequency) or a transition state (with one imaginary frequency), and to provide free energies at 298.15 K. Intrinsic reaction coordinate (IRC) analysis was applied to confirm that the transition state could reach the starting material and the product. All calculations were performed with the Gaussian 09 program.[20] As shown in Figure 2, although the free energy of intermediate **F** is 2.8 kcal/mol greater than that of intermediate **E**, the cyclization energy barrier for **F** is 7.92 kcal/mol less than that for **E**, implying that the cyclization of **F** should occur much more quickly than that of **E**. The free energy of the product *cis*-**11a-30** is 0.72 kcal/mol less than



Scheme 4. Plausible stereochemical models.

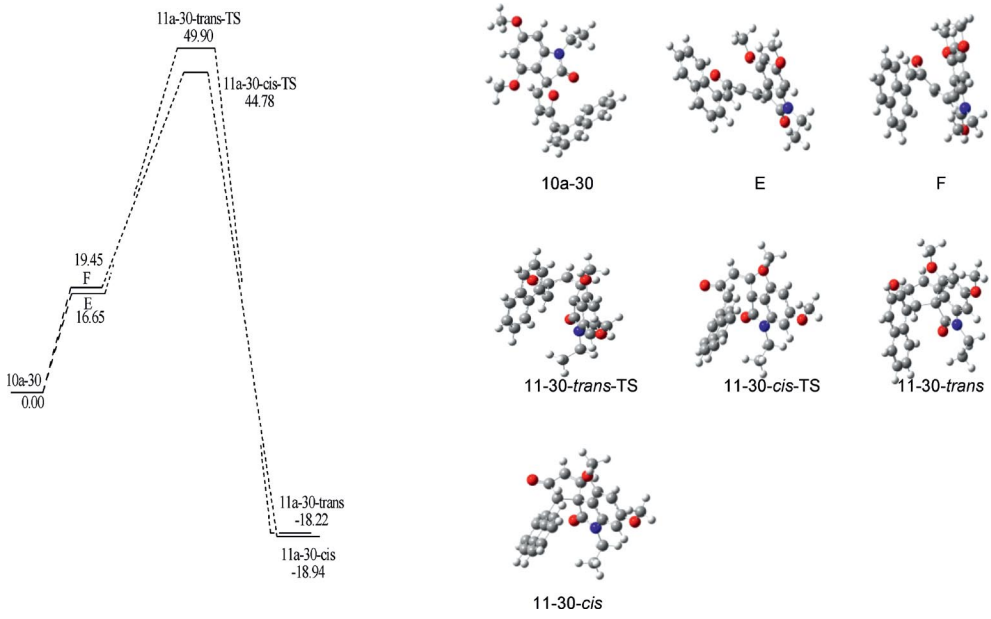
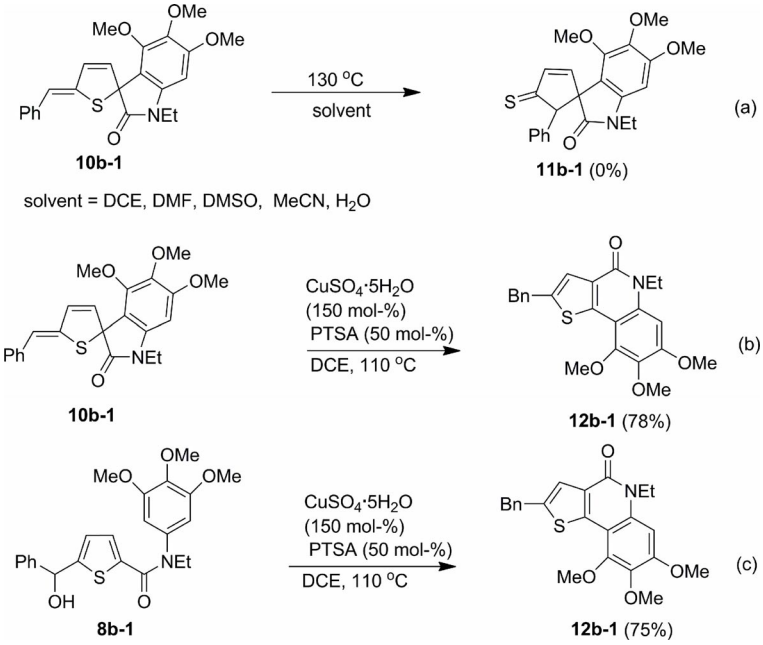


Figure 2. Free-energy profile (in kcal/mol) for the reactions in DCE (left) and the optimized structures of intermediates, transition states, and products (right).

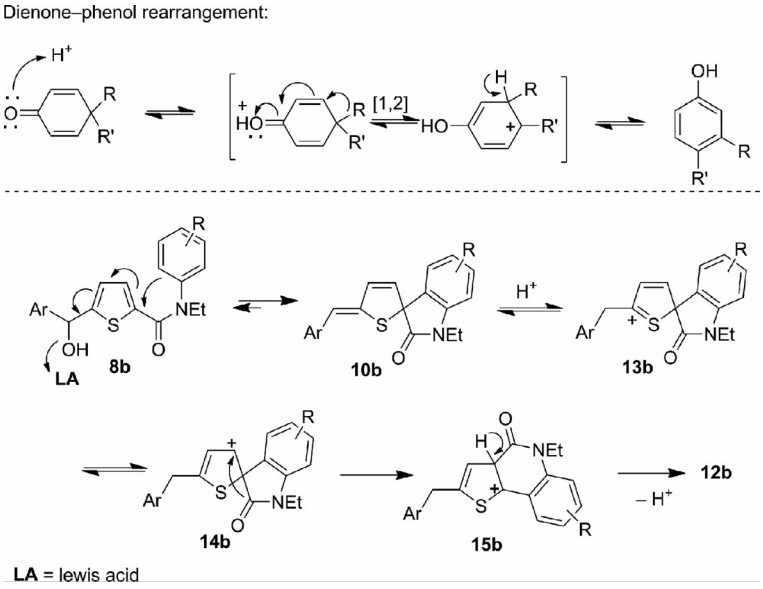
that of *trans*-**11a-30**. Thus, the formation of *cis*-**11a-30** is kinetically and thermodynamically favourable.

1.4. Rearrangement of Spirothienooxindoles 10b into Thieno[2,3-*c*]quinolin-4-ones 12b

Encouraged by the accomplishment of the transformation of **10a** into **11a**, we aimed to achieve the skeletal rearrangement of spirothienooxindoles **10b** into spirothiones **11b**. However, as it is more difficult to cleave the C–S bond than the C–O bond, when **10b-1** was heated in various polar solvents (e.g., DCE, DMF, DMSO, acetonitrile, or H_2O) at 130 °C or higher temperatures, no reaction occurred, and only the starting material was recovered. Interestingly, when **10b-1** was treated with $CuSO_4{\cdot}5H_2O$ (150 mol-%) and PTSA (50 mol-%) in DCE at 110 °C, it was converted into 5*H*-thieno[3,2-*c*]quinolin-4-one (**12b-1**) in 78% yield. The structure of htis product was assigned based on spectroscopic analysis (IR, 2D NMR, and MS, see the Supporting Information). 2-Thienyl-carbinol **8b-1** was also converted into **12b-1** in a comparable 75% yield under the same reaction conditions, and **10b-1** was detected as an intermediate, according to the TLC during the course of the reaction (Scheme 5). The rearrangement of **10b** into **12b** might proceed by a dienone–phenol-like mechanism.[21] Specifically, after protonation at the α position of the enol thioether functionality, **8b** could be converted into carbocation **14** and then into **16**, which could then undergo a 1,2-carbonyl migration to release ring-strain and then deprotonation to form **12b** (Scheme 6). 5*H*-Thieno[3,2-*c*]quinolin-4-ones have been reported to show excellent anticancer activities.[22] They can also be used as building blocks for the construction of biologically active fused heterocycles.[23] A small library of **12b** with various Ar and R groups was prepared



Scheme 5. Synthesis of **12b-1**.



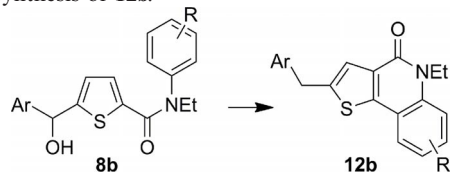
Scheme 6. Possible mechanism for the formation of **12b** from **8b**.

from **8b** concisely and effectively in moderate to good yields (Table 8).

Biological Results and Discussion

To explore the antiproliferative activities of these derivatives, several compounds were selected to test their effects on the human tumor cell lines, such as Du145, LNCaP, and PC3 cells. As shown in Table 9, some of the tested spirooxindoles showed fairly good cytotoxic activities against these tumor cell lines. The cytotoxicity GI_{50} values range from 600 nM against Du145 cells for the most cytotoxic (compound **11a-38**) to no significant inhibition for the least cytotoxic compounds. Four spirofuryloxindoles (**10a**) were more cytotoxic against Du145 and LNCaP cells than against PC3 (Table 9, entries 1–5). Compound **10a-20** (Table 9, entry 4) was the most active, and had the lowest GI_{50} (3.18 μM) against Du145 cells. A comparison of the GI_{50} values of **10a-20** and **10a-1** implies that the introduction of a 2-F group into the Ar ring remarkably improves the cytotoxicity (nearly sevenfold). In contrast, five spirothienooxindoles (**10b**) were more cytotoxic against LNCaP and PC3 cells than against Du145. Notably, compared to **10a-1**, **10b-1** was more cytotoxic against LNCaP (2.31 vs. 21.67 μM; 5.98 vs. > 50 μM), but less cytotoxic against Du145 (21.54 vs. > 50 μM).

Table 8. Synthesis of **12b**.[a]

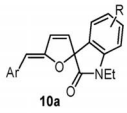
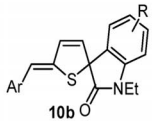
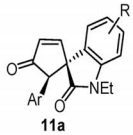
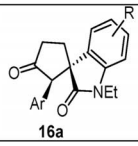


Entry	**8b** (Ar; R)	**11b** (Yield[b] [%])
1	**8b-1** (Ph; 3,4,5-tri-MeO)	**12b-1** (78)
2	**8b-2** (Ph; 3,5-di-MeO)	**12b-2** (72)
3	**8b-3** (Ph; 3,4-di-MeO)	**12b-3** (58)
4	**8b-18** (4-Cl-Ph; 3,4,5-tri-MeO)	**12b-18** (86)
5	**8b-31** (2-Cl-Ph; 3,5-di-MeO)	**12b-31** (77)
6	**8b-32** (2-Cl-Ph; 3,4-di-MeO)	**12b-32** (78)
7	**8b-23** (1-Np; 3,4,5-tri-MeO)	**12b-23** (74)
8	**8b-33** (4-F-Ph; 3,4,5-tri-MeO)	**12b-33** (75)
9	**8b-34** (4-F-Ph;3,5-di-MeO)	**12b-34** (70)
10	**8b-35** (4-F-Ph; 3,4-di-MeO)	**12b-35** (68)
11	**8b-36** (4-F-Ph; 3,5-di-Me)	**12b-36** (53)

[a] All reactions were performed on a 0.3 mmol scale. [b] Isolated yield. 1-Np = 1-naphthyl.

As for spiropentenoneoxindoles **11a**, some of them showed promising cytotoxic activities against Du145, LNCaP, and PC3 cells. Compounds **11a-18**, **11a-31**, and **11a-38** were cytotoxic against Du145 cells in the relatively low micromolar GI_{50} range (0.82 μM, 0.68 μM, and 0.60 μM, respectively), and compound **11a-30** showed clear cytotoxicity against LNCaP cells with a GI_{50} of 0.71 μM. Substitution on the aryl ring influenced the cytotoxicity remarkably. For example, when R = 3,4,5-tri-MeO, compound **11a-18**, bearing one chlorine atom at the *para* position of the phenyl ring, was much more cytotoxic against Du145 cells than was **11a-1**, without substitution on the phenyl ring (19.85 vs. 0.82 μM). Those compounds with 2-Me, 2-Cl, and 4-NO_2 substituents on the phenyl ring also showed good cytotoxicity against Du145 cells (1.13, 1.90, and 2.60 μM, respectively). However, compound **11a-20**, with a 2-fluoro substituent on its phenyl ring, showed no significant inhibition of Du145, LNCaP, or PC3 cells. The cytotoxicity of three spiropentanoneoxindoles **16a**, prepared by hydrogenation of the corresponding compounds **11a**, was also evaluated.

Table 9. The biological activities of the spirooxindole products.[a]

Entry	Structure	Compound	GI_{50} = [μM]		
			Du145	LNCaP	PC3
1		**10a-1**: Ar = Ph; R = 3,4,5-tri-MeO	21.5	21.7	>50
2		**10a-6**: Ar = 4-MeO-Ph; R = 3,4,5-tri-MeO	35.7	28.4	>50
3		**10a-31**: Ar = 2-Cl-Ph; R = 3,5-di-MeO	16.7	18.5	>50
4		**10a-20**: Ar = 2-F-Ph; R = 3,4,5-tri-MeO	3.2	18.2	25.0
5		**10a-21**: Ar = 2-Br-Ph; R = 3,4,5-tri-MeO	10.4	19.1	>50
6		**10b-1**: Ar = Ph; R = 3,4,5-tri-MeO	>50	2.3	6.0
7		**10b-20**: Ar = 2-F-Ph; R = 3,4,5-tri-MeO	>50	7.0	8.2
8		**10b-31**: Ar = 1-Np; R = 3,4,5-tri-MeO	>50	5.0	10.4
9		**10b-40**: Ar = 1-Np; R = 3,4,5-tri-MeO	>50	1.8	7.1
10		**10b-42**: Ar = 4-F-Ph; R = 4,5-di-MeO	>50	2.6	16.4
9		**11a-1**: Ar = Ph; R = 3,4,5-tri-MeO	19.9	10.1	10.0
10		**11a-17**: Ar = 2-Me-Ph; R = 3,4,5-tri-MeO	1.1	13.3	10.9
11		**11a-18**: Ar = 4-Cl-Ph; R = 3,4,5-tri-MeO	0.8	14.9	10.2
12		**11a-19**: Ar = 2-Cl-Ph; R = 3,4,5-tri-MeO	1.9	36.7	11.2
13		**11a-20**: Ar = 2-F-Ph; R = 3,4,5-tri-MeO	>50	>50	>50
14		**11a-22**: Ar = 4-NO_2-Ph; R = 3,4,5-tri-MeO	2.6	6.6	3.3
15		**11a-37**: Ar = 4-Cl-Ph; R = 3,5-di-MeO	2.8	15.2	11.7
16		**11a-31**: Ar = 2-Cl-Ph; R = 3,5-di-MeO	0.7	7.3	8.0
17		**11a-30**: Ar = 1-Np; R = 3,5-di-MeO	3.5	0.7	2.1
18		**11a-38**: Ar = 1-Np; R = 4,5-di-MeO	0.6	2.8	2.6
19		**16a-1**: Ar = Ph; R = 3,4,5-tri-MeO	>50	6.4	>50
20		**16a-39**: 2-F-Ph; R = 4,5-di-MeO	32.7	8.6	>50
21		**16a-30**: Ar = 1-Np; R = 3,5-di-MeO	>50	18.7	>50

[a] The standard error of the GI_{50} was generally less than 10%.

Compared to their unreduced counterparts (i.e., **11a**), compounds **16a** generally showed lower cytotoxicity against the three tumor cell lines, and they did not show significant inhibition of PC3 cells ($GI_{50} > 50$ μM).

Conclusions

In summary, we have shown that 2-furylcarbinols and 2-thienylcarbinols, with a side-chain tethered by an electron-rich phenyl ring, are transformed into spirooxindoles under acidic conditions. This transformation involved an interesting and dearomatizing Friedel–Crafts reaction. The strategy could be valuable for designing some new reactions for the construction of new heterocyclic compounds using five-membered aromatic rings as the starting materials. The skeletal rearrangements of the spirooxindole products were also studied. The rearrangement of spirofurooxindoles into spiropentenoneoxindoles provides additional evidence for the thermal conrotatory electrocyclization of the 4π-electron mechanism. The rearrangement of spirothienooxindoles into thieno[2,3-*c*]quinolin-4-ones proceeded by an interesting and unprecedented dienone–phenol-like mechanism. Finally, some of the spirooxindole products showed promising cytotoxic activities against the DU145 and LNCaP tumor cell lines.

Experimental Section

General Remarks: All reactions were carried out under a nitrogen atmosphere. Unless otherwise specified, all reagents and starting materials were purchased from commercial suppliers and used as received. Solvents were purified according to standard literature procedures. IR spectra were recorded by the FTIR method with samples in the form of thin films or KBr pellets. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded using $CDCl_3$ as a solvent, and ratios of compounds were determined from the ^{1}H NMR spectra. Chemical shifts are reported in ppm downfield from tetramethylsilane. Coupling constants are expressed in Hz; splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and dd (double doublet). Analytical thin-layer chromatography (TLC) was performed on silica gel plates using mixtures of petroleum ether and ethyl acetate as the eluent. Mass spectra were obtained using a high-resolution ESI mass spectrometer.

General Procedure for the Preparation of 10a from 8a: A mixture of **8a** (0.3 mmol), toluene (5 mL), $CuSO_4{\cdot}5H_2O$ (112.5 mg, 0.45 mmol), and acetic acid (1.7 μL) was stirred at 100 °C. After TLC indicated the disappearance of **8a**, the mixture was cooled to room temperature, and the solid was filtered off. The organic solvent was removed from the filtrate, and the residue was purified by flash chromatography on silica gel (EtOAc/petroleum ether, 1:2) to give **10a.**

5-Benzylidene-4′,5′,6′-trimethoxy-1′-methyl-5*H*-spiro[furan-2,3′-indolin]-2′-one (10a-8): Brown oil (100 mg, 88%): IR (thin film, neat): $\tilde{\nu}$ = 2934, 1731, 1613, 1473, 1342, 1274, 1093, 995, 812, 703 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 (d, J = 7.6 Hz, 2 H), 7.23–7.20 (m, 2 H), 7.08–7.04 (m, 1 H), 6.63 (d, J = 5.6 Hz, 1 H), 6.28 (s, 1 H), 6.04 (d, J = 5.6 Hz, 1 H), 5.56 (s, 1 H), 3.92 (s, 3 H), 3.79 (s, 3 H), 3.75 (s, 3 H), 3.21 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.8, 158.9, 156.5, 152.8, 140.2, 138.4, 136.0, 130.5, 130.3, 128.1, 128.0, 125.4, 109.4, 100.8, 92.6, 90.4, 61.8, 61.2, 56.5, 26.7 ppm. HRMS (ESI, ion-trap): calcd. for $C_{22}H_{22}NO_5$ $[M + H]^+$ 380.1498; found 380.1491.

5-Benzylidene-4′,5′,6′-trimethoxy-1′-benzyl-5*H*-spiro[furan-2,3′-indolin]-2′-one (10a-9): Brown oil (68 mg, 50%): IR (thin film, neat): $\tilde{\nu}$ = 2936, 1730, 1616, 1470, 1340, 1261, 1131, 1037, 813, 746 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (d, J = 7.6 Hz, 2 H), 7.37–7.31 (m, 5 H), 7.27–7.23 (m, 2 H), 7.10 (t, J = 7.6 Hz, 1 H), 6.67 (d, J = 5.6 Hz, 1 H), 6.16 (s, 1 H), 6.11 (d, J = 5.6 Hz, 1 H), 5.59 (s, 1 H), 4.97 (d, J = 15.6 Hz, 1 H), 4.83 (d, J = 15.6 Hz, 1 H), 3.76 (br., 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.9, 158.9, 156.3, 152.8, 139.3, 138.5, 136.1, 135.4, 130.6, 130.2, 128.9, 128.2, 128.1, 127.9, 127.4, 125.5, 109.6, 100.9, 92.6, 91.4, 61.8, 61.1, 56.4, 44.1 ppm. HRMS (ESI, ion-trap): calcd. for $C_{28}H_{26}NO_5$ $[M + H]^+$ 456.1811; found 456.1802.

5-(2,6-Dimethylbenzylidene)-1′-ethyl-4′,5′,6′-trimethoxy-5*H*-spiro[furan-2,3′-indolin]-2′-one (10a-16): Brown oil (94 mg, 75%): IR (thin film, neat): $\tilde{\nu}$ = 2936, 1728, 1615, 1469, 1345, 1222, 1134, 933, 798, 626 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.00–6.98 (m, 3 H), 6.68 (d, J = 5.6 Hz, 1 H), 6.17 (s, 1 H), 6.02 (d, J = 5.6 Hz, 1 H), 5.51 (s, 1 H), 3.88 (s, 3 H), 3.78 (s, 3 H), 3.76 (s, 3 H), 3.69 (q, J = 7.2 Hz, 2 H), 2.32 (s, 6 H), 1.25 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.8, 158.2, 156.3, 152.7, 139.3, 138.0, 137.2, 133.9, 130.6, 129.2, 127.0, 126.4, 109.5, 97.4, 91.6, 90.1, 61.4, 61.2, 56.5, 35.1, 20.7, 12.8 ppm. HRMS (ESI, ion-trap): calcd. for $C_{25}H_{28}NO_5$ $[M + H]^+$ 422.1968; found 422.1958.

1′-Ethyl-4′,5′,6′-trimethoxy-5-(2-methylbenzylidene)-5*H*-spiro[furan-2,3′-indolin]-2′-one (10a-17): Brown oil (92 mg, 76%). IR (thin film, neat): $\tilde{\nu}$ = 2936, 1728, 1612, 1473, 1345, 1231, 1133, 1088, 934, 794, 749 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, J = 7.6 Hz, 1 H), 7.11–7.05 (m, 2 H), 6.99 (d, J = 7.6 Hz, 1 H), 6.67 (d, J = 5.6 Hz, 1 H), 6.29 (s, 1 H), 6.05 (d, J = 5.6 Hz, 1 H), 5.67 (s, 1 H), 3.92 (s, 3 H), 3.80 (s, 3 H), 3.78 (s, 3 H), 3.75 (q, J = 7.2 Hz, 2 H), 2.35 (s, 3 H), 1.31 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.4, 159.0, 156.4, 152.9, 139.3, 138.3, 134.8, 134.4, 133.3, 130.7, 130.2, 129.8, 128.3, 125.7, 125.6, 109.7, 97.5, 90.5, 61.7, 61.2, 56.6, 35.2, 20.3, 12.9 ppm. HRMS (ESI, ion-trap): calcd. for $C_{24}H_{26}NO_5$ $[M + H]^+$ 408.1811; found 408.1803.

5-(2-Chlorobenzylidene)-1′-ethyl-4′,5′,6′-trimethoxy-5*H*-spiro[furan-2,3′-indolin]-2′-one (10a-19): Brown oil (108 mg, 85%): IR (thin film, neat): $\tilde{\nu}$ = 2935, 1729, 1613, 1472, 1345, 1229, 1090, 1154, 940, 812, 752 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11–8.09 (m, 1 H), 7.30–7.28 (m, 1 H), 7.12–7.08 (m, 1 H), 7.00–6.96 (m, 1 H), 6.96 (d, J = 6.0 Hz, 1 H), 6.29 (s, 1 H), 6.11 (d, J = 6.0 Hz, 1 H), 5.99 (s, 1 H), 3.92 (s, 3 H), 3.80 (s, 3 H), 3.76 (s, 3 H), 3.75 (q, J = 7.2 Hz, 2 H), 1.31 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.0, 160.4, 156.6, 152.9, 139.3, 133.7, 131.4, 130.6, 129.5, 129.1, 126.5, 126.3, 109.1, 96.0, 92.8, 90.5, 61.6, 61.2, 56.6, 35.3, 12.9 ppm. HRMS (ESI, ion-trap): calcd. for $C_{23}H_{23}ClNO_5$ $[M + H]^+$ 428.1108; found 428.1101.

5′-(2-Fluorobenzylidene)-2-oxo-spiro[1-ethyl-5,6,7-trimethoxyindole-3,2′-(2′,5′-dihydrofuran)] (10a-20): Brown oil (107 mg, 87%): IR (thin film, neat): $\tilde{\nu}$ = 2935, 1727, 1611, 1476, 1344, 1206, 1154, 1088, 937, 795, 754 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06–8.02 (m, 1 H), 7.04–6.94 (m, 3 H), 6.66 (d, J = 5.6 Hz, 1 H), 6.29 (s, 1 H), 6.10 (d, J = 5.6 Hz, 1 H), 5.82 (s, 1 H), 3.94 (s, 3 H), 3.80 (s, 3 H), 3.76 (q, J = 7.2 Hz, 2 H), 3.76 (s, 3 H), 1.33 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.2, 160.5, 160.2, 160.1, 158.0, 156.5, 152.9, 139.4, 138.3, 131.1, 130.5, 129.5, 129.5, 126.6, 126.5, 124.1, 123.9, 123.8, 123.8, 114.7, 114.5, 109.4, 92.8,

91.6, 91.6, 90.5, 61.8, 61.3, 56.6, 35.3, 12.9 ppm. HRMS (ESI, ion-trap): calcd. for $C_{23}H_{23}FNO_5$ $[M + H]^+$ 412.1561; found 412.1554.

5′-(2-Bromobenzylidene)-2-oxo-spiro[1-ethyl-5,6,7-trimethoxyindole-3,2′-(2′,5′-dihydrofuran)] (10a-21): Brown oil (113 mg, 80%): IR (thin film): $\tilde{\nu}$ = 2940, 1729, 1618, 1490, 1326, 1200, 1158, 1098, 940, 798, 749 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.09 (d, J = 7.6 Hz, 1 H), 7.48 (d, J = 8.0 Hz, 1 H), 7.17–7.13 (m, 1 H), 6.90–6.87 (m, 1 H), 6.69 (d, J = 5.6 Hz, 1 H), 6.28 (s, 1 H), 6.12 (d, J = 5.6 Hz, 1 H), 5.97 (s, 1 H), 3.93 (s, 3 H), 3.80 (s, 3 H), 3.77 (q, J = 7.2 Hz, 2 H), 3.72 (s, 3 H), 1.26 1.33 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.1, 160.4, 156.6, 153.0, 139.4, 138.4, 131.3, 129.7, 127.1, 126.7, 122.9, 109.2, 99.0, 92.8, 90.5, 61.7, 61.2, 56.3, 35.3, 12.9 ppm. HRMS (EI, ion-trap): calcd. for $C_{23}H_{23}BrNO_5$ $[M + H]^+$ 412.1561; found 472.0760; found 472.0774.

4′,6′-Dimethoxy-1′-methyl-5-(thiophen-2-ylmethylene)-5*H*-spiro-[furan-2,3′-indolin]-2′-one (10a-25): Brown oil (26 mg, 25%): IR (thin film, neat): $\tilde{\nu}$ = 1628, 1139, 622 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.07–7.05 (m, 2 H), 6.92–6.90 (m, 1 H), 6.57 (d, J = 5.6 Hz, 1 H), 6.13–6.11 (m, 2 H), 6.01 (d, J = 5.6 Hz, 1 H), 5.81 (s, 1 H), 3.84 (s, 3 H), 3.69 (s, 3 H), 3.19 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.9, 163.8, 158.8, 157.9, 146.2, 139.3, 130.7, 129.2, 126.7, 124.6, 123.3, 103.6, 94.1, 93.0, 92.3, 89.1, 55.9, 55.6, 26.8 ppm. HRMS (EI, ion-trap): calcd. for $C_{19}H_{18}NO_4S$ $[M + H]^+$ 356.0957; found 356.0952.

5-(Diphenylmethylene)-1′-ethyl-4′,6′-dimethoxy-5*H*-spiro[furan-2,3′-indolin]-2′-one (10a-28): Brown oil (114 mg, 87%): IR (thin film, neat): $\tilde{\nu}$ = 2357, 1728, 1620, 1456, 1349, 1206, 624 cm^{-1}. ^1H NMR: δ = 7.44–7.42 (m, 2 H), 7.37–7.32 (m, 5 H), 7.22–7.19 (m, 2 H), 7.12–7.08 (m, 1 H), 6.59 (d, J = 5.6 Hz, 1 H), 6.12 (s, 1 H), 6.10 (s, 1 H), 5.98 (d, J = 5.6 Hz, 1 H), 3.83 (s, 3 H), 3.77 (s, 3 H), 3.73 (q, J = 7.2 Hz, 2 H), 1.29 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.9, 163.6, 158.8, 157.9, 145.1, 141.2, 139.6, 131.3, 130.8, 129.9, 129.3, 128.1, 127.6, 126.6, 125.8, 113.4, 104.2, 92.5, 91.6, 89.3, 55.8, 55.7, 35.4, 12.9 ppm. HRMS (ESI, ion-trap): calcd. for $C_{28}H_{26}NO_4$ $[M + H]^+$ 440.1862; found 440.1853.

General Procedure for the Preparation of 11a from 10a: A mixture of **10a** (0.2 mmol) and DCE (3 mL) in a Schlenk flask was stirred at 130 °C for 12 h until TLC indicated the disappearance of **10a**. The mixture was then cooled to room temperature. The organic solvent was removed, and the residue was purified by flash chromatography on silica gel (EtOAc/petroleum ether, 1:1) to give **11a**.

4′,5′,6′-Trimethoxy-1′-methyl-5-phenylspiro[cyclopent[2]ene-1,3′-indoline]-2′,4-dione (11a-8): Brown syrup (69 mg, 92%, *cis*/*trans* = 2.2:1): IR (thin film, neat): $\tilde{\nu}$ = 2932, 1716, 1614, 1468, 1339, 1252, 1123, 697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$; *cis* isomer): δ = 7.28 (d, J = 5.6 Hz, 1 H), 7.16–7.15 (m, 3 H), 6.94–6.92 (m, 2 H), 6.69 (d, J = 5.6 Hz, 1 H), 6.14 (s, 1 H), 4.38 (s, 1 H), 4.01 (s, 3 H), 3.91 (s, 3 H), 3.86 (s, 3 H), 2.82 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$; *cis* isomer): δ = 205.3, 173.5, 158.4, 155.5, 150.8, 139.9, 136.3, 134.7, 133.1, 129.7, 128.0, 127.4, 115.3, 110.7, 89.6, 63.6, 61.4, 61.2, 59.4, 56.4, 26.5 ppm. ^1H NMR (400 MHz, $CDCl_3$; *trans* isomer): δ = 7.24 (d, J = 5.6 Hz, 1 H), 7.09–7.08 (m, 3 H), 6.82–6.81 (m, 2 H), 6.56 (d, J = 5.6 Hz, 1 H), 6.06 (s, 1 H), 4.33 (s, 1 H), 3.78 (s, 3 H), 3.69 (s, 3 H), 3.56 (s, 3 H), 3.22 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$; *trans* isomer): δ = 206.0, 176.7, 156.7, 155.1, 150.8, 139.4, 137.5, 134.0, 133.1, 129.2, 127.8, 127.1, 115.3, 108.6, 89.5, 62.7, 60.8, 60.0, 59.4, 56.3, 26.8 ppm. HRMS (ESI, ion-trap): *m*/*z* calcd. for $C_{22}H_{22}NO_5$ $[M + H]^+$ 380.1492; found 380.1493.

1′-Benzyl-4′,5′,6′-trimethoxy-5-phenylspiro[cyclopent[2]ene-1,3′-indoline]-2′,4-dione (11a-9): Brown syrup (77 mg, 85%, *cis*/*trans* = 5.5:1): IR (thin film, neat): $\tilde{\nu}$ = 1625, 1464, 1134, 624 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$; *cis* isomer): δ = 7.34–7.01 (m, 9 H), 7.02 (d, J = 5.6 Hz, 1 H), 6.39 (d, J = 7.6 Hz, 2 H), 5.90 (s, 1 H), 5.03 (d, J = 16 Hz, 1 H), 4.47 (s, 1 H), 4.16 (d, J = 16 Hz, 1 H), 4.01 (s, 3 H), 3.82 (s, 3 H), 3.68 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$; *cis* isomer): δ = 205.3, 173.6, 158.3, 155.3, 150.7, 138.9, 137.4, 136.4, 134.7, 133.0, 130.4, 128.6, 128.3, 127.6, 127.3, 126.5, 110.6, 90.7, 63.6, 61.4, 61.2, 59.8, 56.1, 44.2 ppm; ^1H NMR (400 MHz, $CDCl_3$; *trans* isomer): δ = 7.34–7.01 (m, 11 H), 6.59 (d, J = 5.6 Hz, 1 H), 5.93 (s, 1 H), 5.12 (d, J = 16 Hz, 1 H), 4.70 (d, J = 16 Hz, 1 H), 4.39 (s, 1 H), 3.71 (s, 3 H), 3.62 (s, 3 H), 3.56 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$; *trans* isomer, selected data): δ = 129.5, 128.8, 127.8, 127.2, 60.7, 60.3, 59.9 ppm. HRMS (ESI, ion-trap): *m*/*z* calcd. for $C_{28}H_{26}NO_5$ $[M + H]^+$ 456.1744; found 456.1743.

General Procedure for the Preparation of 12b from 8b: A mixture of **8b** (0.3 mmol), $ClCH_2CH_2Cl$ (5 mL), $CuSO_4{\cdot}5H_2O$ (112.5 mg, 0.45 mmol), and *p*TsOH (25.8 mg, 0.15 mmol) was stirred at 110 °C for 12 h. After TLC indicated the disappearance of **8b**, the mixture was cooled to room temperature, and the solid was filtered off. The organic solvent was removed from the filtrate, and the residue was purified by flash chromatography on silica gel (EtOAc/petroleum ether, 1:3) to give **12b**.

2-Benzyl-5-ethyl-7,8,9-trimethoxythieno[2,3-*c*]quinolin-4(5*H*)-one (12b-1): White solid (95.7 mg, 78%), m.p. 131.5–132.5 °C. IR (KBr): $\tilde{\nu}$ = 2930, 1644, 1568, 1455, 1288, 1243, 1097, 800.3, 762, 700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.42 (s, 1 H), 7.33–7.22 (m, 5 H), 6.67 (s, 1 H), 4.40 (q, J = 7.2 Hz, 2 H), 4.21 (s, 2 H), 4.07 (s, 3 H), 3.98 (s, 3 H), 3.89 (s, 3 H), 1.38 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.4, 154.0, 148.6, 144.2, 140.3, 139.6, 137.2, 133.3, 128.9, 128.7, 128.6, 126.6, 122.7, 107.6, 94.0, 61.2, 60.7, 56.2, 37.5, 36.2, 12.7 ppm. HRMS (EI, ion-trap): calcd. for $C_{23}H_{24}NO_4S$ $[M + H]^+$ 410.1420; found 410.1415.

2-Benzyl-5-ethyl-7,9-dimethoxythieno[2,3-*c*]quinolin-4(5*H*)-one (12b-2): White solid (81.6 mg, 72%), m.p. 161.5–163.5 °C. IR (KBr): $\tilde{\nu}$ = 2931, 1736, 1644, 1455, 1374, 1318, 1241, 1210, 1157, 1084, 813, 702 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.43 (s, 1 H), 7.32–7.22 (m, 5 H), 6.53 (s, 1 H), 6.38 (s, 1 H), 4.39 (q, J = 7.2 Hz, 2 H), 4.20 (s, 2 H), 3.99 (s, 3 H), 3.91 (s, 3 H), 1.37 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.6, 158.7, 156.4, 143.3, 140.9, 139.8, 138.5, 128.5, 128.6, 127.8, 126.6, 122.5, 104.1, 92.2, 92.0, 55.8, 55.5, 37.7, 36.2, 12.7 ppm. HRMS (ESI, ion-trap): calcd. for $C_{22}H_{22}NO_3S$ $[M + H]^+$ 380.1315; found 380.1311.

2-Benzyl-5-ethyl-7,8-dimethoxythieno[2,3-*c*]quinolin-4(5*H*)-one (12b-3): White solid (65.9 mg, 58%), m.p. 149.5–151.5 °C. IR (KBr): $\tilde{\nu}$ = 2926, 1638, 1572, 1460, 1274, 1168, 1040, 765, 700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.42 (s, 1 H), 7.35–7.24 (m, 5 H), 7.01 (s, 1 H), 6.86 (s, 1 H), 4.41 (q, J = 7.2 Hz, 2 H), 4.21 (s, 2 H), 3.92 (s, 3 H), 3.91 (s, 3 H), 1.38 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.1, 150.7, 145.2, 144.7, 143.0, 139.5, 131.3, 129.1, 128.7, 128.7, 126.9, 123.8, 111.6, 105.5, 98.5, 56.3, 56.2, 37.5, 36.7, 12.9 ppm. HRMS (ESI, ion-trap): calcd. for $C_{22}H_{22}NO_3S$ $[M + H]^+$ 380.1314; found 380.1315.

2-(4-Chlorobenzyl)-5-ethyl-7,8,9-trimethoxythieno[2,3-*c*]quinolin-4(5*H*)-one (12b-18): White solid (110 mg, 86%), m.p. 146–148 °C. IR (KBr): $\tilde{\nu}$ = 2932, 1643, 1496, 1457, 1288, 1243, 1138, 1096, 930, 799 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.38 (s,1 H), 7.26–7.24 (m, 2 H), 7.20–7.18 (m, 2 H), 6.65 (s, 1 H), 4.38 (q, J = 7.2 Hz, 2 H), 4.14 (s, 2 H), 4.05 (s, 3 H), 3.96 (s, 3 H), 3.87 (s, 3 H), 1.36 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.3,

154.1, 148.6, 143.4, 140.4, 138.1, 137.1, 133.3, 132.5, 130.0, 128.9, 128.7, 122.8, 107.5, 93.9, 61.2, 60.7, 56.2, 37.5, 35.5, 12.7 ppm. HRMS (ESI, ion-trap): calcd. for $C_{23}H_{23}ClNO_4S$ [M + H]$^+$ 444.1030; found 444.1024.

2-(2-Chlorobenzyl)-5-ethyl-7,9-dimethoxythieno[2,3-*c*]quinolin-4(5*H*)-one (12b-31): White solid (95 mg, 77%), m.p. 139.5–141.5 °C. IR (KBr): $\tilde{\nu}$ = 2926, 1637, 1510, 1462, 1225, 1040, 764 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.38 (m, 2 H), 7.33–7.31 (m, 1 H), 7.23–7.21 (m, 2 H), 7.02 (s, 1 H), 6.86 (s, 1 H), 4.40 (q, J = 7.2 Hz, 2 H), 4.32 (s, 2 H), 3.99 (s, 3 H), 3.93 (s, 3 H), 1.38 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.0, 150.7, 145.2, 144.6, 141.0, 137.1, 133.9, 131.3, 130.8, 129.8, 129.1, 128.5, 127.2, 124.3, 111.5, 105.5, 98.4, 56.2, 56.2, 37.4, 34.1, 12.9 ppm. HRMS (ESI, ion-trap): calcd. for $C_{22}H_{21}ClNO_3S$ [M + H]$^+$ 414.0925; found 414.0921.

2-(2-Chlorobenzyl)-5-ethyl-7,8-dimethoxythieno[2,3-*c*]quinolin-4(5*H*)-one (12b-32): White solid (96.6 mg, 78%), m.p. 164–166 °C. IR (KBr): $\tilde{\nu}$ = 2926, 1636, 1509, 1460, 1272, 1039, 761 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.39 (m, 2 H), 7.33–7.31 (m, 1 H), 7.24–7.21 (m, 2 H), 7.04 (s, 1 H), 6.86 (s, 1 H), 4.41 (q, J = 7.2 Hz, 2 H), 4.33 (s, 2 H), 4.00 (s, 3 H), 3.94 (s, 3 H), 1.38 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.0, 150.7, 145.2, 144.6, 141.0, 137.1, 133.9, 131.3, 130.8, 129.8, 129.1, 128.5, 127.2, 124.3, 111.5, 105.5, 98.5, 56.3, 56.2, 37.5, 34.1, 12.9 ppm. HRMS (ESI, ion-trap): calcd. for $C_{22}H_{21}ClNO_3S$ [M + H]$^+$ 414.0925; found 414.0922.

5-Ethyl-7,8,9-trimethoxy-2-(naphthalen-2-ylmethyl)thieno[2,3-*c*]-quinolin-4(5*H*)-one (12b-23): White solid (101 mg, 74%), m.p. 159.5–161.5 °C. IR (KBr): $\tilde{\nu}$ = 2932, 1643, 1568, 1457, 1288, 1243, 1096, 1054, 930, 799 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81–7.76 (m, 3 H), 7.73 (s, 1 H), 7.49–7.40 (m, 4 H), 6.66 (s, 1 H), 4.41 (q, J = 7.2 Hz, 2 H), 4.37 (s, 2 H), 4.05 (s, 3 H), 3.98 (s, 3 H), 3.88 (s, 3 H), 1.38 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.4, 154.0, 148.6, 144.1, 140.4, 137.2, 137.1, 133.6, 133.3, 132.3, 128.9, 128.4, 127.7, 127.6, 127.1, 126.9, 126.1, 125.6, 122.9, 107.6, 93.9, 61.2, 60.7, 56.1, 37.5, 36.4, 12.7 ppm. HRMS (ESI, ion-trap): calcd. for $C_{27}H_{26}NO_4S$ [M + H]$^+$ 460.1577; found 460.1567.

5-Ethyl-2-(4-fluorobenzyl)-7,8,9-trimethoxythieno[2,3-*c*]quinolin-4(5*H*)-one (12b-33): White solid (96 mg, 75%), m.p. 149–150 °C. IR (KBr): $\tilde{\nu}$ = 1644, 1508, 1457, 1400, 1286, 1053, 820, 766 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (s, 1 H), 7.25–7.22 (m, 2 H), 7.01–6.97 (m, 2 H), 6.67 (s, 1 H), 4.40 (q, J = 7.2 Hz, 2 H), 4.17 (s, 2 H), 4.07 (s, 3 H), 3.98 (s, 3 H), 3.89 (s, 3 H), 1.38 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.9, 160.5, 158.4, 154.1, 148.6, 143.9, 140.4, 137.2, 135.4, 135.4, 133.3, 130.2, 130.1, 128.9, 122.7, 115.5, 115.4, 107.5, 93.9, 61.2, 60.7, 56.2, 37.5, 35.4, 12.7 ppm. HRMS (ESI, ion-trap): calcd. for $C_{23}H_{23}FNO_4S$ [M + H]$^+$ 428.1326; found 428.1319.

5-Ethyl-2-(4-fluorobenzyl)-7,9-dimethoxythieno[2,3-*c*]quinolin-4(5*H*)-one (12b-34): White solid (83 mg, 70%), m.p. 192.5–194.5 °C. IR (KBr): $\tilde{\nu}$ = 1699, 1650, 1518, 1244, 823, 753 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 (s, 1 H), 7.24–7.22 (m, 2 H), 7.01–6.97 (m, 2 H), 6.54 (s, 1 H), 6.38 (s, 1 H), 4.39 (q, J = 7.2 Hz, 2 H), 4.17 (s, 2 H), 4.00 (s, 3 H), 3.91 (s, 3 H), 1.37 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.9, 160.6, 158.7, 156.4, 143.1, 140.9, 138.6, 135.6, 130.1, 130.0, 127.8, 122.5, 115.5, 115.3, 104.0, 92.2, 91.9, 55.8, 55.6, 37.7, 35.4, 12.6 ppm. HRMS (ESI, ion-trap): calcd. for $C_{22}H_{21}FNO_3S$ [M + H]$^+$ 398.1221; found 398.1217.

5-Ethyl-2-(4-fluorobenzyl)-7,8-dimethoxythieno[2,3-*c*]quinolin-4(5*H*)-one (12b-35): White solid (81 mg, 68%), m.p. 201.5–202.5 °C. IR (KBr): $\tilde{\nu}$ = 1697, 1654, 1523, 1247, 820, 750 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (s, 1 H), 7.26–7.23 (m, 2 H), 7.04–6.99 (m, 3 H), 6.87 (s, 1 H), 4.42 (q, J = 7.2 Hz, 2 H), 4.18 (s, 2 H), 4.00 (s, 3 H), 3.93 (s, 3 H), 1.39 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.3, 160.6, 158.0, 150.8, 145.3, 144.7, 142.7, 135.2, 131.3, 130.2, 130.1, 129.1, 123.9, 115.7, 115.5, 111.5, 105.5, 98.5, 56.3, 56.2, 37.5, 35.8, 12.9 ppm. HRMS (ESI, ion-trap): calcd. for $C_{22}H_{21}FNO_3S$ [M + H]$^+$ 398.1219; found 398.1218.

5-Ethyl-2-(4-fluorobenzyl)-7,9-dimethylthieno[2,3-*c*]quinolin-4(5*H*)-one (12b-36): White solid (58 mg, 53%), m.p. 190.5–192.5 °C. IR (KBr): $\tilde{\nu}$ = 2888, 1649, 1518, 1397, 820, 763, 735 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53 (s, 1 H), 7.27–7.23 (m, 2 H), 7.16 (s, 1 H), 7.03–6.98 (m, 2 H), 6.96 (s, 1 H), 4.45 (q, J = 7.2 Hz, 2 H), 4.21 (s, 2 H), 2.70 (s, 3 H), 2.47 (s, 3 H), 1.38 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.3, 160.7, 158.2, 143.7, 143.4, 138.1, 137.2, 135.2, 134.6, 130.2, 130.2, 130.1, 126.2, 123.6, 116.0, 115.6, 115.4, 113.5, 37.7, 35.4, 23.4, 21.9, 12.8 ppm. HRMS (ESI, ion-trap): calcd. for $C_{22}H_{21}FNOS$ [M + H]$^+$ 366.1324; found 366.1322.

Biological Assays

Cells and Reagents: The leukemia cell lines (Du145LNCaP, PC3, A549, HepG2NCI-N87,MCF-7) were purchased from ATCC and maintained as recommended by ATCC (Manassas, USA). CCK-8 was purchased from Dojindo Molecular Technologies Inc (Kumamoto, Japan). DMSO and Cremophor were purchased from Sigma–Aldrich (Dorset, USA).

Antiproliferation Assay Using Cell Counting Kit (CCK-8): Cells in the logarithmic phase were placed into 96-well culture dishes (ca. 3000 cells/well). After 24 h, the cells were treated with the compounds or the vehicle control at the indicated concentrations and left for 72 h. CCK-8 was added to the 96-well plates (10 μL/well) and incubated with the cells for 3 h. OD450 and OD650 were determined using a micro-plate reader. Absorbance rate (A) for each well was calculated as OD450 – OD650. The cell viability rate for each well was calculated as V [%] = $(A_s - A_c)/(A_b - A_c) \times 100\%$, and the data were further analysed using Graphpad Prism5 (Graphpad Software, Inc.). The data used were the mean values from three experiments. A_s, Absorbance rate of the test-compound well; A_c, absorbance rate of the well with neither cell nor test compound; A_b, absorbance rate of the well with cell and vehicle control.

Supporting Information (see footnote on the first page of this article): Experimental procedures and characterization data along with copies of the ^{1}H and ^{13}C NMR spectra for all new compounds.

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[1] a) G. Piancatelli, A. Scettri, S. Barbadoro, *Tetrahedron Lett.* **1976**, *17*, 3555–3558; b) G. Piancatelli, *Heterocycles* **1982**, *19*, 1735–1744.

[2] For selected references concerning the mechanism of this rearrangement, see: a) G. Piancatelli, A. Scettri, *Tetrahedron Lett.* **1977**, *13*, 1131–1134; b) G. Piancatelli, A. Scettri, G. Da-

vid, M. D'Auria, *Tetrahedron* **1978**, *34*, 2775–2778; c) M. D'Auria, *Heterocycles* **2000**, *52*, 185–194; d) A. N. Faza, L. S. Lopez, R. Alvarez, I. R. de Lera, *Chem. Eur. J.* **2004**, *10*, 4324–4333.

[3] a) J. H. Dygos, K. A. Babiak, J. R. Behling, J. R. Medich, J. S. Ng, J. J. Wieczorek, *J. Org. Chem.* **1991**, *56*, 2549–2552; b) G. Piancatelli, M. D'Auria, F. D'Onofrio, *Synthesis* **1994**, *9*, 867–889; c) F. G. West, G. U. Gunawardena, *J. Org. Chem.* **1993**, *58*, 2402–2406; d) A. R. Rodriguez, B. W. Spur, *Tetrahedron Lett.* **2003**, *44*, 7411–7415; e) A. G. Csaky, M. Mba, J. Plumet, *Synlett* **2003**, *13*, 2092–2094; f) C.-C. Li, C.-H. Wang, B. Liang, X.-H. Zhang, L.-J. Deng, S. Liang, J.-H. Chen, Y.-D. Wu, Z. Yang, *J. Org. Chem.* **2006**, *71*, 6892–6897; g) M. P. Otero, E. P. Santin, F. Rodriguez-Barrios, B. Vaz, A. R. de Lera, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1883–1886; h) K. Ulbrich, P. Kreitmeier, O. Reiser, *Synlett* **2010**, *13*, 2037–2040.

[4] For selected reviews, see: a) B. A. Keay, J. M. Hopkins, P. W. Dibble, in: *Comprehensive Heterocyclic Chemsitry III*, vol. 3 (Eds.: G. Jones, C. A. Ramsden), Elsevier, Amsterdam, **2008**, p. 571; b) M. d'Ischia, A. Napolitano, A. Pezzella, in: *Comprehensive Heterocyclic Chemsitry III*, vol. 3 (Eds.: G. Jones, C. A. Ramsden), Elsevier, Amsterdam, **2008**, p. 353; c) B. H. Lipshutz, *Chem. Rev.* **1986**, *86*, 795; d) S. P. Roche, J. A. Porco Jr., *Angew. Chem.* **2011**, *123*, 4154–4179; *Angew. Chem. Int. Ed. Engl.* **2011**, *50*, 4068–4093; e) S. K. Bur, A. Padwa, *Chem. Rev.* **2004**, *104*, 2401–2432.

[5] For reviews concerning the synthesis and biological activity of spirooxindoles, see: a) C. Marti, E. M. Carreira, *Eur. J. Org. Chem.* **2003**, 2209–2219; b) R. M. Williams, R. J. Cox, *Acc. Chem. Res.* **2003**, *36*, 127–139; c) J. F. M. da Silva, S. J. Garden, A. C. Pinto, *J. Braz. Chem. Soc.* **2001**, *12*, 273–324; d) R. Rios, *Chem. Soc. Rev.* **2012**, *41*, 1060–1074; e) N. Ball-Jones, J. J. Badillo, A. K. Franz, *Org. Biomol. Chem.* **2012**, *10*, 5165–5181; f) R. Dalpozzo, G. Bartoli, G. Bencivenni, *Chem. Soc. Rev.* **2012**, *41*, 7247–7290; g) C. V. Galliford, K. A. Scheidt, *Angew. Chem.* **2007**, *119*, 8902–8912; *Angew. Chem. Int. Ed.* **2007**, *46*, 8748–8758.

[6] a) K. Ding, Y. Lu, Z. Nikolovska-Koleska, S. Qiu, Y. Ding, W. Gao, J. Stuckey, P. P. Roller, Y. Tomita, J. R. Deschamps, S. Wang, *J. Am. Chem. Soc.* **2005**, *127*, 10130–10131; b) K. Ding, Y. Lu, Z. Nikolovska-Coleska, G. Wang, S. Qiu, S. Shangary, W. Gao, D. Qin, J. Stuckey, K. Krajewski, P. P. Roller, S. Wang, *J. Med. Chem.* **2006**, *49*, 3432–3435.

[7] M. Kitajima, T. Nakamura, N. Kogure, M. Ogawa, Y. Mitsuno, K. Ono, S. Yano, N. Aimi, H. Takayama, *J. Nat. Prod.* **2006**, *69*, 715–718.

[8] S. R. Yong, A. T. Ung, G. S. Pyne, B. W. Skeltonb, A. H. White, *Tetrahedron* **2007**, *63*, 1191–1199.

[9] A. K. Franz, P. D. Dreyfuss, S. L. Schreiber, *J. Am. Chem. Soc.* **2007**, *129*, 1020–1021.

[10] For selected recent papers concerning the synthesis of spirooxindoles, see: a) D. Knueppel, S. F. Martin, *Org. Lett.* **2007**, *9*, 4623–4626; b) X. Chen, Q. Wei, S. Luo, H. Xiao, L. Gong, *J. Am. Chem. Soc.* **2009**, *131*, 13819–13825; c) Y. Zhang, J. S. Panek, *Org. Lett.* **2009**, *11*, 3366–3369; d) B. Alcaide, P. Almendros, T. M. del Campo, M. T. Quirós, *Chem. Eur. J.* **2009**, *15*, 3344–3346; e) S. Jaegli, J. Dufour, H.-L. Wei, T. Piou, X.-H. Duan, J.-P. Vors, L. Neuville, J. P. Zhu, *Org. Lett.* **2010**, *12*, 4498–4501; f) V. Helan, A. Mills, D. Drewry, D. Grant, *J. Org. Chem.* **2010**, *75*, 6693–6695; g) Wei, Q. L.-Z. Gong, *Org. Lett.* **2010**, *12*, 1008–1011; h) X. Companyó, A. Zea, A.-N. R. Alba, A. Mazzanti, A. Moyano, R. Rios, *Chem. Commun.* **2010**, *46*, 6953–6955; i) K. Albertshofer, B. Tan, C. F. Barbas, *Org. Lett.* **2012**, *14*, 1834–1837; j) B. Alcaide, P. Almendros, R. Rodríguez-Acebes, *Chem. Eur. J.* **2005**, *11*, 5708–5712; k) G. Bencivenni, L. Y. Wu, A. Mazzanti, B. Giannichi, F. Pesciaioli, M. P. Song, G. Bartoli, P. Melchiorre, *Angew. Chem.* **2009**, *121*, 7336–7339; *Angew. Chem. Int. Ed.* **2009**, *48*, 7200–7203.

[11] Part of this work has been published elsewhere, see: a) B.-L. Yin, J.-Q. Lai, Z.-R. Zhang, H.-F. Jiang, *Adv. Synth. Catal.* **2011**, *353*, 1961–1965; b) B. Yin, L. Huang, X. Zhang, F. Ji, H. Jiang, *J. Org. Chem.* **2012**, *77*, 6365–6370; c) B. Yin, L. Huang, X. Wang, J. Liu, H. Jiang, *Adv. Synth. Catal.* **2013**, *355*, 370–376.

[12] Further examples of rotational isomerism in *trans*-1,2-diarylethylene derivatives: a) U. Mazzucato, F. MoMichioli, *Chem. Rev.* **1991**, *91*, 1679–1719; b) S. Toyota, *Chem. Rev.* **2010**, *110*, 5398–5424.

[13] For selected examples of Friedel–Crafts reactions using oxocarbenium species as the alkylating agent, see: a) J.-F. Fan, Y. Wu, Y.-L. Wu, *J. Chem. Soc. Perkin Trans. 1* **1999**, 1183–1188; b) M. Spadafora, M. Mehiri, A. Burger, R. Benhida, *Tetrahedron Lett.* **2008**, *49*, 3967–3971; c) D. Martinez-Solorio, M. P. Jennings, *Org. Lett.* **2009**, *11*, 189–192; d) R. R. Castillo, M. Aquino, Z. Gandara, I. Safir, Z. Elkhayat, P. Retailleau, S. Arseniyadis, *Org. Lett.* **2012**, *14*, 1628–1631.

[14] B.-L. Yin, Y. Wu, Y.-L. Wu, *J. Chem. Soc. Perkin Trans. 1* **2002**, 1746–1747.

[15] E. S. Ranganathan, S. K. Bej, L. T. Thompson, *Appl. Catal. A* **2005**, *289*, 153–162.

[16] G. Acres, J. Frost, G. Hards, R. Potter, T. Ralph, D. Thompsett, G. Burstein, G. Hutchings, *Catal. Today* **1997**, *38*, 393–400.

[17] Crystallographic data for **10a**–**30** have been deposited with CCDC-958434. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[18] J. J. Baschuk, X. Li, *Int. J. Energy Res.* **2001**, *25*, 695–713.

[19] S. Ehrlich, J. Moellmann, W. Reckien, T. Bredow, S. Grimme, *ChemPhysChem* **2011**, *12*, 3414–3420.

[20] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, *Gaussian 09*, revision D.01, Gaussian, Inc.,Wallingford, CT, **2009**.

[21] For selected references concerning dienone–phenol rearrangement, see: a) B. Miller, *Acc. Chem. Res.* **1975**, *8*, 245–256; b) Z. Guo, A. G. Schultz, *Org. Lett.* **2001**, *3*, 1177–1180.

[22] For the synthesis and biological activities of 5*H*-thieno[3,2-*c*]-quinolin-4-one, see: a) K. C. Majumdar, M. Ghosh, *Tetrahedron* **2002**, *58*, 10047–10052; b) E. M. Beccalli, G. Broggini, M. Martinelli, G. Paladino, C. Zon, *Eur. J. Org. Chem.* **2005**, 2091–2096; c) F. Nobuhiro, O. Yuya, S. Satoshi, K. Shigeru, WO2009107850, **2009**.

[23] a) F. Pierre, P. C. Chua, S. E. O'Brien, A. Siddiqui-Jain, P. Bourbon, M. Haddach, J. Michaux, J. Nagasawa, M. K. Schwaebe, E. Stefan, A. Vialettes, J. P. Whitten, T. K. Chen, L. Darjania, R. Stansfield, K. Anderes, J. Bliesath, D. Drygin, C. Ho, M. Omori, C. Proffitt, N. Streiner, K. Trent, W. G. Rice, D. M. Ryckman, *J. Med. Chem.* **2011**, *54*, 635–654; b) F. Pierre, C. F. Regan, M.-C. Chevrel, A. Siddiqui-Jain, D. Macalino, N. Streiner, D. Drygin, M. Haddach, S. E. O'Brien, W. G. Rice, D. M. Ryckman, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 3327–3331.

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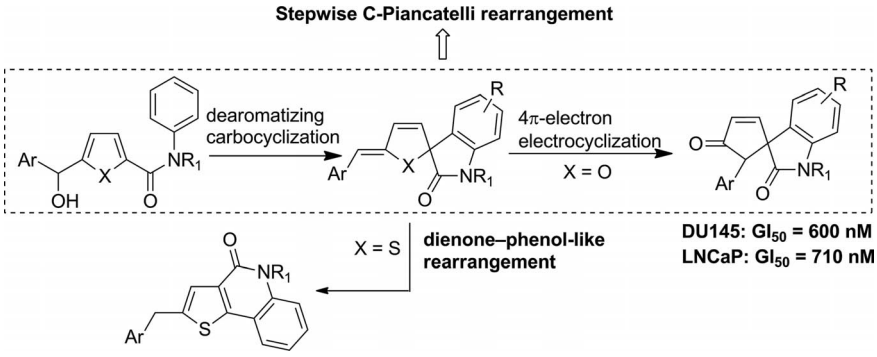

We describe the scope of the transformation of 2-furylcarbinols into spiro[furo-oxindoles], and the skeletal rearrangements of spiro[furo-oxindoles] and spiro[thieno-oxindoles]. The transformation of 2-furylcarbinols into spiro[pentenone-oxindoles] represents the first stepwise *C*-Piancatelli rearrangement. Some of the spirooxindole products showed promising cytotoxic activities against tumor cell lines.

Keywords: Heterocycles / Spiro compounds / Rearrangement / Aromatic substitution / Cyclization

