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Article

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Synthesis of Spiro[indole-3,5'-isoxazoles] with Anticancer Activity via a Formal (4+1)-Spirocyclization of Nitroalkenes to Indoles

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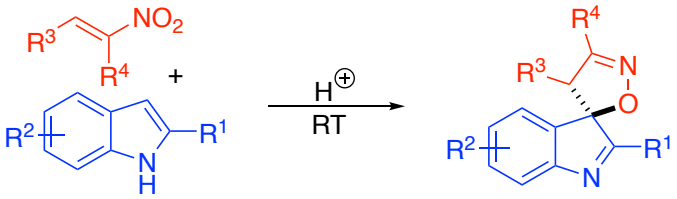
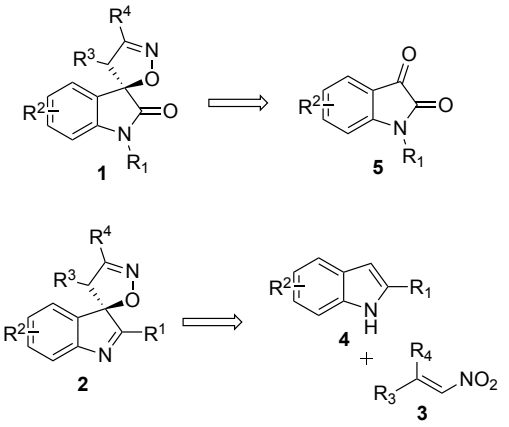


ABSTRACT: An acid-assisted (4+1)-cycloaddition of indoles with nitrostyrenes affords 4'*H*-spiro[indole-3,5'-isoxazoles] in a diastereomerically pure form. Several of these spirocyclic molecules exhibit promising anti-cancer activity by reducing viability and inducing differentiation of neuroblastoma cells.

INTRODUCTION

Natural and synthetic spiro-heterocycles are important synthetic targets due to their diverse biological profiles and manifold reactivity.[1] Although the subject of the present study, 4'*H*-spiro[indole-3,5'-isoxazoles] (**2**), do not occur in nature and have not been obtained synthetically, they share the privileged polycyclic framework with an array of highly potent natural products (Scheme 1).[2,3] Related 4'H-spiro[indoline-3,5'-isoxazol]-2-one (**1**) have received some attention from the synthetic community and methods toward their synthesis have been developed. These rely on ready availability of isatin precursors **5** and include an acid-assisted 1,5-spiro-cyclization of monooximes of 3-ene-2,5-diones,[4] [3+2]-cycloaddition of nitrileoxides to 3-methyleneoxindoles,[5] and metal-catalyzed selective vinylation of isatin oximes with vinylboronic acids.[6] Any subsequent manipulations at the carbonyl moiety, should they be required, are limited by the vulnerability of the alpha-spirocyclic fragment in **1**. Recently, we communicated on the novel, efficient and highly diastereoselective route to 4'*H*-spiro[indole-3,5'-isoxazoles] (**2**) proceeding via a formal [4+1] cycloaddition reaction of nitroalkene **3** as 1,4-*CCNO*-dipole and the C-3 of indole **4** as the dipolarophilic C_1-moiety.[7] To the best of our knowledge, this is the only direct spirocyclization approach to 4'*H*-spiro[indole-3,5'-isoxazoles] substituted with an alkyl, aryl or hetaryl group at C-2 (Scheme 1). Herein we report a full account of this unusual transformation, which includes studies on the scope and limitations, assessment of the side processes, and biological evaluation of the spirocyclic products for anti-cancer activities.

Scheme 1



RESULTS AND DISCUSSION

Our groups have been exploring polyphosphoric acid (PPA)-assisted cascade heterocyclizations of indoles with nitro compounds (Scheme 2).[8] For example, we discovered conditions allowing for a selective rearrangement of the

nitro group into hydroxamic acid **6**,[9] or under modified conditions, an unusual ANRORC[10] cascade to give 2-quinolones **7**.[8] In other examples, substitution of PPA with PCl_3 resulted in in situ conversion of the nitro-group into a nitrile **8**[11] or a carboxamide **9**.[12] During this work, we came across a poor quality batch of P_2O_5 containing notable amounts of red phosphorus (arising from incomplete combustion during reagent manufacturing). Polyphosphoric acid prepared from this material had a distinct pink color. In this medium, the reaction between nitrostyrene **3a** and 2-phenylindole (**4a**) carried out at room temperature led to the formation of notable amounts of unexpected spirocyclic structure **2aa** (Table 1). The molecular structure of **2aa** was unambiguously confirmed by single crystal X-ray crystallography.[13] Remarkably, this product was formed with complete (3*R**,4'*S**)-diastereoselectivity, as shown. This finding justified further efforts towards the optimization of the reaction conditions for the selective synthesis of spirocycles **2**. We further tested the reaction in the presence of 2 equiv. of phosphorous acid (H_3PO_3, pK_a 1.30) in various organic media. It was discovered that reactions carried out in ethyl alcohol, THF or dimethoxyethane afforded nitroalkane **5aa** as the sole product (Table 1, entries 1-3). Formation of spirocyclic product **2aa** in minute amounts was observed in such solvents as DMF and acetonitrile (entries 4,5), but the best results were obtained when reactions were carried out at room temperature in solutions of acetic or formic acid (entries 6,7). Indeed, it was found that H_3PO_3-assisted reaction in formic acid affords **2aa** as the sole product in nearly quantitative yield (entry 7). We also tested the reaction mediated by *ortho*-phosphoric acid (H_3PO_4, pK_a 2.16), which also proceeded smoothly affording **2aa** in 76% yield along with 13% of nitroalkane **10aa** (entry 8). This prompted us to test a number of different Brønsted acids. It was found that weaker carboxylic acids such as CH_3COOH (pK_a 4.75) mediate Michael type addition to afford nitroalkane **10aa** exclusively (entry 9). Reactions mediated by stronger acids, such as formic (pK_a 3.75, entry 10), trifluoroacetic (pK_a 0.00, entry 11), afforded **5aa** as the major product along with minute amounts of spirocyclic material **2aa**. Even stronger acid such as methanesulphonic (pK_a -2.00, entry 12) allowed for predominant formation of **2aa.** In the presence of sulfuric acid, whose acidity could be estimated using the pK_a of the protonated carboxylic acid (c.a. -6.0), compound **2aa** was formed exclusively, albeit in marginal yield, due to partial decomposition of the products, but importantly, no nitroalkane **10aa** was detected (entry 13). Taking into account the supreme performance of phosphorous acid, which provided nearly quantitative yield of the target product, we made it a reagent of choice.With optimized conditions in hand, we evaluated the featured transformation on preparative scale employing 2-phenyl-1*H*-indole (**4a**) and aromatic nitrostyrenes **3a**-**f**. We were pleased to find that these reactions proceeded smoothly affording the corresponding spirocyclic products **2aa**-**2af** in high yields and diastereoselectivities (Scheme 4, entries 1-6). Next, the possibility to employ aliphatic nitroalkenes bearing primary (**3g**) or secondary (**3h**) alkyl substituents was assessed. These reactions proved to be somewhat less efficient and sluggish, requiring about 2 h for complete conversion, but the corresponding spirocyclic indolines **2ag** and **2ah** were also obtained as sole diastereomers in good yields.

Scheme 2

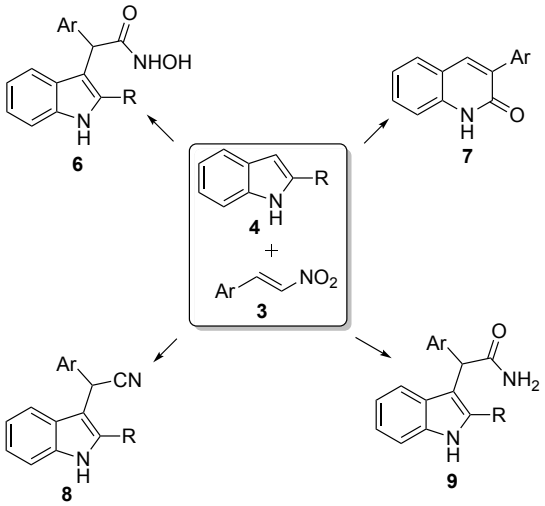
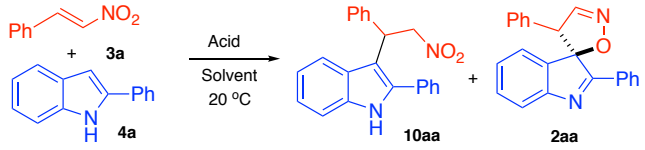


Table 1. Optimization of spiro-cyclization towards **2aa**



	Acid[a] (Time, h)	Solvent	2aa:10aa (yields, %)[c]
1	H_3PO_3 (0.75)	EtOH	0:91
2	H_3PO_3 (0.75)	DME	0:92
3	H_3PO_3 (0.75)	THF	0:91
4	H_3PO_3 (0.75)	DMF	7:87
5	H_3PO_3 (0.75)	MeCN	16:81
6	H_3PO_3 (0.75)	CH_3COOH	95:0
7	**H_3PO_3 (0.75)**	**HCOOH**	**98:0**
8	H_3PO_4 (1.5)	HCOOH	76:13
9	CH_3COOH (15)		0:95
10	HCOOH (15)		8:83
11	CF_3COOH (1.5)	HCOOH	10:82
12	CH_3SO_3H (1.5)	HCOOH	60:8
13	H_2SO_4 (1.5)[b]	HCOOH	33:0

a) All acids were used as 1:1 mixture with 85% formic acid, unless specified otherwise.

b) A mixture of 150 mg of 98% sulfuric acid and 500 mg of 85% formic acid.

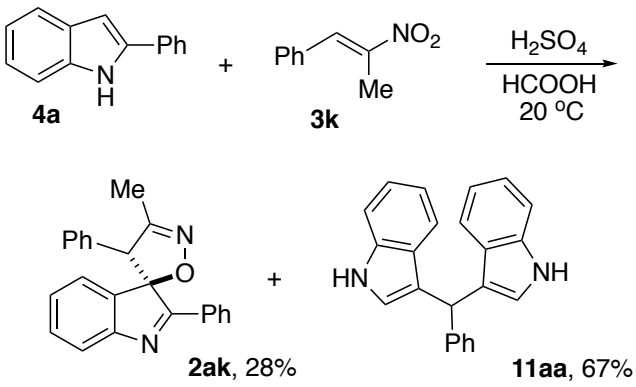
c) Yields were determined by ^{1}H NMR analysis of crude reaction mixtures.

Reaction of **4a** with (*E*)-2-(2-nitrovinyl)furan (**3i**) allowed the preparation of 4'-(furan-2-yl)-substituted analog **2ai**, thus showing the possibility of introducing even acid-sensitive heteroaryl groups to the featured scaffold (entry 9). Next, the influence of the substituent at C-2 of indole was investigated. Facile and highly efficient spirocyclization was shown to proceed with indole substrates bearing electron rich substituents (**4b**,**d**,**g**,**h**). Typically, these reactions progressed to completion within 30-40 min, affording the corresponding spirocyclic products in good yields (**2ba**, **2da**, **2ga**, **2ha**: entries 10, 12, 15, 16). Indoles bearing moderately electron poor (**4c**) or sterically encumbered (**4e**,**f**) aryl substituents at C-2 reacted more sluggishly requiring extended reaction time (about 2 h) for complete conversion, but the yields of the corresponding products **2ac**, **2ae**, and **2af** were still reasonably high (entries 11, 13, 14). The introduction of heteroaryl substituents was also tolerated as demonstrated by the preparation of the thienyl substituted derivative **2ja** (entry 17). Replacing the phenyl group at C-2 with a methyl group resulted in complex reaction mixtures and total decomposition of the initially formed spirocyclic product **2ka**, but lowering the temperature to 10 °C allowed for isolation of **2ka** in marginal yield (entry 18). Also, it should be pointed out that 2-(trifluoromethyl)- (**4o**) and 2-(methoxycarbonyl)- (**4p**) 1*H*-indoles did not provide any spirocyclic products at all, even at 50 °C. Starting materials were recovered unchanged in both cases.

Next, we evaluated tolerance of this transformation to the presence of other substituents at C-5 or C-7 of indole core. To this end, indoles bearing 5-isopropyl (**4l**), 5-methoxy (**4m**), and 7-chloro (**4n**) substituent were subjected to the reaction with nitrostyrene **3a** under standard reaction conditions. All these reactions proceeded uneventfully affording spirocyclic products **2ia**, **2ma** and **2na** efficiently with high selectivity (entries 19-21). Finally, for further evaluation of the reaction scope, several variously substituted indoles were tested in reactions with different nitrostyrenes to obtain more complex representatives of this class of compounds (entries 22-25).

Next, we tested the possibility to involve β-alkyl nitrostyrenes in order to access spirocyclic compounds **2** with additional substituents at C-3'. To this end, (2-nitroprop-1-en-1-yl)benzene (**3k**) was subjected to the reaction with 2-phenyl-1*H*-indole (**4a**) in the presence of H_3PO_3 in formic acid. Unfortunately, this reaction did not proceed at all with the recovery of the starting materials even after heating at 80 °C. Similar lack of reactivity was observed in an attempted reaction carried out in the presence of H_3PO_4. Evidently, such a modification in the nitrostyrene structure introduces unfavorable steric demands and reduces polarization of the double bond making it inefficient as a Michael acceptor. To address this issue, we enforced the reaction by applying stronger acids, such as sulfuric or methanesulfonic. In the presence of H_2SO_4, the reaction between **3k** and **4a** proceeded at room temperature affording spirocyclic product **2ak** in low yield and an unexpected formation of triarylmethane **11aa** as the major product (Scheme 3). By carrying out the reaction the presence of $MeSO_3H$ we managed to improve the **2ak**/**11aa** selectivity ratio and isolated

Scheme 3



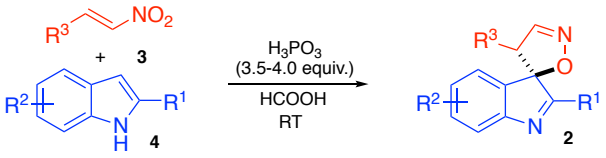
2ak in 58% yield as a mixture of diastereomers 93:7 (Scheme 5, entry 1). However, formation of **11aa** (38% yield) still represents a challenge as we failed to identify conditions for the spirocyclization that avoid the formation of this byproduct.

Reaction of indole **4a** with (2-nitrobut-1-en-1-yl)benzene (**3l**) also proceed uneventfully affording a mixture of 54% of spirocyclic product **2al** and 42% of the same triarylmethane **11aa** (Scheme 5, entry 2). Reaction of indole **4a** with 1-chloro-4-(2-nitroprop-1-en-1-yl)benzene (**3m**) afforded comparable amounts of spirocyclic product **2am** along with triarylmethane **11ac** (Scheme 5, entry 3). Interestingly, byproduct **11** incorporates only the substituent R^3 with the adjacent olefinic carbon atom, while the other olefinic carbon, together with the NO_2 group and substituent R^4, are absent. Testing this reaction with substituted nitroalkenes **3k**-**m** and indoles **4a**,**e**,**g** always gave the spirocyclic product in marginal yield with lower diastereoselectivity, along with notable amounts of triarylmethane byproduct **11** (Scheme 5, entries 4-8).

In the next stage of our investigation we designed a three-component one-pot transformation involving the assembly of indoles **4** from arylhydrazines **12** and acetophenones **13** via the Fischer reaction, followed by spirocyclization towards structure **2** (Scheme 6). To this end, equimolar mixtures of **12a** and **13a** were first refluxed in glacial acetic acid to obtain the corresponding hydrazones **14a** (R^2 = H, R^1 = Ph). Here, acetic acid was used instead of formic acid since the latter notably decomposes upon contact with H_2SO_4 upon heating. Addition of sulfuric acid triggered the Fischer indolization, which proceeded smoothly at 90 °C furnishing intermediate indole **4a** (Scheme 6). Upon completion of this process, nitroalkene **3a** was added at room temperature and spirocyclic product **2aa** was formed in isolated 79% yield. The one-pot transformation was also successful with diversely substituted **12**, **13** and **3** (Scheme 6). Expectedly, triarylmethane byproducts **11** were formed in reactions involving β-alkyl nitrostyrenes **3k**-**m**. In this one-pot version of the reaction

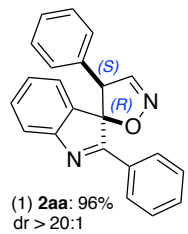
it was not possible to employ H_3PO_3, which provides the best results for spirocyclization reaction, since this acid failed to mediate the Fischer indolization step. The overall yield of the one-pot process is somewhat lower compared to the normal synthetic routine involving isolation and purification of the intermediate indoles. Nevertheless,

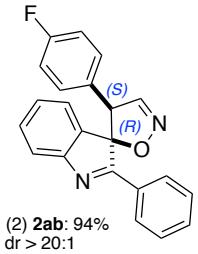
Scheme 4

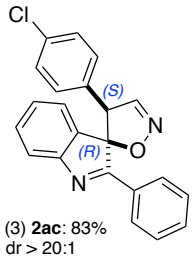


3a: R^3 = Ph;
3b: R^3 = 4-FC_6H_4;
3c: R^3 = 4-ClC_6H_4;
3d: R^3 = 4-$MeOC_6H_4$;
3e: R^3 = 4-$Me_2NC_6H_4$;
3f: R^3 = 2-FC_6H_4;
3g: R^3 = *n*-C_6H_{13};
3h: R^3 = *i*-Pr;
3i: R^3 = 2-furyl;
3j: 4-EtC_6H_4

4a: R^1 = Ph, R^2 = H;
4b: R^1 = 4-MeC_6H_4, R_2 = H;
4c: R_1 = 4-ClC_6H_4, R_2 = H;
4d: R^1 = 4-EtC_6H_4, R^2 = H;
4e: R^1 = 2-naphthyl, R^2 = H;
4f: R^1 = (5,6,7,8-tetrahydro-naphthalen-2-yl), R^2 = H;
4g: R^1 = 2,3-dihydrobenzo[*b*]-[1,4]dioxin-6-yl, R^2 = H;
4h: R^1 = 3,4-$(MeO)_2C_6H_3$, R^2 = H;
4i: R^1 = 4-MeC_6H_4, R^2 = H;
4j: R^1 = 2-thienyl, R^2 = H;
4k: R^1 = Me, R^2 = H;
4l: R^1 = Ph, R^2 = 5-*i*-Pr;
4m: R^1 = Ph, R^2 = 5-MeO;
4n: R^1 = Ph, R^2 = 7-Cl;
4o: R^1 = CF_3, R^2 = H;
4p: R^1 = CO_2Me, R^2 = H.


(1) **2aa**: 96%
dr > 20:1


(2) **2ab**: 94%
dr > 20:1


(3) **2ac**: 83%
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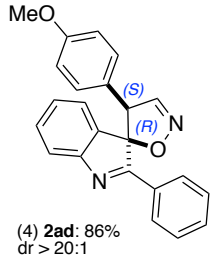
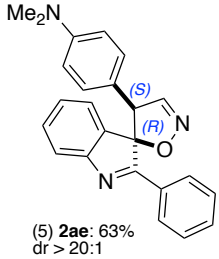
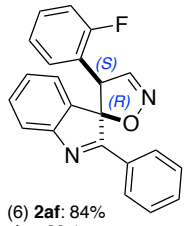

(4) **2ad**: 86%
dr > 20:1


(5) **2ae**: 63%
dr > 20:1


(6) **2af**: 84%
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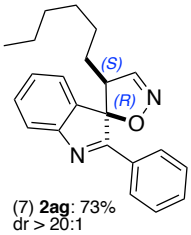
(7) **2ag**: 73%
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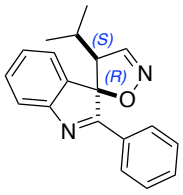
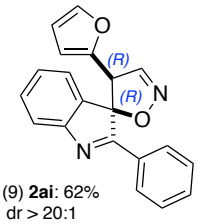
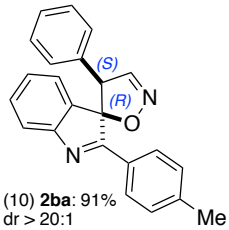

(8) **2ah**: 71%
dr > 20:1


(9) **2ai**: 62%
dr > 20:1


(10) **2ba**: 91%
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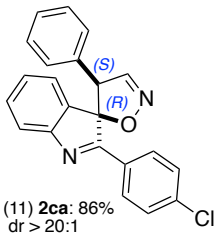
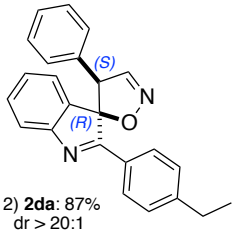
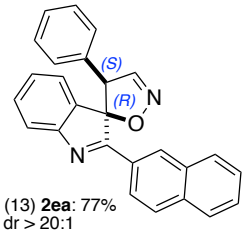
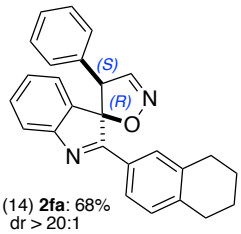
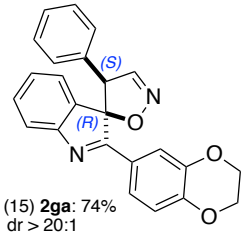
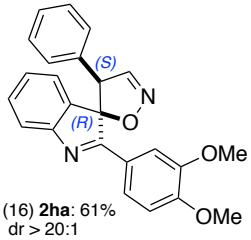

(11) **2ca**: 86%
dr > 20:1

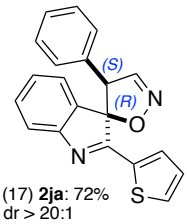

(12) **2da**: 87%
dr > 20:1

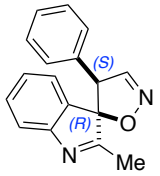

(13) **2ea**: 77%
dr > 20:1

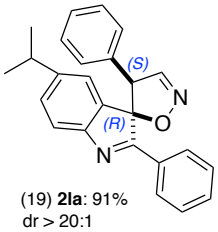

(14) **2fa**: 68%
dr > 20:1

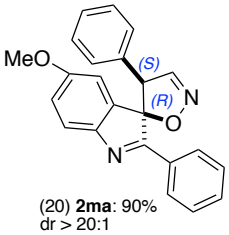

(15) **2ga**: 74%
dr > 20:1

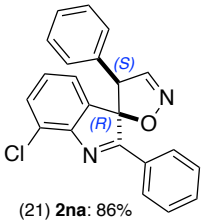

(16) **2ha**: 61%
dr > 20:1

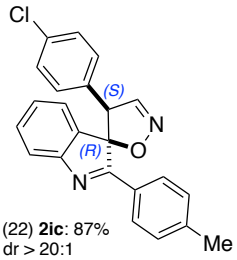

(17) **2ja**: 72%
dr > 20:1

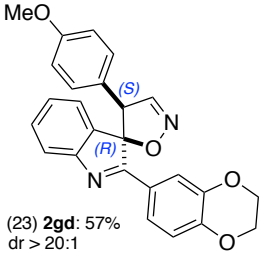

(18) **2ka**: 44%
(at 10 °C)
dr > 20:1

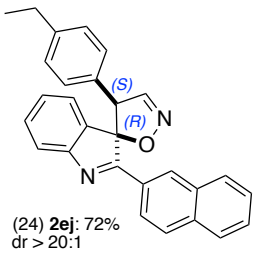

(19) **2la**: 91%
dr > 20:1

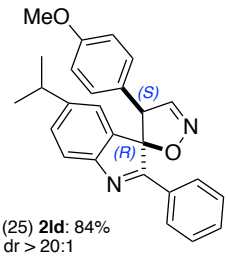

(20) **2ma**: 90%
dr > 20:1


(21) **2na**: 86%
dr > 20:1

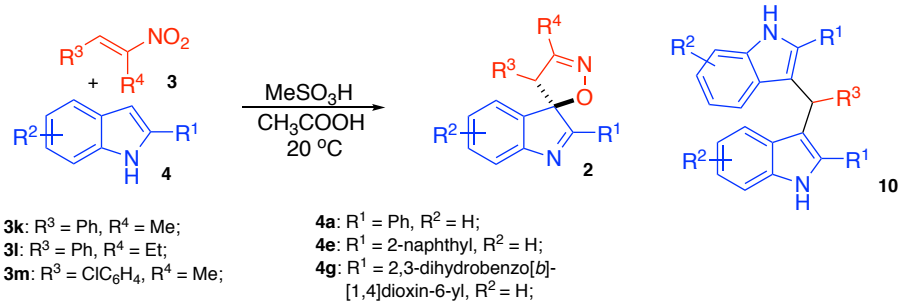

(22) **2ic**: 87%
dr > 20:1

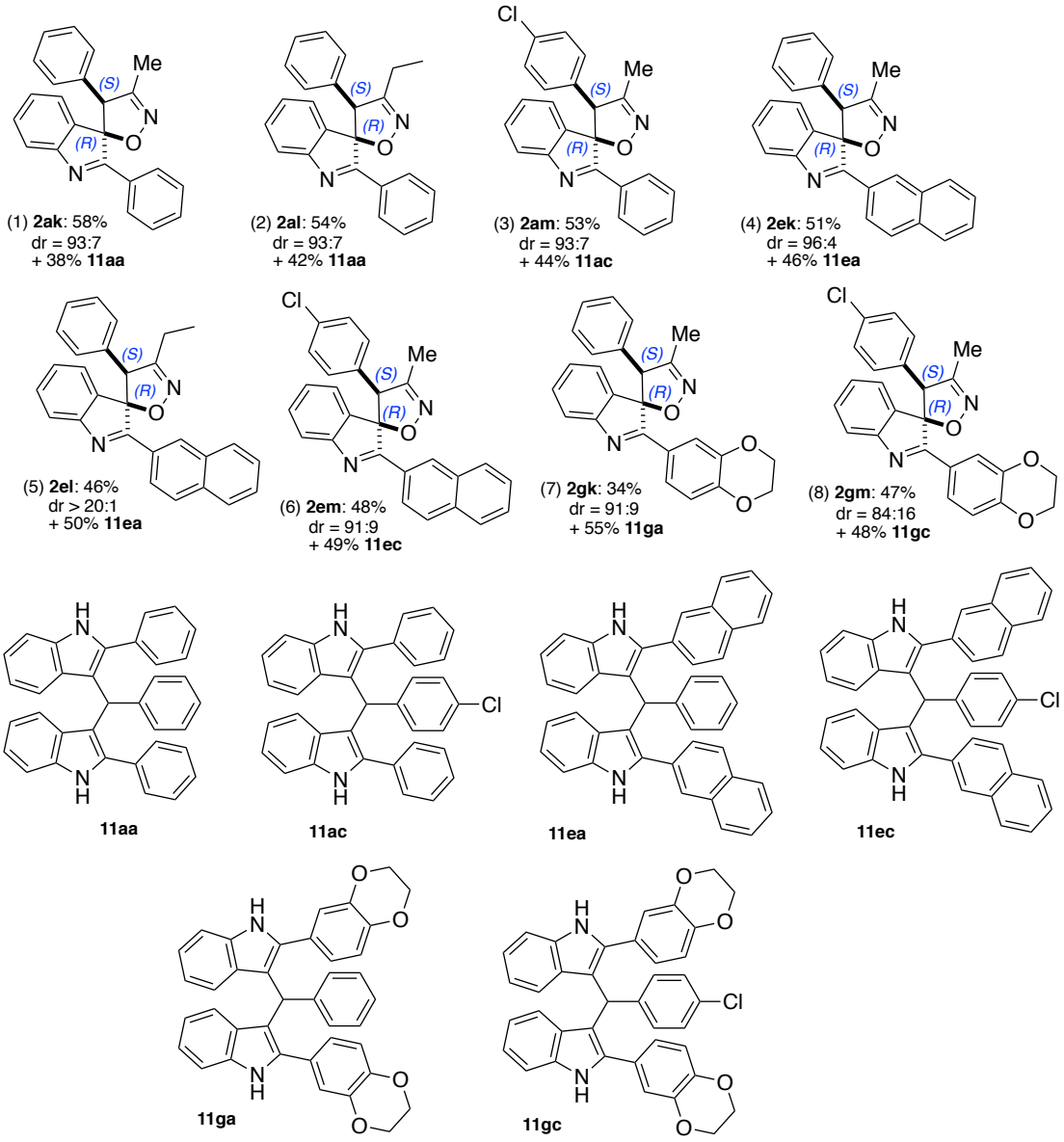

(23) **2gd**: 57%
dr > 20:1


(24) **2ej**: 72%
dr > 20:1


(25) **2ld**: 84%
dr > 20:1

Scheme 5

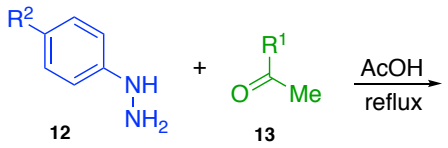




the one-pot approach still looks attractive as it allows for the reduction of the number of synthetic operations and elimination of waste products.

Analysis of the experimental observations has led us to propose the following mechanistic rationale (Scheme 7). Initial protonation of nitroalkene **3** leads to the formation of activated *N*-oxo-*N*-vinylhydroxylammonium **15** (which can be *O*-phosphorylated in H_3PO_3 or H_3PO_4 media, making it even more stable).[14] This species is highly susceptible to Michael-type attack by C-3 of indole **4**, affording iminium species **16**, which upon deprotonation is transformed into nitronate form **17**. It should be pointed out, that species

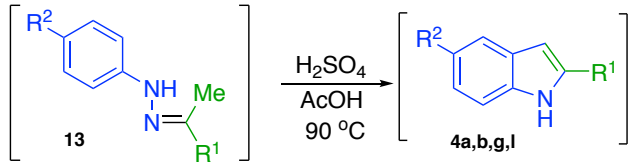
Scheme 6



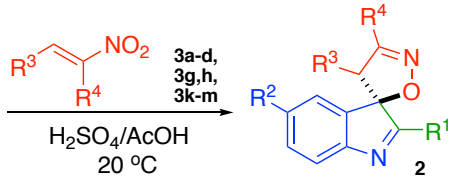
12 **13**

12a: R^2 = H; **12l**: R^2 = *i*-Pr

13a: R^1 = Ph; **13b**: R^1 = 4-MeC_6H_4; **13g**: R^1 = 2,3-dihydrobenzo[*b*]-[1,4]dioxin-6-yl



13 **4a,b,g,l**



2

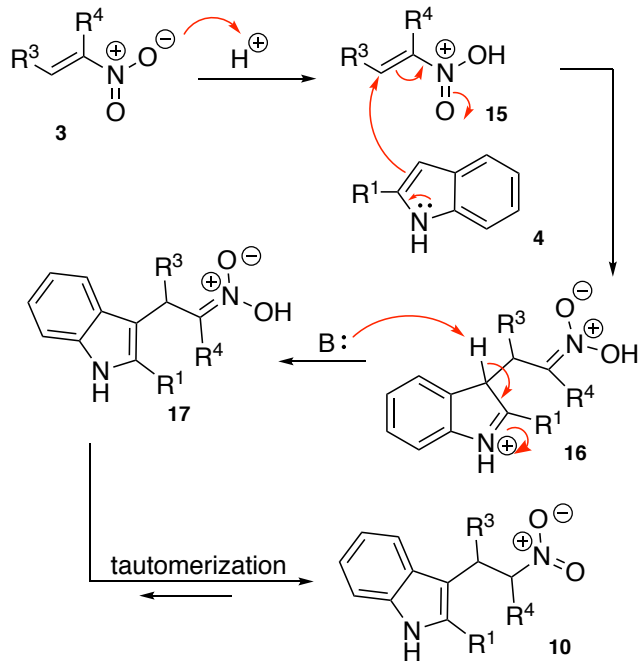
2aa: R^1 = R^3 = Ph, R^2 = R^4 = H, 79%;
2ab: R^1 = Ph, R^3 = 4-FC_6H_4, R^2 = R^4 = H, 72%;
2ac: R^1 = Ph, R^3 = 4-ClC_6H_4, R^2 = R^4 = H, 68%;
2ad: R^1 = Ph, R^3 = 4-MeOC_6H_4, R^2 = R^4 = H, 74%;
2ag: R^1 = Ph, R^3 = *n*-C_6H_{13}, R^2 = R^4 = H, 49%;
2ah: R^1 = Ph, R^3 = *i*-Pr, R^2 = R^4 = H, 53%;
2ak: R^1 = R^3 = Ph, R^2 = H, R^4 = Me, 41% + **11aa**, 27%;
2al: R^1 = R^3 = Ph, R^2 = H, R^4 = Et, 42% + **11aa**, 31%;
2ba: R^1 = 4-MeC_6H_4, R^2 = R^4 = H, R^3 = Ph, 77%;
2ga: R^1 = 2,3-dihydrobenzo[*b*]-[1,4]dioxin-6-yl, R^2 = R^4 = H, R^3 = Ph, 59%;
2gm: R^1 = 2,3-dihydrobenzo[*b*]-[1,4]dioxin-6-yl, R^2 = H, R^3 = 4-ClC_6H_4, R^4 = Me, 36% + **11gc**, 32%;
2la: R^1 = R^3 = Ph, R^2 = *i*-Pr, R^4 = H, 73%.

17 can tautomerize to form nitroalkane form **10**. Unlike **17**, form **10** is non-reactive in the spirocyclization reaction. Indeed, when pre-isolated compound **10aa** was subjected to the action of H_3PO_3 in formic acid (best optimized reaction conditions), it failed to provide any spiro-product **2aa**, and was recovered unchanged (Scheme 8). At the same time, when potassium nitronates **18**, generated upon basic treatment of nitroalkanes **10** in EtOH, were isolated and re-subjected to the spirocyclization under the same conditions spiro-products were formed, albeit in marginal yields along with recovered nitroalkanes **10** (Scheme 8). These experiments are consistent with the idea that nitronates **17** are essential intermediates in the featured process.

It could be further reasoned, that protonation of nitronate **17** under acidic conditions should provide nitronic acid **20**, which is susceptible to acid-mediated dehydration to afford conjugated oxime **21**. Subsequent acid-assisted 5-*endo-trig* cyclization should provide spiro-2,5-dihydroisoxazole species **22**, which under the reaction conditions may isomerize into either (3*R**,4'*S**)- (**2**) or (3*R**,4'*R**)-4,5- dihydroisoxazole **23** (Scheme 9).

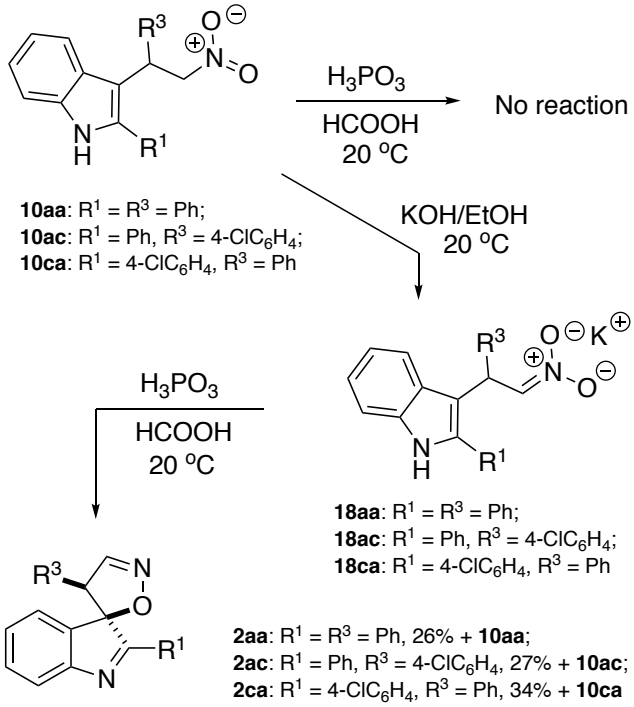
Our DFT modeling[13] suggests that diastereomer **2** is more thermodynamically favored by about 4.1 kcal/mol, which explains high diastereoselectivity of the featured transformation.

Scheme 7



3 **15** **4** **17** **16** **10**

Scheme 8



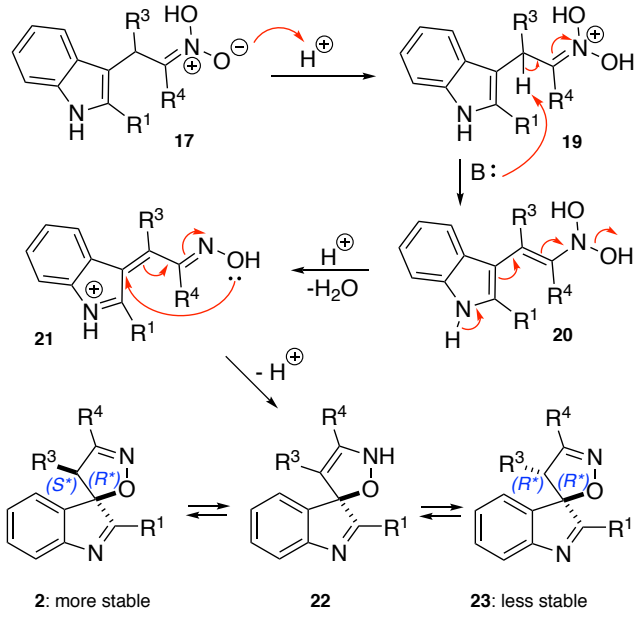
10aa: R^1 = R^3 = Ph;
10ac: R^1 = Ph, R^3 = 4-ClC_6H_4;
10ca: R^1 = 4-ClC_6H_4, R^3 = Ph

18aa: R^1 = R^3 = Ph;
18ac: R^1 = Ph, R^3 = 4-ClC_6H_4;
18ca: R^1 = 4-ClC_6H_4, R^3 = Ph

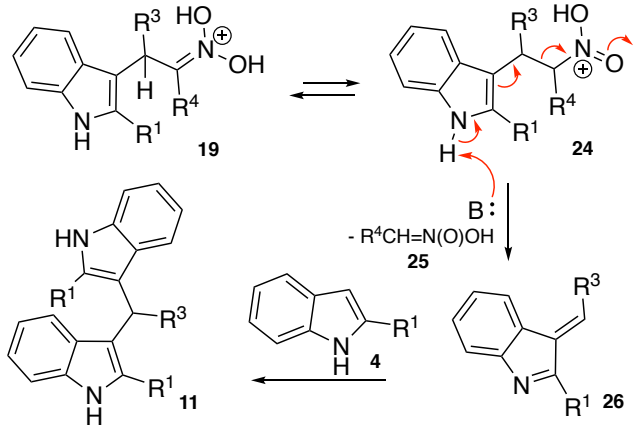
2aa: R^1 = R^3 = Ph, 26% + **10aa**;
2ac: R^1 = Ph, R^3 = 4-ClC_6H_4, 27% + **10ac**;
2ca: R^1 = 4-ClC_6H_4, R^3 = Ph, 34% + **10ca**

It could be also envisioned that *N*-alkylidene-*N*-hydroxyhydroxylammonium species **19** formed upon protonation of nitronate **17** exists in tautomeric equilibrium with *N*-alkyl-*N*-oxohydroxylammonium form **24** (Scheme 10). The latter species should be susceptible to a fragmentation with extrusion of nitronic (azinic) acid **25** to afford highly electrophilic (*E*)-3-alkylidene-2-methyl-3*H*-indole species **26**.

Scheme 9



Scheme 10



In the presence of excess amount of slowly reacting indole starting material **4** nucleophilic attack of this species is expected to furnish alkylation product **11**. It should be pointed out, that intermediates **24** derived from nitrostyrenes substituted at C-β ($R^4 \neq H$) should experience significant unfavorable steric repulsion between groups R^3 and R^4, and thus are expected to be more prompt to the extrusion of **25**. This might be the reason that formation of by-products **11** was detected only in such cases. An alternative reason for the observed phenomenon might be in the unfavored formation of key intermediate **20** in reaction of substrates bearing bulky R^4.

The above considerations also provide an explanation to the observed dependence of the reaction outcome on the strength of the employed Brønsted acid. Indeed, in the presence of weak acids (such as AcOH) protonation of nitronate **17** to afford nitronic acid **19** is not expected to be efficient. Instead, tautomerization would take place to yield non-reactive nitoalkane **10**. Employment of Lewis-basic solvents (alcohols, ethers, amides) provides the same effect. In the presence of stronger acids (H_3PO_3, H_3PO_4), kinetically controlled protonation of negatively charged oxygen moiety in structure **17** should take place much to a greater extent, and key intermediate **19** would be generated in significant concentrations. The following spirocyclization can also be additionally assisted by phosphorylation of the hydroxylamine functions in both **19** and **20**, which should promote the elimination step leading to formation of oxime **20**. However, for sterically hindered nitrostyrenes **3k-m** ($R^4 \neq H$) the initial Michael addition step in such acids is not efficient, probably, also due to the phosphorylation of the anionic oxygen atom in species **3**, introducing additional steric encumbrance. With strongest Brønsted acids, such as sulfuric or methanesulfonic, an alternative route for the thermodynamically controlled protonation of species **17** at carbon atom should also take place to afford species **24**, which ultimately leads to the formation of triarylmethane byproduct **11**.

Table 2. The effects of the synthesized compounds on the viability of neuroblastoma cells

compound #	% mean cell viability [a]	% SD
2aa	75	2
2ab	95	8
2ac	97	6
2ad	47	10
2ae	58	4
2af	92	7
2ag	93	2
2ah	102	7
2ai	95	8
2ba	65	7
2ca	74	8
2da	20	2
2ea	49	7
2fa	48	4
2ga	26	8
2ha	94	6
2ja	18	3
2ka	96	7
2la	40	7
2ma	73	9
2na	94	5
2ic	73	6
2ld	56	4
2gd	18	0
2ej	37	1
2ak	101	3
2ek	92	4
2em	101	7

[a] BE(2)-C cells were treated with the indicated compounds (25 μM) in triplicates for 4 days. Cell viability was then determined by the MTT assay. Shown are the compound name, % mean cell viability relative to DMSO control, and standard deviation (SD).

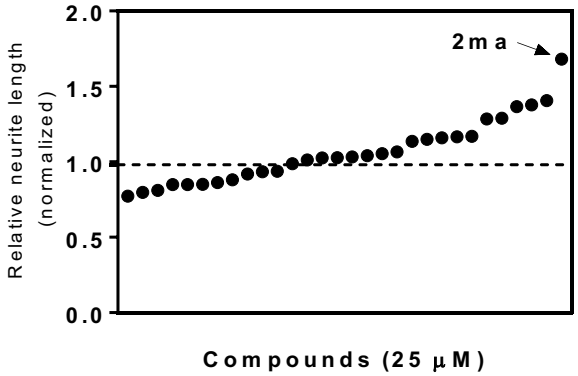


Figure 1. Effect of compounds on neurite outgrowth in neuroblastoma cell line BE(2)-C. 1,000 cells were treated with the compounds (25 μM) for 8 days. Shown is the scatter plot of normalized neurite lengths, sorted in ascending order, associated with individual compounds. Black dashed line is the mean of the library.

Due to their interesting natural product-like framework, the synthesized compounds were tested for biological activities. For example, they were found to reduce viability of BE(2)-C human neuroblastoma cells (Table 2). The effect was particularly pronounced with compounds **2da**, **2ga**, **2ja** and **2gd**, which at the concentration of 25 μM reduced cell viability to 20, 26, 18 and 18%, respectively. Although a more extensive testing with the determination IC_{50} values against several cancer cell lines would be necessary to understand the structure-activity relationship (SAR) trends in this series of compounds, it is interesting that two of these four compounds (**2ga** and **2gd**) contain the benzodioxane moiety at the C2-position of the indole ring revealing the initial SAR.

In another assay, the synthesized compounds were tested for their ability to induce differentiation of the BE(2)-C neuroblastoma cells. Neuroblastoma is a major type of childhood cancer responsible for ~15% of cancer-related deaths among children. [15] It is believed that neuroblastoma tumors result the from the failure of neural crest precursor cells to undergo differentiation and lead to uncontrolled cell proliferation cycle.[16] Retinoic acid has been a mainstay therapy for neuroblastoma that works by inducing differentiation of cancer cells. However, resistance of this type of cancer to treatment with retinoic acid is common and generates the need for identification of new classes of differentiation agents.[17]

As shown in quantitatively in Figure 1 and visually in Figure 2, compound **2ma** induced visible neurite outgrowth, the morphological marker of neuroblastoma cell differentiation, in BE(2)-C cells. Although its effect was not as potent as that of retinoic acid.

CONCLUSION

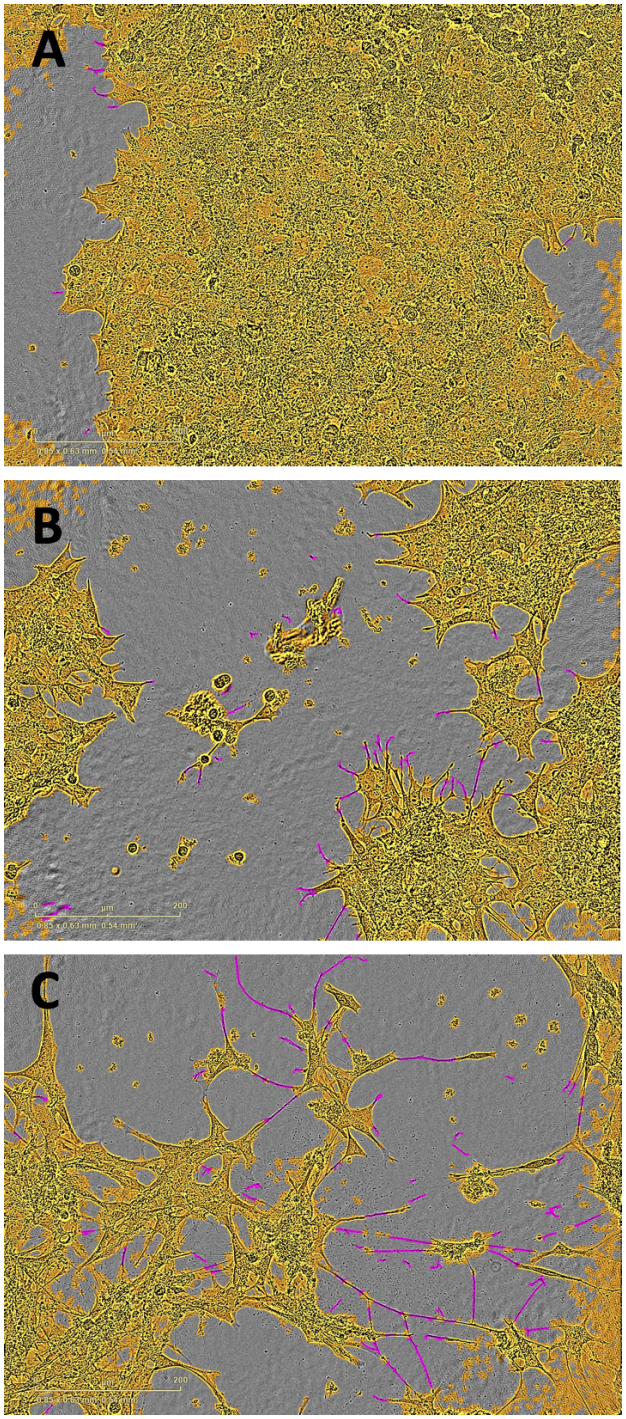


Figure 2. Compound 2ma induces neurite outgrowth in BE(2)-C cells. Shown are representative phase-contrast images for cells treated with (**A**) DMSO control, (**B**) **2ma** (25 μM) and (**C**) retinoic acid (2 μM) for 8 days. Neurites are highlighted in pink and cell bodies in yellow color.

affords *H*-spiro[indole-3,5-isoxazole] derivatives in a highly diastereoselective formal (4+1)-cycloaddition process. Here, we describe the preparation of a small library of spirocyclic compounds, reaction scope and limitations, effects

of the medium acidity and propose a plausible mechanistic rationale. Several of the synthesized compounds reduced the viability of neuroblastoma cells to 20, 26, 18 and 18%, respectively, at the concentration of 25 μM. Furthermore, compound **2ma** was found to induce differentiation of neuroblastoma cells in a manner similar to the clinically used drug, retinoic acid. Given the rapid development of resistance to retinoic acid, this promising finding warrants further exploration of compounds with this spirocyclic skeleton as potential agents to combat neuroblastoma, a deadly childhood cancer.

EXPERIMENTAL PART

General

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance-III spectrometer (400 or 100 MHz, respectively) equipped with BBO probe in $CDCl_3$ or DMSO-d_6, using TMS as internal standard. High-resolution mass spectra were registered with a Bruker Maxis spectrometer (electrospray ionization, in MeCN solution, using HCO_2Na–HCO_2H for calibration). Melting points were measured with a Stuart smp30 apparatus. All reactions were performed in oven-dried 3 mL Weaton microreactor equipped with magnetic spin-vane and Mininert valve, employing magnetic stirring. Reaction progress and purity of isolated compounds were controlled by TLC on Silufol UV-254 plates, eluting with hexanes/EtOAc mixture 4:1. Indoles **4d**,[18] **4h**,[19] and **4j**,[20] as well as nitroalkene **3e**[21] were synthesized according to known procedures. All other reagents and solvents were purchased from commercial vendors and used as received.

Detection of Neurite outgrowth

Human neuroblastoma cell line BE(2)-C cells were grown in DMEM / F-12 (Corning Cellgro) supplemented with 10% Equafetal bovine serum (Atlas Biologicals). 1,000 cells were plated and treated in 96-well plates with different concentration of compounds in triplicates for 4 days. Cell images were taken under 20X magnification using IncuCyte ZOOM Live Cell Imaging System (Essen BioScience). Neurite lengths were analyzed in the acquired images using the neurite definition defined by NeuroTrack system (Essen BioScience) as described previously.[22]

Cell viability measured by MTT Assay

The effect of compound treatment of cell viability was measured by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay, which is based on measuring the metabolic (mitochondrial dehydrogenase) activity in viable cells. Briefly, BE(2)-C cells were treated with compounds in 96 well plates for 4 days, the MTT reagent (15 μl at 2.5 mg/ml in 1X PBS) was then added into each well and incubated for 1 hour at 37 °C. Precipitates were spun down and dissolved in DMSO. Optical density values at wavelength 570 nm and 630 nm were measured using SpectroMAX 190 (Molecular Device), and the difference in the two optical density values was used to determine the relative cell survival.

Preparative procedures

(3*R,4'*S**)-2,4'-Diphenyl-4'*H*-spiro[indole-3,5'-isoxazole]** (**2aa**), **Typical Procedure A**: Reaction vessel was charged with 2-phenyl-1*H*-indole (**4a**) (97 mg, 0.50 mmol), (2-nitrovinyl)benzene (**3a**) (82 mg, 0.55 mmol), phosphorous acid (500 mg), and formic acid (500 mg). The mixture was vigorously stirred for 2 h at room temperature. Resulting dark-red homogenous solution was poured into water (50 mL), and the formed precipitate was filtered and washed consecutively with water (4 times), 10% aqueous ammonia, and once again with water. After drying, the resulting crystalline material was sufficiently pure for any practical purposes, but it could be additionally purified by Flash column chromatography on Silica gel eluting with a mixture of hexane and ethyl acetate (4:1), or by re-crystallization from a mixture of hexane and benzene (1:1). The titled material was obtained as light-grey solid, m.p. 103-105 °C (benzene/hexanes), R_f 0.47 (hexanes/EtOAc, 1:4). Yield 156 mg, (0.48 mmol, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (dd, *J* = 7.8, 1.8 Hz, 2H), 7.70 (d, *J* = 1.6 Hz, 1H), 7.59 – 7.49 (m, 3H), 7.40 (d, *J* = 7.7 Hz, 1H), 7.15 (td, *J* = 7.6, 1.3 Hz, 1H), 7.12 – 7.08 (m, 3H), 6.94 (d, *J* = 6.7 Hz, 1H), 6.91 – 6.82 (m, 3H), 5.10 (d, *J* = 1.4 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 177.4, 152.9, 149.5, 135.7, 133.1, 131.8, 131.7, 130.1, 129.2 (2C), 128.7 (2C), 128.4 (2C), 128.2, 127.8 (2C), 126.0, 124.7, 121.2, 97.7, 61.8; FT IR (KBr, film, cm^{-1}): 3059, 3034, 2360, 1691, 1657, 1561, 1544, 1461, 1198; HRMS (ES TOF) calc`d for $C_{22}H_{16}N_2NaO$ $(M+Na)^+$ 347.1155, found 347.1167 (3.4 ppm).

(3*R,4'*S**)-4'-(4-Fluorophenyl)-2-phenyl-4'*H*-spiro[indole-3,5'-isoxazole]** (**2ab**): This compound was obtained via Typical Procedure A from 2-phenyl-1*H*-indole (**4a**) (97 mg, 0.50 mmol) and 1-fluoro-4-(2-nitrovinyl)benzene (**3b**) (92 mg, 0.55 mmol). The titled material was obtained as light yellow crystals, m.p. 94-96 °C (benzene/hexanes), R_f 0.41 (hexanes/ EtOAc, 1:4). Yield 161 mg (0.47 mmol, 94%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (dd, *J* = 7.9, 1.5 Hz, 2H), 7.68 (d, *J* = 1.5 Hz, 1H), 7.61 – 7.49 (m, 3H), 7.42 (d, *J* = 7.7 Hz, 1H), 7.22 – 7.15 (m, 1H), 6.96 – 6.88 (m, 2H), 6.86 – 6.76 (m, 4H), 5.08 (d, *J* = 1.0 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 177.2, 162.3 (d, *J* = 242.1 Hz), 161.1, 152.9, 149.2, 135.6, 131.9, 131.5, 130.2, 129.4 (d, *J* = 8.2 Hz), 129.2 (2C), 128.9 (2C, d, *J* = 3.3 Hz), 128.3 (2C), 126.2, 124.5, 121.3, 115.7 (2C, d, *J* = 21.8 Hz), 97.7, 61.0; FT IR (KBr, film, cm^{-1}): 3062, 2923, 2855, 2210, 1696, 1603, 1509, 1460, 1235, 1160, 1104; HRMS (ES TOF) calc'd for $C_{22}H_{16}FN_2O$ $(M+H)^+$ 343.1241, found 343.1231 (2.9 ppm); calc'd for $C_{22}H_{15}FN_2ONa$ $(M+Na)^+$ 365.1061, found 365.1058 (0.8 ppm).

(3*R,4'*S**)-4'-(4-Chlorophenyl)-2-phenyl-4'*H*-spiro[indole-3,5'-isoxazole]** (**2ac**): This compound was obtained via Typical Procedure A from 2-phenyl-1*H*-indole (**4a**) (97 mg, 0.50 mmol) and 1-chloro-4-(2-nitrovinyl)benzene (**3c**) (101 mg, 0.55 mmol). The titled material was obtained as yellow crystals, m.p. 125-128 °C (benzene/ hexanes), R_f 0.22 (hexanes/benzene, 5:2). Yield 148 mg. (0.42 mmol, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 7.1 Hz, 2H), 7.67 (s, 1H), 7.59 – 7.49 (m, 3H), 7.42 (d, *J* = 7.6 Hz, 1H), 7.23 – 7.14 (m, 1H), 7.08 (d, *J* = 8.1 Hz, 2H), 6.93 (d, *J* = 4.0 Hz, 2H), 6.78 (d, *J* = 8.1 Hz, 2H), 5.06 (s, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 177.1, 152.7, 149.0, 135.4, 134.1, 131.9, 131.6, 131.4, 130.4, 129.3 (2C), 129.0 (2C), 128.9 (2C), 128.3 (2C), 126.3, 124.5, 121.4, 97.6, 61.1; FT IR (KBr, film, cm^{-1}): 3649, 3568, 3061, 2360, 1682, 1652, 1513, 1455, 1242; HRMS (ES TOF) calc`d for $C_{22}H_{15}ClN_2NaO$ $(M+Na)^+$ 381.0765, found 381.0763 (0.5 ppm).

(3*R,4'*S**)-4'-(4-Methoxyphenyl)-2-phenyl-4'*H*-spiro[indole-3,5'-isoxazole]** (**2ad**): This compound was obtained via Typical Procedure A from 2-phenyl-1*H*-indole (**4a**) (97 mg, 0.50 mmol) and 1-methoxy-4-(2-nitrovinyl)benzene (**3d**) (99 mg, 0.55 mmol). The titled material was obtained as grey crystals, m.p. 122-123 °C (benzene/hexanes), R_f 0.20 (benzene). Yield 152 mg, (0.43 mmol, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (dd, *J* = 7.6, 1.4 Hz, 2H), 7.65 (d, *J* = 1.1 Hz, 1H), 7.53 (q, *J* = 6.1 Hz, 3H), 7.41 (d, *J* = 7.7 Hz, 1H), 7.16 (t, *J* = 7.5 Hz, 1H), 6.96 (d, *J* = 7.0 Hz, 1H), 6.91 (t, *J* = 7.4 Hz, 1H), 6.77 (d, *J* = 8.6 Hz, 2H), 6.62 (d, *J* = 8.6 Hz, 2H), 5.05 (s, 1H), 3.66 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 177.4, 159.2, 152.9, 149.9, 135.8, 131.7, 131.7, 130.0, 129.1 (2C), 129.0 (2C), 128.3 (2C), 126.1, 125.0, 124.7, 121.2, 114.0 (2C), 97.8, 61.2, 55.2; FT IR (KBr, film, cm^{-1}): 3069, 2829, 2363, 1895, 1689, 1614, 1513, 1456, 1250, 1179, 1033; HRMS (ES TOF) calc`d for $C_{23}H_{18}N_2NaO_2$ $(M+Na)^+$ 377.1260, found 377.1263 (0.7 ppm).

***N*,*N*-Dimethyl-4-((3*R**,4'*S**)-2-phenyl-4'H-spiro[indole-3,5'-isoxazol]-4'-yl)aniline** (**2ae**): This compound was obtained via Typical Procedure A from 2-phenyl-1*H*-indole (**4a**) (97 mg, 0.50 mmol) and *N*,*N*-dimethyl-4-(2-nitrovinyl)aniline (**3e**) (106 mg, 0.55 mmol). Yield 116 mg, (0.32 mmol, 63%), yellow solid, m.p.147.4-150.5 °C (benzene), R_f 0.19 (benzene); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 – 8.10 (m, 2H), 7.62 (s, 1H), 7.53 (q, *J* = 5.5 Hz, 3H), 7.41 (d, *J* = 7.6 Hz, 1H), 7.16 (t, *J* = 7.5 Hz, 1H), 7.01 (d, *J* = 7.3 Hz, 1H), 6.92 (t, *J* = 7.4 Hz, 1H), 6.72 (d, *J* = 8.5 Hz, 2H), 6.43 (d, *J* = 8.5 Hz, 2H), 5.01 (s, 1H), 2.82 (s, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 177.7, 153.1, 150.4, 150.1, 136.0, 131.9, 131.6, 129.9, 129.1 (2C), 128.7 (2C), 128.3 (2C), 126.0, 124.9, 121.1, 120.1, 112.2 (2C), 97.9, 61.4, 40.4 (2C); IR (KBr, film, cm^{-1}): 2976, 1744, 1618 ,1527, 1458, 1363, 1241; HRMS (ES TOF) calc`d for $C_{24}H_{22}N_3O$ $(M+H)^+$ 368.1757, found 368.1749 (2.4 ppm);

(3*R*,4'*S*)-4'-(2-Fluorophenyl)-2-phenyl-4'*H*-spiro[indole-3,5'-isoxazole] (**2af**): This compound was obtained via Typical Procedure A from 2-phenyl-1*H*-indole (**4a**) (97 mg, 0.50 mmol) and 1-fluoro-2-(2-nitrovinyl)benzene (**3f**) (92 mg, 0.55 mmol). Yield 144 mg (0.42 mmol, 84%), R_f 0.54 (benzene/petroleum ether, 5:2). Light yellow crystals, mp 143-145 °C (benzene/hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 6.7 Hz, 2H), 7.69 (s, 1H), 7.57 – 7.49 (m, 3H), 7.45 (d, *J* = 7.7 Hz, 1H), 7.18 (t, *J* = 7.5 Hz, 1H), 7.14 – 7.05 (m, 2H), 7.00 (t, *J* = 7.4 Hz, 1H), 6.90 (dt, *J* = 14.7, 7.2 Hz, 2H), 6.74 (t, *J* = 9.1 Hz, 1H), 5.23 (s, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 177.1, 160.4 (d, *J* = 248.1 Hz), 153.4, 148.5, 135.3, 131.8, 131.7, 130.3, 130.2 (d, *J* = 8.2 Hz), 129.1 (2C), 128.9 (d, *J* = 3.6 Hz), 128.2 (2C), 126.0, 124.3, 124.2 (d, *J* = 3.6 Hz), 121.3, 121.1 (d, *J* = 15.2 Hz), 115.6 (d, *J* = 21.3 Hz), 97.0, 55.9 (d, *J* = 1.4 Hz); IR (KBr, film, cm^{-1}): 3065, 2368, 1614, 1542, 1501, 1460, 1246, 1220, 1201, 1100. HRMS (ES TOF) calc'd for $C_{22}H_{16}FN_2O$ $(M + H)^+$ 343.1241, found 343.1235 (1.8 ppm).

(3*R,4'*S**)-4'-Hexyl-2-phenyl-4'H-spiro[indole-3,5'-isoxazole]** (**2ag**): This compound was obtained via Typical Procedure A from 2-phenyl-1*H*-indole (**4a**) (97 mg, 0.50 mmol) and 1-nitrooct-1-ene (**3g**) (86 mg, 0.55 mmol). The titled material was obtained as yellowish oil, R_f 0.33 (hexane/acetone 6:1). Yield 122 mg (0.37 mmol, 73%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 – 8.03 (m, 2H), 7.61 (d, *J* = 7.7 Hz, 1H), 7.53 – 7.44 (m, 3H), 7.44 – 7.38 (m, 2H), 7.37 – 7.33 (m, 1H), 7.22 (td, *J* = 7.5, 1.0 Hz, 1H), 3.73 (td, *J* = 7.9, 1.4 Hz, 1H), 1.50 (tdd, *J* = 13.2, 6.7, 4.1 Hz, 1H), 1.29 – 1.18 (m, 1H), 1.12 – 0.78 (m, 8H), 0.75 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 177.7, 153.4, 151.1, 135.8, 131.6, 131.5, 130.4, 128.9 (2C), 128.1 (2C), 126.2, 124.0, 121.7, 96.4, 56.2, 31.2, 28.7, 28.3, 27.5, 22.3, 13.9; FT IR (KBr, film, cm^{-1}): 3043, 2979, 2972, 2930, 2882, 1719, 1614, 1543, 1453, 1374, 1355, 1262, 1033; HRMS (ES TOF) calc`d for $C_{22}H_{25}N_2O$ $(M+H)^+$ 333.1961, found 333.1969 (2.3 ppm); calc`d for $C_{22}H_{24}N_2NaO$ $(M+Na)^+$ 355.1781, found 355.1783 (0.5 ppm).

(3*R,4'*S**)-4'-Isopropyl-2-phenyl-4'*H*-spiro[indole-3,5'-isoxazole]** (**2ah**): This compound was obtained via Typical Procedure A from 2-phenyl-1*H*-indole (**4a**) (97 mg, 0.50 mmol) and 3-methyl-1-nitrobut-1-ene (**3h**) (63 mg, 0.55 mmol). The titled material was obtained as colorless solid, m.p. 148-150 °C (benzene/hexanes), R_f 0.21 (hexane/ acetone 7:1). Yield 103 mg (0.35 mmol, 71%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 6.9 Hz, 2H), 7.62 (d, *J* = 7.7 Hz, 1H), 7.55 – 7.45 (m, 4H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.38 (d, *J* = 7.2 Hz, 1H), 7.22 (t, *J* = 7.4 Hz, 1H), 3.45 (dd, *J* = 11.1, 0.8 Hz, 1H), 1.99 – 1.83 (m, 1H), 1.03 (d, *J* = 6.6 Hz, 3H), 0.29 (d, *J* = 6.4 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 178.0, 153.9, 150.2, 135.9, 131.8, 131.6, 130.7, 129.0 (2C), 128.2 (2C), 126.5, 123.8, 121.9, 96.3, 63.9, 28.1, 22.5, 20.3; FT IR (KBr, film, cm^{-1}): 3039, 2972, 2930, 2874, 1723, 1543, 1456, 1374, 1273, 1036 cm-1; HRMS (ES TOF) calc`d for $C_{19}H_{19}N_2O$ $(M+H)^+$ 291.1492, found 291.1485 (2.5 ppm).

(3*R,4'*R**)-4'-(Furan-2-yl)-2-phenyl-4'*H*-spiro[indole-3,5'-isoxazole]** (**2ai**): This compound was obtained via Typical Procedure A from 2-phenyl-1*H*-indole (**4a**) (97 mg, 0.50 mmol) and 2-(2-nitrovinyl)furan (**3i**) (77 mg, 0.55 mmol). The titled material was obtained as yellow oil, R_f 0.21 (hexane/ acetone 6:1). Yield 97 mg (0.31 mmol, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 7.0 Hz, 2H), 7.61 (d, *J* = 0.8 Hz, 1H), 7.56 – 7.46 (m, 4H), 7.27 (t, *J* = 7.6 Hz, 1H), 7.11 (dd, *J* = 9.0, 4.1 Hz, 2H), 7.01 (d, *J* = 7.5 Hz, 1H), 6.17 – 6.08 (m, 1H), 6.01 (d, *J* = 3.2 Hz, 1H), 5.10 (s, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 176.5, 153.1, 147.1, 146.0, 142.9, 135.4, 131.8, 131.4, 130.4, 129.2 (2C), 128.2 (2C), 126.3, 124.2, 121.3, 110.6, 109.0, 96.5, 55.9; FT IR (film, cm^{-1}): 3073, 2930, 2855, 1606, 1539, 1505, 1464, 1445, 1318, 1269, 1246, 1201, 1145, 1073; HRMS (ES TOF) calc`d for $C_{20}H_{15}N_2O_2$ $(M+H)^+$ 315.1128, found 315.1137 (2.9 ppm); calc`d for $C_{20}H_{14}N_2NaO_2$ $(M+Na)^+$ 337.0947, found 337.0940 (2.2 ppm).

(3*R,4'*S**)-4'-Phenyl-2-(*p*-tolyl)-4'*H*-spiro[indole-3,5'-isoxazole]** (**2ba**): This compound was obtained via Typical Procedure A from 2-(*p*-tolyl)-1*H*-indole (**4b**) (104 mg, 0.50 mmol) and (2-nitrovinyl)benzene (**3a**) (82 mg, 0.55 mmol). The titled material was obtained as light grey solid, m.p. 55-57 °C (benzene/hexanes), R_f 0.27 (hexane/benzene 2:5). Yield 154 mg, (0.46 mmol, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.0 Hz, 2H), 7.70 (s, 1H), 7.38 (d, *J* = 7.6 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.20 – 7.03 (m, 4H), 6.94 (d, *J* = 7.3 Hz, 1H), 6.91 – 6.80 (m, 3H), 5.10 (s, 1H), 2.45 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 177.3, 153.0, 149.4, 142.4, 135.7, 133.1, 130.0, 129.9 (2C), 128.9, 128.6, 128.3, 128.1, 127.7 (2C), 125.8, 124.6, 121.0, 97.7, 62.0, 21.8; FT IR (KBr, film, cm^{-1}): 3032, 2882, 2589, 2364, 1925, 1813, 1614, 1543, 1516, 1456, 1190; HRMS (ES TOF) calc`d for $C_{23}H_{18}N_2NaO$ $(M+Na)^+$: 361.1311, found 361.1311 (0.2 ppm).

(3*R,4'*S**)-2-(4-Chlorophenyl)-4'-phenyl-4'*H*-spiro[indole-3,5'-isoxazole]** (**2ca**): This compound was obtained via Typical Procedure A from 2-(4-chlorophenyl)-1*H*-indole (**4c**) (114 mg, 0.50 mmol) and (2-nitrovinyl)benzene (**3a**) (82 mg, 0.55 mmol). The titled material was obtained as light-yellow solid, m.p. 152-153 °C (benzene/hexanes), R_f 0.32 (hexane/ benzene 2:5). Yield 154 mg (0.43 mmol, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.4 Hz, 2H), 7.71 (s, 1H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 7.7 Hz, 1H), 7.10 (d, *J* = 4.4 Hz, 4H), 6.97 – 6.79 (m, 4H), 5.04 (s, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 176.2, 152.8, 149.6, 138.0, 135.6, 132.9, 130.2, 130.1, 129.6 (2C), 129.5 (2C), 128.7 (2C), 128.3, 127.7 (2C), 126.2, 124.7, 121.3, 97.6, 61.7; FT IR (KBr, film, cm^{-1}): 2994, 2360, 1749, 1655, 1490, 1456, 1377, 1250, 1096; HRMS (ES TOF) calc`d for $C_{22}H_{16}ClN_2O$ $(M+H)^+$ 359.0946, found 359.0940 (1.4 ppm); calc`d for $C_{22}H_{15}ClN_2NaO$ $(M+Na)^+$ 381.0765, found 381.0751 (3.7 ppm).

(3*R,4'*S**)-2-(4-Ethylphenyl)-4'-phenyl-4'*H*-spiro[indole-3,5'-isoxazole]** (**2da**): This compound was obtained via Typical Procedure A from 2-(4-ethylphenyl)-1*H*-indole (**4d**) (111 mg, 0.50 mmol) and (2-nitrovinyl)benzene (**3a**) (82 mg, 0.55 mmol). Yield 118 mg (0.33 mmol, 67%). Light yellow crystals, mp 92-94 °C (benzene/hexane), R_f 0.21 (benzene/hexane, 5:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.2 Hz, 2H), 7.71 (s, 1H), 7.37 (t, *J* = 7.6 Hz, 3H), 7.13 (t, *J* = 7.7 Hz, 1H), 7.11 – 7.07 (m, 3H), 6.93 (d, *J* = 7.2 Hz, 1H), 6.89 – 6.84 (m, 3H), 5.12 (s, 1H), 2.75 (q, *J* = 7.6 Hz, 2H), 1.30 (t, *J* = 7.6 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 177.4, 153.0, 149.5, 148.6, 135.7, 133.2, 130.0, 129.1, 128.7 (2C), 128.6 (2C), 128.4 (2C), 128.2, 127.7 (2C), 125.8, 124.6, 121.0, 97.7, 62.0, 29.1, 15.4; IR (KBr, film, cm^{-1}) 2942, 2356, 1685, 1610, 1539, 1498, 1453, 1273, 1198; HRMS (ES TOF) calc'd for $C_{24}H_{21}N_2O$ $(M + H)^+$ 353.1648, found 353.1641 (2.0 ppm).

(3*R,4'*S**)-2-(Naphthalen-2-yl)-4'-phenyl-4'*H*-spiro[indole-3,5'-isoxazole]** (**2ea**): This compound was obtained via Typical Procedure A from 2-(naphthalen-2-yl)-1*H*-indole (**4e**) (122 mg, 0.50 mmol) and (2-nitrovinyl)benzene (**3a**) (82 mg, 0.55 mmol). The titled material was obtained as green solid, m.p. 154-156 °C (benzene/hexanes), R_f 0.32 (benzene). Yield 144 mg (0.38 mmol, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (s, 1H), 8.35 (d, *J* = 8.6 Hz, 1H), 8.04 – 7.95 (m, 2H), 7.91 (d, *J* = 7.6 Hz, 1H), 7.76 (s, 1H), 7.64 – 7.54 (m, 2H), 7.45 (d, *J* = 7.7 Hz, 1H),

7.17 (t, *J* = 7.5 Hz, 1H), 7.14 – 7.05 (m, 3H), 7.00 (d, *J* = 7.2 Hz, 1H), 6.94 – 6.83 (m, 3H), 5.19 (s, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 177.3, 152.9, 149.6, 135.8, 134.9, 133.1, 133.0, 130.1, 129.4, 129.0, 129.0, 128.8, 128.6 (2C), 128.2, 128.0, 127.9, 127.7 (2C), 126.9, 126.0, 124.9, 124.6, 121.2, 97.8, 62.2. FT IR (KBr, film, cm^{-1}): 3058, 2360, 1693, 1509, 1456, 1231, 909; HRMS (ES TOF) calc`d for $C_{26}H_{18}N_2NaO$ $(M+Na)^+$ 397.1311, found 397.1324 (3.2 ppm).

(3*R,4'*S**)-4'-Phenyl-2-(5,6,7,8-tetrahydronaphthalen-2-yl)-4'*H*-spiro[indole-3,5'-isoxazole]** (**2fa**): This compound was obtained via Typical Procedure A from 2-(5,6,7,8-tetrahydronaphthalen-2-yl)-1*H*-indole (**4f**) (124 mg, 0.50 mmol) and (2-nitrovinyl)benzene (**3a**) (82 mg, 0.55 mmol). Yield 129 mg (0.34 mmol, 68%), green crystals, mp 122-125 °C (benzene/hexane), R_f 0.17 (benzene/hexane, 5:2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.86 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.70 (d, *J* = 1.3 Hz, 1H), 7.39 (d, *J* = 7.7 Hz, 1H), 7.22 (d, *J* = 8.0 Hz, 1H), 7.13 (ddd, *J* = 7.8, 7.4, 0.8 Hz, 1H), 7.10 – 7.05 (m, 3H), 6.94 (d, *J* = 7.2 Hz, 1H), 6.89 – 6.83 (m, 3H), 5.14 (d, *J* = 0.7 Hz, 1H), 2.90 – 2.84 (m, 4H), 1.89 – 1.82 (m, 4H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 177.5, 153.0, 149.3, 141.8, 138.1, 135.6, 133.1, 129.91, 129.85, 128.9, 128.7, 128.5 (2C), 128.0, 127.6 (2C), 125.6, 125.2, 124.5, 120.8, 97.6, 62.0, 29.7, 29.5, 23.1, 23.0; IR (KBr, film, cm^{-1}): 2930, 2855, 2364, 1741, 1606, 1538, 1464, 1246, 1194; HRMS (ES TOF) calc'd for $C_{26}H_{23}N_2O$ $(M + H)^+$ 379.1805, found 379.1808 (0.8 ppm).

(3*R,4'*S**)-2-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-4'-phenyl-4'*H*-spiro[indole-3,5'-isoxazole]** (**2ga**): This compound was obtained via Typical Procedure A from 2-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-1*H*-indole (**4g**) (126 mg, 0.50 mmol) and (2-nitrovinyl)benzene (**3a**) (82 mg, 0.55 mmol). The titled material was obtained as yellow solid, m.p. 116-119 °C (benzene/hexanes); R_f 0.22 (hexane/benzene 2:5). Yield 141 mg (0.37 mmol, 74%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 2H), 7.68 (s, 1H), 7.34 (d, *J* = 7.8 Hz, 1H), 7.18 – 7.05 (m, 4H), 6.99 (d, *J* = 8.3 Hz, 1H), 6.92 (d, *J* = 7.4 Hz, 1H), 6.87 – 6.80 (m, 3H), 5.12 (s, 1H), 4.31 (d, *J* = 5.6 Hz, 4H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 176.7, 153.0, 149.5, 147.0, 143.9, 135.6, 133.1, 130.0, 128.6 (2C), 128.1, 127.7 (2C), 125.6, 125.0, 124.5, 122.1, 120.8, 118.0, 117.4, 97.6, 64.8, 64.3, 62.1; FT IR (KBr, film, cm^{-1}): 3065, 2360, 1681, 1565, 1513, 1288, 1246, 1066; HRMS (ES TOF) calc`d for $C_{24}H_{19}N_2O_3$ $(M+H)^+$ 383.1390, found 383.1393 (0.8 ppm); calc`d for $C_{24}H_{18}N_2NaO_3$ $(M+Na)^+$ 405.1210, found 405.1208 (0.3 ppm).

(3*R,4'*S**)-2-(3,4-Dimethoxyphenyl)-4'-phenyl-4'*H*-spiro-[indole-3,5'-isoxazole]** (**2ha**): This compound was obtained via Typical Procedure A from 2-(3,4-dimethoxyphenyl)-1*H*-indole (**4h**) (127 mg, 0.50 mmol) and (2-nitrovinyl)benzene (**3a**) (82 mg, 0.55 mmol). Yield 117 mg, (0.31 mmol, 61%), orange solid, m.p. 158.7-161.2 °C (benzene/hexanes), R_f 0.43 (EtOAc/hexanes 1:3); ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 1.9 Hz, 1H), 7.72 (d, *J* = 1.5 Hz, 1H), 7.68 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.36 (d, *J* = 7.6 Hz, 1H), 7.15 – 7.07 (m, 4H), 6.98 (d, *J* = 8.5 Hz, 1H), 6.93 (d, *J* = 7.0 Hz, 1H), 6.88 – 6.81 (m, 3H), 5.14 (d, *J* = 1.2 Hz, 1H), 4.02 (s, 3H), 3.97 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 177.0, 153.0, 152.3, 149.47, 149.45, 135.7, 133.2, 130.0, 128.6 (2C), 128.2, 127.7 (2C), 125.6, 124.6, 124.4, 122.0, 120.8, 111.0, 110.6, 97.7, 62.6, 56.21, 56.17; IR (KBr, film, cm^{-1}): 3065, 2937, 2041, 1703, 1602, 1509, 1457, 1351, 1273, 1228, 1145, 1021; HRMS (ES TOF) calc`d for $C_{24}H_{21}N_2NaO_3$ $(M+H)^+$ 385.1547, found 385.1559 (3.1 ppm); calc`d for $C_{24}H_{20}N_2NaO_3$ $(M+Na)^+$ 407.1366, found 407.1375 (2.1 ppm);

(3*R,4'*S**)-4'-(4-Chlorophenyl)-2-(*p*-tolyl)-4'*H*-spiro[indole-3,5'-isoxazole]** (**2ic**): This compound was obtained via Typical Procedure A from 2-(*p*-tolyl)-1*H*-indole (**4i**) (104 mg, 0.50 mmol) and 1-chloro-4-(2-nitrovinyl)benzene (**3c**) (101 mg, 0.55 mmol). Yield 153 mg, (0.41 mmol, 82%), grey solid, m.p. 178.8-181.3 °C (benzene/hexanes), R_f 0.27 (benzene/hexanes 2:1); ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.1 Hz, 2H), 7.66 (d, *J* = 0.8 Hz, 1H), 7.39 (d, *J* = 7.7 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.21 – 7.13 (m, 1H), 7.06 (d, *J* = 8.3 Hz, 2H), 6.91 (d, *J* = 6.1 Hz, 2H), 6.77 (d, *J* = 8.3 Hz, 2H), 5.06 (s, 1H), 2.44 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 177.1, 152.9, 149.0, 142.5, 135.4, 134.0, 131.6, 130.3, 129.9, 129.0 (2C), 128.8 (2C), 128.7 (2C), 128.2 (2C), 126.0, 124.4, 121.1, 97.6, 61.3, 21.8; IR (KBr, film, cm^{-1}): 3036, 2937, 1748, 1607, 1508, 1462, 1244, 1191, 1092; HRMS (ES TOF) calc`d for $C_{23}H_{18}ClN_2O$ (M+H)+ 373.1102, found 373.1107 (1.3 ppm);

(3*R,4'*S**)-4'-Phenyl-2-(thiophen-2-yl)-4'*H*-spiro[indole-3,5'-isoxazole]** (**2ja**): This compound was obtained via Typical Procedure A from 2-(thiophen-2-yl)-1*H*-indole (**4j**) (100 mg, 0.50 mmol) and (2-nitrovinyl)benzene (**3a**) (82 mg, 0.55 mmol). The titled material was obtained as green solid, m.p. 57-60 °C (benzene/hexanes), R_f 0.27 (benzene). Yield 119 mg (0.36 mmol, 72%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 1.6 Hz, 1H), 7.69 (dd, *J* = 3.8, 1.0 Hz, 1H), 7.62 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.37 (dt, *J* = 7.7, 0.8 Hz, 1H), 7.20 (dd, *J* = 5.0, 3.8 Hz, 1H), 7.15 – 7.08 (m, 4H), 6.91 – 6.79 (m, 4H), 5.19 (d, *J* = 1.6 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 173.2, 153.2, 149.2, 135.4, 135.0, 133.1, 131.3, 130.3, 130.1, 128.7 (2C), 128.7, 128.3, 127.8 (2C), 125.7, 124.7, 120.9, 97.1, 62.9; FT IR (KBr, film, cm^{-1}): 3080, 2360, 1753, 1550, 1505, 1423, 1243, 1190, 1059 cm-1; HRMS (ES TOF): calc`d for $C_{20}H_{14}N_2NaOS$ $(M+Na)^+$ 353.0719, found 353.0706 (3.8 ppm).

(3*R,4'*S**)-2-Methyl-4'-phenyl-4'*H*-spiro[indole-3,5'-isoxazole]** (**2ka**): This compound was obtained via Typical Procedure A from 2-methyl-1*H*-indole (**4k**) (66 mg, 0.50 mmol) and (2-nitrovinyl)benzene (**3a**) (82 mg, 0.55 mmol). The reaction was carried out at 10 °C. The titled material was obtained as red solid, m.p. 64-65°C (benzene/ hexanes), R_f 0.70 (benzene). Yield 58 mg (0.22 mmol, 44%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 1.4 Hz, 1H), 7.24 (d, *J* = 7.7 Hz, 1H), 7.20 – 7.13 (m, 3H), 7.07 (t, *J* = 7.6 Hz, 1H), 6.82 (dd, *J* = 6.4, 2.8 Hz, 2H), 6.65 (t, *J* = 7.5 Hz, 1H), 6.28 (d, *J* = 7.4 Hz, 1H), 4.51 (d, *J* = 1.2 Hz, 1H), 2.27 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 181.1, 154.25, 149.3, 133.0, 132.8, 130.3, 129.0 (2C), 128.7, 128.5 (2C), 125.6, 125.3, 120.3, 96.4, 58.6, 15.4; FT IR (KBr, film, cm^{-1}): 3062, 3039, 2930, 2863, 1726, 1595, 1464, 1381, 1246, 1194, 1074; HRMS (ES TOF) calc'd for $C_{17}H_{15}N_2O$ (M + H)+ 263.1179, found 263.1176 (0.9 ppm).

(3*R,4'*S**)-5-Isopropyl-2,4'-diphenyl-4'*H*-spiro[indole-3,5'-isoxazole]** (**2la**): This compound was obtained via Typical Procedure A from 5-isopropyl-2-phenyl-1*H*-indole (**4l**) (118 mg, 0.50 mmol) and (2-nitrovinyl)benzene (**3a**) (82 mg, 0.55 mmol). The titled material was obtained as grey solid, m.p. 108-110°C (benzene/hexanes), R_f 0.43 (hexanes/ benzene, 2:5). Yield 166 mg, (0.46 mmol, 91%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (dd, *J* = 7.5, 1.7 Hz, 2H), 7.70 (d, *J* = 1.1 Hz, 1H), 7.53 (d, *J* = 6.8 Hz, 3H), 7.30 (d, *J* = 7.9 Hz, 1H), 7.09 (d, *J* = 6.5 Hz, 3H), 7.02 – 6.92 (m, 1H), 6.88 – 6.81 (m, 2H), 6.75 (s, 1H), 5.07 (s, 1H), 2.69 (hept, *J* = 6.9 Hz, 1H), 1.04 (d, *J* = 6.9 Hz, 3H), 1.01 (d, *J* = 6.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 176.6, 150.9, 149.4, 147.1, 135.7, 133.4, 131.8, 131.5, 129.1 (2C), 128.6 (2C), 128.2 (2C), 128.1, 128.1, 127.8 (2C), 122.9, 120.8, 97.5, 61.6, 34.1, 24.3, 23.6; FT IR (KBr, film, cm^{-1}): 2960, 2360, 1955, 1670, 1494, 1381, 1186; HRMS (ES TOF) calc`d for $C_{25}H_{23}N_2O$ $(M+H)^+$ 367.1805, found 367.1794 (2.9 ppm).

(3*R,4'*S**)-5-Isopropyl-4'-(4-methoxyphenyl)-2-phenyl-4'*H*-spiro[indole-3,5'-isoxazole]** (**2ld**): This compound was obtained via Typical Procedure A from 5-isopropyl-2-phenyl-1*H*-indole (**4l**) (118 mg, 0.50 mmol) and 1-methoxy-4-(2-nitrovinyl)benzene (**3d**) (99 mg, 0.55 mmol). The titled material was obtained as green solid, m.p. 61-63°C (benzene/ hexanes), R_f 0.33 (benzene). Yield 166 mg (0.42 mmol, 84%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (dd, *J* = 7.7, 1.9 Hz, 2H), 7.66 (d, *J* = 1.5 Hz, 1H), 7.55 – 7.47 (m, 3H), 7.31 (d, *J* = 7.9 Hz, 1H), 6.98 (dd, *J* = 7.9, 1.5 Hz, 1H), 6.77 (d, *J* = 8.6 Hz, 3H), 6.65 – 6.58 (m, 2H), 5.02 (d, *J* = 1.2 Hz, 1H), 3.66 (s, 3H), 2.71 (hept, *J* = 6.9 Hz, 1H), 1.07 (d, *J* = 6.9 Hz, 3H), 1.04 (d, *J* = 6.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 176.7, 159.3, 151.0, 149.7, 147.1, 135.8, 131.9, 131.5, 129.1 (2C), 129.0 (2C), 128.2 (2C), 128.2, 125.4, 122.9, 120.7, 114.0 (2C),

97.6, 61.1, 55.3, 34.1, 24.3, 23.6; FT IR (KBr, film, cm^{-1}): 2957, 2919, 2364, 1749, 1606, 1516, 1254, 1179, 1033; HRMS (ES TOF), calc`d for $C_{26}H_{25}N_2O_2$ $(M+H)^+$ 397.1911, found 397.1901 (2.5 ppm); calc`d for $C_{26}H_{24}N_2NaO_2$ $(M+Na)^+$ 419.1730, found 419.1737 (1.7 ppm).

(3*R,4'*S**)-5-methoxy-2,4'-diphenyl-4'*H*-spiro[indole-3,5'-isoxazole]** (**2ma**): This compound was obtained via Typical Procedure A from 5-methoxy-2-phenyl-1*H*-indole (**4m**) (112 mg, 0.50 mmol) and (2-nitrovinyl)benzene (**3a**) (82 mg, 0.55 mmol). The titled material was obtained as yellow oil, R_f 0.33 (hexane/acetone 6:1). Yield 160 mg (0.45 mmol, 90%), ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 – 8.08 (m, 2H), 7.71 (d, *J* = 1.6 Hz, 1H), 7.56 – 7.49 (m, 3H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.17 – 7.10 (m, 3H), 6.87 (dd, *J* = 6.5, 3.0 Hz, 2H), 6.66 (dd, *J* = 8.4, 2.5 Hz, 1H), 6.46 (d, *J* = 2.5 Hz, 1H), 5.10 (d, *J* = 1.5 Hz, 1H), 3.61 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 175.6, 158.3, 149.4, 146.2, 137.2, 133.1, 131.7, 131.5, 129.2 (2C), 128.7 (2C), 128.3, 128.1 (2C), 127.8 (2C), 121.7, 115.3, 111.0, 97.5, 61.7, 55.8; FT IR (KBr, film, cm^{-1}): 3065, 3035, 2964, 2934, 2837, 1606, 1546, 1475, 1359, 1292, 1201, 1175, 1028; HRMS (ES TOF) calc`d for $C_{23}H_{19}N_2O_2$ $(M+H)^+$ 355.1441, found 355.1438 (0.7 ppm); calc`d for $C_{23}H_{18}N_2NaO_2$ $(M+Na)^+$: 377.1260, found 377.1268, (2.0 ppm).

(3*R,4'*S**)-4'-(4-Ethylphenyl)-2-(naphthalen-2-yl)-4'*H*-spiro[indole-3,5'-isoxazole]** (**2ej**): This compound was obtained via Typical Procedure A from 2-(naphthalen-2-yl)-1*H*-indole (**4e**) (122 mg, 0.50 mmol) and 1-ethyl-4-(2-nitrovinyl)benzene (**3j**) (97 mg, 0.55 mmol). Yield 145 mg, (0.36 mmol, 72%), white solid, m.p. 144.6-149.8 °C (benzene/hexanes), R_f 0.38 (benzene/hexanes 2:1); ^1H NMR (400 MHz, $CDCl_3$) δ 8.61 (s, 1H), 8.34 (dd, *J* = 8.6, 1.0 Hz, 1H), 7.99 (d, *J* = 8.8 Hz, 2H), 7.91 (d, *J* = 7.6 Hz, 1H), 7.73 (d, *J* = 0.7 Hz, 1H), 7.62 – 7.53 (m, 2H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.17 (t, *J* = 7.5 Hz, 1H), 7.00 (d, *J* = 7.2 Hz, 1H), 6.92 (t, *J* = 8.3 Hz, 3H), 6.78 (d, *J* = 7.9 Hz, 2H), 5.15 (s, 1H), 2.47 (q, *J* = 7.6 Hz, 2H), 1.09 (t, *J* = 7.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 177.4, 153.0, 149.9, 144.3, 135.9, 134.9, 133.1, 130.1, 130.0, 129.4, 129.1, 128.9, 128.8, 128.1 (2C), 128.0, 127.9, 127.7 (2C), 126.9, 126.0, 125.0, 124.7, 121.2, 97.8, 62.0, 28.4, 15.4; IR (KBr, film, cm^{-1}): 3028, 2966, 2937, 2854, 2361, 1743, 1540, 1511, 1457, 1271, 1250; HRMS (ES TOF) calc`d for $C_{28}H_{23}N_2O$ $(M+H)^+$ 403 1805, found 403.1814 (2.2 ppm); calc`d for $C_{28}H_{22}N_2NaO$ $(M+Na)^+$ 425.1624, found 425.1624 (0.1 ppm);

(3*R,*4*'S*)-7-Chloro-2,4'-diphenyl-4'H-spiro[indole-3,5'-isoxazole]** (**2na**): This compound was obtained via Typical Procedure A from 7-chloro-2-phenyl-1*H*-indole (**4j**) (114 mg, 0.50 mmol) and (2-nitrovinyl)benzene (**3a**) (82 mg, 0.55 mmol). The titled material was obtained as pink solid, m.p. 162-165°C (benzene/hexanes), R_f 0.34 (benzene/hexanes 1:0.4). Yield 154 mg, (0.43 mmol, 86%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 7.1 Hz, 2H), 7.70 (s, 1H), 7.59 – 7.50 (m, 3H), 7.16 – 7.09 (m, 4H), 6.89 – 6.78 (m, 4H), 5.12 (s, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 178.3, 149.7, 149.5, 137.8, 132.8, 132.2, 131.3, 130.6, 129.2 (2C), 128.8 (2C), 128.6 (2C), 128.4, 127.7 (2C), 127.0, 126.3, 123.0, 98.3, 62.2; FT IR (KBr, film, cm^{-1}): 2923, 2360, 1749, 1531, 1460, 1246, 1190, 1044; HRMS (ES TOF) calc`d for $C_{22}H_{15}ClN_2NaO$ $(M+Na)^+$ 381.0765, found 381.0751 (3.8 ppm);

(3*R,4'*S**)-2-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-4'-(4-methoxyphenyl)-4'*H*-spiro[indole-3,5'-isoxazole]** (**2gd**): This compound was obtained via Typical Procedure A from 2-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-1*H*-indole (**4g**) (126 mg, 0.50 mmol) and 1-methoxy-4-(2-nitrovinyl)benzene (**3d**) (99 mg, 0.55 mmol). Yield 111 mg, (0.29 mmol, 57%), orange solid, m.p.161.1-163.4 °C (benzene); R_f 0.35 (EtOAc/hexanes 1:1). ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.63 (m, 3H), 7.35 (d, *J* = 7.7 Hz, 1H), 7.17 – 7.09 (m, 1H), 7.03 – 6.92 (m, 3H), 6.91 – 6.84 (m, 1H), 6.77 (d, *J* = 8.6 Hz, 2H), 6.61 (d, *J* = 8.7 Hz, 1H), 5.07 (d, *J* = 1.0 Hz, 1H), 4.39 – 4.28 (m, 4H), 3.67 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, CDCl3) δ 176.8, 159.2, 153.0, 149.9, 146.9, 143.9, 135.8, 130.0 (2C), 129.0, 125.7, 125.1 (2C), 124.6, 122.2, 120.9, 118.0, 117.5, 114.0 (2C), 97.8, 64.8, 64.3, 61.7, 55.3; IR (KBr, film, cm^{-1}): 3065, 2929, 2849, 1739, 1540, 1507, 1462, 1283, 1242, 1192, 1130, 1063; HRMS (ES TOF) calc`d for $C_{25}H_{21}N_2O_4$ $(M+H)^+$ 413.1496, found 413.1492 (0.9 ppm);

(3*R,4'*S**)-3'-Methyl-2,4'-diphenyl-4'*H*-spiro[indole-3,5'-isoxazole]** (**2ak**), **Typical Procedure B**: Reaction vessel was charged with 2-phenyl-1*H*-indole (**4a**) (97 mg, 0.50 mmol), (2-nitroprop-1-en-1-yl)benzene (**3k**) (90 mg, 0.55 mmol), and glacial acetic acid (500 mg, 0.48 mL). Methanesulfonic acid (13 mg, 0.14 mmol) was added in a single portion and the resulting mixture was stirred at room temperature for 6 hr. Then, the mixture was quenched with water (50 mL) and 33% aqueous ammonia (1 mL). The product was extracted with ethyl acetate (3 x 50 mL), concentrated and separated by preparative column chromatography on Silica gel eluting with a mixture of hexanes and ethyl acetate 3:1. Unreacted nitro compound **3k** was eluted first R_f 0.65 (EtOAc/hexanes 1:3), then compound **11aa** (see below, R_f 0.52 (EtOAc/hexanes 1:4)), followed by the title compound **2ak**, which was obtained as light-brown solid, m.p. 87.7-90.3 °C (benzene), R_f 0.44 (EtOAc/hexanes 1:3), dr 14.3:1. Yield 98 mg (0.29 mmol, 58%), ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (dd, *J* = 7.7, 1.7 Hz, 2H), 7.57 – 7.50 (m, 3H), 7.37 (d, *J* = 7.7 Hz, 1H), 7.18 – 7.10 (m, 4H), 6.98 (d, *J* = 7.2 Hz, 1H), 6.90 (t, *J* = 7.4 Hz, 1H), 6.86 – 6.80 (m, 2H), 4.76 (s, 1H), 2.10 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 177.9, 157.9, 152.9, 136.0, 132.6, 132.1, 131.6, 130.0, 129.1 (2C), 129.0 (2C), 128.6 (2C), 128.4 (2C), 128.2, 125.8, 125.0, 121.1, 99.0, 64.6, 12.9; IR (KBr, film, cm^{-1}): 3037, 2933, 2854, 1967, 1743, 1540, 1466, 1366, 1267; HRMS (ES TOF) calc`d for $C_{23}H_{18}N_2NaO$ $(M+Na)^+$: 361.1311, found 361.1313 (0.4 ppm);

3,3'-(Phenylmethylene)bis(2-phenyl-1*H*-indole) (**11aa**): Was isolated as a byproduct along with material **2ak**, as greenish solid, m.p. 234.4-237.0 °C (benzene), R_f 0.52 (EtOAc/hexanes 1:3); yield 45 mg, (0.095 mmol, 38%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 2H), 7.33 (d, *J* = 8.1 Hz, 4H), 7.28 – 7.07 (m, 15H), 7.00 (d, *J* = 8.1 Hz, 2H), 6.83 (t, *J* = 7.6 Hz, 2H), 6.12 (s, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 145.0 (2C), 136.1 (2C), 135.6, 133.1 (2C), 129.4 (2C), 129.0 (2C), 128.5 (4C), 128.39 (2C), 128.35 (4C), 127.6 (2C), 126.2, 121.9 (2C), 121.8 (2C), 119.7 (2C), 115.8 (2C), 110.7 (2C), 40.1; IR (KBr, film, cm^{-1}): 3422, 2937, 2862, 1702, 1561, 1457, 1238; HRMS (ES TOF) calc`d for $C_{35}H_{25}N_2$ $(M-H)^-$ 473.2023, found 473.2029 (1.1 ppm);

(3*R*,4'*S*)-3'-Ethyl-2,4'-diphenyl-4'*H*-spiro[indole-3,5'-isoxazole] (**2al**): This compound was obtained via Typical Procedure B from 2-phenyl-1*H*-indole (**4a**) (97 mg, 0.50 mmol) and (2-nitrobut-1-en-1-yl)benzene (**3l**) (97 mg, 0.55 mmol) as colorless oil, R_f 0.51 (EtOAc/ hexanes 1:4), dr 12.5:1. Yield 95 mg, (0.27 mmol, 54%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 – 8.08 (m, 2H), 7.53 (t, *J* = 6.6 Hz, 3H), 7.39 (d, *J* = 7.7 Hz, 1H), 7.21 – 7.06 (m, 4H), 7.00 – 6.78 (m, 4H), 4.75 (s, 1H), 2.65 (dq, *J* = 15.1, 7.5 Hz, 1H), 2.23 (dq, *J* = 15.1, 7.5 Hz, 1H), 1.09 (t, *J* = 7.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 178.2, 162.4, 153.0, 135.8, 132.9, 132.1, 131.5, 129.9, 129.0 (2C), 128.9 (2C), 128.6 (2C), 128.5 (2C), 128.2, 125.8, 125.1, 121.1, 98.8, 63.1, 20.9, 10.9; IR (KBr, film, cm^{-1}): 3057, 2979, 1962, 1540, 1457, 1263, 1188; HRMS (ES TOF) calc`d for $C_{24}H_{21}N_2O$ $(M+H)^+$ 353.1648, found 353.1647 (0.5 ppm). In addition, compound **11aa** was also isolated as a byproduct, yield 50 mg (0.105 mmol, 42%). Physical and spectral properties of this material were identical to those described above for the sample of **11aa** isolated along with spirocyclic compound **2ak**.

(3*R,4'*S**)-4'-(4-Chlorophenyl)-3'-methyl-2-phenyl-4'*H*-spiro[indole-3,5'-isoxazole]** (**2am**): This compound was obtained via Typical Procedure B from 2-phenyl-1*H*-indole (**4a**) (97 mg, 0.50 mmol) and 1-chloro-4-(2-nitroprop-1-en-1-yl)benzene (**3m**) (109 mg, 0.55 mmol) as yellowish oil, R_f 0.47 (EtOAc/hexanes 1:3), dr 14.3:1. Yield 99 mg, (0.27 mmol, 53%), ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (dd, *J* = 7.8, 1.3 Hz, 2H), 7.58 – 7.48 (m, 3H), 7.40 (d, *J* = 7.7 Hz, 1H), 7.24 – 7.16 (m, 1H), 7.12 (d, *J* = 8.4 Hz, 2H), 7.02 – 6.92 (m, 2H), 6.76 (d, *J* = 8.4 Hz, 2H), 4.73 (s,

1H), 2.07 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 177.7, 157.5, 152.7, 135.7 (2C), 134.2, 131.8, 131.1, 130.34 (2C), 130.29, 129.2 (2C), 128.9 (2C), 128.4 (2C), 126.1, 124.8, 121.3, 99.0, 64.0, 12.9; IR (KBr, film, cm^{-1}): 3061, 2933, 2365, 1743, 1557, 1540, 1499, 1461, 1246; HRMS (ES TOFF) calc`d for $C_{23}H_{18}ClN_2O$ $(M+H)^+$ 373.1102, found 373.1100 (0.7 ppm); calc`d for $C_{23}H_{17}ClN_2NaO$ $(M+Na)^+$ 395.0922, found 395.0927 (1.3 ppm); In addition, compound **11ac** was isolated as a byproduct, yield 56 mg (0.11 mmol, 44%).

3,3'-((4-Chlorophenyl)methylene)bis(2-phenyl-1*H*-indole) (**11ac**): Was isolated as a byproduct along with material **2al** as colorless solid, m.p. 238.6-240.4 °C (benzene/hexanes), R_f 0.48 (EtOAc/hexanes 1:2); Yield 56 mg, (0.11 mmol, 44%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 2H), 7.32 (t, *J* = 9.4 Hz, 2H), 7.25 – 7.10 (m, 16H), 7.04 (d, *J* = 8.1 Hz, 2H), 6.86 (t, *J* = 7.6 Hz, 2H), 6.06 (s, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 143.6 (2C), 136.1 (2C), 135.8 (1C), 133.0 (2C), 131.8 (1C), 130.7 (2C), 128.7 (2C), 128.54 (4C), 128.49 (2C), 128.3 (4C), 127.7 (2C), 122.0 (2C), 121.7 (2C), 119.8 (2C), 115.1 (2C), 110.8 (2C), 39.6 (1C); IR (KBr, film, cm^{-1}): 3401, 2933, 1706, 1557, 1254; HRMS (ES TOF) calc`d for $C_{35}H_{24}ClN_2$ $(M-H)^-$ 507.1634, found 507.1629 (0.9 ppm);

(3*R,4'*S**)-3'-methyl-2-(naphthalen-2-yl)-4'-phenyl-4'*H*-spiro[indole-3,5'-isoxazole]** (**2ek**): This compound was obtained via Typical Procedure B from 2-(naphthalen-2-yl)-1*H*-indole (**4e**) (122 mg, 0.50 mmol) and (2-nitroprop-1-en-1-yl)benzene (**3k**) (90 mg, 0.55 mmol) as light grey solid, m.p. 92-94.2 °C (hexanes), R_f 0.48 (EtOAc/hexanes 1:3). Yield 99 mg, (0.26 mmol, 51%), dr 25:1. ^1H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.32 (dd, *J* = 8.7, 1.4 Hz, 1H), 8.00 (s, 2H), 7.91 (d, *J* = 7.5 Hz, 1H), 7.65 – 7.54 (m, 2H), 7.42 (d, *J* = 7.7 Hz, 1H), 7.15 (dt, *J* = 12.2, 6.5 Hz, 4H), 7.05 (d, *J* = 7.3 Hz, 1H), 6.93 (t, *J* = 7.4 Hz, 1H), 6.84 (dd, *J* = 7.4, 1.5 Hz, 2H), 4.87 (s, 1H), 2.14 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, CDCl3) δ 177.8, 158.1, 153.0, 136.1, 134.8, 133.2, 132.6, 130.0, 129.42, 129.36, 129.0 (2C), 128.9, 128.8, 128.6 (2C), 128.1, 128.0, 127.9, 126.9, 125.9, 125.1, 125.0, 121.1, 99.2, 65.1, 12.9; IR (KBr, film, cm^{-1}): 3045, 2929, 1739, 1706, 1540, 1462, 1275, 1238, 1192; HRMS (ES TOF) calc`d for $C_{27}H_{20}N_2NaO$ $(M+Na)^+$ 411.1468, found 411.1466 (0.6 ppm). In addition, compound **11ea** was isolated as a byproduct.

3,3'-(Phenylmethylene)bis(2-(naphthalen-2-yl)-1*H*-indole) (**11ea**): Was isolated as a byproduct along with material **2ek**, as colorless solid, m.p. 237.4-238.9 °C (benzene), R_f 0.49 (EtOAc/hexanes 1:3). Yield 66 mg, (0.12 mmol, 46%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 2H), 7.64 (d, *J* = 8.3 Hz, 2H), 7.50 – 7.28 (m, 17H), 7.18 (d, *J* = 8.5 Hz, 2H), 7.11 (t, *J* = 7.6 Hz, 2H), 7.01 (d, *J* = 8.1 Hz, 2H), 6.86 (t, *J* = 7.6 Hz, 2H), 6.35 (s, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 144.8 (2C), 136.2 (2C), 135.7 (1C), 133.0 (2C), 132.5 (2C), 130.4 (2C), 129.6 (2C), 129.0 (2C), 128.5 (2C), 128.2 (2C), 127.9 (2C), 127.6 (2C), 127.5 (2C), 126.4 (1C), 126.1 (4C), 126.0 (2C), 121.84 (2C), 121.77 (2C), 119.7 (2C), 116.2 (2C), 110.7 (2C), 40.3 (1C); IR (KBr, film, cm^{-1}): 3405, 3057, 1702, 1602, 1490, 1461, 1317, 1035; HRMS calc`d for $C_{43}H_{29}N_2$ $(M-H)^-$ 573.2336, found 573.2341 (0.9 ppm);

(3*R,4'*S**)-3'-Ethyl-2-(naphthalen-2-yl)-4'-phenyl-4'*H*-spiro[indole-3,5'-isoxazole]** (**2el**): This compound was obtained via Typical Procedure B from 2-(naphthalen-2-yl)-1*H*-indole (**4e**) (122 mg, 0.50 mmol) and (2-nitrobut-1-en-1-yl)benzene (**3l**) (97 mg, 0.55 mmol) as greenish solid, m.p. 134.7-138.5 °C (benzene/hexanes); R_f 0.55 (EtOAc/ hexanes 1:4). Yield 92 mg, (0.23 mmol, 46%), dr 20:1. ^1H NMR (400 MHz, $CDCl_3$) δ 8.60 (s, 1H), 8.31 (d, *J* = 8.6 Hz, 1H), 7.98 (d, *J* = 8.4 Hz, 2H), 7.91 (d, *J* = 7.7 Hz, 1H), 7.63 – 7.52 (m, 2H), 7.42 (d, *J* = 7.7 Hz, 1H), 7.20 – 7.10 (m, 4H), 6.99 (d, *J* = 7.4 Hz, 1H), 6.91 (t, *J* = 7.4 Hz, 1H), 6.84 (d, *J* = 7.1 Hz, 2H), 4.87 (s, 1H), 2.71 (dq, *J* = 15.1, 7.5 Hz, 1H), 2.26 (dq, *J* = 15.1, 7.4 Hz, 1H), 1.13 (t, *J* = 7.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 178.2, 162.6, 153.1, 136.1, 134.8, 133.2, 132.9, 130.0, 129.4, 129.3, 129.0 (2C), 128.9, 128.8, 128.6 (2C), 128.2, 128.0, 127.9, 126.9, 125.9, 125.23, 125.15, 121.1, 98.9, 63.7, 21.1, 11.2; IR (KBr, film, cm^{-1}): 3675, 2979, 2361, 1706, 1536, 1457; HRMS (ES TOF) calc`d for $C_{28}H_{23}N_2O$ $(M+H)^+$ 403.1805, found 403.1815, (2.4. ppm); In addition, compound **11ea** was also isolated as a byproduct, yield 72 mg (0.125 mmol, 50%). Physical and spectral properties of this material were identical to those described above for the sample of **11ea** isolated along with spirocyclic compound **2ek**.

(3*R,4'*S**)-4'-(4-Chlorophenyl)-3'-methyl-2-(naphthalen-2-yl)-4'*H*-spiro[indole-3,5'-isoxazole]** (**2em**): This compound was obtained via Typical Procedure B from 2-(naphthalen-2-yl)-1*H*-indole (**4e**) (122 mg, 0.50 mmol) and 1-chloro-4-(2-nitroprop-1-en-1-yl)benzene (**3m**) (109 mg, 0.55 mmol) as greenish solid, m.p. 188.1-191.5 °C (benzene/hexanes), R_f 0.35 (EtOAc/hexanes 1:3). Yield 102 mg, (0.24 mmol, 48%), dr 91:9. ^1H NMR (400 MHz, CDCl3) δ 8.62 (s, 1H), 8.29 (d, *J* = 8.6 Hz, 1H), 7.99 (d, *J* = 8.2 Hz, 2H), 7.91 (d, *J* = 7.8 Hz, 1H), 7.63 – 7.53 (m, 2H), 7.43 (d, *J* = 7.7 Hz, 1H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.12 (d, *J* = 7.9 Hz, 2H), 7.04 (d, *J* = 7.3 Hz, 1H), 6.98 (t, *J* = 7.4 Hz, 1H), 6.77 (d, *J* = 7.9 Hz, 2H), 4.83 (s, 1H), 2.11 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, CDCl3) δ 177.6, 157.7, 152.9, 135.9, 134.9, 134.2, 133.2, 131.1, 130.4 (2C), 130.3, 129.5, 129.2, 129.0, 128.92, 128.90 (2C), 128.1, 128.0, 126.9, 126.1, 125.1, 124.9, 121.4, 99.1, 64.5, 12.9; IR (KBr, film, cm^{-1}): 2925, 2858, 1913, 1747, 1548, 1494, 1469, 1288, 1208; HRMS (ES TOF) calc`d for $C_{27}H_{20}ClN_2O$ $(M+H)^+$ 423.1259, found 423.1247 (2.8 ppm). In addition, compound **11ec** was isolated as a byproduct.

3,3'-((4-Chlorophenyl)methylene)bis(2-(naphthalen-2-yl)-1*H*-indole) (**11ec**): Was isolated as a byproduct along with material **2em**, as grey solid, m.p. 245.8-247.3 °C (benzene/hexanes), R_f 0.55 (EtOAc/hexanes 1:3). Yield 75 mg, (0.12 mmol, 49%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 2H), 7.65 (d, *J* = 8.0 Hz, 2H), 7.48 – 7.27 (m, 16H), 7.16 (d, *J* = 8.5 Hz, 2H), 7.12 (t, *J* = 7.6 Hz, 2H), 7.03 (d, *J* = 8.1 Hz, 2H), 6.88 (t, *J* = 7.6 Hz, 2H), 6.30 (s, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 143.4 (2C), 136.2 (2C), 135.9, 133.0 (2C), 132.6 (2C), 132.0, 130.9 (2C), 130.3 (2C), 128.7 (2C), 128.6 (2C), 128.1 (2C), 128.0 (2C), 127.6 (2C), 127.5 (2C), 126.2 (4C), 126.0 (2C), 122.0 (2C), 121.6 (2C), 119.9 (2C), 115.5 (2C), 110.8 (2C), 39.8; IR (KBr, film, cm^{-1}): 3389, 2933, 1756, 1507, 1453, 1308, 1288, 1250; HRMS (ES TOF) calc`d for $C_{43}H_{28}ClN_2$ $(M-H)^-$ 607.1947, found 607.1934 (2.1 ppm);

(3*R,4'*S**)-2-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-3'-methyl-4'-phenyl-4'*H*-spiro[indole-3,5'-isoxazole]** (**2gk**): This compound was obtained via Typical Procedure B from 2-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-1*H*-indole (**4g**) (126 mg, 0.50 mmol) and (2-nitroprop-1-en-1-yl)benzene (**3k**) (90 mg, 0.55 mmol) as yellowish oil, R_f 0.47 (EtOAc/hexanes 1:3). Yield 67 mg, (0.17 mmol, 34%), dr 10:1. ^1H NMR (400 MHz, DMSO-d_6) δ 7.59 (d, *J* = 8.5 Hz, 1H), 7.54 (s, 1H), 7.27 (d, *J* = 7.6 Hz, 1H), 7.16 – 7.06 (m, 6H), 6.91 (t, *J* = 7.5 Hz, 1H), 6.86 (d, *J* = 7.3 Hz, 2H), 5.04 (s, 1H), 4.43 – 4.30 (m, 4H), 2.08 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 176.4, 158.2, 152.4, 146.7, 143.6, 136.1, 132.4, 129.8, 129.2 (2C), 128.3 (2C), 127.7, 125.3, 125.0, 124.4, 121.5, 120.3, 117.9, 116.5, 97.9, 64.6, 64.5, 64.1, 12.4; IR (KBr, film, cm^{-1}): 3066, 2945, 1739 ,1589, 1503, 1462, 1436, 1325, 1292, 1263, 1200, 1134, 1072; HRMS (ES TOF) calc`d for $C_{25}H_{21}N_2O_3$ $(M+H)^+$ 397.1547, found 397.1537 (2.3 ppm); In addition, compound **11ga** was isolated as a byproduct.

3,3'-(Phenylmethylene)bis(2-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-1*H*-indole) (**11ga**): Was isolated as a byproduct along with material **2gk**, as yellowish oil, R_f 0.61 (EtOAc). Yield 81 mg, (0.14 mmol, 55%), ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 2H), 7.30 (d, *J* = 7.6 Hz, 4H), 7.23 (t, *J* = 6.5 Hz, 3H), 7.07 (t, *J* = 7.5 Hz, 2H), 6.99 (d, *J* = 8.1 Hz, 2H), 6.81 (t, *J* = 7.6 Hz, 2H), 6.74 – 6.68 (m, 4H), 6.65 (d, *J* = 8.2 Hz, 2H), 6.06 (s, 1H), 4.21 (s, 8H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 145.0 (2C), 143.27 (2C), 143.26 (2C), 135.9 (2C), 135.4, 129.3 (2C), 128.9 (2C), 128.3 (2C), 126.6 (2C), 126.0, 121.9 (2C), 121.7 (2C), 121.5 (2C), 119.5 (2C), 117.5 (2C), 117.2 (2C), 115.3 (2C), 110.6 (2C),

64.5 (2C), 64.3 (2C), 40.0; IR (KBr, film, cm^{-1}): 2929, 2858, 1747, 1702, 1461, 1288, 1246; HRMS (ES TOF) calc`d for $C_{39}H_{29}N_2O_4$ (M-H)$^-$ 589.2133, found 589.2129 (0.7 ppm);

(3*R,4'*S**)-4'-(4-Chlorophenyl)-2-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-3'-methyl-4'*H*-spiro[indole-3,5'-isoxazole]** (**2gm**): This compound was obtained via Typical Procedure B from 2-(2,3-dihydrobenzo[*b*][1,4]-dioxin-6-yl)-1*H*-indole (**4g**) (126 mg, 0.50 mmol) and 1-chloro-4-(2-nitroprop-1-en-1-yl)benzene (**3m**) (109 mg, 0.55 mmol) as colorless solid, m.p. 209.2-211.8 °C (EtOAc/hexanes), R_f 0.61 (EtOAc/hexanes 1:1). Yield 101 mg, (0.24 mmol, 47%), dr 5.3:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.67 (d, *J* = 8.5 Hz, 1H), 7.33 (d, *J* = 7.7 Hz, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 7.10 (d, *J* = 8.2 Hz, 2H), 6.99 (t, *J* = 6.8 Hz, 2H), 6.92 (t, *J* = 7.0 Hz, 1H), 6.75 (d, *J* = 8.2 Hz, 2H), 4.79 (s, 1H), 4.38 – 4.28 (m, 4H), 2.10 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 176.9, 157.4, 152.8, 147.0, 144.0, 135.7, 134.1, 131.1, 130.4 (2C), 130.2, 128.8 (2C), 125.6, 125.1, 124.7, 122.2, 121.0, 118.0, 117.5, 98.9, 64.8, 64.5, 64.3, 12.9; IR (KBr, film, cm^{-1}): 3070, 2933, 1747, 1507, 1457, 1296, 1250, 1122; HRMS calc`d for $C_{25}H_{20}ClN_2O_3$ (M+H)$^+$ 431.1157, found 431.1150 (1.6 ppm); In addition, compound **11gc** was isolated as a byproduct.

3,3'-((4-Chlorophenyl)methylene)bis(2-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-1*H*-indole) (**11gc**): Was isolated as a byproduct along with material **2gm**, as light-brown amorphous solid with m.p. 152.3-173.0 °C, R_f 0.33 (EtOAc/hexanes 1:1). Yield 75 mg, (0.12 mmol, 48%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 7.21 (q, *J* = 8.6 Hz, 4H), 7.09 (t, *J* = 7.6 Hz, 2H), 7.04 (d, *J* = 8.1 Hz, 2H), 6.85 (t, *J* = 7.6 Hz, 2H), 6.73 – 6.63 (m, 6H), 6.02 (s, 1H), 4.20 (d, *J* = 2.4 Hz, 8H); ^{13}C{^{1}H} NMR (101 MHz, CDCl3) δ 143.6 (2C), 143.3 (2C), 143.2 (2C), 135.8 (2C), 135.5, 131.6, 130.7 (2C), 128.6 (2C), 128.4 (2C), 126.4 (2C), 121.8 (2C), 121.6 (2C), 121.5 (2C), 119.6 (2C), 117.5 (2C), 117.2 (2C), 114.6 (2C), 110.7 (2C), 64.4 (2C), 64.3 (2C), 39.5; IR (KBr, film, cm^{-1}): 3401, 3070, 2986, 2870, 1735, 1499, 1466, 1288, 1250; HRMS (ES TOF) calc`d for $C_{39}H_{28}ClN_2O_4$ (M-H)$^-$ 623.1743, found 623.1740 (0.6 ppm);

Preparation of authentic samples of nitroalkanes 10

3-(2-Nitro-1-phenylethyl)-2-phenyl-1*H*-indole (**10aa**),[23] **Typical Procedure C**: Reaction vessel was charged with 2-phenyl-1*H*-indole (**4a**) (97 mg, 0.50 mmol), (2-nitrovinyl)benzene (**3a**) (82 mg, 0.55 mmol), phosphorous acid (500 mg), and ethanol (500 mg). The mixture was vigorously stirred for 2 h at room temperature. Resulting dark-red homogenous solution was poured into water (50 mL), and the formed precipitate was filtered and washed consecutively with water (4 times), 10% aqueous ammonia, and once again with water. After drying, the resulting crystalline material was purified by Flash column chromatography on Silica gel eluting with a mixture of hexane and ethyl acetate (4:1), or by re-crystallization from a mixture of hexane and benzene (1:1). Yield 156 mg, (0.46 mmol, 91%), colorless solid, m.p. 142.3-143.4 °C (benzene/hexanes), R_f 0.63 (EtOAc/hexanes 1:1), R_f 0.65 (benzene/CH_2Cl_2 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.38 – 7.06 (m, 12H), 7.01 (t, *J* = 7.4 Hz, 1H), 5.22 (t, *J* = 7.9 Hz, 1H), 5.13 – 4.91 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 140.0, 137.1, 136.2, 132.3, 129.03 (2C), 128.97 (2C), 128.9 (2C), 128.7, 127.6 (2C), 127.3, 127.1, 122.6, 120.4, 120.0, 111.6, 109.6, 79.2, 40.9; IR (KBr, film, cm^{-1}): 3414, 3057, 2357, 1544, 1457, 1370, 1304; HRMS (ES TOF) calc`d for $C_{22}H_{18}N_2NaO_2$ (M+Na)$^+$ 365.1260, found 365.1257 (1.0 ppm);

3-(1-(4-Chlorophenyl)-2-nitroethyl)-2-phenyl-1*H*-indole (**10ac**):[23] This compound was obtained via Typical Procedure C from 2-phenyl-1*H*-indole (**4a**) (97 mg, 0.50 mmol) and 1-chloro-4-(2-nitrovinyl)benzene (**3c**) (101 mg, 0.55 mmol). Yield 169 mg, (0.45 mmol, 90%), yellowish solid, m.p. 118.0-123.2 °C (EtOH), R_f 0.40 (benzene), R_f 0.57 (EtOAc/hexanes 1:4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.52 – 7.39 (m, 7H), 7.29 – 7.21 (m, 5H), 7.14 (t, *J* = 7.6 Hz, 1H), 5.29 (t, *J* = 7.9 Hz, 1H), 5.14 (ddd, *J* = 30.3, 12.5, 8.0 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 138.6, 137.2, 136.2, 133.2, 132.1, 129.19 (2C), 129.18 (2C), 129.0 (2C), 128.94, 128.89 (2C), 126.9, 122.8, 120.6, 119.9, 111.6, 109.3, 79.0, 40.4; IR (KBr, film, cm^{-1}): 3434, 3057, 2920, 1553, 1478, 1453, 1382, 1317, 1250; HRMS (ES TOF) calc`d for $C_{22}H_{17}ClN_2NaO_2$ (M+Na)$^+$ 399.0871, found 399.0872 (0.3 ppm);

2-(4-Chlorophenyl)-3-(2-nitro-1-phenylethyl)-1*H*-indole (**10ca**):[24] This compound was obtained via Typical Procedure C from 2-(4-chlorophenyl)-1*H*-indole (**4c**) (114 mg, 0.50 mmol) and (2-nitrovinyl)benzene (**3a**) (82 mg, 0.55 mmol). The titled material was obtained as yellowish solid, m.p. 164.3-167.8 °C (EtOH), R_f 0.60 (EtOAc/hexanes 1:4); R_f 0.43 (benzene). Yield 162 mg, (0.43 mmol, 86%), ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.43 (t, *J* = 6.8 Hz, 2H), 7.41 – 7.20 (m, 9H), 7.14 (t, *J* = 7.5 Hz, 1H), 5.26 (t, *J* = 7.9 Hz, 1H), 5.17 (d, *J* = 7.8 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 139.7, 136.3, 135.9, 134.9, 130.7, 130.2 (2C), 129.4 (2C), 129.1 (2C), 127.6 (2C), 127.5, 127.0, 123.0, 120.7, 120.2, 111.6, 110.1, 79.2, 41.0; IR (KBr, film, cm^{-1}): 3410, 3066, 1548, 1499, 1461, 1432, 1383, 1317; HRMS (ES TOF) calc`d for $C_{22}H_{17}ClN_2NaO_2$ (M+Na)$^+$ 399.0871, found 399.0861 (2.5 ppm).

Base-assisted spirocyclization of nitroalkanes 10

(3*R,4'*S**)-2,4'-Diphenyl-4'H-spiro[indole-3,5'-isoxazole]** (**2aa**), **Typical Procedure D**: Reaction vessel was charged with potassium hydroxide (56 mg, 1.00 mmol), 3-(2-nitro-1-phenylethyl)-2-phenyl-1*H*-indole (**10aa**) (68 mg, 0.20 mmol) and ethanol (0.40 mL). The mixture was stirred for 60 min at room temperature, and then the resulted solution was added over 5 min to another vessel, containing a mixture of phosphorous acid (320 mg) and formic acid (0.30 mL) stirred at room temperature. After 30 min the mixture was quenched with water (10 mL) and brine (20 mL) and extracted with ethyl acetate (3 x 15 mL). Combined organic phases were concentrated in vacuum and the residual oil was separated by column chromatography to afford two fractions: unreacted nitroalkane **5aa** was eluting first with R_f 0.63 (EtOAc/hexanes 1:1), yield 47 mg (0.14 mmol, 69%) followed by spirocyclic product **2aa** R_f 0.47 (hexanes/EtOAc, 1:4), yield 17 mg (0.052 mmol, 26%). Chromatographical and spectral properties of compounds **2aa** and **10aa** isolated in this experiment were identical to those of authentic samples described above.

(3*R,4'*S**)-4'-(4-Chlorophenyl)-2-phenyl-4'*H*-spiro[indole-3,5'-isoxazole]** (**2ac**): This compound was obtained via Typical Procedure D from 3-(1-(4-chlorophenyl)-2-nitroethyl)-2-phenyl-1*H*-indole (**10ac**) (75 mg, 0.2 mmol). The title compound was obtained as yellow solid, yield 19 mg (0.054 mmol, 27%) along with unreacted **5ac** isolated back in a yield of 53 mg (0.14 mmol, 70%). Chromatographical and spectral properties of compounds **2ac** and **5ac** isolated in this experiment were identical to those of authentic samples described above.

(3*R,4'*S**)-2-(4-Chlorophenyl)-4'-phenyl-4'*H*-spiro[indole-3,5'-isoxazole]** (**2ca**): This compound was obtained via Typical Procedure D from 2-(4-chlorophenyl)-3-(2-nitro-1-phenylethyl)-1*H*-indole (**10ca**) (75 mg, 0.2 mmol). The title compound was obtained as off-white solid, yield 24 mg (0.068 mmol, 34%) along with unreacted **5ca** isolated back in a yield of 47 mg (0.126 mmol, 63%).

Three-component one-pot procedure involving Fischer indolization

(3*R,4'*S**)-2,4'-Diphenyl-4'H-spiro[indole-3,5'-isoxazole]** (**2aa**), **Typical Procedure E**: Reaction wessel was charged with phenylhydrazine (**12a**) (98 μL, 108 mg, 1.00 mmol), acetophenone (**13a**) (117 μL, 120 mg, 1.00 mmol), and glasial acetic acid (1.00 g). The reaction mixture was refluxed for 20 min monitoring the reaction progress by TLC. When hydrazone

formation was complete, the mixture was cooled down to room temperatre and concentrated sulfuric acid (125 mg) was added in a single portion. The mixture was heated to 90 °C in oil bath for 4 hr monitoring the indolization step by TLC. Then the mixture was cooled down, (2-nitrovinyl)benzene (**3a**) (149 mg, 1.00 mmol) was added, and the stirring at room temperature was continued for 4 hr. After purification by column chromatography the titled compound was afforded as off-white solid identical to the sample obtained via method A. Yield 256 mg (0.79 mmol, 79%).

(3*R,4'*S**)-4'-(4-Fluorophenyl)-2-phenyl-4'*H*-spiro[indole-3,5'-isoxazole]** (**2ab**): This compound was obtained via Typical Procedure E starting from phenylhydrazine (**12a**) (98 μL, 108 mg, 1.00 mmol), acetophenone (**13a**) (117 μL, 120 mg, 1.00 mmol), and 1-fluoro-4-(2-nitrovinyl)benzene (**3b**) (167 mg, 1.00 mmol). The titled material was afforded as light-yellow crystals identical to the sample obtained via method A. Yield 246 mg (0.72 mmol, 72%).

(3*R,4'*S**)-4'-(4-Chlorophenyl)-2-phenyl-4'*H*-spiro[indole-3,5'-isoxazole]** (**2ac**): This compound was obtained via Typical Procedure E starting from phenylhydrazine (**12a**) (98 μL, 108 mg, 1.00 mmol), acetophenone (**13a**) (117 μL, 120 mg, 1.00 mmol), and 1-chloro-4-(2-nitrovinyl)benzene (**3c**) (184 mg, 1.00 mmol). The titled material was afforded as yellow crystals identical to the sample obtained via method A. Yield 243 mg (0.68 mmol, 68%).

(3*R,4'*S**)-4'-(4-Methoxyphenyl)-2-phenyl-4'*H*-spiro[indole-3,5'-isoxazole]** (**2ad**): This compound was obtained via Typical Procedure E starting from phenylhydrazine (**12a**) (98 μL, 108 mg, 1.00 mmol), acetophenone (**13a**) (117 μL, 120 mg, 1.00 mmol), and 1-methoxy-4-(2-nitrovinyl)benzene (**3d**) (180 mg, 0.55 mmol). The titled material was afforded as grey crystals identical to the sample obtained via method A. Yield 261 mg, (0.74 mmol, 74%).

(3*R,4'*S**)-4'-Hexyl-2-phenyl-4'H-spiro[indole-3,5'-isoxazole]** (**2ag**): This compound was obtained via Typical Procedure E starting from phenylhydrazine (**12a**) (98 μL, 108 mg, 1.00 mmol), acetophenone (**13a**) (117 μL, 120 mg, 1.00 mmol), and 1-nitrooct-1-ene (**3g**) (156 mg, 1.00 mmol). The titled material was afforded as yellowish oil identical to the sample obtained via method A. Yield 162 mg (0.49 mmol, 49%).

(3*R,4'*S**)-4'-Isopropyl-2-phenyl-4'*H*-spiro[indole-3,5'-isoxazole]** (**2ah**): This compound was obtained via Typical Procedure E starting from phenylhydrazine (**12a**) (98 μL, 108 mg, 1.00 mmol), acetophenone (**13a**) (117 μL, 120 mg, 1.00 mmol), and 3-methyl-1-nitrobut-1-ene (**3h**) (115 mg, 1.00 mmol). The titled material was afforded as colorless solid identical to the sample obtained via method A. Yield 156 mg (0.53 mmol, 53%).

(3*R,4'*S**)-3'-Methyl-2,4'-diphenyl-4'*H*-spiro[indole-3,5'-isoxazole]** (**2ak**): This compound was obtained via Typical Procedure E starting from phenylhydrazine (**12a**) (98 μL, 108 mg, 1.00 mmol), acetophenone (**13a**) (117 μL, 120 mg, 1.00 mmol), and (2-nitroprop-1-en-1-yl)benzene (**3k**) (163 mg, 1.00 mmol). The titled material was afforded as light-brown solid identical to the sample obtained via method B. Yield 139 mg (0.41 mmol, 41%). In addition, compound **11aa** was isolated in a yield of 64 mg (0.14 mmol, 27%).

(3*R*,4'*S*)-3'-Ethyl-2,4'-diphenyl-4'*H*-spiro[indole-3,5'-isoxazole] (**2al**): This compound was obtained via Typical Procedure E starting from phenylhydrazine (**12a**) (98 μL, 108 mg, 1.00 mmol), acetophenone (**13a**) (117 μL, 120 mg, 1.00 mmol), and (2-nitrobut-1-en-1-yl)benzene (**3l**) (176 mg, 1.00 mmol). The titled material was afforded as colorless oil identical to the sample obtained via method B. Yield 148 mg, (0.42 mmol, 42%). In addition, compound **11aa** was isolated in a yield of 73 mg (0.16 mmol, 31%).

(3*R,4'*S**)-4'-Phenyl-2-(*p*-tolyl)-4'*H*-spiro[indole-3,5'-isoxazole]** (**2ba**): This compound was obtained via Typical Procedure E starting from phenylhydrazine (**12a**) (98 μL, 108 mg, 1.00 mmol), 4′-methylacetophenone (**13b**) (133 μL, 134 mg, 1.00 mmol), and (2-nitrovinyl)benzene (**3a**) (149 mg, 1.00 mmol). The titled material was afforded as light grey solid identical to the sample obtained via method A. Yield 258 mg, (0.77 mmol, 77%).

(3*R,4'*S**)-2-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-4'-phenyl-4'*H*-spiro[indole-3,5'-isoxazole]** (**2ga**): This compound was obtained via Typical Procedure E starting from phenylhydrazine (**12a**) (98 μL, 108 mg, 1.00 mmol), 1-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)ethan-1-one (**13g**) (150 μL, 178 mg, 1.00 mmol), and (2-nitrovinyl)benzene (**3a**) (82 mg, 0.55 mmol). The titled material was afforded as yellow solid identical to the sample obtained via method A. Yield 225 mg (0.59 mmol, 59%).

(3*R,4'*S**)-4'-(4-Chlorophenyl)-2-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-3'-methyl-4'*H*-spiro[indole-3,5'-isoxazole]** (**2gm**): This compound was obtained via Typical Procedure E starting from phenylhydrazine (**12a**) (98 μL, 108 mg, 1.00 mmol), 1-(2,3-dihydrobenzo-[*b*][1,4]dioxin-6-yl)ethan-1-one (**13g**) (150 μL, 178 mg, 1.00 mmol), 1-chloro-4-(2-nitroprop-1-en-1-yl)benzene (**3m**) (198 mg, 1.00 mmol). The titled material was afforded as colorless solid identical to the sample obtained via method A. Yield 152 mg, (0.36 mmol, 36%). In addition, compound **11gc** was isolated as a byproduct in a yield of 100 mg, (0.16 mmol, 32%).

(3*R,4'*S**)-5-Isopropyl-2,4'-diphenyl-4'*H*-spiro[indole-3,5'-isoxazole]** (**2la**): This compound was obtained via Typical Procedure E starting from (4-isopropylphenyl)hydrazine (**12l**) (146 μL, 150 mg, 1.00 mmol), acetophenone (**13a**) (117 μL, 120 mg, 1.00 mmol), and (2-nitrovinyl)benzene (**3a**) (82 mg, 0.55 mmol). The titled material was afforded as grey solid identical to the sample obtained via method A. Yield 263 mg, (0.73 mmol, 73%).

ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectral data (PDF)
HRMS data (PDF)
Computational data (PDF)
X-Ray crystallography data (CIF)

The Supporting Information is available free of charge on the ACS Publications website.

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Notes

The authors declare no competing financial interest.

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