Structure−Activity Relationship Study of Tricyclic Necroptosis Inhibitors

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Necroptosis is a regulated caspase-independent cell death mechanism that can be induced in multiple cell types and is characterized by morphological features resembling necrosis. Here we describe a series of tricyclic heterocycles (i.e., 3-phenyl-3,3a,4,5-tetrahydro-2*H*-benz[*g*]indazoles, 3-phenyl-2,3,3a,4-tetrahydro-[1]benzopyrano[4,3-*c*]pyrazoles, 3-phenyl-2,3,3a,4-tetrahydro[1]benzothiopyrano[4,3-*c*]pyrazoles, and 5,5-dioxo-3-phenyl-2,3,3a,4-tetrahydro[1]benzothiopyrano[4,3-*c*]pyrazoles], collectively termed Nec-3, that can potently inhibit necroptosis. For example, compounds **8**, **22**, **41**, **53**, and **55** inhibit necroptosis in an FADD-deficient variant of human Jurkat T cells treated for 24 h with TNF-α with EC_{50} values in the range 0.15−0.29 μM. Distinct from the previously described series of hydantoin-containing indole derivatives (Nec-1), the Nec-3 series exhibits specificity in inhibiting TNF-α-induced necroptosis. A structure−activity relationship (SAR) study revealed that the (3*R*,3a*R*)-*rel*-diastereomers were more active than the (3*R*,3a*S*)-*rel*-diastereomers for all four ring systems. Introduction of fluorine or methoxy to the 8-position of the tricyclic ring and a methoxy to the 4-position of the pendent phenyl ring increased activity. Amides at the 2-position of the tricyclic ring were best. The Nec-3 series provides new tools for elucidating caspase-independent cell death pathways and potentially lead compounds for therapeutic development.

Introduction

Cell death plays a prominent role in the pathophysiology of many acute and chronic diseases. The complex mechanisms of cell death are only beginning to be revealed. A complete understanding of these mechanisms is essential to design strategies for effectively treating many human diseases. Historically, cell death has been categorized morphologically as either apoptosis or necrosis.[1] However, the cellular mechanisms leading to these two morphologically distinct cell death phenotypes are more interrelated than previously realized. The ultimate manner of cell death following an insult is dependent on many factors, including but not limited to the cell death signal initiator and the signaling pathway existing in a particular cell type.

Apoptosis is a genetically regulated process required for both development and tissue homeostasis.[2] Extensive studies of apoptosis during the past decade revealed that it is characterized by multiple highly regulated steps including caspase activation and mitochondrial damage that leads to downstream events such as concomitant nucleus and cytoplasm condensation, DNA degradation, membrane blebbing, and caspase-mediated cleavage of various cellular proteins.[3,4] Apoptotic cell bodies are efficiently removed by engulfment processes that function to eliminate the debris of dead cells and to prevent the activation of inflammation. Abnormal regulation of apoptosis may lead to inappropriate cell death, which may underlie the etiology of many human diseases.

Necrosis represents types of cell death morphologically and mechanistically distinct from apoptosis. Necrosis is characterized by cell membrane and organelle disruption, cell swelling, and mitochondrion impairment followed by cell lysis, which is accompanied by a host inflammatory response.[5] Although in recent years multiple studies have demonstrated apoptosis activation in various diseases, necrosis remains the prevalent form of acute cell death in many pathologies, including stroke,[6] myocardial infarction,[7] trauma, and possibly some forms of neurodegeneration.[8] Very few attempts, however, have been made to develop therapeutics specifically targeting necrosis because of the conventional notion that, unlike apoptosis, necrotic cell death is a nonregulated response to overwhelming stress.

This notion is directly challenged by a number of recent studies demonstrating the existence of regulated caspase-independent cell death mechanisms[9−16] with morphological features resembling necrosis. Previously we have defined one type of necrosis as necroptosis.[17] Necroptosis represents a type of regulated caspase-independent cell death pathway that may offer an unprecedented opportunity to selectively target pathological necrotic cell death.

Our laboratories have been seeking to identify and optimize low molecular weight molecules capable of inhibiting necroptosis to elucidate caspase-independent cell death pathways and their roles in disease pathophysiology and to provide lead compounds (i.e., necrostatins) for therapeutic development. A series of hydantoin-containing indole derivatives (referred to as the Nec-1 series) have recently been described as potent in vitro necroptosis inhibitors (exemplified by **1**, $EC_{50} = 0.05$ μM) that also were efficacious in an animal model of ischemic stroke (Figure 1).[17,18] Herein, we report the structure−activity relationship (SAR) study for a new series of inhibitors (referred to as the Nec-3 series) that block tumor necrosis factor α (TNF-α) induced necroptosis. The Nec-3 series of compounds contain a tricyclic heterocycle with an appended aryl substituent (i.e., **2**). Distinct from the Nec-1 compounds, the Nec-3 series show

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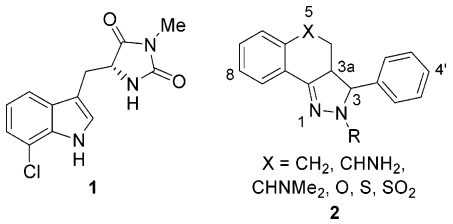


1 **2**

Figure 1. Necrostatins.

specificity in inhibiting necroptosis induced by TNF-α and thus may provide valuable tools in the elucidation of TNF-α-specific signaling steps in caspase-independent cell death pathways.

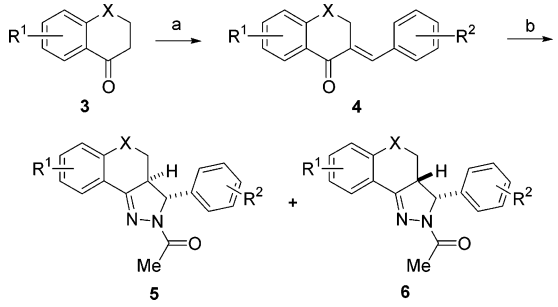
Results and Discussion

Chemistry. The 3-phenyl-3,3a,4,5-tetrahydro-2*H*-benz[*g*]-indazoles (**2**, X = CH_2), 3-phenyl-2,3,3a,4-tetrahydro[1]-benzopyrano[4,3-*c*]pyrazoles (**2**, X = O), and 3-phenyl-2,3,3a,4-tetrahydro[1]benzothiopyrano[4,3-*c*]pyrazoles (**2**, X = S) were prepared from 1-tetralones, 4-chromanones, and 4-thiochromanones, respectively, according to the procedures outlined in Scheme 1.[19] For example, compounds **3** (X = CH_2, O, or S) were condensed with aromatic aldehydes in the presence of sodium hydroxide to give chalcones **4**. In the cases of 7-nitro-1-tetralone and 7-methoxy-4-chromanone, condensations with 4-anisaldehyde were accomplished under acidic conditions. Treatment of **4** with hydrazine hydrate in acetic acid gave a mixture of readily separable diastereomers **5** (i.e., (3*R*,3a*S*)-*rel*-isomer] and **6** (i.e., (3*R*,3a*R*)-*rel*-isomer].[20−27] This general procedure was used in the preparation of **7**−**41**. The stereochemical assignments were confirmed using ^{1}H NMR, 1-D NOE, and HH-COSY experiments. For example, **8** was assigned as the (3*R*,3a*R*)-*rel*-isomer due to an NOE between the 3a-position (δ 3.47−3.55) and the 3-position (δ 5.66) protons and a large coupling constant (J = 11.2 Hz) indicative of a *syn*-relationship. The (3*R*,3a*S*)-*rel*-isomer, **7**, lacked a similar NOE between the protons at the 3a-position (δ 3.16−3.23) and at the 3-position (δ 4.91) and had a smaller coupling constant (J = 9.2 Hz), and the proton at the 3a-position (δ 3.20) was shielded by the 4′-methoxyphenyl ring compared to the corresponding proton in the (3*R*,3a*R*)-*rel*-isomer. The 5,5-dioxo-3-phenyl-2,3,3a,4-tetrahydro[1]benzothiopyrano[4,3-*c*]pyrazoles (**2**, X = SO_2), such as **42** and **43**, were readily prepared by oxidizing the corresponding 3-phenyl-2,3,3a,4-tetrahydro[1]-benzothiopyrano[4,3-*c*]pyrazoles with *m*-chloroperoxybenzoic acid (MCPBA).

The 5-position of the 3,3a,4,5-tetrahydro-2*H*-benz[*g*]indazole ring system of **8** was modified as shown in Scheme 2. Introduction of an azide to this benzylic position utilizing Me_3SiN_3 in the presence of [bis(trifluoroacetoxy)iodo]benzene was accomplished following the procedure of Kita and co-workers to give **44** in 29% yield.[28] This reaction was also accompanied by an elimination−oxidation reaction giving **45** in 31% yield. The azide **44** was subsequently reduced by hydrogenation to amine **46** and then converted to the tertiary amine **47** by reductive amination with formaldehyde. The relative stereochemistry at the 5-position of **47** was established by ^{1}H NMR and HH-COSY experiments. The dimethylamine protons of **47** (δ 2.21) had a coupling interaction with the proton at the 3a-position (δ 4.03−4.09) indicative of a *syn*-relationship.

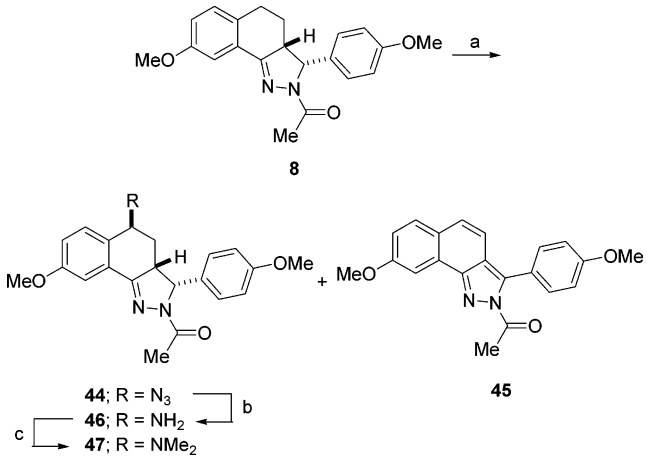
Derivatives with various substituents on the 2-position of the tricyclic ring were also prepared. Compounds **52** and **53** were synthesized according to Scheme 1, except that formic acid and propionic acid, respectively, were used as the solvent in place of acetic acid. When chalcone **48** was allowed to react with

Scheme 1. Synthesis of 3-Acetyl Tricyclic Derivatives[a]



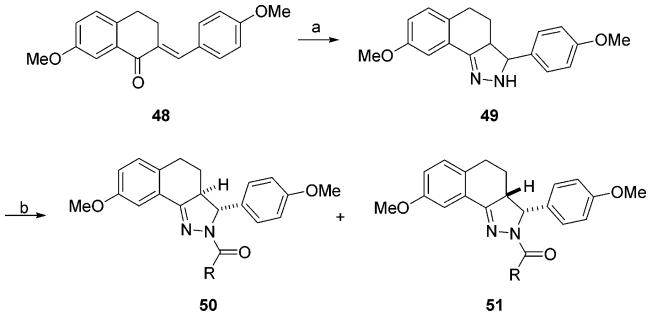
[a] X = CH_2, O, or S. Reagents and conditions: (a) ArCHO, 8 N NaOH, EtOH, rt, 2 h; (b) CH_3CO_2H, $NH_2NH_2{\cdot}xH_2O$, 120 °C, 15 h.

Scheme 2. Synthesis of 5-Substituted Tricyclic Derivatives[a]



[a] Reagents and conditions: (a) Me_3SiN_3, $[CF_3CO_2]_2PhI$, rt, 24 h (29% **44** and 31% **45**); (b) H_2 (1 atm), 10% Pd−C, EtOH, rt, 24 h (59%); (c) aq CH_2O, HCO_2H, THF, Δ, 24 h (47%).

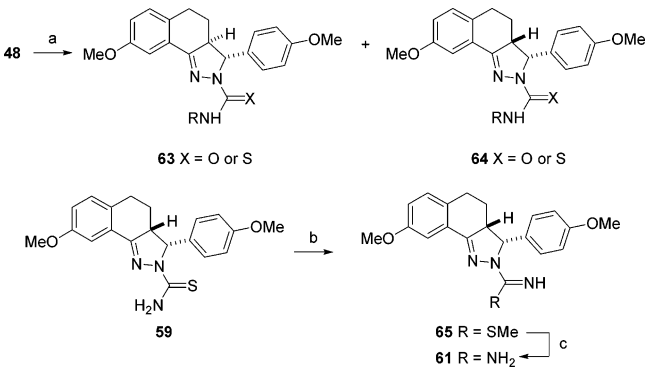
Scheme 3. Synthesis of 3-Amido-Substituted Tricyclic Derivatives[a]



[a] Reagents and conditions: (a) $NH_2NH_2{\cdot}xH_2O$, t-$BuCO_2H$, EtOH, Δ, 6 h; (b) RC(O)Cl, EtOAc, saturated aqueous $NaHCO_3$, rt, 30 min.

hydrazine hydrate in the presence of trimethylacetic acid, as shown in Scheme 3, amine **49** was isolated as a mixture of diastereomers (the material was subsequently used without purification). Unlike the case with acetic acid, utilizing a sterically demanding acid such as trimethylacetic acid prevented direct amide formation and allowed for the isolation of the amine. Treatment of **49** with various acid chlorides yielded amide derivatives **50** and **51**. Amide **55** was subsequently generated from **54** upon treatment with NaOH in methanol. Cyclization of **48** with various semicarbazides and thiosemicarbazides gave **58**−**60** (Scheme 4). In all cyclization reactions reported herein where both the (3*R*,3a*R*)-*rel*- and (3*R*,3a*S*)-*rel*-isomers were formed, they could be separated by column chromatography on silica gel. Compound **59** was subsequently converted to **61** by a sequence of reactions involving alkylation

Scheme 4. Synthesis of 3-Non-Amido-Substituted Tricyclic Derivatives[a]



[a] Reagents and conditions: (a) $NH_2NHC(O)NHR$ or $NH_2NHC(S)NHR$, EtOH, concd HCl, Δ, 6 h; (b) MeI, EtOH, Δ, 2 h (85%); (c) NH_3 (2.0 N in EtOH), 60 °C, 16 h (88%).

with methyl iodide to give intermediate **65** followed by treatment with ammonia in ethanol. Finally, **62** was prepared from **8** by reduction with lithium aluminum hydride.

Biology. Evaluation of necroptosis inhibitory activity was performed using an FADD-deficient variant of human Jurkat T cells treated for 24 h with TNF-α as previously described.[17] Under these conditions the cells underwent necroptosis (the DMSO control had ~40% viability), which was inhibited by (±)-**1** ($EC_{50} = 0.21 \pm 0.2$ μM) as a positive control.[18] For EC_{50} value determinations, cells were treated with 10 ng/mL human TNF-α in the presence of increasing concentrations of test compounds (0.029, 0.058, 0.12, 0.23, 0.46, 0.93, 1.9, 3.7, 11.1, 33, and 100 μM) in duplicate for 24 h followed by ATP-based viability assessment. EC_{50} values ± SD were determined from at least two independent experiments.

In four cases where both isomers were examined with the 3,3a,4,5-tetrahydro-2*H*-benz[*g*]indazole ring system, the (3*R*,3a*R*)-*rel*-isomers were more active than the corresponding (3*R*,3a*S*)-*rel*-isomers at inhibiting necroptosis (Table 1). For example, **8** was 22 times more potent than **7**. In addition, introduction of the methoxy group at the 8-position of the tricyclic ring gave increased activity (e.g., **9** vs **11** and **13** vs **8**).

Translocation of the methoxy group to the 6-, 7-, or 9-position of the tricyclic ring (e.g., **14**, **16**, and **18**) resulted in loss of or reduced activity. Increasing the size (**19**) or introduction of an amine onto the ether (**20**) at the 8-position of the tricyclic ring also resulted in diminished activity. An electron-withdrawing fluorine (**22**) was well tolerated at the 8-position of the tricyclic ring. However, replacing the fluorine with a nitro group (**24**) diminished inhibitory activity. An electron-donating methoxy group on the 4′-position of the pendent phenyl ring resulted in increased activity compared to a fluorine or nitro substituent (**8** vs **11** and **25**). However, increasing the size of the ether (**26**), transposition to the 2′-position (**27**), or replacing it with a hydroxyl (**28**) or a thioether (**29**) was detrimental to activity to varying degrees. Introduction of a primary amine (**46**) or a tertiary amine (**47**) on the 5-position of the tricyclic ring also resulted in activity erosion.

Replacing the 3,3a,4,5-tetrahydro-2*H*-benz[*g*]indazole ring with a 2,3,3a,4-tetrahydro[1]benzopyrano[4,3-*c*]pyrazole ring (Table 2) only resulted in a slight decrease in activity (**8** vs **37** and **22** vs **39**). However, the difference in activities between the (3*R*,3a*R*)-*rel*- and (3*R*,3a*S*)-*rel*-isomers in some cases appeared to be more dramatic in the 2,3,3a,4-tetrahydro[1]-benzopyrano[4,3-*c*]pyrazole ring system (**38** vs **39**). The SAR of the pendent phenyl group appeared to be comparable between the two ring systems. Replacing the 3,3a,4,5-tetrahydro-2*H*-benz[*g*]indazole ring with a 2,3,3a,4-tetrahydro[1]benzothiopyrano-[4,3-*c*]pyrazole (**8** vs **41**) was well tolerated, but replacement with a 5,5-dioxo-3-phenyl-2,3,3a,4-tetrahydro[1]benzothiopyrano-[4,3-*c*]pyrazole ring resulted in a slight decrease in activity (**8** vs **43**).

Next, the SAR of various nitrogen substituents on the 2-position of the 3,3a,4,5-tetrahydro-2*H*-benz[*g*]indazole ring was examined (Table 3). In general, amides were best, with the ethyl and hydroxymethyl amides (i.e., **53** and **55**) being more active than **8**. Introduction of ureas or thioureas to the 2-position of the tricyclic ring was detrimental to activity. Likewise, replacing the amide with an alkyl group (**62**) resulted in complete loss of necroptosis inhibitory activity.

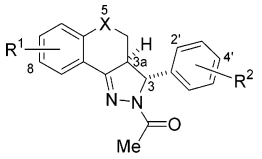
In the FADD-deficient variant of human Jurkat T cells treated for 24 h with TNF-α, representative compounds from the Nec-1 series, (±)-**1**, and the Nec-3 series, **8**, had very similar inhibitory activities ($EC_{50} = 0.21 \pm 0.02$[18] and 0.29 ± 0.07 μM, respectively). Similar to FADD-deficient Jurkat cells, mouse fibrosarcoma L929 cells were previously shown to undergo necroptosis upon treatment with TNF-α.[17] Both (±)-**1** and **8** at 30 μM completely protected L929 cells from TNF-α-induced necroptosis (Figure 2). In addition to TNF-α, the pan-caspase inhibitor benzyloxycarbonyl-Val-Ala-Asp(OMe)-fluoromethylketone (zVAD.fmk) has also been found to induce necrosis in L929 cells,[29,30] which was efficiently inhibited by (±)-**1** (Figure 2). However, **8** was ineffective against zVAD.fmk-induced necroptosis in L929 cells. Parenthetically, zVAD.fmk was incapable of inducing necroptosis in the FADD-deficient variant of human Jurkat T cells. These results further demonstrate that the mechanism(s) resulting in necroptotic cell death are dependent on both the initiator of cell death and the cell type. Furthermore, these results suggest that the Nec-1 and Nec-3 series of compounds most likely modulate different molecular targets in the necroptosis pathway. As previously demonstrated, the Nec-1 series of inhibitors have worked in a board range of cell types utilizing various cell death initiators.[17] In contrast, the Nec-3 series exhibit specificity toward necroptosis induced by TNF-α. More selective compounds, such as the Nec-3 series, may be advantageous in treating certain conditions.

One model of the necroptosis cell death pathway to explain the observed results described herein is shown in Figure 3. Cell death can be activated via different initiators, including TNF-α agonism of the TNF-α receptor, followed by initial signal transduction through various pathways, some of which are cell type dependent. These pathways may then converge downstream into a common signaling pathway leading to the characteristic necrotic morphology, accompanied by plasma membrane permeability, mitochondrion dysfunction, and autophagy. The Nec-1 series may target a step in the universal part of the pathway, resulting in broad activity, whereas the Nec-3 series may target a more upstream step that is not activated by zVAD.fmk in L929 cells, but that is activated by TNF-α in both the FADD-deficient variant of human Jurkat T cells and L929 cells. Identification of the molecular targets for both series of compounds will assist the elucidation of this emerging complex cell death pathway and may help guide compound selection for treating various diseases.

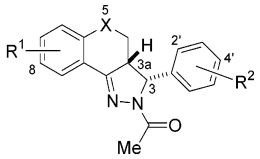
Conclusions

A series of tricyclic heterocycles were found to inhibit TNF-α-induced necroptosis in both the FADD-deficient variant of human Jurkat T cells and mouse fibrosarcoma L929 cells. An

Table 1. EC_{50} Determinations for Inhibition of Necroptosis in FADD-Deficient Jurkat T Cells Treated with TNF-α



A = (3*R*,3a*S*)-rel-isomer

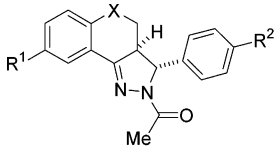


B = (3*R*,3a*R*)-rel-isomer

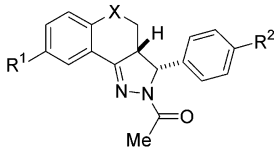
compd	R^1	R^2	X	isomer	$EC_{50}^{a,b}$ (μM)
7	8-OMe	4′-OMe	CH_2	A	6.4 ± 2
8	8-OMe	4′-OMe	CH_2	B	0.29 ± 0.07
9	H	4′-F	CH_2	B	5.4 ± 1
10	8-OMe	4′-F	CH_2	A	3.7 ± 0.8
11	8-OMe	4′-F	CH_2	B	0.96 ± 0.09
12	8-OMe	3′-F	CH_2	B	0.68 ± 0.01
13	H	4′-OMe	CH_2	B	0.84 ± 0.3
14	6-OMe	4′-OMe	CH_2	B	>100
15	7-OMe	4′-F	CH_2	A	>100
16	7-OMe	4′-F	CH_2	B	>100
17	7,8-di-OMe	4′-F	CH_2	B	>100
18	9-OMe	4′-OMe	CH_2	B	>50
19	8-OBn	4′-OMe	CH_2	B	5.0 ± 0.7
20	8-O$(CH_2)_2$R[c]	4′-OMe	CH_2	B	>50
21	8-F	4′-OMe	CH_2	A	2.7 ± 0.8
22	8-F	4′-OMe	CH_2	B	0.28 ± 0.03
23	8-NO_2	4′-OMe	CH_2	A	>100
24	8-NO_2	4′-OMe	CH_2	B	3.5 ± 2
25	8-OMe	4′-NO_2	CH_2	B	1.8 ± 0.4
26	8-OMe	4′-OBn	CH_2	B	>100
27	8-OMe	2′-OMe	CH_2	B	>100
28	8-OMe	4′-OH	CH_2	B	5.9 ± 1
29	8-OMe	4′-SMe	CH_2	B	1.1 ± 0.7
30	8-OH	4′-OH	CH_2	B	>100
31	8-OMe	3′,4′-OCH_2O−	CH_2	B	2.6 ± 1[d]
32	8-OMe	3′,4′-O$(CH_2)_2O$−	CH_2	B	2.1 ± 0.7
46[e]	8-OMe	4′-OMe	$CHNH_2$[f]	B	1.2 ± 0.4
47	8-OMe	4′-OMe	$CHNMe_2$[f]	B	5.1 ± 2

[a] Positive control: (±)-**1**, EC_{50} = 0.21 ± 0.02 μM, N = 3. [b] EC_{50} ± SD values were determined from two independent experiments, unless otherwise noted. [c] R = morpholine. [d] EC_{50} ± SD values were determined from three independent experiments. [e] Oxalate salt. [f] (5*S*)-*rel*-Isomer.

Table 2. EC_{50} Determinations for Inhibition of Necroptosis in FADD-Deficient Jurkat T Cells Treated with TNF-α



A = (3*R*,3a*S*)-rel-isomer



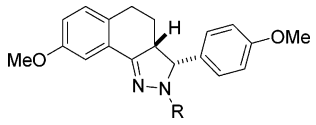
B = (3*R*,3a*R*)-rel-isomer

compd	R^1	R^2	X	isomer	$EC_{50}^{a,b}$ (μM)
33	Me	F	O	A	>100
34	Me	F	O	B	11.6 ± 6[c]
35	OMe	F	O	B	4.8 ± 1
36	OMe	OMe	O	A	9.9 ± 0.1
37	OMe	OMe	O	B	0.46 ± 0.001
38	F	OMe	O	A	>100
39	F	OMe	O	B	0.70 ± 0.1
40	OMe	OMe	S	A	5.1 ± 2
41	OMe	OMe	S	B	0.28 ± 0.07
42	OMe	OMe	SO_2	A	>100
43	OMe	OMe	SO_2	B	0.75 ± 0.1

[a] Positive control: (±)-**1**, EC_{50} = 0.21 ± 0.02 μM, N = 3. [b] EC_{50} ± SD values were determined from two independent experiments, unless otherwise noted. [c] EC_{50} ± SD values were determined from three independent experiments.

SAR study revealed that the (3*R*,3a*R*)-*rel*-diastereomers were more active then the corresponding (3*R*,3a*S*)-*rel*-diastereomers. Introduction of fluorine or methoxy to the 8-position of the tricyclic ring increased activity, while substitution at the 6-, 7-, and 9-positions was detrimental. Also, introduction of a methoxy group to the 4-position of the pendent phenyl ring increased activity, while placing the methoxy at the 2-position of the phenyl ring eliminated activity. Amides at the 2-position of the tricyclic ring systems were best. The tricyclic necroptosis inhibitors were not effective at inhibiting zVAD.fmk-induced necroptosis in L929 cells. This is in contract to a hydantoin−indole necrostatin, suggesting that the two series of compounds are mechanistically distinct. Overall, in this paper we report a second novel class of small-molecule necroptosis inhibitors that can further assist in the elucidation of caspase-independent cell

Table 3. EC_{50} Determinations for Inhibition of Necroptosis in FADD-Deficient Jurkat T Cells Treated with TNF-α



compd	R	$EC_{50}^{a,b}$ (μM)	compd	R	$EC_{50}^{a,b}$ (μM)
52	HC═O	0.92 ± 0.09	**58**	C(═O)NH_2	4.3 ± 3[c]
53	C(═O)Et	0.15 ± 0.01	**59**	C(═S)NH_2	8.8 ± 3
54	C(═O)CH_2OAc	3.1 ± 0.2	**60**	C(═S)NHMe	7.9 ± 2
55	C(═O)CH_2OH	0.16 ± 0.02	**61**	C(═NH)NH_2	>100
56	C(═O)CH_2OMe	0.44 ± 0.2	**62**	Et	>100
57	C(═O)CF_3	0.39 ± 0.2			

[a] Positive control: (±)-**1**, EC_{50} = 0.21 ± 0.02 μM, N = 3. [b] EC_{50} ± SD values were determined from two independent experiments, unless otherwise noted. [c] EC_{50} ± SD values were determined from three independent experiments.

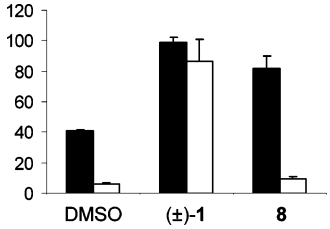


Figure 2. L929 cells were treated with 10 ng/mL human TNF-α (black bars) or 100 μM zVAD.fmk (white bars) in the presence of DMSO (control), 30 μM (±)-**1**, or **8**. After 24 h, cell viability was determined using a luminescent ATP-based assay. Average cell viabilities (%) ± SD for two independent experiments are shown.

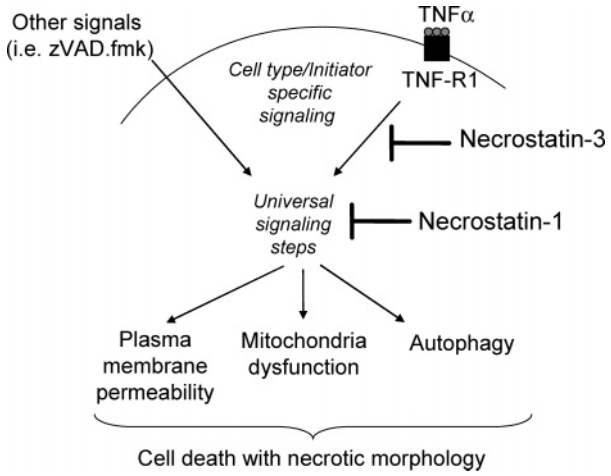


Figure 3. A model of the necroptosis cell death pathway.

death pathways and potentially provide lead compounds for therapeutic development.

Experimental Section

Chemistry Materials and Methods. Unless otherwise noted, all reagents and solvents were purchased from commercial sources and used without further purification. The NMR spectra were obtained using a Bruker 400 MHz or Varian 400 or 500 MHz spectrometer. All ^{1}H NMR spectra are reported in δ units (ppm) and are referenced to the peak for tetramethylsilane (TMS) if conducted in $CDCl_3$, to the central line of the quintet at 3.30 ppm for samples in CD_3OD, or to the central line of the quintet at 2.49 ppm for samples in d_6-DMSO. All ^{13}C NMR spectra are reported in δ units (ppm) and are referenced to the central line of the triplet at 77.23 ppm if conducted in $CDCl_3$, to the central line of the septet at 49.0 ppm for samples in CD_3OD, or to the central line of the septet at 39.5 ppm for samples in d_6-DMSO. Coupling constants (J) are reported in hertz. Column chromatography was performed on silica gel (Merck, grade 60, 230−400 mesh) or utilizing a CombiFlash Sg 100c separation system (ISCO) with RediSep disposable silica gel columns (ISCO). High-resolution mass spectra were obtained by using an SX-102A mass spectrometer (JEOL USA, Inc., Peabody, MA) or an LCT mass spectrometer (Micromass Inc., Beverly, MA). All melting points were taken in glass capillary tubes on a Mel-Temp apparatus and are uncorrected. The elemental compositions of the compounds agreed to within ±0.4% of the calculated values.

General Procedure for the Synthesis of 2-Arylidene-1-tetralones, 2-(Arylidene)chroman-4-ones, and 2-(Arylidene)-thiochroman-4-ones under Basic Conditions. Exemplified for 2-(4-Fluorobenzylidene)-7-methoxy-1-tetralone. To a solution of 7-methoxy-1-tetralone (1.760 g, 0.01 mol) and 4-fluorobenzaldehyde (1.240 g, 0.01 mol) in ethanol (20 mL) was slowly added an aqueous solution of NaOH (0.012 mol, 8 N) at room temperature. The mixture was stirred for 2 h. The solid precipitate was collected by filtration and then washed sequentially with ethanol, with water, and again with ethanol. The solid was dried in vacuo to give 2-(4-fluorobenzylidene)-7-methoxy-1-tetralone (2.485 g, 88%): mp 129−30 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.88−2.91 (m, 2H), 3.06−3.10 (m, 2H), 3.87 (s, 3H), 7.06−7.13 (m, 3H), 7.17 (d, J = 8.4 Hz, 1H), 7.42 (d, J = 5.2 Hz, 1H), 7.44 (d, J = 5.6 Hz, 1H), 7.61 (d, J = 3.2 Hz, 1H), 7.81 (s, 1H); HFABMS m/z 283.1134 (calcd for $C_{18}H_{16}FO_2$, MH^+, 283.1134).

For characterization of other 2-arylidene-1-tetralones, 2-(arylidene)-chroman-4-ones, and 2-(arylidene)thiochroman-4-ones, see the Supporting Information.

General Procedure for the Synthesis of 2-Arylidene-1-tetralones and 2-(Arylidene)chroman-4-ones under Acidic Conditions. Exemplified for 2-(4-Methoxybenzylidene)-7-nitro-1-tetralone. A mixture of 7-nitro-1-tetralone (0.382 g, 2.0 mmol), 4-methoxybenzaldehyde (0.243 mL, 2.0 mmol), and concentrated HCl (10 mL) in methanol (5.4 mL) was heated at reflux for 4 h. The mixture was allowed to cool to room temperature and then filtered. The residue was washed with a small amount of methanol and dried in vacuo to give 2-(4-methoxybenzylidene)-7-nitro-1-tetralone (2.485 g, 88%) as a pale yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.04−3.9 (m, 2H), 3.19−3.22 (m, 2H), 3.87 (s, 3H), 6.96−6.99 (m, 2H), 7.44−7.47 (m, 3H), 7.93 (s, 1H), 8.32 (dd, J_1 = 8.5 Hz, J_2 = 2.5 Hz, 1H), 8.94 (d, J = 2.0 Hz, 1H).

General Procedure for the Preparation of (3*R*,3a*S*)-*rel*- and (3*R*,3a*R*)-*rel*-2-Acetyl-3,3a,4,5-tetrahydro-3-(aryl)-2*H*-benz[*g*]-indazoles, 2-Acetyl-2,3,3a,4-tetrahydro[1]benzopyrano[4,3-*c*]-pyrazoles, and 2-Acetyl-2,3,3a,4-tetrahydro[1]benzothiopyrano-[4,3-c]pyrazoles. Exemplified for (3*R*,3a*S*)-*rel*-2-Acetyl-3,3a,4,5-tetrahydro-3-(4-fluorophenyl)-8-methoxy-2*H*-benz[*g*]indazole (10) and (3*R*,3a*R*)-*rel*-2-Acetyl-3,3a,4,5-tetrahydro-3-(4-fluorophenyl)-8-methoxy-2*H*-benz[*g*]indazole (11). A solution of 2-(4-fluorobenzylidene)-7-methoxy-1-tetralone (0.300 g, 1.0 mmol) and hydrazine hydrate (0.3 mL) in acetic acid (3 mL) was refluxed at 120 °C for 15 h. The reaction mixture was concentrated and then dissolved in ethyl acetate. The organic layer was washed sequentially with water, saturated aqueous $NaHCO_3$, water, and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue obtained was purified by silica gel column chromatography using ethyl acetate−hexane (3:7) to give **10** (0.051 g, 15%) and **11** (0.109 g, 32%), in addition to recovered starting material (95 mg).

Data for 10: mp 165−67 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.94−1.99 (m, 1H), 2.29−2.31 (m, 1H), 2.32 (s, 3H), 2.40−2.42 (m, 2H), 3.16−3.22 (m, 1H), 3.89 (s, 3H), 4.95 (d, J = 9.6 Hz, 1H), 6.93−6.96 (dd, J = 2.8 and 8.4 Hz, 1H), 7.04−7.08 (t, J = 8.8 Hz, 2H), 7.12 (d, J = 8.4 Hz, 1H), 7.28−7.32 (m, 2H), 7.46 (d, J = 2.4 Hz, 1H). Anal. ($C_{20}H_{19}FN_2O_2$) C, H, N.

Data for 11: mp 182−85 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02−1.06 (m, 1H), 1.75−1.78 (m, 1H), 2.48 (s, 3H), 2.81−2.87 (m, 2H), 3.54−3.57 (m, 1H), 3.90 (s, 3H), 5.72 (d, J = 12.0 Hz, 1H), 6.93−7.11 (m, 6H), 7.56 (d, J = 4.0 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 22.13, 24.50, 28.30, 48.77, 55.73, 62.61, 107.83, 112.70, 115.62, 118.72, 127.99, 128.21, 130.26, 132.25, 132.92, 155.79, 158.35, 161.13, 163.58, 168.72. Anal. ($C_{20}H_{19}FN_2O_2$) C, H, N.

Data for (3*R*,3a*S*)-*rel*-2-acetyl-3,3a,4,5-tetrahydro-3-(4-methoxyphenyl)-8-methoxy-2*H*-benz[*g*]indazole (7): yield 25%; mp 146−48 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.89−1.95 (m, 1H), 2.25−2.29 (m, 1H), 2.39 (s, 3H), 2.85−2.87 (m, 2H), 3.16−3.23 (m, 1H), 3.79 (s, 3H), 3.86 (s, 3H), 4.91 (d, J = 9.2 Hz, 1H), 6.87−6.93 (m, 3H), 7.09 (d, J = 8.4 Hz, 1H), 7.22−7.25 (m, 2H), 7.44 (d, J = 2.4 Hz, 1H). Anal. ($C_{21}H_{22}N_2O_3$) C, H, N.

Data for (3*R*,3a*R*)-*rel*-2-acetyl-3,3a,4,5-tetrahydro-3-(4-methoxyphenyl)-8-methoxy-2*H*-benz[*g*]indazole (8): yield 30%; mp 151−53 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03−1.11 (m, 1H), 1.72−1.76 (m, 1H), 2.44 (s, 3H), 2.77−2.91 (m, 2H), 3.47−3.55 (m, 1H), 3.75 (s, 3H), 3.87 (s, 3H), 5.66 (d, J = 11.2 Hz, 1H), 6.80 (d, J = 8.8 Hz, 2H), 6.89−6.92 (dd, J = 3.2 and 8.8 Hz, 1H), 6.99 (d, J = 8.4 Hz, 2H), 7.06 (d, J = 8.4 Hz, 1H), 7.54 (d, J = 2.8 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 22.15, 24.42, 28.93, 48.84, 55.42, 55.70, 63.03, 107.76, 112.66, 114.15, 118.56, 127.44,

127.88, 128.39, 129.26, 130.24, 132.32, 155.60, 158.28, 159.14, 168.56. Anal. ($C_{21}H_{22}N_2O_3$) C, H, N.

Data for (3*R*,3a*R*)-*rel*-2-acetyl-3,3a,4,5-tetrahydro-3-(4-fluorophenyl)-2*H*-benz[*g*]indazole (9): yield 23%; mp 166−68 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06−1.11 (m, 1H), 1.77−1.81 (m, 1H), 2.47 (s, 3H), 2.87−2.95 (m, 2H), 3.56−3.63 (m, 1H), 5.72 (d, J = 12.0 Hz, 1H), 7.00 (t, J = 8.0 Hz, 2H), 7.06−7.10 (m, 2H), 7.19 (d, J = 8.0 Hz, 1H), 7.28−7.36 (m, 2H), 8.09 (d, J = 8.0 Hz, 1H). Anal. ($C_{19}H_{17}FN_2O$) C, H, N.

Data for (3*R*,3a*R*)-*rel*-2-acetyl-3,3a,4,5-tetrahydro-3-(3-fluorophenyl)-8-methoxy-2*H*-benz[*g*]indazole (12): yield 39%; mp 176−77 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00−1.08 (m, 1H), 1.75−1.80 (m, 1H), 2.46 (s, 3H), 2.75−2.83 (m, 2H), 3.52−3.60 (m, 1H), 3.87 (s, 3H), 5.69 (d, J = 11.2 Hz, 1H), 7.76−6.79 (dd, J = 2.4 and 9.6 Hz, 1H), 6.86−6.95 (m, 3H), 7.06 (d, J = 8.8 Hz, 1H), 7.23−7.28 (m, 1H), 7.53 (d, J = 3.2 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 22.18, 24.54, 28.97, 46.79, 55.75, 62.97, 107.18, 113.16, 114.65, 118.71, 121.92, 128.05, 130.27, 132.13, 139.57, 155.62, 156.22, 161.60, 164.24, 168.50. Anal. ($C_{20}H_{19}FN_2O_2$) C, H, N.

Data for (3*R*,3a*R*)-*rel*-2-acetyl-3,3a,4,5-tetrahydro-3-(4-methoxyphenyl)-2*H*-benz[*g*]indazole (13): yield 30%; mp 257−60 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01−1.11 (m, 1H), 1.70−1.75 (m, 1H), 2.40 (s, 3H), 2.76−2.89 (m, 2H), 3.47−3.54 (m, 1H), 3.71 (s, 3H), 5.63 (d, J = 11.2 Hz, 1H), 6.76 (d, J = 8.4 Hz, 2H), 6.96 (d, J = 8.8 Hz, 2H), 7.11 (d, J = 6.8 Hz, 1H), 7.23−7.29 (m, 2H), 8.02−8.04 (dd, J = 1.6 and 7.6 Hz, 1H). Anal. ($C_{20}H_{20}N_2O_2$) C, H, N.

Data for (3*R*,3a*R*)-*rel*-2-acetyl-3,3a,4,5-tetrahydro-3-(4-methoxyphenyl)-6-methoxy-2*H*-benz[*g*]indazole (14): yield 43%; mp 203−207 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.98−1.07 (m, 1H), 1.74−1.79 (m, 1H), 2.43 (s, 3H), 2.45−2.52 (m, 1H), 3.04−3.09 (m, 1H), 3.48−3.54 (m, 1H), 3.76 (s, 3H), 3.82 (s, 3H), 5.68 (d, J = 11.0 Hz, 1H), 6.80 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 8.0 Hz, 1H), 7.00 (d, J = 8.5 Hz, 2H), 7.24 (t, J = 8.0 Hz, 1H), 7.68 (d, J = 8.0 Hz, 1H). Anal. ($C_{21}H_{22}N_2O_3$) C, H, N.

Data for (3*R*,3a*S*)-*rel*-2-acetyl-3,3a,4,5-tetrahydro-3-(4-fluorophenyl)-7-methoxy-2*H*-benz[*g*]indazole (15): yield 18%; mp 228−30 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.89−2.00 (m, 1H), 2.24−2.30 (m, 1H), 2.38 (s, 3H), 2.88−2.94 (m, 2H), 3.12−3.19 (m, 1H), 3.83 (s, 3H), 4.89 (d, J = 9.6 Hz, 1H), 6.68 (d, J = 2.4 Hz, 1H), 6.83−6.85 (dd, J = 2.4 and 8.4 Hz, 1H), 7.00−7.06 (m, 2H), 7.26−7.29 (m, 2H), 7.90 (d, J = 8.8 Hz, 1H). Anal. ($C_{20}H_{19}FN_2O_2$) C, H, N.

Data for (3*R*,3a*R*)-*rel*-2-acetyl-3,3a,4,5-tetrahydro-3-(4-fluorophenyl)-7-methoxy-2*H*-benz[*g*]indazole (16): yield 20%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00−1.07 (m, 1H), 1.74−1.76 (m, 1H), 2.42 (s, 3H), 2.76−2.89 (m, 2H), 3.49−3.56 (m, 1H), 3.81 (s, 3H), 5.67 (d, J = 10.8 Hz, 1H), 6.65 (s, 1H), 6.83−6.85 (dd, J = 6.0 and 2.4 Hz, 1H), 6.94−7.06 (m, 4H), 7.99 (d, J = 9.2 Hz, 1H). Anal. ($C_{20}H_{19}FN_2O_2$) C, H, N.

Data for (3*R*,3a*R*)-*rel*-2-acetyl-3,3a,4,5-tetrahydro-3-(4-fluorophenyl)-7,8-dimethoxy-2*H*-benz[*g*]indazole (17): yield 33%; mp 189−93 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01−1.08 (m, 1H), 1.72−1.77 (m, 1H), 1.44 (s, 3H), 2.72−2.93 (m, 2H), 3.48−3.55 (m, 1H), 3.88 (s, 3H), 3.95 (s, 3H), 5.67 (d, J = 10.8 Hz, 1H), 6.60 (s, 1H), 6.94−6.99 (dd, J = 9.2 and 8.8 Hz, 2H), 7.04−7.07 (m, 2H), 7.47 (s, 1H). Anal. ($C_{21}H_{21}FN_2O_3$) C, H, N.

Data for (3*R*,3a*R*)-*rel*-2-acetyl-3,3a,4,5-tetrahydro-3-(4-methoxyphenyl)-9-methoxy-2*H*-benz[*g*]indazole (18): yield 27%; mp 157−60 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.09−1.18 (m, 1H), 1.67−1.72 (m, 1H), 2.49 (s, 3H), 2.83−2.95 (m, 2H), 3.53−3.59 (m, 1H), 3.78 (s, 3H), 3.98 (s, 3H), 5.57 (d, J = 11.0 Hz, 1H), 6.77 (d, J = 7.0 Hz, 1H), 6.80 (d, J = 9.0 Hz, 2H), 6.84 (d, J = 9.0 Hz, 1H), 7.04 (d, J = 9.0 Hz, 2H), 7.25 (t, J = 9.0 Hz, 1H). Anal. ($C_{21}H_{22}N_2O_3$) C, H, N.

Data for (3*R*,3a*R*)-*rel*-2-acetyl-3,3a,4,5-tetrahydro-3-(4-methoxyphenyl)-8-benzyloxy-2*H*-benz[*g*]indazole (19): yield 36%; mp 155−57 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.03−1.12 (m, 1H), 1.72−1.77 (m, 1H), 2.44 (s, 3H), 2.74−2.86 (m, 2H), 3.48−3.54 (m, 1H), 3.75 (s, 3H), 5.12 (s, 2H), 5.66 (d, J = 10.5 Hz, 1H), 6.80 (d, J = 8.5 Hz, 2H), 6.96 (d, J = 3.0 Hz, 1H), 6.99 (d, J = 8.5 Hz, 2H), 7.07 (d, J = 8.0 Hz, 2H), 7.33−7.47 (m, 4H), 7.64 (d, J = 3.0 Hz, 1H). Anal. ($C_{27}H_{26}N_2O_3$) C, H, N.

Data for (3*R*,3a*R*)-*rel*-2-acetyl-3,3a,4,5-tetrahydro-3-(4-methoxyphenyl)-8-(4-morpholino)ethoxy-2*H*-benz[*g*]indazole (20): yield 33%; mp 122−26 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02−1.11 (m, 1H), 1.72 (m, 1H), 2.44 (s, 3H), 2.60 (t, J = 4.5 Hz, 4H), 2.76−2.84 (m, 4H), 3.48−3.54 (m, 1H), 3.74−3.79 (m, 7H), 4.16−4.19 (m, 2H), 5.66 (d, J = 10.5 Hz, 1H), 6.80 (d, J = 8.5 Hz, 2H), 6.90−6.93 (dd, J = 3.0 and 9.0 Hz, 1H), 6.99 (d, H = 8.5 Hz, 2H), 7.06 (d, J = 9.0 Hz, 1H), 7.55 (d, J = 3.0 Hz, 1H); HFABMS m/z 450.2391 (calcd for $C_{26}H_{31}N_3O_4$, MH^+, 450.2393).

Data for (3*R*,3a*S*)-*rel*-2-acetyl-3,3a,4,5-tetrahydro-3-(4-methoxyphenyl)-8-fluoro-2*H*-benz[*g*]indazole (21): required a second silica gel column chromatography purification using 2% MeOH in CH_2Cl_2; yield 26%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.89−1.99 (m, 1H), 2.27−2.32 (m, 1H), 2.38 (s, 3H), 2.85−2.95 (m, 2H), 3.18−3.24 (m, 1H), 3.70 (s, 3H), 4.92 (d, J = 9.0 Hz, 1H), 6.88−6.91 (m, 2H), 7.01−7.05 (m, 1H), 7.14−7.16 (m, 1H), 7.23−7.25 (m, 2H), 7.63 (dd, J = 9.5 and 2.5 Hz, 1H); HFABMS m/z 339.1523 (calcd for $C_{20}H_{20}FN_2O_2$, MH^+, 339.1509).

Data for (3*R*,3a*R*)-*rel*-2-acetyl-3,3a,4,5-tetrahydro-3-(4-methoxyphenyl)-8-fluoro-2*H*-benz[*g*]indazole (22): yield 29%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.03−1.12 (m, 1H), 1.74−1.79 (m, 1H), 2.44 (s, 3H), 2.78−2.89 (m, 2H), 3.49−3.55 (m, 1H), 3.76 (s, 3H), 5.67 (d, J = 11.0 Hz, 1H), 6.81 (d, J = 9.0 Hz, 2H), 6.97−7.04 (m, 3H), 7.11−7.13 (m, 1H), 7.72 (dd, J = 9.5 and 3.0 Hz, 1H); HFABMS m/z 339.1493 (calcd for $C_{20}H_{20}FN_2O_2$, MH^+, 339.1509).

Data for (3*R*,3a*S*)-*rel*-2-acetyl-3,3a,4,5-tetrahydro-3-(4-methoxyphenyl)-8-nitro-2*H*-benz[*g*]indazole (23): yield 25%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.94−2.05 (m, 1H), 2.34−2.38 (m, 1H), 2.42 (s, 3H), 2.97−3.09 (m, 2H), 3.23−3.29 (m, 1H), 3.71 (s, 3H), 4.98 (d, J = 9.5 Hz, 1H), 6.90 (d, J = 9.0 Hz, 2H), 7.24 (d, J = 7.0 Hz, 2H), 7.36 (d, J = 8.5 Hz, 1H), 8.14 (dd, J = 8.5 and 2.5 Hz, 1H), 8.79 (d, J = 2.0 Hz, 1H); HFABMS m/z 366.1467 (calcd for $C_{20}H_{20}N_3O_4$, MH^+, 366.1454).

Data for (3*R*,3a*R*)-*rel*-2-acetyl-3,3a,4,5-tetrahydro-3-(4-methoxyphenyl)-8-nitro-2*H*-benz[*g*]indazole (24): yield 45%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.07−1.16 (m, 1H), 1.81−1.86 (m, 1H), 2.47 (s, 3H), 2.95−2.97 (m, 2H), 3.56−3.62 (m, 1H), 3.76 (s, 3H), 5.72 (d, J = 11.5 Hz, 1H), 6.82 (d, J = 9.0 Hz, 2H), 6.97 (d, J = 8.5 Hz, 2H), 7.33 (d, J = 8.5 Hz, 1H), 8.13 (dd, J = 8.5 and 2.5 Hz, 1H), 8.89 (d, J = 2.5 Hz, 1H); HFABMS m/z 366.1467 (calcd for $C_{20}H_{20}N_3O_4$, MH^+, 366.1454).

Data for (3*R*,3a*R*)-*rel*-2-acetyl-3,3a,4,5-tetrahydro-3-(4-nitroxyphenyl)-8-methoxy-2*H*-benz[*g*]indazole (25): yield 29%; mp 219−21 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91−1.01 (m, 1H), 1.71−1.75 (m, 1H), 2.43 (s, 3H), 2.75−2.82 (m, 2H), 3.57−3.64 (m, 1H), 3.84 (s, 3H), 5.74 (d, J = 11.6 Hz, 1H), 6.88−6.91 (dd, J = 3.2 and 8.4 Hz, 1H), 7.22 (d, J = 9.6 Hz, 2H), 7.48 (d, J = 3.2 Hz, 1H), 8.13 (d, J = 9.6 Hz, 2H). Anal. ($C_{20}H_{19}N_3O_4$) C, H, N.

Data for (3*R*,3a*R*)-*rel*-2-acetyl-3,3a,4,5-tetrahydro-3-(4-benzyloxyphenyl)-8-methoxy-2*H*-benz[*g*]indazole (26): yield 41%; mp 156−61 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01−1.14 (m, 1H), 1.72−1.79 (m, 1H), 2.45 (s, 3H), 2.75−2.83 (m, 2H), 3.56−3.64 (m, 1H), 3.87 (s, 3H), 4.99 (s, 2H), 5.67 (d, J = 10.8 Hz, 1H), 6.87−6.92 (m, 2H), 6.99 (d, J = 8.4 Hz, 1H), 7.06 (d, J = 8.8 Hz, 1H), 7.30−7.40 (m, 7H), 7.54 (d, J = 3.2 Hz, 1H). Anal. ($C_{27}H_{26}N_2O_3$) C, H, N.

Data for (3*R*,3a*R*)-*rel*-2-acetyl-3,3a,4,5-tetrahydro-2-(2-methoxyphenyl)-8-methoxy-2H-benz[g]indazole (27): yield 24%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.01−1.10 (m, 1H), 1.84−1.90 (m, 1H), 2.40 (s, 3H), 2.68−2.89 (m, 2H), 3.54−3.60 (m, 1H), 3.85 (s, 3H), 6.15 (d, J = 11.4 Hz, 1H), 6.75−6.90 (m, 4H), 7.04 (d, J = 8.5 Hz, 1H), 7.18−7.21 (m, 1H), 7.52 (d, J = 2.5 Hz, 1H).

Data for (3*R*,3a*R*)-*rel*-2-acetyl-3,3a,4,5-tetrahydro-3-(4-thiomethoxyphenyl)-8-methoxy-2*H*-benz[*g*]indazole (29): yield 22%; mp 144−47 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02−1.09 (m, 1H), 1.73−1.76 (m, 1H), 2.43 (s, 3H), 2.45 (s, 3H), 2.74−2.86

(m, 2H), 3.50−3.56 (m, 1H), 3.87 (s, 3H), 5.66 (d, J = 10.5 Hz, 1H), 6.90−6.92 (dd, J = 3.0 and 8.5 Hz, 1H), 6.99 (d, J = 8.5 Hz, 2H), 7.06 (d, J = 8.5 Hz, 1H), 7.16 (d, J = 8.5 Hz, 2H), 7.53 (d, J = 3.0 Hz, 1H). Anal. ($C_{21}H_{22}N_2O_2S$) C, H, N.

Data for (3*R*,3a*R*)-*rel*-2-acetyl-3,3a,4,5-tetrahydro-3-(3,4-methylenedioxyphenyl)-8-methoxy-2*H*-benz[*g*]indazole (31): yield 41%; mp 206−209 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.08−1.17 (m, 1H), 1.75−1.80 (m, 1H), 2.42 (s, 3H), 2.76−2.84 (m, 2H), 3.47−3.53 (m, 1H), 3.87 (s, 3H), 5.62 (d, J = 11.4 Hz, 1H), 5.90 (s, 2H), 6.52 (d, J = 1.5 Hz, 1H), 6.57−6.59 (dd, J = 1.5 and 8.0 Hz, 1H), 6.72 (d, J = 7.5 Hz, 1H), 6.90−6.92 (dd, J = 3.0 and 8.5 Hz, 1H), 7.07 (d, J = 8.2 Hz, 1H), 7.52 (d, J = 2.5 Hz, 1H). Anal. ($C_{21}H_{20}N_2O_4$) C, H, N.

Data for (3*R*,3a*R*)-*rel*-2-acetyl-3,3a,4,5-tetrahydro-3-(3,4-ethylenedioxyphenyl)-8-methoxy-2*H*-benz[*g*]indazole (32): yield 17%; mp 189−93 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.06−1.15 (m, 1H), 1.78−1.80 (m, 1H), 2.41 (s, 3H), 2.75−2.86 (m, 2H), 3.46−3.52 (m, 1H), 3.87 (s, 3H), 4.22 (s, 4H), 5.60 (d, J = 11.5 Hz, 1H), 6.55−6.58 (m, 2H), 6.76 (d, J = 8.5 Hz, 1H), 6.89−6.91 (dd, J = 3.0 and 9.0 Hz, 1H), 7.06 (d, J = 8.0 Hz, 1H), 7.52 (d, J = 3.0 Hz, 1H). Anal. ($C_{22}H_{22}N_2O_4$) C, H, N.

Data for (3*R*,3a*S*)-*rel*-2-acetyl-2,3,3a,4-tetrahydro-3-(4-fluorophenyl)-8-methyl[1]benzopyrano[4,3-*c*]pyrazole (33): yield 15%; mp 218−20 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (s, 3H), 2.42 (s, 3H), 3.53−3.57 (m, 1H), 4.13−4.19 (m, 1H), 4.60−4.64 (m, 1H), 4.99 (d, J = 8 Hz, 1H), 6.85 (d, J = 8 Hz, 1H), 7.05−7.09 (m, 2H), 7.16−7.31 (m, 3H), 7.63 (s, 1H); HFABMS *m*/*z* 325.1354 (calcd for $C_{19}H_{17}FN_2O_2$, MH^+, 325.1352).

Data for (3*R*,3a*R*)-*rel*-2-acetyl-2,3,3a,4-tetrahydro-3-(4-fluorophenyl)-8-methyl[1]benzopyrano[4,3-*c*]pyrazole (34): required a second silica gel column chromatography purification using hexane−EtOAc−MeCN (65:25:10); yield 42%; mp 243−46 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (s, 3H), 2.48 (s, 3H), 3.29 (t, J = 12 Hz, 1H), 3.72−3.83 (m, 1H), 4.14−4.18 (m, 1H), 5.77 (d, J = 12 Hz, 1H), 6.82 (d, J = 8 Hz, 1H), 7.0−7.15 (m, 5H), 7.78 (s, 1H); HFABMS *m*/*z* 325.1359 (calcd for $C_{19}H_{17}FN_2O_2$, MH^+, 325.1352).

Data for (3*R*,3a*R*)-*rel*-2-acetyl-2,3,3a,4-tetrahydro-3-(4-fluorophenyl)-8-methoxy[1]benzopyrano[4,3-*c*]pyrazole (35): yield 32%; mp 245 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.45 (s, 3H), 3.21−3.27 (m, 1H), 3.84 (s, 3H), 3.82−3.87 (m, 1H), 4.10−4.14 (dd, J = 10.5 and 12.5 Hz, 1H), 4.55−4.59 (dd, J = 6.0 and 10.5 Hz, 1H), 5.75 (d, J = 10.5 Hz, 1H), 6.82 (d, J = 9.0 Hz, 1H), 6.91−6.94 (dd, J = 3.5 and 9.5 Hz, 1H), 6.98−7.01 (dd, J = 8.5 and 8.5 Hz, 2H), 7.06−7.08 (m, 2H), 7.33 (d, J = 3.5 Hz, 1H); HFABMS *m*/*z* 341.1304 (calcd for $C_{19}H_{17}FN_2O_3$, MH^+, 341.1301).

Data for (3*R*,3a*S*)-*rel*-2-acetyl-2,3,3a,4-tetrahydro-3-(4-methoxyphenyl)-8-methoxy[1]benzopyrano[4,3-*c*]pyrazole (36): yield 39%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.39 (s, 3H), 3.53−3.59 (m, 1H), 3.80 (s, 3H), 3.84 (s, 3H), 4.11 (dd, 1H, J = 10.3, 12.8 Hz), 4.57 (dd, 1H, J = 6.0, 10.5 Hz), 4.95 (d, 1H, J = 10.0 Hz), 6.86 (d, 1H, J = 9.0 Hz), 6.88−6.91 (m, 2H), 6.93 (dd, 1H, J = 2.8, 9.3 Hz), 7.21−7.24 (m, 2H), 7.26−7.27 (m, 1H); HFABMS *m*/*z* 353.1485 (calcd for $C_{20}H_{21}N_2O_4$, MH^+, 353.1501).

Data for (3*R*,3a*R*)-*rel*-2-acetyl-2,3,3a,4-tetrahydro-3-(4-methoxyphenyl)-8-methoxy[1]benzopyrano[4,3-*c*]pyrazole (37): yield 50%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.45 (s, 3H), 3.30 (dd, 1H, J = 11.0, 13.0 Hz), 3.76 (s, 3H), 3.78−3.83 (m, 1H), 3.85 (s, 3H), 4.13 (dd, 1H, J = 5.8, 10.8 Hz), 5.72 (d, 1H, J = 11.0 Hz), 6.81−6.84 (m, 3H), 6.91 (dd, 1H, J = 3.0, 9.5 Hz), 7.00−7.02 (m, 2H), 7.34 (d, 1H, J = 3.5 Hz); HFABMS *m*/*z* 353.1492 (calcd for $C_{20}H_{21}N_2O_4$, MH^+, 353.1501).

Data for (3*R*,3a*S*)-*rel*-2-acetyl-2,3,3a,4-tetrahydro-3-(4-methoxyphenyl)-8-fluoro[1]benzopyrano[4,3-c]pyrazole (38): yield 33%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.38 (s, 3H), 3.53−3.59 (m, 1H), 3.80 (s, 3H), 4.13 (dd, 1H, J = 10.3, 12.8 Hz), 4.60 (dd, 1H, J = 5.8, 10.3 Hz), 4.97 (d, 1H, J = 9.5 Hz), 6.87−6.91 (m, 3H), 7.02−7.06 (m, 1H), 7.21−7.24 (m, 2H), 7.49 (dd, 1H, J = 3.0, 8.0 Hz); HFABMS *m*/*z* 341.1312 (calcd for $C_{19}H_{18}FN_2O_3$, MH^+, 341.1301).

Data for (3*R*,3a*R*)-*rel*-2-acetyl-2,3,3a,4-tetrahydro-3-(4-methoxyphenyl)-8-fluoro[1]benzopyrano[4,3-c]pyrazole (39): yield 53%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.44 (s, 3H), 3.31 (dd, 1H, J = 11.0, 13.0 Hz), 3.76 (s, 3H), 3.78−3.84 (m, 1H), 4.16 (dd, 1H, J = 5.8, 11.3 Hz), 5.73 (d, 1H, J = 11.0 Hz), 6.82−6.86 (m, 3H), 6.98−7.05 (m, 3H), 7.57 (dd, 1H, J = 3.0, 8.5 Hz); HFABMS *m*/*z* 341.1310 (calcd for $C_{19}H_{18}FN_2O_3$, MH^+, 341.1301).

Data for (3*R*,3a*S*)-*rel*-2-acetyl-2,3,3a,4-tetrahydro-3-(4-methoxyphenyl)-8-methoxy[1]benzothiopyrano[4,3-*c*]pyrazole (40): yield 36%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.39 (s, 3H), 3.07 (dd, 1H, J = 4.5, 12.3 Hz), 3.33 (dd, 1H, J = 12.3 Hz), 3.57−3.62 (m, 1H), 3.79 (s, 3H), 3.86 (s, 3H), 5.02 (d, 1H, J = 8.5 Hz), 6.87−6.90 (m, 2H), 7.09 (d, 1H, J = 9.0 Hz), 7.20−7.23 (m, 2H), 7.52 (d, 1H, J = 3.0 Hz); HFABMS *m*/*z* 369.1273 (calcd for $C_{20}H_{21}N_2O_3S$, MH^+, 369.1273).

Data for (3*R*,3a*R*)-*rel*-2-acetyl-2,3,3a,4-tetrahydro-3-(4-methoxyphenyl)-8-methoxy[1]benzothiopyrano[4,3-*c*]pyrazole (41): yield 52%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.41−2.51 (m, 2H), 2.45 (s, 3H), 3.77 (s, 3H), 3.86 (s, 3H), 3.89−3.95 (m, 1H), 5.67 (d, 1H, J = 11.0 Hz), 6.83−6.85 (m, 2H), 6.88 (dd, 1H, J = 3.0, 8.8 Hz), 7.00−7.03 (m, 2H), 7.09 (d, 1H, J = 9.0 Hz), 7.65 (d, 1H, J = 3.0 Hz); HFABMS *m*/*z* 369.1267 (calcd for $C_{20}H_{21}N_2O_3S$, MH^+, 369.1273).

Preparation of (3*R*,3a*R*)-*rel*-2-Acetyl-3,3a,4,5-tetrahydro-3-(4-hydroxyphenyl)-8-methoxy-2*H*-benz[*g*]indazole (28). A mixture of **26** (0.370 mg, 0.86 mmol) and 5% Pd−C (10 mg) in ethyl acetate (20 mL) was stirred under a hydrogen atmosphere for 20 h and then filtered though a pad of Celite. The Celite was then washed sequentially with ethyl acetate and acetic acid. The combined filtrates were concentrated. The solid obtained was recrystallized from ethyl acetate to give **28** (0.185 g, 63%): mp 240−41 °C; ^{1}H NMR (400 MHz, d_6-DMSO−$CDCl_3$) δ 0.99−1.11 (m, 1H), 1.72−1.76 (m, 1H), 2.43 (s, 3H), 2.67−2.83 (m, 2H), 3.46−3.53 (m, 1H), 3.87 (s, 3H), 5.61 (d, J = 10.8 Hz, 1H), 6.74 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 6.61 (m, 1H), 7.07 (d, J = 8.4 Hz, 1H), 7.43−7.46 (m,1H), 7.52 (d, J = 3.2 Hz, 1H). Anal. ($C_{20}H_{20}N_2O_3$) C, H, N.

Preparation of (3*R*,3a*R*)-*rel*-2-Acetyl-3,3a,4,5-tetrahydro-3-(4-hydroxyphenyl)-8-hydroxy-2*H*-benz[*g*]indazole (30). To a solution of **28** (0.100 g, 0.28 mmol) under an argon atmosphere in dichloromethane (5 mL) was added BBr_3 (1.0 mL, 1.0 M solution in dichloromethane) at −78 °C. The reaction mixture was stirred at room temperature for 1 h and then poured into an ice cold solution of HCl (1.0 N). The mixture was extracted in ethyl acetate. The organic layer was washed with water, dried over anhydrous Na_2SO_4, filtered, and concentrated. The solid obtained was recrystallized from ethyl acetate to give **30** (62 mg, 67%): mp 164−67 °C; ^{1}H NMR (400 MHz, DMSO−$CDCl_3$) δ 0.70−0.90 (m, 1H), 1.41−1.46 (m, 1H), 2.41−2.57 (m, 5H), 3.15−3.22 (m, 1H), 5.29 (d, J = 11.2 Hz, 1H), 6.43 (d, J = 6.8 Hz, 2H), 6.53−6.57 (m, 3H), 6.68 (d, J = 8.4 Hz, 1H), 7.19 (s, 1H); HFABMS *m*/*z* 323.1399 (calcd for $C_{19}H_{18}N_2O_3$, MH^+, 323.1396).

Preparation of (3*R*,3a*S*)-*rel*-2-Acetyl-2,3,3a,4-tetrahydro-3-(4-methoxyphenyl)-5,5-dioxo-8-methoxy[1]benzothiopyrano[4,3-*c*]pyrazole (42) and (3*R*,3a*R*)-*rel*-2-Acetyl-2,3,3a,4-tetrahydro-3-(4-methoxyphenyl)-5,5-dioxo-8-methoxy[1]benzothiopyrano[4,3-*c*]pyrazole (43). A solution of **40** (21 mg, 0.057 mmol) in dichloromethane (5 mL) at 0 °C was treated with MCPBA (60 mg). The reaction mixture was stirred at room temperature for 16 h, then diluted with ethyl acetate (50 mL), washed sequentially with saturated $NaHCO_3$ and brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel using ethyl acetate−hexane (2:3) as the eluent to give **42** (96%) as a white solid. **43** (92%) was prepared in a similar manner from **41**.

Data for 42: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.41 (s, 3H), 3.54−3.62 (m, 2H), 3.81 (s, 3H), 3.95 (s, 3H), 4.09−4.15 (m, 1H), 5.03 (d, 1H, J = 10.5 Hz), 6.89−6.92 (m, 2H), 7.14 (dd, 1H, J = 2.3, 8.8), 7.21−7.24 (m, 2H), 7.56 (d, 1H, J = 2.5 Hz), 7.88 (d, 1H, J = 9.0 Hz); HFABMS *m*/*z* 401.1159 (calcd for $C_{20}H_{21}N_2O_5S$, MH^+, 401.1171).

Data for 43: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.48 (s, 3H), 2.68 (dd, 1H, J = 13.8 Hz), 3.11 (dd, 1H, J = 4.3, 13.8 Hz), 3.77 (s, 3H), 3.95 (s, 3H), 4.40−4.46 (m, 1H), 5.80 (d, 1H, J = 11.5 Hz), 6.84−6.86 (m, 2H), 6.96−6.98 (m, 2H), 7.14 (dd, 1H, J = 3.0, 9.0 Hz), 7.64 (d, 1H, J = 2.5 Hz), 7.86 (d, 1H, J = 9.5 Hz); HFABMS m/z 401.1160 (calcd for $C_{20}H_{21}N_2O_5S$, MH^+, 401.1171).

Preparation of (3*R*,3a*S*)-*rel*-2-Formyl-3,3a,4,5-tetrahydro-3-(4-methoxyphenyl)-8-methoxy-2*H*-benz[*g*]indazole ((3*R*,3a*S*)-*rel*-52) and (3*R*,3a*R*)-*rel*-2-Formyl-3,3a,4,5-tetrahydro-3-(4-methoxyphenyl)-8-methoxy-2*H*-benz[*g*]indazole (52). A solution of 2-(4-methoxybenzylidene)-7-methoxy-1-tetralone (2.0 g, 0.0068 mol) and hydrazine hydrate (2.0 mL) in formic acid (20 mL) was heated at 120 °C for 2 days. The reaction mixture was concentrated and then extracted with ethyl acetate. The organic layer was washed sequentially with water, saturated aqueous $NaHCO_3$, water, and brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated. The residue was purified by column chromatography on silica gel using ethyl acetate−hexane (3:7) as the eluent to give (3*R*,3a*S*)-*rel*-**52** (0.740 g, 32%) and **52** (0.905 g, 40%).

Data for (3*R*,3a*S*)-*rel*-52: mp 166−68 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.90−1.99 (m, 1H), 2.27−2.31 (m, 1H), 2.86−2.90 (m, 2H), 3.21−3.28 (m, 1H), 3.80 (s, 3H), 3.86 (s, 3H), 4.89 (d, J = 9.6 Hz, 1H), 6.90−6.98 (m, 3H), 7.10 (d, J = 8.8 Hz, 1H), 7.25−7.27 (m, 2H), 7.43 (d, J = 2.4 Hz, 1H), 8.97 (s, 1H). Anal. ($C_{20}H_{20}N_2O_3$) C, H, N.

Data for 52: mp 155−59 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01−1.12 (m, 1H), 1.69−1.74 (m, 1H), 2.68−2.85 (m, 2H), 3.49−3.76 (m, 1H), 3.76 (s, 3H), 3.81 (s, 3H), 5.58 (d, J = 11.2 Hz, 1H), 6.78−7.04 (m, 6H), 7.48 (d, J = 3.2 Hz, 1H), 8.94 (s, 1H). Anal. ($C_{20}H_{20}N_2O_3$) C, H, N.

Preparation of (3*R*,3a*S*)-*rel*-2-Propionyl-3,3a,4,5-tetrahydro-3-(4-methoxyphenyl)-8-methoxy-2*H*-benz[*g*]indazole ((3*R*,3a*S*)-*rel*-53) and (3*R*,3a*R*)-*rel*-2-Propionyl-3,3a,4,5-tetrahydro-3-(4-methoxyphenyl)-8-methoxy-2*H*-benz[*g*]indazole (53). A solution of 2-(4-methoxybenzylidene)-7-methoxy-1-tetralone (0.500 g, 1.7 mmol) and hydrazine hydrate (0.5 mL) in propionic acid (5 mL) was refluxed at 140 °C for 2 days. The reaction mixture was concentrated and the residue dissolved in ethyl acetate (25 mL). The mixture was washed sequentially with water, saturated aqueous $NaHCO_3$, and water, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel using ethyl acetate−hexane (3:7) as the eluent to give (3*R*,3a*S*)-*rel*-**53** (0.217 g, 35%) and **53** (0.252 g, 41%).

Data for (3*R*,3a*S*)-*rel*-53: mp 133−36 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (t, J = 7.6 Hz, 3H), 1.85−1.96 (m, 1H), 2.23−2.29 (m, 1H), 2.74−2.87 (m, 4H), 3.15−3.22 (m, 1H), 3.78 (s, 3H), 3.86 (s, 3H), 4.89 (d, J = 9.6 Hz, 1H), 6.87−6.92 (m, 3H), 7.08 (d, J = 8.4 Hz, 1H), 7.23 (d, J = 8.8 Hz, 2H), 7.44 (d, J = 2.4 Hz, 1H). Anal. ($C_{22}H_{24}N_2O_3$) C, H, N.

Data for 53: mp 150−52 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05−1.10 (m, 1H), 1.21 (t, J = 8.0 Hz, 3H), 1.70−1.78 (m, 1H), 2.74−2.88 (m, 4H), 3.47−3.52 (m, 1H), 3.75 (s, 3H), 3.87 (s, 3H), 5.65 (d, J = 11.2 Hz, 1H), 6.80 (d, J = 8.4 Hz, 2H), 6.89−6.92 (dd, J = 3.2 and 8.4 Hz, 1H), 6.98 (d, J = 8.8 Hz, 2H), 7.06 (d, J = 8.4 Hz, 1H), 7.54 (d, J = 3.2 Hz, 1H). Anal. ($C_{22}H_{24}N_2O_3$) C, H, N.

General Procedure for the Preparation of 2-Substituted (3*R*,3a*S*)-*rel*- and (3*R*,3a*R*)-*rel*-3,3a,4,5-Tetrahydro-3-(4-methoxyphenyl)-8-methoxy-2*H*-benz[*g*]indazoles. Exemplified for (3*R*,3a*S*)-*rel*-2-(Acetoxyacetyl)-3,3a,4,5-tetrahydro-3-(4-methoxyphenyl)-8-methoxy-2*H*-benz[*g*]indazole ((3*R*,3a*S*)-*rel*-54) and (3*R*,3a*R*)-*rel*-2-(Acetoxyacetyl)-3,3a,4,5-tetrahydro-3-(4-methoxyphenyl)-8-methoxy-2*H*-benz[*g*]indazole (54). A solution of 2-(4-methoxybenzylidene)-1-tetralone (1.0 g, 3.4 mmol), trimethylacetic acid (5.0 g), and hydrazine hydrate (1.0 mL) in ethanol (5 mL) was refluxed for 6 h and then concentrated. The residue obtained was dissolved in ethyl acetate (10 mL) and then washed with water. The organic layer was slowly poured into a saturated $NaHCO_3$ solution (10 mL). The resulting solution was slowly treated with acetoxyacetyl chloride (1.83 mL, 17 mmol). The mixture was stirred at room temperature for 30 min. The ethyl acetate layer was separated, washed sequentially with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel column using ethyl acetate−hexane (2:3) as the eluent to give (3*R*,3a*S*)-*rel*-**54** (11%) and **54** (68%).

Data for (3*R*,3a*S*)-*rel*-54: mp 159−61 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.87−1.98 (m, 1H), 2.13 (s, 3H), 2.26−2.31 (m, 1H), 2.86−2.89 (m, 2H), 3.17−3.24 (m, 1H), 3.78 (s, 3H), 3.86 (s, 3H), 4.90 (d, J = 9.2 Hz, 1H), 5.09 (d, J = 15.6 Hz, 1H), 5.22 (d, J = 15.6 Hz, 1H), 6.87−6.95 (m, 3H), 7.10 (d, J = 8.8 Hz, 1H), 7.24 (d, J = 8.8 Hz, 2H), 7.41 (d, J = 3.2 Hz, 1H). Anal. ($C_{23}H_{24}N_2O_5$) C, H, N.

Data for 54: mp 201−204 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05−1.16 (m, 1H), 1.73−1.77 (m, 1H), 2.16 (s, 3H), 2.72−2.89 (m, 2H), 3.48−3.55 (m, 1H), 3.75 (s, 3H), 3.87 (s, 3H), 5.16−5.25 (m, 2H), 5.64 (d, J = 11.2 Hz, 1H), 6.80 (d, J = 8.8 Hz, 2H), 6.91−6.94 (dd, J = 2.0 and 8.4 Hz, 1H), 6.99 (d, J = 8.8 Hz, 2H), 7.07 (d, J = 8.4 Hz, 1H), 7.49 (d, J = 3.2 Hz, 1H). Anal. ($C_{23}H_{24}N_2O_5$) C, H, N.

Data for (3*R*,3a*R*)-*rel*-2-(methoxyacetyl)-3,3a,4,5-tetrahydro-3-(4-methoxyphenyl)-8-methoxy-2*H*-benz[*g*]indazole (56): yield 16%; mp 157−59 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.06−1.12 (m, 1H), 1.75−1.77 (m, 1H), 2.76−2.88 (m, 2H), 3.46−3.50 (m, 1H), 3.51 (s, 3H), 3.75 (s, 3H), 3.87 (s, 3H), 4.54 (d, J = 16.0 Hz, 1H), 4.66 (d, J = 16.0 Hz, 1H), 5.68 (d, J = 11.0 Hz, 1H), 6.80 (d, J = 9.5 Hz, 2H), 6.91−6.93 (dd, J = 3.0 and 9.0 Hz, 1H), 6.98 (d, J = 9.5 Hz, 2H), 7.07 (d, J = 8.0 Hz, 1H), 7.50 (d, J = 3.0 Hz, 1H); HFABMS m/z 381.1810 (calcd for $C_{22}H_{24}N_2O_4$, MH^+, 381.1814).

Data for (3*R*,3a*R*)-*rel*-2-(trifluoroacetyl)-3,3a,4,5-tetrahydro-3-(4-methoxyphenyl)-8-methoxy-2*H*-benz[*g*]indazole (57): yield 22%; mp 220−22 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.09−1.18 (m, 1H), 1.75−1.80 (m, 1H), 2.77−2.89 (m, 2H), 3.53−3.59 (m, 1H), 3.76 (s, 3H), 3.87 (s, 3H), 5.68 (d, J = 10 Hz, 1H), 6.84 (d, J = 8.5 Hz, 2H), 6.94−6.97 (dd, J = 3.0 and 8.5 Hz, 1H), 7.01 (d, J = 8.5 Hz, 2H), 7.07 (d, J = 8.5 Hz, 1H), 7.56 (d, J = 3.0 Hz, 1H); HFABMS m/z 405.1432 (calcd for $C_{21}H_{19}F_3N_2O_3$, MH^+, 405.1426).

Preparation of (3*R*,3a*R*)-*rel*-2-(Hydroxyacetyl)-3,3a,4,5-tetrahydro-3-(4-methoxyphenyl)-8-methoxy-2*H*-benz[*g*]indazole (55). To a solution of **54** (0.150 g, 0.36 mmol) in methanol (10 mL) was added NaOH (50%, 2 mL) at room temperature. The reaction mixture was stirred at room temperature for 24 h before being diluted with ethyl acetate. The organic layer was washed with water, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue obtained was purified by column chromatography on a silica gel column using ethyl acetate−hexane (2:3) as the eluent to furnish **55** (0.105 g, 78%): mp 163−64 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06−1.17 (m, 1H), 1.72−1.78 (m, 1H), 2.76−2.89 (m, 2H), 3.76 (s, 3H), 3.87 (s, 3H), 4.55−7.70 (m, 2H), 5.66 (d, J = 10.0 Hz, 1H), 6.82 (d, J = 9.2 Hz, 2H), 6.92−6.95 (dd, J = 2.4 and 8.8 Hz, 1H), 6.99 (d, J = 9.2 Hz, 2H), 7.07 (d, J = 8.4 Hz, 1H), 7.50 (d, J = 2.4 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 24.38, 28.90, 48.57, 55.46, 55.76, 61.40, 69.61, 108.02, 114.34, 119.12, 127.53, 127.84, 128.47, 130.32, 132.61, 157.67, 158.36, 159.42, 168.66. Anal. ($C_{21}H_{22}N_2O_4$) C, H, N.

General Procedure for the Preparation of 2-Carbothioamides and 2-Carboxamides of (3*R*,3a*R*)-*rel*-3,3a,4,5-Tetrahydro-3-(4-methoxyphenyl)-8-methoxy-2*H*-benz[*g*]indazoles. Exemplified for (3*R*,3a*R*)-*rel*-2-Carbothioamide-3,3a,4,5-tetrahydro-3-(4-methoxyphenyl)-8-methoxy-2*H*-benz[*g*]indazole (59). A suspension of 2-(4-methoxybenzylidene)-7-methoxy-1-tetralone (0.850 g, 0.0028 mol) and thiosemicarbazide (0.790 g, 0.0084 mol) in ethanol (30 mL) and concentrated HCl (2 mL) was refluxed for 6 h. The resulting solution was cooled to room temperature. The solid precipitate was isolated by filtration, washed with ethanol, and then recrystallized from ethanol to give **59** (0.985 g, 96%): mp 236−39 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.04−1.13 (m, 1H), 1.76−1.81 (m, 1H), 2.75−2.87 (m, 2H), 3.60−3.66 (m, 1H), 3.76 (s, 3H), 3.85 (s, 3H), 6.07 (d, J = 10.5 Hz, 1H), 6.83 (d, J = 9.0 Hz, 2H), 6.93−6.95 (dd, J = 3.0 and 8.5 Hz, 1H), 6.99 (d, J = 9.0 Hz,

2H), 7.08 (d, $J = 8.5$ Hz, 1H), 7.49 (d, $J = 3.0$ Hz, 1H); HFABMS *m*/*z* 368.1439 (calcd for $C_{20}H_{21}N_3O_2S$, MH^+, 368.1433).

Data for (3*R*,3a*R*)-*rel*-2-carboxamide-3,3a,4,5-tetrahydro-3-(4-methoxyphenyl)-8-methoxy-2*H*-benz[*g*]indazole (58): yield 75%; mp 217−20 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02−1.11 (m, 1H), 1.74−1.79 (m, 1H), 2.73−2.86 (m, 2H), 3.54−3.60 (m, 1H), 3.75 (s, 3H), 3.86 (s, 3H), 5.58 (d, $J = 10.5$ Hz, 1H), 6.81 (d, $J = 8.5$ Hz, 2H), 6.88−6.90 (dd, $J = 3.0$ and 8.5 Hz, 1H), 7.01 (d, $J = 8.5$ Hz, 2H), 7.05 (d, $J = 8.5$ Hz, 1H), 7.47 (d, $J = 3.0$ Hz, 1H); HFABMS *m*/*z* 352.1663 (calcd for $C_{20}H_{21}N_3O_3$, MH^+, 352.1663).

Data for (3*R*,3a*R*)-*rel*-2-carbothioamide-3,3a,4,5-tetrahydro-3-(4-methoxyphenyl)-8-methoxy-*N*-methyl-2*H*-benz[*g*]indazole (60): yield 28%; mp 199−200 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02−1.11 (m, 1H), 1.76−1.81 (m, 1H), 2.75−2.86 (m, 2H), 3.21 (d, $J = 5.0$ Hz, 3H), 3.56−3.62 (m, 1H), 3.75 (s, 3H), 3.87 (s, 3H), 6.10 (d, $J = 11.0$ Hz, 1H), 6.80 (d, $J = 8.5$ Hz, 2H), 6.91−6.94 (dd, $J = 3.0$ and 8.5 Hz, 1H), 6.96 (d, $J = 8.5$ Hz, 2H), 7.07 (d, $J = 8.5$ Hz, 1H), 7.46 (m, 1H), 7.48 (d, $J = 3.0$ Hz, 1H); HFABMS *m*/*z* 382.1579 (calcd for $C_{21}H_{23}N_3O_2S$, MH^+, 382.1589).

Preparation of (3*R*,3a*R*)-*rel*-2-Carboxamidine-3,3a,4,5-tetrahydro-3-(4-methoxyphenyl)-8-methoxy-2*H*-benz[*g*]indazole (61). A solution of **59** (0.5 g, 1.3 mmol) and methyl iodide (1.0 mL) in ethanol (10 mL) was refluxed for 2 h. When the reaction mixture was concentrated to one-fourth of its volume, a solid precipitate formed. The mixture was filtered, and the solid was washed with cold ethanol to give **65** (565 mg, 85%), which was used without further purification. A solution of **65** (175 mg, 0.34 mmol) and ammonia (2.0 N solution in ethanol, 15 mL) in ethanol (15 mL) was stirred at 60 °C for 16 h. The reaction mixture was concentrated. The solid was recrystallized from methanol−diethyl ether to give **61** (105 mg, 88%): mp 170−75 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.07−1.15 (m, 1H), 1.74−1.78 (m, 1H), 2.76−2.89 (m, 2H), 3.77 (s, 3H), 3.79−3.84 (m, 1H), 3.88 (s, 3H), 6.19 (d, $J = 10.5$ Hz, 1H), 6.86 (d, $J = 8.5$ Hz, 2H), 6.97−6.99 (dd, $J = 3.0$ and 8.5 Hz, 1H), 7.10 (d, $J = 8.5$ Hz, 2H), 7.50 (d, $J = 3.0$ Hz, 1H); HFABMS *m*/*z* 351.1825 (calcd for $C_{20}H_{22}N_4O_2$, MH^+, 351.1821).

Preparation of (3*R*,3a*R*,5*S*)-*rel*-2-Acetyl-5-azido-3,3a,4,5-tetrahydro-3-(4-methoxyphenyl)-8-methoxy-2*H*-benz[*g*]indazole (44) and 2-Acetyl-3-(4-methoxyphenyl)-8-methoxy-2*H*-benz[*g*]indazole (45). To a solution of **8** (800 mg, 2.2 mmol) in acetonitrile (10 mL) under an argon atmosphere was added trimethylsilyl azide (1.517 mL, 5.0 equiv) followed by slow addition of [bis(trifluoroacetoxy)iodo]benzene (2.948 g, 3.0 equiv). The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was concentrated to give a dark brown residue that was purified by column chromatography on silica gel using ethyl acetate−hexane (1:3) as the eluent to give **44** (252 mg, 29%), **45** (239 mg, 31%), and recovered starting material **8** (45 mg).

Data for 44: thick oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24−1.28 (m, 1H), 1.82−1.88 (m, 1H), 2.46 (s, 3H), 3.74 (s, 3H), 3.86−3.89 (m, 1H), 3.91 (s, 3H), 4.66 (m, 1H), 5.70 (d, $J = 11.5$ Hz, 1H), 6.80 (d, $J = 8.5$ Hz, 2H), 6.96 (d, $J = 8.5$ Hz, 2H), 7.0−7.02 (dd, $J = 3.0$ and 9.0 Hz, 1H), 7.19 (d, $J = 9.0$ Hz, 1H), 7.60 (d, $J = 3.0$ Hz, 1H); HFABMS *m*/*z* 392.1722 (calcd for $C_{21}H_{22}N_5O_3$, MH^+, 392.1723).

Data for 45: mp 169−73 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.02 (s, 3H), 3.91 (s, 3H), 4.04 (s, 3H), 7.10 (d, $J = 8.5$ Hz, 2H), 7.27−7.29 (dd, $J = 3.0$ and 8.5 Hz, 1H), 7.74 (d, $J = 2.5$ Hz, 2H), 7.87 (d, $J = 8.5$ Hz, 1H), 7.92 (d, $J = 8.5$ Hz, 2H), 8.96 (d, $J = 2.5$ Hz, 1H); HFABMS *m*/*z* 347.1365 (calcd for $C_{21}H_{19}N_2O_3$, MH^+, 347.1396).

Preparation of (3*R*,3a*R*,5*S*)-*rel*-2-Acetyl-5-amino-3,3a,4,5-tetrahydro-3-(4-methoxyphenyl)-8-methoxy-2*H*-benz[*g*]indazole Oxalate Salt (46). A solution of **44** (0.240 g, 0.61 mmol) and 10% Pd−C (50 mg) in ethanol (10 mL) was stirred under hydrogen (1 atm) for 24 h. The solvent was evaporated, and the residue was purified by silica gel column chromatography utilizing 5% methanol in dichloromethane to afford the free base of **46** (85 mg, 38%). The free base of **46** (44 mg) in ethyl acetate (20 mL) was treated with a solution of oxalic acid (12 mg, 1.1 equiv) in ethyl acetate (5 mL). The solvent was evaporated, and the residue was washed with ether (20 mL) three times and dried to afford the oxalate salt of **46**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.06−1.12 (m, 1H), 1.95−1.98 (m, 1H), 2.36 (s, 3H), 3.71 (s, 3H), 3.86 (s, 3H), 3.95−4.01 (m, 1H), 4.52−4.53 (m, 1H), 5.73 (d, $J = 11.0$ Hz, 1H), 6.86−6.89 (m, 2H), 6.93−6.95 (m, 2H), 7.14 (dd, $J = 3.0$, 8.5 Hz, 1H), 7.46 (d, $J = 8.5$ Hz, 1H), 7.49 (d, $J = 3.0$ Hz, 1H); HFABMS *m*/*z* 366.1818 (calcd for $C_{21}H_{24}N_3O_3$, MH^+, 366.1818).

Preparation of (3*R*,3a*R*,5*S*)-*rel*-2-Acetyl-5-(*N*,*N*-dimethylamino)-3,3a,4,5-tetrahydro-3-(4-methoxyphenyl)-8-methoxy-2*H*-benz[*g*]indazole (47). To a solution of **46** (210 mg, 0.57 mmol) in THF (10 mL) was added formic acid (0.150 mL) at 0 °C, followed by slow addition of aqueous formaldehyde (37 wt %). The reaction mixture was refluxed for 24 h. The solution was allowed to cool, made basic with aqueous NaOH (25 wt %), and extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel using ethyl acetate as the eluent to give **47** (105 mg, 47%): mp 123−28 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.9−1.02 (m, 1H), 2.21 (s, 6H), 2.43 (s, 3H), 3.23 (m, 1H), 3.73 (s, 3H), 3.89 (s, 3H), 4.03−4.09 (m, 1H), 5.66 (d, $J = 11.0$ Hz, 1H), 6.78 (d, $J = 8.5$ Hz, 2H), 6.90−6.92 (dd, $J = 2.5$ and 8.5 Hz, 1H), 6.96 (d, $J = 8.5$ Hz, 2H), 7.12 (d, $J = 8.5$ Hz, 1H), 7.58 (d, $J = 2.5$ Hz, 1H). Anal. ($C_{23}H_{27}N_3O_3$) C, H, N.

Preparation of (3*R*,3a*R*)-*rel*-2-Ethyl-3,3a,4,5-tetrahydro-3-(4-methoxyphenyl)-8-methoxy-2*H*-benz[*g*]indazole (62). To a solution of **8** (180 mg, 0.51 mmol) in THF (5 mL) under an argon atmosphere was added $LiAlH_4$ (2.056 mL, 2.056 mmol, 1 M in THF) at room temperature. The reaction mixture was stirred at room temperature for 1 h and then quenched with methanol followed by ice. The reaction mixture was extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel using 25% ethyl acetate−hexane as the eluent to give **62** (30 mg, 17%): thick oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.40 (t, $J = 7.0$ Hz, 3H), 1.72−2.04 (m, 2H), 2.62−2.85 (m, 2H), 3.87 (s, 6H), 4.15 (q, $J = 7.0$ Hz, 2H), 4.75 (d, $J = 10.5$ Hz, 1H), 6.75−6.77 (dd, $J = 8.0$ and 3.0 Hz, 1H), 7.01 (d, $J = 8.0$ Hz, 2H), 7.12 (d, $J = 8.5$ Hz, 1H), 7.29 (d, $J = 8.0$ Hz, 2H), 7.44 (d, $J = 3.0$ Hz, 1H); LRMS *m*/*z* 336.3 (calcd for $C_{21}H_{24}N_2O_2$, M^+, 336.2).

Evaluation of Necroptosis Inhibitory Activity in an FADD-Deficient Variant of Human Jurkat T Cells Treated with TNF-α. Necroptosis activity was performed using an FADD-deficient variant of human Jurkat T cells treated with TNF-α as previously described.[17] For EC_{50} value determinations, cells (500000 cells/mL, 100 μL/well in a 96-well plate) were treated with 10 ng/mL human TNF-α in the presence of increasing concentrations of test compounds for 24 h at 37 °C in a humidified incubator with 5% CO_2 followed by ATP-based viability assessment. Stock solutions (30 mM) in DMSO were initially prepared and then diluted with DMSO to give testing solutions, which were added to each test well. The final DMSO concentration was 0.5%. Eleven compound test concentrations (0.029, 0.058, 0.12, 0.23, 0.46, 0.93, 1.9, 3.7, 11.1, 33, and 100 μM) were used. Each concentration was done in duplicate. Cell viability assessments were performed using a commercial luminescent ATP-based assay kit (CellTiter-Glo, Promega, Madison, WI) according to the manufacturer's instructions. Briefly, 40 μL of the cell lysis/ATP detection reagent was added to each well. The plates were incubated on a rocking platform for 10 min at room temperature, and luminescence was measured using a Wallac Victor 3 plate reader (Perkin-Elmer, Wellesley, MA). Cell viability was expressed as a ratio of the signal in the well treated with TNF-α and compound to the signal in the well treated with compound alone. This was done to account for nonspecific toxicity, which in most cases was <10%. EC_{50} values were calculated using nonlinear regression analysis of sigmoid dose−response (variable slope) curves from plots of log(*I*) verses viability values. The reported EC_{50} values ± SD were determined from at least two independent experiments.

Evaluation of Necroptosis Inhibitory Activity in L929 Cells Treated with TNF-α or zVAD.fmk. L929 cells (100000 cells/mL, 100 μL/well in a 96-well plate) were treated with 10 ng/mL human TNF-α or 100 μM zVAD.fmk in the presence of DMSO (control), 30 μM (±)-**1**, or **8** for 24 h at 37 °C in a humidified incubator with 5% CO_2 followed by ATP-based viability assessment as described in the previous experiment. Stock solutions (30 mM) in DMSO were initially prepared and then diluted with DMSO to give testing solutions. Each sample was done in duplicate. The final DMSO concentration was 0.5%. Cell viability values were adjusted to account for nonspecific toxicity, which in most cases was <10%. The reported cell viability values (%) ± SD were determined from two independent experiments.

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Supporting Information Available: Detailed experimental procedures for the preparation of tetralones, characterization of 2-arylidene-1-tetralones, 2-(arylidene)chroman-4-ones, and 2-(arylidene)-thiochroman-4-ones, combustion analyses, HPLC methods, purity assessments, and characterization of the (3*R*,3a*S*)-*rel*-isomers of **9**, **12**−**14**, **17**−**20**, **25**, **26**, **29**, **31**, **32**, **35**, and **56**. This material is available free of charge via the Internet at http://pubs.acs.org.

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