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Indol-3-ylcycloalkyl Ketones: Effects of N1 Substituted Indole Side Chain Variations on CB_2 Cannabinoid Receptor Activity

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Several 3-acylindoles with high affinity for the CB_2 cannabinoid receptor and selectivity over the CB_1 receptor have been prepared. A variety of 3-acyl substituents were investigated, and the tetramethylcyclopropyl group was found to lead to high affinity CB_2 agonists (**5**, **16**). Substitution at the N1-indole position was then examined. A series of aminoalkylindoles was prepared and several substituted aminoethyl derivatives were active (**23**−**27**, **5**) at the CB_2 receptor. A study of N1 nonaromatic side chain variants provided potent agonists at the CB_2 receptor (**16**, **35**−**41**, **44**−**47**, **49**−**54**, and **57**−**58**). Several polar side chains (alcohols, oxazolidinone) were well-tolerated for CB_2 receptor activity (**41**, **50**), while others (amide, acid) led to weaker or inactive compounds (**55** and **56**). N1 aromatic side chains also afforded several high affinity CB_2 receptor agonists (**61**, **63**, **65**, and **69**) but were generally less potent in an in vitro CB_2 functional assay than were nonaromatic side chain analogues.

Introduction

The cannabinoid 1 receptor (CB_1[a]) and the cannabinoid 2 receptor (CB_2) are members of the G-protein-coupled receptor family of receptors. While there is some evidence of the CB_2 receptor in the central nervous system,[1] the CB_2 receptor is found primarily in the immune system.[2] The psychotropic effects associated with nonselective cannabinoid agonists are thought to be mediated through the CB_1 receptor, which is present in the central and peripheral nervous system as well as the periphery. Activation of either the CB_1 or CB_2 receptor has been shown to result in analgesic activity in animals.[3] CB_2-selective agonists exhibit activity against both neuropathic and inflammatory pain[4,5] and lack the psychotropic side effects that limit the ultility of nonselective cannabinoid agonists.[6] Another avenue being explored to treat pain without inducing CB_1 centrally mediated side effects is the use of peripherally restricted CB_1 agonists.[7] In addition to pain, cannabinoid ligands are being investigated for the potential to treat numerous other disease states including liver disease,[8] osteoporosis,[9] Alzheimer's disease,[10] cancer,[11] multiple sclerosis,[12] and diabetes.[13]

Indoles have long been a popular framework for cannabinoid receptor ligands beginning with early work by Sterling-Winthrop that led to pravadoline and WIN-55,212-2 (**1**) (Figure 1).[14] Huffman and co-workers also did early groundbreaking work on indole cannabinoid ligands including the identification of the CB_2-selective agonist **2**.[15] More recently, numerous companies have reported indole-related cannabinoid ligands.[15−23] Our laboratories have also reported a series of indole CB_2 receptor agonists wherein the effect of substitution around the indole ring was reported.[24]

Several groups have reported work on the structure−activity relationships (SAR) of the N1 substituted indole side chain in cannabinoid receptor ligands.[15,25,26] Some of the earliest work in this area, by Eissenstat and co-workers, described activity at the CB_1 receptor.[25] They found that aminoethyl substitution was optimal, especially the now familiar morpholinylethyl substituent. Other aminoethyl groups were also found to have activity at the CB_1 receptor, including thiomorpholinylethyl, piperidinylethyl, and α-methylmorpholinylethyl. More polar substituents such as the morpholinoethyl *N*-oxide, piperazinylethyl, and carboxylmethyl were inactive.

Huffman and co-workers have extensively investigated indole cannabinoid ligands and were the first to describe that simple N1 alkyl side chains are tolerated in place of the aminoalkyl side chains previously thought to be necessary for activity at the cannabinoid receptors.[15] Huffman and co-workers also found that the size of the N1 alkyl side chain had a significant impact on activity at both the CB_1 and CB_2 receptors and on selectivity between the two. Generally, the Huffman group observed that the propyl side chain resulted in ligands with higher selectivity for the CB_2 receptor (**2**), while an N1 pentyl substituent gave analogues with increased affinity for the CB_1 receptor.

Makriyannis and co-workers have also disclosed many aminoalkylindoles including the well-known CB_2-selective ligand AM1241 (**3**).[26] Compound **3** is efficacious in a range of preclinical pain models[26,27] but also exhibits unique

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[a] Abbreviations: CB_1, cannabinoid 1 receptor; CB_2, cannabinoid 2 receptor; FLIPR, fluorescence imaging plate reader; HEK, human embryonic kidney, HEPES, 4-(2-hydroxyethyl)piperazine-1-ethanesulfonic acid; BSA, bovine serum albumin; CHO, Chinese hamster ovary; Tris-HCl, 2-Amino-2-(hydroxymethyl)-1,3-propanediol hydrochloride; EDTA, ethylenediaminetetraacetic acid; SEM, standard error of the mean; PBS, D-phosphate buffered saline.

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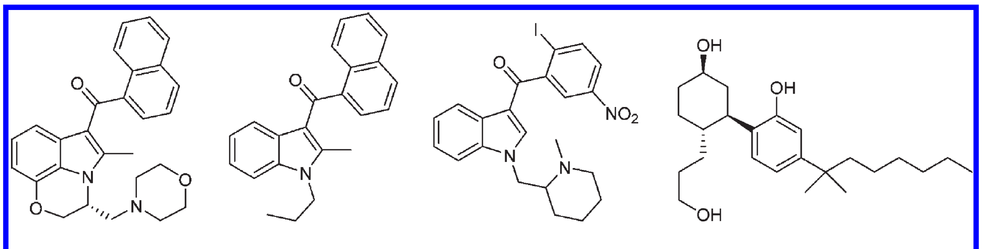


Figure 1. Literature compounds.

characteristics including an opioid receptor dependency[28] not observed in other CB_2-selective ligands[29] and varied activities in in vitro functional assays.[30,31] In their patent, Makriyannis and co-workers focus on two N1 side chains, the 1-(*N*-methyl-2-piperidinyl)methyl side chain of **3** and 1-(*N*-methyl-3-morpholinyl)methyl side chain, with the latter resulting in significantly weaker analogues than the former.

Hynes and co-workers at Bristol-Myers Squibb reported a series of C3-amidoindoles CB_2 agonists.[17] In their (*S*)-fenchylamide series, they report that an N1 pentyl substituent has higher affinity for the CB_2 receptor than the corresponding N1 morpholinylethyl side chain. However, the pentyl derivative was not active in their lipopolysaccharide stimulated TNF-α functional assay. Other N1 side chains such as methoxyethyl, *N*-morpholinylpropyl, *N*-piperidinylethyl, and *N*,*N*-dimethylaminylethyl demonstrated affinity for the CB_2 receptor but were weaker than the morpholinylethyl substituent. An *N*-pyrrolidinylethyl did not exhibit binding affinity for the CB_2 receptor.

In an early aminoalkylindole patent, Bell reported indol-3-yl cyclohexyl ketones; however, since then, the vast majority of work on cannabinoid indole ligands has focused on 3-acyl derivatives with aryl substituents.[32] One notable exception is in the work of Makriyannis who reports a 3-acyladamantane indole ligand.[26c] As we described previously,[24] work in our laboratories led to a reexamination of nonaromatic acyl substitution.

Here we report the SAR of the N1 side chain as well as indol-3-yl cycloalkyl ketones (Figure 2). The investigation of the 3-acyl substituent was limited to N1 substitutions of the well-known morpholinylethyl (**A**) and the tetrahydropyranylmethyl group (**B**), which were chosen on the basis of their potency and selectivity (vide infra). The N1 side chain study was limited to tetramethylcyclopropyl ketones derivatives (**C**). All ligands were assessed for human CB_1 and human CB_2 binding affinity as well as activity in an in vitro CB_2 functional assay. Rat and human CB_1 and CB_2 cyclase assay results for several compounds are also reported to compare activity and selectivity across the two species.

Chemistry

The 3-acyl variants (Table 1) were synthesized by one of the routes shown in Scheme 1. Acylation proceeded by treatment of the unsubstituted indole core with EtMgBr, $ZnCl_2$, and an acid chloride[33] followed by N-alkylation with the appropriate mesylate. Alternatively, the indole was first N-alkylated and then underwent Friedel–Crafts acylation with $AlCl_3$ and an acid chloride. The N1 side chain analogues (Tables 2–5) were all synthesized by first coupling indole with 2,2,3,3-tetramethylcyclopropanecarbonyl chloride (Scheme 2) using EtMgBr and $ZnCl_2$.[33] The C-3 acylated product then underwent N-alkylation with the appropriate mesylate or halide.

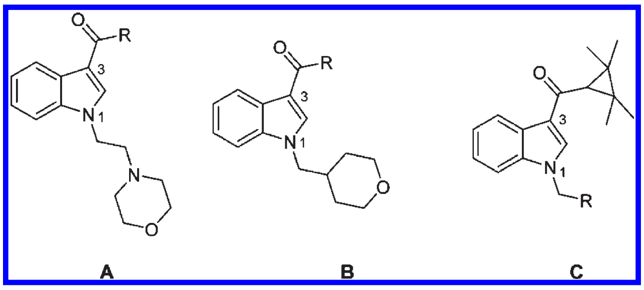


Figure 2. Scaffolds for investigation of 3-acyl substituent (A and B) and N1 side chain (C).

Biology

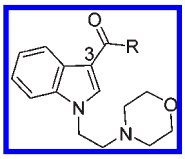
The binding affinity of this series of indole ligands was evaluated at recombinant human CB_1 and human CB_2 receptors through competition binding against [^{3}H]CP-55,940 (**4**).[34] In vitro functional activity was assessed in an human embryonic kidney (HEK) 293 cell line coexpressing the human CB_2 receptor and a chimeric $G_{\alpha q/o5}$ protein to facilitate redirection of the $G_{\alpha i/o}$ signaling to intracellular calcium release responses and enable measurement of calcium mobilization using a fluorescence imaging plate reader (FLIPR) as previously described.[30,35] The activity of several compounds was also assessed in the human CB_1, human CB_2, rat CB_1, and rat CB_2 cyclase assays using procedures previously described.[30,36] Maximal efficacy (% max) in the FLIPR and cyclase assays was determined relative to the response elicited by 10 μM CP-55,940 (**4**).

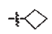
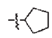
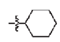
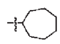
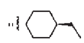
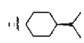
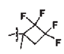
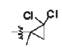
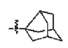
Results and Discussion

The study of 3-acylindole substituents was carried out with morpholinylethyl and tetrahydropyranylmethyl side chains. The morpholinylethyl group was chosen because it generally led to compounds with high affinity and selectivity for the CB_2 receptor. The tetrahydropyranylmethyl side chain also resulted in compounds that had high affinity for CB_2. When direct comparisons can be made, the tetrahydropyranylmethyl substituted ligands exhibit higher affinity for the CB_2 receptor than the corresponding morpholinylethyl analogues; however, selectivity for the CB_2 receptor often declined.[24]

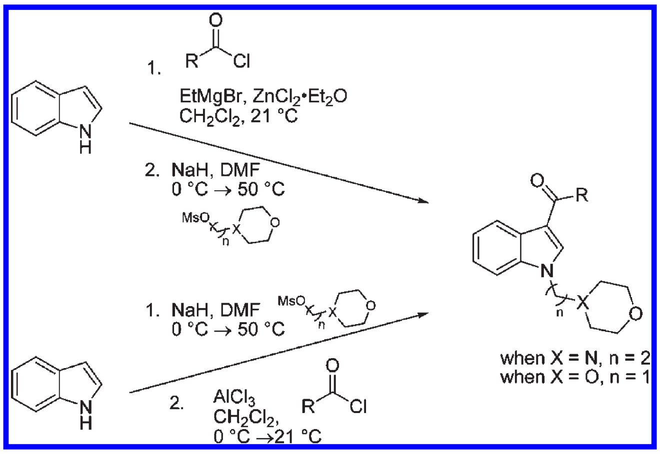
As shown in Tables 1 and 2, several 3-acyl variants were investigated. In both the morpholinylethyl and tetrahydropyranylmethyl series, the tetramethylcyclopropyl ligands exhibit the highest affinity for the CB_2 receptor as well as the best potency in the FLIPR assay (**5**, **16**) relative to all other acyl substituents investigated. Several other acyl substitutions result in ligands with good affinity for the CB_2 receptor (**8**–**11**, **14**, **15**, **17**–**22**), but CB_2/CB_1 selectivity varied. Two interesting derivatives, other than the tetramethylcyclopropyl analogues, were noradamantane derivative **15** and oxaadamantane

Table 1. In Vitro Biological Activity of Morpholinylethyl 3-Acyl Variants

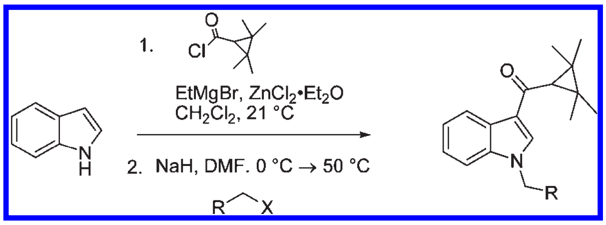


	R	Human CB_2 Binding pK$_i$ ± SEM	Human CB_2 Binding K$_i$ (nM)	Human CB_1 Binding pK$_i$ ± SEM	Human CB_1 Binding K$_i$ (nM)	CB_1/CB_2	Human CB_2 FLIPR EC$_{50}$ (nM) (SEM range)	Human CB_2 FLIPR % max
1	**WIN-55,212-2**	8.89 ± 0.06	1.3	7.88 ± 0.12	13.3	10	86-163	74± 4
2	**JWH-015**	7.45 ± 0.06	35	5.92 ± 0.10	1204	34	634-961	75 ± 5
3	**AM1241**	7.94 ± 0.10	11.5	5.90 ± 0.25	1269	110	>10,000	
5		8.34 ± 0.15	4.6	6.02 ± 0.10	945	205	16-24	71 ± 3
6		<6	>1000	<5	>10,000		>10,000	
7		<6	>1000	<5	>10,000		819-1437	35 ± 7
8		6.86 ± 0.07	138	5.79 ± 0.11	1630	12	86-189	44 ± 9
9		7.95 ± 0.17	11	6.44 ± 0.41	362	33	31-59	48 ± 8
10		7.80 ± 0.10	16	6.21 ± 0.09	616	39	85-91	59 ± 5
11		6.72 ± 0.03	190	<5	>10,000	>53	>10,000	
12		<6	>1000	<5	>10,000		>10,000	
13		<6	>1000	<5	>10,000		716-1086	33 ± 6
14		7.46 ± 0.08	35	5.51 ± 0.01	3057	87	42-182	50 ± 6
15		7.65 ± 0.19	23	<5	>10,000	>435	68-194	66 ± 9

Scheme 1. General Synthesis of 3-Acyl Variants



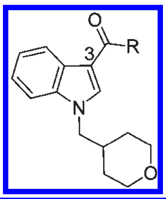
Scheme 2. General Synthesis of N1 Side Chain Derivatives



22. These ligands demonstrate high affinity and good functional potency for the CB_2 receptor and are more selective for the CB_2 receptor than the other 3-acyl variants investigated. Increasing size of 3-cycloalkyl ketones resulted in ligands with increasing affinity for the CB_2 receptor (**6**−**9**). Ultimately, the tetramethylcyclopropyl ketone was chosen as the template for investigation of the N1 side chain.

The N1-amine side chain analogues (aminoalkylindoles) investigated are shown in Table 3. Several aminoalkylindoles possess high affinity, good potency, and good selectivity for the CB_2 receptor. The most interesting ligands were those with a substituted aminoethyl group. Specifically, analogues **24**−**27** and analogue **5** all exhibit high affinity for the CB_2 receptor; however, azepine **27**, with its larger side chain, is less potent in the FLIPR functional assay. Unsubstituted aminoethyl derivative **23** is inactive at the CB_2 receptor, as are analogues with amine functionality further away from the indole ring (**28**−**33**). The full characterization of morpholinylethyl ligand **5** has been reported previously by our laboratories.[24,36] Interestingly, the homologue of **5**, **32**, exhibits very little affinity for the CB_2 receptor. Analogue **34** has the same *N*-methylpiperidinyl side chain as AM1241 (**3**), and while **34**

Table 2. In Vitro Biological Activity of Tetrahydrofuranylmethyl 3-Acyl Variants



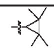
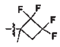
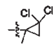
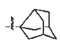
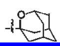
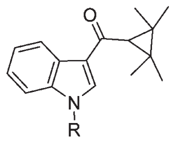
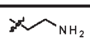
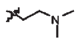
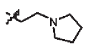
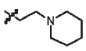
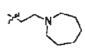
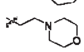
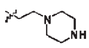
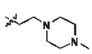
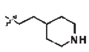
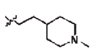
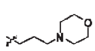
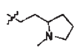
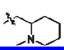
	R	Human CB_2 Binding		Human CB_1 Binding			Human CB_2 FLIPR	
		$pK_i \pm$ SEM	K_i (nM)	$pK_i \pm$ SEM	K_i (nM)	CB_1/CB_2	EC_{50} (nM) (SEM range)	% max
16		9.67 ± 0.12	0.21	7.91 ± 0.18	12	57	7-12	131 ± 10
17		7.96 ± 0.25	11	6.88 ± 0.21	131	12	20-32	64 ± 11
18		7.33 ± 0.18	47	5.84 ± 0.19	1450	31	197-734	46 ± 4
19		6.74 ± 0.03	181	5.47 ± 0.06	3360	19	782-1484	32 ± 7
20		8.59 ± 0.20	2.6	7.21 ± 0.6	62	24	14-17	86 ± 2
21		8.67 ± 0.08	2.1	7.14 ± 0.22	73	35	7-12	93 ± 2
22		8.23 ± 0.07	5.9	6.27 ± 0.14	538	91	8-10	97 ± 3

Table 3. In Vitro Biological Activity of Aminoalkylindoles

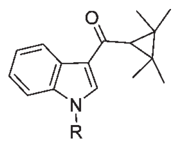


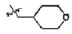
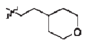
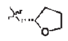
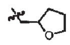
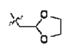
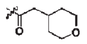
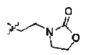
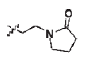
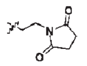
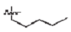
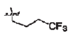
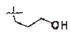
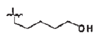
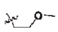
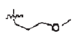
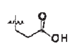
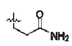
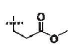
	R	Human CB_2 Binding		Human CB_1 Binding			Human CB_2 FLIPR	
		$pK_i \pm$ SEM	K_i (nM)	$pK_i \pm$ SEM	K_i (nM)	CB_1/CB_2	EC_{50} (nM) (SEM range)	% max
23		<6	>1000	<5	>10,000		>10,000	
24		8.72 ± 0.10	1.9	<5	>10,000	>5263	35-63	105 ± 6
25		8.23 ± 0.23	5.8	<5	>10,000	>1724	70-146	84 ± 8
26		8.65 ± 0.04	2.3	6.25 ± 0.23	556	242	56-85	93 ± 10
27		7.59 ± 0.24	26	6.10 ± 0.09	790	30	1020-1527	49 ± 10
5		8.34 ± 0.15	4.6	6.02 ± 0.10	945	205	16-24	71 ± 3
28		<6	>1000	<5	>10,000		2200-6783	30 ± 4
29		<6	>1000	5.67 ± 0.33	2150			
30		<6	>1000	<5	>10,000			
31		<6	>1000	<5	>10,000			
32		<6	>1000	<5	>10,000		1524-3391	56 ± 6
33		<6	>1000	<5	>10,000			
34		9.32 ± 0.22	0.48	8.26 ± 0.22	5.5	11	628-916	48 ± 3

does exhibit affinity for the CB_2 receptor, it also has high affinity for CB_1 and is only a weak partial agonist in the FLIPR assay.

Many N1 side chains in addition to amines were also investigated (Tables 4 and 5). Looking first at the nonaromatic side chains (Table 4), one of the highest affinity CB_2 receptor

Table 4. In Vitro Biological Activity of N1 Nonaromatic Side Chain Analogues

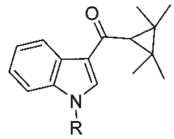


	R	Human CB_2 Binding pK$_i$ ± SEM	Human CB_2 Binding K$_i$ (nM)	Human CB_1 Binding pK$_i$ ± SEM	Human CB_1 Binding K$_i$ (nM)	CB_1/CB_2	Human CB_2 FLIPR EC$_{50}$ (nM) (SEM range)	Human CB_2 FLIPR % max
16		9.67 ± 0.12	0.21	7.91 ± 0.18	12	57	7-12	131 ± 10
35		8.56 ± 0.18	2.8	7.04 ± 0.02	92	33	15-32	90 ± 4
36		9.31 ± 0.14	0.14	6.20 ± 0.27	630	4500	6-7	102 ± 5
37		8.48 ± 0.10	3.3	6.67 ± 0.28	220	67	14-43	117 ± 7
38		8.42 ± 0.15	3.8	6.14 ± 0.12	720	189	11-33	99 ± 3
39		8.99 ± 0.25	1.0	6.55 ± 0.06	280	280	7-9	133 ± 14
40		<6	>1000	<5	>10,000			
41		9.74 ± 0.30	0.18	6.45 ± 0.15	350	1944	2-4	81 ± 7
42		7.27 ± 0.12	55	<5	>10,000	>182	55-163	97 ± 6
43		6.77 ± 0.01	170	<5	>10,000	>59	77-173	34 ± 0.2
44		8.04 ± 0.08	9.2	5.37 ± 0.06	4300	467	36-38	114 ± 4
45		8.70 ± 0.04	2.0	7.04 ± 0.06	91	46	5-13	102 ± 0.5
46		8.74 ± 0.05	1.8	6.84 ± 0.09	150	83	29-43	93 ± 4
47		10.07 ± 0.19	0.09	7.83 ± 0.29	15	167	6-10	104 ± 5
48		7.25 ± 0.28	56	<5	>10,000	>179	440-1600	85 ± 1
49		8.67 ± 0.30	2.1	5.67 ± 0.33	2200	1048	27-43	140 ± 15
50		8.66 ± 0.22	2.2	<5.25	>5600	>2500	8-23	105 ± 6
51		9.15 ± 0.49	0.71	6.17 ± 0.25	680	958	11-24	79 ± 6
52		8.50 ± 0.19	3.1	6.15 ± 0.05	710	229	14-28	117 ± 8
53		8.87 ± 0.30	1.3	6.18 ± 0.31	660	508	26-32	108 ± 2
54		9.40 ± 0.36	0.40	7.41 ± 0.04	39	98	22-54	74 ± 6
55		<6	>1000	<5	>10,000			
56		6.66 ± 0.06	220	<5	>10,000	<46	294-492	107 ± 9
57		8.53 ± 0.26	2.9	5.74 ± 0.08	1830	631	17-45	109 ± 8
58		9.00 ± 0.04	0.99	6.42 ± 0.30	380	384	6-14	89 ± 8

ligands is tetrahydropyranylmethyl analogue **16**, which has been reported previously.[24] Unfortunately, **16** also has high affinity for the CB_1 receptor. There are numerous additional high affinity CB_2 receptor agonists in this series, and many of these ligands also exhibit good selectivity for the CB_2 receptor versus the CB_1 receptor. One analogue of note is the (*R*)-tetrahydrofuranylmethyl ligand **38**, which was 3-fold more selective for the CB_2 receptor than the corresponding (*S*)-enantiomer, **37**. Also of interest is oxazolidinone **41**, which exhibits very high affinity and selectivity for the CB_2 receptor (CB_1/CB_2 = 1944). Consistent with the work of Huffman and co-workers, the *n*-propyl side chain ligand (**44**) is more selective for the CB_2 receptor (CB_1/CB_2 = 467) than the *n*-pentyl analogue **46** (CB_1/CB_2 = 83).

Several alcohols (**48**–**51**), ethers (**52**, **53**), and a thioether (**54**) were all well-tolerated with all analogues exhibiting high affinity and good potency in the CB_2 functional assay. A carboxylic acid side chain (**55**) is not tolerated, but the corresponding amide (**56**) did exhibit moderate affinity at the CB_2 receptor and is an agonist in the FLIPR assay. Ester

Table 5. In Vitro Biological Activity of N1 Aromatic Side Chain Analogues



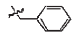
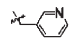
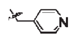
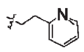
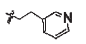
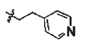
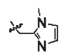
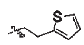
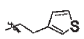
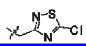
	R	Human CB_2 Binding pKi ± SEM	Human CB_2 Binding K_i (nM)	Human CB_1 Binding pKi ± SEM	Human CB_1 Binding K_i (nM)	CB_1/CB_2	Human CB_2 FLIPR EC_{50} (nM) (SEM range)	Human CB_2 FLIPR % max
59		8.09 ± 2.1	8.2	6.67 ± 0.27	210	26	93-130	59 ± 16
60		7.52 ± 0.05	30	5.69 ± 0.12	2030	68	75-187	103 ± 6
61		8.44 ± 0.14	3.7	7.32 ± 0.76	48	13	30-68	99 ± 1
62		7.16 ± 0.13	68	5.72 ± 0.05	1900	28	542-600	59 ± 3
63		7.71 ± 0.14	20	<5	>10,000	>500	62-97	78 ± 19
64		7.51 ± 0.17	31	5.65 ± 0.17	2200	71	162-329	100 ± 12
65		8.75 ± 0.14	1.8	6.51 ± 0.09	310	172	54-80	97 ± 7
66		6.81 ± 0.05	160	<5	>10,000	>63	1619-3515	63 ± 4
67		8.56 ± 0.07	2.8	6.16 ± 0.8	700	250	96-257	86 ± 5
68		8.75 ± 0.09	1.8	6.83 ± 0.12	148	82	70-103	108 ± 7
69		7.74 ± 0.20	18	5.70 ± 0.06	2000	111	49-111	49 ± 5
70		8.08 ± 0.10	8.3	5.37 ± 0.08	4200	506	109-201	97 ± 4

Table 6. Activities of Select Ligands in Human and Rat Cyclase Assays

	human CB_1 cyclase		human CB_2 cyclase		rat CB_1 cyclase		rat CB_2 cyclase	
	EC_{50} (nM) (SEM range)	% max	EC_{50} (nM) (SEM range)	% max	EC_{50} (nM) (SEM range)	% max	EC_{50} (nM) (SEM range)	% max
1	37−61	113 ± 6	0.39−1.1	98 ± 9	10−19	108 ± 3	1.5−5.8	46 ± 2
5	811−1186	118 ± 10	0.52−0.97	78 ± 4	248−328	97 ± 2	1.6−3.9	70 ± 4
16	4−8	111 ± 8	2.7−7.7	103 ± 1	12−17	91 ± 3	0.17−0.27	93 ± 4
41	3593−3745	133 ± 1	0.97−1.1	114 ± 1			0.07−0.41	99 ± 1
50	1881−3383	98 ± 1	2.1−2.2	100 ± 4	2077−3257	113 ± 11	4.4−5.6	104 ± 6

(**57**) and ketone (**58**) functionalities are well-tolerated. Overall, numerous side chains exhibit high affinity and good selectivity for the CB_2 receptor and are potent agonists in the CB_2 FLIPR functional assay.

Finally, as shown in Table 5, aromatic side chains were also investigated. While most of the analogues in this series exhibit high affinity for the CB_2 receptor, many have relatively weak potency and/or efficacy in the FLIPR assay (i.e., **59**, **62**, **67**, and **69**). Interestingly, the location of the heteroatoms in these aryl side chains influence both binding affinities and potency in the FLIPR assay (i.e., **60** vs **61** and **62** vs **63** vs **64**). Although most aryl side chains investigated exhibit good to moderate affinity for the CB_2 receptor, they are generally less potent in the CB_2 FLIPR assay. As with the N1 nonaromatic series, CB_2/CB_1 selectivity varied from moderate (i.e., **61**) to good (i.e., **63**).

Cyclase Activity. The activity of several compounds was also assessed in the human and rat cyclase assays. Activity of the reference compound WIN-55,212-2 (**1**), is shown for comparison. As shown in Table 6, ligand **5** exhibits a high degree of selectivity for the CB_2 receptor in the human (CB_1/CB_2 = 1385) and rat (CB_1/CB_2 = 115) cyclase assay. The more potent **16** was somewhat less selective for the CB_2 receptor in the human assays than the rat, but the ligand was very potent in all assays, as had been observed in the FLIPR and binding assays. Two additional analogues, **41** and **50**, exhibited potent and efficacious agonist activity in the human and rat CB_2 cyclase assays, and both are highly selective for the human CB_2 receptor. Overall, activity in the cyclase assays demonstrated that compounds were generally more selective for the CB_2 receptor in the human cyclase assays compared to the rat assays; however, the activity and selectivity trends were consistent across species.

In Vitro SAR Summary. Numerous high affinity CB_2-selective ligands with potent agonist activity were identified. Several 3-cycloalkyl ketone substituents generated high affinity, CB_2 selective agonists, including a noradamantyl analogue (**15**), an oxaadamantyl derivative (**22**), and tetramethylcyclopropylcyclopropyl analogues (**5**, **16**). On the basis of preliminary measures of CB_2 potency and selectivity against the CB_1 receptor, the latter was chosen for use in the N1 side chain investigation.

Several N1 amino side chains exhibit good activity at the CB_2 receptor, but it was noted that an amine group further from the indole ring (**28**−**33**) is not tolerated. A variety of functionality was well-tolerated in the non-amine side chain analogues (Table 4), and this series had numerous high affinity CB_2 receptor agonists (i.e., **16**, **38**, **41**, **44**, **47**, **51**, **53**, and **58**). Overall, these compounds also demonstrate good selectivity for CB_2 versus CB_1 in binding assays. Finally, aromatic side chains were also tolerated, but their activity at and selectivity for the CB_2 receptor were sensitive to heteroatom location (**61** vs **62** vs **63**).

The results reported here were also generally consistent with previous work reported on indole cannabinoid ligands. Specifically, in agreement with the work of Huffman and co-workers,[15] it was observed that the *n*-propyl analogue was more selective for the CB_2 receptor relative to the CB_1 receptor than the corresponding *n*-pentyl analogue. Also, Eissenstat and co-workers reported that the aminoethyl side chain was optimal[25] and, in the amine side chain series investigated here, the substituted aminoethyl analogues (**5**, **24**−**27**) were the only active amine side chain ligands. Hynes and co-workers reported that an N1-pentyl analogue did not exhibit agonist activity in their C3-amidoindole series; however, in our system, the *n*-pentyl ligand **46** was a potent, full agonist.

Overall, a good correlation between binding affinity and activity in the FLIPR assay was observed. However, any discrepancies between the two assays may be due to the artifical coupling of the receptor to the chimeric G-protein in the FLIPR assay resulting in a reduction of intrinsic ligand affinity or to the nonequilibrium conditions of the FLIPR assay. Also, in the FLIPR assay, several ligands exhibited efficacy greater than that of CP-55,940 (**4**)[34] (i.e., **16**, **37**, **44**, **49**). These ligands are believed to be full agonists at the CB_2 receptor as is CP-55,940 (**4**) and would be anticipated to behave as such in vivo.

Despite there being only an 81% homology between the rat and human CB_2 receptors,[35] activity in the cyclase assays generally confirmed the activity and selectivity trends observed in the binding and FLIPR assays. For example, the literature standard, WIN-55,212-2 (**1**), and analogue **16** both exhibit high affinity for the CB_1 and CB_2 receptors in the human binding assays, and this is also observed in the rat and human cyclase assays. Ligands **5**, **41**, and **50** all demonstrated reasonable selectivity for the CB_2 receptor in the binding assays, which was also observed in the cyclase assays in both species. Generally, higher levels of selectivity for the CB_2 receptor relative to the CB_1 receptor were observed in the human cyclase assays than in the rat assays.

In summary, the 3-acyl substituent was investigated in two series, the morpholinylethyl and the tetrahydrofuranylmethyl series. There were several analogues of interest, including the adamantyl derivatives **15** and **22**, but the 3-tetramethylcyclopropyl ketone led to the ligands with the highest affinity for the CB2 receptor (**5** and **16**). The N1-indole side chain was also investigated. In the aminoalkylindole series, several ligands exhibit high affinity for the CB_2 receptor as well as moderate to good levels of binding selectivity for the CB_2 receptor versus the CB_1 receptor (**5**, **24**−**27**). Analogue **34**, with the same *N*-methylpiperidinyl side chain as **3**, exhibits notably higher affinity for both the CB_2 and CB_1 receptors compared with the other aminoalkylindoles.

Many N1 aromatic and nonaromatic side chains were also investigated, and numerous high affinity CB_2 receptor agonists with moderate to very good selectivity for the CB_2 receptor were identified. A stereochemical effect was noted on binding selectivity, with the *R*-tetrahydrofuranylmethyl analogue **38** exhibiting more selectivity for the CB_2 receptor than did its *S*-enantiomer **37**. Some polarity was tolerated in the N1 side chain with oxazolidinone **41** demonstrating very high affinity for the CB_2 receptor (K_i = 0.18 nM) and good potency with full agonist activity in FLIPR assay (EC_{50} = 3 nM, 81% response). However, carboxylic acid **55** was inactive at both the CB_2 and CB_1 receptors. Consistent with the literature, the *n*-propyl ligand, **44**, was more selective for the CB_2 receptor than was the *n*-butyl (**45**) or the *n*-pentyl (**46**) ligand. Several N1 aromatic side chain ligands exhibit good affinity for the CB_2 receptor. As seen with the pyridinylethyl analogues (**62**−**64**), CB_2 receptor activity varied with heteroatom location. Data generated in the human and rat cyclase assay confirmed the activity and selectivity trends observed in the binding and FLIPR assays and demonstrated the activity of these series across two species. We have previously reported that **5** exhibited activity in several pain models,[24,36] demonstrating the potential of CB_2 selective agonists for the treatment of pain.

Experimental Section

Radioligand Binding Assays. Membrane samples prepared from HEK cells stably expressing human CB_2 receptor and the Chinese hamster ovary (CHO) cells stably expressing the human CB_1 receptor were used to perform radioligand binding assays using [^{3}H]CP-55,940 (**4**) as previously described.[35] Briefly, competition experiments were conducted using 0.5 nM [^{3}H]CP-55,940 (**4**) in the presence of variable concentrations of test compounds in an assay buffer containing 50 mM 2-amino-2-(hydroxymethyl)-1,3-propanediol, hydrochloride (Tris-HCl), pH 7.4, 2.5 mM EDTA, 5 mM $MgCl_2$, and 0.05% fatty acid free BSA. After 90 min of incubation at 30 °C, the reactions were terminated by rapid vacuum filtration through UniFilter-96 GF/C filter plates (Perkin-Elmer Boston, MA) and six washes with cold assay buffer, and the filter plates were air-dried. The bound activity was counted in a TopCount using Microscint-20 (Perkin-Elmer, Boston, MA). Nonspecific binding was defined by 10 μM unlabeled CP-55,940 (**4**). K_i values from competition binding assays were determined with one site binding or one site competition curve fitting using the MDL Assay Explorer software (San Ramon, CA). Data are presented as mean values $\pm$ standard error of the mean (SEM) of at least three independent experiments, each of which was performed in duplicate.

Fluorescence Imaging Plate Reader (FLIPR) Functional Assays. FLIPR assays were performed using HEK cells stably coexpressing the chimeric Gαq/o5 protein with the human CB_2 receptor.[35] Briefly, cells were seeded at 75 000 cells per well 1 day prior to the assay and assays performed with no-wash dye (FLIPR calcium assay kit, Molecular Devices, Sunnyvale, CA) following the vendor's instruction. Variable concentrations of test compounds (0.3 nM to 10 μM), CP-55,940 (**4**) (at 10 μM final concentration) positive control, or vehicle negative control were added to cells in the presence of assay buffer (10 mM HEPES, pH 7.4, 130 mM NaCl, 5 mM KCl, 0.05% BSA), and fluorescence responses were measured immediately with a FLIPR machine. Net peak responses were compared with that of 10 μM CP-55,940 (**4**) and expressed as percentages of the CP-55,940 (**4**) evoked response. EC_{50} values were analyzed with sigmoidal dose response curve fitting using MDL Assay Explorer software (San Ramon, CA). Data are presented as mean values ± SEM of at least three independent experiments, each of which was performed in duplicate.

Cyclase Functional Assays. The cyclase functional assays were performed using the HitHunter cAMP assay kit from DiscoveRx (Fremont, CA) in suspension forms according to the manufacturer's protocol and as described previously.[30,36] Briefly, cell suspensions were incubated at 37 °C for 20 min with variable concentrations of test ligands or 10 mM CP-55,940 (**4**)[34] as a positive control in the presence of a fixed concentration of forskolin (18 mM for the rat CB_2 line and 37 mM for human CB_1 and CB_2 and rat CB_1 lines) in D-phosphate buffered saline (PBS) buffer (Invitrogen) supplemented with BSA (0.01% final concentration). The reactions were terminated by the addition of lysis buffer, and the luminescence was detected following the procedure according to the manufacturer's instructions. The positive control, CP-55,940 (**4**) (10 mM), produced significant inhibition of cAMP levels induced by forskolin in the cell lines expressing the human CB_1 (84% inhibition, n = 10), human CB_2 (71% inhibition, n = 10), rat CB_1 (90% inhibition, n = 10), and rat CB_2 receptors (63% inhibition, n = 10). Receptor activation by ligands is expressed as percent response compared to that of 10 mM CP-55,940 (**4**). EC_{50} values were calculated by sigmoidal dose-response curve fitting using Prism (GraphPad) software.

Chemistry. Proton NMR spectra were obtained on a General Electric QE 300 or QZ 300 MHz instrument with chemical shifts (δ) reported relative to tetramethylsilane as an internal standard. Elemental analyses were performed by Robertson Microlit Laboratories or Quantitative Technologies, Inc. Column chromatography was carried out on silica gel 60 (230-400 mesh). Thin-layer chromatography was performed using 250 mm silica gel 60 glass-backed plates with F_{254} as indicator. All starting materials were commercially available and were obtained from Aldrich unless otherwise specified. The purity of all final compounds was assessed to be ≥95% by spectral data and elemental analysis.

2,2,3,3-Tetramethylcyclopropanecarbonyl Chloride. To a flask containing 2,2,3,3-tetramethylcyclopropane carboxylic acid (13.5 g, 95 mmol) was added 30 mL of thionyl chloride (410 mmol, excess). This solution was warmed to reflux and was stirred for 2 h. The mixture was then cooled to ambient temperature and concentrated under reduced pressure. The residue was diluted with 10 mL of benzene and concentrated to remove any remaining thionyl chloride. This was repeated two additional times, and the material was used without further purification or characterization.

1*H*-Indol-3-yl(2,2,3,3-tetramethylcyclopropyl)methanone. To a solution of indole (11 g, 95 mmol) in 30 mL of dichloromethane at ambient temperature was added 105 mL of a 1 M solution of ethylmagnesium bromide in tetrahydrofuran (THF) (105 mmol) dropwise via syringe pump. After the addition was complete, the solution was stirred for 15 min at which time 105 mL of a 1 M solution of $ZnCl_2$ in Et_2O (105 mmol) was added. The mixture was stirred for an additional 30 min, and then 2,2,3,3-tetramethylcyclopropanecarbonyl chloride (95 mmol) in 50 mL of dichloromethane was added via cannula. The mixture was stirred for 6 h at ambient temperature and then was quenched with 50 mL of saturated, aqueous NH_4Cl and diluted with 50 mL of dichloromethane. The layers were separated, and the aqueous layer was extracted with dichloromethane (3 × 30 mL). The combined organics were washed with 20 mL of H_2O and then were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified via column chromatography (SiO_2, 50% ethyl acetate/hexanes) to give 9.7 g of the major regioisomer 1*H*-indol-3-yl(2,2,3,3-tetramethylcyclopropyl)methanone (40 mmol, 42% yield) and 6.1 g of the minor regioisomer of 1-[(2,2,3,3-tetramethylcyclopropyl)carbonyl]-1*H*-indole (25 mmol, 27% yield). ^{1}H NMR (major product) (300 MHz, CD_3OD) δ ppm 1.32 (s, 6 H), 1.33 (s, 6 H), 2.14 (s, 1 H), 7.12-7.24 (m, 2 H), 7.38-7.46 (m, 1 H), 8.02 (s, 1 H), 8.19-8.25 (m, 1 H); ^{1}H NMR (minor product) (300 MHz, CD_3OD) δ ppm 1.29 (s, 6 H), 1.34 (s, 6 H), 1.94 (s, 1 H), 6.66 (dd, J = 3.7, 0.7 Hz, 1 H), 7.16-7.32 (m, 2 H), 7.51-7.58 (m, 1 H), 7.67 (d, J = 3.7 Hz, 1 H), 8.32-8.39 (m, 1 H); MS (major and minor regioisomers) (DCI/NH_3) m/z 242 $(M + H)^+$.

2-Morpholin-4-ylethyl Methanesulfonate. A solution of 4-(2-hydroxylethyl)morpholine (5.1 mL, 42 mmol) and triethylamine (17 mL, 124 mmol) in 100 mL of THF was cooled to 0 °C, and methanesulfonyl chloride (4.8 mL, 62 mmol) was added dropwise over 5 min. The mixture was stirred at 0 °C for 10 min. Then the ice bath was removed and the reaction mixture was stirred at 23 °C for an additional 2 h. The reaction mixture was filtered though Celite with THF and concentrated under reduced pressure. The crude 2-morpholin-4-ylethyl methanesulfonate was used without further purification or characterization.

4-(2-(1*H*-Indol-1-yl)ethyl)morpholine. To indole (10 g, 85.4 mmol) in 400 mL of dimethylformamide at 0 °C was added NaH (60% dispersion in mineral oil, 10.2 g, 256 mmol) portionwise over 15 min. The mixture was stirred for 10 min at 0 °C and then was allowed to warm to ambient temperature. The mixture was stirred for 1 h at ambient temperature and then was cooled to 0 °C. The 2-morpholin-4-ylethyl methanesulfonate in 10 mL of DMF was added rapidly via cannula. After the addition was complete, the ice bath was removed and the mixture was stirred for 4 h at ambient temperature. The mixture was then cooled to 0 °C, was quenched with 30 mL of saturated, aqueous NH_4Cl and was diluted with 30 mL of EtOAc. The layers were separated, and the aqueous layer was extracted EtOAc (3 × 15 mL). The combined organics were washed with water (1 × 10 mL) and brine (1 × 10 mL) and then were dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by column chromatography (SiO_2, 9:1:0.1 CH_2Cl_2/MeOH/NH_4OH) to give the title compound (17.4 g, 75.6 mmol, 88% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.49 (dd, J = 4.8, 4.8 Hz, 4 H), 2.76 (t, J = 7.0 Hz, 2 H), 3.71 (dd, J = 4.7, 4.7 Hz, 4 H), 4.25 (t, J = 7.1 Hz, 2 H), 6.49 (dd, J = 3.1, 0.7 Hz, 1 H), 7.06-7.26 (m, 3 H), 7.33-7.38 (m, 1 H), 7.62 (d, J = 7.8 Hz, 1 H); MS (DCI/NH_3) m/z 231 $(M + H)^+$.

[1-(2-Morpholin-4-ylethyl)-1*H*-indol-3-yl](2,2,3,3-tetramethylcyclopropyl)methanone *p*-Toluenesulfonic Acid (5). A solution of 4-(2-hydroxylethyl)morpholine (5.1 mL, 42 mmol) and triethylamine (17 mL, 124 mmol) in 100 mL of THF was cooled to 0 °C, and methanesulfonyl chloride (4.8 mL, 62 mmol) was added dropwise over 5 min. The mixture was stirred at 0 °C for 10 min. Then the ice bath was removed and the reaction mixture was stirred at 23 °C for an additional 2 h. The reaction mixture was filtered though Celite with THF and concentrated under reduced pressure. The crude 2-morpholin-4-ylethyl methanesulfonate was used without further purification or characterization.

To a solution of 1*H*-indol-3-yl(2,2,3,3-tetramethylcyclopropyl)methanone (5.0 g, 21 mmol) in 40 mL of dimethylformamide at 0 °C was added NaH (60% dispersal in mineral oil, 4.2 g, 104 mmol). This mixture was stirred at 0 °C for 10 min and then was warmed to ambient temperature and allowed to stir for 30 min. The solution was again cooled to 0 °C, and 2-morpholin-4-ylethyl methanesulfonate (42 mmol) in 10 mL of DMF was added via cannula. The ice bath was removed after the addition was complete, and the reaction mixture was warmed to 45 °C at which temperature it was stirred for 2 h. The mixture was cooled to ambient temperature, diluted with ethyl acetate (10 mL), and quenched with saturated, aqueous NH_4Cl (20 mL) and H_2O (10 mL). The layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 mL), and the combined organics were dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified via column chromatography (SiO_2, 50% hexanes in EtOAc) to provide 6.6 g of [1-(2-morpholin-4-ylethyl)-1*H*-indol-3-yl](2,2,3,3-tetramethylcyclopropyl)methanone (18.6 mmol, 90% yield). ^{1}H NMR (300 MHz, CD_3OD) δ ppm 1.33 (s, 12 H), 2.13 (s, 1 H), 2.46-2.54 (m, 4 H), 2.79 (t, J = 6.4 Hz, 2 H), 3.61−3.71 (m, 4 H), 4.37 (t, J = 6.4 Hz, 2 H), 7.16−7.30 (m, 2 H), 7.45−7.53 (m, 1 H), 8.11 (s, 1 H), 8.20−8.30 (m, 1 H); MS (DCI/NH_3) m/z 355 (M + H)$^+$.

To [1-(2-morpholin-4-ylethyl)-1*H*-indol-3-yl](2,2,3,3-tetramethylcyclopropyl)methanone (6.6 g, 19 mmol) in 25 mL of EtOAc and 5 mL of EtOH was added *p*-toluenesulfonic acid monohydrate (3.5 g, 19 mmol). No precipitate formed after 10 min of stirring so the crude material was concentrated under reduced pressure and dried under reduced pressure to give 9.4 g of **5** (18 mmol, 96% yield). ^{1}H NMR (300 MHz, CD_3OD) δ ppm 1.33 (s, 6H), 1.34 (s, 6H), 2.15 (s, 1H), 2.36 (s, 3H), 3.40 (m, 4H), 3.68 (dd, J = 7.1, 7.1 Hz, 2H), 3.90 (m, 4H), 4.73 (dd, J = 7.1, 7.1 Hz, 2H), 7.23 (br d, J = 7.8 Hz, 2H), 7.26 (ddd, J = 8.1, 8.1, 1.4 Hz, 1H), 7.33 (ddd, J = 7.1, 7.1, 1.0 Hz, 1H), 7.56 (br d, J = 8.1 Hz, 1H), 7.72 (br d, J = 8.5 Hz, 2H), 8.15 (s, 1H), 8.29 (dt, J = 7.8, 1.0 Hz, 1H); MS (DCI/NH_3) m/z 355 (M + H)$^+$. Anal. ($C_{22}H_{30}N_2O_2\cdot C_7H_8O_3S$) C, H, N.

Cyclobutyl(1-(2-morpholinoethyl)-1*H*-indol-3-yl)methanone (6). To a solution of cyclobutanecarbonyl chloride (0.22 mL, 2.0 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added $AlCl_3$ (0.26 g, 2.0 mmol). This mixture was allowed to warm to ambient temperature and was stirred for 15 min. The 4-(2-(1*H*-indol-1-yl)ethyl)-morpholine (0.15 g, 0.65 mmol) in CH_2Cl_2 (4 mL) was added dropwise over 25 min. The mixture was then allowed to stir at ambient temperature for 18 h. The mixture was quenched with saturated, aqueous NH_4Cl (5 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL), and the combined organics were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was recrystallized with EtOAc, MeOH, and Et_2O to give **6** (0.11 g, 0.35 mmol, 54% yield). ^{1}H NMR (300 MHz, CD_3OD) δ ppm 1.85−2.02 (m, 1 H), 2.03−2.22 (m, 1 H), 2.23−2.50 (m, 4 H), 3.18−3.29 (m, 1 H), 3.37−3.59 (m, 2 H), 3.68 (t, J = 7.1 Hz, 2 H), 3.78−3.96 (m, 4 H), 3.96−4.09 (m, 2 H), 4.75 (t, J = 7.1 Hz, 2 H), 7.29 (dt, J = 7.5, 1.0 Hz, 1 H), 7.36 (dt, J = 7.6, 1.4 Hz, 1 H), 7.60 (d, J = 8.1 Hz, 1 H), 8.18 (s, 1 H), 8.31 (d, J = 7.1 Hz, 1 H); MS (DCI/NH_3) m/z 313 (M + H)$^+$. Anal. ($C_{19}H_{24}N_2O_2\cdot 1.3HCl$) C, H, N.

Cyclopentyl(1-(2-morpholinoethyl)-1*H*-indol-3-yl)methanone (7). A mixture of cyclopentanecarboxylic acid (1.1 g, 10 mmol) and $SOCl_2$ (5 mL) was warmed to reflux and was allowed to stir for 2 h. The mixture was then cooled to ambient temperature and concentrated under reduced pressure. The residue was diluted with 10 mL of benzene and concentrated to remove any remaining thionyl chloride. This was repeated two additional times, and the crude cyclopentanecarbonyl chloride was used without further purification or characterization.

To a solution of indole (1.2 g, 10 mmol) in CH_2Cl_2 (30 mL) at ambient temperature was added EtMgBr (11 mL of 1 M solution in THF, 11 mmol) dropwise over 10 min. The solution was stirred for 30 min at which time $ZnCl_2$ (11 mL of a 1 M solution in Et_2O, 11 mmol) was added. The mixture was stirred for an additional 1 h. Then cyclopentanecarbonyl chloride (10 mmol) in CH_2Cl_2 (5 mL) was added dropwise over 10 min. The mixture was stirred for 18 h and then was quenched with saturated, aqueous NH_4Cl (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organics were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude solid which was recrystallized with 20% EtOAc in hexanes to give cyclopentyl(1*H*-indol-3-yl)methanone (0.51 g, 2.4 mmol, 24% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.62−1.72 (m, 2 H), 1.74−1.84 (m, 2 H), 1.88−2.09 (m, 4 H), 3.48−3.62 (m, 1 H), 7.27−7.31 (m, 2 H), 7.39−7.44 (m, 1 H), 7.88 (d, J = 3.1 Hz, 1 H), 8.41−8.47 (m, 1 H), 8.57 (s, 1 H); MS (DCI/NH_3) m/z 214 (M + H)$^+$.

To a mixture of NaH (60% dispersion in mineral oil, 57 mg, 1.4 mmol) in DMF (5 mL) at 0 °C was added cyclopentyl(1*H*-indol-3-yl)methanone (0.10 g, 0.47 mmol) in DMF (3 mL). The mixture was allowed to warm to ambient temperature and was stirred for 1 h. The reaction mixture was cooled to 0 °C, and 2-morpholin-4-ylethyl methanesulfonate (0.94 mmol) in DMF (2 mL) was added. This mixture was warmed to 35 °C and was stirred for 1 h. Then the mixture was warmed to 40 °C and was stirred for 20 h. The mixture was cooled to ambient temperature and was quenched with saturated, aqueous NH_4Cl (5 mL). After dilution with EtOAc (5 mL), the layers were separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organics were dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified via flash column chromatography (SiO_2, 20% hexanes/EtOAc) to provide **7** (14 mg, 0.043 mmol, 9.1% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.61−1.84 (m, 4 H), 1.88−2.05 (m, 4 H), 2.40−2.57 (m, 4 H), 2.72−2.85 (m, 2 H), 3.45−3.60 (m, 1 H), 3.66−3.75 (m, 4 H), 4.21−4.33 (m, 2 H), 7.28−7.41 (m, 2 H), 7.82−7.91 (m, 1 H), 8.02 (s, 1 H), 8.40−8.46 (m, 1 H); MS (DCI/NH_3) m/z 327 (M + H)$^+$. Anal. ($C_{20}H_{26}N_2O_2\cdot 0.2H_2O$) C, H, N.

Cyclohexyl(1-(2-morpholinoethyl)-1*H*-indol-3-yl)methanone (8). A mixture of 4-(2-(1*H*-indol-1-yl)ethyl)morpholine (0.15 g, 0.65 mmol), cyclohexanecarbonyl chloride (0.11 mL, 0.78 mmol), and $AlCl_3$ (0.16 g, 1.2 mmol) in CH_2Cl_2 (5 mL) was processed as described in the procedure for **6** to give **8** (0.12 g, 0.35 mmol, 54% yield). ^{1}H NMR (300 MHz, CD_3OD) δ ppm 1.23−1.39 (m, 1 H), 1.41−1.65 (m, 4 H), 1.73−1.93 (m, 5 H), 2.50 (dd, J = 4.4, 4.4 Hz, 4 H), 2.79 (t, J = 6.4 Hz, 2 H), 3.14−3.27 (m, 1 H), 3.65 (dd, J = 4.8 Hz, 4 H), 4.38 (t, J = 6.4 Hz, 2 H), 7.19−7.33 (m, 2 H), 7.49−7.53 (m, 1 H), 8.23−8.28 (m, 1 H), 8.27 (s, 1 H); MS (DCI/NH_3) m/z 341 (M + H)$^+$. Anal. ($C_{21}H_{28}N_2O_2$) C, H, N.

Cycloheptyl(1-(2-morpholinoethyl)-1*H*-indol-3-yl)methanone (9). A mixture of cycloheptanecarboxylic acid (1.4 mL, 10 mmol) and $SOCl_2$ (5 mL) was warmed to reflux and was allowed to stir for 2 h. The mixture was then cooled to ambient temperature and concentrated under reduced pressure. The residue was diluted with 10 mL of benzene and concentrated to remove any remaining thionyl chloride. This was repeated two additional times, and the crude cycloheptanecarbonyl chloride was used without further purification or characterization.

To a solution of indole (1.2 g, 10 mmol) in CH_2Cl_2 (30 mL) at ambient temperature was added EtMgBr (11 mL of 1 M solution in THF, 11 mmol) dropwise over 10 min. The solution was stirred for 30 min at which time $ZnCl_2$ (11 mL of a 1 M solution in Et_2O, 11 mmol) was added. The mixture was stirred for an additional 1 h. Then cycloheptanecarbonyl chloride (10 mmol) in CH_2Cl_2 (5 mL) was added dropwise over 10 min. The mixture was stirred for 18 h and then was quenched with saturated, aqueous NH_4Cl (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organics were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude solid which was recrystallized with 20% EtOAc in hexanes to give cycloheptyl(1*H*-indol-3-yl)methanone (0.92 g, 3.8 mmol, 38% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.56−2.04 (m, 12 H), 3.33−3.43 (m, 1 H), 7.14−7.26 (m, 2 H), 7.40−7.47 (m, 1 H), 8.14 (s, 1 H), 8.21−8.29 (m, 1 H); MS (DCI/NH_3) m/z 242 (M + H)$^+$.

To a mixture of NaH (60% dispersion in mineral oil, 50 mg, 1.2 mmol) in DMF (5 mL) at 0 °C was added cycloheptyl(1*H*-indol-3-yl)methanone (0.10 g, 0.42 mmol) in DMF (2 mL). The mixture was allowed to warm to ambient temperature and was stirred for 1 h. The reaction mixture was cooled to 0 °C, and 2-morpholin-4-ylethyl methanesulfonate (0.83 mmol) in DMF (2 mL) was added. This mixture was warmed to 35 °C and was stirred for 1 h. The mixture was cooled to ambient temperature and was quenched with saturated, aqueous NH_4Cl (5 mL). After dilution with EtOAc (5 mL), the layers were separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organics were dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified via flash column chromatography (SiO_2, 20% hexanes/EtOAc) to provide **9** (78 mg, 0.22 mmol, 52% yield). ^{1}H NMR (300 MHz,

$CDCl_3$) δ ppm 1.59−1.69 (m, 6 H), 1.74−1.91 (m, 4 H), 1.92−2.04 (m, 2 H), 2.44−2.57 (m, 4 H), 2.79 (t, J = 6.1 Hz, 2 H), 3.13−3.25 (m, 1 H), 3.63−3.75 (m, 4 H), 4.26 (t, J = 5.9 Hz, 2 H), 7.27−7.40 (m, 3 H), 7.86 (s, 1 H), 8.38−8.47 (m, 1 H); MS (DCI/NH_3) m/z 355 $(M + H)^+$. Anal. ($C_{20}H_{26}N_2O_2$· 0.2H_2O) C, H, N.

(*trans*-4-Ethylcyclohexyl)(1-(2-morpholinoethyl)-1*H*-indol-3-yl)-methanone (10). A mixture of *trans*-(4-ethylcyclohexane)carboxylic acid (0.19 g, 1.2 mmol) and $SOCl_2$ (5 mL) was warmed to reflux and was allowed to stir for 2 h. The mixture was then cooled to ambient temperature and concentrated under reduced pressure. The residue was diluted with 10 mL of benzene and concentrated to remove any remaining thionyl chloride. This was repeated two additional times, and the crude *trans*-(4-ethylcyclohexane)carbonyl chloride was used without further purification or characterization.

A mixture of 4-(2-(1*H*-indol-1-yl)ethyl)morpholine (0.23 g, 1.0 mmol), *trans*-(4-ethylcyclohexane)carbonyl chloride (1.2 mmol), and $AlCl_3$ (0.24 g, 1.8 mmol) in CH_2Cl_2 (5 mL) was processed as described in the procedure for **6** to give **10** (0.28 g, 0.76 mmol, 76% yield). ^1H NMR (300 MHz, $CDCl_3$) δ ppm 0.92 (t, J = 7.1 Hz, 3 H), 0.96−1.11 (m, 2 H), 1.16−1.34 (m, 3 H), 1.53−1.76 (m, 2 H), 1.86−2.02 (m, 4 H), 2.44−2.56 (m, 4 H), 2.78 (t, J = 5.9 Hz, 2 H), 2.98 (tt, J = 11.9, 3.4 Hz, 1 H), 3.62−3.78 (m, 4 H), 4.26 (t, J = 5.9 Hz, 2 H), 7.27−7.41 (m, 3 H), 7.88 (s, 1 H), 8.36−8.45 (m, 1 H); MS (DCI/NH_3) m/z 369 $(M + H)^+$. Anal. ($C_{23}H_{32}N_2O_2$) C, H, N.

(*trans*-4-Isopropylcyclohexyl)(1-(2-morpholinoethyl)-1*H*-indol-3-yl)methanone (11). A mixture of *trans*-(isopropylhexane)carboxylic acid (0.32 g, 2.0 mmol) and $SOCl_2$ (5 mL) was warmed to reflux and was allowed to stir for 2 h. The mixture was then cooled to ambient temperature and concentrated under reduced pressure. The residue was diluted with 10 mL of benzene and concentrated to remove any remaining thionyl chloride. This was repeated two additional times, and the crude *trans*-(isopropylhexane)carbonyl chloride was used without further purification or characterization.

A mixture of 4-(2-(1*H*-indol-1-yl)ethyl)morpholine (0.15 g, 0.65 mmol), *trans*-(isopropylhexane)carbonyl chloride (2.0 mmol), and $AlCl_3$ (0.26 g, 2.0 mmol) in CH_2Cl_2 (10 mL) was processed as described in the procedure for **6** to give **11** (0.18 g, 0.43 mmol, 66% yield). ^1H NMR (300 MHz, CD_3OD) δ ppm 0.93 (d, J = 7.1 Hz, 6 H), 1.13−1.31 (m, 3 H), 1.40−1.67 (m, 3 H), 1.83−2.00 (m, 4 H), 3.14 (tt, J = 11.9, 3.3 Hz, 1 H), 3.21−3.61 (m, 4 H), 3.69 (t, J = 7.3 Hz, 2 H), 3.77−4.14 (m, 4 H), 4.75 (t, J = 7.1 Hz, 2 H), 7.29 (dt, J = 7.5, 1.4 Hz, 1 H), 7.36 (dt, J = 7.6, 1.4 Hz, 1 H), 7.57−7.63 (m, 1 H), 8.27−8.32 (m, 1 H), 8.33 (s, 1 H); MS (DCI/NH_3) m/z 383 $(M + H)^+$. Anal. ($C_{24}H_{34}N_2O_2$·HCl) C, H, N.

(1-(2-Morpholinoethyl)-1*H*-indol-3-yl)(2,2,3,3-tetrafluoro-1-methylcyclobutyl)methanone (12). To a solution of indole (0.57 g, 4.9 mmol) in CH_2Cl_2 (50 mL) at ambient temperature was added EtMgBr (5.4 mL of 1 M solution in THF, 5.4 mmol) dropwise over 10 min. The solution was stirred for 30 min at which time $ZnCl_2$ was added (5.4 mL of a 1 M solution in Et_2O, 5.4 mmol). The mixture was stirred for an additional 1 h. Then 2,2,3,3-tetrafluoro-1(methyl)cyclobutanecarbonyl chloride (ABCR, 1.0 g, 4.9 mmol) in CH_2Cl_2 (5 mL) was added dropwise over 10 min. The mixture was stirred for 3 h and then was quenched with saturated, aqueous NH_4Cl (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organics were dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified via flash column chromatography (SiO_2, 50% hexanes/EtOAc) to give (1*H*-indol-3-yl)-(2,2,3,3-tetrafluoro-1-methylcyclobutyl)methanone (0.40 g, 1.4 mmol, 29% yield). ^1H NMR (300 MHz, $CDCl_3$) δ ppm 1.71 (s, 3 H), 2.26−2.44 (m, 1 H), 3.26−3.49 (m, 1 H), 7.30−7.39 (m, 2 H), 7.40−7.49 (m, 1 H), 7.83−7.91 (m, 1 H), 8.39−8.47 (m, 1 H), 8.70 (s, 1 H); MS (DCI/NH_3) m/z 303 $(M + NH_4)^+$.

To a mixture of NaH (60% dispersion in mineral oil, 84 mg, 2.1 mmol) in DMF (15 mL) at 0 °C was added (1*H*-indol-3-yl)(2,2,3,3-tetrafluoro-1-methylcyclobutyl)methanone (0.15 g, 0.53 mmol) in DMF (2 mL). The mixture was allowed to warm to ambient temperature and was stirred for 1 h. The reaction mixture was cooled to 0 °C, and 2-morpholin-4-ylethyl methanesulfonate (0.16 mmol) in DMF (2 mL) was added. This mixture was warmed to 35 °C and was stirred for 1 h. The mixture was cooled to ambient temperature and was quenched with saturated, aqueous NH_4Cl (5 mL). After dilution with EtOAc (5 mL), the layers were separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organics were dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified via flash column chromatography (SiO_2, 20% hexanes/EtOAc) to provide **12** (39 mg, 0.10 mmol, 19% yield). ^1H NMR (300 MHz, $CDCl_3$) δ ppm 1.72 (s, 3 H), 2.27−2.44 (m, 1 H), 2.47−2.55 (m, 4 H), 2.80 (t, J = 5.6 Hz, 2 H), 3.26−3.50 (m, 1 H), 3.64−3.77 (m, 4 H), 4.28 (t, J = 5.6 Hz, 2 H), 7.31−7.40 (m, 3 H), 7.96 (s, 1 H), 8.43 (dd, J = 5.8, 4.1 Hz, 1 H); MS (DCI/NH_3) m/z 399 $(M + H)^+$. Anal. ($C_{20}H_{22}F_4N_2O_2$) C, H, N.

(2,2-Dichloro-1-methylcyclopropyl)(1-(2-morpholinoethyl)-1*H*-indol-3-yl)methanone (13). A mixture of 2,2-dichloro-1-methylcycloproanecarboxylic acid (1 g, 5.9 mmol) and $SOCl_2$ (10 mL) was warmed to reflux and was allowed to stir for 2 h. The mixture was then cooled to ambient temperature and concentrated under reduced pressure. The residue was diluted with 10 mL of benzene and concentrated to remove any remaining thionyl chloride. This was repeated two additional times, and the crude 2,2-dichloro-1-methylcycloproanecarbonyl chloride was used without further purification or characterization.

To a solution of indole (0.69 g, 5.9 mmol) in CH_2Cl_2 (30 mL) at ambient temperature was added EtMgBr (6.5 mL of 1 M solution in THF, 6.5 mmol) dropwise over 10 min. The solution was stirred for 30 min at which time $ZnCl_2$ was added (6.5 mL of a 1 M solution in Et_2O, 6.5 mmol). The mixture was stirred for an additional 1 h. Then 2,2-dichloro-1-methylcycloproanecarbonyl chloride (5.9 mmol) in CH_2Cl_2 (5 mL) was added dropwise over 10 min. The mixture was stirred for 17 h and then was quenched with saturated, aqueous NH_4Cl (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organics were dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified via flash column chromatography (SiO_2, 50% hexanes in EtOAc) to give (2,2-dichloro-1-methylcyclopropyl)-(1*H*-indol-3-yl)methanone (0.36 g, 1.3 mmol, 23% yield). ^1H NMR (300 MHz, $CDCl_3$) δ ppm 1.48 (d, J = 7.1 Hz, 1 H), 1.77 (s, 3 H), 2.27 (d, J = 7.5 Hz, 1 H), 7.29−7.38 (m, 2 H), 7.42−7.50 (m, 1 H), 7.93 (d, J = 3.1 Hz, 1 H), 8.32−8.41 (m, 1 H), 8.69 (s, 1 H); MS (DCI/NH_3) m/z 267 $(M + H)^+$.

To a mixture of NaH (60% dispersion in mineral oil, 72 mg, 1.8 mmol) in DMF (10 mL) at 0 °C was added (2,2-dichloro-1-methylcyclopropyl)(1*H*-indol-3-yl)methanone (0.16 g, 0.60 mmol) in DMF (2 mL). The mixture was allowed to warm to ambient temperature and was stirred for 1 h. The reaction mixture was cooled to 0 °C, and 2-morpholin-4-ylethyl methanesulfonate (1.0 mmol) in DMF (2 mL) was added. This mixture was warmed to 40 °C and was stirred for 1 h. The mixture was cooled to ambient temperature and was quenched with saturated, aqueous NH_4Cl (5 mL). After dilution with EtOAc (5 mL), the layers were separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organics were dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified via flash column chromatography (SiO_2, 20% hexanes/EtOAc) to provide **13** (0.22 g, 0.58 mmol, 96% yield). ^1H NMR (300 MHz, $CDCl_3$) δ ppm 1.48 (d, J = 7.5 Hz, 1 H), 1.78 (s, 3 H), 2.26 (d, J = 7.5 Hz, 1 H), 2.46−2.60 (m, 4 H), 2.84 (t, J = 5.4 Hz, 2 H), 3.67−3.78 (m, 4 H), 4.32 (t, J = 5.4 Hz, 2 H), 7.30−7.45 (m, 3 H), 8.00 (s, 1 H), 8.33−8.42 (m, 1 H); MS (DCI/NH_3) m/z 381 $(M + H)^+$. Anal. ($C_{19}H_{22}Cl_2N_2O_2$) C, H, N.

(*R*)-(1-(2-Morpholinoethyl)-1*H*-indol-3-yl)(spiro[2.5]octan-1-yl)-methanone (14). A mixture of (1*R*)-spiro[2.5]octane-1-carboxylic acid (1.5 g, 10 mmol, Chemstep) and $SOCl_2$ (5 mL) was warmed to reflux and was allowed to stir for 2 h. The mixture was then cooled to ambient temperature and concentrated under reduced pressure. The residue was diluted with 10 mL of benzene and concentrated to remove any remaining thionyl chloride. This was repeated two additional times, and the crude (1*R*)-spiro[2.5]octane-1-carbonyl chloride was used without further purification or characterization.

To a solution of indole (1.2 g, 10 mmol) in CH_2Cl_2 (30 mL) at ambient temperature was added EtMgBr (11 mL of 1 M solution in THF, 11 mmol) dropwise over 10 min. The solution was stirred for 30 min at which time $ZnCl_2$ was added (11 mL of a 1 M solution in Et_2O, 11 mmol). The mixture was stirred for an additional 1 h. Then (1*R*)-spiro[2.5]octane-1-carbonyl chloride (10 mmol) in CH_2Cl_2 (5 mL) was added dropwise over 10 min. The mixture was stirred for 17 h and then was quenched with saturated, aqueous NH_4Cl (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organics were dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified via flash column chromatography (SiO_2, 40% hexanes in EtOAc) to give (*R*)-(1*H*-indol-3-yl)(spiro[2.5]octan-1-yl)methanone (0.75 g, 3.0 mmol, 30% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 0.87 (dd, *J* = 7.5, 4.1 Hz, 1 H), 1.40−1.66 (m, 11 H), 2.36 (dd, *J* = 7.5, 5.4 Hz, 1 H), 7.24−7.33 (m, 2 H), 7.36−7.47 (m, 1 H), 7.96 (d, *J* = 3.1 Hz, 1 H), 8.42 (dd, *J* = 6.3, 2.5 Hz, 1 H), 8.65 (s, 1 H); MS (DCI/NH_3) *m*/*z* 254 $(M + H)^+$.

To a mixture of NaH (60% dispersion in mineral oil, 95 mg, 2.4 mmol) in DMF (10 mL) at 0 °C was added (*R*)-(1*H*-indol-3-yl)(spiro[2.5]octan-1-yl)methanone (0.20 g, 0.79 mmol) in DMF (2 mL). The mixture was allowed to warm to ambient temperature and was stirred for 1 h. The reaction mixture was cooled to 0 °C, and 2-morpholin-4-ylethyl methanesulfonate (1.6 mmol) in DMF (2 mL) was added. This mixture was stirred at ambient temperature for 2 h. The mixture was cooled to ambient temperature and was quenched with saturated, aqueous NH_4Cl (5 mL). After dilution with EtOAc (5 mL), the layers were separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organics were dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified via flash column chromatography (SiO_2, 20% hexanes/EtOAc) to provide **14** (0.21 g, 0.57 mmol, 73% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 0.86 (dd, *J* = 7.3, 3.9 Hz, 1 H), 1.19−1.32 (m, 1 H), 1.40−1.69 (m, 6 H), 2.32 (dd, *J* = 7.5, 5.4 Hz, 1 H), 2.43−2.59 (m, 4 H), 2.78−2.85 (m, 2 H), 3.62−3.81 (m, 4 H), 3.70 (s, 4 H), 4.22−4.34 (m, 2 H), 7.27−7.40 (m, 3 H), 7.95 (s, 1 H), 8.37−8.46 (m, 1 H); MS (DCI/NH_3) *m*/*z* 367 $(M + H)^+$. Anal. ($C_{23}H_{30}N_2O_2 \cdot H_2O$) C, H, N.

[1-(2-Morpholin-4-ylethyl)-1*H*-indol-3-yl](3-noradamantane)-methanone (14). A mixture of 3-noradamantanecarboxylic acid (1.1 g, 6.4 mmol) and $SOCl_2$ (10 mL) was warmed to reflux and was allowed to stir for 2 h. The mixture was then cooled to ambient temperature and concentrated under reduced pressure. The residue was diluted with 10 mL of benzene and concentrated to remove any remaining thionyl chloride. This was repeated two additional times, and the crude 3-noradamantanecarbonyl chloride was used without further purification or characterization.

To a solution of indole (0.5 g, 4.3 mmol) in CH_2Cl_2 (20 mL) at ambient temperature was added EtMgBr (5.1 mL of 1 M solution in THF, 5.1 mmol) dropwise over 10 min. The solution was stirred for 30 min at which time $ZnCl_2$ was added (5.1 mL of a 1 M solution in Et_2O, 5.1 mmol). The mixture was stirred for an additional 1 h. Then 3-noradamantanecarbonyl chloride (6.4 mmol) in CH_2Cl_2 (5 mL) was added dropwise over 10 min. The mixture was stirred for 18 h and then was quenched with saturated, aqueous NH_4Cl (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organics were dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified via column chromatography (SiO_2, 60% hexanes in EtOAc) to give (1*H*-indol-3-yl)(3-noradamantyl)methanone (0.88 g, 3.3 mmol, 77% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.57−1.88 (m, 4 H), 1.92−2.03 (m, 3 H), 2.06−2.14 (m, 1 H), 2.25−2.33 (m, 3 H), 2.41 (s, 2 H), 7.27−7.33 (m, 2 H), 7.37−7.43 (m, 1 H), 7.91 (d, *J* = 2.7 Hz, 1 H), 8.44 (s, 1 H), 8.52−8.58 (m, 1 H); MS (DCI/NH_3) *m*/*z* 266 $(M + H)^+$.

To a mixture of NaH (60% dispersion in mineral oil, 0.24 g, 6.1 mmol) in DMF (20 mL) at 0 °C was added 1*H*-indol-3-yl)(3-noradamantyl)methanone (0.54 g, 2.0 mmol) in DMF (2 mL). The mixture was allowed to warm to ambient temperature and was stirred for 1 h. The reaction mixture was cooled to 0 °C, and 2-morpholin-4-ylethyl methanesulfonate (4.1 mmol) in DMF (2 mL) was added. This mixture was stirred at 40 °C for 16 h. The mixture was cooled to ambient temperature and was quenched with saturated, aqueous NH_4Cl (5 mL). After dilution with EtOAc (5 mL), the layers were separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organics were dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified via flash column chromatography (SiO_2, 20% hexanes/EtOAc) to provide **15** (0.43 g, 1.1 mmol, 56% yield). ^{1}H NMR (300 MHz, CD_3OD) δ ppm 1.74−1.85 (m, 3 H), 2.03−2.12 (m, 2 H), 2.26 (d, *J* = 11.5 Hz, 2 H), 2.41 (s, 2 H), 2.46−2.55 (m, 5 H), 2.77 (t, *J* = 5.9 Hz, 2 H), 3.08 (t, *J* = 6.6 Hz, 1 H), 3.62−3.70 (m, 6 H), 4.39 (t, *J* = 5.9 Hz, 2 H), 7.18−7.30 (m, 2 H), 7.49 (d, *J* = 7.8 Hz, 1 H), 8.19 (s, 1 H), 8.34 (d, *J* = 7.5 Hz, 1 H); MS (DCI/NH_3) *m*/*z* 379 $(M + H)^+$. Anal. ($C_{24}H_{30}N_2O_2$) C, H, N.

[1-(Tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-indol-3-yl](2,2,3,3-tetramethylcyclopropyl)methanone (16). To tetrahydropyran-4-methanol (Combi-Blocks, Inc., 0.15 g, 1.2 mmol) in 10 mL of THF was added triethylamine (0.56 mL, 4.1 mmol) followed by methanesulfonyl chloride (0.15 mL, 1.9 mmol). The mixture was stirred at 0 °C for 10 min. Then the ice bath was removed and the reaction mixture was stirred at 23 °C for an additional 1.5 h. The reaction mixture was filtered though Celite with THF and concentrated under reduced pressure. The crude tetrahydro-2*H*-pyran-4-ylmethyl methanesulfonate was used without further purification or characterization.

To a solution of 1*H*-indol-3-yl(2,2,3,3-tetramethylcyclopropyl)methanone (0.15 g, 0.62 mmol) in 8 mL of DMF at 0 °C was added NaH (60% dispersion in mineral oil, 0.12 g, 3.1 mmol). This mixture was stirred at 0 °C for 10 min and then was warmed to ambient temperature and allowed to stir for 30 min. The solution was again cooled to 0 °C, and tetrahydro-2*H*-pyran-4-ylmethyl methanesulfonate (2.1 mmol) in 5 mL DMF was added via cannula. The ice bath was removed after the addition was complete, and the reaction mixture was warmed to 45 °C at which temperature it was stirred for 2 h. The mixture was cooled to ambient temperature, diluted with 10 mL of ethyl acetate, and quenched with 10 mL of saturated, aqueous NH_4Cl, and 5 mL of H_2O. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 5 mL). The combined organics were dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified via column chromatography (SiO_2, 50% hexanes in EtOAc) to give 0.19 g of **16** (0.56 mmol, 90% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.31 (s, 6H), 1.35 (s, 6H), 1.46 (m, 4H), 1.94 (s, 1H), 2.16 (m, 1H), 3.33 (dt, *J* = 11.5, 2.4 Hz, 2H), 3.98 (dd, *J* = 10.5, 3.1 Hz, 2H), 4.04 (d, *J* = 7.5 Hz, 2H), 7.27 (m, 2H), 7.33 (m, 1H), 7.61 (s, 1H), 8.40 (m, 1H); MS (DCI/NH_3) *m*/*z* 340 $(M + H)^+$. Anal. ($C_{22}H_{29}NO_2$) C, H, N.

Cyclopentyl(1-((tetrahydro-2*H*-pyran-4-yl)methyl)-1*H*-indol-3-yl)methanone (17). To a mixture of NaH (60% dispersion in mineral oil, 57 mg, 1.4 mmol) in DMF (5 mL) at 0 °C was added cyclopentyl(1*H*-indol-3-yl)methanone (0.10 g, 0.47 mmol, as described in the procedure for **7**) in DMF (3 mL). The mixture was allowed to warm to ambient temperature and was stirred for 1 h. The reaction mixture was cooled to 0 °C, and tetrahydro-2*H*-pyran-4-ylmethyl methanesulfonate (0.94 mmol, as described in the procedure for **16**) in DMF (2 mL) was added. This mixture was warmed to 35 °C and was stirred for 1 h. Then the mixture was warmed to 40 °C and was stirred for 20 h. The mixture was cooled to ambient temperature and was quenched with saturated, aqueous NH_4Cl (5 mL). After dilution with EtOAc (5 mL), the layers were separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organics were dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified via flash column chromatography (SiO_2, 50% hexanes/EtOAc) to provide **17** (48 mg, 0.15 mmol, 33% yield). ^1H NMR (300 MHz, $CDCl_3$) δ ppm 1.35−1.48 (m, 2 H), 1.50−1.55 (m, 2 H), 1.60−1.72 (m, 2 H), 1.74−1.83 (m, 2 H), 1.88−2.04 (m, 4 H), 2.08−2.22 (m, 1 H), 3.33 (dt, J = 11.6, 2.5 Hz, 2 H), 3.46−3.61 (m, 1 H), 3.98 (dd, J = 11.2, 3.4 Hz, 2 H), 4.05 (d, J = 7.1 Hz, 2 H), 7.28−7.38 (m, 3 H), 7.72 (s, 1 H), 8.38−8.46 (m, 1 H); MS (DCI/NH_3) m/z 312 $(M + H)^+$. Anal. ($C_{20}H_{25}NO_2 \cdot 0.2H_2O$) C, H, N.

(2,2,3,3-Tetrafluoro-1-methylcyclobutyl)(1-((tetrahydro-2*H*-pyran-4-yl)methyl)-1*H*-indol-3-yl)methanone (18). To a mixture of NaH (60% dispersion in mineral oil, 84 mg, 2.1 mmol) in DMF (15 mL) at 0 °C was added (1*H*-indol-3-yl)(2,2,3,3-tetrafluoro-1-methylcyclobutyl)methanone (0.15 g, 0.53 mmol, as described in the procedure for **12**) in DMF (2 mL). The mixture was allowed to warm to ambient temperature and was stirred for 1 h. The reaction mixture was cooled to 0 °C, and tetrahydro-2*H*-pyran-4-ylmethyl methanesulfonate (1.05 mmol, as described in the procedure for **16**) in DMF (2 mL) was added. This mixture was warmed to 35 °C and was stirred for 1 h. The mixture was cooled to ambient temperature and was quenched with saturated, aqueous NH_4Cl (5 mL). After dilution with EtOAc (5 mL), the layers were separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organics were dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified via flash column chromatography (SiO_2, 50% hexanes/EtOAc) to provide **18** (37 mg, 0.10 mmol, 18% yield). ^1H NMR (300 MHz, $CDCl_3$) δ ppm 1.37−1.55 (m, 4 H), 1.71 (s, 3 H), 2.07−2.22 (m, 1 H), 2.25−2.44 (m, 1 H), 3.26−3.39 (m, 3 H), 3.95−4.03 (m, 2 H), 4.03−4.19 (m, 2 H), 7.31−7.41 (m, 3 H), 7.67 (d, J = 1.7 Hz, 1 H), 8.37−8.47 (m, 1 H); MS (DCI/NH_3) m/z 384 $(M + H)^+$. Anal. ($C_{20}H_{21}F_4NO_2$) C, H, N.

(2,2-Dichloro-1-methylcyclopropyl)(1-((tetrahydro-2*H*-pyran-4-yl)methyl)-1*H*-indol-3-yl)methanone (19). To a mixture of NaH (60% dispersion in mineral oil, 82 mg, 2.0 mmol) in DMF (10 mL) at 0 °C was added (2,2-dichloro-1-methylcyclopropyl)(1*H*-indol-3-yl)methanone (0.18 g, 0.68 mmol, as described in the procedure for **13**) in DMF (2 mL). The mixture was allowed to warm to ambient temperature and was stirred for 1 h. The reaction mixture was cooled to 0 °C, and tetrahydro-2*H*-pyran-4-ylmethyl methanesulfonate (1.2 mmol, as described in the procedure for **16**) in DMF (2 mL) was added. This mixture was warmed to 40 °C and was stirred for 16 h. The mixture was cooled to ambient temperature and was quenched with saturated, aqueous NH_4Cl (5 mL). After dilution with EtOAc (5 mL), the layers were separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organics were dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified via flash column chromatography (SiO_2, 20% hexanes/EtOAc) to provide **19** (60 mg, 0.16 mmol, 24% yield). ^1H NMR (300 MHz, $CDCl_3$) δ ppm 1.38−1.59 (m, 5 H), 1.76 (s, 3 H), 2.10−2.21 (m, 1 H), 2.25 (d, J = 7.5 Hz, 1 H), 3.34 (dq, J = 11.6, 6.2, 2.5 Hz, 2 H), 3.99 (dt, J = 11.6, 2.2 Hz, 2 H), 4.12 (td, J = 24.6, 14.2, 7.3 Hz, 2 H), 7.30−7.42 (m, 3 H), 7.73 (s, 1 H), 8.36 (dd, J = 5.6, 3.6 Hz, 1 H); MS (DCI/NH_3) m/z 366 $(M + H)^+$. Anal. ($C_{19}H_{21}Cl_2NO_2 \cdot 0.1C_6H_{14}$) C, H, N.

(*R*)-Spiro[2.5]octan-1-yl(1-((tetrahydro-2*H*-pyran-4-yl)methyl)-1*H*-indol-3-yl)methanone (20). To a mixture of NaH (60% dispersion in mineral oil, 70 mg, 1.7 mmol) in DMF (10 mL) at 0 °C was added (*R*)-(1*H*-indol-3-yl)(spiro[2.5]octan-1-yl)methanone (0.15 g, 0.58 mmol, as described in the procedure for **14**) in DMF (2 mL). The mixture was allowed to warm to ambient temperature and was stirred for 1 h. The reaction mixture was cooled to 0 °C, and tetrahydro-2*H*-pyran-4-ylmethyl methanesulfonate (1.2 mmol, as described in the procedure for **16**) in DMF (2 mL) was added. This mixture was stirred at ambient temperature for 2 h. The mixture was cooled to ambient temperature and was quenched with saturated, aqueous NH_4Cl (5 mL). After dilution with EtOAc (5 mL), the layers were separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organics were dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified via flash column chromatography (SiO_2, 20% hexanes/EtOAc) to provide **20** (96 mg, 0.27 mmol, 47% yield). ^1H NMR (300 MHz, $CDCl_3$) δ ppm 0.85 (dd, J = 7.6, 3.9 Hz, 1 H), 1.17−1.29 (m, 1 H), 1.38−1.69 (m, 14 H), 2.09−2.24 (m, 1 H), 2.33 (dd, J = 7.8, 5.4 Hz, 1 H), 3.25−3.41 (m, 2 H), 3.93−4.02 (m, 2 H), 4.07 (d, J = 7.1 Hz, 2 H), 7.26−7.36 (m, 3 H), 7.79 (s, 1 H), 8.38−8.44 (m, 1 H); MS (DCI/NH_3) m/z 352 $(M + H)^+$. Anal. ($C_{23}H_{29}NO_2$) C, H, N.

[1-((Tetrahydro-2*H*-pyran-4-yl)methyl](3-noradamantane)methanone (21). To a mixture of NaH (60% dispersion in mineral oil, 0.14 g, 3.6 mmol) in DMF (10 mL) at 0 °C was added (1*H*-indol-3-yl)(3-noradamantyl)methanone (0.32 g, 1.2 mmol, as described in the procedure for **15**) in DMF (5 mL). The mixture was allowed to warm to ambient temperature and was stirred for 1 h. The reaction mixture was cooled to 0 °C, and tetrahydro-2*H*-pyran-4-ylmethyl methanesulfonate (2.4 mmol, as described in the procedure for **16**) in DMF (2 mL) was added. This mixture was stirred at 40 °C for 16 h. The mixture was cooled to ambient temperature and was quenched with saturated, aqueous NH_4Cl (5 mL). After dilution with EtOAc (5 mL), the layers were separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organics were dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified via flash column chromatography (SiO_2, 20% hexanes/EtOAc) to provide **21** (0.18 g, 0.50 mmol, 41% yield). ^1H NMR (300 MHz, CD_3OD) δ ppm 1.37−1.56 (m, 4 H), 1.57−1.67 (m, 2 H), 1.70−1.73 (m, 1 H), 1.77 (dd, J = 11.4, 2.9 Hz, 2 H), 1.93−2.06 (m, 3 H), 2.07−2.20 (m, 1 H), 2.26 (d, J = 11.5 Hz, 2 H), 2.42 (s, 2 H), 3.07 (t, J = 6.4 Hz, 1 H), 3.33 (dt, J = 11.7, 2.4 Hz, 2 H), 3.93−4.02 (m, 2 H), 4.05 (d, J = 7.1 Hz, 2 H), 7.28−7.37 (m, 3 H), 7.73 (s, 1 H), 8.49−8.63 (m, 1 H); MS (DCI/NH_3) m/z 364 $(M + H)^+$. Anal. ($C_{24}H_{29}NO_2$) C, H, N.

(2-Oxatricyclo[3.3.1.13,7]dec-1-yl)-[1-(tetrahydropyran-4-ylmethyl)-1*H*-indol-3-yl]methanone (22). The 2-oxaadamantane-1-carboxylic acid methyl ester was obtained as described in the literature.[37] The 2-oxaadamantane-1-carboxylic acid methyl ester (7.1 g, 36 mmol) was dissolved in 50 mL of CH_3OH and 50 mL of H_2O, and 5 N NaOH was added (11 mL, 54.3 mmol). This mixture was stirred at ambient temperature for 2 h and then was concentrated under reduced pressure to remove the methanol. The remaining aqueous material was extracted with CH_2Cl_2 (1 × 10 mL) to remove any remaining ester. The aqueous material was then cooled to 0 °C and acidified with 6 N HCl until pH ≈ 2 was obtained. The resulting solution was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organics were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give 2-oxaadamantane-1-carboxylic acid (5.5 g, 30 mmol, 83% yield). ^1H NMR (300 MHz, $CDCl_3$) δ ppm 1.57−1.72 (m, 2 H), 1.85−2.18 (m, 8 H), 2.24 (s, 2 H), 4.21−4.35 (m, 1 H); MS (DCI/NH_3) m/z 200 $(M + NH_4)^+$.

A solution of 2-oxaadamantane-1-carboxylic acid (0.21 g, 1.1 mmol) in 3 mL of $SOCl_2$ was warmed to reflux and was allowed to stir for 2 h. The mixture was cooled to ambient temperature and concentrated under reduced pressure. The crude material was diluted with 5 mL of toluene and concentrated under reduced pressure. This dilution with toluene and concentration were repeated two additional times to give the crude 2-oxaadamantane-1-carbonyl chloride which was used without additional purification or characterization.

To a solution of indole (88 mg, 0.75 mmol) in CH_2Cl_2 (10 mL) at ambient temperature was added EtMgBr (0.90 mL of 1 M solution in THF, 0.90 mmol) dropwise over 10 min. The solution was stirred for 30 min at which time $ZnCl_2$ was added (0.90 mL of 1 M solution in Et_2O, 0.90 mmol). The mixture was stirred for an additional 1 h. Then 2-oxaadamantane-1-carbonyl chloride (1.1 mmol) in CH_2Cl_2 (5 mL) was added dropwise over 10 min. The mixture was stirred for 18 h and then was quenched with saturated, aqueous NH_4Cl (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organics were dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified via column chromatography (SiO_2, 60% hexanes in EtOAc) to give (2-oxatricyclo[3.3.1.13,7]dec-1-yl)-[1*H*-indol-3-yl]methanone (90 mg, 0.32 mmol, 43% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.59−2.33 (m, 7 H), 3.44 (t, J = 6.4 Hz, 1 H), 4.16−4.27 (m, 3 H), 4.34 (t, J = 3.7 Hz, 2 H), 7.27−7.30 (m, 2 H), 7.37−7.43 (m, 1 H), 8.37−8.51 (m, 1 H), 8.48−8.55 (m, 1 H), 8.65 (d, J = 2.7 Hz, 1 H); MS (DCI/NH_3) m/z 282 $(M + H)^+$.

To a mixture of NaH (60% dispersion in mineral oil, 60 mg, 1.5 mmol) in DMF (10 mL) at 0 °C was added (2-oxatricyclo-[3.3.1.13,7]dec-1-yl)-[1*H*-indol-3-yl]methanone (88 mg, 0.31 mmol) in DMF (5 mL). The mixture was allowed to warm to ambient temperature and was stirred for 1 h. The reaction mixture was cooled to 0 °C, and tetrahydro-2*H*-pyran-4-yl-methyl methanesulfonate (0.53 mmol, as described in the procedure for **16**) in DMF (2 mL) was added. This mixture was stirred at 40 °C for 24 h. The mixture was cooled to ambient temperature and was quenched with saturated, aqueous NH_4Cl (5 mL). After dilution with EtOAc (5 mL), the layers were separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organics were dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified via flash column chromatography (SiO_2, 20% hexanes/EtOAc) to provide **22** (24 mg, 0.063 mmol, 20% yield). ^{1}H NMR (300 MHz, CD_3OD) δ ppm ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.39−1.52 (m, 2 H), 1.50−1.57 (m, 3 H), 1.70−1.81 (m, 2 H), 1.91−1.99 (m, 2 H), 2.02−2.18 (m, 6 H), 2.23−2.34 (m, 2 H), 3.33 (dt, J = 11.7, 2.4 Hz, 2 H), 3.94−4.01 (m, 2 H), 4.04 (d, J = 7.5 Hz, 2 H), 4.36 (s, 1 H), 7.26−7.36 (m, 3 H), 8.45 (s, 1 H), 8.48−8.55 (m, 1 H); MS (DCI/NH_3) m/z 380 $(M + H)^+$. Anal. ($C_{24}H_{29}NO_3 \cdot 0.3H_2O$) C, H, N.

(1-(2-Aminoethyl)-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)-methanone (23). To a mixture of **48** (0.46 g, 1.6 mmol) in THF (15 mL) at 0 °C was added Et_3N (0.74 mL, 5.3 mmol) followed by methanesulfonyl chloride (0.27 mL, 3.6 mmol). This mixture was stirred at 0 °C for 1.5 h and then was filtered through Celite, and the filtrate was concentrated under reduced pressure. The crude mesylate was dissolved in DMF (10 mL), and NaN_3 (0.31 g, 4.8 mmol) was added. This mixture was warmed to 50 °C and was stirred for 2.5 h. The material was cooled to ambient temperature and was quenched with saturated, aqueous $NaHCO_3$ (10 mL). The mixture was diluted with EtOAc (10 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 5 mL), and the combined organics were dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified via flash column chromatography (SiO_2, 70% hexanes/EtOAc) to provide (1-(2-azidoethyl)-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone (0.32 g, 1.0 mmol, 64% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.31 (s, 6 H), 1.35 (s, 6 H), 1.95 (s, 1 H), 3.74 (t, J = 5.8 Hz, 2 H), 4.32 (t, J = 5.9 Hz, 2 H), 7.26−7.35 (m, 3 H), 7.70 (s, 1 H), 8.39−8.47 (m, 1 H); MS (DCI/NH_3) m/z 311 $(M + H)^+$.

To a solution of (1-(2-azidoethyl)-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone (0.28 g, 0.90 mmol) in THF (10 mL) and water (0.5 mL) was added PPh_3 (0.26 g, 0.99 mmol). This mixture was stirred at ambient temperature for 48 h. Then the mixture was quenched with saturated, aqueous $NaHCO_3$ (10 mL). The mixture was diluted with EtOAc (10 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 5 mL) and the combined organics were dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified via column chromatography (SiO_2, (9:1:0.1 $CH_2Cl_2/CH_3OH/NH_4OH$) to give **23**. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.29 (s, 12 H), 2.03 (s, 1 H), 3.30−3.41 (m, 2 H), 4.43−4.49 (m, 2 H), 7.19−7.24 (m, 2 H), 7.39−7.45 (m, 1 H), 7.86 (s, 1 H), 8.18−8.28 (m, 1 H); MS (DCI/NH_3) m/z 285 $(M + H)^+$. Anal. ($C_{18}H_{24}N_2O \cdot 0.24H_2O$) C, H, N.

(1-(2-(Dimethylamino)ethyl)-1*H*-indol-3-yl)(2,2,3,3-tetramethyl-cyclopropyl)methanone *p*-Toluenesulfonic Acid (24). The *N*,*N*-dimethylethanolamine (0.11 g, 1.2 mmol), triethylamine (0.56 mL, 4.1 mmol), and methanesulfonyl chloride (0.15 mL, 1.9 mmol) in 10 mL of THF were processed as described in the procedure for 2-morpholin-4-ylethyl methanesulfonate to provide 2-(dimethyl-amino)ethyl methanesulfonate which was carried on without purification or characterization.

The 2-(dimethylamino)ethyl methanesulfonate (1.2 mmol), 1*H*-indol-3-yl(2,2,3,3-tetramethylcyclopropyl)methanone (0.15 g, 0.62 mmol), and NaH (60% dispersion in mineral oil, 0.12 g, 3.1 mmol) in DMF (8 mL) were processed as described in the procedure for **5** to provide (1-(2-(dimethylamino)ethyl)-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone (0.12 g, 0.38 mmol, 62% yield). This free base was carried on to the salt without characterization.

p-Toluenesulfonic acid monohydrate (71 mg, 0.37 mmol) and (1-(2-(dimethylamino)ethyl)-1*H*-indol-3-yl)(2,2,3,3-tetramethyl-cyclopropyl)methanone (0.12 g, 0.38 mmol) were combined in EtOAc (1 mL). The crude material was recrystallized with CH_3OH, EtOAc, and Et_2O to give **24** (0.12 g, 0.30 mmol, 81% yield). ^{1}H NMR (300 MHz, CD_3OD) δ ppm 1.33 (s, 6H), 1.34 (s, 6H), 2.16 (s, 1H), 2.36 (s, 3H), 2.98 (s, 6H), 3.68 (t, J = 6.8 Hz, 2H), 4.70 (t, J = 7.1 Hz, 2H), 7.22 (br d, J = 8.1 Hz, 2H), 7.26 (m, 1H), 7.33 (ddd, J = 8.1, 7.1, 1.4 Hz, 1H), 7.57 (br d, J = 8.1 Hz, 1H), 7.70 (br d, J = 8.1 Hz, 2H), 8.17 (s, 1H), 8.30 (ddd, J = 7.8, 1.4, 0.7 Hz, 1H); MS (DCI/NH_3) m/z 313 $(M + H)^+$. Anal. ($C_{20}H_{28}N_2O \cdot C_7H_8O_3S$) C, H, N.

(1-(2-(Pyrrolidin-1-yl)ethyl)-1*H*-indol-3-yl)(2,2,3,3-tetramethyl-cyclopropyl)methanone *p*-Toluenesulfonic Acid (25). The 1-(2-hydroxyethyl)pyrrolidine (0.14 g, 1.2 mmol), triethylamine (0.56 mL, 4.1 mmol), and methanesulfonyl chloride (0.15 mL, 1.9 mmol) in 10 mL of THF were processed as described in the procedure for 2-morpholin-4-ylethyl methanesulfonate to provide 2-(pyrrolidin-1-yl)ethyl methanesulfonate which was carried on without purification or characterization.

The 2-(pyrrolidin-1-yl)ethyl methanesulfonate (1.2 mmol), 1*H*-indol-3-yl(2,2,3,3-tetramethylcyclopropyl)methanone (0.15 g, 0.62 mmol), and NaH (60% dispersion in mineral oil, 62 mg, 1.6 mmol) in DMF (8 mL) were processed as described in the procedure for **5** to provide (1-(2-(pyrrolidin-1-yl)ethyl)-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone (45 mg, 0.13 mmol, 21% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.30 (s, 6 H), 1.34 (s, 6 H), 1.83 (s, 4 H), 1.94 (s, 1 H), 2.49−2.70 (m, 4 H), 2.92−3.06 (m, 2 H), 4.27−4.43 (m, 2 H), 7.23−7.40 (m, 3 H), 7.79 (s, 1 H), 8.35−8.46 (m, 1 H); MS (DCI/NH_3) m/z 339 $(M + H)^+$.

p-Toluenesulfonic acid monohydrate (24 mg, 0.12 mmol) and (1-(2-(pyrrolidin-1-yl)ethyl)-1*H*-indol-3-yl)(2,2,3,3-tetramethyl-cyclopropyl)methanone (41 mg, 0.12 mmol) were combined in a mixture of CH_3OH, EtOAc, and Et_2O. The resulting solids were isolated via filtration to provide **25** (44 mg, 0.086 mmol, 14% yield). ^{1}H NMR (300 MHz, CD_3OD) δ ppm 1.33 (s, 6H), 1.34 (s, 6H), 2.06 (m, 4H), 2.17 (s, 1H), 2.36 (s, 3H), 3.16 (m, 2H), 3.59 (m, 2H), 3.75 (t, J = 6.8 Hz, 2H), 4.67 (t, J = 6.8 Hz, 2H), 7.23 (br d, J = 8.1 Hz, 2H), 7.30 (m, 2H), 7.56 (m, 1H), 7.71 (br d, J = 8.1 Hz, 2H) 8.16 (s, 1H), 8.30 (m, 1H); MS (DCI/NH_3) m/z 339 $(M + H)^+$. Anal. ($C_{22}H_{30}N_2O \cdot C_7H_8O_3S$) C, H, N.

(1-(2-(Piperidin-1-yl)ethyl)-1*H*-indol-3-yl)(2,2,3,3-tetramethyl-cyclopropyl)methanone (26). The 1-piperidineethanol (0.16 g, 1.2 mmol), triethylamine (0.56 mL, 4.1 mmol), and methanesulfonyl chloride (0.15 mL, 1.9 mmol) in 10 mL of THF were processed as described in the procedure for 2-morpholin-4-ylethyl methanesulfonate to provide 2-(piperidin-1-yl)ethyl methanesulfonate which was carried on without purification or characterization.

The 2-(piperidin-1-yl)ethyl methanesulfonate (1.2 mmol), 1*H*-indol-3-yl(2,2,3,3-tetramethylcyclopropyl)methanone (0.15 g, 0.62 mmol), and NaH (60% dispersion in mineral oil, 0.12 g, 3.1 mmol) in DMF (8 mL) were processed as described in the procedure for **5** to provide **26** (0.21 g, 0.60 mmol, 96% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.31 (s, 6 H), 1.35 (s, 6 H), 1.42−1.70 (m, 6 H), 1.94 (s, 1 H), 2.41−2.54 (m, 4 H), 2.69−2.83 (m, 2 H), 4.18−4.35 (m, 2 H), 7.22−7.30 (m, 2 H), 7.35 (s, 1 H), 7.82 (s, 1 H), 8.36−8.46 (m, 1 H); MS (DCI/NH_3) *m*/*z* 353 (M + H)$^+$. Anal. ($C_{23}H_{32}N_2O\cdot 0.1C_6H_{14}\cdot 0.5H_2O$) C, H, N.

(1-(2-(Azepan-1-yl)ethyl)-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone (27). The *N*-(2-hydroxyethyl)hexamethyleneimine (Acros, 0.18 g, 1.2 mmol), triethylamine (0.56 mL, 4.1 mmol), and methanesulfonyl chloride (0.15 mL, 1.9 mmol) in 10 mL of THF were processed as described in the procedure for 2-morpholin-4-ylethyl methanesulfonate to provide 2-(azepan-1-yl)ethyl methanesulfonate which was carried on without purification or characterization.

The 2-(azepan-1-yl)ethyl methanesulfonate (1.2 mmol), 1*H*-indol-3-yl(2,2,3,3-tetramethylcyclopropyl)methanone (0.15 g, 0.62 mmol), and NaH (60% dispersion in mineral oil, 0.12 g, 3.1 mmol) in DMF (8 mL) were processed as described in the procedure for **5** to provide **27** (0.19 g, 0.52 mmol, 84% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.30 (s, 6 H), 1.35 (s, 6 H), 1.49−1.68 (m, 8 H), 1.95 (s, 1 H), 2.64−2.80 (m, 4 H), 2.87−2.98 (m, 2 H), 4.12−4.32 (m, 2 H), 7.21−7.30 (m, 2 H), 7.30−7.40 (m, 1 H), 7.84 (s, 1 H), 8.37−8.48 (m, 1 H); MS (DCI/NH_3) *m*/*z* 367 (M + H)$^+$. Anal. ($C_{24}H_{34}N_2O\cdot 0.2H_2O$) C, H, N.

(1-(2-(Piperazin-1-yl)ethyl)-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone Trifluoroacetic Acid (28). The *tert*-butyl-4-(2-hydroxyethyl)piperazine-1-carboxylate (0.29 g, 1.2 mmol), triethylamine (0.56 mL, 4.1 mmol), and methanesulfonyl chloride (0.15 mL, 1.9 mmol) in 10 mL of THF were processed as described in the procedure for 2-morpholin-4-ylethyl methanesulfonate to provide *tert*-butyl 4-(2-(methylsulfonyloxy)ethyl)-piperazine-1-carboxylate which was carried on without purification or characterization.

The *tert*-butyl 4-(2-(methylsulfonyloxy)ethyl)piperazine-1-carboxylate (1.2 mmol), 1*H*-indol-3-yl(2,2,3,3-tetramethylcyclopropyl)methanone (0.15 g, 0.62 mmol), and NaH (60% dispersion in mineral oil, 0.12 g, 3.1 mmol) in DMF (10 mL) were processed as described in the procedure for **5** to provide *tert*-butyl 4-(2-(3-(2,2,3,3-tetramethylcyclopropanecarbonyl)-1*H*-indol-1-yl)ethyl)piperazine-1-carboxylate (0.22 g, 0.49 mmol, 78% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.35 (s, 9 H), 1.45 (s, 12 H), 1.90−1.98 (m, 1 H), 2.36−2.52 (m, 4 H), 2.69−2.91 (m, 2 H), 3.33−3.53 (m, 4 H), 4.19−4.34 (m, 2 H), 7.22−7.40 (m, 3 H), 7.70−7.84 (m, 1 H), 8.32−8.52 (m, 1 H); MS (DCI/NH_3) *m*/*z* 454 (M + H)$^+$.

A mixture of *tert*-butyl 4-(2-(3-(2,2,3,3-tetramethylcyclopropanecarbonyl)-1*H*-indol-1-yl)ethyl)piperazine-1-carboxylate (0.17 g, 0.38 mmol) and TFA (4 mL) in CH_2Cl_2 (3 mL) was stirred at 0 °C for 5 min. The mixture was then allowed to warm to ambient temperature and was stirred for 20 min. The mixture was concentrated under reduced pressure, the residue was diluted with toluene (5 mL), and the mixture was concentrated under reduced pressure. This dilution and concentration were repeated two additional times with toluene. The resulting solids were dried under reduced pressure to give **28** (0.23 g, 0.33 mmol, 86% yield). ^{1}H NMR (300 MHz, CD_3OD) δ ppm 1.34 (s, 12 H), 1.69 (s, 1 H), 2.70−2.77 (m, 4 H), 2.92 (t, J = 6.1 Hz, 2 H), 3.12−3.16 (m, J = 5.1, 5.1 Hz, 4 H), 4.40 (t, J = 6.3 Hz, 2 H), 7.16−7.33 (m, 2 H), 7.51 (d, J = 7.8 Hz, 1 H), 8.09 (s, 1 H), 8.25 (d, J = 7.5 Hz, 1 H); MS (DCI/NH_3) *m*/*z* 354 (M + H)$^+$. Anal. ($C_{22}H_{31}N_3O\cdot 3CF_3CO_2H\cdot 0.5H_2O$) C, H, N.

(1-(2-(4-Methylpiperazin-1-yl)ethyl)-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone (29). A mixture of **28** (0.19 g, 0.36 mmol), $NaBH(OAc)_3$(0.10 g, 0.47 mmol), and HCHO (37% aqueous solution, 10 mL) was stirred at ambient temperature for 3.5 h. The mixture was quenched with saturated, aqueous $NaHCO_3$ (10 mL) and was diluted with CH_2Cl_2 (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organics were dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and puified via flash column chromatography (SiO_2, 95% CH_2Cl_2/4% CH_3OH/1% NH_4OH) to give **29** (65 mg, 0.17 mmol, 47% yield). ^{1}H NMR (300 MHz, CD_3OD) δ ppm 1.33 (s, 6 H), 1.33 (s, 6 H), 2.13 (s, 1 H), 2.27 (s, 3 H), 2.39−2.66 (m, 8 H), 2.80 (t, J = 6.4 Hz, 2 H), 4.37 (t, J = 6.4 Hz, 2 H), 7.15−7.31 (m, 2 H), 7.44−7.52 (m, 1 H), 8.10 (s, 1 H), 8.20−8.28 (m, 1 H); MS (DCI/NH_3) *m*/*z* 368 (M + H)$^+$. Anal. ($C_{23}H_{33}N_3O\cdot 0.5CH_3OH$) C, H, N.

(1-(2-(Piperidin-4-yl)ethyl)-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone (30). The *tert*-butyl 4-(2-hydroxyethyl)-piperidine-1-carboxylate (0.50 g, 2.2 mmol), triethylamine (0.91 mL, 6.5 mmol), and methanesulfonyl chloride (0.25 mL, 3.3 mmol) in 5 mL of THF were processed as described in the procedure for 2-morpholin-4-ylethyl methanesulfonate to provide *tert*-butyl 4-(2-(methylsulfonyloxy)ethyl)piperidine-1-carboxylate which was carried on without purification or characterization.

The *tert*-butyl 4-(2-(methylsulfonyloxy)ethyl)piperidine-1-carboxylate (2.2 mmol), 1*H*-indol-3-yl(2,2,3,3-tetramethylcyclopropyl)methanone (0.26 g, 1.1 mmol), and NaH (60% dispersion in mineral oil, 0.22 g, 5.5 mmol) in DMF (10 mL) were processed as described in the procedure for **5** to provide *tert*-butyl 4-(2-(3-(2,2,3,3-tetramethylcyclopropanecarbonyl)-1*H*-indol-1-yl)ethyl)piperidine-1-carboxylate (0.50 g, 1.1 mmol, 51% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.18−1.28 (m, 2 H), 1.31 (s, 6 H), 1.35 (s, 6 H), 1.34−1.36 (m, 1 H), 1.46 (s, 9 H), 1.65−1.77 (m, 2 H), 1.79−1.91 (m, 2 H), 1.93 (s, 1 H), 2.60−2.75 (m, 2 H), 4.04−4.15 (m, 2 H), 4.16−4.24 (m, 2 H), 7.25−7.33 (m, 3 H), 7.64 (s, 1 H), 8.35−8.45 (m, 1 H); MS (DCI/NH_3) *m*/*z* 453 (M + H)$^+$.

A mixture of *tert*-butyl 4-(2-(3-(2,2,3,3-tetramethylcyclopropanecarbonyl)-1*H*-indol-1-yl)ethyl)piperidine-1-carboxylate (0.40 g, 0.88 mmol) and TFA (3 mL) in CH_2Cl_2 (5 mL) was stirred at 0 °C for 5 min. The mixture was then allowed to warm ambient temperature and was stirred for 20 min. The mixture was concentrated under reduced pressure, and the residue was puified via column chromatography (SiO_2, 95% CH_2Cl_2/4% CH_3OH/1% NH_4OH). The free base (0.15 g, 0.43 mmol) was dissolved in EtOAc (3 mL), and *p*-TSA-H_2O (0.43 mmol) in EtOAc (1 mL) was added. The resulting solids were isolated via filtration to give **30** (0.16 g, 0.30 mmol, 70% yield). ^{1}H NMR (300 MHz, CD_3OD) δ ppm 1.33 (s, 12 H), 1.37−1.54 (m, 2 H), 1.57−1.66 (m, 1 H), 1.85−1.94 (m, 2 H), 1.91−2.04 (m, 2 H), 2.15 (s, 1 H), 2.35 (s, 3 H), 2.87−2.99 (m, 2 H), 3.32−3.41 (m, 2 H), 4.29−4.36 (m, 2 H), 7.17−7.26 (m, 1 H), 7.17−7.25 (m, 2 H), 7.24−7.30 (m, 1 H), 7.46−7.51 (m, 1 H), 7.67−7.73 (m, 2 H), 8.08 (s, 1 H), 8.23−8.28 (m, 1 H); MS (DCI/NH_3) *m*/*z* 353 (M + H)$^+$. Anal. ($C_{23}H_{32}N_2O\cdot 1.25C_7H_8O_3S\cdot 0.25H_2O$) C, H, N.

(1-(2-(4-Methylpiperazin-1-yl)ethyl)-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone (31). A mixture of the free base of **30** (0.15 g, 0.54 mmol), $NaBH(OAc)_3$ (0.17 g, 0.81 mmol), and HCHO (37% aqueous solution, 5 mL) were processed as described in the experiment for **29** to give the desired free base (0.15 g, 0.41 mmol, 76% yield). The free base (0.15 g, 0.41 mmol) was dissolved in EtOAc (2 mL), and fumaric acid (0.41 mmol) in EtOAc (1 mL) was added. The resulting solids were isolated via filtration to give **31** (0.15 g, 0.41 mmol, 76% yield). ^{1}H NMR (300 MHz, CD_3OD) δ ppm 1.33 (s, 12 H), 1.43−1.60 (m, 3 H), 1.92 (q, J = 6.9 Hz, 2 H), 1.97−2.08 (m, 2 H), 2.15 (s, 1 H), 2.79−2.83 (m, 3 H), 2.86−3.04 (m, 2 H), 3.36−3.53 (m, 2 H), 4.29−4.40 (m, 2 H), 6.70 (s, 2 H), 7.18−7.32 (m, 2 H), 7.49 (d, J = 8.1 Hz, 1 H), 8.09 (s, 1 H), 8.23−8.29 (m, 1 H); MS (DCI/NH_3) *m*/*z* 367 (M + H)$^+$. Anal. ($C_{23}H_{33}N_3O\cdot 1.5C_4H_4O_4$) C, H, N.

(1-(3-Morpholinopropyl)-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone (32). The 3-morpholinopropan-1-ol (0.18 g, 1.2 mmol), triethylamine (0.56 mL, 4.1 mmol), and methanesulfonyl chloride (0.15 mL, 1.9 mmol) in 10 mL of THF were processed as described in the procedure for 2-morpholin-4-ylethyl methanesulfonate to provide 3-morpholinopropyl methanesulfonate which was carried on without purification or characterization.

The 3-morpholinopropyl methanesulfonate (1.2 mmol), 1*H*-indol-3-yl(2,2,3,3-tetramethylcyclopropyl)methanone (0.15 g, 0.62 mmol), and NaH (60% dispersion in mineral oil, 0.12 g, 3.1 mmol) in DMF (8 mL) were processed as described in the procedure for **5** to provide **32** (0.15 g, 0.41 mmol, 33% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.30 (s, 6 H), 1.35 (s, 6 H), 1.93 (s, 1 H), 2.00−2.09 (m, 2 H), 2.29 (t, J = 6.1 Hz, 2 H), 2.41 (d, J = 0.7 Hz, 4 H), 3.70−3.78 (m, 4 H), 4.28 (t, J = 6.6 Hz, 2 H), 7.21−7.31 (m, 2 H), 7.33−7.42 (m, 1 H), 7.71 (s, 1 H), 8.37−8.43 (m, 1 H); MS (DCI/NH_3) m/z 369 $(M + H)^+$. Anal. ($C_{23}H_{32}N_2O_2$) C, H, N.

(1-(2-(1-Methylpyrrolidin-2-yl)ethyl)-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone (33). The 2-(1-methylpyrrolidin-2-yl)ethanol (0.16 g, 1.2 mmol), triethylamine (0.56 mL, 4.1 mmol), and methanesulfonyl chloride (0.15 mL, 1.9 mmol) in 10 mL of THF were processed as described in the procedure for 2-morpholin-4-ylethyl methanesulfonate to provide 2-(1-methylpyrrolidin-2-yl)ethyl methanesulfonate which was carried on without purification or characterization.

The 2-(1-methylpyrrolidin-2-yl)ethyl methanesulfonate (1.2 mmol), 1*H*-indol-3-yl(2,2,3,3-tetramethylcyclopropyl)methanone (0.15 g, 0.62 mmol), and NaH (60% dispersion in mineral oil, 0.12 g, 3.1 mmol) in DMF (8 mL) were processed as described in the procedure for **5** to provide the desired free base (85 mg, 0.24 mmol, 20%). The free base (85 mg, 0.23 mmol) was dissolved in EtOAc (1 mL), MeOH (0.5 mL), and Et_2O (1 mL), and *p*TSA-H_2O (0.23 mmol) was added. The resulting solids were isolated via filtration to give **33** (70 mg, 0.13 mmol, 58% yield). ^{1}H NMR (300 MHz, CD_3OD) δ ppm 1.33 (s, 12 H), 1.72−1.90 (m, 1 H), 2.00−2.14 (m, 3 H), 2.16 (s, 1 H), 2.28−2.40 (m, 1 H), 2.35 (s, 3 H), 2.52−2.66 (m, 1 H), 2.88 (s, 3 H), 3.06−3.20 (m, 1 H), 3.31−3.34 (m, 1 H), 3.58−3.73 (m, 1 H), 4.41 (t, J = 7.5 Hz, 2 H), 7.18−7.26 (m, 2 H), 7.22−7.34 (m, 2 H), 7.53 (d, J = 7.8 Hz, 1 H), 7.66−7.75 (m, 2 H), 8.12 (s, 1 H), 8.27 (d, J = 8.1 Hz, 1 H); MS (DCI/NH_3) m/z 353 $(M + H)^+$. Anal. ($C_{23}H_{32}N_2O \cdot C_7H_8O_3S \cdot 0.2H_2O$) C, H, N.

(1-((1-Methylpiperidin-2-yl)methyl)-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone (34). The (1-methylpiperidin-2-yl)methanol (0.27 g, 2.1 mmol), triethylamine (0.87 mL, 6.2 mmol), and methanesulfonyl chloride (0.24 mL, 3.1 mmol) in 10 mL of THF were processed as described in the procedure for 2-morpholin-4-ylethyl methanesulfonate to provide (1-methylpiperidin-2-yl)methyl methanesulfonate which was carried on without purification or characterization.

The (1-methylpiperidin-2-yl)methyl methanesulfonate (2.1 mmol), 1*H*-indol-3-yl(2,2,3,3-tetramethylcyclopropyl)methanone (0.25 g, 1.0 mmol), and NaH (60% dispersion in mineral oil, 0.10 g, 2.6 mmol) in DMF (10 mL) were processed as described in the procedure for **5** to provide the desired free base (0.18 mg, 0.51 mmol, 49%). The free base (0.18 mg, 0.51 mmol) was dissolved in EtOAc (1 mL) and MeOH (0.5 mL), and *p*TSA-H_2O (0.51 mmol) was added. The resulting solids were isolated via filtration to give **34** (0.21 mg, 0.40 mmol, 78% yield). ^{1}H NMR (300 MHz, CD_3OD) δ ppm 1.33 (s, 12 H), 1.48−1.66 (m, 2 H), 1.72−2.02 (m, 3 H), 2.17 (s, 1 H), 2.36 (s, 3 H), 3.01−3.22 (m, 2 H), 3.08 (s, 3 H), 3.32−3.39 (m, 1 H), 3.52−3.66 (m, 1 H), 3.67−3.80 (m, 1 H), 4.37 (dd, J = 14.2, 8.5 Hz, 1 H), 7.19−7.24 (m, 2 H), 7.26−7.38 (m, 2 H), 7.52 (d, J = 8.1 Hz, 1 H), 7.68−7.74 (m, 2 H), 8.12 (s, 1 H), 8.30 (d, J = 7.8 Hz, 1 H); MS (DCI/NH_3) m/z 353 $(M + H)^+$. Anal. ($C_{23}H_{32}N_2O \cdot C_7H_8O_3S \cdot 0.1H_2O$) C, H, N.

(1-(2-(Tetrahydro-2*H*-pyran-4-yl)ethyl)-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone (35). The 2-(tetrahydro-2*H*-pyran-4-yl)ethanol (Biofine, 0.38 g, 2.9 mmol), triethylamine (1.2 mL, 8.7 mmol), and methanesulfonyl chloride (0.34 mL, 4.4 mmol) in 10 mL of THF were processed as described in the procedure for 2-morpholin-4-ylethyl methanesulfonate to provide 2-(tetrahydro-2*H*-pyran-4-yl)ethyl methanesulfonate which was carried on without purification or characterization.

The 2-(tetrahydro-2*H*-pyran-4-yl)ethyl methanesulfonate (2.9 mmol), 1*H*-indol-3-yl(2,2,3,3-tetramethylcyclopropyl)methanone (0.35 g, 1.5 mmol), and NaH (60% dispersion in mineral oil, 0.29 g, 7.3 mmol) in DMF (10 mL) were processed as described in the procedure for **5** to provide **35** (0.36 mg, 1.0 mmol, 70% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.31 (s, 6 H), 1.35 (s, 6 H), 1.42 (dt, J = 12.3, 4.6 Hz, 2 H), 1.51−1.71 (m, 3 H), 1.82−1.91 (m, 2 H), 1.94 (s, 1 H), 3.37 (dt, J = 11.6, 1.9 Hz, 2 H), 3.97 (dd, J = 11.5, 4.7 Hz, 2 H), 4.20 (dd, J = 7.5 Hz, 2 H), 7.26−7.34 (m, 3 H), 7.65 (s, 1 H), 8.36−8.45 (m, 1 H); MS (DCI/NH_3) m/z 354 $(M + H)^+$. Anal. ($C_{23}H_{31}NO_2$) C, H, N.

(1-((Tetrahydrofuran-3-yl)methyl)-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone (36). The (tetrahydrofuran-3-yl)methanol (0.13 g, 1.2 mmol), triethylamine (0.56 mL, 4.1 mmol), and methanesulfonyl chloride (0.15 mL, 1.9 mmol) in 10 mL of THF were processed as described in the procedure for 2-morpholin-4-ylethyl methanesulfonate to provide (tetrahydrofuran-3-yl)methyl methanesulfonate which was carried on without purification or characterization.

The (tetrahydrofuran-3-yl)methyl methanesulfonate (1.2 mmol), 1*H*-indol-3-yl(2,2,3,3-tetramethylcyclopropyl)methanone (0.15 g, 0.62 mmol), and NaH (60% dispersion in mineral oil, 0.12 g, 3.1 mmol) in DMF (10 mL) were processed as described in the procedure for **5** to provide **36** (0.16 mg, 0.48 mmol, 77% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.31 (s, 6 H), 1.34 (s, 3 H), 1.35 (s, 3 H), 1.64−1.78 (m, 1 H), 1.94 (s, 1 H), 1.99−2.15 (m, 1 H), 2.81−2.97 (m, 1 H), 3.62−3.76 (m, 2 H), 3.75−3.84 (m, 1 H), 3.96−4.06 (m, 1 H), 4.13 (d, J = 7.8 Hz, 2 H), 7.26−7.32 (m, 2 H), 7.33−7.40 (m, 1 H), 7.66 (s, 1 H), 8.37−8.45 (m, 1 H); MS (DCI/NH_3) m/z 326 $(M + H)^+$. Anal. ($C_{21}H_{27}NO_2$) C, H, N.

(*S*)-(1-((Tetrahydrofuran-2-yl)methyl)-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone (37). The (*S*)-(tetrahydrofuran-2-yl)methanol (Julich/Codexis, 0.30 g, 3.7 mmol), triethylamine (0.70 mL, 5.0 mmol), and methanesulfonyl chloride (0.34 mL, 4.4 mmol) in 15 mL of THF were processed as described in the procedure for 2-morpholin-4-ylethyl methanesulfonate to provide (*S*)-(tetrahydrofuran-2-yl)methyl methanesulfonate which was carried on without purification or characterization.

The (*S*)-(tetrahydrofuran-2-yl)methyl methanesulfonate (3.7 mmol), 1*H*-indol-3-yl(2,2,3,3-tetramethylcyclopropyl)methanone (0.30 g, 1.2 mmol), and NaH (60% dispersion in mineral oil, 0.15 g, 3.7 mmol) in DMF (12 mL) were processed as described in the procedure for **5** to provide **37** (0.23 mg, 0.71 mmol, 57% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.29−1.31 (m, 6 H), 1.34 (s, 3 H), 1.35 (s, 3 H), 1.54−1.62 (m, 1 H), 1.73−1.94 (m, 2 H), 1.95 (s, 1 H), 1.97−2.08 (m, 1 H), 3.73−3.91 (m, 2 H), 4.12−4.34 (m, 3 H), 7.24−7.29 (m, 2 H), 7.33−7.39 (m, 1 H), 7.79 (s, 1 H), 8.38−8.45 (m, 1 H); MS (DCI/NH_3) m/z 326 $(M + H)^+$. Anal. ($C_{21}H_{27}NO_2$) C, H, N.

(*R*)-(1-((Tetrahydrofuran-2-yl)methyl)-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone (38). The (*R*)-(tetrahydrofuran-2-yl)methanol (Lancaster, 0.33 g, 3.4 mmol), triethylamine (0.78 mL, 5.6 mmol), and methanesulfonyl chloride (0.35 mL, 4.5 mmol) in 10 mL of THF were processed as described in the procedure for 2-morpholin-4-ylethyl methanesulfonate to provide (*R*)-(tetrahydrofuran-2-yl)methyl methanesulfonate which was carried on without purification or characterization.

The (*R*)-(tetrahydrofuran-2-yl)methyl methanesulfonate (3.4 mmol), 1*H*-indol-3-yl(2,2,3,3-tetramethylcyclopropyl)methanone (0.27 g, 1.1 mmol), and NaH (60% dispersion in mineral oil, 0.13 g, 3.4 mmol) in DMF (10 mL) were processed as described in the procedure for **5** to provide **38** (0.28 mg, 0.85 mmol, 76% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.30 (s, 6 H), 1.33 (s, 3 H), 1.35 (s, 3 H), 1.49−1.63 (m, 1 H), 1.73−1.92 (m, 2 H), 1.95 (s, 1 H), 1.98−2.07 (m, 1 H), 3.73−3.90 (m, 2 H), 4.15−4.35 (m, 3 H), 7.23−7.28 (m, 2 H), 7.34−7.39 (m, 1 H), 7.78 (s, 1 H), 8.39−8.45 (m, 1 H); MS (DCI/NH_3) *m*/*z* 326 (M + H)$^+$. Anal. ($C_{21}H_{27}NO_2$) C, H, N.

(1-((1,3-Dioxolan-2-yl)methyl)-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone (39). The glycerol formal (Fluka, 40% *desired* 4-hydroxymethyl-1,3-dioxolane and 60% 5-hydroxy-1,3-dioxane, 0.43 g, 4.1 mmol), triethylamine (1.7 mL, 12.4 mmol), and methanesulfonyl chloride (0.48 mL, 6.2 mmol) in 25 mL of THF were processed as described in the procedure for 2-morpholin-4-ylethyl methanesulfonate to provide (1,3-dioxolan-2-yl)methyl methanesulfonate which was carried on without purification or characterization.

The (1,3-dioxolan-2-yl)methyl methanesulfonate (1.6 mmol), 1*H*-indol-3-yl(2,2,3,3-tetramethylcyclopropyl)methanone (0.50 g, 2.1 mmol), and NaH (60% dispersion in mineral oil, 0.33 g, 8.3 mmol) in DMF (20 mL) were processed as described in the procedure for **5** to provide **39** (0.27 g, 0.81 mmol, 50% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.31 (s, 6 H), 1.34 (s, 3 H), 1.35 (s, 3 H), 1.95 (s, 1 H), 3.71 (dd, *J* = 8.6, 5.6 Hz, 1 H), 3.98 (dd, *J* = 8.6, 6.6 Hz, 1 H), 4.26−4.30 (m, 2 H), 4.41−4.51 (m, 1 H), 4.89 (s, 1 H), 5.09 (s, 1 H), 7.26−7.31 (m, 2 H), 7.32−7.39 (m, 1 H), 7.75 (s, 1 H), 8.38−8.45 (m, 1 H); MS (DCI/NH_3) *m*/*z* 328 (M + H)$^+$. Anal. ($C_{20}H_{25}NO_3$) C, H, N.

2-(Tetrahydro-2*H*-pyran-4-yl)-1-(3-(2,2,3,3-tetramethylcyclopropanecarbonyl)-1*H*-indol-1-yl)ethanone (40). A mixture of 2-(tetrahydro-2*H*-pyran-4-yl)acetic acid (0.18 g, 1.2 mmol) and $SOCl_2$ (7 mL) was warmed to reflux and was allowed to stir for 2 h. The mixture was then cooled to ambient temperature and concentrated under reduced pressure. The residue was diluted with 10 mL of benzene and concentrated to remove any remaining thionyl chloride. This was repeated two additional times, and the crude 2-(tetrahydro-2*H*-pyran-4-yl)acetyl chloride was used without further purification or characterization.

The 2-(tetrahydro-2*H*-pyran-4-yl)acetyl chloride (1.2 mmol), 1*H*-indol-3-yl(2,2,3,3-tetramethylcyclopropyl)methanone (0.15 g, 0.62 mmol), and NaH (60% dispersion in mineral oil, 75 mg, 3.1 mmol) in DMF (10 mL) were processed as described in the procedure for **5** to provide **40** (0.16 g, 0.44 mmol, 70% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.35 (s, 6 H), 1.36 (s, 6 H), 1.41−1.55 (m, 2 H), 1.77−1.87 (m, 2 H), 2.00 (s, 1 H), 2.28−2.45 (m, 1 H), 2.88−2.98 (m, 2 H), 3.49 (dt, *J* = 11.7, 2.0 Hz, 2 H), 4.01 (dd, *J* = 11.0, 4.2 Hz, 2 H), 7.34−7.43 (m, 2 H), 7.97 (s, 1 H), 8.30−8.35 (m, 1 H), 8.38−8.44 (m, 1 H); MS (DCI/NH_3) *m*/*z* 368 (M + H)$^+$. Anal. ($C_{23}H_{29}NO_3$) C, H, N.

3-(2-(3-(2,2,3,3-Tetramethylcyclopropanecarbonyl)-1*H*-indol-1-yl)ethyl)oxazolidin-2-one (41). The 3-(2-hydroxyethyl)oxazolidin-2-one (0.33 g, 2.5 mmol), triethylamine (1.1 mL, 7.5 mmol), and methanesulfonyl chloride (0.29 mL, 3.7 mmol) in 20 mL of THF were processed as described in the procedure for 2-morpholin-4-ylethyl methanesulfonate to provide 2-(2-oxooxazolidin-3-yl)ethyl methanesulfonate which was carried on without purification or characterization.

The 2-(2-oxooxazolidin-3-yl)ethyl methanesulfonate (2.5 mmol), 1*H*-indol-3-yl(2,2,3,3-tetramethylcyclopropyl)methanone (0.30 g, 1.2 mmol), and NaH (60% dispersion in mineral oil, 0.15 g, 3.7 mmol) in DMF (15 mL) were processed as described in the procedure for **5** to provide **41** (0.20 g, 0.56 mmol, 45% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.31 (s, 6 H), 1.35 (s, 6 H), 1.93 (s, 1 H), 2.91 (dd, *J* = 8.1 Hz, 2 H), 3.68 (dd, *J* = 6.1 Hz, 2 H), 4.06 (dd, *J* = 7.8 Hz, 2 H), 4.44 (t, *J* = 5.9 Hz, 2 H), 7.28−7.34 (m, 2 H), 7.36−7.42 (m, 1 H), 7.68 (s, 1 H), 8.36−8.47 (m, 1 H); MS (DCI/NH_3) *m*/*z* 355 (M + H)$^+$. Anal. ($C_{21}H_{26}N_2O_3$) C, H, N.

1-(2-(3-(2,2,3,3-Tetramethylcyclopropanecarbonyl)-1*H*-indol-1-yl)ethyl)pyrrolidin-2-one (42). The 1-(2-hydroxyethyl)pyrrolidin-2-one (0.16 g, 1.2 mmol), triethylamine (0.56 mL, 4.1 mmol), and methanesulfonyl chloride (0.15 mL, 1.9 mmol) in 10 mL of THF were processed as described in the procedure for 2-morpholin-4-ylethyl methanesulfonate to provide 2-(2-oxopyrrolidin-1-yl)ethyl methanesulfonate which was carried on without purification or characterization.

The 2-(2-oxopyrrolidin-1-yl)ethyl methanesulfonate (1.2 mmol), 1*H*-indol-3-yl(2,2,3,3-tetramethylcyclopropyl)methanone (0.15 g, 0.62 mmol), and NaH (60% dispersion in mineral oil, 0.12 g, 3.1 mmol) in DMF (8 mL) were processed as described in the procedure for **5** to provide **42** (0.12 g, 0.34 mmol, 55% yield). ^{1}H NMR (300 MHz, CD_3OD) δ ppm 1.33 (s, 12 H), 1.73−1.86 (m, 2 H), 2.15 (s, 1 H), 2.23 (t, *J* = 8.1 Hz, 2 H), 3.04 (dd, *J* = 6.8 Hz, 2 H), 3.70 (t, *J* = 5.9 Hz, 2 H), 4.45 (dd, *J* = 5.8 Hz, 2 H), 7.18−7.24 (m, 1 H), 7.28 (dt, *J* = 7.5, 1.5 Hz, 1 H), 7.50 (dt, *J* = 8.0, 1.2, 1.0 Hz, 1 H), 8.07 (s, 1 H), 8.26 (dq, *J* = 7.8, 0.7 Hz, 1 H); MS (DCI/NH_3) *m*/*z* 353 (M + H)$^+$. Anal. ($C_{22}H_{28}N_2O_2$) C, H, N.

1-(2-(3-(2,2,3,3-Tetramethylcyclopropanecarbonyl)-1*H*-indol-1-yl)ethyl)pyrrolidin-2-one (43). The 1-(2-hydroxyethyl)pyrrolidin-2-one (0.19 g, 1.2 mmol), triethylamine (0.56 mL, 4.1 mmol), and methanesulfonyl chloride (0.15 mL, 1.9 mmol) in 10 mL of THF were processed as described in the procedure for 2-morpholin-4-ylethyl methanesulfonate to provide 2-(2-oxopyrrolidin-1-yl)ethyl methanesulfonate which was carried on without purification or characterization.

The 2-(2-oxopyrrolidin-1-yl)ethyl methanesulfonate (1.2 mmol), 1*H*-indol-3-yl(2,2,3,3-tetramethylcyclopropyl)methanone (0.15 g, 0.62 mmol), and NaH (60% dispersion in mineral oil, 0.12 g, 3.1 mmol) in DMF (8 mL) were processed as described in the procedure for **5** to provide **43** (60 mg, 0.16 mmol, 26% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.32 (s, 6 H), 1.35 (s, 6 H), 1.93−1.95 (m, 1 H), 2.57 (s, 4 H), 3.98 (t, *J* = 7.0 Hz, 2 H), 4.38 (t, *J* = 7.0 Hz, 2 H), 7.22−7.33 (m, 2 H), 7.35−7.41 (m, 1 H), 7.67 (s, 1 H), 8.36−8.44 (m, 1 H); MS (DCI/NH_3) *m*/*z* 366 (M + H)$^+$. Anal. ($C_{22}H_{26}N_2O_3 \cdot 0.5H_2O$) C, H, N.

(1-Propyl-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone (44). The 1-bromopropane (0.19 mL, 2.1 mmol), 1*H*-indol-3-yl(2,2,3,3-tetramethylcyclopropyl)methanone (0.50 g, 2.1 mmol), and NaH (60% dispersion in mineral oil, 0.25 g, 6.2 mmol) in DMF (10 mL) were processed as described in the procedure for **5** to provide **44** (0.57 g, 2.0 mmol, 97% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 0.98 (t, *J* = 7.5 Hz, 3 H), 1.30 (s, 6 H), 1.35 (s, 6 H), 1.86−2.02 (m, 2 H), 1.94 (s, 1 H), 4.13 (t, *J* = 6.8 Hz, 2 H), 7.24−7.29 (m, 2 H), 7.31−7.39 (m, 1 H), 7.66 (s, 1 H), 8.36−8.44 (m, 1 H); MS (DCI/NH_3) *m*/*z* 284 (M + H)$^+$. Anal. ($C_{19}H_{25}NO$) C, H, N.

(1-Butyl-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone (45). The 1-bromobutane (0.27 mL, 2.5 mmol), 1*H*-indol-3-yl(2,2,3,3-tetramethylcyclopropyl)methanone (0.30 g, 1.2 mmol), and NaH (60% dispersion in mineral oil, 0.20 g, 5.0 mmol) in DMF (10 mL) were processed as described in the procedure for **5** to provide **45** (0.33 g, 1.1 mmol, 89% yield). ^{1}H NMR (300 MHz, CD_3OD) δ ppm 0.97 (t, *J* = 7.3 Hz, 3 H), 1.32 (s, 12 H), 1.32−1.43 (m, 2 H), 1.81−1.93 (m, 2 H), 2.13 (s, 1 H), 4.25 (t, *J* = 7.1 Hz, 2 H), 7.16−7.30 (m, 2 H), 7.46 (dt, *J* = 8.2, 1.0 Hz, 1 H), 8.04 (s, 1 H), 8.22−8.29 (m, 1 H); MS (DCI/NH_3) *m*/*z* 298 (M + H)$^+$. Anal. ($C_{20}H_{27}NO$) C, H, N.

(1-Pentyl-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone (46). The 1-bromopentane (0.26 mL, 2.1 mmol), 1*H*-indol-3-yl(2,2,3,3-tetramethylcyclopropyl)methanone (0.50 g, 2.1 mmol), and NaH (60% dispersion in mineral oil, 0.25 g, 6.2 mmol) in DMF (10 mL) were processed as described in the procedure for **5** to provide **46** (0.59 g, 1.9 mmol, 91% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 0.87−0.94 (m, 3 H), 1.31 (s, 6 H), 1.35 (s, 6 H), 1.35−1.39 (m, 4 H), 1.83−1.93 (m, 2 H), 1.94 (s, 1 H), 4.15 (t, *J* = 7.3 Hz, 2 H), 7.24−7.28 (m, 2 H), 7.31−7.37 (m, 1 H), 7.66 (s, 1 H), 8.36−8.44 (m, 1 H); MS (DCI/NH_3) *m*/*z* 312 (M + H)$^+$. Anal. ($C_{21}H_{29}NO$) C, H, N.

(2,2,3,3-Tetramethylcyclopropyl)(1-(4,4,4-trifluorobutyl)-1*H*-indol-3-yl)methanone (47). The 4,4,4-trifluorobutan-1-ol (0.16 g, 1.2 mmol), triethylamine (0.56 mL, 4.1 mmol), and methanesulfonyl chloride (0.15 mL, 1.9 mmol) in 10 mL of THF were processed as described in the procedure for 2-morpholin-4-ylethyl methanesulfonate to provide 4,4,4-trifluorobutyl methanesulfonate which was carried on without purification or characterization.

The 4,4,4-trifluorobutyl methanesulfonate (1.2 mmol), 1*H*-indol-3-yl(2,2,3,3-tetramethylcyclopropyl)methanone (0.15 g, 0.62 mmol), and NaH (60% dispersion in mineral oil, 0.12 g, 3.1 mmol) in DMF (10 mL) were processed as described in the procedure for **5** to provide **47** (0.19 g, 0.54 mmol, 86% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.31 (s, 6 H), 1.35 (s, 6 H), 1.94 (s, 1 H), 2.02−2.26 (m, 4 H), 4.26 (t, J = 6.8 Hz, 2 H), 7.25−7.33 (m, 3 H), 7.64 (s, 1 H), 8.37−8.45 (m, 1 H); MS (DCI/NH_3) m/z 352 (M + H)$^+$. Anal. ($C_{20}H_{24}F_3NO$) C, H, N.

[1-(2-Hydroxyethyl)-1*H*-indol-3-yl](2,2,3,3-tetramethylcyclopropyl)methanone (48). A mixture of 2-benzyloxyethanol (0.25 g, 1.7 mmol), triethylamine (0.67 mL, 5.0 mmol), and methanesulfonyl chloride (0.19 mL, 2.5 mmol) in 20 mL of THF was processed as described in the procedure for 2-morpholin-4-ylethyl methanesulfonate to provide 2-(benzyloxy)ethyl methanesulfonate which was carried on without purification or characterization.

A mixture of 2-(benzyloxy)ethyl methanesulfonate (1.7 mmol), 1*H*-indol-3-yl(2,2,3,3-tetramethylcyclopropyl)methanone (0.20 g, 0.83 mmol), and NaH (60% dispersion in mineral oil, 0.17 g, 4.1 mmol) in DMF (10 mL) was processed as described in the procedure for **5** to provide (1-(2-(benzyloxy)-ethyl)-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone (0.20 g, 0.54 mmol, 65% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.27 (s, 6H), 1.34 (s, 6H), 1.92 (s, 1H), 3.84 (t, J = 5.4 Hz, 2H), 4.36 (t, J = 5.1 Hz, 2H), 4.47 (s, 2H), 7.23 (m, 4H), 7.29 (m, 4H), 7.77 (s, 1H), 8.43 (m, 1H); MS (DCI/NH_3) m/z 376 (M + H)$^+$.

To (1-(2-(benzyloxy)ethyl)-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone (0.19 g, 0.51 mmol) in 20 mL of ethanol (200 proof) was added Pd/C (0.10 g, 10 wt % palladium on activated carbon). This mixture was stirred under 1 atm of H_2 (balloon) for 2 h after which time the reaction mixture was degassed three times with a N_2 backflush. The mixture was then filtered through Celite, concentrated under reduced pressure, and purified via flash column chromatography (SiO_2, 30% ethyl acetate/hexanes) to give **48** (68 mg, 0.24 mmol, 47% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm 1.30 (s, 6H), 1.35 (s, 6H), 1.95 (s, 1H), 4.03 (m, 2H), 4.33 (t, J = 5.1 Hz, 2H), 7.28 (m, 2H), 7.36 (m, 1H), 7.76 (s, 1H), 8.43 (m, 1H); MS (DCI/NH_3) m/z 286 (M + H)$^+$. Anal. ($C_{18}H_{23}NO_2$) C, H, N.

(1-(3-Hydroxypropyl)-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone (49). A mixture of 2-benzyloxypropanol (0.26 g, 1.7 mmol), triethylamine (0.67 mL, 5.0 mmol), and methanesulfonyl chloride (0.19 mL, 2.5 mmol) in 20 mL of THF was processed as described in the procedure for 2-morpholin-4-ylethyl methanesulfonate to provide 3-(benzyloxy)propyl methanesulfonate which was carried on without purification or characterization.

A mixture of 3-(benzyloxy)propyl methanesulfonate (1.7 mmol), 1*H*-indol-3-yl(2,2,3,3-tetramethylcyclopropyl)methanone (0.20 g, 0.83 mmol), and NaH (60% dispersion in mineral oil, 0.17 g, 4.1 mmol) in DMF (10 mL) was processed as described in the procedure for **5** to provide (1-(3-(benzyloxy)propyl)-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)-methanone (0.27 g, 0.69 mmol, 84% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.27 (s, 6 H), 1.34 (s, 6 H), 1.90 (s, 1 H), 2.09−2.22 (m, 2 H), 3.43 (t, J = 5.6 Hz, 2 H), 4.33 (t, J = 6.8 Hz, 2 H), 4.49 (s, 2 H), 7.24−7.28 (m, 2 H), 7.30−7.39 (m, 6 H), 7.67 (s, 1 H), 8.38−8.47 (m, 1 H); MS (DCI/NH_3) m/z 390 (M + H)$^+$.

A mixture of (1-(3-(benzyloxy)propyl)-1*H*-indol-3-yl)(2,2,-3,3-tetramethylcyclopropyl)methanone (0.24 g, 0.62 mmol), Pd/C (0.20 g, 10 wt % palladium on activated carbon), and H_2 (1 atm balloon) in EtOH (40 mL) were processed as in the procedure for **48** to provide **49** (0.13 g, 0.43 mmol, 70% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm 1.30 (s, 6 H), 1.35 (s, 6 H), 1.94 (s, 1 H), 2.06−2.20 (m, 2 H), 3.67 (t, J = 5.8 Hz, 2 H), 4.35 (t, J = 7.0 Hz, 2 H), 7.24−7.29 (m, 2 H), 7.37−7.41 (m, 1 H), 7.71 (s, 1 H), 8.36−8.44 (m, 1 H); MS (DCI/NH_3) m/z 300 (M + H)$^+$. Anal. ($C_{19}H_{25}NO_2\cdot 0.2H_2O$) C, H, N.

(1-(4-Hydroxybutyl)-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone (50). A mixture of 4-(benzyloxy)butan-1-ol (0.44 g, 2.5 mmol), triethylamine (1.1 mL, 7.9 mmol), and methanesulfonyl chloride (0.30 mL, 3.8 mmol) in 20 mL of THF was processed as described in the procedure for 2-morpholin-4-ylethyl methanesulfonate to provide 4-(benzyloxy)-butyl methanesulfonate which was carried on without purification or characterization.

A mixture of 4-(benzyloxy)butyl methanesulfonate (2.5 mmol), 1*H*-indol-3-yl(2,2,3,3-tetramethylcyclopropyl)methanone (0.30 g, 1.2 mmol), and NaH (60% dispersion in mineral oil, 0.25 g, 6.3 mmol) in DMF (15 mL) was processed as described in the procedure for **5** to provide (1-(4-(benzyloxy)-butyl)-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone (0.47 g, 1.16 mmol, 94% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.29 (s, 6 H), 1.34 (s, 6 H), 1.61−1.73 (m, 2 H), 1.93 (s, 1 H), 1.96−2.06 (m, 2 H), 3.50 (t, J = 6.1 Hz, 2 H), 4.19 (t, J = 7.1 Hz, 2 H), 4.49 (s, 2 H), 7.23−7.39 (m, 8 H), 7.66 (s, 1 H), 8.35−8.46 (m, 1 H); MS (DCI/NH_3) m/z 404 (M + H)$^+$.

A mixture of (1-(4-(benzyloxy)butyl)-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone (0.47 g, 1.16 mmol), Pd/C (0.25 g, 10 wt % palladium on activated carbon), and H_2 (1 atm balloon) in EtOH (60 mL) were processed as in the procedure for **48** to provide **50** (0.22 g, 0.78 mmol, 67% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm 1.31 (s, 6 H), 1.35 (s, 6 H), 1.57−1.69 (m, 2 H), 1.95 (s, 1 H), 1.96−2.07 (m, 2 H), 2.17 (s, 1 H), 3.70 (t, J = 6.3 Hz, 2 H), 4.22 (t, J = 7.1 Hz, 2 H), 7.24−7.29 (m, 2 H), 7.32−7.39 (m, 1 H), 7.68 (s, 1 H), 8.36−8.44 (m, 1 H); MS (DCI/NH_3) m/z 313 (M + H)$^+$. Anal. ($C_{20}H_{27}NO_2\cdot 0.1C_6H_{14}\cdot 0.2H_2O$) C, H, N.

(1-(5-Hydroxypentyl)-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone (51). A mixture of 5-(benzyloxy)pentan-1-ol (0.34 g, 1.7 mmol), triethylamine (0.67 mL, 5.0 mmol), and methanesulfonyl chloride (0.19 mL, 2.5 mmol) in 10 mL of THF was processed as described in the procedure for 2-morpholin-4-ylethyl methanesulfonate to provide 5-(benzyloxy)pentyl methanesulfonate which was carried on without purification or characterization.

A mixture of 5-(benzyloxy)pentyl methanesulfonate (1.7 mmol), 1*H*-indol-3-yl(2,2,3,3-tetramethylcyclopropyl)methanone (0.20 g, 0.83 mmol), and NaH (60% dispersion in mineral oil, 0.17 g, 4.1 mmol) in DMF (10 mL) was processed as described in the procedure for **5** to provide (1-(5-(benzyloxy)-pentyl)-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone (0.30 g, 0.72 mmol, 87% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.30 (s, 6 H), 1.34 (s, 6 H), 1.42−1.52 (m, 2 H), 1.60−1.73 (m, 2 H), 1.85−1.97 (m, 2 H), 1.94 (s, 1 H), 3.46 (t, J = 6.3 Hz, 2 H), 4.15 (t, J = 7.3 Hz, 2 H), 4.48 (s, 2 H), 7.24−7.37 (m, 8 H), 7.65 (s, 1 H), 8.35−8.46 (m, 1 H); MS (DCI/NH_3) m/z 418 (M + H)$^+$.

A mixture of (1-(5-(benzyloxy)pentyl)-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone (0.29 g, 0.69 mmol), Pd/C (0.20 g, 10 wt % palladium on activated carbon), and H_2 (1 atm balloon) in EtOH (50 mL) was processed as in the procedure for **48** to provide **51** (0.16 g, 0.49 mmol, 71% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm 1.31 (s, 6 H), 1.35 (s, 6 H), 1.41−1.53 (m, 2 H), 1.56−1.68 (m, 2 H), 1.88−2.00 (m, 2 H), 1.95 (s, 1 H), 3.65 (t, J = 6.3 Hz, 2 H), 4.17 (t, J = 7.1 Hz, 2 H), 7.24−7.28 (m, 2 H), 7.32−7.36 (m, 1 H), 7.66 (s, 1 H), 8.36−8.42 (m, 1 H); MS (DCI/NH3) m/z 328 (M + H)$^+$. Anal. ($C_{21}H_{29}NO_2\cdot 0.5H_2O$) C, H, N.

(1-(2-Methoxyethyl)-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone (52). The 2-methoxyethanol (0.094 g, 1.2 mmol), triethylamine (0.56 mL, 4.1 mmol), and methanesulfonyl chloride (0.15 mL, 1.9 mmol) in 10 mL of THF were processed as described in the procedure for 2-morpholin-4-ylethyl methanesulfonate to provide 2-methoxyethyl methanesulfonate which was carried on without purification or characterization.

The 2-methoxyethyl methanesulfonate (1.2 mmol), 1*H*-indol-3-yl(2,2,3,3-tetramethylcyclopropyl)methanone (0.15 g, 0.62 mmol), and NaH (60% dispersion in mineral oil, 0.12 g, 3.1 mmol) in DMF (8 mL) were processed as described in the procedure for **5** to provide **52** (0.12 g, 0.40 mmol, 65% yield). ^{1}H NMR (300 MHz, CD_3OD) δ ppm 1.32 (s, 6 H), 1.33 (s, 6 H), 2.11 (s, 1 H), 3.31 (s, 3 H), 3.76 (dd, J = 5.4 Hz, 2 H), 4.41 (dd, J = 5.1 Hz, 2 H), 7.16−7.28 (m, 2 H), 7.46−7.50 (m, 1 H), 8.03 (s, 1 H), 8.21−8.27 (m, 1 H); MS (DCI/NH_3) m/z 300 $(M + H)^+$. Anal. ($C_{19}H_{25}NO_2$) C, H, N.

(1-(3-Methoxypropyl)-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone (53). The 1-bromo-3-methoxypropane (0.19 g, 1.2 mmol), 1*H*-indol-3-yl(2,2,3,3-tetramethylcyclopropyl)methanone (0.15 g, 0.62 mmol), and NaH (60% dispersion in mineral oil, 62 mg, 1.6 mmol) in DMF (10 mL) were processed as described in the procedure for **5** to provide **53** (0.12 g, 0.38 mmol, 62% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.30 (s, 6 H), 1.35 (s, 6 H), 1.94 (s, 1 H), 2.05−2.18 (m, 2 H), 3.31 (t, J = 5.8 Hz, 2 H), 3.35 (s, 3 H), 4.30 (t, J = 6.8 Hz, 2 H), 7.24−7.29 (m, 2 H), 7.33−7.39 (m, 1 H), 7.67 (s, 1 H), 8.37−8.45 (m, 1 H); MS (DCI/NH_3) m/z 314 $(M + H)^+$. Anal. ($C_{20}H_{27}NO_2$) C, H, N.

(1-(4-(Methylthio)butyl)-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone (54). The 4-(methylthio)butan-1-ol (0.15 g, 1.2 mmol), triethylamine (0.56 mL, 4.1 mmol), and methanesulfonyl chloride (0.15 mL, 1.9 mmol) in 10 mL of THF were processed as described in the procedure for 2-morpholin-4-ylethyl methanesulfonate to provide 4-(methylthio)butyl methanesulfonate which was carried on without purification or characterization.

The 4-(methylthio)butyl methanesulfonate (1.2 mmol), 1*H*-indol-3-yl(2,2,3,3-tetramethylcyclopropyl)methanone (0.15 g, 0.62 mmol), and NaH (60% dispersion in mineral oil, 0.12 g, 3.1 mmol) in DMF (8 mL) were processed as described in the procedure for **5** to provide **54** (0.19 g, 0.55 mmol, 89% yield). ^{1}H NMR (300 MHz, CD_3OD) δ ppm 1.31 (s, 6 H), 1.35 (s, 6 H), 1.60−1.72 (m, 2 H), 1.95 (s, 1 H), 1.97−2.05 (m, 2 H), 2.06 (s, 3 H), 2.53 (t, J = 6.8 Hz, 2 H), 4.19 (t, J = 7.1 Hz, 2 H), 7.26−7.28 (m, 2 H), 7.32−7.38 (m, 1 H), 7.67 (s, 1 H), 8.35−8.45 (m, 1 H); MS (DCI/NH_3) m/z 344 $(M + H)^+$. Anal. ($C_{21}H_{29}NOS$) C, H, N.

3-(3-(2,2,3,3-Tetramethylcyclopropanecarbonyl)-1*H*-indol-1-yl)propanoic Acid (55). A mixture of **57** and KOH (3 mL, 10% aqueous solution) in EtOH (6 mL) was warmed to reflux and was allowed to stir for 30 min. The mixture was cooled to ambient temperature and was concentrated under reduced pressure. The crude material was diluted with H_2O (5 mL) and EtOAc (5 mL). The layers were separated, the organic layer was discarded, and the aqueous layer was acidified with 5% aqueous HCl (5 mL). The aqueous layer was extracted with EtOAc (3 × 5 mL), and the combined organics were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The material was recrystallized with Et_2O and hexanes to provide **55** (0.11 g, 0.35 mmol, 81% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.30 (s, 6 H), 1.33 (s, 6 H), 1.93 (s, 1 H), 2.95 (t, J = 6.6 Hz, 2 H), 4.50 (t, J = 6.6 Hz, 2 H), 7.27−7.37 (m, 3 H), 7.75 (s, 1 H), 8.38−8.44 (m, 1 H); MS (DCI/NH_3) m/z 314 $(M + H)^+$. Anal. ($C_{19}H_{23}NO_3$) C, H, N.

3-(3-(2,2,3,3-Tetramethylcyclopropanecarbonyl)-1*H*-indol-1-yl)propanamide (56). The 3-chloropropanamide (0.18 g, 1.7 mmol), 1*H*-indol-3-yl(2,2,3,3-tetramethylcyclopropyl)methanone (0.20 g, 0.83 mmol), and NaH (60% dispersion in mineral oil, 100 mg, 2.5 mmol) in DMF (5 mL) were processed as described in the procedure for **5** to provide **56** (33 mg, 0.11 mmol, 13% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.30 (s, 6 H), 1.33 (s, 6 H), 1.92 (s, 1 H), 2.75 (t, J = 6.4 Hz, 2 H), 4.55 (t, J = 6.4 Hz, 2 H), 5.23−5.30 (m, 2 H), 7.26−7.30 (m, 2 H), 7.32−7.37 (m, 1 H), 7.75 (s, 1 H), 8.39−8.47 (m, 1 H); MS (DCI/NH_3) m/z 313 $(M + H)^+$. Anal. ($C_{19}H_{24}N_2O_2$) C, H, N.

Methyl 3-(3-(2,2,3,3-Tetramethylcyclopropanecarbonyl)-1*H*-indol-1-yl)propanoate (57). The methyl 3-bromopropanoate (0.26 g, 1.7 mmol), 1*H*-indol-3-yl(2,2,3,3-tetramethylcyclopropyl)methanone (0.20 g, 0.83 mmol), and NaH (60% dispersion in mineral oil, 83 mg, 2.1 mmol) in DMF (5 mL) were processed as described in the procedure for **5** to provide **57** (0.15 g, 0.46 mmol, 55% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.31 (s, 6 H), 1.33 (s, 6 H), 1.92 (s, 1 H), 2.89 (t, J = 6.6 Hz, 2 H), 3.68 (s, 3 H), 4.50 (t, J = 6.6 Hz, 2 H), 7.27−7.31 (m, 2 H), 7.31−7.35 (m, 1 H), 7.73 (s, 1 H), 8.38−8.46 (m, 1 H); MS (DCI/NH_3) m/z 328 $(M + H)^+$. Anal. ($C_{20}H_{25}NO_3$) C, H, N.

6-(3-(2,2,3,3-Tetramethylcyclopropanecarbonyl)-1*H*-indol-1-yl)hexan-2-one (58). The 6-chlorohexan-2-one (0.22 g, 1.7 mmol), 1*H*-indol-3-yl(2,2,3,3-tetramethylcyclopropyl)methanone (0.20 g, 0.83 mmol), and NaH (60% dispersion in mineral oil, 100 mg, 2.5 mmol) in DMF (5 mL) were processed as described in the procedure for **5** to provide **58** (43 mg, 0.13 mmol, 15% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.31 (s, 6 H), 1.35 (s, 6 H), 1.59−1.69 (m, 2 H), 1.82−1.94 (m, 2 H), 1.95 (s, 1 H), 2.12−2.12 (m, 3 H), 2.46 (t, J = 7.0 Hz, 2 H), 4.17 (t, J = 7.1 Hz, 2 H), 7.25−7.29 (m, 2 H), 7.31−7.34 (m, 1 H), 7.67 (s, 1 H), 8.37−8.46 (m, 1 H); MS (DCI/NH_3) m/z 340 $(M + H)^+$. Anal. ($C_{22}H_{29}NO_2$) C, H, N.

(1-Benzyl-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone (59). The benzyl bromide (0.15 mL, 1.2 mmol), 1*H*-indol-3-yl(2,2,3,3-tetramethylcyclopropyl)methanone (0.15 g, 0.62 mmol), and NaH (60% dispersion in mineral oil, 0.12 g, 3.1 mmol) in DMF (10 mL) were processed as described in the procedure for **5** to provide **59** (0.19 g, 0.57 mmol, 92% yield). ^{1}H NMR (300 MHz, CD_3OD) δ ppm 1.31 (s, 6 H), 1.32 (s, 6 H), 2.13 (s, 1 H), 5.47 (s, 2 H), 7.14−7.23 (m, 3 H), 7.25−7.43 (m, 5 H), 8.12 (s, 1 H), 8.18−8.32 (m, 1 H); MS (DCI/NH_3) m/z 332 $(M + H)^+$. Anal. ($C_{23}H_{25}NO$) C, H, N.

(1-(Pyridin-3-ylmethyl)-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone (60). The pyridin-3-ylmethanol (0.24 g, 2.1 mmol), triethylamine (0.93 mL, 6.7 mmol), and methanesulfonyl chloride (0.33 mL, 4.2 mmol) in 20 mL of THF were processed as described in the procedure for 2-morpholin-4-ylethyl methanesulfonate to provide pyridin-3-ylmethyl methanesulfonate which was carried on without purification or characterization.

The pyridin-3-ylmethyl methanesulfonate (2.1 mmol), 1*H*-indol-3-yl(2,2,3,3-tetramethylcyclopropyl)methanone (0.30 g, 1.2 mmol), and NaH (60% dispersion in mineral oil, 0.23 g, 5.8 mmol) in DMF (25 mL) were processed as described in the procedure for **5** to provide **60** (0.31 g, 0.94 mmol, 76% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.29 (s, 6 H), 1.35 (s, 6 H), 1.94 (s, 1 H), 5.44 (s, 2 H), 7.20−7.32 (m, 3 H), 7.36 (dd, J = 7.6, 5.3 Hz, 1 H), 7.44−7.52 (m, 1 H), 7.71 (s, 1 H), 8.39−8.47 (m, 1 H), 8.54−8.71 (m, 2 H); MS (DCI/NH_3) m/z 333 $(M + H)^+$. Anal. ($C_{22}H_{24}N_2O \cdot 0.2H_2O$) C, H, N.

(1-(Pyridin-4-ylmethyl)-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone (61). The pyridin-4-ylmethanol (0.24 g, 2.1 mmol), triethylamine (0.93 mL, 6.7 mmol), and methanesulfonyl chloride (0.33 mL, 4.2 mmol) in 20 mL of THF were processed as described in the procedure for 2-morpholin-4-ylethyl methanesulfonate to provide pyridin-4-ylmethyl methanesulfonate which was carried on without purification or characterization.

The pyridin-4-ylmethyl methanesulfonate (2.1 mmol), 1*H*-indol-3-yl(2,2,3,3-tetramethylcyclopropyl)methanone (0.30 g, 1.2 mmol), and NaH (60% dispersion in mineral oil, 0.23 g, 5.8 mmol) in DMF (25 mL) were processed as described in the procedure for **5** to provide **61** (0.31 g, 0.94 mmol, 76% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.30 (s, 6 H), 1.36 (s, 6 H), 1.95 (s, 1 H), 5.43 (s, 2 H), 7.08 (d, J = 5.4 Hz, 2 H), 7.11−7.19 (m, 1 H), 7.21−7.34 (m, 2 H), 7.71 (s, 1 H), 8.41−8.49 (m, 1 H), 8.52−8.68 (m, 2 H); MS (DCI/NH_3) m/z 333 $(M + H)^+$. Anal. ($C_{22}H_{24}N_2O$) C, H, N.

(1-(2-(Pyridin-2-yl)ethyl)-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone (62). The 2-(pyridin-2-yl)ethanol (0.11 mL, 0.99 mmol), triethylamine (0.42 mL, 3.0 mmol), and methanesulfonyl chloride (0.12 mL, 1.5 mmol) in 5 mL of THF were processed as described in the procedure for 2-morpholin-4-ylethyl methanesulfonate to provide 2-(pyridin-2-yl)ethyl methanesulfonate which was carried on without purification or characterization.

The 2-(pyridin-2-yl)ethyl methanesulfonate (0.99 mmol), 1*H*-indol-3-yl(2,2,3,3-tetramethylcyclopropyl)methanone (0.12 g, 0.50 mmol), and NaH (60% dispersion in mineral oil, 0.10 g, 2.5 mmol) in DMF (10 mL) were processed as described in the procedure for **5** to provide the free base of **62**. The free base was dissolved in EtOAc and EtOH, and *p*-TSA (1 equiv) in EtOAc was added. The resulting solids were isolated via filtration to give **62** (78 mg, 0.15 mmol, 30% yield). ^{1}H NMR (300 MHz, CD_3OD) δ ppm 1.29 (s, 6 H), 1.30 (s, 6 H), 2.01 (s, 1 H), 2.36 (s, 3 H), 3.59 (t, J = 6.6 Hz, 2 H), 4.75 (t, J = 6.6 Hz, 2 H), 7.16−7.28 (m, 4 H), 7.33−7.40 (m, 1 H), 7.70 (dt, J = 8.6, 2.0 Hz, 2 H), 7.74−7.79 (m, 1 H), 7.82−7.86 (m, 1 H), 7.88 (s, 1 H), 8.21−8.27 (m, 1 H), 8.38 (dt, J = 7.8, 1.7 Hz, 1 H), 8.65 (dd, J = 5.8, 0.7 Hz, 1 H); MS (DCI/NH_3) m/z 347 (M + H)$^+$. Anal. ($C_{23}H_{26}N_2O\cdot C_7H_8O_3S$) C, H, N.

(1-(2-(Pyridin-3-yl)ethyl)-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone (63). The 2-(pyridin-2-yl)ethanol (0.15 mL, 1.2 mmol), triethylamine (0.56 mL, 4.1 mmol), and methanesulfonyl chloride (0.15 mL, 1.9 mmol) in 10 mL of THF were processed as described in the procedure for 2-morpholin-4-ylethyl methanesulfonate to provide 2-(pyridin-3-yl)ethyl methanesulfonate which was carried on without purification or characterization.

The 2-(pyridin-3-yl)ethyl methanesulfonate (1.2 mmol), 1*H*-indol-3-yl(2,2,3,3-tetramethylcyclopropyl)methanone (0.15 g, 0.62 mmol), and NaH (60% dispersion in mineral oil, 0.12 g, 3.1 mmol) in DMF (8 mL) were processed as described in the procedure for **5** to provide **63** (74 mg, 0.21 mmol, 34% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.25 (s, 6 H), 1.32 (s, 6 H), 1.79 (s, 1 H), 3.23 (t, J = 6.8 Hz, 2 H), 4.44 (t, J = 6.6 Hz, 2 H), 7.20−7.31 (m, 5 H), 7.36 (s, 1 H), 8.40−8.45 (m, 1 H), 8.46−8.62 (m, 2 H); MS (DCI/NH_3) m/z 347 (M + H)$^+$. Anal. ($C_{23}H_{26}N_2O\cdot 0.2C_6H_{14}\cdot 0.3H_2O$) C, H, N.

(1-(2-(Pyridin-4-yl)ethyl)-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone (64). The 2-(pyridin-4-yl)ethanol (0.15 mL, 1.2 mmol), triethylamine (0.56 mL, 4.1 mmol), and methanesulfonyl chloride (0.15 mL, 1.9 mmol) in 10 mL of THF were processed as described in the procedure for 2-morpholin-4-ylethyl methanesulfonate to provide 2-(pyridin-4-yl)ethyl methanesulfonate which was carried on without purification or characterization.

The 2-(pyridin-4-yl)ethyl methanesulfonate (1.2 mmol), 1*H*-indol-3-yl(2,2,3,3-tetramethylcyclopropyl)methanone (0.15 g, 0.62 mmol), and NaH (60% dispersion in mineral oil, 0.12 g, 3.1 mmol) in DMF (8 mL) were processed as described in the procedure for **5** to provide **64** (42 mg, 0.12 mmol, 20% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.25 (s, 6 H), 1.31 (s, 6 H), 1.78 (s, 1 H), 3.20 (t, J = 7.0 Hz, 2 H), 4.44 (t, J = 7.0 Hz, 2 H), 7.03 (d, J = 5.4 Hz, 2 H), 7.27−7.32 (m, 3 H), 7.35 (s, 1 H), 8.36−8.46 (m, 1 H), 8.51 (d, J = 4.7 Hz, 2 H); MS (DCI/NH_3) m/z 347 (M + H)$^+$. Anal. ($C_{23}H_{26}N_2O\cdot 0.3H_2O$) C, H, N.

(1-(2-(1*H*-Pyrrol-1-yl)ethyl)-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone (65). The 2-(1*H*-pyrrol-1-yl)ethanol (0.13 mL, 1.2 mmol), triethylamine (0.56 mL, 4.1 mmol), and methanesulfonyl chloride (0.15 mL, 1.9 mmol) in 10 mL of THF were processed as described in the procedure for 2-morpholin-4-ylethyl methanesulfonate to provide 2-(1*H*-pyrrol-1-yl)ethyl methanesulfonate which was carried on without purification or characterization.

The 2-(1*H*-pyrrol-1-yl)ethyl methanesulfonate (1.2 mmol), 1*H*-indol-3-yl(2,2,3,3-tetramethylcyclopropyl)methanone (0.15 g, 0.62 mmol), and NaH (60% dispersion in mineral oil, 0.12 g, 3.1 mmol) in DMF (8 mL) were processed as described in the procedure for **5** to provide **65** (40 mg, 0.12 mmol, 19% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.24 (s, 6 H), 1.31 (s, 6 H), 1.71 (s, 1 H), 4.23−4.27 (m, 2 H), 4.40−4.50 (m, 2 H), 6.13 (t, J = 2.0 Hz, 2 H), 6.41 (t, J = 2.0 Hz, 2 H), 6.92 (s, 1 H), 7.26−7.33 (m, 3 H), 8.39−8.47 (m, 1 H); MS (DCI/NH_3) m/z 335 (M + H)$^+$. Anal. ($C_{23}H_{26}N_2O\cdot 0.1C_6H_{14}\cdot 0.7H_2O$) C, H, N.

(1-((1-Methyl-1*H*-imidazol-2-yl)methyl)-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone (66). The (1-methyl-1*H*-imidazol-2-yl)methanol (66 mg, 0.59 mmol), triethylamine (0.25 mL, 1.8 mmol), and methanesulfonyl chloride (69 μL, 0.89 mmol) in 5 mL of THF were processed as described in the procedure for 2-morpholin-4-ylethyl methanesulfonate to provide (1-methyl-1*H*-imidazol-2-yl)methyl methanesulfonate which was carried on without purification or characterization.

The (1-methyl-1*H*-imidazol-2-yl)methyl methanesulfonate (0.59 mmol), 1*H*-indol-3-yl(2,2,3,3-tetramethylcyclopropyl)methanone (0.10 g, 0.41 mmol), and NaH (60% dispersion in mineral oil, 60 mg, 1.5 mmol) in DMF (5 mL) were processed as described in the procedure for **5** to provide the free base of **66**. The free base was dissolved in EtOAc and EtOH, and *p*-TSA (1 equiv) in EtOAc was added. The resulting solids were isolated via filtration to give **66** (20 mg, 0.06 mmol, 15% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.24 (s, 6 H), 1.31 (s, 6 H), 1.79 (s, 3 H), 1.99 (s, 1 H), 2.35 (s, 3 H), 3.58 (s, 2 H), 6.06−6.20 (m, 1 H), 6.96 (s, 1 H), 7.18 (d, J = 8.1 Hz, 2 H), 7.23−7.43 (m, 3 H), 7.79 (d, J = 8.1 Hz, 2 H), 8.05−8.16 (m, 1 H), 8.41 (dd, J = 7.5, 1.4 Hz, 1 H); MS (DCI/NH_3) m/z 336 (M + H)$^+$. Anal. ($C_{23}H_{26}N_2O\cdot 1.3C_7H_8O_3S\cdot H_2O$) C, H, N.

(2,2,3,3-Tetramethylcyclopropyl)(1-(2-(thiophen-2-yl)ethyl)-1*H*-indol-3-yl)methanone (67). The 2-(thiophen-2-yl)ethanol (0.14 mL, 1.2 mmol), triethylamine (0.56 mL, 4.1 mmol), and methanesulfonyl chloride (0.15 mL, 1.9 mmol) in 10 mL of THF were processed as described in the procedure for 2-morpholin-4-ylethyl methanesulfonate to provide 2-(thiophen-2-yl)ethyl methanesulfonate which was carried on without purification or characterization.

The 2-(thiophen-2-yl)ethyl methanesulfonate (1.2 mmol), 1*H*-indol-3-yl(2,2,3,3-tetramethylcyclopropyl)methanone (0.15 g, 0.62 mmol), and NaH (60% dispersion in mineral oil, 0.12 g, 3.1 mmol) in DMF (8 mL) were processed as described in the procedure for **5** to provide **67** (0.12 g, 0.34 mmol, 55% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.26 (s, 6 H), 1.31 (s, 6 H), 1.81 (s, 1 H), 3.37 (t, J = 6.8 Hz, 2 H), 4.42 (t, J = 7.1 Hz, 2 H), 6.66 (dd, J = 3.6, 0.8 Hz, 1 H), 6.90 (dd, J = 5.3, 3.6 Hz, 1 H), 7.19 (dd, J = 5.1, 1.4 Hz, 1 H), 7.26−7.32 (m, 2 H), 7.30−7.36 (m, 1 H), 7.43 (s, 1 H), 8.37−8.48 (m, 1 H); MS (DCI/NH_3) m/z 352 (M + H)$^+$. Anal. ($C_{22}H_{25}NOS$) C, H, N.

(2,2,3,3-Ttetramethylcyclopropyl)(1-(2-(thiophen-3-yl)ethyl)-1*H*-indol-3-yl)methanone (68). The 2-(thiophen-3-yl)ethanol (0.14 mL, 1.2 mmol), triethylamine (0.56 mL, 4.1 mmol), and methanesulfonyl chloride (0.15 mL, 1.9 mmol) in 10 mL of THF were processed as described in the procedure for 2-morpholin-4-ylethyl methanesulfonate to provide 2-(thiophen-3-yl)ethyl methanesulfonate which was carried on without purification or characterization.

The 2-(thiophen-3-yl)ethyl methanesulfonate (1.2 mmol), 1*H*-indol-3-yl(2,2,3,3-tetramethylcyclopropyl)methanone (0.15 g, 0.62 mmol), and NaH (60% dispersion in mineral oil, 0.12 g, 3.1 mmol) in DMF (8 mL) were processed as described in the procedure for **5** to provide **68** (0.15 g, 0.43 mmol, 69% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.25 (s, 6 H), 1.32 (s, 6 H), 1.79 (s, 1 H), 3.18 (t, J = 7.0 Hz, 2 H), 4.38 (t, J = 6.8 Hz, 2 H), 6.81−6.86 (m, 2 H), 7.25−7.29 (m, 3 H), 7.30−7.34 (m, 1 H), 7.35 (s, 1 H), 8.37−8.45 (m, 1 H); MS (DCI/NH_3) m/z 352 (M + H)$^+$. Anal. ($C_{22}H_{25}NOS$) C, H, N.

(1-(2-(4-Methylthiazol-5-yl)ethyl)-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone (69). The 2-(4-methylthiazol-5-yl)ethanol (0.15 mL, 1.2 mmol), triethylamine (0.56 mL, 4.1 mmol), and methanesulfonyl chloride (0.15 mL, 1.9 mmol) in

10 mL of THF were processed as described in the procedure for 2-morpholin-4-ylethyl methanesulfonate to provide 2-(4-methylthiazol-5-yl)ethyl methanesulfonate which was carried on without purification or characterization.

The 2-(4-methylthiazol-5-yl)ethyl methanesulfonate (1.2 mmol), 1*H*-indol-3-yl(2,2,3,3-tetramethylcyclopropyl)methanone (0.15 g, 0.62 mmol), and NaH (60% dispersion in mineral oil, 0.12 g, 3.1 mmol) in DMF (8 mL) were processed as described in the procedure for **5** to provide **69** (73 mg, 0.20 mmol, 32% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.26 (s, 6 H), 1.32 (s, 6 H), 1.81 (s, 1 H), 2.15 (s, 3 H), 3.33 (t, J = 5.8 Hz, 2 H), 4.39 (t, J = 6.3 Hz, 2 H), 7.26−7.31 (m, 3 H), 7.39 (s, 1 H), 8.36−8.46 (m, 1 H), 8.57−8.71 (m, 1 H); MS (DCI/NH_3) m/z 367 $(M + H)^+$. Anal. ($C_{22}H_{26}N_2OS$) C, H, N.

(1-(2-(5-Chloro-1,2,4-thiadiazol-3-yl)ethyl)-1*H*-indol-3-yl)(2,2,3,-3-tetramethylcyclopropyl)methanone (70). The 5-chloro-3-(chloromethyl)-1,2,4-thiadiazole (0.21 g, 1.2 mmol), 1*H*-indol-3-yl(2,2,3,3-tetramethylcyclopropyl)methanone (0.15 g, 0.62 mmol), and NaH (60% dispersion in mineral oil, 0.12 g, 3.1 mmol) in DMF (10 mL) were processed as described in the procedure for **5** to provide **70** (50 mg, 0.13 mmol, 22% yield). ^{1}H NMR (300 MHz, CD_3OD) δ ppm 1.36 (s, 6 H), 1.37 (s, 6 H), 2.07 (s, 1 H), 4.79 (s, 2 H), 7.43 (dt, J = 7.5, 1.2 Hz, 1 H), 7.50 (dt, J = 7.7, 1.5 Hz, 1 H), 7.83−7.91 (m, 1 H), 8.34 (s, 1 H), 8.47−8.52 (m, 1 H); MS (DCI/NH_3) m/z 373 $(M + H)^+$. Anal. ($C_{19}H_{20}ClN_3OS \cdot 0.4H_2O$) C, H, N.

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