Structure-Based Design, Synthesis, and Biological Evaluation of Indomethacin Derivatives as Cyclooxygenase-2 Inhibiting Nitric Oxide Donors[§]

Shiow-Jyi Wey,* Michael E. Augustyniak, Edward D. Cochran, James L. Ellis, Xinqin Fang, David S. Garvey, David R. Janero, L. Gordon Letts, Allison M. Martino, Terry L. Melim, Madhavi G. Murty, Steward K. Richardson, Joseph D. Schroeder, William M. Selig, A. Mark Trocha, Roseanne S. Wexler, Delano V. Young, Irina S. Zemtseva, and Brian M. Zifcak

NitroMed, Inc., 125 Spring Street, Lexington, Massachusetts 02421

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Indomethacin, a nonselective cyclooxygenase (COX) inhibitor, was modified in three distinct regions in an attempt both to increase cyclooxygenase-2 (COX-2) selectivity and to enhance drug safety by covalent attachment of an organic nitrate moiety as a nitric oxide donor. A human whole-blood COX assay shows the modifications on the 3-acetic acid part of the indomethacin yielding an amide-nitrate derivative **32** and a sulfonamide-nitrate derivative **61** conferred COX-2 selectivity. Along with their respective *des*-nitrate analogs, for example, **31** and **62**, the nitrates **32** and **61** were effective antiinflammatory agents in the rat air-pouch model. After oral dosing, though, only **32** increased nitrate and nitrite levels in rat plasma, indicating that its nitrate tether served as a nitric oxide donor in vivo. In a rat gastric injury model, examples **31** and **32** both show a 98% reduction in gastric lesion score compared to that of indomethacin. In addition, the nitrated derivative **32** inducing 85% fewer gastric lesions when coadministered with aspirin as compared to the combination of aspirin and valdecoxib.

Introduction

Common adverse effects of nonsteroidal anti-inflammatory drugs (NSAIDs) (e.g., aspirin, indomethacin, naproxen, and ibuprofen) are gastrointestinal (GI) bleeding, ulceration, and more severely, perforation. Prostaglandins (PGs) synthesized by the "housekeeping" cyclooxygenase-1 (COX-1) enzyme mediate many physiological functions, including GI cytoprotection. The immediate hypothesis after the discovery of the "inducible" COX-2 enzyme and its increased expression at the sites of inflammation was that the proinflammatory PGs produced by COX-2 caused pain and fever.[1–3] Therefore, a selective COX-2 inhibitor was expected to exert the anti-inflammatory, analgesic and antipyretic effects of conventional NSAIDs without the undesired GI side effects associated with COX-1 inhibition. The subsequent discovery that COX-2 is constitutively expressed in the brain, the spinal cord, and the kidneys[4,5] suggested that the COX-2 derived PGs have beneficial effects in, for example, ulcer healing[6] and regulation of renal function.[7] The physiological importance of COX-2 was subsequently manifested in the clinic as increased cardiovascular and renal risks associated with COX-2 inhibitors,[8,9] particularly, when administered concurrently with aspirin.[10,11] The cardio-renal liability of COX-2 inhibitor drugs has severely restricted their use as anti-inflammatory agents, especially for those with very high selectivity for the COX-2 isoform that may obviate physiological effects of COX-2 derived PGs and induced a prothrombotic state.

Nitric oxide (NO) also plays many important physiological roles, including, vasoregulation, GI tissue protection,[12] wound healing,[13] and inhibition of platelet activity.[14] Because of its cyctoprotective effects and its potent antiplatelet and vasorelaxant properties, adjunctive NO has been considered a plausible means for improving the GI safety of traditional NSAIDs. COX-inhibiting nitric oxide donors (CINODs) are currently under laboratory and clinical investigation for using NO to improve and enhance traditional NSAIDs,[13,15–28] as well as for COX-2 selective inhibitors.[29,30] Especially in predisposed cardiovascular patients, the increased cardiovascular risk of COX-2 selective inhibitors and their gastric toxicity when administered with aspirin prophylaxis might be ameliorated by supplementary NO.

The crystal structures of the inhibitor-bound COXs show that the catalytic binding site is a long hydrophobic channel. From a combination of the information from the 3-D crystal structures, site-directed mutation studies, and kinetic experiments, the rationale for inhibitor binding and COX-2 selectivity are summarized as follows: Arg120[31] at the entrance of the catalytic active site forms a salt bridge with the carboxylic acid end of the traditional NSAIDs, an interaction important for COX-1 inhibition by traditional NSAIDs, but not crucial for COX-2 inhibition.[32,33] Therefore, carboxylic acids are not a structural requirement for COX-2 selective inhibitors. Other amino acids involved in the hydrogen-bonding network at the entrance for binding inhibitors are Tyr355 and Glu524.[34] In COX-1, Ile523 blocks the diaryl-heterocycle-type selective inhibitors from entering the catalytic site.[35] Because of the shorter side chain of Val523 in COX-2, a side-pocket is created (17% increased size) next to the main catalytic binding site. This side pocket is referred to as the "selective binding site" because traditional NSAIDs do not use this space. In the crystal structures of 1CX2 and 6COX, the aryl-sulfonamide group of SC-558, a bromo-analog of the COX-2 selective inhibitor celecoxib, penetrates deep into this side pocket and interacts with polar groups His90, Glu192, and Arg513.[36] There is a possibility that the hydrogen-bonding network extends to nearby Glu524, which is part of the hydrogen-bonding network at the entrance. In COX-1, His513's side chain is shorter, so even if the inhibitor can bypass Ile523, it likely cannot interact with His513. The use of this side-pocket and established hydrogen bonding to form a tight-binding slowly reversible complex was suggested to be the

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* To whom correspondence should be addressed. Phone: 978-362-1812. E-mail: swey@comcast.net.

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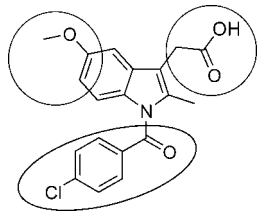


Figure 1. Three regions of modification on indomethacin.

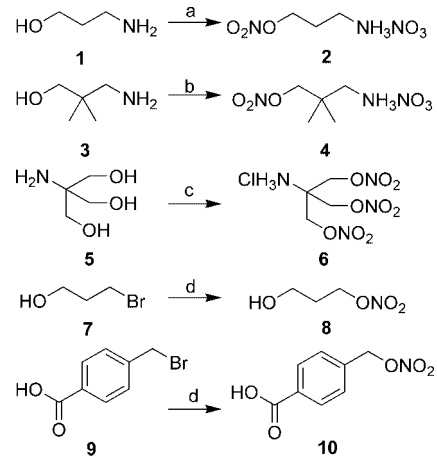
reason for the selectivity. In the report on the modification of meclofenamic acid, Kalgutkar et al.[37] found that Tyr355 showed a more important role in COX-2 inhibition than did Arg120 from their mutation binding studies. Since Try355 is conserved in both isoforms, the authors suggest the selectivity must arise from outside the entrance of the binding site, commonly, referred to as the "lobby" region. The specific sequence differences responsible for the selectivity of the amide derivatives of meclofenamic acid were not identified.

Induced COX conformational changes after binding with inhibitors caused by the flexibility and sequence differences of the peptide chain have also been suggested to play a role in isoform selectivity. For example, one of the sequence differences between COX-1 and COX-2 is located at the junction of α-helices C and D, which is the framework in front of the catalytic binding site.[38] As a result of an extra amino acid inserted between α-helices C and D in COX-2, the α-helix D that contains Arg120 has more flexibility at the entrance of the binding site. The combination of these observations with the kinetic data leads to a possible inhibition profile being proposed: $E + I \leftrightarrows [EI] \leftrightarrows EI^*$.[39–43] The induced conformational change resulted a tight-binding, slowly reversible enzyme (E)−inhibitor (I) complex, EI*. COX-1 inhibition is usually time independent, whereas COX-2 inhibition is time dependent. Therefore, the equilibrium between weak complex [EI] and tight complex EI* can influence selectivity, as may multiple stages of binding complexes.[44,45]

There have been several reports of using traditional NSAID as pharmacophores for the design and syntheses of new COX-2 selective inhibitors, including aspirin,[46] meloxicam,[47] nimesulide,[48] meclofenamic acid,[37] ketoprofen,[49] flurbiprofen,[50] and indomethacin.[51–56] Herein, we report the design and synthesis of a nitric oxide-donating COX-2 selective inhibitor modified from indomethacin that showed modest COX-2 selectivity in a human whole-blood assay with improved GI safety, especially when coadministered with aspirin.

Molecule Design. As shown in Figure 1, three regions of modifications were preformed with the goal of enhancing the COX-2 selectivity based on the information just summarized, and improving its safety profile as a COX-2 selective inhibitor by attaching a NO donor. From a comparison of the crystal structures of inhibitor-bound COX-2 enzymes, 4COX (with indomethacin) and 1CX2 (with SC-558), the 5-methoxy group and the 6-position of the indomethacin are very close to Val523 and the methoxy group lines up with the sulfonamide group of SC-558. Thus, the modifications on the 5- or 6-positions of the indole ring were intended to increase the steric interaction with Ile523 in COX-1, the probability of establishing a hydrogen-bond with Arg513 in the selective binding site of COX-2, or both. The second region of modification was at the N-1 position of the indole ring. The 4-chlorobenzoyl group of the indomethacin, which binds in the apical pocket of the binding site, will be replaced with cycloalkylalkyl and arylalkyl groups to explore other hydrophobic residues that can bind in this cavity. Although the specific sequence differences outside the binding site that are responsible for the selectivity were not identified by Kalgutkar et al.,[37] there are two uncharged polar amino acids just outside the entrance on α-helix D, Tyr115 and Ser119 in COX-2 instead of Leu115 and Val119 in COX-1,[35] that may influence the inhibitor binding by establishing hydrogen bonds with a polar-end tether. Finally, since a carboxylic acid-end is not a structural requirement for COX-2 inhibition, the 3-acetic acid group of indomethacin was converted to alternative functional groups and attached with either an alcohol or a nitrate as a NO donor. These polar-end tethers may also serve to establish possible hydrogen-bonding with Tyr115, Ser119, or both outside the binding channel and, hence, may increase the COX-2 selectivity.

Scheme 1. Synthesis of Nitrate Tethers As Nitric Oxide Donors[a]



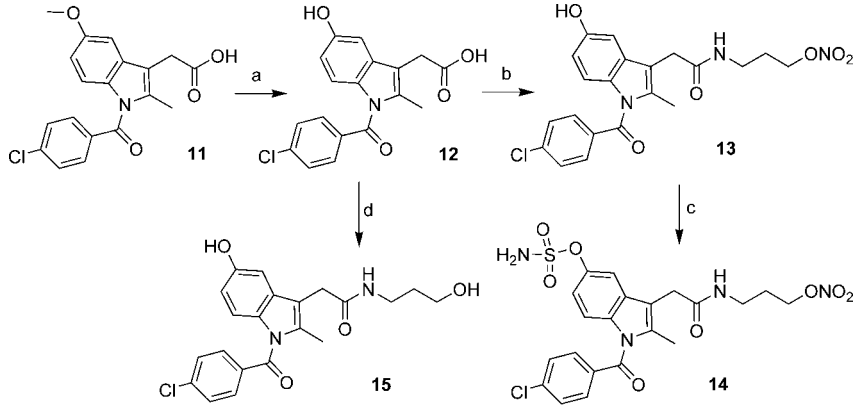
[a] Reagents and conditions: (a) 90% fuming HNO_3, Ac_2O, 0°C; (b) 90% fuming HNO_3, Ac_2O, EtOAc, 0°C; (c) i. 90% fuming HNO_3, Ac_2O, AcOH, 0°C; ii. 2 N NaON; iii. HCl/Et_2O; (d) $AgNO_3$, acetonitrile.

Syntheses. The nitrate tethers for use as potential NO donors were synthesized either according to or modified from literature procedures. As shown in Scheme 1, the nitric acid salts of 3-(nitrooxy)propylamine **2** and 2,2-dimethyl-3-(nitrooxy)propylamine **4** were prepared from the nitration of the corresponding amino alcohols with acetyl nitrate, prepared in situ from 90% fuming nitric acid and acetic anhydride. The free base of Tris−trinitrate **6** was prepared according to a literature procedure and was treated with dry hydrochloride in ethyl ether to afford the salt for storage.[57] All amine-nitrate derivatives were not stable at room temperature for a long period of time and therefore were kept in the freezer as ammonium salts. 3-(Nitrooxy)propan-1-ol[58] **8** and 4-[(nitrooxy)methyl]benzoic acid **10** were prepared from the corresponding bromo-derivatives and silver nitrate in acetonitrile.

The 5-*O*-sulfamate compound **14** was prepared as shown in Scheme 2. Demethylation of indomethacin with boron tribromide in methylene chloride afforded the phenolic compound **12**,[59] a possible indomethacin metabolite. The amine-nitrate tether **2** and 3-aminopropanol **1** were coupled to the 3-acetic acid in the presence of *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDAC) to give examples **13** and **15**, respectively. The phenolic group was then transformed to *O*-sulfamate **14** by reaction with sulfamoyl chloride in *N*-methyl-2-pyrrolidinone.[60]

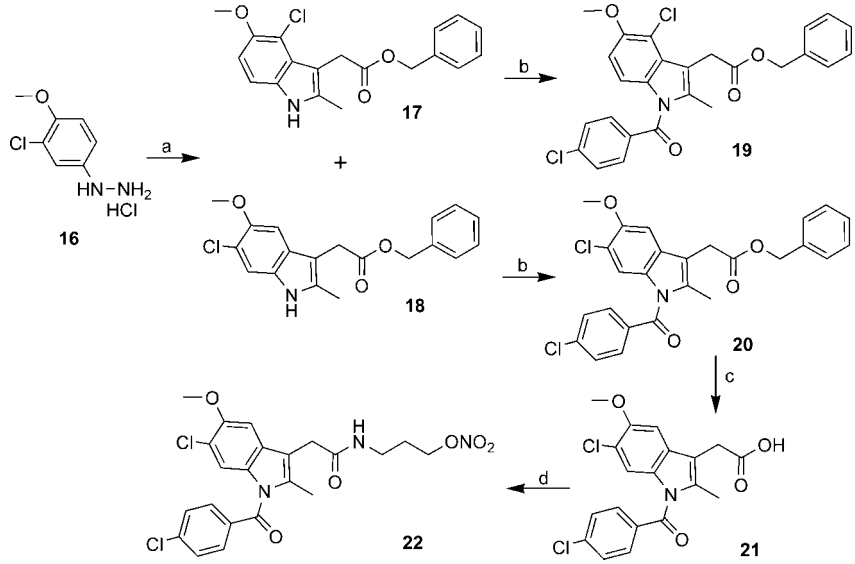
The 4- and 6-chloro derivatives of indomethacin were prepared starting from a Fisher indole synthesis as shown in Scheme 3. Condensation between 3-chloro-4-methoxyphenylhydrazine **16**, which was prepared from 3-chloro-*p*-anisidine following a literature procedure,[61] and benzyl levulinate in

Scheme 2. Synthesis of 5-Position Modified Indomethacin and its Derivatives[a]



[a] Reagents and conditions: (a) BBr_3, CH_2Cl_2; (b) **2**, NEt_3, DMAP, EDAC; (c) $ClSO_2NH_2$, *N*-methyl-2-pyrrolidinone; (d) **1**, NEt_3, DMAP, EDAC.

Scheme 3. Synthesis of 4- and 6-Chloro-indomethacin Derivatives[a]



[a] Reagents and conditions: (a) benzyl levulinate, AcOH, reflux; (b) 4-chlorobenzoyl chloride, DMAP, NEt_3, CH_2Cl_2; (c) 10%Pd/C, H_2 (30 psi), EtOAc, MeOH; (d) **2**, NEt_3, DMAP, EDAC.

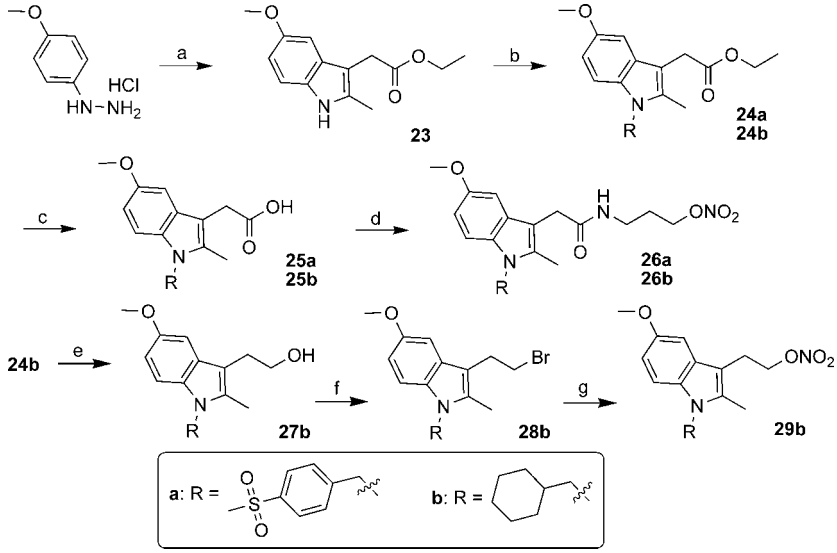
refluxing acetic acid gave compounds **17** and **18** in a ratio of 1:2. These two regioisomers were separated by column chromatography and were reacted with 4-chlorobenzoyl chloride in the presence of 4-dimethylaminopyridine (DMAP) to obtain **19** and **20**, respectively. 6-Chloro indomethacin **21** was obtained by hydrogenation of benzyl ester **20** in the presence of 10% Pd on carbon. The amine-nitrate tether **2** was then coupled to the carboxylic acid to afford compound **22**.

Syntheses to replace the 4-chlorobenzoyl group of indomethacin are shown in Scheme 4. Fisher indole synthesis using 4-methoxyphenylhydrazine and ethyl levulinate in acetic acid, followed by N-1 alkylation with 4-(bromomethyl)-1-(methylsulfonyl)benzene[62] using potassium *t*-butoxide as base, gave compound **24a**. After hydrolysis with aqueous sodium hydroxide in THF, the acid **25a** was coupled with amine-nitrate tether **2** to give example **26a**. The *N*-cyclohexylmethyl derivatives **26b** was synthesized using the same procedure as **26a** except (bromomethyl)cyclohexane was used for N-1 alkylation of compound **23**. The nitrate **29b** was prepared from the reduction of ethyl ester **24b** with lithium aluminum hydride, followed by the bromination with hydrobromic acid and then reaction with silver nitrate.

As shown in Scheme 5, the amide derivatives of indomethacin, compounds **30**−**33**, were all prepared in the same manner by coupling with an amine-alcohol or an amine-nitrate in the presence of EDAC. The amide derivative **34** and hydroxamic acid **35** were prepared from the reaction of the acyl chloride of indomethacin[63] with Tris−trinitrate **6** or hydroxylamine. Acetyl-derivatives of hydroxamic acid, examples **36** and **37**, were obtained by controlling the amount of acetic anhydride used in the reaction. The *O*-alkyl hydroxamic acid derivatives, examples **38**−**40**, were prepared from the coupling reaction with the corresponding *O*-alkyl hydroxylamines. The *O*-alkyl-hydroxylamines **43** and **44** were prepared from O-alkylation of *N*-hydroxyphthalimide with bromoalcohols in the presence of sodium acetate followed by deprotection with hydrazine.[64]

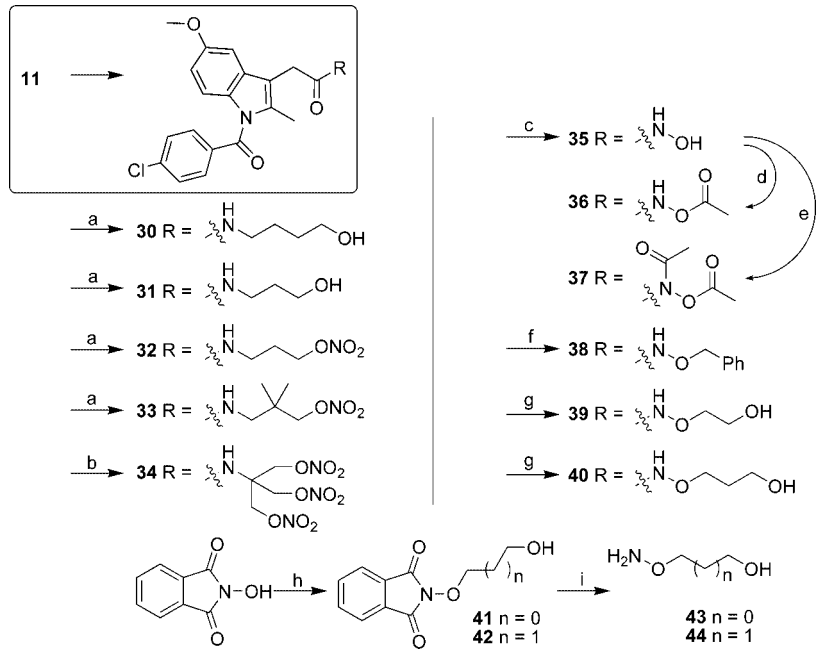
Other modifications on the 3-acetic acid of indomethacin started from borane reduction of indomethacin to give ethanol derivative **45**, as shown in Scheme 6. The ethanol derivative **45** was then transformed to nitrate **47**, bromide **48**, and azide **54** through a common intermediate, mesylate **46**. The phosphonic acid **50** were synthesized via an Abuzov reaction by reacting bromide **48** with trimethyl phosphite, followed by hydrolysis with bromotrimethylsilane.[65] The carboxylsulfamide **51** and carboxylsulfamate **52** were prepared from the reaction of ethanol derivative **45** and chlorosulfonyl isocyanate followed by the addition of nitrate tethers **2** or **8**. Phosgene was used in the preparation of carbamate **53** through the formation of the chloroformate of **45**. The amine

Scheme 4. Synthesis of N-Modified Indomethacin and its Derivatives[a]



[a] Reagents and conditions: (a) ethyl levulinate, AcONa, AcOH, reflux; (b) *t*-BuOK, 4-(bromomethyl)-1-(methylsulfonyl)benzene for **24a** or (bromomethyl)cyclohexane for **24b**; (c) 2 N NaOH, THF; (d) **2**, NEt_3, EDAC; (e) $LiAlH_4$; (f) HBr; (g) $AgNO_3$, acetonitrile.

Scheme 5. Preparation of Indomethacin Amide and Hydroxamic Acid Derivatives[a]



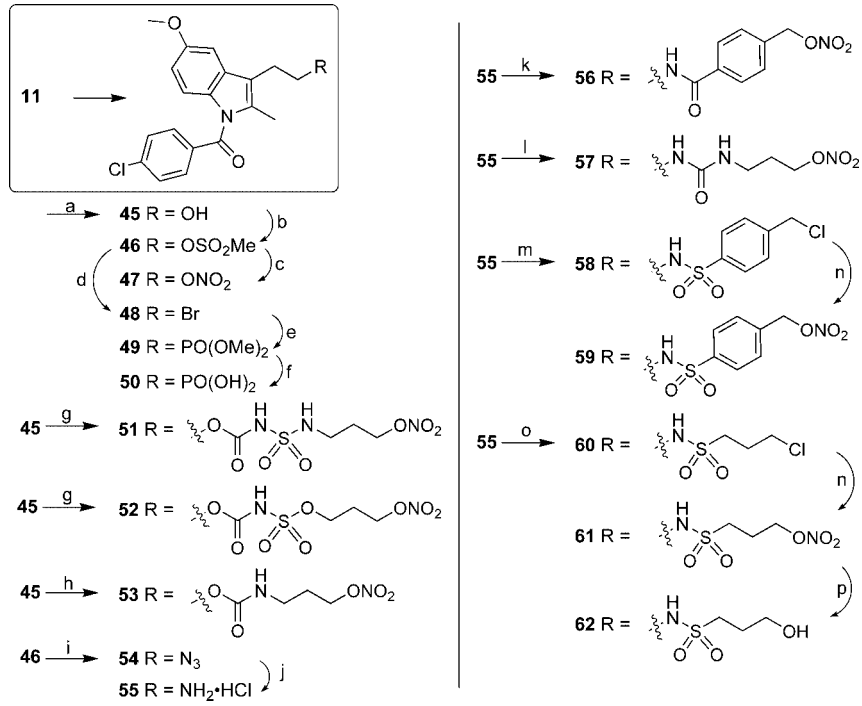
[a] Reagents and conditions: (a) amines, NEt_3, DMAP, EDAC; (b) i. $(COCl)_2$, CH_2Cl_2; ii. **6**, NEt_3; (c) i. $(COCl)_2$, CH_2Cl_2; ii. $NH_2OH \cdot HCl$, DMAP; (d) Ac_2O (1.3 equiv), DMAP, DMSO; (e) Ac_2O (large excess), DMSO; (f) *O*-benzylhydroxylamine, EDAC, NEt_3, CH_2Cl_2; (g) **43** or **44**, EDAC, NEt_3, CH_2Cl_2; (h) AcONa, 2-bromoethanol or 3-bromopropan-1-ol, DMSO, 70°C; (i) $N_2H_4 \cdot H_2O$, MeOH, 70°C.

derivative **55** was prepared from the hydrogenation of azide **54** in the presence of acetic acid and was converted to the hydrochloride salt to prevent possible N-1 benzoyl group transposition to the primary amine. The benzyl nitrate tether **10** was coupled to the amine **55** in the presence of triethylamine and EDAC to afford the inverse amide **56**. The urea derivative **57** was prepared through the formation of the carbamoyl imidazole intermediate of amine **55,** followed by the addition of amine-nitrate tether **2**. The sulfonamide derivatives **58** and **60** were obtained from the reaction of the corresponding sulfonyl chloride with amine **55** and were converted to their nitrate derivatives, examples **59** and **61**, with silver nitrate in refluxing acetonitrile. Although 4-(bromomethyl) benzenesulfonyl chloride was used in the preparation of sulfonamide derivative **58**, the chloromethyl derivative was isolated because of the halogen exchange in the reaction mixture. Initial attempts to prepare alcohol **62**, not shown in the scheme, through the conversion of chloride **60** to acetate, followed by hydrolysis, proved unsuccessful. Under the basic conditions for hydrolysis of the acetate, a mixture of a cyclic sulfonamide, removal of 4-chlorobenzoyl group product, or both were obtained. The alcohol derivative **62** was prepared from the hydrogenation of the nitrate **61** using 10% Pd/C as catalyst. Hydrogenation usually will reduce chlorobenzene, but in our preparation of examples **55** and **62**, the N-1 chlorobenzoyl group remains intact.

Results and Discussion

COX Inhibitory Activity. Compounds were assayed for COX inhibition using a human whole-blood assay.[66,67] After

Scheme 6. Modifying the 3-Acetic Acid of Indomethacin to Ethanol or Ethyl Amine Derivatives[a]



[a] Reagents and conditions: (a) $BH_3 \cdot SMe_2$, THF; (b) CH_3SO_2Cl, NEt_3; (c) $(Bu_4N)^+NO_3^-$, toluene, 100°C; (d) LiBr, acetone, 55°C; (e) $P(OMe)_3$, 110°C; (f) TMSBr, CH_2Cl_2; (g) chlorosulfonyl isocyanate, NEt_3, **2** or **8**; (h) i. phosgene/toluene, K_2CO_3, THF, 50°C; ii. **2**, DMAP, THF; (i) NaN_3, DMSO, 50°C; (j) i. 10% Pd/C, H_2 (30 psi), AcOH; ii. Na_2CO_3 then HCl/Et_2O; (k) EDAC, NEt_3, DMAP, **10**; (l) CDI then **2**, NEt_3; (m) 4-(bromomethyl)benzenesulfonyl chloride, NEt_3; (n) $AgNO_3$, reflux; (o) 3-chloropropanesulfonyl chloride, NEt_3; (p) 10% Pd/C, H_2 (35 psi).

Table 1. Selected Examples of COX Inhibitory Activity and Selectivity

example[a]	COX-1 IC_{50} (μM)	COX-2 IC_{50} (μM)	COX-1/ COX-2
11	0.5	0.7	0.7
11[b]	0.19	0.44	0.4
12	15.6	5.0	3.1
13	4.7	3.5	1.4
14	>100	26.3	>4
15	5.4	3.0	1.8
21	1.6	4.1	0.4
22	15.9	5.8	2.7
30	2.4	1.2	2.0
31	3.3	1.8	1.8
32	6.0	1.2	5.0
33	2.6	1.2	2.1
40	<0.3	0.7	<0.4
57	3.0	10	0.3
61	11	1.2	9.1
62	3.7	1.1	3.5
celecoxib	14	1.2	11.7
celecoxib[b]	6.7	0.87	7.6

[a] See Supporting Information for screening data of all examples. [b] Values as reported in ref 67.

initial screening at three concentrations, COX-1 (100 μM) and COX-2 (1 and 10 μM), the active compounds were selected for IC_{50} determination. The complete screening data of all compounds is available as Supporting Information. The most promising compounds were further examined using in vivo experiments for antiinflammatory activity, gastric tolerability, and NO donor activity.

In our studies, as shown in Table 1, indomethacin (**11**) slightly favors COX-1 inhibition and celecoxib showed 11.7-fold COX-2 selectivity. The demethylated indomethacin, example **12**, favors COX-2 inhibition by 3-fold, and incorporation of an amide tether as in examples **13** and **15** slightly decreases the selectivity. The 5-*O*-sulfamate group in example **14** does restore COX-2 selectivity by greater than 4-fold. This suggests the 5-*O*-sulfamate group might be entering the selective binding site and interacting with Arg513 as we anticipated, but simultaneously lowering the COX inhibitory potency. Both benzyl esters of 4- and 6-chloro-indomethacin, examples **19** and **20**, showed weak inhibitory activity (data not shown in Table 1). 6-Chloro-indomethacin **21** appears to more favor inhibition of COX-1 but is not as potent as indomethacin. A chlorine atom at the 6-position is either not large enough to cause unfavorable interaction with Ile523 or, perhaps, is too big and causes indomethacin to adopt another binding mode. As suggested by Loll et al., another possible conformation for 4′-iodo-indomethacin binding in COX-1 is a trans form, as depicted in the crystal structure of 1PGG.[68] Example **22**, attaching an amide linker to 6-chloro indomethacin favors COX-2 inhibition by almost 3-fold.

Replacement of the 4-chlorobenzoyl group of indomethacin with a 4-bromobenzyl group was reported to give excellent COX-2 selectivity.[51] In our series, replacement of the 4-chlorobenzoyl group with a (methylsulfonyl)benzyl, example **25a**, or a cyclohexylmethyl group, example **25b**, severely compromised the inhibition of both COX isozymes. The attachment of an amide-nitrate linker did not improve the inhibitory activity for the (methylsulfonyl)benzyl derivative, example **26a**, but did cause a minor improvement for the cyclohexylmethyl derivative **26b**. The ethanol derivative of cyclohexylmethyl series, example **27b**, and its nitrate derivative **29b** also show weak inhibitory activity.

The indomethacin alkyl-amide derivatives **30**−**33** increased COX-2 inhibition from 2- to 5-fold. Decreased selectivity of compound **33** is most likely caused by the branched side chain still fitting well in the lobby region of COX-1 and thus exhibiting better affinity for this subtype. However, this size effect did not impart a selectivity advantage for COX-2 because the lobby region of COX-2 has more flexibility.[38] An alkyl group with

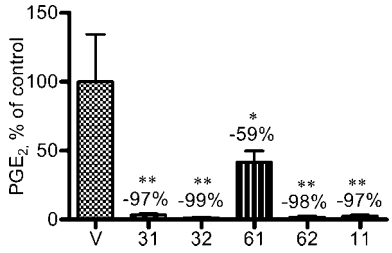


Figure 2. Anti-inflammatory activity: Rat carrageenan air-pouch model (intrapouch dosing). Values are means ± SEM ($n = 8$–15). Statistical analysis by ANOVA ,followed by Dunnett's multiple comparison test ((*) $p < 0.05$ vs vehicle, (**) $p < 0.01$ vs vehicle). V: vehicle (0.5% methylcellulose). Dose for all examples was 45 μmol/kg.

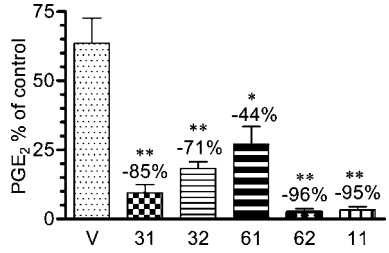


Figure 3. Anti-inflammatory activity: Rat carrageenan air-pouch model (oral dosing). Values are means ± SEM ($n = 6$–22). Statistical analysis by ANOVA, followed by Dunnett's multiple comparison test ((*) $p < 0.05$ vs vehicle, (**) $p < 0.01$ vs. vehicle). V: vehicle (0.5% methylcellulose). Dose for all examples was 45 μmol/kg, except for indomethacin (**11**), whose dose was 22.5 μmol/kg.

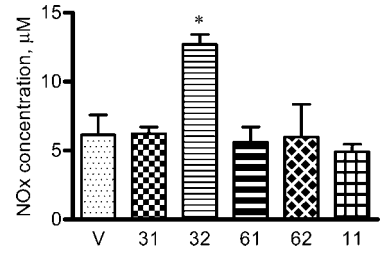


Figure 4. NO_x concentration in rat plasma. Values are means ± SEM ($n = 3$). Statistical analysis by ANOVA, followed by Dunnett's multiple comparison test ((*) $p < 0.05$ vs vehicle). V: vehicle (0.5% methylcellulose). Oral dose for all examples was 45 μmol/kg, except for indomethacin (**11**), whose dose was 22.5 μmol/kg.

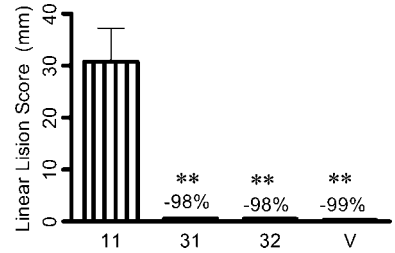


Figure 5. Rat gastric lesion scores. Values are means ± SEM ($n =$ 4–12). Statistical analysis by ANOVA, followed by Dunnett's multiple comparison test ((**) $p < 0.01$ vs indomethacin **11**). V: vehicle (0.5% methylcellulose). Dose concentration for all examples was 45 μmol/kg.

increased steric bulk, example **34**, diminishes the COX-2 selectivity in this series. These results contrast with data from a purified enzyme assay in which a two-carbon alkyl amide analogue of compound **31** was reported to have a 290-fold selectivity for COX-2.[54] The derivatives of hydroxamic acid **35**−**37** showed no COX-2 selectivity. Because the immediate binding site for the acid group is conserved in both COX enzymes, a short aliphatic chain most likely will not have a strong influence on COX selectivity. However, hydroxamic acid derivatives **38**−**40** favor COX-1 inhibition as opposed to the amide derivatives **30**−**33**. Perhaps the preferred binding conformation of hydroxamic acid directs the alkyl chain to the surface of the enzyme instead of in-line with binding channel to the lobby region.

The nitrate **47**, phosphoric acid **50**, carboxylsulfamide **51**, carboxylsulfamate **52**, carbamate **53**, and amine **55** derived from alcohol **45** lost their ability to inhibit COX isozymes. The inverse amide **56**, urea **57**, and aryl-sulfonamide **59** derived from amine **55** also showed no COX-2 selectivity. However, the nitrate of alkyl-sulfonamides, example **61**, showed 9-fold selectivity, and its alcohol, example **62**, showed 4-fold COX-2 selectivity. Both nitrate derivatives **32** and **61** showed better COX-2 selectivity than the corresponding alcohols, examples **31** and **62**. The improved selectivity of nitrate derivatives was also reported previously in pyrazoles derivatives.[29]

In Vivo Pharmacological Profiling. In the rat air pouch model, amide derivatives **31** and **32** and alkyl-sulfonamide derivatives **61** and **62** significantly reduced the PGE_2 level when administered intrapouch by 97%, 99%, 59% and 98%, respectively, as shown in Figure 2. The oral dosing air pouch experiment, as shown in Figure 3, also showed these four compounds significantly reduced the PGE_2 level as evidence of their antiinflammatory activity. These two sets of experiments suggested example **62** has the best bioavailability and least protein binding affinity followed by **31**, **32** and **61**. However, only example **32** increased rat plasma nitrite plus nitrate (NO_x) concentration, as shown in Figure 4, indicating that the nitrate tether acted as a NO donor. Since the attachment of a NO donor to improve the safety profiles of COX-2 inhibitor drugs is the primary goal of this research, the pair of propoxy-amide derivatives, examples **31** and **32**, were further examined for GI tolerance.

The amide derivatives, **31** and **32**, both show a 98% reduction in gastric lesion score when compared to equimolar indomethacin as shown in Figure 5. Although low-dose aspirin is routinely used for cardiovascular prophylaxis, concomitant use of aspirin and a COX-2 inhibitor increases gastric damage when compared to using either aspirin or the COX-2 inhibitor alone.[10,11,69] This adverse effect was not significant for example **32** when administered with background aspirin treatment compared to the valdecoxib and aspirin treatment group as shown in Figure 6. The gastric-sparing effect (85% reduction) is especially noteworthy given the 4.7-fold greater dose of **32** versus valdecoxib when coadministered with aspirin.

Conclusion

We have identified several modifications of indomethacin yielding derivatives that increase this NSAID's COX-2 selectivity and safety: the 5-phenol **12** and 5-*O*-sulfamate **14** derivatives, the alkyl-amide derivatives **30–33**, and the inversed alkyl-sulfonamide derivatives **61** and **62**. The 5-*O*-sulfamate derivative **14** was COX-2 selective but at higher concentration. The nitrated sulfonamide derivative **61** showed the highest COX-2 selectivity, but the nitrate tether did not increase plasma NO_x concentration in vivo. With the assumption that the binding mode did not change because of these modifications, a straight-chain, polar-end tether might have some influence on COX binding and selectivity. Potential interactions between the straight-chain polar group and Tyr115, Ser119, or both in the lobby region would need to be confirmed through mutation studies. Nevertheless,

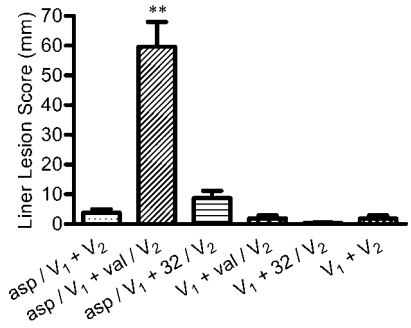


Figure 6. Aspirin-induced rat gastric lesions. Values are means ± SEM (n = 3–11). Statistical analysis by ANOVA, followed by Newman−Keuls multiple comparison test ((**) $p < 0.001$ vs all other groups). V_1: vehicle (1.0% methylcellulose). V_2: vehicle (0.5% methylcellulose). asp: aspirin (139 μmol/kg). val: valdecoxib (9.5 μmol/kg). Compound **32** (45 μmol/kg).

we have successfully designed and synthesized a NO-enhanced COX-2 selective inhibitor, example **32** (IC_{50} = 1.2 μM with 5-fold selectivity), from indomethacin which is an effective antiinflammatory agent in vivo, while being exceptionally well tolerated without apparent GI liability by itself and, most notably, when coadministered with aspirin. On the basis of a prior detailed analysis of indomethacin phenethylamide metabolism in the rat,[70] the amide linker of example **32** should be virtually immune to amidase hydrolysis such that negligible indomethcin would be generated. Consequently, our approach toward an NO-enhanced anti-inflammatory agent differs from the "pro-drug" approach commonly use in the synthesis of nitrated NSAID esters.

Experimental Section

Reagents and solvents were used as obtained from commercial suppliers. ^{1}H and ^{13}C NMR spectra were recorded on a 300 (Bruker AMX) or 400 MHz (Bruker AVANCE) spectrometer, and the chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane. Mass spectra were recorded on a PE SCIEX, API 150EX instrument using the turbo ion spray atmospheric pressure ionization method. Melting points were determined on a MEL-TEMP apparatus and are uncorrected. Elemental analyses were performed by Robertson Microlit Laboratories (Madison, NJ). Flash column chromatography was performed using EMD silica gel 60H. Thin-layer chromatography was carried out on EMD silica gel 60 F_{254} TLC plates and visualized under UV or by staining with phosphomolybdate or $KMnO_4$ solution.

Human Whole-Blood COX Inhibition Assay.[66] Human whole blood from consenting donors of either sex who had not taken any NSAIDs for two weeks were collected in sodium heparin (20 units/mL). Test compounds at various concentrations, dissolved and diluted in DMSO at 1000 times the final concentrations, were added in duplicate to 1 mL per well aliquots of blood in a 24-well plate. After 15 min of incubation at 37 °C in a CO_2 incubator, LPS at 10 μg/mL was added to the appropriate wells to induce COX-2. At 4.5 h after test compound addition, A23187 was added at 25 μM to other wells to activate COX-1. Vehicle control wells received equal volumes of DMSO. At 30 min after A23187 activation, that is, 5 h after LPS addition, reactions were terminated by placing the 24-well plates on ice and addiing 2 mM EGTA. Plasma was collected and extracted with methanol overnight at −20 °C. After evaporation, the thromboxane B_2 (TXB_2) in each sample was measured in duplicate with an enzyme-linked immunoassay kit (Cayman Chemical, Ann Arbor, MI). The results were normalized against vehicle (control) values and expressed as % control of COX activity, and an IC_{50} was determined over the concentration range tested.

Rat Carrageenan Air Pouch Studies.[2] Male Sprague–Dawley rats (180–200 g) were purchased from Charles River Laboratories (Kingston or Raleigh). Animal care and use were in accord with NitroMed's IACUC guidelines. Rats were randomly housed 5 per cage and allowed to acclimate on a 12/12 reverse light/dark cycle with standard chow and water available ad libitum for at least 48 h before the experiment. Air pouches were produced by subcutaneous injection of 20 mL of sterile air on day (−6) into the intrascapular area on the back of the anesthetized rats. An additional 10 mL of sterile air was injected into the pouch on day (−3) to keep the pouch open and allow the interior membrane to develop. On day (−1), rats were fasted 18 h before the experiment (water ad libitum) in cages equipped with metal floor racks. On day 0, the pulverized test compounds in 0.5% methocel or vehicle were either injected into the pouch or dosed orally in blinded fashion, 1 h prior to carrageenan injection (1 mL of 1.0% carrageenan in saline). After 4 h, PBS/heparin (Invitrogen Corporation, Carlsbad, CA) was injected into the pouch, which was then massaged gently for 15–20 s. The rat was then quickly sacrificed using carbon dioxide, and the inflammatory exudate was collected from the pouch. The exudates were assayed for PGE_2 with an enzyme-linked immunoassay kit (Cayman).

NO_x in Rat Plasma. Rat plasma was collected by heart puncher at the termination of the air-pouch (4 h after oral dosing) described above. Plasma NO_x (the sum of inorganic nitrite and nitrate) was quantified with a fluorometric kit (Cayman).

Rat Gastric Injury Model. Rats were acclimated as described for the air pouch model (above) and were fasted 18 h before the experiment (water ad libitum) in cages equippedwith metal floor racks. Water was removed 1 h before the experiment and returned after dosing and removed again 1 h prior to examination of the stomach. The pulverized test compounds were homogenized with a glass/Teflon pestle homogenizer in 0.5% methocel and were prepared immediately before dosing. The test compounds were administered intragastrically (p.o.) at a dose volume of 1 mL/kg using an 18-gauge gavage needle. The rats were sacrificed 3 h after dosing using carbon dioxide. The stomach was removed, opened along the greater curvature, rinsed, mounted on a Petri dish, and digitally photographed. The images were analyzed by staff blinded to drug treatment using Image J Analysis software for visible hemorrhagic lesions. The length of each lesion was recorded, and all lesion lengths were summed as the total lesion score. Values are given as the means ± SEM over 4–12 animals. The significance of differences between means was evaluated using a one-way analysis of variance (ANOVA), followed by Dunnett's multiple comparison test. $P < 0.05$ was considered significant.

Aspirin-Induced Rat Gastric Damage Model. A minimum of 72 h was allowed for acclimation of rats, as described above. The experiment was performed in six groups with 3–11 animals per group. All test compounds including aspirin were pulverized with a mortar and pestle and homogenized by vortexing with 2–3 layers of glass beads in sufficient amount of vehicle. All compounds were prepared immediately before dosing and were administered intragastrically using gavage needles at a dose volume of 1.0 mL/kg. Aspirin was suspended in 1.0% methocel, whereas test compounds were suspended in 0.5% methocel. Four groups of animals were dosed intragastrically with aspirin (25 mg/kg); then the test compounds were dosed 2 min later. After 3 h, the rats were sacrificed and subjected to gastric lesion scoring as described above.

3-(Nitrooxy)propylamine Nitric Acid Salt (2). A solution of 3-amino-1-propanol (6.17 g, 82.2 mmol) was added, dropwise, to an ice-cooled solution of fuming nitric acid (90%, 12 mL) in acetic anhydride (50 mL). The reaction was stirred in an ice-bath for 10 min and then at room temperature for 10 min. The solvent was evaporated under vacuum at 40 °C. The residue was stirred in Et_2O (200 mL) until the product precipitated. The mixture was filtered, and the white crystalline solid was dried in vacuo to give the title compound (12.1 g, 80% yield). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 4.57 (br. t, 2 H), 2.8–3.0 (m, 2H), 1.98–1.93 (m, 2H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 70.9, 36.1, 24.5. MS (API-TIS): m/z 121 $(M - NO_3)^+$.

2,2-Dimethyl-3-(nitrooxy)propylamine Nitric Acid Salt (4). A solution of 3-amino-2,2-dimethylpropanol (6.0 g, 82.2 mmol) in EtOAc (40 mL) was added, dropwise, to an ice-cooled solution of fuming HNO_3 (90%, 8 mL) in acetic anhydride (50 mL). The reaction was stirred in an ice-bath for 10 min and an additional 10 min at room temperature. The solvent was evaporated under vacuum at 40 °C. The residue was stirred in Et_2O (200 mL) until the product precipitated. The mixture was filtered, and the white solid was dried in vacuo to give the title compound (6.55 g, 53% yield). mp: 114–115 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.92 (br, 3H), 4.37 (s, 2H), 2.81 (br. s, 2 H), 1.03 (s, 6H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 77.5, 45.6, 33.3, 21.9. MS (API-TIS): *m*/*z* 149 $(M - NO_3)^+$.

3-(Nitrooxy)propan-1-ol (8). A solution of 3-bromo-1-propanol (5.42 g, 39.0 mmol) in acetonitrile (20 mL) was added to a solution of $AgNO_3$ (10.16 g, 59.8 mmol) in acetonitrile (50 mL) and stirred at room temperature for 24 h. To the reaction mixture was added brine (350 mL), and the mixture was stirred for 1 h. The silver salts were filtered off through Celite, and the filtrate was extracted with Et_2O (200 mL × 3). The organic layer was washed with brine, dried over Na_2SO_4, filtered, concentrated, and dried under vacuum to give the title compound (4.08 g, 86% yield, > 95% purity) that was used in the next step without purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.61 (t, J = 6.4 Hz, 2H), 3.78 (t, J = 6.4 Hz, 2H), 1.99 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 70.3, 58.5, 29.5.

4-[(Nitrooxy)methyl]benzoic Acid (10). A solution of $AgNO_3$ (17.73 g, 104.4 mmol) and α-bromo-*p*-toluic acid (10.84 g, 50.4 mmol) in THF (150 mL) and acetonitrile (150 mL) was stirred at room temperature overnight and then at 50 °C for 1 h. The reaction mixture was then cooled to room temperature and stirred with brine (150 mL) for 1 h. The resulting mixture was filtered through Celite and washed with water. The filtrate was concentrated and then extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried over Na_2SO_4, filtered, concentrated, and dried under vacuum. The crude product was washed with CH_2Cl_2 (50 mL) on a Buchner funnel and then dried under vacuum to give the title compound as a white solid (7.27 g, 73% yield). mp: 159–161 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.02 (d, J = 8.1 Hz, 2H), 7.60 (d, J = 8.1 Hz, 2H), 5.67 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 166.9, 137.3, 131.4, 129.7, 129.0, 74.3. MS (API-TIS): *m*/*z* 196 $(MH)^+$.

2-{1-[(4-Chlorophenyl)carbonyl]-5-hydroxy-2-methylindol-3-yl}acetic Acid (12). A solution of BBr_3 (54 mL, 1 M in CH_2Cl_2, 54 mmol) was added slowly to an ice-cold solution of indomethacin (9.4 g, 26.3 mmol) in CH_2Cl_2 (100 mL) and stirred at room temperature overnight. The resulting mixture was poured onto crushed ice (250 g) and extracted with EtOAc (200 mL × 3). The combined organic extracts were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated. The resulting solid was washed with Et_2O and dried under vacuum to obtain the title compound as a yellowish solid (6.49 g, 72% yield). mp: >205 °C (dec.). ^{1}H NMR (300 MHz, CD_3OD): δ 7.65 (d, J = 8.5 Hz, 2H), 7.53 (d, J = 8.5 Hz, 2H), 6.89 (d, J = 2.4 Hz, 1H), 6.82 (d, J = 8.9 Hz, 1H), 6.54 (dd, J = 8.9, 2.4 Hz, 1H), 3.62 (s, 2H), 2.34 (s, 3H). ^{13}C NMR (75 MHz, CD_3OD): δ 175.2, 170.0, 154.6, 140.0, 136.6, 135.9, 132.5, 132.3, 131.8, 130.2, 115.9, 114.6, 113.0, 104.5, 30.8, 13.5. MS (API-TIS): *m*/*z* 344 $(MH)^+$. Anal. ($C_{18}H_{14}ClNO_4$) C, H, N.

2-{1-[(4-Chlorophenyl)carbonyl]-5-hydroxy-2-methylindol-3-yl}-*N*-[3-(nitrooxy)propyl]acetamide (13). A solution of **12** (1.46 g, 4.3 mmol), **2** (0.87 g, 4.8 mmol), DMAP (100 mg, 0.82 mmol), EDAC (1.07 g, 5.6 mmol), and NEt_3 (1.8 mL, 12.9 mmol) in CH_2Cl_2 (50 mL) was stirred at room temperature for 4 h. The reaction mixture was partitioned between 3 N HCl (30 mL) and CH_2Cl_2 (50 mL × 2). The combined organic extracts were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated. The crude material was dissolved in EtOAc (5 mL) and CH_2Cl_2 (5 mL) and triturated with Et_2O (80 mL). The solid was collected and dried under vacuum to obtain the title compound as a white solid (0.89 g, 47% yield). mp: 135–137 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.19 (s, 1H), 8.02 (br. t, 1H), 7.67 (d, J = 8.5 Hz, 2H), 7.61 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 8.8 Hz, 1H), 6.84 (d, J = 2.1 Hz, 1H), 6.54 (dd, J = 8.9, 2.4 Hz, 1H), 4.47 (t, J = 6.4 Hz, 2H), 3.43 (s, 2H), 3.13 (br. q, 2H), 2.19 (s, 3H), 1.79 (m, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 169.8, 167.9, 153.4, 137.5, 134.9, 134.5, 131.1, 129.6, 129.1, 114.6, 114.0, 112.0, 103.7, 71.7, 35.3, 31.3, 26.5, 13.4. MS (API-TIS): *m*/*z* 446 $(MH)^+$.

1-[(4-Chlorophenyl)carbonyl]-2-methyl-3-({*N*-[3-(nitrooxy)-propyl]carbamoyl}methyl)indol-5-yl Aminosulfonate (14). A solution of sulfamoyl chloride (0.19 g, 1.7 mmol) and **13** (0.19 g, 0.4 mmol) in *N*-methyl-2-pyrrolidinone (NMP, 3 mL) was stirred at room temperature for 4 h. The reaction was quenched with brine and extracted with a mixture of EtOAc (20 mL) and $CHCl_3$ (50 mL). The organic extracts were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated. The crude material was dissolved in $CHCl_3$ (50 mL) and stirred with water (30 mL) overnight to remove trace amounts of NMP. The white solid suspended in the $CHCl_3$ layer was collected and dried under vacuum (0.105 g, 48% yield). mp: 146–148 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.11 (br. t, 1H), 7.90 (br. s, 2H), 7.71 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 2.1 Hz, 1H), 7.11 (d, J = 8.9 Hz, 1H), 7.01 (dd, J = 8.9, 2.1 Hz, 1H), 4.47 (t, J = 6.2 Hz, 2H), 3.52 (s, 2H), 3.13 (br. q, 2H), 2.22 (s, 3H), 1.79 (m, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 169.8, 167.9, 153.4, 137.5, 134.9, 134.5, 131.1, 129.6, 129.1, 114.6, 114.0, 112.0, 103.7, 71.7, 35.3, 31.3, 26.5, 13.4. MS(API-TIS): *m*/*z* 525 $(MH)^+$. Anal. ($C_{21}H_{21}ClN_4O_8S$) C, H, N.

2-{1-[(4-Chlorophenyl)carbonyl]-5-hydroxy-2-methylindol-3-yl}-*N*-(3-hydroxypropyl)acetamide (15). A solution of **12** (0.84 g, 2.4 mmol), 3-amino-1-propanol (0.2 mL, 2.6 mmol), DMAP (35 mg, 0.29 mmol), EDAC (0.57 g, 2.97 mmol), and NEt_3 (0.37 mL, 2.7 mmol) in CH_2Cl_2 (100 mL) was stirred at room temperature overnight. The reaction mixture was partitioned between 3 N HCl (30 mL) and CH_2Cl_2 (50 mL × 2). The combined organic extracts were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated. The product was separated by silica gel column chromatography eluted with MeOH/$CHCl_3$ (gradient from 1:20 to 1:15) to obtain the title compound (0.56 g, 57% yield). ^{1}H NMR (300 MHz, 10% CD_3OD/$CDCl_3$): δ 7.65 (d, J = 8.5 Hz, 2H), 7.48 (d, J = 8.5 Hz, 2H), 6.81–6.8 (m, 2H), 6.68 (br. t, 1H), 6.61 (dd, J = 8.9, 2.4 Hz, 1H), 3.57 (s, 2H), 3.54 (t, J = 5.8 Hz, 2H), 3.32 (q, J = 5.8 Hz, 2H), 2.36 (s, 3H), 1.61 (m, 2H). ^{13}C NMR (75 MHz, 10% CD_3OD/$CDCl_3$): δ 171.8, 168.6, 153.1, 139.4, 136.0, 133.6, 131.0, 130.4, 130.3, 129.1, 115.0, 112.5, 102.8, 59.5, 36.9, 31.9, 31.4, 13.0. MS (API-TIS): *m*/*z* 401 (MH^+).

3-Chloro-4-methoxyphenylhydrazine Hydrochloride (16). A solution of $NaNO_2$ (4.77 g, 69.1 mmol) in water (15 mL) was added to an ice-cold mixture of 3-chloro-*p*-anisidine in 6 N HCl (100 mL) and stirred for 20 min. The resulted solution was added slowly to a solution of $SnCl_2 \cdot 2H_2O$ in HCl (conc., 250 mL) at −5 °C. The reaction mixture was stirred at room temperature for 1 h. The crude material was collected by filtration, dissolved in MeOH (500 mL), dried over Na_2SO_4, filtered, and concentrated. The resulting yellowish solid was washed with Et_2O (300 mL) and dried under vacuum to obtain the title compound (13.62 g, 99% yield). ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.4 (br, 4H), 7.24 (d, J = 2.1 Hz, 1H), 7.2–7.0 (m, 2H), 3.8 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 149.8, 139.6, 121.2, 117.4, 115.4, 113.5, 56.4.

Phenylmethyl 2-(4-chloro-5-methoxy-2-methylindol-3-yl)acetate (17) and Phenylmethyl 2-(6-chloro-5-methoxy-2-methylindol-3-yl)acetate (18). Benzyl levulinate (7.23 g, 35.1 mmol) and **16** (7.53 g, 36.0 mmol) was heated to reflux in acetic acid (100 mL) for 3 h. After the mixture was cooled down to room temperature, acetic acid was removed under vacuum. The residue was partitioned between water (100 mL) and EtOAc (100 mL × 2). The combined organic extracts were washed with saturated $NaHCO_3$, 3 N HCl, water, and brine, dried over Na_2SO_4, filtered, and concentrated. The product was separated by silica gel column chromatography eluted with EtOAc/hexane (gradient from 1:3 to 1:2, R_f = 0.2, 0.1). The data for the more-polar compound **17** (1.96 g, 16% yield) follow. mp: 124–125 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.93 (br, 1H), 7.4–7.3 (m, 5H), 6.98 (d, J = 8.7 Hz,

1H), 6.78 (d, $J = 8.7$ Hz, 1H), 5.17 (s, 2H), 3.99 (s, 2H), 3.88 (s, 3H), 2.21 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.0, 148.9, 136.0, 135.7, 131.7, 128.4, 128.0, 125.9, 112.7, 109.1, 108.7, 103.9, 66.5, 55.9, 30.7, 11.3. MS (API-TIS): *m/z* 344 (MH^+). The less-polar compound **18** (4.11 g, 33% yield) can be recrystallized from Et_2O and hexane. mp: 94–95 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74 (br, 1H), 7.3–7.2 (m, 6H), 6.97 (s, 1H), 5.11 (s, 2H), 3.81 (s, 3H), 3.68 (s, 2H), 2.33 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.8, 149.3, 135.8, 134.0, 129.6, 128.4, 128.2, 128.0, 117.1, 111.7, 104.1, 100.8, 66.5, 56.5, 30.4, 11.6. MS(API-TIS): *m/z* 344 $(MH)^+$. Anal. ($C_{19}H_{18}ClNO_3$) C, H, N.

Phenylmethyl 2-{4-Chloro-1-[(4-chlorophenyl)carbonyl]-5-methoxy-2-methylindol-3-yl}acetate (19). A solution of **17** (1.25 g, 3.6 mmol), 4-chlorobenzoyl chloride (0.55 mL, 4.3 mmol), DMAP (0.23 g, 1.9 mmol), and NEt_3 (2.6 mL, 18.7 mmol) in CH_2Cl_2 (20 mL) was stirred at room temperature for 24 h. The reaction was partitioned between 3 N HCl (50 mL) and CH_2Cl_2 (100 mL). The organic layer was washed with 3 N HCl, water, and brine, dried over Na_2SO_4, filtered, concentrated, and dried under vacuum. The crude material was dissolved in CH_2Cl_2 (2 mL) and triturated with Et_2O (70 mL). The off white solid was collected, washed with Et_2O, and dried under vacuum to obtain the title compound (1.52 g, 87% yield). mp: 147–148 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (d, $J = 8.5$ Hz, 2H), 7.45 (d, $J = 8.5$ Hz, 2H), 7.33 (m, 5H), 6.99 (d, $J = 9.0$ Hz, 1H), 6.73 (d, $J = 9.0$ Hz, 1H), 5.18 (s, 2H), 4.05 (s, 2H), 3.87 (s, 3H), 2.26 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2, 168.1, 151.3, 139.6, 137.3, 135.9, 133.6, 132.1, 131.2, 129.2, 128.5, 128.1, 127.6, 113.3, 112.7, 112.2, 108.9, 66.8, 57.2, 31.0, 13.2. MS (API-TIS): *m/z* 482 $(MH)^+$.

Phenylmethyl 2-{6-Chloro-1-[(4-chlorophenyl)carbonyl]-5-methoxy-2-methylindol-3-yl}acetate (20). A solution of **18** (0.68 g, 2.0 mmol), 4-chlorobenzoyl chloride (0.28 mL, 2.2 mmol), DMAP (0.12 g, 1.0 mmol), and NEt_3 (1.5 mL, 10.8 mmol) in CH_2Cl_2 (20 mL) was stirred at room temperature for 24 h. The reaction mixture was partitioned between 3 N HCl (10 mL) and CH_2Cl_2 (100 mL). The organic layer was washed with 3 N HCl, water, and brine, dried over Na_2SO_4, filtered, concentrated, and dried under vacuum. The product was separated by silica gel column chromatography, eluted with EtOAc/hexane (1:3, $R_f = 0.3$), to obtain the title compound as a white solid (0.75 g, 79% yield). mp: 104–105 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 (d, $J = 8.5$ Hz, 2H), 7.46 (d, $J = 8.5$ Hz, 2H), 7.34–7.2 (m, 5H), 7.20 (s, 1H), 6.94 (s, 1H), 5.13 (s, 2H), 3.81 (s, 3H), 3.69 (s, 2H), 2.28 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.2, 167.8, 151.3, 139.2, 135.5, 135.4, 133.3, 130.9, 130.1, 129.0, 128.7, 128.3, 128.2, 128.0, 118.8, 115.6, 112.1, 100.6, 66.6, 56.1, 30.2, 13.3. MS(API-TIS): *m/z* 482 (MH^+). Anal. ($C_{26}H_{21}Cl_2NO_4$) C, H, N.

2-{6-Chloro-1-[(4-chlorophenyl)carbonyl]-5-methoxy-2-methylindol-3-yl}acetic Acid (21). Compound **20** (0.37 g, 0.76 mmol) was hydrogenated in EtOAc (30 mL) and MeOH (5 mL) in presence of 10% Pd/C (33 mg) at 30 psi for 2.5 h. The reaction mixture was filtered through Celite, and the filter cake was washed with EtOAc. The filtrate was concentrated, and the residue was separated by silica gel column chromatography eluted with CH_2Cl_2/MeOH (20:1, $R_f = 0.1$) to obtain the title compound (0.26 g, 87% yield). mp: 69–71 °C. ^{1}H NMR (300 MHz, $CDCl_3$); δ 7.63 (d, $J = 8.5$ Hz, 2H), 7.47 (d, $J = 8.5$ Hz, 2H), 7.15 (s, 1H), 6.97 (s, 1H), 3.93 (s, 3H), 3.66 (s, 2H), 2.30 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.8, 168.0, 151.6, 139.7, 136.0, 133.2, 131.1, 130.2, 129.2, 128.7, 119.2, 115.8, 111.5, 100.6, 56.5, 30.0, 13.4. MS (API-TIS): *m/z* 392 (MH^+).

2-{6-Chloro-1-[(4-chlorophenyl)carbonyl]-5-methoxy-2-methylindol-3-yl}-N-[3-(nitrooxy)propyl]acetamide (22). A solution of **21** (1.11 g, 2.8 mmol), **2** (0.51 g, 3.1 mmol), DMAP (63 mg, 0.5 mmol), EDAC (0.71 g, 3.7 mmol), and NEt_3 (1.4 mL, 10.0 mmol) in CH_2Cl_2 (150 mL) was stirred at room temperature for 5 h. The reaction mixture was partitioned between 3 N HCl (50 mL) and CH_2Cl_2 (50 mL × 2). The combined organic extracts were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated. The crude material was dissolved in MeOH (5 mL) and triturated with Et_2O (80 mL). The solid was collected, washed with 5% MeOH/Et_2O, and dried under vacuum to obtain the title compound as a yellowish solid (0.61 g, 59% yield). mp: 154–155 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66 (d, $J = 8.5$ Hz, 2H), 7.51 (d, $J = 8.5$ Hz, 2H), 7.15 (s, 1H), 6.92 (s, 1H), 5.73 (br. t, 1H), 4.42 (t, $J = 6.2$ Hz, 2H), 3.92 (s, 3H), 3.64 (s, 2H), 3.34 (br. q, 2H), 2.33 (s, 3H), 1.89 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.5, 167.8, 151.0, 137.7, 135.5, 133.9, 131.2, 129.7, 129.6, 129.0, 117.2, 115.2, 114.1, 101.6, 71.6, 56.4, 35.2, 31.1, 26.4, 13.5. MS (API-TIS): *m/z* 494 $(MH)^+$.

Ethyl 2-(5-methoxy-2-methylindol-3-yl)acetate (23). A stirred mixture of 4-methoxyphenylhydrazine hydrochloride (26 g, 0.149 mol), ethyl levulinate (21.5 g, 0.149 mol), and sodium acetate (12.2 g, 0.149 mol) in glacial acetic acid (200 mL) was heated at reflux for 3 h. The reaction mixture was concentrated to dryness. The residue was dissolved in ethanol (120 mL), treated with 4 M HCl in 1,4-dioxane (80 mL), and heated at a gentle reflux for 15 h. The mixture was concentrated to remove the volatiles, and the residue was taken up with EtOAc, washed with water, aqueous K_2CO_3, and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated. Chromatography of the residue (1:1 EtOAc/hexane, silica gel) afforded the title compound (28 g, 76% yield) as a viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.83 (br. s, 1H), 7.06 (d, $J = 8.7$ Hz, 1H), 7.00 (d, $J = 2.4$ Hz, 1H), 6.77–6.73 (m, 1H), 4,12 (q, $J = 7.1$ Hz, 2H), 3.84 (s, 3H), 3.64 (m, 2H), 1.23 (t, $J = 7.1$ Hz, 3H). MS (API-TIS): *m/z* 248 $(MH)^+$.

Ethyl 2-(5-Methoxy-2-methyl-1-{[4-(methylsulfonyl)phenyl]methyl}indol-3-yl)acetate (24a). To a stirred solution of **23** (1.45 g, 5.87 mmol) and 4-(bromomethyl)-1-(methylsulfonyl)benzene (1.46 g, 5.87 mmol) in THF (80 mL) was added *t*-BuOK (1.0 M in THF, 5.87 mL, 5.87 mmol) via syringe at room temperature under N_2. The mixture was heated at a gentle reflux for 16 h. After it was cooled, the mixture was poured onto ice, neutralized with 1 N HCl, and extracted with EtOAc twice. The organics were dried over Na_2SO_4, filtered, and concentrated. Chromatography of the residue (1:1 EtOAc/hexane, silica gel) furnished the title compound (2.01 g, 82% yield) as a solid. mp: 123–124 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82 (d, $J = 8.3$ Hz, 2H), 7.13–6.99 (m, 4H), 6.78 (m, 1H), 5.34 (s, 2H), 4.14 (q, $J = 7.1$ Hz, 2H), 3.86 (s, 3H), 3.71 (s, 2H), 3.00 (s, 3H), 2.31 (s, 3H), 1.25 (t, $J = 7.1$ Hz, 3H). MS (API-TIS): *m/z* 416 $(MH)^+$.

2-(5-Methoxy-2-methyl-1-{[4-(methylsulfonyl)phenyl]methyl}indol-3-yl)acetic Acid (25a). To a stirred solution of **24a** (2.01 g, 4.84 mmol) in THF (50 mL) was added 2 N NaOH (50 mL). The mixture was stirred at room temperature for 4 h and concentrated to remove the volatiles. After acidification to pH 2 with 2 N HCl, the mixture was extracted with EtOAc twice. The organics were dried over Na_2SO_4, filtered, and concentrated to give a solid. Recrystallization from THF/EtOAc (1:4) afforded the title compound (1.80 g, 95% yield) as a beige solid. mp: 168 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.84 (d, $J = 8.3$ Hz, 2H), 7.12 (d, $J = 8.3$ Hz, 2H), 7.05–7.00 (m, 1H), 6.81–6.76 (m, 1H), 5.35 (s, 2H), 3.86 (s, 3H), 3.76 (s, 2H), 3.01 (s, 3H), 2.31 (s, 3H). MS (API-TIS): *m/z* 388 (MH^+).

2-(5-Methoxy-2-methyl-1-{[4-(methylsulfonyl)phenyl]methyl}indol-3-yl)-*N*-[3-(nitrooxy)propyl]acetamide (26a). To a stirred mixture of **2** (0.240 g, 1.31 mmol), **25a** (0.465 g, 1.20 mmol), and EDAC (0.251 g, 1.31 mmol) in THF (15 mL) was added triethylamine (0.366 mL, 2.62 mmol). After 15 h, the mixture was diluted with EtOAc, washed with 1 N HCl, dried over Na_2SO_4, filtered, and concentrated. Chromatography (EtOAc/hexane = 1:1, neutral Al_2O_3) afforded the title compound (106 mg, 18% yield). mp: 106 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88 (d, $J = 8.3$ Hz, 2H), 7.28 (m, 1H), 7.21 (d, $J = 8.3$ Hz, 2H), 7.02 (m, 1H), 6.75–6.70 (m, 1H), 5.53 (s, 2H), 4.63 (t, $J = 6.1$ Hz, 2H), 3.79 (s, 3H), 3.66 (s, 2H), 3.19 (s, 3H), 2.94 (m, 2H), 2.54 (m, 1H), 2.31 (m, 3H), 2.01 (m, 2H). MS (API-TIS): *m/z* 490.0 $(MH)^+$. Anal. ($C_{23}H_{27}N_3O_7S$) C, H, N.

Ethyl 2-[1-(cyclohexylmethyl)-5-methoxy-2-methylindol-3-yl]acetate (24b). To a stirred solution of **23** (5.40 g, 21.9 mmol) and (bromomethyl)cyclohexane (3.87 g, 21.9 mmol) in THF at room temperature was added potassium *t*-butoxide (1.0 M in THF, 21.9 mL) under N_2. The reaction was heated at reflux for 15 h. After it

was cooled, the mixture was poured onto ice, acidified to pH 2 with 2 N HCl, and extracted with EtOAc twice. The organics were dried over Na_2SO_4, filtered, and concentrated. Chromatography (2−10% EtOAc in hexane gradient, silica gel) afforded the title compound (3.88 g, 52% yield) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.15 (d, J = 8.8 Hz, 1H), 7.04 (d, J = 2.4 Hz, 1H), 6.83–6.79 (m, 1H), 4.14 (q, J = 7.1 Hz, 2H), 3.88 (s, 3H), 3.85 (m, 2H), 3.69 (s, 2H), 2.40 (s, 3H), 1.73–1.67 (m, 6H), 1.26 (t, J = 7.1 Hz, 3H), 1.23–1.00 (m, 5H). MS (API-TIS): m/z 344 $(MH)^+$.

2-[1-(Cyclohexylmethyl)-5-methoxy-2-methylindol-3-yl]acetic Acid (25b). To a stirred solution of **24b** (740 mg, 2.16 mmol) in 1:1 THF:MeOH (20 mL) was added 2 N NaOH (5 mL). After the mixture was stirred at room temperature overnight, it was acidified to pH 1 with 1 N HCl and extracted with EtOAc twice. The organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated to give a tan solid. Recrystalization from EtOAc (10 mL) afforded the title compound (560 mg, 82% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.6–9.5 (br, 1H), 7.13 (d, J = 8.8 Hz, 1H), 6.97 (d, J = 2.3 Hz, 1H), 6.78 (dd, J = 6.4, 2.4 Hz, 1H), 3.84 (s, 3H), 3.82 (m, 2H), 3.69 (s, 2H), 2.35 (s, 3H), 1.7–1.5 (m, 6H), 1.2–0.9 (m, 5H). MS (API-TIS): m/z 316.2 $(MH)^+$.

2-[1-(Cyclohexylmethyl)-5-methoxy-2-methylindol-3-yl]-N-[3-(nitrooxy)propyl]acetamide (26b). To a stirred solution of **24b** (230 mg, 0.73 mmol), EDAC (280 mg, 1.46 mmol), and **2** (161 mg, 0.88 mmol) in CH_2Cl_2 was added NEt_3 (0.418 mL, 3.00 mmol) and DMAP (10 mg). After it was stirred at room temperature for 3 h, the reaction mixture was concentrated. The solid residue was taken up with EtOAc and washed with 2 N HCl and water. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The resulting tan solid was recrystallized from EtOAc/hexane (1:5) to afford the title compound (282 mg, 92% yield) as a white solid. mp: 38 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.17 (d, J = 8.8 Hz, 1H), 6.9–6.8 (m, 2H), 5.83 (br. t, 1H), 4.35 (t, J = 6.3 Hz, 2H), 3.85 (d, J = 7.4 Hz, 2H), 3.82 (s, 3H), 3.65 (m, 2H), 3.25 (m, 2H), 2.33 (m, 3H), 1.84 (t, J = 6.5 Hz, 2H), 1.8–1.5 (m, 6H), 1.2–1.0 (m, 6H). MS (API-TIS): m/z 418 $(MH)^+$. Anal. ($C_{22}H_{31}N_3O_5$) C, H, N.

2-[1-(Cyclohexylmethyl)-5-methoxy-2-methylindol-3-yl]ethan-1-ol (27b). To a stirred solution of **24b** (0.520 g, 1.52 mmol) in THF (15 mL) was added 1 M $LiAlH_4$ in THF (3 mL, 3 mmol), and the mixture was stirred at room temperature for 45 min. The mixture was poured onto solid $Na_2SO_4 \cdot 10H_2O$ and aged for 10 min before filtration. The filter cake was washed several times with EtOAc. The combined filtrate and EtOAc washings were concentrated, and the residue was purified by chromatography (1:2 EtOAc/hexane, silica gel) to give the title compound (0.450 g, 98% yield) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.14 (d, J = 8.8 Hz, 1H), 6.99 (d, J = 2.4 Hz, 1H), 6.80 (dd, J = 8.8, 2.4 Hz, 1H), 3.86 (s, 3H), 3.90–3.81 (m, 4H), 2.97 (t, J = 6.5 Hz, 2H), 2.05 (s, 3H), 1.8–0.99 (m, 12 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.6, 134.7, 131.7, 128.0, 110.1, 110.0, 106.2, 100.1, 62.7, 55.8, 49.7, 38.9, 31.1, 28.0, 26.2, 25.8, 10.5. MS (API-TIS): m/z 302 $(MH)^+$.

3-(2-Bromoethyl)-1-(cyclohexylmethyl)-5-methoxy-2-methylindole (28b). To a stirred solution of **27b** (0.430 g, 1.43 mmol) in toluene (15 mL) was added 48% aqueous HBr (1.59 mL, 14.3 mmol), and the mixture was heated at reflux for 2 h. After it was cooled, the mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$, and water. The organic layer was dried over Na_2SO_4, filtered, and concentrated. Chromatography (1:19 EtOAc/hexane, silica gel) of the residue afforded the title compound (0.45 g, 86% yield) as a foam. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.16 (d, J = 8.8 Hz, 1H), 6.95 (d, J = 2.4 Hz, 1H), 6.81 (dd, J = 8.8, 2.4 Hz, 1H), 3.87 (s, 3H), 3.86–3.83 (m, 2H), 3.52 (m, 2H), 3.26 (t, J = 8.3 Hz, 2H), 2.36 (s, 3H), 1.8–0.99 (m, 11H). MS (API-TIS): m/z 364, 366 (MH^+ for ^{79}Br and ^{81}Br, respectively).

{2-[1-(Cyclohexylmethyl)-5-methoxy-2-methylindol-3-yl]ethyl} nitrooxy (29b). To a stirred solution of **28b** (0.450 g, 1.23 mmol) in acetonitrile (10 mL) was added $AgNO_3$ (0.419 g, 2.46 mmol). The mixture was stirred at for 15 h, at which point the bromide had been completely consumed, as indicated by TLC. Upon concentration to dryness, the residue was taken up with EtOAc, treated with brine, and agitated for 10 min. The reaction mixture was filtered, and the organic layer was separated from the filtrate, dried over Na_2SO_4, filtered, and concentrated. Chromatography (1:9 EtOAc/hexane, silica gel) of the residue afforded the title compound (0.345 g, 81% yield) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.16 (d, J = 8.8 Hz, 1H), 6.97 (d, J = 2.0 Hz, 1H), 6.82 (dd, J = 8.8, 2.0 Hz, 1H), 4.58 (t, J = 7.5 Hz, 2H), 3.90 (s, 3H), 3.88–3.84 (m, 2H), 3.12 (t, J = 7.3 Hz, 2H), 2.36 (s, 3H), 1.74–1.57 (m, 6H), 1.19–1.01 (m, 5H). MS (API-TIS): m/z 347 $(MH)^+$. Anal. ($C_{19}H_{26}N_2O_4$) C, H, N.

2-{1-[(4-Chlorophenyl)carbonyl]-5-methoxy-2-methylindol-3-yl}-*N*-(4-hydroxybutyl)acetamide (30). A solution of indomethacin (1.6 g, 4.5 mmol), 4-aminobutan-1-ol (1.02 g, 4.7 mmol), DMAP (0.12 g, 1.0 mmol), EDAC (0.97 g, 5.1 mmol), and NEt_3 (1.5 mL, 10.8 mmol) in CH_2Cl_2 (60 mL) was stirred at room temperature for 6 h. The reaction was partitioned between 3 N HCl (50 mL) and CH_2Cl_2 (100 mL). The organic layer was washed with 3 N HCl, water, and brine, dried over Na_2SO_4, filtered, concentrated, and dried under vacuum. The product was separated by silica gel column chromatography eluted with MeOH/$CHCl_3$ (1:15, R_f = 0.17). The product was further purified by washing with EtOAc and Et_2O to obtain the title compound as a off-white solid (1.02 g, 53% yield). mp: 134–136 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 (d, J = 8.3 Hz, 2H), 7.48 (d, J = 8.3 Hz, 2H), 6.90 (d, J = 2.0 Hz, 1H), 6.86 (d, J = 9.0 Hz, 1H), 6.69 (dd, J = 9.0, 2.0 Hz, 1H), 6.0 (br. t, 1H), 3.81 (s, 3H), 3.62 (s, 2H), 3.55 (t, J = 5.4 Hz, 2H), 3.23 (br. q, 2H), 2.58 (s, 3H), 1.49 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.0, 168.4, 156.2, 139.6, 136.3, 133.5, 131.2, 130.9, 130.3, 129.2, 115.0, 112.9, 112.1, 101.0, 62.1, 55.7, 39.3, 32.2, 29.6, 26.1, 13.2. MS(API-TIS) m/z 429 $(MH)^+$. Anal. ($C_{23}H_{25}ClN_2O_4$) C, H, N.

2-{1-[(4-Chlorophenyl)carbonyl]-5-methoxy-2-methylindol-3-yl}-*N*-(3-hydroxypropyl)acetamide (31). A solution of indomethacin (1.55 g, 4.3 mmol), 3-aminopropan-1-ol (0.35 mL, 4.6 mmol), DMAP (65 mg, 0.5 mmol), EDAC (1.02 g, 5.3 mmol), and NEt_3 (1.2 mL, 8.6 mmol) in CH_2Cl_2 (70 mL) was stirred at room temperature overnight. The reaction was partitioned between 3 N HCl (50 mL) and CH_2Cl_2 (100 mL). The organic layer was washed with 3 N HCl, water, and brine, dried over Na_2SO_4, filtered, concentrated and dried under vacuum. The product was separated by silica gel column chromatography eluted with MeOH/$CHCl_3$ (1:15, R_f = 0.25) to obtain the title compound as a off-white solid (1.23 g, 68% yield). mp: 106–107 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H), 6.90 (d, J = 2.2 Hz, 1H), 6.85 (d, J = 9.0 Hz, 1H), 6.66 (dd, J = 9.0, 2.2 Hz, 1H), 6.48 (br. t, 1H), 3.80 (s, 3H), 3.61 (s, 2H), 3.54 (t, J = 5.4 Hz, 2H), 3.45 (br, 1H), 3.32 (br. q, 2H), 2.35 (s, 3H), 1.57 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.9, 168.2, 156.1, 139.3, 136.2, 133.4, 131.0, 130.7, 130.3, 129.0, 115.0, 112.7, 112.0, 100.8, 59.4, 55.6, 36.6, 31.8, 31.7, 13.1. MS (API-TIS): m/z 415 $(MH)^+$. Anal. ($C_{22}H_{23}ClN_2O_4$) C, H, N.

2-{1-[(4-Chlorophenyl)carbonyl]-5-methoxy-2-methylindol-3-yl}-*N*-[3-(nitrooxy)propyl]acetamide (32). A solution of indomethacin (1.55 g, 4.3 mmol), **2** (0.78 g, 5.0 mmol), DMAP (125 mg, 1.02 mmol), EDAC (1.09 g, 5.7 mmol), and NEt_3 (1.6 mL, 11.5 mmol) in CH_2Cl_2 (60 mL) was stirred at room temperature for 3.5 h. The reaction was partitioned between 3 N HCl (50 mL) and CH_2Cl_2 (100 mL). The organic extract was washed with 3 N HCl, water, and brine, dried over Na_2SO_4, filtered, concentrated, and dried under vacuum. The crude material was dissolved in CH_2Cl_2 (3 mL) and triturated with Et_2O (60 mL). The solid was collected and dried under vacuum to obtain the title compound as a yellowish solid (1.17 g, 59% yield). mp: 122–124 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 (d, J = 8.5 Hz, 2H), 7.48 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 2.3 Hz, 1H), 6.85 (d, J = 9.0 Hz, 1H), 6.69 (dd, J = 9.0, 2.3 Hz, 1H), 5.86 (br. t, 1H), 4.39 (t, J = 6.2 Hz, 2H), 3.82 (s, 3H), 3.65 (s, 2H), 3.31 (br. q, 2H), 2.39 (s, 3H), 1.88 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.3, 168.3, 156.3, 139.6, 136.5, 133.5, 131.1, 130.9, 130.2, 129.2, 115.2, 112.5, 112.2, 100.8, 70.9, 55.7, 36.4, 32.2, 28.6, 27.0, 13.2. MS (API-TIS): m/z 460 $(MH)^+$. Anal. ($C_{22}H_{22}ClN_3O_6$) C, H, N.

***N*-[2,2-Dimethyl-3-(nitrooxy)propyl]-2-{1-[(4-chlorophenyl)-carbonyl]-5-methoxy-2-methylindol-3-yl}acetamide (33).** A solution of indomethacin (1.15 g, 3.2 mmol), **4** (0.70 g, 3.3 mmol), EDAC (0.74 g, 3.9 mmol), and NEt_3 (0.95 mL, 6.8 mmol) in CH_2Cl_2 (40 mL) was stirred at room temperature for 2 h. The reaction was partitioned between 3 N HCl (50 mL) and CH_2Cl_2 (100 mL). The organic layer was washed with 3 N HCl, water, and brine, dried over Na_2SO_4, filtered, concentrated, and dried under vacuum. The crude material was dissolved in CH_2Cl_2 (3 mL) and triturated with Et_2O (60 mL). The solid was collected, washed with MeOH, and dried under vacuum to obtain the title compound as a white solid (0.57 g, 37% yield). mp: 148 °C (dec.). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66 (d, J = 8.5 Hz, 2H), 7.49 (d, J = 8.5 Hz, 2H), 6.90 (d, J = 2.4 Hz, 1H), 6.86 (d, J = 9.0 Hz, 1H), 6.69 (dd, J = 9.0, 2.4 Hz, 1H), 5.80 (br. t, 1H), 4.08 (s, 2H), 3.81 (s, 3H), 3.67 (s, 2H), 3.16 (br. d, 2H), 2.42 (s, 3H), 0.89 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.3, 168.2, 156.3, 139.5, 136.4, 133.5, 131.1, 130.9, 130.1, 129.1, 115.2, 112.5, 112.3, 100.7, 79.1, 55.6, 46.6, 35.7, 32.1, 22.2, 13.1. MS (API-TIS): m/z 488 $(MH)^+$.

***N*-{1,1-Bis[(nitrooxy)methyl]-2-(nitrooxy)ethyl}-2-{1-[(4-chlorophenyl)-carbonyl]-5-methoxy-2-methylindol-3-yl}acetamide (34).** Oxalyl chloride (0.19 mL, 2.2 mmol) was added to an ice-cold solution of indomethacin (0.6 g, 1.7 mmol) in CH_2Cl_2 (50 mL) and DMF (10 μL). The reaction was stirred in the ice-bath for 15 min then at room temperature for 2 h. The reaction mixture was evaporated to dryness under reduced pressure, and the resulting crude material was dissolved in CH_2Cl_2 (50 mL). Compound **6** was added to the above solution followed by the addition of NEt_3 (0.5 mL, 3.6 mmol) and stirred at room temperature for 3 h. The reaction was partitioned between 3 N HCl (50 mL) and CH_2Cl_2 (100 mL × 2). The combined organic extracts were washed with water, saturated $NaHCO_3$, and brine, dried over Na_2SO_4, filtered, and concentrated. The product was separated by silica gel column chromatography eluted with EtOAc/hexane (1:3, R_f = 0.2). The resulting yellowish solid, after evaporation of the solvents, was washed with Et_2O and dried under vacuum to obtain the title compound as a white solid (0.16 g, 16% yield). mp: >122 °C (dec.). ^{1}H NMR (300 MHz, acetone-d_6): δ 7.75 (d, J = 8.4 Hz, 2H), 7.72 (br, 1H), 7.62 (d, J = 8.4 Hz, 2H), 7.10 (d, J = 2.4 Hz, 1H), 7.02 (d, J = 9.0 Hz, 1H), 6.70 (dd, J = 9.0, 2.4 Hz, 1H), 5.04 (s, 6H), 3.82 (s, 3H), 3.70 (s, 2H), 2.31 (s, 3H). ^{13}C NMR (75 MHz, acetone-d_6): δ 171.9, 168.9, 157.2, 139.2, 136.7, 133.6, 132.1, 131.9, 131.8, 129.9, 115.7, 114.1, 112.6, 102.0, 70.8, 57.2, 55.9, 32.5, 13.6. MS (API-TIS): m/z 596 $(MH)^+$.

2-{1-[(4-Chlorophenyl)carbonyl]-5-methoxy-2-methylindol-3-yl}ethanehydroxamic Acid (35). Oxalyl chloride (0.8 mL, 9.2 mmol) was added to an ice-cold solution of indomethacin (2.51 g, 7.0 mmol) in CH_2Cl_2 (50 mL) and DMF (20 μL). The reaction was stirred in the ice-bath for 30 min then at room temperature for 2 h. The reaction mixture was evaporated to dryness under reduced pressure, and the resulting crude acid chloride was dissolved in CH_2Cl_2 (50 mL). Hydroxylamine hydrochloride (0.51 g, 7.3 mmol) and DMAP (1.71 g, 14.0 mmol) were added to the above solution and stirred at room temperature overnight. To the reaction mixture was added 3 N HCl (100 mL), and the solid precipitating out from the solution was collected, washed with CH_2Cl_2 and Et_2O, and then dried under vacuum to obtain a white solid (1.04 g, 40% yield). ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.6 (s, 1H), 8.7 (br., 1H), 7.68–7.65 (m, 4H), 7.15 (d, J = 2.3 Hz, 1H), 6.92 (d, J = 9.0 Hz, 1H), 6.71 (dd, J = 9.0, 2.3 Hz, 1H), 3.77 (s, 3H), 3.40 (s, 2H), 2.25 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.9, 166.4, 155.5, 137.6, 135.3, 134.2, 131.2, 130.8, 130.3, 129.1, 114.5, 113.8, 111.2, 102.1, 55.5, 28.4, 13.3. MS (API-TIS): m/z 373 $(MH)^+$.

(2-{1-[(4-Chlorophenyl)carbonyl]-5-methoxy-2-methylindol-3-yl}acetylamino) Acetate (36). A solution of **35** (0.49 g, 1.3 mmol), DMAP (20 mg), and acetic anhydride (0.16 mL, 1.7 mmol) in DMSO (5 mL) was stirred at room temperature for 3 days. The solvents were evaporated under vacuum. The residue was dissolved in EtOAc (60 mL), washed with 3 N HCl, water, and brine, dried over Na_2SO_4, filtered, and concentrated. The product was separated by silica gel column chromatography eluted with MeOH/$CHCl_3$ (1:20, R_f = 0.3). The crude purified material was washed with MeOH to obtain the title compound as a solid (0.24 g, 44% yield). mp: 153–156 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.1 (br, 1H), 7.62 (d, J = 8.5 Hz, 2H), 7.46 (d, J = 8.5 Hz, 2H), 6.99 (d, J = 2.3 Hz, 1H), 6.90 (d, J = 9.0 Hz, 1H), 6.69 (dd, J = 9.0, 2.3 Hz, 1H), 3.84 (s, 3H), 3.73 (s, 2H), 2.38 (s, 3H), 2.16 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.4, 168.3, 156.2, 139.4, 136.4, 133.4, 131.1, 130.8, 130.1, 129.1, 115.0, 112.3, 111.1, 100.9, 55.6, 29.4, 18.0, 13.2. MS(API-TIS): m/z 415 $(MH)^+$. Anal. ($C_{21}H_{19}ClN_2O_5$) C, H, N.

(*N*-Acetyl-2-{1-[(4-chlorophenyl)carbonyl]-5-methoxy-2-methylindol-3-yl}acetylamino) Acetate (37). A solution of **35** (0.42 g, 1.13 mmol) in a mixture of THF (10 mL), DMSO (2 mL), and acetic anhydride (5 mL) was stirred at room temperature overnight. The solvents were evaporated under vacuum. The residue was dissolved in EtOAc (100 mL), washed with saturated $NaHCO_3$, 3 N HCl, water, and brine, dried over Na_2SO_4, filtered, and concentrated. The residue was triturated with Et_2O, and the solid was collected and dried under vacuum to obtain the title compound (0.32 g, 61% yield). mp: 156–158 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 9.0 Hz, 1H), 6.84 (d, J = 2.3 Hz, 1H), 6.66 (dd, J = 9.0, 2.3 Hz, 1H), 4.06 (br. s, 2H), 3.82 (s, 3H), 2.42 (s, 3H), 2.33 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.2, 167.9, 167.4, 155.1, 139.2, 136.4, 133.8, 131.2, 130.8, 130.5, 129.1, 115.0, 111.8, 111.2, 101.0, 55.7, 32.2, 24.3, 17.9, 13.4. MS (API-TIS): m/z 457 $(MH)^+$. Anal. ($C_{23}H_{21}ClN_2O_6$) C, H, N.

2-{1-[(4-Chlorophenyl)carbonyl]-5-methoxy-2-methylindol-3-yl}-*N*-(phenylmethoxy)acetamide (38). A solution of indomethacin (4.01 g, 11.2 mmol), *O*-benzylhydroxylamine (0.70 g, 3.3 mmol), EDAC (2.76 g, 14.4 mmol), and NEt_3 (3.6 mL, 25.8 mmol) in CH_2Cl_2 (100 mL) was stirred at room temperature overnight. The reaction was partitioned between 3 N HCl (100 mL) and CH_2Cl_2 (100 mL). The organic layer was washed with 3 N HCl, water, and brine, dried over Na_2SO_4, filtered, concentrated, and dried under vacuum. The product was separated by silica gel column chromatography eluted with EtOAc/hexane (1:1, R_f = 0.2). The resulting yellowish solid, after evaporation of solvents, was washed with Et_2O and dried under vacuum to obtain the title compound as a white solid (1.98 g, 38% yield). mp: 152–153 °C (dec.). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.3 (br, 1H), 7.57 (d, J = 8.5 Hz, 2H), 7.45 (d, J = 8.5 Hz, 2H), 7.40–7.20 (m, 5H), 6.88 (d, J = 2.4 Hz, 1H), 6.83 (d, J = 9.0 Hz, 1H), 6.69 (dd, J = 9.0, 2.4 Hz, 1H), 4.84 (s, 2H), 3.80 (s, 3H), 3.58 (s, 2H), 2.28 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.2, 167.3, 156.2, 139.5, 136.1, 134.7, 133.5, 131.1, 130.8, 129.3, 129.1, 128.7, 128.5, 115.0, 112.1, 111.5, 100.9, 78.2, 55.7, 29.2, 13.2. MS(API-TIS): m/z 463 $(MH)^+$.

2-{1-[(4-Chlorophenyl)carbonyl]-5-methoxy-2-methylindol-3-yl}-*N*-(2-hydroxyethoxy)acetamide (39). A solution of indomethacin (6.23 g, 17.4 mmol), **43** (1.35 g, 17.5 mmol), EDAC (4.32 g, 22.5 mmol), and NEt_3 (5.6 mL, 40.2 mmol) in CH_2Cl_2 (100 mL) was stirred at room temperature for 2 h. The reaction was partitioned between 3 N HCl (100 mL) and CH_2Cl_2 (100 mL × 2). The combined organic extracts were washed with 3 N HCl, water, and brine, dried over Na_2SO_4, filtered, and concentrated. The resulting crude material was washed with methanol, filtered, and dried under vacuum to obtain the title compound as a yellowish solid (5.32 g, 73% yield). mp: 146–148 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.69 (br. s, 1H), 7.62 (d, J = 8.5 Hz, 2H), 7.46 (d, J = 8.5 Hz, 2H), 6.90 (d, J = 2.4 Hz, 1H), 6.84 (d, J = 9.0 Hz, 1H), 6.69 (dd, J = 9.0, 2.4 Hz, 1H), 3.90–3.70 (m, 2H), 3.80 (s, 3H), 3.60–3.50 (m, 4H), 2.29 (s, 3H). ^{13}C NMR (75 MHz, 20% $CD_3OD/CDCl_3$): δ 169.2, 168.4, 155.8, 139.2, 136.0, 133.4, 130.9, 130.6, 130.2, 128.9, 114.7, 111.8, 111.4, 101.0, 77.6, 59.0, 55.3, 28.6, 12.8. MS(API-TIS): m/z 417 $(MH)^+$. Anal. ($C_{21}H_{21}ClN_2O_5$) C, H, N.

2-{1-[(4-Chlorophenyl)carbonyl]-5-methoxy-2-methylindol-3-yl}-*N*-(3-hydroxypropoxy)acetamide (40). A solution of indomethacin (2.1 g, 5.9 mmol), **44** (0.64 g, 7.1 mmol), EDAC (1.45 g, 22.5 mmol), and NEt_3 (1.6 mL, 11.5 mmol) in CH_2Cl_2 (50 mL) was stirred at room temperature overnight. The reaction was partitioned between 3 N HCl (50 mL) and CH_2Cl_2 (50 mL × 2).

The combined organic extracts were washed with 3 N HCl, water, and brine, dried over Na_2SO_4, filtered, and concentrated. The resulting crude material was dissolved in ethyl acetate and triturated with hexane. The solid was collected and dried under vacuum to obtain the title compound as a yellowish solid (2.40 g, 95% yield). mp: 112–114 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.15 (br. s, 1H), 7.62 (d, J = 8.5 Hz, 2H), 7.47 (d, J = 8.5 Hz, 2H), 6.92 (d, J = 2.4 Hz, 1H), 6.84 (d, J = 9.0 Hz, 1H), 6.67 (dd, J = 9.0, 2.4 Hz, 1H), 3.99 (t, J = 5.7 Hz, 2H), 3.81 (s, 3H), 3.74 (t, J = 5.7 Hz, 2H), 3.59 (s, 2H), 2.37 (s, 3H), 1.80–1.73 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 168.2, 156.0, 139.3, 136.3, 133.4, 131.1, 130.7, 130.2, 129.0, 114.9, 111.7, 101.1, 74.5, 59.4, 55.6, 30.4, 29.2, 13.2. MS(API-TIS): m/z 431 $(MH)^+$.

2-(2-Hydroxyethoxy)benzo[c]azolidine-1,3-dione (41). A solution of sodium acetate (33.21 g, 0.4 mol), *N*-hydroxyphthalimide (22.0 g, 0.135 mol), and 2-bromoethanol (50.6 g, 0.4 mol) in DMSO (400 mL) was heated to 70 °C for 6 h. After it was cooled down to room temperature, water (400 mL) was added to the reaction mixture, and it was extracted with CH_2Cl_2 (250 mL × 3). The combined organic extracts were washed with water (250 mL × 2), 3 N HCl (150 mL), and brine, dried over Na_2SO_4, filtered, and concentrated. The resulting crude material was washed with 50% ethanol in water (120 mL), filtered, and dried under vacuum to obtained the title compound as a white solid (17.76 g, 64% yield). mp: 82–84 °C. ^{1}H NMR (300 MHz, CD_3OD): δ 7.9–7.8 (m, 4H), 4.30–4.25 (m, 2H), 3.90–3.82 (m, 2H). ^{13}C NMR (75 MHz, CD_3OD): δ 165.2, 135.8, 130.2, 124.3, 80.5, 60.8. MS(API-TIS): m/z 208 $(MH)^+$.

2-(3-Hydroxypropoxy)benzo[c]azolidine-1,3-dione (42). The title compound was prepared as a white solid (70% yield) from 3-bromopropan-1-ol by following the procedure for **41**. mp: 78–80 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.9–7.75 (m, 4H), 4.39 (t, J = 6.0 Hz, 2H), 3.93 (t, J = 6.0 Hz, 2H), 3.04 (br. s, 1H), 2.02 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.7, 134.5, 128.6, 123.5, 75.8, 58.8, 30.7. MS (API-TIS): m/z 222 $(MH)^+$.

2-(Aminooxy)ethan-1-ol (43). A solution of **41** (15.57 g, 75.2 mmol) and hydrazine hydrate (5.4 mL, 0.11 mol) in MeOH (150 mL) was heated to 70 °C for 1.5 h. After the mixture was cooled down to room temperature, $CHCl_3$ (100 mL) was added to the reaction mixture. The resulting slurry was filtered and washed with $CHCl_3$ (100 mL × 2). The filtrate was concentrated, and the residue was distilled under vacuum (0.025 mmHg) at 75−80 °C to obtain a colorless oil (4.54 g, 78% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.78 (s, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 76.3, 60.7.

3-(Aminooxy)propan-1-ol (44). The title compound was prepared as a colorless oil (87% yield), by following the procedure for **43**, and was distilled under vacuum (0.05 mmHg) at 90–95 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.0–5.0 (br, 3H), 3.79 (t, J = 6.1 Hz, 2H), 3.67 (t, J = 6.1 Hz, 2H), 1.81 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 73.0, 59.2, 31.2.

4-Chlorophenyl 3-(2-hydroxyethyl)-5-methoxy-2-methylindolyl Ketone (45). A solution of BH_3·SMe_2 in THF (2 M, 15 mL, 30 mmol) was added slowly to an ice-cold solution of indomethacin (10.2 g, 28.6 mmol) in THF (150 mL). The reaction was warmed up slowly from the ice-bath and stirred at room temperature overnight. Excess BH_3 was destroyed by the slow addition of MeOH (2 mL). The reaction mixture was evaporated to dryness under reduced pressure. The crude material was dissolved in CH_2Cl_2 (200 mL), washed with saturated $NaHCO_3$, water, 3 N HCl, water, and brine, dried over Na_2SO_4, filtered, and concentrated. The residue was dissolved in Et_2O (50 mL) and triturated with hexane (200 mL). The yellowish solid was collected and dried under vacuum to obtain the title compound (8.01 g, 81% yield). mp: 111–113 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (d, J = 8.5 Hz, 2H), 7.45 (d, J = 8.5 Hz, 2H), 6.94 (d, J = 2.4 Hz, 1H), 6.87 (d, J = 9.0 Hz, 1H), 6.65 (dd, J = 9.0, 2.4 Hz, 1H), 3.86 (t, J = 6.7 Hz, 2H), 3.83 (s, 3H), 2.94 (t, J = 6.7 Hz, 2H), 2.35 (s, 3H), 1.81 (br., 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.3, 156.0, 139.1, 135.4, 134.0, 131.08, 131.04, 130.97, 129.0, 116.0, 115.0, 111.3, 101.3, 62.1, 55.7, 27.6, 13.3. MS (API-TIS): m/z 344 $(MH)^+$. Anal. ($C_{19}H_{18}ClNO_3$) C, H, N.

2-{1-[(4-Chlorophenyl)carbonyl]-5-methoxy-2-methylindol-3-yl}ethyl Methylsulfonate (46). Triethylamine (0.22 mL, 1.6 mmol) and methanesulfonyl chloride (0.15 mL, 1.9 mmol) were added to a solution of **45** (0.44 g, 1.3 mmol) in CH_2Cl_2 (15 mL), and the mixture was stirred at room temperature for 2 h. The reaction was partitioned between 3 N HCl (10 mL) and CH_2Cl_2 (30 mL). The organic extract was washed with water and brine, dried over Na_2SO_4, filtered, concentrated, and dried under vacuum. The product, >95% purity from NMR analysis, was used in the next step without purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64 (d, J = 8.5 Hz, 2H), 7.47 (d, J = 8.5 Hz, 2H), 6.95 (d, J = 2.4 Hz, 1H), 6.89 (d, J = 9.0 Hz, 1H), 6.67 (dd, J = 9.0, 2.4 Hz, 1H), 4.39 (t, J = 7.0 Hz, 2H), 3.83 (s, 3H), 3.13 (t, J = 7.0 Hz, 2H), 2.92 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.1, 155.9, 139.1, 135.6, 133.7, 131.0, 130.7, 130.3, 129.0, 114.9, 113.7, 111.4, 100.8, 68.5, 55.6, 37.2, 24.4, 13.1. MS(API-TIS): m/z 422 $(MH)^+$.

4-Clorophenyl 5-methoxy-2-methyl-3-[2-(nitrooxy)ethyl]-indolyl Ketone (47). The crude product of **46** and tetrabutylammonium nitrate (0.47 g, 1.54 mmol) was heated to 100 °C overnight in toluene (15 mL). After it was cooled to room temperature, the reaction mixture was dissolved in EtOAc (100 mL), washed with water and brine, dried over Na_2SO_4, filtered, and concentrated. The product was separated by silica gel column chromatography eluted with EtOAc/hexane (1:5, R_f = 0.25) to obtain the title compound as a sticky oil (0.12 g, 24% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 (d, J = 8.6 Hz, 2H), 7.45 (d, J = 8.6 Hz, 2H), 6.92 (d, J = 2.5 Hz, 1H), 6.88 (d, J = 9.0 Hz, 1H), 6.68 (dd, J = 9.0, 2.5 Hz, 1H), 4.62 (t, J = 7.1 Hz, 2H), 3.83 (s, 3H), 3.09 (t, J = 7.1 Hz, 2H), 2.36 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.2, 156.1, 139.3, 135.8, 133.8, 131.1, 130.9, 130.3, 129.1, 115.1, 113.5, 111.6, 100.7, 71.6, 55.7, 22.1, 13.1. MS (API-TIS): m/z 389 $(MH)^+$.

3-(2-Bromoethyl)-5-methoxy-2-methylindolyl 4-chlorophenyl Ketone (48). To the crude product of **46** (1.03 g 3.0 mmol) was added LiBr (0.55 g, 6.4 mmol) and heated to 55 °C in acetone (100 mL) for 24 h. After the mixture was cooled to room temperature, the acetone was evaporated under vacuum. The residue was dissolved in CH_2Cl_2 (100 mL), washed with water and brine, dried over Na_2SO_4, filtered, and concentrated. The product was separated by silica gel column chromatography eluted with EtOAc/hexane (1:10, R_f = 0.25) to obtain the title compound (0.96 g, 79% yield). The product can be recrystallized from Et_2O and hexane. mp: 92–93 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (d, J = 8.5 Hz, 2H), 7.44 (d, J = 8.5 Hz, 2H), 6.90 (d, J = 2.5 Hz, 1H), 6.90 (d, J = 8.9 Hz, 1H), 6.66 (dd, J = 8.9, 2.5 Hz, 1H), 3.82 (s, 3H), 3.56 (t, J = 7.6 Hz, 2H), 3.21 (t, J = 7.6 Hz, 2H), 2.34 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.1, 155.9, 139.1, 135.4, 133.9, 131.0, 130.9, 130.2, 129.0, 116.6, 115.0, 111.3, 100.9, 55.7, 31.4, 27.9, 13.3. MS (API-TIS): m/z 406 $(MH)^+$.

(2-{1-[(4-Chlorophenyl)carbonyl]-5-methoxy-2-methylindol-3-yl}ethyl)-dimethoxyphosphino-1-one (49). A solution of **48** (0.43 g, 1.1 mmol) in $P(OMe)_3$ (3 mL) was heated to 110 °C for 2 days. The reaction mixture was evaporated to dryness under vacuum. The product was separated by silica gel column chromatography eluted with MeOH/ EtOAc (1:10, R_f = 0.3) to obtain the title compound (0.32 g, 70% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (d, J = 8.5 Hz, 2H), 7.46 (d, J = 8.5 Hz, 2H), 6.92 (d, J = 2.5 Hz, 1H), 6.89 (d, J = 9.0 Hz, 1H), 6.66 (dd, J = 9.0, 2.5 Hz, 1H), 3.83 (s, 3H), 3.76 (d, J_{PH}= 10.7 Hz, 6H), 2.96 (m, 2H), 2.35 (s, 3H), 2.06 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.0, 155.8, 138.9, 134.0, 133.9, 130.9, 130.8, 130.1, 128.9, 118.2 (d, J_{CP} = 16.7 Hz), 114.9, 111.1, 100.9, 55.6, 52.2 (d, J_{CP} = 6.5 Hz), 24.5 (d, J_{CP} = 137.4 Hz), 16.84 (d, J_{CP} = 4.3 Hz), 13.0. MS (API-TIS): m/z 436 $(MH)^+$.

4-Chlorophenyl 5-methoxy-2-methyl-3-(2-phosphonoethyl)indolyl Ketone (50). Bromotrimethylsilane (0.65 mL, 4.9 mmol) was added to an ice-cold solution of **49** (0.96 g, 2.2 mmol) in CH_2Cl_2 (30 mL) and stirred at room temperature overnight. The reaction mixture was partitioned between 1 N HCl (80 mL) and CH_2Cl_2 (100 mL × 2). The combined organic extracts were washed with water and brine, dried over Na_2SO_4, filtered, concentrated, and dried under vacuum. The residue was dissolved in $CHCl_3$ (5 mL) and

triturated with Et_2O (100 mL). The off-white solid was collected, washed with Et_2O, and then dried under vacuum (0.51 g, 57% yield). mp: 165–167 °C. ^{1}H NMR (300 MHz, CD_3OD): δ 7.62 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 8.4 Hz, 2H), 7.01 (d, J = 2.1 Hz, 1H), 6.92 (d, J = 9.0 Hz, 1H), 6.64 (dd, J = 9.0, 2.1 Hz, 1H), 3.81 (s, 3H), 2.95 (m, 2H), 2.27 (s, 3H), 1.99 (m, 2H). ^{13}C NMR (75 MHz, CD_3OD): δ 169.9, 157.7, 140.0, 135.9, 134.9, 132.4, 132.2, 131.8, 130.2, 120.5 (d, J_{CP} = 18 Hz), 116.1, 112.5, 102.1, 55.1, 28.4 (d, J_{CP} = 134.3 Hz), 18.5 (d, J_{CP} = 3.8 Hz), 13.4. MS (API-TIS): m/z 408 $(MH)^+$.

(2-{1-[(4-Chlorophenyl)carbonyl]-5-methoxy-2-methylindol-3-yl}ethoxy)-*N*-({[3-(nitrooxy)propyl]amino}sulfonyl)carboxamide (51). Chlorosulfonyl isocyanate (115 μL, 1.3 mmol) and NEt_3 (180 μL, 1.3 mmol) were added to an ice-cold solution of **45** (0.40 g, 1.2 mmol) in CH_2Cl_2 (15 mL) and stirred in the ice-bath for 30 min. Compound **2** (0.26 g, 1.4 mmol) and NEt_3 (250 μL, 1.8 mmol) were added to the reaction, and the temperature allowed to warm slowly in the ice-bath to room temperature. After 3 h, the reaction mixture was diluted with CH_2Cl_2 (80 mL), washed with 3 N HCl, water, and brine, and dried over Na_2SO_4, filtered, and concentrated. The products were separated by silica gel column chromatography eluted with EtOAc/hexane (1:1, R_f = 0.32) to obtain the title compound (0.15 g, 23% yield). The product can be recrystallized from $CHCl_3$/hexane. mp: 127–129 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.66 (d, J = 8.6 Hz, 2H), 7.60 (d, J = 8.6 Hz, 2H), 7.09 (d, J = 2.4 Hz, 1H), 6.99 (d, J = 9.0 Hz, 1H), 6.70 (dd, J = 9.0, 2.4 Hz, 1H), 4.54 (t, J = 6.3 Hz, 2H), 4.31 (t, J = 6.9 Hz, 2H), 3.80 (s, 3H), 3.03–2.97 (m, 4H), 2.23 (s, 3H), 1.86 (m, 2H). ^{13}C NMR (75 MHz, 5% $CDCl_3$/DMSO-d_6): δ 168.0, 155.9, 151.8, 137.8, 135.2, 134.3, 131.3, 130.7, 130.6, 129.2, 115.0, 114.8, 111.5, 101.5, 71.0, 64.4, 55.5, 39.8, 26.2, 23.4, 13.2. MS (API-TIS): m/z 569 $(MH)^+$.

3-(Nitrooxy)propyl [(2-{1-[(4-chlorophenyl)carbonyl]-5-methoxy-2-methylindol-3-yl}ethoxy)carbonylamino]sulfonate (52). Chlorosulfonyl isocyanate (130 μL, 1.5 mmol) and NEt_3 (210 μL, 1.5 mmol) were added to an ice-cold solution of **45** (0.52 g, 1.5 mmol) in CH_2Cl_2 (20 mL) and stirred in the ice-bath for 30 min. Compound **8** (0.25 g, 2.1 mmol) and NEt_3 (210 μL, 1.5 mmol) were added to the reaction; the temperature allowed to increase slowly in the ice-bath to room temperature, and the mixture was stirred overnight. The reaction mixture was partitioned between 3 N HCl (20 mL) and CH_2Cl_2 (50 mL). The organic extract was washed with water and brine, dried over Na_2SO_4, filtered, and concentrated. The products were separated by silica gel column chromatography eluted with EtOAc/hexane (1:1, R_f = 0.1) to obtain the title compound as a solid (0.143 g, 17% yield). mp: 44–46 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61 (d, J = 8.5 Hz, 2H), 7.43 (d, J = 8.5 Hz, 2H), 6.94 (d, J = 2.3 Hz, 1H), 6.89 (d, J = 9.0 Hz, 1H), 6.65 (dd, J = 9.0, 2.3 Hz, 1H), 4.48 (t, J = 6.0 Hz, 2H), 4.36 (t, J = 6.9 Hz, 2H), 4.31 (t, J = 6.0 Hz, 2H), 3.82 (s, 3H), 3.02 (br. t, 2H), 2.31 (s, 3H), 2.07 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.5, 156.0, 150.9, 139.2, 135.6, 133.6, 131.1, 130.9, 130.6, 129.0, 115.0, 114.5, 111.3, 101.2, 69.0, 68.5, 66.1, 55.7, 26.3, 23.4, 13.1. MS (API-TIS): m/z 570 $(MH)^+$.

(2-{1-[(4-Chlorophenyl)carbonyl]-5-methoxy-2-methylindol-3-yl}ethoxy)-*N*-[3-(nitrooxy)propyl]carboxamide (53). A solution of **45** (0.39 g, 1.1 mmol) in THF (5 mL) was added to a mixture of phosgene (20% in toluene, 10 mL) and K_2CO_3 (0.16 g, 1.2 mmol). The reaction was stirred at room temperature for 1 h then heated to 50 °C for an additional 0.5 h. The reaction was cooled down to room temperature. The excess phosgene was removed by evaporation of the reaction mixture to half the volume under reduced pressure. The resulting crude intermediate was dissolved in THF (20 mL), and **2** (0.20 g, 1.1 mmol) and DMAP (0.44 g, 3.6 mmol) were added and stirred at room temperature for 1.5 h. The reaction was quenched with 3 N HCl (100 mL) and extracted with EtOAc (50 mL × 2). The combined organic layers were washed with 3 N HCl, water, and brine, dried over Na_2SO_4, filtered, and concentrated. The product was separated by silica gel column chromatography eluted with EtOAc/hexane (2:3, R_f = 0.25) to obtain the title compound as a solid (0.47 g, 83% yield). The product can be recrystallized from $CHCl_3$ /hexane. mp: 51–52 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61 (d, J = 8.5 Hz, 2H), 7.43 (d, J = 8.5 Hz, 2H), 6.96 (d, J = 2.1 Hz, 1H), 6.87 (d, J = 9.0 Hz, 1H), 6.64 (dd, J = 9.0, 2.1 Hz, 1H), 5.15 (br, 1H), 4.44 (t, J = 5.9 Hz, 2H), 4.23 (t, J = 6.7 Hz, 2H), 3.81 (s, 3H), 3.24 (br. q, 2H), 2.96 (t, J = 6.7 Hz, 2H), 2.32 (s, 3H), 1.88 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.1, 156.4, 155.8, 138.9, 135.1, 133.9, 130.9, 130.7, 128.9, 115.3, 114.8, 111.0, 101.2, 70.6, 55.5, 37.3, 27.2, 23.9, 13.0. MS (API-TIS): m/z 490 $(MH)^+$.

3-(2-Azidoethyl)-5-methoxy-2-methylindolyl 4-chlorophenyl Ketone (54). To the crude product **46** (1.51 g, 4.4 mmol), was added NaN_3 (0.58 g, 8.9 mmol), and the mixture was heated to 70 °C in DMSO (50 mL) for 2 h. After the mixture was cooled to room temperature, the DMSO was evaporated under vacuum. The residue was dissolved in CH_2Cl_2 (150 mL), washed with water and brine, dried over Na_2SO_4, filtered, concentrated, and dried under vacuum to obtain the title compound. The product, >95% purity from NMR analysis, was used in the next step without purification. An analytical sample was obtained by silica gel column chromatography eluted with EtOAc/hexane (1:5, R_f = 0.45). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64 (d, J = 8.5 Hz, 2H), 7.45 (d, J = 8.5 Hz, 2H), 6.91 (d, J = 2.5 Hz, 1H), 6.89 (d, J = 9.0 Hz, 1H), 6.67 (dd, J = 9.0, 2.5 Hz, 1H), 3.83 (s, 3H), 3.49 (t, J = 7.0 Hz, 2H), 2.94 (t, J = 7.0 Hz, 2H), 2.37 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.2, 155.9, 139.1, 135.4, 133.9, 131.1, 130.9, 130.5, 129.0, 115.5, 115.0, 111.2, 101.0, 55.7, 50.7, 24.1, 13.1.

3-(2-Aminoethyl)-5-methoxy-2-methylindolyl 4-chlorophenyl Ketone Hydrochloride (55). The crude product **54** was hydrogenated in EtOAc (30 mL) in the presence of 10% Pd/C (0.14 g) and acetic acid (0.5 mL) at 30 psi for 2 h. The reaction mixture was filtered through Celite, and the filter cake was washed with MeOH (100 mL). The filtrate was concentrated, and the residue was partitioned between CH_2Cl_2 (200 mL) and water (100 mL). The organic layer was washed with saturated Na_2CO_3, water, and brine, dried over Na_2SO_4, filtered, concentrated, and dried under vacuum. The product was dissolved in Et_2O and treated with HCl/Et_2O. The brown solid was collected, washed with Et_2O, and then dried under vacuum (1.21 g, 73% yield for 4 steps). mp: >200 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.30 (br, 3H), 7.71 (d, J = 8.7 Hz, 2H), 7.63 (d, J = 8.7 Hz, 2H), 7.26 (d, J = 2.1 Hz, 1H), 6.96 (d, J = 9.0 Hz, 1H), 6.71 (dd, J = 9.0, 2.1 Hz, 1H), 3.80 (s, 3H), 3.00 (m, 4H), 2.23 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.0, 155.7, 137.6, 134.9, 134.2, 131.2, 130.5, 130.3, 129.0, 114.7, 111.5, 101.5, 55.6, 38.5, 21.6, 13.1. MS (API): m/z 343 $(M - Cl)^+$.

***N*-(2-{1-[(4-Chlorophenyl)carbonyl]-5-methoxy-2-methylindol-3-yl}ethyl){4-[(nitrooxy)methyl]phenyl}carboxamide (56).** A mixture of **55** (1.01 g, 2.7 mmol), **10** (0.59 g, 3.0 mmol), DMAP (0.4 g, 3.3 mmol), EDAC (0.67 g, 3.5 mmol), and NEt_3 (1.6 mL, 11.5 mmol) in CH_2Cl_2 (30 mL) and THF (20 mL) was stirred at room temperature for 2 days. The reaction mixture was partitioned between 3 N HCl (30 mL) and EtOAc (50 mL × 2). The combined organic extracts were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated. The product was separated by silica gel column chromatography eluted with EtOAc/hexane (2:3, R_f = 0.25 in 1:1) to obtain the title compound (0.28 g, 20% yield). The product can be recrystallized from Et_2O and hexane. mp: 141–144 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70 (d, J = 8.2 Hz, 2H), 7.61 (d, J = 8.5 Hz, 2H), 7.43 (d, J = 8.5 Hz, 2H), 7.41 (d, J = 8.2 Hz, 2H), 6.98 (d, J = 2.5 Hz, 2H), 6.89 (d, J = 9.0 Hz, 1H), 6.67 (dd, J = 9.0, 2.5 Hz, 1H), 6.4 (br. t, 1H), 5.43 (s, 2H), 3.74 (s, 3H), 3.67 (br. q, 2H), 3.00 (t, J = 6.6 Hz, 2H), 2.30 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.2, 166.8, 156.0, 139.1, 136.0, 135.3, 135.0, 133.8, 131.0, 130.88, 130.85, 129.0, 128.8, 127.4, 116.6, 115.0, 111.5, 101.0, 55.6, 39.9, 23.9, 13.2. MS (API-TIS): m/z 522 $(MH)^+$. Anal. ($C_{27}H_{24}ClN_3O_6$) C, H, N.

***N*-(2-{1-[(4-Chlorophenyl)carbonyl]-5-methoxy-2-methylindol-3-yl}ethyl){[3-(nitrooxy)propyl]amino}carboxamide (57).** *N*,*N*′-Carbonyldiimidazole (79 mg, 0.49 mmol) and **55** (0.16 g, 0.46 mmol) in CH_2Cl_2 (10 mL) were stirred at room temperature for 45 min. Compound **2** (85 mg, 0.46 mmol) and NEt_3 (0.07 mL, 0.5 mmol) in THF (5 mL) was added to the resulting solution, and

the mixture was stirred for an additional 5 h. The reaction mixture was partitioned between 3 N HCl (30 mL) and CH_2Cl_2 (50 mL). The organic extract was washed with water and brine, dried over Na_2SO_4, filtered, and concentrated. The product was separated by silica gel column chromatography eluted with EtOAc/hexane (gradient from 2:1 to 4:1, $R_f = 0.33$ in 2:1) to obtain the title compound (0.081 g, 40% yield). The product can further purified by washing with Et_2O. mp: 112–114 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60 (d, $J = 8.4$ Hz, 2H), 7.44 (d, $J = 8.4$ Hz, 2H), 6.94 (d, $J = 2.1$ Hz, 1H), 6.87 (d, $J = 9.0$ Hz, 1H), 6.66 (dd, $J = 9.0$, 2.1 Hz, 1H), 4.58 (br, 2H), 4.46 (t, $J = 6.0$ Hz, 2H), 3.83 (s, 3H), 3.40 (br. q, 2H), 3.23 (br. q, 2H), 2.86 (t, $J = 6.6$ Hz, 2H), 2.30 (s, 3H), 1.87 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.4, 158.0, 156.1, 139.3, 135.1, 133.9, 131.1, 131.0, 129.1, 128.8, 116.8, 115.0, 111.2, 101.4, 71.0, 55.7, 40.1, 36.9, 27.8, 24.8, 13.2. MS (API-TIS): *m/z* 489 $(MH)^+$.

3-[2-({[4-(Chloromethyl)phenyl]sulfonyl}amino)ethyl]-5-methoxy-2-methylindolyl 4-chlorophenyl Ketone (58). 4-(Bromomethyl)benzenesulfonyl chloride (1.15 g, 4.3 mmol) and NEt_3 (1.0 mL, 7.2 mmol) were added to **55** in CH_2Cl_2 (50 mL), and the mixture was stirred at room temperature overnight. The reaction was partitioned between 3 N HCl (30 mL) and CH_2Cl_2 (50 mL × 3). The combined organic extracts were washed with 3 N HCl, saturated $NaHCO_3$, water, and brine, dried over Na_2SO_4, filtered, and concentrated. The product was separated by silica gel column chromatography eluted with EtOAc/hexane (1:2, $R_f = 0.25$) to obtain the title compound (0.83 g, 53% yield). mp: 58–60 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.73 (d, $J = 8.3$ Hz, 2H), 7.57 (d, $J = 8.4$ Hz, 2H), 7.43 (d, $J = 8.4$ Hz, 2H), 7.42 (d, $J = 8.3$ Hz, 2H), 6.86 (d, $J = 9.0$ Hz, 1H), 6.85 (d, $J = 2.4$ Hz, 1H), 6.64 (dd, $J = 9.0$, 2.4 Hz, 1H), 5.15 (br. t, 1H), 4.57 (s, 2H), 3.80 (s, 3H), 3.21 (br. q, 2H), 2.88 (t, $J = 6.9$ Hz, 2H), 2.25 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.2, 155.9, 142.0, 139.7, 139.1, 135.3, 133.7, 131.0, 130.8, 130.4, 129.0, 128.95, 127.2, 115.3, 115.0, 111.4, 100.9, 55.6, 44.8, 42.5, 24.8, 13.2. MS (API-TIS): *m/z* 531 $(MH)^+$.

4-Chlorophenyl 5-methoxy-2-methyl-3-{2-[({4-[(nitrooxy)methyl]phenyl}-sulfonyl)amino]ethyl}indolyl Ketone (59). A solution of **58** (0.83 g, 1.6 mmol) and $AgNO_3$ (0.61 g, 3.95 mmol) in acetonitrile (60 mL) was heated to 70 °C for 6 h. The reaction was cooled down to room temperature and stirred with brine (50 mL) for 1 h. The silver salts were filtered off through Celite, and the filtrate was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, filtered, concentrated, and dried under vacuum. The product was separated by silica gel column chromatography eluted with EtOAc/hexane (1:2, $R_f = 0.15$) to obtain the title compound. The product was washed with 10% EtOAc/hexane to obtain a light yellowish solid (0.50 g, 57% yield). mp: 143–146 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.9–7.7 (m, 3H), 7.7–7.6 (m, 6H), 6.99 (d, $J = 2.4$ Hz, 1H), 6.97 (d, $J = 9.0$ Hz, 1H), 6.71 (dd, $J = 9.0$, 2.4 Hz, 1H), 5.65 (s, 2H), 3.78 (s, 3H), 3.01 (br. q, 2H), 2.79 (t, $J = 6.6$ Hz, 2H), 2.15 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.8, 155.6, 141.2, 137.6, 136.9, 134.5, 134.2, 131.2, 130.5, 130.4, 129.5, 129.0, 126.8, 116.1, 114.7, 111.3, 101.2, 73.8, 55.4, 42.4, 24.4, 13.2. MS (API-TIS): *m/z* 558 $(MH)^+$. Anal. ($C_{26}H_{24}ClN_3O_7S$) C, H, N.

4-Chlorophenyl 3-(2-{[(3-chloropropyl)sulfonyl]amino}ethyl)-5-methoxy-2-methylindolyl Ketone (60). 3-Chloropropanesulfonyl chloride (0.24 mL, 2.0 mmol) and NEt_3 (0.5 mL, 3.6 mmol) was added to **55** in $CHCl_3$ (20 mL), and the mixture was stirred at room temperature overnight. The reaction mixture was partitioned between 3 N HCl (30 mL) and CH_2Cl_2 (50 mL × 2). The combined organic extracts were washed with 3 N HCl, saturated $NaHCO_3$, water, and brine, dried over Na_2SO_4, filtered, and concentrated. The product was separated by silica gel column chromatography eluted with EtOAc/hexane (1:2, $R_f = 0.12$) to obtain the title compound (0.55 g, 77% yield). mp: 108–111 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59 (d, $J = 8.4$ Hz, 2H), 7.43 (d, $J = 8.4$ Hz, 2H), 6.98 (d, $J = 2.4$ Hz, 1H), 6.90 (d, $J = 9.0$ Hz, 1H), 6.65 (dd, $J = 9.0$, 2.4 Hz, 1H), 5.00 (t, $J = 6.3$ Hz, 1H), 3.82 (s, 3H), 3.55 (t, $J = 6.0$ Hz, 2H), 3.35 (br. q, 2H), 3.06 (m, 2H), 2.94 (t, $J = 6.9$ Hz, 2H), 2.33 (s, 3H), 2.12 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.2, 155.9, 139.0, 135.2, 133.7, 130.9, 130.5, 128.9, 115.4, 114.9, 111.3, 101.0, 55.6, 49.7, 42.6, 26.6, 25.5, 13.2. MS (API-TIS): *m/z* 483 $(MH)^+$. Anal. ($C_{22}H_{24}Cl_2N_2O_4S$) C, H, N.

4-Chlorophenyl 5-methoxy-2-methyl-3-[2-({[3-(nitrooxy)-propyl]sulfonyl}-amino)ethyl]indolyl Ketone (61). A solution of **60** (3.08 g, 6.4 mmol) and $AgNO_3$ (3.14 g, 18.5 mmol) in acetonitrile (100 mL) was heated to reflux for 3 days. The reaction was cooled down to room temperature and stirred with brine (50 mL) for 30 min. The silver salts were filtered off through Celite, and the filtrate was extracted with CH_2Cl_2. The organic extracts were washed with brine, dried over Na_2SO_4, filtered, concentrated, and dried under vacuum. The product was separated by silica gel column chromatography eluted with EtOAc/hexane (2:3, $R_f = 0.19$) to obtain the title compound as a yellowish solid (1.96 g, 60% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61 (d, $J = 8.5$ Hz, 2H), 7.45 (d, $J = 8.5$ Hz, 2H), 6.97 (d, $J = 2.4$ Hz, 1H), 6.89 (d, $J = 9.0$ Hz, 1H), 6.67 (dd, $J = 9.0$, 2.4 Hz, 1H), 4.73 (t, $J = 6.3$ Hz, 1H), 4.47 (t, $J = 6.2$ Hz, 2H), 3.83 (s, 3H), 3.36 (br. q, 2H), 2.92–3.0 (m, 4H), 2.34 (s, 3H), 2.10 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.3, 156.0, 139.3, 135.5, 133.7, 131.1, 130.9, 130.5, 129.1, 115.3, 115.0, 101.1, 70.5, 55.7, 49.0, 42.8, 25.6, 21.6, 13.3. MS (API-TIS): *m/z* 510 $(MH)^+$. Anal. ($C_{22}H_{24}ClN_3O_7S$) C, H, N.

4-Chlorophenyl 3-(2-{[(3-hydroxypropyl)sulfonyl]amino}ethyl)-5-methoxy-2-methylindolyl Ketone (62). Compound **61** (0.36 g, 0.71 mmol) was hydrogenated in EtOAc (20 mL) in presence of 10% Pd/C (55 mg) at 35 psi for 3.5 h. The reaction mixture was filtered through Celite, and the filter cake was washed with EtOAc. The filtrate was concentrated, and the residue was separated by silica gel column chromatography eluted with EtOAc/hexane (2:1, $R_f = 0.1$) to obtain the title compound (0.27 g, 80% yield). mp: 116–118 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, $J = 8.0$ Hz, 2H), 7.47 (d, $J = 8.0$ Hz, 2H), 6.97 (d, $J = 2.4$ Hz, 1H), 6.89 (d, $J = 8.8$ Hz, 1H), 6.67 (dd, $J = 8.8$, 2.4 Hz, 1H), 4.64 (br. t, 1H), 3.84 (s, 3H), 3.67 (t, $J = 6.0$ Hz, 2H), 3.37 (br. q, 2H), 3.07 (m, 2H), 2.96 (t, $J = 6.8$ Hz, 2H), 2.36 (s, 3H), 2.00–1.90 (m, 2H), 1.80–1.70 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4, 156.1, 139.4, 135.5, 133.8, 131.2, 131.0, 130.6, 129.1, 115.5, 115.0, 111.5, 101.2, 60.6, 55.8, 49.8, 42.8, 26.8, 25.6, 13.4. MS (API-TIS): *m/z* 465 $(MH)^+$. Anal. ($C_{22}H_{25}ClN_2O_5S$) C, H, N.

Supporting Information Available: COX inhibition screening data of all compounds and combustion analyses results. This material is available free of charge via the Internet at http://pubs.acs.org.

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