Synthesis and Structure−Activity Relationship of Novel, Highly Potent Metharyl and Methcycloalkyl Cyclooxygenase-2 (COX-2) Selective Inhibitors

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A novel series of benzo-1,3-dioxolane metharyl derivatives was synthesized and evaluated for cyclooxygenase-2 (COX-2) and cyclooxygenase-1 (COX-1) inhibition in human whole blood (HWB). In the present study, structure−activity relationships (SAR) in the metharyl analogues were investigated. The spacer group and substitutions in the spacer group were found to be quite important for potent COX-2 inhibition. Compounds in which a methylene group (**8a**−**c**), carbonyl group (**12a**−**c**), or methylidene group (**7a**−**c**) connected cycloalkyl groups to the central benzo-1,3-dioxolane template were found to be potent and selective COX-2 inhibitors. Aryl-substituted compounds linked to the central ring by either a methylene or a carbonyl spacer resulted in potent, highly selective COX-2 inhibitors. In this series of substituted-(2*H*-benzo-[3,4-*d*]1,3-dioxolan-5-yl))-1-(methylsulfonyl)benzene compounds, SAR studies demonstrated that substitution at the 3-position of the aryl group optimized COX-2 selectivity and potency, whereas substitution at the 4-position attenuated COX-2 inhibition. Mono- or difluoro substitution at meta position(s), as in **22c** and **22h**, was advantageous for both in vitro COX-2 potency and selectivity (e.g., COX-2 IC_{50} for **22c** = 1 μM and COX-1 IC_{50} for **22c** = 20 μM in HWB assay). Several novel compounds in the (2*H*-benzo[3,4-*d*]1,3-dioxolan-5-yl))-1-(methylsulfonyl)benzene series, as shown in structures **7c**, **8a**, **12a**, **21c**, **22c**, **22e**, and **22h**, selectively inhibited COX-2 activity by 40−50% at a test concentration of 1 μM in an in vitro HWB assay.

Introduction

Cyclooxygenases (COXs) and lipoxygenases (LOXs) are key enzymes in arachidonic acid (AA) metabolism. Eicosanoid mediators derived from COX and LOX pathways profoundly influence the development and progression of several inflammatory diseases. Prostaglandins (PGs) produced by COXs play physiological and pathophysiological roles in inflammation and in nociceptive transmission. COX exists in two isoforms: COX-1 and COX-2. Both COX isoforms metabolize AA to PGH_2, the common substrate for thromboxane-A_2 (TXA_2), prostacyclin (PGI_2), and prostaglandin-E_2 (PGE_2) synthesis. TXA_2, PGI_2, and PGE_2 play important roles in the maintenance of cardiovascular homeostasis. TXA_2 is primarily synthesized by COX-1 in platelets. COX-1-derived constitutive PGs are cytoprotective in the gastrointestinal (GI) tract. Inducible COX-2 is expressed at sites of inflammation by monocytes and macrophages and plays a key role in mediating the inflammatory process.[1] PGE_2 and leukotriene-B_4 (LTB_4) are the predominant eicosanoid inflammatory mediators.

Under basal physiological conditions, LOX-derived leukotrienes (LTs) are not produced by the GI mucosa in appreciable quantities. However, LTs are generated under inflammatory conditions[2] in the GI tract.[3] LT production during COX-1 inhibition due to diversion of the substrate AA to 5-LOX may contribute to GI mucosal injury by increasing microvascular permeability. In addition, one of the mediators produced by this pathway, LTB_4, is a potent chemotactic agent[4] that exerts its biological activity via BLT-1 and recently identified BLT-2 receptors.[5,6] At the site of inflammation, increased LTB_4 production also leads to activation of proinflammatory cytokines, e.g., tissue necrosis factor-α (TNF-α) and interleukin-1β (IL-1β). After the discovery of COX-2, it has been confirmed that IL-1β-stimulated chondrocytes from normal as well as osteoarthritic human cartilage induced COX-2 expression,[7] whereas, COX-1 was not detected in either normal or osteoarthritic chondrocytes.[8] Since there is no COX-1 in chondrocytes, traditional nonselective nonsteroidal antiinflammatory drugs (NSAIDs) are effective in reducing pain in arthritis by inhibiting COX-2.

NSAIDs are widely used for reducing pain and inflammation. However, chronic NSAID use may cause serious GI side effects, such as ulceration. NSAIDs induce GI damage by multiple mechanisms and vary in ulcerogenic activity in different regions of the GI tract. Both PG-dependent and -independent factors are responsible for the NSAID gastric toxicity. PG-dependent factors include the influences of PGs on mucus−bicarbonate secretion, regulation of acid secretion, and blood flow. Since the discovery of inducible COX-2, it has been possible to separate the roles of constitutive COX-1 and inducible COX-2 isozymes. Selective inhibition of COX-2 has proved to be a useful therapeutic target.[9] As a result, pharmaceutical companies have developed and tested extensive libraries of COX-2-selective inhibitors[1,10] with the hypothesis that selective

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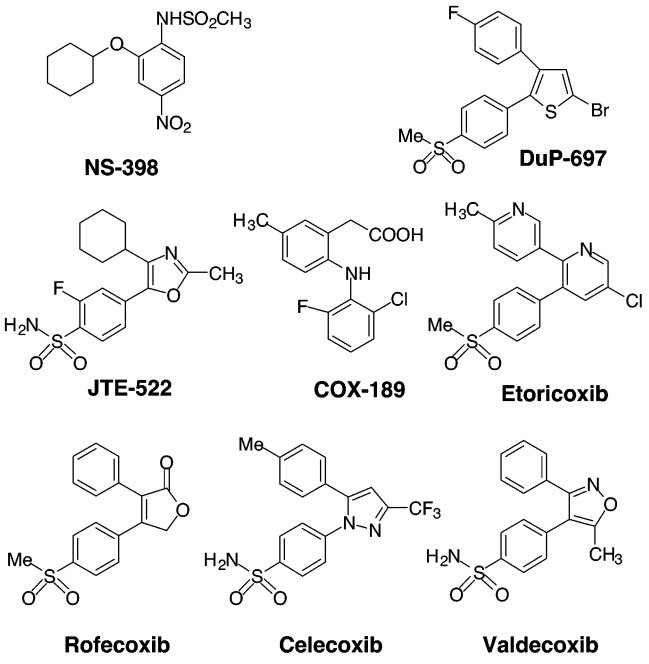
Chart 1



COX-2 inhibiton should block the prostaglandin production in inflammatory cells, while not interfering with the production of gastroprotective PGs in the GI tract by COX-1.

A number of pharmaceutical companies directed their research efforts and resources for the development of potent and selective COX-2 inhibitors. The clinical efficacy and impressive GI safety of COX-2 inhibitors resulted in the United States Food and Drug Administration (FDA) approval of two COXIBs, celecoxib and rofecoxib (Chart 1), as the first-generation, selective COX-2 inhibitors marketed for the treatment of inflammatory diseases. Specifically, for the treatment of acute pain, osteoarthritis, and rheumatoid arthritis,[11−14] they seem to be as effective as classical NSAIDs with reduced deleterious GI side effects.[15] Recently, valdecoxib received FDA approval as a COX-2 selective antiinflammatory drug,[16,17] and another COX-2 selective inhibitor, JTE-522,[18] is in a phase II clinical trial while COX-189[19] and etoricoxib are completing phase III clinical studies.

Prior to the proposal and confirmation of the COX-2 hypothesis, compounds such as NS-398 and DuP-697 demonstrated antiinflammatory activity with GI-sparing profiles in animal models.[20−22] Later, it was confirmed that DuP-697 and NS-398 preferentially inhibited COX-2 over COX-1.[23,24] These two compounds were the early lead candidates of COX-2-selective inhibitors, and especially, the central thiophene ring of DuP-697 provided a five-member ring template for the development of COX-2 inhibitors.

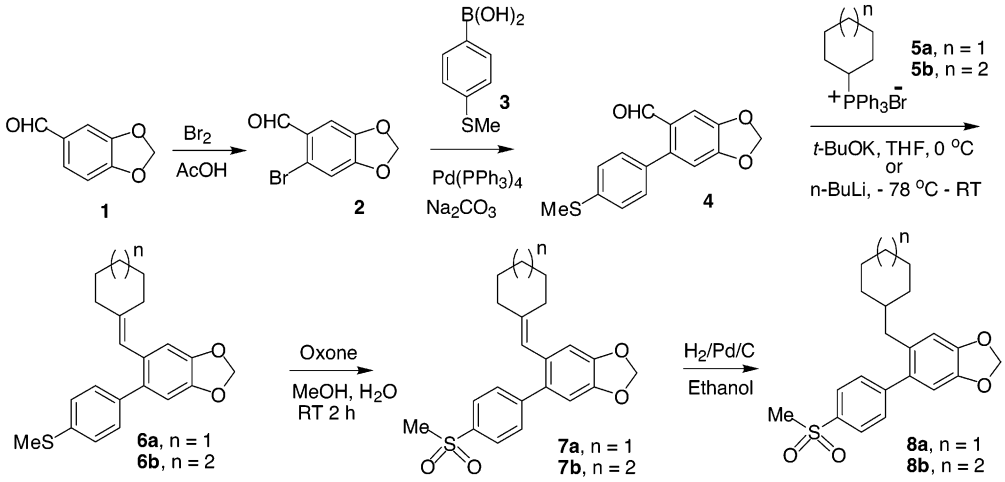
Structural biology[25,26] and X-ray crystallography[27,28] provided more useful information for the development of COX-2 inhibitors. Generally, for good COX-2 inhibitory activity and selectivity, compounds require a key pharmacophore,[29] the 4-methylsulfonylphenyl group, attached to a five-membered ring in which additional vicinal aryl ring substitution is present. The methyl sulfone group may be replaced by a sulfonamide, whereas the COX-2 inhibitory potency can be tuned-up by various substitutions on the other aryl ring. By utilizing a variety of five-member ring templates to give *o*-diaryl-substituted compounds with rigid conformation, many COX-2 selective inhibitors have been identified. Several interesting five-member ring templates include pyrazoles,[11,30] furanones,[12] cyclopentenes,[31,32] cyclopentenones,[33] imidazoles,[34,35] isoxazoles,[17] pyrroles,[36] oxazoles,[37] oxazolones,[38] and spiroheptenes.[39] The three FDA approved drugs, e.g., celecoxib, rofecoxib, and valdecoxib, are representative examples of the diaryl-substituted pyrazole, diaryl-substituted furanone, and diaryl-substituted isoxazole series, respectively. The five-member rings have also been replaced by six-member aryl[40] and heteroaryl rings.[41] Etoricoxib is an example of a diaryl-substituted pyridine COX-2 selective inhibitor.[41,42] A few bicyclic systems have been explored as central templates for the development of COX-2-selective inhibitors. Among the bicyclic systems, diaryl-substituted indanones[43] and pyrazolopyrimidines[44] have been reported. Classical NSAID templates have also been used to convert a COX-1-selective compound into a COX-2 selective inhibitor by slight modification. For example, conversion of indomethacin into various amide derivatives has generated COX-2 selective inhibitors.[45] On the basis of the COX-1 and COX-2 crystal structures, rationally designed COX-2 selectivity was achieved in flurbiprofen analogues.[46] Molecular modeling experiments also provide a better understanding of COX-2 enzyme−inhibitor interactions and possible guidelines to predict structure−activity relationships for novel COX-2 inhibitor design.[47−49]

As a part of our ongoing program to explore novel classes of COX-2 inhibitors, we report a new series of metharyl COX-2 selective inhibitors. In a novel approach to ortho-substituted aryl or cycloalkyl COX-2-selective inhibitors, we determined the effect of incorporating a spacer group between the cycloalkyl, aryl, or heteroaryl ring and central ring. Primarily, we have used a one-carbon spacer between the central benzo-1,3-dioxolane ring (template) and the aryl, heteroaryl, or cycloalkyl rings; therefore, as a generic name we refer to these compounds as the metharyl and the methcycloalkyl series compounds. In the present study, benzo-1,3-dioxolane was selected as the central ring for the SAR study in view of the easier access to substituent variation. Herein, we report that analogues of the vicinal-substituted benzo-1,3-dioxolanes are potent COX-2 inhibitors and a spacer group between the central ring and the cycloalkyl-, aryl- or heteroaryl group plays an important role in COX-2 inhibitory potency. Details of the synthetic studies and structure−activity relationships among these compounds are presented.

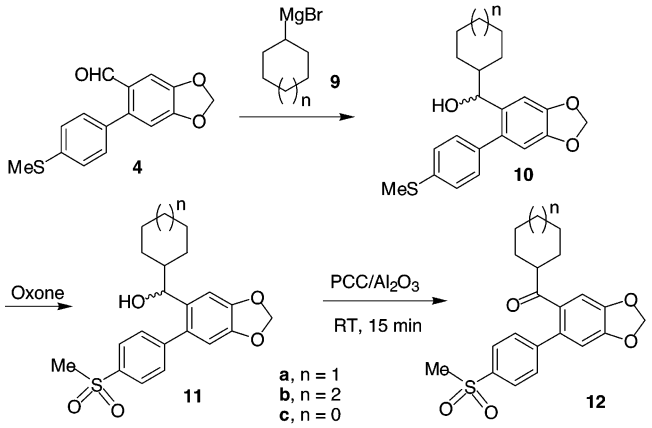
Chemistry

Our initial strategy was to investigate 1-(6-(cycloalkylmethyl)(2*H*-benzo[3,4-*d*]1,3-dioxolen-5-yl))-4-(methylsulfonyl)benzene analogues such as **8a** and **8b** in an effort to determine if incorporating a methylene spacer group between the central benzo-1,3-dioxolane ring and the cycloalkyl ring might improve in vitro COX-2 inhibitory potency. Synthesis of a series of (cycloalkylmethyl)benzo-1,3-dioxolanes **8a** and **8b** was conveniently accomplished as shown in Scheme 1. The known bromopiperonal **2** was prepared by bromination of

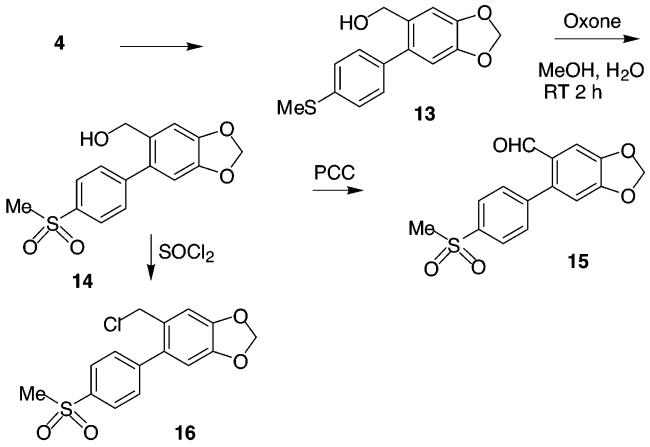
Scheme 1



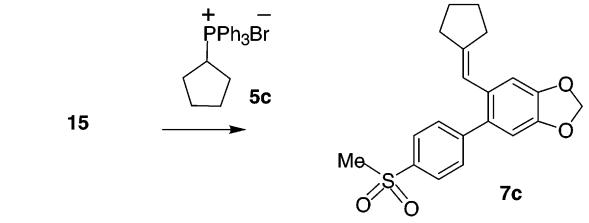
Scheme 2



Scheme 3



Scheme 4



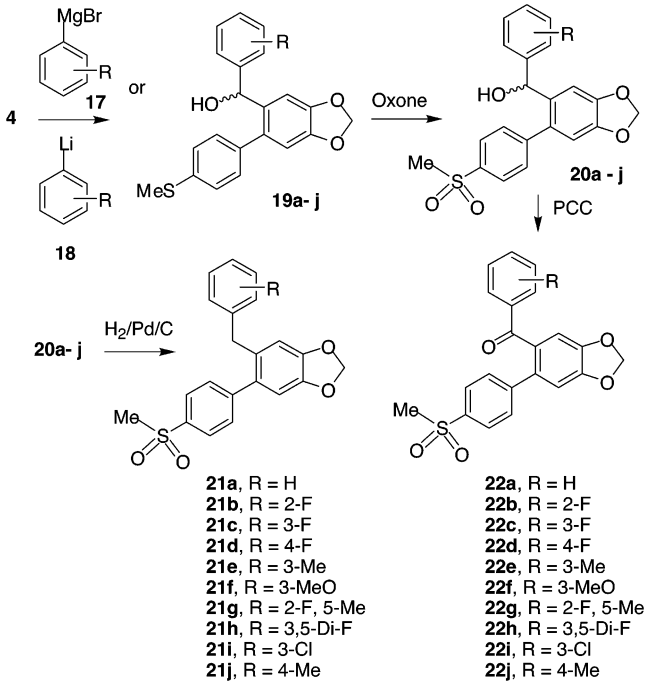
piperonal **1** using bromine in acetic acid.[50] The resulting bromoaldehyde **2** was converted to the key synthon 6-(4-methylthiophenyl)-2*H*-benzo[*d*]1,3-dioxolane-5-carbaldehyde **4** in high yield by Suzuki cross-coupling with 4-(methylthio)phenyl boronic acid **3** using standard conditions.[51] The Wittig coupling of carbaldehyde **4** with the ylides generated from **5a** or **5b** afforded the desired tricyclic compounds **6a** or **6b** in good yields. Oxidation of methylthio compounds **6a** and **6b** with Oxone gave the corresponding methyl sulfones **7a** and **7b** in excellent yields. Hydrogenation of **7a** and **7b** using Pd/C catalyst at 25−40 psi pressure provided **8a** and **8b** in nearly quantitative yields.

The synthetic method for the preparation of **12a**−**c** is outlined in Scheme 2. Reaction of aldehyde **4** with appropriately substituted Grignard reagents gave tricyclic compounds **10a**−**c**. These compounds **10a**−**c** were then oxidized with Oxone to give the corresponding methyl sulfones **11a**−**c**. The benzylic hydroxyl groups in **11a**−**c** were either deoxygenated by hydrogenolysis to give **8a**−**c** or oxidized to give the corresponding carbonyl compounds **12a**−**c**.

As shown in Scheme 3, an initial focus of our strategy was to prepare appropriately substituted key synthons, e.g., (6-(4-methylsulfonyl)phenyl)-2*H*-benzo[*d*]1,3-dioxolane-5-carbaldehyde) **15**, 1-(6-(chloromethyl) (2*H*-benzo-[3,4-*d*]1,3-dioxolan-5-yl))-4-(methylsulfonyl)phenyl)-2*H*-benzene **16**, and use these intermediates in a convergent manner to prepare the planned target compounds for COX in vitro screening and SAR studies. One such example is illustrated in Scheme 4. Wittig condensation of methylsulfonyl aldehyde **15** with the ylide derived from phosphonium **5c** gave **7c** in one step.

As will be discussed below, our attention was next focused toward alternative core structures related to **21** and **22**. The syntheses of these compounds were accomplished as shown in Scheme 5. Aldehyde **4** (Scheme 1) was prepared in large quantities (200−300 g) in two steps from commercially available piperonal in 62% overall yield. Lithio derivatives **18a**−**j** were conveniently prepared by metal halogen exchange of the corresponding haloarenes with *n*-BuLi or *t*-BuLi at −78 °C and subsequently quenched by addition of aldehyde **4** in THF to provide alcohols **19a**−**j**. Alternatively, Grignard reagents **17a**−**j** were prepared from the corresponding haloarenes and then treated with aldehyde **4** to give **19a**−**j**. These compounds **19a**−**j** were then oxidized with Oxone to form the corresponding sulfones **20a**−**j**. The

Scheme 5



21a, R = H
21b, R = 2-F
21c, R = 3-F
21d, R = 4-F
21e, R = 3-Me
21f, R = 3-MeO
21g, R = 2-F, 5-Me
21h, R = 3,5-Di-F
21i, R = 3-Cl
21j, R = 4-Me

22a, R = H
22b, R = 2-F
22c, R = 3-F
22d, R = 4-F
22e, R = 3-Me
22f, R = 3-MeO
22g, R = 2-F, 5-Me
22h, R = 3,5-Di-F
22i, R = 3-Cl
22j, R = 4-Me

doubly benzylic hydroxyl groups in **20a**−**j** were converted to the ketones by treatment with pyridinium chlorochromate (PCC) in dichloromethane to give the desired compounds **22a**−**j**. Alternatively, the hydroxyl groups in **20a**−**j** were deoxygenated by hydrogenolysis to give **21a**−**j**.

Attention was also focused on preparing (pyridylmethyl)benzo-1,3-dioxolane derivatives. Benzo-1,3-dioxolane-2-, 3-, and 4-(pyridylmethyl) derivatives were synthesized from **4** utilizing the same methodology, as depicted in Scheme 4. In Scheme 6, details of the preparation of the 3-(pyridylmethyl)-substituted analogue **27** are illustrated. 3-Lithiated-pyridine **24** was prepared by metal halogen exchange of 3-bromopyridine **23** with *t*-BuLi at −78 °C, followed by quenching the 3-lithiopyridine **24** by the aldehyde **4** to give the sulfide **25**. Oxidation of sulfide **25**, with Oxone proceeded smoothly to yield methyl sulfone **26**. Deoxygenation of **26** was carried out at room temperature by treating **26** with triethylsilane in dichloromethane/TFA to give **27**.[52]

Oxidation of **26** using PCC gave the compound **28**, with a carbonyl spacer group.

Using a similar reaction sequence as that shown in Scheme 6, the methyl-substituted 2-pyridyl analogue **31**, with a carbonyl spacer group was prepared as shown in Scheme 7. However, the same methodology when used to prepare 6-(4-(methylsulfonyl)phenyl)(2*H*-benzo[*d*]1,3-dioxolan-5-yl) 3-pyridyl ketone **36**, unexpectedly gave two products, **35** and **36** (Scheme 8). Initial metalation of 4-bromopyridine **32** gave a mixture of two lithiated species, 4-bromo-3-lithio- and 4-lithiopyridine, which upon quenching with **4** resulted in a mixture of **33** and **34**. The mixture was separated by flash column chromatography to give pure compounds **33** and **34**, each one was independently converted to the corresponding methyl sulfone, and subsequently the alcohol was oxidized to give compounds **35** and **36**, respectively.

A number of other alternative piperidinyl-substituted structures were pursued as well. The preparations of **38a**−**f** are illustrated in Scheme 9. Chloro compound **16** was reacted with various substituted piperidine derivatives **37** using potassium carbonate as base, giving the corresponding diaryl sulfones **38a**−**f** in good yields.

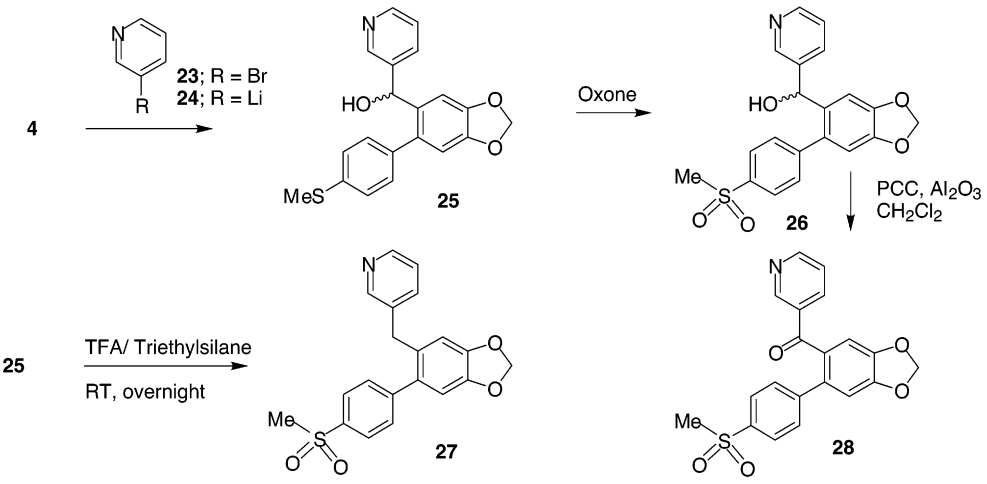
To decrease the basicity of the nitrogen in **38a**, the heterocyclic pattern of **38a** was modified. Compound **42** was synthesized by a straightforward transformation of the methylthio compound **4** as shown in Scheme 10.

An alternative approach to decrease the basicity of nitrogen in **38a** was achieved by preparing compounds as **45a,b** and **46a,b**. Carboxylic acid **43a** was prepared in two steps. It was then converted to the corresponding acid chloride **43b** and coupled with heterocycles **44a,b** to give the heterocycloalkyl-substituted benzo-1,3-dioxalane analogues **46a**, **46b**, and **45b** in which a carbonyl group spacer is introduced between the heterocyclic ring and the central benzo-1,3-dioxolane ring, as shown in Scheme 11.

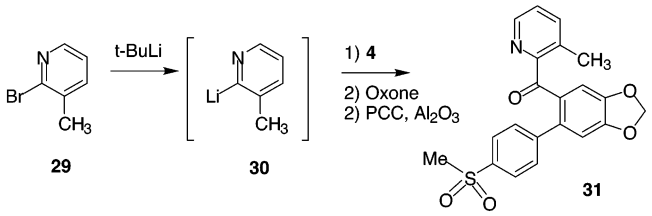
To examine the effect of sulfonamide pharmacophore on the COX-2 potency and selectivity, the methyl sulfone in **21a** was transformed into a sulfonamide to give **47** as shown in Scheme 12.

To study the effects of fluoro substitution on the phenylmethyl sulfone pharmacophore, the corresponding (fluoromethyl)phenyl sulfone **50** was prepared as

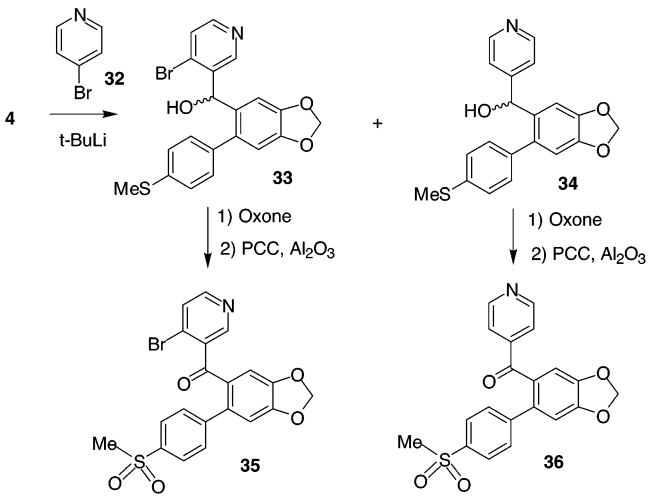
Scheme 6



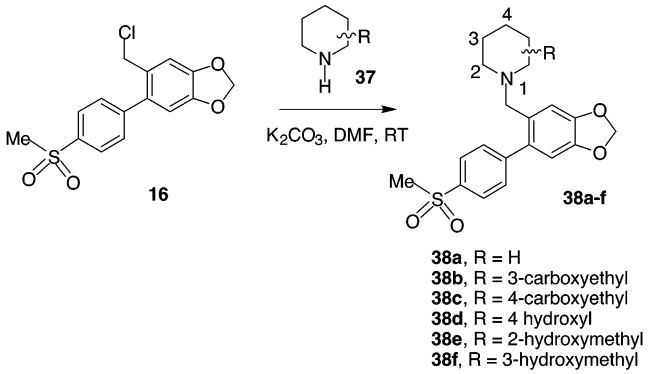
Scheme 7



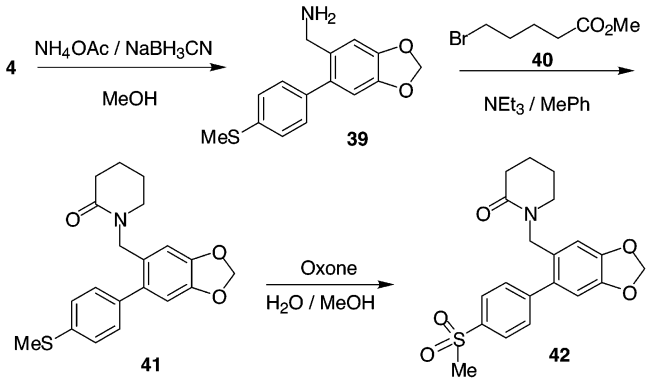
Scheme 8



Scheme 9

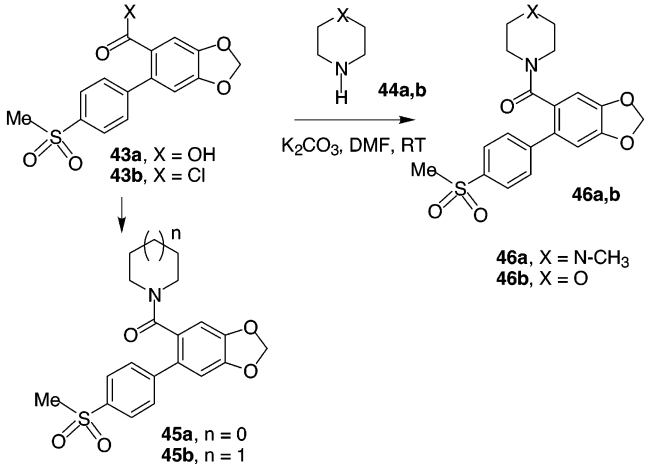


Scheme 10

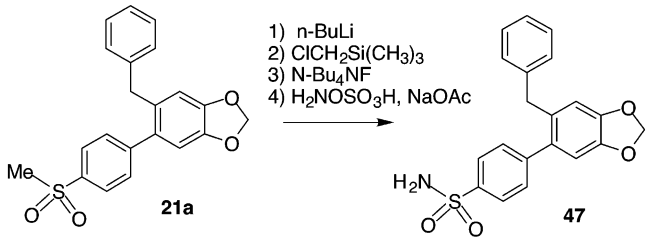


shown in Scheme 13.[53] Hydroxyl compound **19a** was hydrogenated overnight at 40 psi pressure to give the deoxygenated product **49a**. Interestingly, when compound **19a** was treated with sodium borohydride in the presence of trifluoroacetic acid, the desired product **49a** was not obtained. Instead, tricyclic compound **48** was

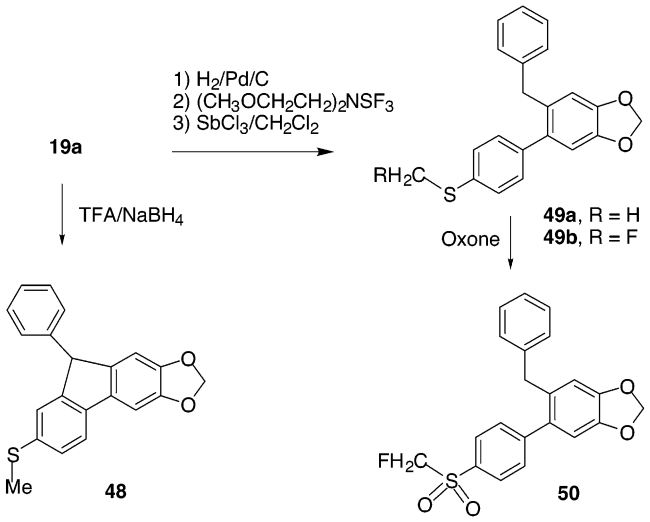
Scheme 11



Scheme 12



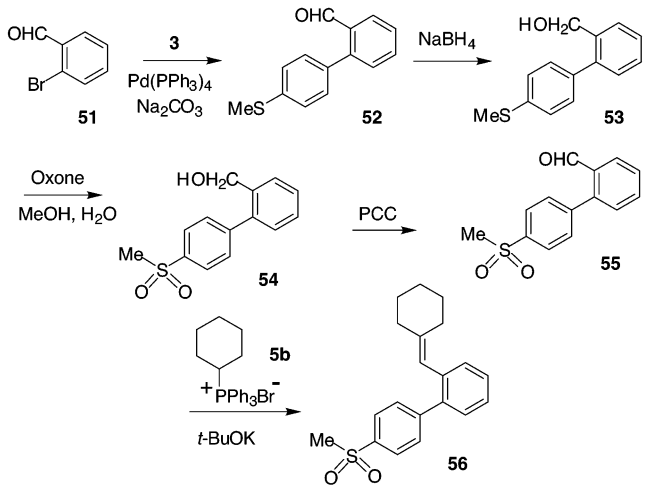
Scheme 13



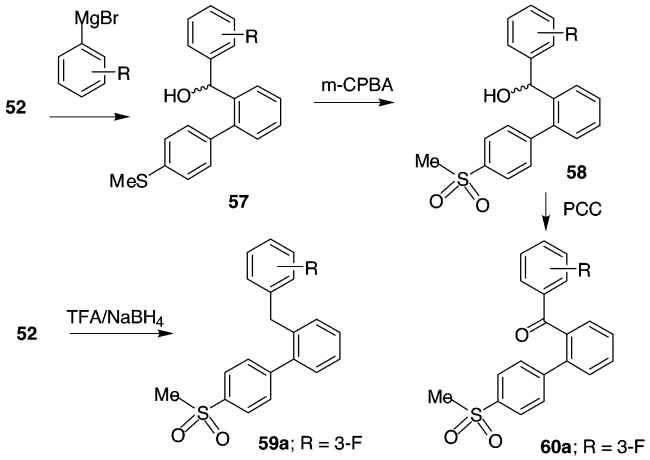
obtained in nearly quantitative yield. The formation of **48** can be rationalized on the basis of stable doubly benzylic carbocation formation followed by ring closure. Fluorination of thiomethyl group in **49a** was performed by treating **49a** with [bis(2-methoxyethyl)amino] sulfur trifluoride in the presence of a catalytic amount of $SbCl_3$ to furnish **49b**, which was subsequently oxidized with *m*-chloroperbenzoic acid to give **50**.

For studying the SAR of the dioxolane ring, compounds not containing this ring, such as **56** and **60**, were prepared. The details are outlined in Schemes 14 and 15. Compounds containing no spacer group between the central ring and the aryl ring, such as **65**, were prepared as shown in Scheme 16.[40] To study the effect of lengthening the spacer (linker) between the aryl and central ring, as in **21a**, compound **67** with a three-

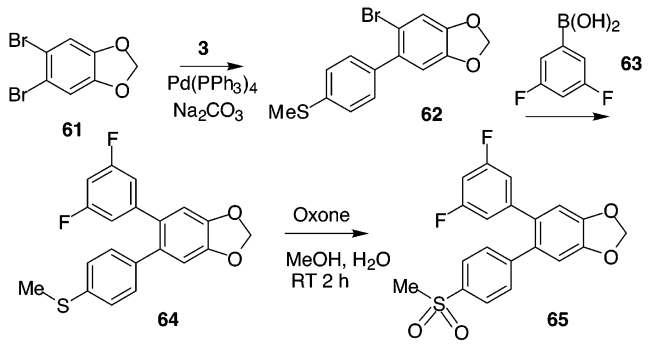
Scheme 14



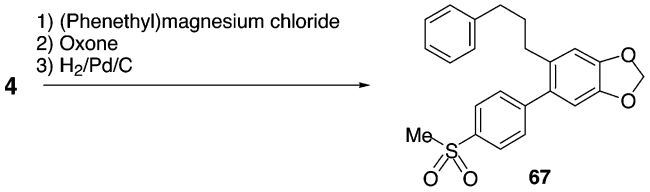
Scheme 15



Scheme 16



Scheme 17



carbon spacer group was prepared, as shown in Scheme 17. In addition, the dimethoxy compound **72** and benzo[*e*]1,4-dioxin-2-yl compound **74** were also prepared (Scheme 18).

Results and Discussion

As an initial screen to determine the in vitro COX-1 and COX-2 inhibitory activity, we evaluated compounds for their ability to inhibit recombinant human or ovine COX-1 at a 100 μM test concentration and COX-2 at both 10 and 1 μM test concentrations (Tables 1 and 2). Compounds that showed good COX-2 inhibition at 1 μM were also evaluated at various concentrations as COX-2 and COX-1 inhibitors to assess COX-2 selectivity (Table 3). Once initial lead compounds were so identified, they were evaluated in a human whole blood (HWB) assay, which takes into account the interactions of inhibitors with blood proteins and the ability of test compounds to traverse cellular membranes in a physiological setting. Eventually, all newly synthesized compounds were evaluated only in the HWB assay.

Recently, it has been reported that the bulky cyclohexyl group, as compared to the aryl group, enhances the COX-2 selectivity of JTE-522, an oxazole series COX-2 inhibitor.[18] In our initial SAR studies, we used 4-(methylsulfonylphenyl)benzo-1,3-dioxolane as a template and explored the effects of cycloalkyl groups of various sizes at the vicinal position as well as the linkage between the central ring and the cycloalkyl ring. We were gratified to find that several of the initial compounds screened in the recombinant enzyme assay were very potent, highly selective COX-2 inhibitors. Compounds **7a**, **7b**, and **8a** did not inhibit COX-1, even at 100 μM in the enzyme assay. Our studies demonstrated that, by connecting the cycloalkyl substituent to the central benzo-1,3-dioxolane template by a one-carbon spacer group, it was possible to prepare potent, selective COX-2 inhibitors. Evaluation of compounds **7a**−**c** and **8a**−**c** in the HWB assay confirmed that these compounds are potent COX-2 inhibitors; however, under these conditions some COX-1 inhibition was also detected (Table 1). Introduction of a double bond between the cycloalkyl substituent and the central ring improved the COX-2 inhibitor profile. When connected by a rigid double bond, the corresponding compounds such as **7a**−**c** were found to be slightly more potent COX-2 inhibitors than **8a**−**c** having a methylene group in the linkage. At a 10 μM concentration, **7a**−**c** and **8a**−**c** exerted substantial (75−90%) COX-2 inhibition in HWB.

SAR of Aryl-Substituted Analogues. Aryl group substitution is commonly incorporated into *o*-diaryl substituted COX-2 inhibitor design. It is well-established that *p*-methyl sulfone or sulfonamide on one of the phenyl rings is required for good COX-2 potency and selectivity. A variety of substituents could be added to the other phenyl ring to secure or enhance the COX-2 inhibitory potency. To investigate the SAR of the aryl-substituted analogues, we next focused attention on the preparation of aryl-substituted analogues of **8a**. In most of the known diaryl-substituted COX-2 inhibitors, the two rings are periplanar to the central ring. We expected that in the metharyl-substituted compound **21a** the methylene linkage that acts as a spacer between the aryl ring and the central benzo-1,3-dioxolane ring should give the molecule more flexibility to adopt a conformation suitable for the interaction at the enzyme's active site. Unsubstituted-aryl-ring compound **21a** exhibited modest COX-2 inhibitory potency ($IC_{50} = 10\ \mu M$), as well as a 6-fold COX-2/COX-1 selectivity (IC_{50} for

Scheme 18

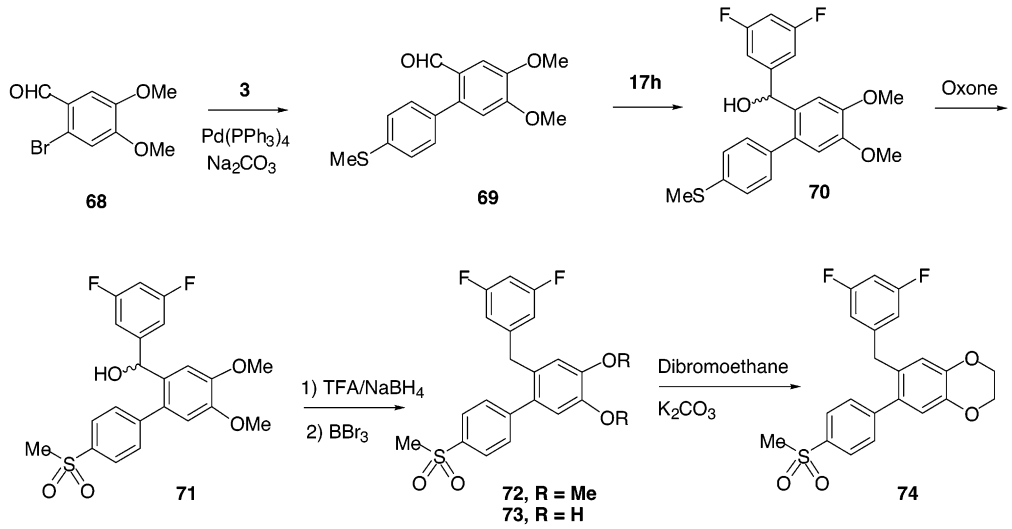
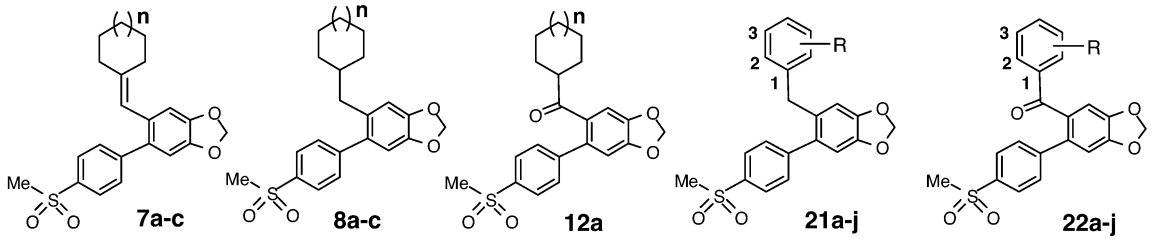


Table 1. Percent Inhibition of Recombinant COX-1 (Human or Ovine), COX-2 (Human) Enzyme Activity and Human COX-1 and COX-2 Enzyme Activity in HWB



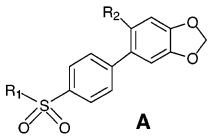
		recombinant[a]			HWB[d]		
compd	substituent	COX-1 (100 μM)[b]	COX-2 (10 μM)[b]	COX-2 (1 μM)[b]	COX-1 (100 μM)[b]	COX-2 (10 μM)[b]	COX-2 (1 μM)[b]
7a	n = 1	0	90	90	50	90	40
7b	n = 2	0[c]	100	100	35	90	25
7c	n = 0	80[c]	90	65	70	90	55
8a	n = 1	0	100	100	50	75	20
8b	n = 2	10[c]	100	90	40	80	25
8c	n = 0	20[c]	70	40			
12a	n = 1				55	85	40
20a		0	0	0			
21a	R = H	0	85	85	65	50	10
21b	R = 2-F				75	40	5
21c	R = 3-F				25	90	40
21d	R = 4-F	10[c]	0	10			
21e	R = 3-Me				10	40	10
21f	R = 3-MeO				35	10	0
21g	R= 2-F, 5-Me				40	50	25
21h	R = 3,5-di-F	15[c]	90	90	70	40	15
21i	R = 3-Cl				65	100	40
21j	R = 4-Me	25[c]	80	50	45	10	0
22a	R = H	0	90	10	75	65	25
22b	R = 2-F				70	95	30
22c	R = 3-F				50	95	50
22d	R = 4-F				95	5	0
22e	R = 3-Me	0[c]	40	10	95	85	40
22f	R = 3-MeO				95	75	10
22g	R = 2-F, 5-Me				90	90	25
22h	R = 3,5-di-F				50	95	50
22i	R = 3-Cl				90	100	15
22j	R = 4-Me				60	10	0
celecoxib		80	100	90	NT	100	50
rofecoxib		0	100	40	75	100	75

[a] Unless indicated otherwise, percent inhibition of recombinant human COX-1. [b] Concentration of test inhibitor. [c] Inhibition of recombinant ovine COX-1. [d] Average percent inhibition of two donors.

COX-1 = 60 μM) in HWB (Table 4). The length of the spacer between the central ring and the aryl group is also critical for COX-2 inhibition. Lengthening the spacer to three carbons, as in **67** (Table 2), resulted in the loss of COX-2 inhibitory potency.

Next we explored the effects of aryl substitution at ortho-, meta-, and para-positions on the phenyl ring of compound **21a** on COX inhibitor potency and selectivity in the HWB assay. As shown in Table 1, differences in COX-2 inhibitory potencies were observed when the aryl

Table 2. Percent Inhibition of Recombinant COX-1 (Human or Ovine), COX-2 (Human) Enzyme Activity and Human COX-1 and COX-2 Enzyme Activity in HWB



A

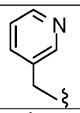
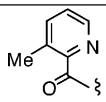
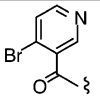
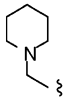
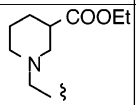
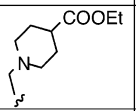
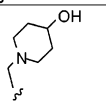
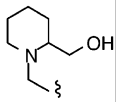
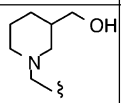
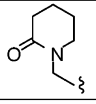
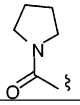
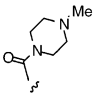
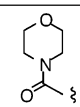
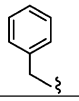
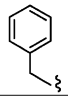
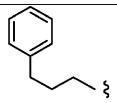
Comp. #	R_1	R_2	COX-1[a] Recomb. (100 μM)[b]	COX-2 Recomb. (10 μM)[b]	COX-2 Recomb. (1 μM)[b]	COX-1 HWB[d] (100 μM)[b]	COX-2 HWB[d] (10 μM)[b]	COX-2 HWB[d] (1 μM)[b]
27	Me		30	65	0	35	15	15
28	Me		20	20	0			
31	Me		0	10	0			
35	Me		40[c]	0	10			
38a	Me		0	30	0			
38b	Me		10	40	40			
38c	Me		0	20	20			
38d	Me		0	25	10			
38e	Me		0	30	25			
38f	Me		0	30	20			
42	Me		70	90	20	50	35	15
45a	Me		0	20	0			
45b	Me		15	40	20			
46a	Me		15	15	20			
46b	Me		10	10	35			

Table 2. (Continued)

Comp. #	R_1	R_2	COX-1[a] Recomb. (100 μM)[b]	COX-2 Recomb. (10 μM)[b]	COX-2 Recomb. (1 μM)[b]	COX-1 HWB[d] (100 μM)[b]	COX-2 HWB[d] (10 μM)[b]	COX-2 HWB[d] (1 μM)[b]
47	NH_2		90	90	85	90	0	0
50	$-CH_2F$		50[c]	50	25			
56						60	90	40
59a						35	10	0
60a						45	40	10
65						65	35	0
67	Me		10	0	15	65	35	15
72						0	15	15
74						70	40	15

[a] Unless indicated otherwise, percent inhibition of recombinant human COX-1. [b] Concentration of test inhibitor. [c] Percent inhibition of recombinant ovine COX-1. [d] Average percent inhibition of two donors.

Table 3. IC_{50} Values of Various Compounds in Recombinant COX-1 (Human), COX-2 (Human) Enzyme Assay

compd	IC_{50} (μM) COX-1	IC_{50} (μM) COX-2	COX-2/COX-1 selectivity
7a	>100 (nd[a])	0.07	>1400
7b	>100 (nd)	0.2	>500
47	25	0.05	500
celecoxib	<100	0.054	nd
rofecoxib	>100	1.0	>100

[a] nd = not determined.

Table 4. IC_{50} Values of Various Compounds and Standard COX-2 Inhibitors for COX-1 and COX-2 Enzymes in Human Blood

compd	IC_{50} (μM) COX-1	IC_{50} (μM) COX-2	COX-2/COX-1 selectivity
21a	60	10	10
22c	20	1.0	20
47	60	nd[a]	nd
celecoxib	14	1.2	11
rofecoxib	40	0.3	133

[a] nd = not determined.

ring was substituted at position 2-, 3-, or 4 with, for instance, halogen, methoxy, or methyl groups. In this bicyclic system, incorporation of substituent at the para-position of the phenyl ring had a deleterious effect on COX-2 inhibitory potency. Compounds **21j** and **22j**, with a 4-Me substituent, were not COX-2 inhibitors at a 1 μM test concentration in HWB. It is important to note the differences in COX-2 potency of **21j** in the enzyme assay and in HWB. In the enzyme assay **21j** exhibited 50% inhibition at 1 μM test concentration, whereas at this concentration it did not exhibit COX-2 inhibition in HWB. Surprisingly, 4-fluoro substitution in compound **21d** abrogated the COX-2 inhibitory activity. In general, 4-fluoro substitution on the aryl ring increases COX-2 potency. The active site of COX-2 offers more accessible space than that of COX-1, due to substitution of the amino acid valine for isoleucine at position 523.[25,26] The valine substitution opens up additional space that has proven to be important for the binding of selective COX-2 inhibitors, as thoroughly explored in the development of COX-2-selective inhibitors. Nonetheless, the steric requirement by the enzyme for the inhibitor is also critical. In the benzo-1,3-dioxolane system, the spacer group combined with 4-substitution on the aryl ring presumably exceeded the steric requirement for significant COX-2 affinity. We have also observed a similar difference in COX-2 potency for 4-fluoro-substituted compounds **22a** and **22d**. In contrast, compounds substituted at the meta-positions were potent COX-2 inhibitors. Among the meta-substituents, compounds substituted with electron-withdrawing groups such as **21e**, **21h**, and **21i** were moderately potent, whereas an electron-donating substituent, as in **21f**, decreased the COX-2 inhibitory potency. COX-2 inhibitory potency and selectivity are extremely sensitive to minor changes in chemical structure within the same chemical series. In this series, 3-fluoro substitution on the aryl ring as in **21c** resulted in a potent COX-2 inhibitor, whereas fluorine substitution at the 2-position decreased the COX-2 potency.

SAR of Aryl Analogues with Substituted Spacers. We found significant differences in COX-2 inhibitor potencies when the spacer group was substituted. Hydroxyl substitution as in **20a** resulted in the loss of COX-2 inhibitory potency (0% inhibition at 10 μM concentration in recombinant enzyme assay), but carbonyl

substitution in the spacer (e.g., compound **22a**) retained the COX-2 inhibitory potency (Table 1). It is noteworthy that compounds **22a** and **22e**, with a carbonyl spacer, exhibited significantly less (10%) COX-2 inhibition at 1 μM concentration in the enzyme assay, whereas the inhibition observed for the same concentration (1 μM) in HWB was considerably higher (25% and 40%, respectively). The carbonyl spacer can increase the polarity of the molecule and/or may have some effect on the hydrophobicity of the compounds. The theoretical *C* log *P* values for the compounds with carbonyl spacer are approximately 1 unit less than the corresponding compounds with methylene spacer (*C* log *P* values: **21a**, 4.41; **22a**, 3.53; **21e**, 4.96; **22e**, 4.09). The 3-aryl-substituted compounds **22c**, **22e**, and **22h** with carbonyl spacer exhibited good COX-2 inhibition (40−50%) at 1 μM concentration in HWB and modest COX-1 inhibition (50−65%) at a very high (100 μM) concentration. In contrast, 4-aryl-substituted compounds **22d** and **22j** did not exhibit any significant COX-2 inhibition (5−10%), even at a high 10 μM concentration in HWB. The COX inhibition by compounds with a carbonyl spacer, **22a**−**j**, is given in Table 1.

SAR of Methyl Sulfone COX-2 Pharmacophore. Replacement of the methyl sulfone group by a sulfonamide moiety usually decreases COX-2 selectivity but enhances oral bioavailability.[32,54] For the SAR study of this pharmacophore in the bicyclic system, we screened only one sulfonamide (**47**, Scheme 12) analogue of methyl sulfone **21a**. Its COX-2 and COX-1 inhibitory potencies were first determined in the enzyme assay and then in the HWB assay. Sulfonamide substitution, as in **47**, increased the COX-2 inhibitory potency in the enzyme assay. In this series, both the methyl sulfone **21a** and the sulfonamide **47** exhibited excellent COX-2 inhibition in the enzyme assay (Table 3). Sulfonamide **47** was found to be even more potent in the enzyme assay than the corresponding methyl sulfone **21a** with an IC_{50} of 0.05 μM against COX-2 and an IC_{50} of 25 μM against COX-1 (a 500-fold COX-2 selectivity). In the HWB assay, in contrast to methyl sulfone **21a**, the sulfonamide group in **47** abrogated the COX-2 inhibitory activity completely, yet **47** exhibited weak COX-1 inhibitory activity. To confirm this unexpected finding, we repeated the experiment using a known reference sample as a control and obtained the same results. Methyl sulfone and sulfonamide are the two well-known pharmacophores used in the development of COX-2 inhibitors. Even before the HWB assay was developed for the evaluation of COX-2 inhibitors, based on the potency in the enzyme assay, it has been reported and subsequently always presumed that sulfonamide in general increases the oral bioavailability and decreases COX-2 selectivity, which does not seem to be the general case. The sulfonamide **47** did not inhibit COX-2 even at high concentration (100 μM) in HWB, yet inhibited the COX-1 at higher concentrations. We even attempted to determine its IC_{50s} for COX-2 and COX-1 in HWB. For concentrations up to 100 μM, no COX-2 inhibition was observed. The COX-1 IC_{50} for sulfonamide **47** in HWB was 60 μM (Table 4). This divergence in results depending upon assay conditions underscores the importance of screening the compounds in an assay that more accurately reflects the physiological conditions. These data also show that interchangeability of the methyl sulfone group and the sulfonamide group for COX-2 inhibition is dependent upon other structural components, including the central ring system present within a particular inhibitor.

We also studied the effect of fluorine substitution on the methyl sulfone moiety. In this benzo-1,3-dioxolane bicyclic series, when the methyl sulfone was changed to a (fluoromethyl)sulfone as in compound **50**, an approximately 10-fold decrease of COX-2 inhibitory potency was observed in the enzyme assay.

SAR of Pyridyl Analogues. The pyridyl moiety imparts more hydrophilicity to a molecule. It can form a salt in the acidic pH of the GI tract, increasing aqueous solubility and helping to improve the absorption and bioavailability of a molecule, giving rise to enhanced in vivo potency.[55] We evaluated substituted 2- and 3-(pyridylmethyl) analogues for their COX-2 and COX-1 inhibition in the HWB assay. In this series, only the 3-(pyridylmethyl) analogue **27** (Table 2) was active in the enzyme assay: 65% COX-2 inhibition at 10 μM test concentration. The COX-2 inhibitory potency observed for **27** in the enzyme assay was much higher than that observed in the HWB assay. In the HWB assay, **27** showed only 15% COX-2 inhibition at a concentration of 10 μM. The 3-(pyridylmethyl) analogue **28** with a carbonyl spacer was also found to be inactive. The substituted 3-(pyridylmethyl) analogue **35** and the 2-(pyridylmethyl) analogue **31** were not COX-2 inhibitors.

SAR of Nitrogen-Containing Analogues. Since earlier SAR studies demonstrated that cyclohexyl substitution (as in **8a**) resulted in a potent and selective COX-2 inhibitor, another variation was introduced with the aim of retaining COX-2 potency and improving bioavailability. The cyclohexyl ring in **8a** was replaced by piperidine, as in **38a** (Table 2). Introduction of the amine nitrogen into **38a** was detrimental to COX-2 potency. While cyclohexyl analogue **8a** (Table 1) showed 100% COX-2 inhibition at 1 μM in the enzyme assay, its N-containing analogue **38a** was inactive. Substituted analogues **38b**−**f** exhibited low COX-2 potency in the recombinant enzyme assay; 25−40% inhibitions at 10 μM were observed. The loss in COX-2 inhibitory potency of **38a**−**f** was postulated to reflect the basicity of the nitrogen. If COX-2 inhibitory potency were compromised to be due to basicity of nitrogen in **38a**−**f**, then addition of a carbonyl into either the six-member ring as in **42** or into the spacer as in **45b** to give the corresponding amides should be beneficial for COX-2 inhibition. This modification was also guided by the good COX-2 inhibitory potency of **12a** and **22a**, which contain a carbonyl spacer (**12a**: 40% inhibition at 1 μM and 90% inhibition at 10 μM in HWB assay). Unlike compound **12a**, the nitrogen-containing analogue **45b** was a weak COX-2 inhibitor. Interestingly, the lactam **42** showed reasonably potent COX-2 inhibition in the enzymatic assay. However, once again this inhibition profile was not reproduced in the HWB assay (Table 2).

SAR of Spacer and 1,3-Dioxolane Ring. To determine the contribution of the spacer and the dioxolane ring, compounds **65** with no spacer (Scheme 16) and **56**, **59a**, and **60a** with no dioxolane ring (Scheme 15) were screened in the HWB assay, and their potencies were

compared to the corresponding compounds containing those groups. Compounds **21h** and **22h** with methylene and carbonyl spacer groups, respectively, showed excellent COX-2 inhibition in HWB. In contrast, compound **65**, without a spacer group, did not show any COX-2 inhibition at a 10 μM concentration in the HWB assay. Similarly, we also found that the 1,3-dioxolane ring contributed to COX-2 inhibitory potency. Compounds with no dioxolane rings, such as **56**, **59a**, and **60a**, were less potent than the corresponding compounds **7a**, **21c**, and **22c**. Compound **60a** showed weak COX-2 inhibition at a 1 μM concentration in the HWB assay compared to **22c**, which showed 50% inhibition at a 1 μM concentration in WHB. When dimethoxy groups, as in **72**, replaced the 1,3-dioxolane ring in **21h**, the COX-2 inhibitory potency was considerably decreased. Replacement of the 1,3-dioxolane ring in **22c** by 1,4-dioxinyl ring as in **74** also reduced COX-2 inhibitory potency considerably.

In Vivo Activity. To assess the oral activity of benzo-1,3-dioxolane COX-2 inhibitors, selected methyl sulfones **7c** and **21c** were evaluated in an acute inflammation model (the air pouch assay) and were found to be inactive (0% inhibition at 16 mg/kg). The reason for the lack of oral in vivo activity for **7c** and **21c** may reflect limited oral bioavailability. For the purpose of quick evaluation, we decided to directly administer the compound into the air pouch and determine the activity. The potent 3-fluorophenyl-substituted analogue **22c** inhibited 80% of the PGE_2 production in the air pouch (80% inhibition at 2 mg/kg) when administered directly into the air pouch.

Conclusions

We have designed and synthesized a series of novel disubstituted metharyl benzo-1,3-dioxolane compounds, many of which are highly potent and selective COX-2 inhibitors. Our SAR studies demonstrate for the first time that incorporation of a one-carbon spacer group between the central benzo-1,3-dioxolane ring and the cycloalkyl or aryl substituent provides more flexibility and leads to more potent COX-2 inhibitors. In this series, fluorine substitution at meta-position(s) of a phenyl ring, e.g., **21c**, **22c**, and **22h** generated potent and selective COX-2 inhibitors.

Experimental Section

General Comments. Reagents and solvents were generally used as obtained from commercial suppliers. Dry tetrahydrofuran (THF), ethyl ether, hexanes, dichloromethane, dimethylformamide (DMF), and methylsulfoxide (DMSO) were obtained from VWR or Fisher Scientific. Reactions were routinely performed under a nitrogen atmosphere in oven-dried glassware. Melting points were determined with an electrothermal heating block and are uncorrected. ^1H and ^{13}C NMR spectra were determined at 300 and 75.45 MHz, respectively. NMR spectra were recorded in $CDCl_3$ unless otherwise indicated, and chemical shifts are reported relative to tetramethylsilane (δ = 0.00). Routine mass spectra were obtained on a PE SCIEX, API 150 EX instrument with Turbo ion spray injector coupled with a Perkin-Elmer autosampler HPLC unit and 785A UV/vis detector, using an atmospheric pressure ionization method. Elemental microanalyses were performed by Robertson Microlit Laboratories (Madison, NJ). Flash column chromatography was performed using Merck silica gel 60 (270−400 mesh). TLC was performed on a 250 μm precoated Merck silica gel 60 F254 glass-backed plates. Spots were visualized under 254 nm UV light or by staining with phosphomolybdate (10% solution in ethanol) spray reagent.

Assay for Inhibition of Recombinant COX-1 (Human or Ovine) and COX-2 (Human) Enzyme Activity. Inhibition of recombinant human or ovine COX-1 and human COX-2 enzyme activities was measured using either the COX (human) inhibitor screening assay or the COX (ovine) inhibitor screening assay (Cayman Chemical, Ann Arbor, MI, cat. no. 560121 or 560101, respectively), which also contained the prostaglandin screening EIA used for quantification of the prostaglandin product. These commercial assays supplied the COX enzymes. The instructions provided with the assay were followed with some modification. Glass test tubes placed in a 25 °C water bath received 950 μL of reaction buffer (0.1 M Tris-HCl, pH 8.0, containing 5 mM EDTA and 2 mM phenol), 10 μL of a 100 μM heme solution, and 10 μL (5 units) of either human or ovine COX-1 or human COX-2 enzyme, and the resulting mixture was incubated for 2 min. Twenty microliters of test compound or solvent (e.g., DMSO) was added. Each tube was mixed vigorously immediately after this addition. The enzyme was incubated with the inhibitor for 20 min at 25 °C. The enzymatic reaction was then initiated by the addition of 10 μL of freshly prepared 10 mM arachidonic acid (neutralized with KOH) and mixing. After 2 min at 37 °C, the reaction was terminated by addition of 50 μL of 1 M HCl, mixing, and cooling to room temperature. One hundred microliters of a saturated stannous chloride solution (50 mg/mL of 0.1 M HCl) was added and the reaction mixture was allowed to stand at room temperature for at least 5 min. PGs produced in the COX-mediated reactions were quantified by EIA. Activity is expressed as percent inhibition relative to the control reaction containing solvent only (i.e., without test compound).

Assay for Inhibition of COX-1 and COX-2 Enzyme Activity in Human Whole Blood. The assay for COX-1 and COX-2 enzyme activity in human whole blood was performed essentially as described by Young et al.[56] Briefly, human blood from nonfasted, male or female donors who had not taken any aspirin or NSAIDs for 14 days was collected in sodium heparin (20 units per mL blood) and distributed in 1 mL aliquots per well of a 24-well tissue culture plate. The plate was placed on a gently rotating platform shaker in a 5% CO_2 incubator at 37° C for 15 min. Test compounds were dissolved and diluted in DMSO and 1 μL of each dilution of the test compound was added per well in duplicate wells.

To induce COX-2, lipopolysaccharide (LPS) from *Escherichia coli* (LPS, serotype 026:B6 or serotype 0127:B8, Sigma Chemical Co., St. Louis, MO, cat. no. L3755 or L3129, respectively) was added at 10 μg/mL (2 μL of 5 mg/mL LPS in DMSO) to appropriate wells 15 min after the addition of the test compounds. For the stimulation of COX-1, the calcium ionophore A23187 (Sigma Chemical Co., St. Louis, MO, cat. no. C7522) was added to a final concentration of 25 μM (1 μL of 25 mM stock in DMSO) to separate wells 4.5 h after the addition of the test compounds. (All control wells not receiving test compounds, LPS, or A23187 received equal volumes of DMSO) At 30 min after A23187 addition or 5 h after LPS addition, all incubations were terminated by cooling on ice and adding EGTA to a final concentration of 2 mM. The blood samples were then transferred by polyethylene transfer pipets to 15 mL polypropylene centrifuge tubes and centrifuged at 1200*g* for 10 min at 4 °C. One hundred microliters of plasma was removed from each blood sample and added to 1 mL of methanol in a 15 mL polypropylene centrifuge tube, mixed vigorously, and stored overnight at −20 °C. The next day, the samples were centrifuged at 2000*g* for 10 min at 4 °C, and the supernatants were transferred to glass tubes and evaporated to dryness. After reconstitution with EIA buffer and appropriate dilution (2000-fold for COX-1 and 500-fold for COX-2), the samples were assayed for TXB_2 using EIA kits supplied by Cayman Chemical Co. (Ann Arbor, MI, cat. no. 519031) in duplicate wells.

Air Pouch Model of Inflammation.[57] Male SD rats (175−200 g, Charles River Laboratories) were used, and the rats were fasted with free access to water at 24 h prior to

experiment. On day zero, animals received subcutaneous injections of 20 mL of sterile air into the intrascapular area of the back. An additional 10 mL of air was injected into the pouch on day −3 to keep the pouch open, allowing the interior membrane to be developed. On day six, vehicle or the test compound in 0.5% methyl cellulose was administered by oral gavage. One hour later inflammation was induced by injecting 1 mL of 1% carrageenan into the air pouch. Three hours after carrageenan injection, rats were sacrificed. Pouch exudates were collected, washed, and the number of leukocytes in the exudate were determined by cell counting with a Coulter counter. The total white blood cells (WBC) counts and percent inhibition of the cell infiltration were calculated. The exudate samples were also assayed for PGE_2 by specific ELISAs (Cayman Chemical Co.).

For determining the activity of COX-2 inhibitor in the air pouch directly, on day six, vehicle or the test compounds in 0.5% methylcellulose were administered by an injection into the air pouch, 1 h prior to the carrageenan injection.

6-Bromo-2*H*-benzo[d]1,3-dioxolene-5-carbaldehyde-(methylsulfonyl)benzene (2). The title compound was synthesized as described.[50] Treatment of piperonal **1** (60 g) with bromine (60 mL) in acetic acid (750 mL) and carbon disulfide (75 mL) containing a catalytic amount of iodine at room temperature, overnight, gave the title compound (69 g, 70% yield): mp 128−130 °C; ^{1}H NMR ($CDCl_3$) δ 10.17 (s, 1H, 7.33 (s, 1H), 7.03 (s, 1H), 6.06 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 190.3, 153.3, 148.1, 128.0, 121.5, 113.2, 108.1, 102.7; LRMS (APIMS) *m*/*z* 229 (Br 79) and 231 (Br 81) $(M + H)^+$ LRMS (APIMS) *m*/*z* 229 $(M + H)^+$ and 231 $((M + H) + 2)^+$.

General Procedures. Suzuki Coupling Reaction: Method A. The bromo compound (50 mmol) and 4-(methylthio)benzeneboronic acid **3** (8.4 g, 50 mmol) were dissolved in toluene (500 mL), and sodium carbonate (2 M, 50 mL, 100 mmol) was added. To this reaction mixture was added ethanol (20 mL) followed by tetrakis(triphenylphosphine)-palladium (3.4 g, 2.5 mmol). The reaction mixture was refluxed overnight under a nitrogen atmosphere and then diluted with water (250 mL), the organic layer was separated, and the aqueous layer was extracted with EtOAc (2 × 150 mL). The combined organic extracts were washed with water (4 × 250 mL) and brine (1 × 250 mL), dried over sodium sulfate, and filtered. The filtrate was evaporated under reduced pressure to give the crude product. The product was either purified by trituration with ethyl acetate/hexane or by chromatography on silica gel and elution with hexanes:EtOAc (19:1) to give the title compound as a white solid.

Wittig Reaction: Method B. A suspension of cycloalkyl-(triphenyl)phosphonium bromide (20 mmol) in anhydrous THF (125 mL) was stirred at −78 °C. *n*-BuLi (7 mL of 2.5 M in hexane, 17.5 mmol) was added dropwise to the stirred suspension under nitrogen atmosphere. The reaction mixture was stirred at −78 to −60 °C for over a period of 1 h. The suspension of ylide was then cooled to −78 °C, and the aldehyde (5 mmol) in THF (25 mL) was added dropwise to the ylide solution. The reaction mixture was gently stirred for 1.5 h at −78 °C, slowly allowed to warm to room temperature, and stirred at room temperature overnight. The reaction mixture was then quenched with saturated aqueous ammonium chloride and extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with water (1 × 50 mL) and brine (1 × 50 mL), dried over sodium sulfate, and filtered. The filtrate was evaporated and the residue was purified by chromatography on silica gel and elution with hexanes:EtOAc (9:1). This gave the desired product as a white powder in yields varying from 57% to 75%.

Oxone Oxidation Reaction: Method C. The thiomethyl compound (4 mmol) was dissolved in methanol (60 mL) with stirring at room temperature. A solution of Oxone (8 mmol) in water (20 mL) was added. The reaction mixture was stirred at room temperature for 2 h. The solvent methanol was evaporated at reduced pressure and the remainder was diluted with water (25 mL), neutralized with ammonium hydroxide, and extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with water (2 × 50 mL) and brine (1 × 25 mL), dried over sodium sulfate, and filtered. The filtrate was evaporated under reduced pressure, and the product was either purified by trituration with ethyl acetate/hexane or by chromatography on silica gel and elution with hexanes:EtOAc (19:1) to give the desired (methylsulfonyl) compound as a white solid in excellent yield.

Grignard Reaction: Method D. The desired Grignard reagent (4 mmol), if not commercially available, was freshly prepared by refluxing the equimolar amounts of haloarene and magnesium in the presence of a catalytic amount of iodine in THF (20 mL). The solution of the corresponding magnesium bromide (4 mmol) in THF (20 mL) was then added to a precooled (0 °C) solution of carbaldehyde (4 mmol) in anhydrous THF (40 mL) under nitrogen atmosphere. The reaction mixture was stirred at 0 °C for 10 min and then at room temperature for 2 h. It was quenched with saturated aqueous ammonium chloride, acidified with 1 N HCl, and then extracted with ethyl acetate (2 × 50 mL). The combined organic extracts were washed with water (1 × 25 mL) and brine (1 × 25 mL), dried over sodium sulfate, and filtered, and the filtrate was evaporated under reduced pressure to give the crude product. Purification by silica gel column chromatography using 20% ethyl acetate in hexane gave the desired compound as a white solid.

Hydrogenation Reaction: Method E. The product to be hydrogenated (1 mmol) was dissolved in a mixture of EtOAc (5 mL) and EtOH (25 mL). The catalyst, 10% palladium on carbon (250 mg), was added under a stream of nitrogen. The hydrogenation was performed at 20 psi of hydrogen for 3 h. The solution was filtered to remove the catalyst, and the filtrate was evaporated under reduced pressure to give the crude product that was triturated with hexanes:EtOAc (5:1) to give the title compound in good yield.

Deoxygenation Reaction Using $NaBH_4$/TFA: Method F. The hydroxyl compound (8 mmol) was dissolved in a minimal amount of CH_2Cl_2 and under argon atmosphere was added to trifluoroacetic acid at 0 °C. The reaction mixture was stirred at 0 °C for 15 min. To the resulting solution was then added, in small portions, sodium borohydride (1.39 g, 36.72 mmol). The reaction mixture was stirred at 0 °C for an additional 30 min. The solvent and trifluoroacetic acid were evaporated under reduced pressure to give a gray foam. Ice-cold water (20 mL) was added to the foam, and the aqueous layer was made basic (pH 8−9) by addition of NaOH (50%). The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic layers were dried over sodium sulfate and filtered. The filtrate was evaporated under reduced pressure to give the crude product that was either purified by recrystallization from CH_2Cl_2:hexanes or by silica gel column chromatography using 20% ethyl acetate in hexane to give the desired compound as a white solid.

PCC Oxidation Reaction: Method G. A suspension of the hydroxyl compound (1 mmol) and alumina (2 g) in anhydrous CH_2Cl_2 (50 mL) was stirred at room temperature. While stirring, pyridinium chlorochromate (3 mmol) was added, and the reaction mixture was stirred at room temperature for 1 h. The mixture was diluted with CH_2Cl_2, and the alumina was removed by filtration. The filtrate was washed with water (1 × 50 mL), saturated aqueous sodium bicarbonate (2 × 50 mL), and brine (1 × 50 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was evaporated under reduced pressure. Purification by flash column chromatography on silica gel and elution with hexanes:EtOAc (19:1) gave the desired compound as a white solid.

N-Alkylation Reaction: Method H. The appropriately substituted halo compound (1.2 mmol) and substituted piperidinyl compound (138 mg, 1.2 mmol) were dissolved in anhydrous DMF (5 mL). Potassium carbonate (830 mg, 6 mmol) was added, and reaction mixture was stirred at room temperature overnight. The reaction mixture was then treated with ice-cold water and extracted with ethyl acetate (2 × 75 mL). The combined organic extracts were washed with water (1 × 50 mL) and brine (1 × 50 mL), dried over sodium sulfate,

and filtered. The filtrate was evaporated under reduced pressure to give the crude product that was purified by flash column chromatography using methanol:dichloromethane (5:95) to give the desired compound as a white solid in high yield.

$NaBH_4$ Reduction: Method I. The carbaldehyde (4 mmol) was dissolved in ethanol (50 mL), and to this solution was added sodium borohydride (12 mmol). The reaction mixture was stirred at room temperature for 2 h. The solvent was evaporated under reduced pressure and the residue was treated with water (25 mL), neutralized with 1 N HCl, and extracted with ethyl acetate (2 × 50 mL). The combined organic extracts were washed with water and brine, dried over sodium sulfate, and filtered. The filtrate was evaporated under reduced pressure to give the crude product. Trituration with 10% ethyl acetate in hexane gave the pure desired compound as a white solid.

6-(4-Methylthiophenyl)-2*H*-benzo[d]1,3-dioxolane-5-carbaldehyde (4). This compound was prepared using method A. It was obtained as a white solid in 88% yield: mp 111−112 °C; ^{1}H NMR ($CDCl_3$) δ 9.74 (s, 1H), 7.41 (s, 1H), 7.29 (m, 4H), 6.80 (s, 1H), 6.07 (s, 2H), 2.52 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 190.3, 152.3, 148.5, 143.3, 140.8, 140.2, 130.9, 128.8, 127.4, 110.1, 106.7; 102.4, 44.4; LRMS (APIMS) *m/z* 273 $(M + H)^+$.

1-(6-(Cyclohexylidenemethyl)(2*H*-benzo[3,4-d]1,3-dioxolan-5-yl))-4-methylthiobenzene (6a). Using method B, compound **6a** was obtained as a white powder in 67% yield: mp 83−84 °C; ^{1}H NMR ($CDCl_3$) δ 7.31 (m, 4H), 6.79 (s, 1H), 6.72 (s, 1H), 5.92 (s, 2H), 5.88 (s, 1H), 2.51 (s, 3H), 2.23 (t, J = 5.6 Hz, 2H), 2.11 (m, 2H), 1.45−1.55 (m, 6H).

4-(6-(Cycloheptylidenemethyl)(2*H*-benzo[3,4-d]1,3-dioxolan-5-yl))-1-methylthiobenzene (6b). Using (cycloheptyl)triphenyl phosphine bromide and following method B, the title compound **6b** was obtained as oil in 57% yield: ^{1}H NMR ($CDCl_3$) δ 7.22 (s, 4H), 6.77 (d, J = 3.1 Hz, 2H), 5.94 (s, 3H), 2.48 (s, 3H), 2.40−2.36 (m, 2H), 2.25−2.20 (m, 2H), 1.63−1.32 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 146.2, 146.0, 143.4, 138.2, 136.6, 134.0, 130.4, 130.2, 125.9, 125.4, 109.9, 109.5, 100.9, 37.4, 31.1, 29.9, 28.9, 28.9, 27.0, 15.8.

1-(6-(Cyclohexylidenemethyl)(2*H*-benzo[3,4-d]1,3-dioxolan-5-yl))-4-(methylsulfonyl)benzene (7a). The compound **7a** was prepared from **6a** by using method C in 56% yield. It was obtained as crystalline solid: mp 147−151 °C; ^{1}H NMR ($CDCl_3$) δ 7.89 (d, J = 8.3 Hz, 2H), 7.84 (d, J = 8.3 Hz, 2H), 6.77 (s, 1H), 6.72 (s, 1H), 5.98 (s, 2H), 5.84 (s, 1H), 3.07 (s, 3H), 2.14 (t, J = 5.6 Hz, 2H), 2.08 (m, 2H), 1.51−1.30 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 147.2, 147.1, 146.4, 143.2, 138.3, 135.5, 130.6, 130.5, 126.8, 120.9, 110.5, 109.4, 101.2, 44.5, 36.9, 29.5, 28.2. 27.3, 26.4; LRMS (APIMS) *m/z* 371 $(M + H)^+$. Anal. ($C_{21}H_{22}SO_4$) C, H.

4-(6-(Cycloheptylidenemethyl)(2*H*-benzo[3,4-d]1,3-dioxolan-5-yl))-1-(methylsulfonyl)benzene (7b). The compound **7b** was prepared from **6b** using method C in 75% yield. It was obtained as a white solid: mp 168−169 °C; ^{1}H NMR ($CDCl_3$) δ 7.91 (d, J = 8.3 Hz, 2H), 7.51 (d, J = 8.2 Hz, 2H), 6.79 (d, J = 2.1 Hz, 2H), 6.00 (s, 2H), 5.92 (s, 1H), 3.09 (s, 3H), 2.32 (t, J = 14.4 Hz, 2H), 2.23−2.17 (m, 2H), 1.61−1.51 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 147.3, 146.4, 145.0, 138.4, 132.5, 131.0, 130.7, 126.8, 124.5, 110.3, 109.5, 101.3, 44.6, 37.5, 31.2, 29.9, 29.0, 28.9, 26.9; LRMS (APIMS) *m/z* 402 $(M + NH_4)^+$. Anal. ($C_{22}H_{24}SO_4$) C, H.

4-(6-(Cyclopentylidenemethyl)(2*H*-benzo[3,4-d]1,3-dioxolan-5-yl))-1-(methylsulfonyl)benzene (7c). A suspension of cyclopentyltriphenylphosphine bromide **5c** (1.24 g, 3 mmol) in anhydrous THF (15 mL) was stirred at 0 °C under nitrogen atmosphere. A solution of *t*-BuOK (2.5 mL of 1M in THF, 2.5 mmol) was added dropwise and stirred for 15 min. To the resulting dark orange colored mixture was added the carbaldehyde **15** (3.04 g, 3 mmol) in anhydrous THF (10 mL) and DMF (10 μL) dropwise. The reaction mixture was stirred at 0 °C for 30 min and then slowly allowed to warm to room temperature and stirred for 3 h at room temperature. The reaction was quenched with saturated aqueous ammonium chloride, and the organic layer was separated. The aqueous layer was diluted and extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. Purification by flash column chromatography using 20% ethyl acetate in hexanes as the eluant gave the title compound **7c** as a white solid (280 mg, 72% yield): mp 145−147 °C; ^{1}H NMR ($CDCl_3$) δ 7.94−7.91 (m, 2H), 7.51−7.48 (m, 2H), 6.97 (s, 1H), 6.75 (s, 1H), 6.00−5.97 (m, 3H), 3.11 (s, 3H), 2.41 (t, J = 6.8 Hz, 2H), 2.31 (t, J = 7.0 Hz, 2H), 1.77−1.54 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 147.4, 147.3, 146.9, 146.0, 138.5, 132.3, 131.1, 130.7, 126.9, 111.0, 109.6, 108.8, 101.2, 44.5, 34.8, 30.9, 26.8, 25.4; LRMS (APIMS) *m/z* 374 $(M + NH_4)^+$. Anal. ($C_{20}H_{20}SO_4$) C, H.

1-(6-(Cyclohexylmethyl)(2*H*-benzo[3,4-d]1,3-dioxolen-5-yl))-4-(methylsulfonyl)benzene (8a). The product **7a** was converted to **8a** using method E to give the title compound **8a** in 54% yield: mp 112−116 °C; ^{1}H NMR ($CDCl_3$) δ 7.94 (d, J = 8.2 Hz, 2H), 7.43 (d, J = 8.2 Hz, 2H), 6.75 (s, 1H), 6.61 (s, 1H), 5.97 (s, 2H), 3.10 (s, 3H), 2.34 (d, J = 5.1 Hz, 2H), 1.6−0.80 (m, 11H); ^{13}C NMR ($CDCl_3$) δ 148.1, 147.4, 145.5, 138.7, 133.3, 132.5, 130.7, 127.1, 109.8, 109.5, 101.1, 44.5, 40.2, 39.8, 32.9 (2 × C), 26.3, 26.2 (2 × C); LRMS (APIMS) *m/z* 390 $(M + NH_4)$. Anal. ($C_{21}H_{24}SO_4$) C, H.

4-(6-(Cycloheptylsmethyl)(2*H*-benzo[3,4-d]1,3-dioxolan-5-yl))-1-(methylsulfonyl)benzene (8b). As described above, the product **8a** was similarly converted to **8b** using method E to give the title compound **8b** in 80% yield: mp 89−92 °C; ^{1}H NMR ($CDCl_3$) δ 7.91 (d, J = 8.3 Hz, 2H), 7.39 (d, J = 8.3 Hz, 2H), 6.72 (s, 1H), 6.57 (s, 1H), 5.92 (s, 2H), 3.07 (s, 3H), 2.33 (d, J = 7.1 Hz, 2H), 1.53−1.14 (m, 11H), 0.90 (q, J = 10.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 147.9, 147.4, 145.4, 138.6, 133.3, 132.8, 130.6, 127.0, 109.6, 109.4, 101.0, 44.4, 41.1, 40.4, 33.9, 28.1, 26.0; LRMS (APIMS) *m/z* 404 $(M + NH_4)^+$. Anal. ($C_{22}H_{26}SO_4$) C, H.

4-(6-(Cyclopenthylmethyl)(2*H*-benzo[3,4-d]1,3-dioxolan-5-yl))-1-(methylsulfonyl)benzene (8c). Compound **8c** was prepared by method E. The pure compound was obtained a white solid, in 83% yield: mp 103−105 °C; ^{1}H NMR ($CDCl_3$) δ 7.98−7.94 (m, 2H), 7.48−7.44 (m, 2H), 6.80 (s, 1H), 6.64−6.61 (m, 1H), 5.98 (s, 2H), 3.10 (s, 3H), 2.49−2.43 (m, 2H), 1.98−1.83 (m, 1H), 1.59−1.40 (m, 6H), 0.98−0.78 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 148.0, 147.5, 145.5, 138.7, 133.5, 133.0, 130.7, 127.1, 109.7, 109.6, 101.1, 44.6, 41.9, 38.3, 32.3, 24.6; LRMS (APIMS) *m/z* 376 $(M + NH_4)^+$. Anal. ($C_{20}H_{22}SO_4$) C, H.

Cyclohexyl(6-(4-methylthiophenyl)(2*H*-benzo[d]1,3-dioxolan-5-yl))methan-1-ol (10a). The compound **10a** was prepared by using method D. The product was obtained as a white solid in 93% yield: mp 110−112 °C; ^{1}H NMR ($CDCl_3$) δ 7.26 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 8.4 Hz, 2H), 7.01 (s, 1H), 6.64 (s, 1H), 5.97 (dd, J = 4.1 and 1.3 Hz, 2H), 4.4 (dd, J = 8.7 and 3.2 Hz, 1H), 2.52 (s, 3H), 2.0 (m, 1H, OH), 1.80−1.50 (m, 5H), 1.20−0.5 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 147.3, 146.4, 137.9, 137.0, 135.0, 134.8, 130.0 (2 × C), 126.2 (2 × C), 109.7, 106.2, 101.1, 74.9, 44.9, 29.3, 29.2, 26.2, 26.0, 28.9, 15.7; LRMS (APIMS) *m/z* 730 $(2\ M + NH_4)^+$, 339 $(M - OH)^+$.

1-(6-(Cyclohexylhydroxymethyl)(2*H*-benzo[3,4-d]1,3-dioxolan-5-yl))-4-(methylsulfonyl)benzene (11a). The thiomethyl compound **10a** was converted to **11a** using method C. The product **11a** was obtained in 92% yield: mp 140−142 °C; ^{1}H NMR ($CDCl_3$) δ 7.93 (d, J = 8.3 Hz, 2H), 7.46 (d, J = 8.4 Hz, 2H), 7.03 (s, 1H), 6.60 (s, 1H), 5.98 (s, 2H), 4.21 (d, J = 6.8 Hz, 1H), 3.1 (s, 3H), 2.85 (br s, 1H, OH), 2.0 (m, 1H), 1.7−0.5 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 148.1, 147.1, 146.7, 139.0, 134.8, 133.4, 130.7 (2 × C), 127.3 (2 × C), 109.2, 106.6, 101.4, 74.8, 45.0, 44.5, 29.3, 29.1, 26.1, 25.9, 25.8; LRMS (APIMS) *m/z* 406 $(M + NH_4)^+$.

Cyclohexyl 6-(4-(Methylsulfonyl)phenyl)(2*H*-benzo-[d]1,3-dioxolan-5-yl) Ketone (12a). Oxidation of **11a** using method G gave **12a** in 82% yield: mp 172−174 °C; ^{1}H NMR ($CDCl_3$) δ 7.93 (d, J = 8.3 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H), 7.03 (s, 1H), 6.80 (s, 1H), 6.05 (s, 2H), 3.06 (s, 3H), 2.25 (m, 1H), 1.7−1.5 (m, 5H), 1.30−0.80 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 149.4, 147.7, 139.3, 134.0, 133.8, 129.6 (2 × C), 127.4 (2 × C), 110.2, 108.6, 102.0, 49.7, 44.5 (2 × C), 29.1 (2 × C), 25.6 (2 ×

C); LRMS (APIMS) *m/z* 404 (M + NH_4), 387 (M + H)$^+$. Anal. ($C_{21}H_{22}SO_5$) C, H.

(6-(4-Methylthiophenyl)-2*H*-benzo[d]1,3-dioxolen-5-yl-)methan-1-ol (13). The carbaldehyde **4** was reduced to **13** by method I. The title compound **13** was obtained as a white solid in 66% yield: mp 95−97 °C; ^{1}H NMR ($CDCl_3$) δ 7.25 (m, 4H), 6.99 (s, 1H), 6.72 (s, 1H), 5.96 (s, 2H), 4.41 (s, 2H), 2.50 (s, 3H), 1.95 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 147.0, 146.8, 137.3, 137.1, 134.6, 131.7, 129.6 (2 × C), 126.2 (2 × C), 109.9, 108.7, 101.1, 62.7, 15.7; LRMS (APIMS) *m/z* 292 (M + NH_4)$^+$.

1-(6-(Hydroxymethyl)(2*H*-benzo[3,4-d]1,3-dioxolen-5-yl)-4-(methylsulfonyl)benzene (14). The compound **13** was converted to **14** by method **C**. The pure product **14** was obtained as a white crystalline solid, in 97% yield: mp 163 °C; ^{1}H NMR ($CDCl_3$) δ 7.95 (d, *J* = 8.1 Hz, 2H), 7.55 (d, *J* = 8.2 Hz, 2H), 7.03 (s, 1H), 6.72 (s, 1H), 6.00 (s, 2H), 4.43 (s, 2H), 3.09 (s, 3H), 2.1 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 147.9, 147.3, 146.3, 139.1, 133.3, 131.8, 130.3, 127.3, 109.7, 109.3, 101.4, 62.6, 44.5; LRMS (APIMS) *m/z* 324 (M + NH_4)$^+$.

6-(4-(Methylsulfonyl)phenyl)-2*H*-benzo[d]1,3-dioxolane-5-carbaldehyde (15). Compound **14** was oxidized using method G to give the title compound as a white solid, in 68% yield: mp 152−153 °C; ^{1}H NMR ($CDCl_3$) δ 9.74 (s, 1H), 8.06 (d, *J* = 8.2 Hz, 2H), 7.59 (d, *J* = 8.2 Hz, 2H), 7.51 (s, 1H), 6.86 (s, 1H), 6.16 (s, 2H), 3.16 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 189.3, 152.3, 148.5, 143.3, 140.9, 130.9 (2 × C), 128.8, 127.4 (2 × C), 110.0, 106.7, 102.4, 49.7, 44.4; LRMS (APIMS) *m/z* 322 (M + NH_4)$^+$, 305 (M + H)$^+$. Anal. ($C_{14}H_{12}SO_3$) C, H.

1-(6-(Chloromethyl)(2*H*-benzo[3,4-d]1,3-dioxolan-5-yl))-4-(methylsulfonyl)benzene (16). To a solution of methyl sulfone **14** (1.53 g, 5 mmol) in anhydrous benzene (35 mL) was added thionyl chloride (0.8 mL) followed by a catalytic amount of pyridine (3 or 4 drops). The reaction mixture was stirred at room-temperature overnight. The solvent was evaporated under reduced pressure, and the residue on addition of hexane gave a white solid. The product was used without further purification. The sample was characterized after purification by silica gel column chromatography using ethyl acetate hexane (1:1): mp 146−148 °C; ^{1}H NMR ($CDCl_3$) δ 8.00 (d, *J* = 8.3 Hz, 2H), 7.6 (d, *J* = 8.3 Hz, 2H), 6.99 (s, 1H), 6.71 (s, 1H), 6.02 (s, 2H), 4.38 (s, 2H), 3.11 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 148.1, 145.7, 139.6, 134.1, 130.2, (2 × C), 128.5, 127.4 (2 × C), 110.3, 109.7, 101.7, 44.4; LRMS (APIMS) *m/z* 342 (M + NH_4)$^+$. Anal. ($C_{14}H_{14}SO_3$) C, H.

Using methods D, C, E, G, and I and carbaldehyde **4** as a starting material, compounds **21a**−**j** and compounds **22a**−**j** were prepared good yields. Spectral data for the few representative examples are given below.

(6-(4-Methylthiophenyl)(2*H*-benzo[d]1,3-dioxolan-5-yl))phenylmethan-1-ol (19a): white solid; mp 96−99 °C; ^{1}H NMR ($CDCl_3$) δ 7.21 (m, 9H), 6.95 (s, 1H), 6.69 (s, 1H), 5.94 (s, 2H), 5.82 (s, 1H), 2.50 (s, 3H), 2.24 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 147.2, 146.7, 143.9, 137.4, 137.3, 134.9, 134.5, 129.9, 128.2, 127.1, 126.3, 126.2, 109.7, 107.5, 101.1, 72.0, 15.7; LRMS (APIMS) *m/z* 333 (M − OH)$^+$, 718 (2M + NH_4)$^+$.

(2-Fluorophenyl)(6-(4-methylthiophenyl)(2*H*-benzo[d]1,3-dioxolan-5-yl))methan-1-ol (19b): white solid; mp 130−135 °C; ^{1}H NMR ($CDCl_3$) δ 7.51 (t, *J* = 8.3 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.30−7.20 (m, 5H), 6.91 (m, 1H), 6.85 (s, 1H), 6.71 (s, 1H), 6.02 (s, 1H), 5.94 (s, 2H), 2.50 (s, 3H), 2.31 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 161.3, 158.0, 146.8, 137.3, 134.9, 133.4, 130.8, 129.8, 128.8, 127.5, 127.1, 126.2, 123.9, 115.2, 110.0, 107.4, 101.2, 67.0, 15.8; LRMS (APIMS) *m/z* 351 (M − OH)$^+$, 754 (2M + NH_4)$^+$.

(3-Fluorophenyl)(6-(4-methylthiophenyl)(2*H*-benzo[d]1,3-dioxolan-5-yl))methan-1-ol (19c): white solid; mp 97−99 °C; ^{1}H NMR ($CDCl_3$) δ 7.28−7.18 (m, 5H), 6.92 (m, 3H), 6.87 (s, 1H), 6.70 (s, 1H), 5.96 (d, *J* = 1.8 Hz, 2H), 5.79 (d, *J* = 3.6 Hz, 1H), 2.51 (s, 3H), 2.18 (d, *J* = 3.8 Hz, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 164.4, 161.1, 147.4 (d, *J* = 34 Hz), 146.6 (d, *J* = 6.6 Hz), 137.7, 137.2, 134.7, 134.4, 129.8 (2 × C), 126.9 (d, *J* = 8.2 Hz), 126.3 (2 × C), 121.9, 114.0 (d, *J* = 21 Hz), 113.3 (d, *J* = 22 Hz), 109.8, 107.4, 101.3, 71.5, 15.7; LRMS (APIMS) *m/z* 386 (M + NH_4)$^+$, 754 (2M + NH_4)$^+$.

(4-Fluorophenyl)(6-(4-methylthiophenyl)(2*H*-benzo[d]1,3-dioxolan-5-yl))methan-1-ol (19d): colorless thick oil; ^{1}H NMR ($CDCl_3$) δ 7.25 (d, *J* = 8.3 Hz, 2H), 7.15−7.00 (m, 3H), 7.00−6.84 (m, 4H), 6.8 (s, 1H), 5.96 (s, 2H), 5.79 (s, 1H), 2.50 (s, 3H), 2.11 (br s, 1H, OH); LRMS (APIMS) *m/z* 351 (M − OH)$^+$, 754 (2M + NH_4)$^+$.

(3-Methylphenyl)(6-(4-methylthiophenyl)(2*H*-benzo[d]1,3-dioxolan-5-yl))methan-1-ol (19e): colorless thick oil; ^{1}H NMR ($CDCl_3$) δ 7.26−7.12 (m, 5H), 7.02−6.95 (m, 4H) 6.68 (s, 1H), 5.94 (d, *J* = 1.2 Hz, 2H), 5.77 (d, *J* = 3.3 Hz, 1H), 2.50 (s, 3H), 2.29 (s, 3H), 2.16−2.13 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 147.3, 146.7, 143.8, 137.8, 137.4, 135.1, 134.6, 130.0, 128.1, 127.9, 127.0, 126.2, 123.4, 109.8, 107.5, 101.2, 72.1, 21.4, 15.8; LRMS (APIMS) *m/z* 746 (2M + NH_4)$^+$, 347 (M − OH)$^+$.

(3-Methoxyphenyl)(6-(4-methylthiophenyl)(2*H*-benzo[d]1,3-dioxolan-5-yl))methan-1-ol (19f): white solid; mp 95 °C; ^{1}H NMR ($CDCl_3$) δ 7.28−7.25 (m, 2H), 7.21 (s, 2H), 6.95 (d, *J* = 0.5 Hz, 1H), 6.82−6.77 (m, 2H), 6.75 (s, 2H), 6.69 (d, *J* = 0.9 Hz, 1H), 5.97−5.95 (m, 2H), 5.80 (d, *J* = 3.8 Hz, 1H), 3.76 (d, *J* = 0.9 Hz, 3H), 2.51 (d, *J* = 0.9 Hz, 3H), 2.04−2.01 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 159.6, 147.4, 146.8, 145.6, 137.5, 137.4, 134.9, 134.7, 130.0, 129.3, 126.3, 118.7, 112.6, 112.1, 109.8, 107.5, 101.2, 72.0, 55.2, 15.8; LRMS (APIMS) *m/z* 778 (2M + NH_4)$^+$, 363 (M − OH)$^+$.

(2-Fluoro-5-methylphenyl)(6-(4-methylthiophenyl)(2*H*-benzo[d]1,3-dioxolen-5-yl))methan-1-ol (19g): white solid; mp 110 °C; ^{1}H NMR ($CDCl_3$) δ 7.26−7.18 (m, 5H), 7.01−6.98 (m, 1H), 6.87 (s, 1H), 6.82−6.76 (m, 1H), 6.69 (s, 1H), 5.97 (s, 1H), 5.95 (s, 2H), 2.50 (s, 3H), 2.31 (s, 3H), 2.10 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 147.1, 146.8, 137.4, 137.3, 135.0, 133.4, 133.4, 130.2, 129.8, 129.3, 129.2, 128.0, 127.9, 126.2, 115.0, 114.8, 110.0, 107.5, 101.2, 67.2, 20.8, 15.8; LRMS (APIMS) *m/z* 782 (2M + NH_4)$^+$, 365 (M − OH)$^+$.

1-(6-(Hydroxyphenylmethyl)(2*H*-benzo[3,4-d]1,3-dioxolan-5-yl))-4-(methylsulfonyl)benzene (20a): white solid; mp 144−148 °C; ^{1}H NMR ($CDCl_3$) δ 7.89 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.23 (m, 3H), 7.12 (m, 2H), 7.0 (s, 1H), 6.65 (s, 1H), 5.97 (s, 2H), 5.69 (s, 1H), 3.06 (s, 3H), 2.44 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 148.1, 146.9, 146.5, 143.4, 139.2, 134.9, 133.0, 130.5, 128.3, 127.4, 127.1, 126.3, 109.4, 107.8, 101.4, 72.1, 44.5; LRMS (APIMS) *m/z* 400 (M + NH_4)$^+$.

1-(6-((2-Fluorophenyl)hydroxymethyl)(2*H*-benzo[3,4-d]1,3-dioxolan-5-yl))-4-(methylsulfonyl)benzene (20b): white solid; mp 163−169 °C; ^{1}H NMR ($CDCl_3$) δ 7.85 (d, *J* = 6.4 Hz, 2H), 7.46 (d, *J* = 6.5 Hz, 2H), 7.4−7.1 (m, 3H), 6.85 (s, 1H), 6.80 (m, 1H), 6.61 (s, 1H), 5.99 (s, 2H), 5.91 (d, *J* = 3.8 Hz, 1H), 3.07 (s, 3H), 2.44 (d, *J* = 4.1 Hz, 1H, OH); LRMS (APIMS) *m/z* 418 (M + NH_4)$^+$. Anal. ($C_{21}H_{17}SFO_5$) C, H.

1-(6-((3-Fluorophenyl)hydroxymethyl)(2*H*-benzo[3,4-d]1,3-dioxolan-5-yl))-4-(methylsulfonyl)benzene (20c): white solid; mp 163−169 °C; ^{1}H NMR ($CDCl_3$) δ 7.92 (d, *J* = 8.4 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.4 (m, 1H), 6.93 (s, 1H), 6.88 (m, 3H), 6.67 (s, 1H), 5.99 (d, *J* = 1.8 Hz, 2H), 5.68 (d, *J* = 3.2 Hz, 1H), 3.08 (s, 3H), 2.50 (d, *J* = 3.8 Hz, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 164.4, 161.1, 148.2, 147.2, 146.4, 139.4, 134.5, 133.2, 130.5 (2 × C), 129.9 (d, *J* = 8 Hz), 127.3 (2 × C), 121.9, 114.2 (d, *J* = 21 Hz), 113.3 (d, *J* = 22 Hz), 109.5, 107.8, 101.6, 71.5, 44.5; LRMS (APIMS) *m/z* 418 (M + NH_4)$^+$.

1-(6-((4-Fluorophenyl)hydroxymethyl)(2*H*-benzo[3,4-d]1,3-dioxolan-5-yl))-4-(methylsulfonyl)benzene (20d): white solid; mp 85−95 °C; ^{1}H NMR ($CDCl_3$) δ 7.90 (d, *J* = 8.2 Hz, 2H), 7.37 (d, *J* = 8.2 Hz, 2H), 6.89 (d, *J* = 7.1 Hz, 4H), 6.69 (s, 1H), 6.68 (s, 1H), 5.98 (s, 2H), 3.77 (s, 2H), 3.07 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 162.8, 159.6, 147.7, 147.1, 146.8, 139.0, 136.5, 133.3, 131.5 (2 × C), 130.3, 129.8 (2 × C), 129.7, 127.2, 115.0, 110.4, 109.7, 101.3, 44.5, 37.9; LRMS (APIMS) *m/z* 418 (M + NH_4)$^+$.

4-(6-(Hydroxy(3-methylphenyl)methyl)(2*H*-benzo[3,4-d]1,3-dioxolan-5-yl))-1-(methylsulfonyl)benzene (20e): white solid; mp 154 °C; ^{1}H NMR ($CDCl_3$) δ 7.93, (d, *J* = 8.5 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.16 (t, *J* = 7.6 Hz, 1H), 7.05−7.04 (m, 2H), 6.95−6.90 (m, 2H), 6.68 (s, 1H), 6.01−6.00 (m, 2H), 5.68 (d, *J* = 3.5 Hz, 1H), 3.09 (s, 3H), 2.29 (s, 3H), 2.04 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 148.0, 147.0, 146.6, 143.4,

139.2, 138.1, 135.0, 133.0, 130.6, 128.3, 128.3, 127.2, 127.0, 123.4, 109.4, 107.8, 101.5, 72.2, 44.5, 21.4; LRMS (APIMS) *m/z* 414 $(M + NH_4)^+$, 379 $(M - OH)^+$.

1-(6-(Hydroxy(3-methoxyphenyl)methyl)(2*H*-benzo-[3,4-d]1,3-dioxolan-5yl))-4-(methylsulfonyl)benzene (20f): white solid (1.00 g, 93% yield); mp 154 °C; ^{1}H NMR ($CDCl_3$) δ 7.92 (d, J = 8.1 Hz, 2H), 7.47 (d, J = 8.0 Hz, 2H), 7.23−7.1 (m, 1H), 7.01 (s, 1H), 6.77−6.67 (m, 4H), 5.99 (d, J = 2.6 Hz, 2H), 5.67 (s, 1H), 3.75 (s, 3H), 3.08 (s, 3H), 2.32 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 159.6, 148.0, 147.0, 146.5, 145.2, 139.2, 134.8, 133.0, 130.6, 129.4, 127.2, 118.7, 112.5, 112.3, 109.4, 107.7, 101.5, 72.0, 55.2, 44.5; LRMS (APIMS) *m/z* 430 $(M + NH_4)^+$.

4-(6-((2-Fluoro-5-methylphenyl)hydroxymethyl)(2*H*-benzo[3,4-d]1,3-dioxolan-5-yl))-1-(methylsulfonyl)benzene (20g): white solid; mp 169−171 °C; ^{1}H NMR ($CDCl_3$) δ 7.92 (d, J = 8.4 Hz, 2H), 7.49 (d, J = 8.4 Hz, 2H), 7.26−7.22 (m, 1H), 7.00−6.98 (m, 1H), 6.94 (s, 1H), 6.80−6.74 (m, 1H), 6.67 (s, 1H), 6.00−5.99 (m, 2H), 5.88 (s, 1H), 3.10 (s, 3H), 2.31 (s, 3H), 2.25 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 147.9, 147.1, 146.4, 139.2, 133.7, 133.3, 130.5, 130.1, 129.6, 129.5, 127.7, 127.2, 115.0, 114.8, 109.6, 107.7, 101.5, 66.8, 44.5, 20.8; LRMS (APIMS) *m/z* 846 $(2M + NH_4)^+$, 432 $(M + NH_4)^+$.

4-(Methylsulfonyl)-1-(6-benzyl(2*H*-benzo[3,4-d]1,3-dioxolan-5-yl))benzene (21a): white solid; mp 111−114 °C; ^{1}H NMR ($CDCl_3$) δ 8.1 (d, J = 8.4 Hz, 2H), 7.90 (d, J = 8.4 Hz, 2H), 7.40 (d, J = 8.3 Hz, 2H), 7.25−7.10 (m, 3H), 6.94 (d, J = 7.0 Hz, 2H), 6.71 (s, 1H), 6.70 (s, 1H), 5.99 (s, 2H), 3.81 (s, 2H), 3.08 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 147.8, 147.3, 146.2, 140.9, 138.9, 133.8, 133.4, 131.7, 130.4, 130.2, 128.52, 128.48, 127.2, 126.1, 110.6, 109.7, 101.3, 44.6, 38.8; LRMS (APIMS) *m/z* 384 $(M + H)^+$. Anal. ($C_{21}H_{18}SO_4$) C, H.

1-(6-((2-Fluorophenyl)methyl)(2*H*-benzo[3,4-d]1,3-dioxolan-5-yl))-4-(methylsulfonyl)benzene (21b): white solid; mp 98−99 °C; ^{1}H NMR ($CDCl_3$) δ 7.92 (d, J = 6.8 Hz, 2H), 7.42 (d, J = 7.6 Hz, 2H), 7.20 (m, 1H), 7.05−6.80 (m, 3H), 6.69 (s, 1H), 6.68 (s, 1H), 5.97 (s, 2H), 3.81 (s, 2H), 3.08 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 162.3, 159.05, 147.7, 147.2, 146.2, 139.0, 133.4, 130.5, 130.3 (2 × C), 127.9, 127.2 (2 × C), 115.3, 115.0, 110.2, 109.7, 101.3, 44.55, 31.8; LRMS (APIMS) *m/z* 402 $(M + NH_4)^+$. Anal. ($C_{21}H_{17}FSO_4$) C, H.

1-(6-((3-Fluorophenyl)methyl)(2*H*-benzo[3,4-d]1,3-dioxolan-5-yl))-4-(methylsulfonyl)benzene (21c): white solid; mp 110−111 °C; ^{1}H NMR ($CDCl_3$) δ 7.89 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.3 Hz, 2H), 7.15 (m, 1H), 6.83 (dt, J = 5.2 and 2.3 Hz, 1H), 6.70 (m, 3H), 6.60 (d, J = 9.9 Hz, 1H), 5.99 (s, 2H), 3.81 (s, 2H), 3.08 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 164.5, 161.2, 147.9, 146.4, 143.5, 139.1, 133.6, 130.9, 130.4 (2 × C), 129.9 (d, J = 8.2 Hz), 127.2 (2 × C), 124.2, 115.3 (d, J = 21.5 Hz), 113.9 (d, J = 21 Hz), 110.6, 109.8, 101.4, 44.5, 38.6; LRMS (APIMS) *m/z* 402 $(M + NH_4)^+$. Anal. ($C_{21}H_{17}SFO_4$) C, H.

1-(6-((4-Fluorophenyl)methyl)(2*H*-benzo[3,4-d]1,3-dioxolan-5-yl))-4-(methylsulfonyl)benzene (21d): white solid; mp 130−132 °C; ^{1}H NMR ($CDCl_3$) δ 7.9 (d, J = 8.4 Hz, 2H), 7.3 (d, J = 8.4 Hz, 2H), 6.9 (d, J = 8.3 Hz, 4H), 6.9 (s, 1H), 6.8 (s, 1H), 5.97 (s, 2H), 3.80 (s, 2H), 3.1 (s, 3H); LRMS (APIMS) *m/z* 402 $(M + NH_4)^+$. Anal. ($C_{21}H_{17}SFO_4$) C, H.

4-{6-[(3-Methylphenyl)methyl](2*H*-benzo[3,4-d]1,3-dioxolan-5-yl)}-1-(methylsulfonyl)benzene (21e): white solid; mp 84−86 °C; ^{1}H NMR ($CDCl_3$) δ 7.91 (d, J = 8.3 Hz, 2H), 7.42 (d, J = 8.3 Hz, 2H), 7.11 (t, J = 7.8 Hz, 1H), 6.98 (d, J = 7.6 Hz, 1H), 6.76−6.71 (m, 4H), 5.99 (s, 2H), 3.78 (s, 2H), 3.09 (s, 3H), 2.27 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 147.7, 147.4, 146.1, 140.8, 138.9, 138.0, 133.4, 131.9, 130.4, 129.3, 128.3, 127.2, 126.8, 125.6, 110.6, 109.6, 101.3, 44.5, 38.7, 21.4; LRMS (APIMS) *m/z* 398 $(M + NH_4)^+$. Anal. ($C_{22}H_{20}SO_4$) C, H.

4-(6-(3-Methoxyphenyl)methyl)(2*H*-benzo[3,4-d]1,3-dioxolan-5-yl))-1-(methylsulfonyl)benzene (21f): white solid; mp 125−126 °C; ^{1}H NMR ($CDCl_3$) δ 7.90 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 7.14 (t, J = 7.9 Hz, 1H), 6.73−6.70 (m, 3H), 6.56−6.53 (m, 1H), 6.47 (s, 1H), 5.98 (s, 2H), 3.79 (s, 2H), 3.73 (s, 3H), 3.08 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 159.6, 147.7, 147.3, 146.2, 142.6, 138.9, 133.4, 131.5, 130.4, 129.3, 127.2, 120.9, 114.7, 111.0, 110.6, 109.7, 101.3, 55.1, 44.5, 38.7; LRMS (APIMS) *m/z* 810 $(2M + NH_4)^+$, 397 $(M + H)^+$. Anal. ($C_{22}H_{20}SO_5$) C, H.

4-{6-[(2-Fluoro-5-methylphenyl)methyl](2*H*-benzo[3,4-d]1,3-dioxolan-5-yl)}-1-(methylsulfonyl)benzene (21g): white solid; mp 98−100 °C; ^{1}H NMR ($CDCl_3$) δ 7.93 (d, J = 8.2 Hz, 2H), 7.43 (d, J = 8.2 Hz, 2H), 7.00−6.90 (m, 1H), 6.82 (t, J = 9.1 Hz, 1H), 6.69 (s, 2H), 6.64 (d, J = 7.2 Hz, 1H), 5.99 (s, 2H), 3.98 (s, 2H), 3.09 (s, 3H), 2.21 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 157.3, 147.8, 147.3, 146.2, 139.0, 133.4, 131.0, 130.7, 130.4, 128.4, 127.2, 115.0, 114.7, 110.2, 109.7, 101.3, 44.6, 31.9, 20.7; LRMS (APIMS) *m/z* 416 $(M + NH_4)^+$.

4-(1-(3′,5′-Difluorophenyl)-1-hydroxymethyl)-1,2-methylenedioxy-5-(4-methylthiophenyl)benzene. (3,5-Difluorophenyl)(6-(4-methylthiophenyl)(2*H*-benzo[d]1,3-dioxolan-5-yl))methan-1-ol (19h). The resulting product was used for the next reaction without further purification.

4-(1-(3′,5′-Difluorophenyl)-1-hydroxymethyl)-1,2-methylenedioxy-5-(4-methylsulfonylphenyl)benzene (20h). The product was used without purification.

5-(1-(3′,5′-Difluorophenyl)methyl)-1,2-methylenedioxy-4-(4-methylsulfonylphenyl)benzene (21h). Compound **21h** was prepared by method F to give a light brown solid in 63% overall yield for three steps from **19h**): mp 140−141°C; ^{1}H NMR ($CDCl_3$) δ 7.91 (m, 2H), 7.36 (m, 2H), 6.71 (s, 1H), 6.70 (s, 1H), 6.59 (m, 1H), 6.42 (m, 2H), 6.02 (s, 2H), 3.80 (s, 2H), 3.09 (s, 3H); LRMS (APIMS) *m/z* 420 $(M + NH_4)^+$.

4-{6-[(3-Chlorophenyl)methyl](2*H*-benzo[3,4-d]1,3-dioxolan-5-yl)}-1-(methylsulfonyl)benzene (21i): white solid; mp 112−113 °C; ^{1}H NMR ($CDCl_3$) δ 7.91 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.3 Hz, 2H), 7.13−7.12 (m, 2H), 6.87 (s, 1H), 6.82−6.80 (m, 1H), 6.70 (s, 2H), 6.00 (s, 2H), 3.79 (s, 2H), 3.09 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 147.8, 147.1, 146.4, 142.9, 139.1, 134.1, 133.6, 130.8, 130.3, 129.6, 128.5, 127.2, 126.7, 126.3, 110.5, 109.8, 101.4, 44.5, 38.5; LRMS (APIMS) *m/z* 418 $(M + NH_4)^+$. Anal. ($C_{21}H_{17}ClO_4$) C, H.

4-{6-[(4-Methylphenyl)methyl](2*H*-benzo[3,4-d]1,3-dioxolan-5-yl)}-1-(methylsulfonyl)benzene (21j): white solid; mp 153−154 °C; ^{1}H NMR ($CDCl_3$) δ 7.93 (d, J = 7.3 Hz, 2H), 7.43 (d, J = 7.4 Hz, 2H), 7.05 (d, J = 6.9 Hz, 2H), 6.86 (d, J = 7.0 Hz, 2H), 6.72 (s, 2H), 5.99 (s, 2H), 3.79 (s, 2H), 3.10 (s, 3H), 2.31 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 147.7, 147.3, 146.1, 138.9, 137.8, 135.5, 133.3, 132.0, 130.4, 129.1, 128.3, 127.1, 110.5, 109.6, 101.2, 44.5, 38.3, 20.9; LRMS (APIMS) *m/z* 398 $(M + NH_4)^+$. Anal. ($C_{22}H_{20}SO_6$) C, H.

6-(4-(Methylsulfonyl)phenyl)(2*H*-benzo[d]1,3-dioxolan-5-yl) phenyl ketone (22a): white solid; mp 180−184 °C; ^{1}H NMR ($CDCl_3$) δ 7.72 (d, J = 8.0 Hz, 2H), 7.61 (d, J = 7.5 Hz, 2H), 7.41 (m, 3H), 7.27 (m, 2H), 7.03 (s, 1H), 6.89 (s, 1H), 6.10 (s, 2H), 2.93 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 196.8, 149.4, 147.5, 145.9, 139.0, 137.5, 134.9, 132.9, 132.8, 129.9, 129.8, 128.2, 127.2, 110.1, 109.8, 102.1, 44.4; LRMS (APIMS) *m/z* 381 $(M + H)^+$. Anal. ($C_{21}H_{16}SO_5$) C, H.

2-Fluorophenyl 6-(4-(methylsulfonyl)phenyl)(2*H*-benzo[d]1,3-dioxolan-5-yl) ketone (22b): white solid; mp 212−215 °C; ^{1}H NMR ($CDCl_3$) δ 7.74 (d, J = 6.4 Hz, 2H), 7.42−7.3 (m, 4H), 7.13 (s, 1H), 7.02 (t, J = 7.6 Hz, 1H), 6.86 (d, J = 9.3 Hz, 1H), 6.82 (s, 1H), 6.11 (s, 2H), 2.95 (s, 3H); LRMS (APIMS) *m/z* 399 $(M + H)^+$. Anal. ($C_{21}H_{15}FSO_5$) C, H.

3-Fluorophenyl 6-(4-(methylsulfonyl)phenyl)(2*H*-benzo[d]1,3-dioxolan-5-yl) ketone (22c): white solid; mp 205−209 °C; ^{1}H NMR ($CDCl_3$) δ 7.75 (d, J = 8.3 Hz, 2H), 7.38−7.30 (m, 5H), 7.24 (t, J = 5.2 Hz, 1H), 7.04 (s, 1H), 6.89 (s, 1H), 6.12 (s, 2H), 2.95 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 195.5, 163.9, 160.7, 150.0, 147.7, 145.7, 139.7, 139.2, 135.1, 132.2, 130.0, 129.9 (2 × C), 127.3 (2 × C), 125.6, 119.9 (d, J = 21 Hz), 116.4 (d, J = 22 Hz), 110.0 (d, J = 35 H**z**), 102.3, 44.4; LRMS (APIMS) *m/ z* 399 $(M + H)^+$, 416 $(M + NH_4)^+$. Anal. ($C_{21}H_{15}SFO_5$) C, H.

4-Fluorophenyl 6-(4-(methylsulfonyl)phenyl)(2*H*-benzo[d]1,3-dioxolan-5-yl) ketone (22d): white solid; mp 189−190 °C; ^{1}H NMR ($CDCl_3$) δ 7.73 (d, J = 8.4 Hz, 2H), 7.63 (dd, J = 8.8 and 5.3 Hz, 2H), 7.36 (d, J = 8.4 Hz, 2H), 7.0 (m, 4H), 6.1 (s, 2H), 2.94 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 195.5, 167.1, 163.8,

149.8, 147.6, 145.7, 139.7, 139.1, 134.7, 133.8, 132.5 (2 × C), 129.9 (2 × C), 127.3, 115.5, 115.2, 110.2, 109.6, 102.2, 44.4; LRMS (APIMS) *m/z* 399 $(M + H)^+$, 416 $(M + NH_4)^+$. Anal. ($C_{21}H_{15}SFO_5$) C, H.

3-Methylphenyl 6-(4-(methylsulfonyl)phenyl)(2*H*-benzo[d]1,3-dioxolan-5-yl)ketone (22e): white solid; mp 168−170 °C; ^{1}H NMR ($CDCl_3$) δ 7.75 (d, J = 8.3 Hz, 2H), 7.44−7.37 (m, 4H), 7.26−7.18 (m, 2H), 7.18 (s, 1H), 7.04 (s, 1H), 6.12 (s, 2H), 3.00 (s, 3H), 2.36 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 196.9, 149.7, 147.5, 146.0, 139.0, 138.6, 137.5, 134.9, 133.8, 133.0, 130.3, 129.9, 128.2, 127.3, 127.2, 110.2, 109.8, 102.1, 44.4, 21.2; LRMS (APIMS) *m/z* 412 $(M + NH_4)^+$, 395 $(M + H)^+$.

3-Methoxyphenyl 6-(4-(methylsulfonyl)phenyl)(2*H*-benzo[d]1,3-dioxolan-5-yl) ketone (22f): white solid; mp 158 °C; ^{1}H NMR ($CDCl_3$) δ 7.75 (d, J = 8.3 Hz, 2H), 7.39 (d, J = 8.3 Hz, 2H), 7.20−7.16 (m, 3H), 7.03 (s, 1H), 7.00−6.96 (m, 1H), 6.90 (s, 1H), 6.11 (s, 2H), 3.77 (s, 3H). 2.96 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 196.5, 159.4, 149.7, 147.4, 145.9, 139.0, 138.8, 134.9, 132.8, 129.9, 129.2, 127.2, 122.8, 119.3, 114.0, 110.1, 109.7, 102.1, 55.4, 44.4; LRMS (APIMS) *m/z* 411 $(M + H)^+$. Anal. ($C_{22}H_{18}SO_6$) C, H.

2-Fluoro-5-methylphenyl6-[4-(methylsulfonyl)phenyl]-(2*H*-benzo[d]1,3-dioxolan-5-yl) ketone (22g): white solid; mp 153−154 °C; ^{1}H NMR ($CDCl_3$) δ 7.77 (s, 1H), 7.74 (s, 1H), 7.40 (s, 1H), 7.38 (s, 1H), 7.20−7.17 (m, 1H), 7.15−7.10 (m, 2H), 6.83 (s, 1H), 6.78−6.72 (m, 1H), 6.12 (s, 2H), 2.97 (s, 3H), 2.24 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 193.4, 150.2, 147.7, 146.0, 139.1, 135.6, 134.5, 134.4, 133.8, 133.7, 131.2, 130.1, 127.0, 116.04, 115.8, 110.2, 109.8, 102.2, 44.4, 20.3; LRMS (APIMS) *m/z* 842.4 $(2M + NH_4)$, 413 $(M + H)^+$. Anal. ($C_{21}H_{15}ClO_5S$) C, H.

4-(1-(3′,5′-Difluorophenyl)-1-oxomethyl)-1,2-methylenedioxy-5-(4-methylsulfonylphenyl)benzene (22h). The compound **22h** was prepared from **20h** by method G as a white crystalline solid in 43.2% yield overall for three steps: ^{1}H NMR ($CDCl_3$) δ 7.80 (m, 2H), 7.37 (m, 2H), 7.10 (m, 2H), 7.05 (s, 1H), 6.91 (s, 1H), 6.87 (m, 1H), 6.14 (s, 2H), 2.98 (s, 3H); LRMS (APIMS) *m/z* 434 $(M + NH_4)^+$. Anal. ($C_{21}H_{14}SF_2O_5$) C, H.

3-Chlorophenyl 6-[4-(methylsulfonyl)phenyl](2*H*-benzo[d]1,3-dioxolan-5-yl) ketone (22i): white solid; mp 182−183 °C; ^{1}H NMR ($CDCl_3$) δ 7.76 (d, J = 7.7 Hz, 2H), 7.52−7.48 (m, 2H), 7.36 (d, J = 7.5 Hz, 3H), 7.28−7.20 (m, 1H), 7.06 (s, 1H), 6.91 (s, 1H), 6.13 (s, 2H), 2.96 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 195.3, 150.1, 147.7, 145.6, 139.2, 135.2, 134.3, 132.6, 132.0, 129.9 (2 × C), 129.7, 129.5, 127.7, 127.2 (2 × C), 110.1, 109.8, 102.2, 44.3; LRMS (APIMS) *m/z* 846 $(2M + NH_4)^+$, 415 $(M + H)^+$. Anal. ($C_{21}H_{15}ClO_5S$) C, H.

4-Methylphenyl 6-[4-(methylsulfonyl)phenyl](2*H*-benzo[d]1,3-dioxolan-5-yl) ketone (22j): white solid; mp 150−151 °C; ^{1}H NMR ($CDCl_3$) δ 7.75 (d, J = 8.0 Hz, 2H), 7.55 (d, J = 7.7 Hz, 2H), 7.40 (d, J = 7.9 Hz, 2H), 7.10 (d, J = 7.6 Hz, 2H), 6.90 (s, 1H), 6.82 (s, 1H), 6.10 (s, 2H), 2.96 (s, 3H), 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 196.4, 149.5, 147.4, 145.9, 144.0, 138.8, 134.8, 134.5, 133.1, 130.0, 129.8, 128.9, 127.2, 110.1, 109.6, 102.0, 44.4, 21.5; LRMS (APIMS) *m/z* 412 $(M + NH_4)$, 395 $(M + H)^+$. Anal. ($C_{22}H_{18}O_5S$) C, H.

(6-(4-Methylthiophenyl)(2*H*-benzo[d]1,3-dioxolan-5-yl))-3-pyridylmethan-1-ol (25). To a −78 °C precooled solution of 3-bromopyridine **23** (632 mg, 4 mmol) in anhydrous THF (20 mL) was added *t*-BuLi (1.7 M, 4.64 mL, 8 mmol). The resulting dark blue solution of 3-lithiopyridine **24** was stirred at −78 °C for 10 min, and then carbaldehyde **4** (820 mg, 3 mmol) in THF (15 mL) was added dropwise. The reaction mixture was then stirred at −78 °C for 30 min, slowly allowed to warm to room temperature, and stirred for an additional 30 min at room temperature. The reaction was quenched with saturated aqueous ammoniun chloride solution, and the THF layer was separated. The aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and filtered, and the filtrate was evaporated under reduced pressure to give the crude product. Purification by silica gel flash column chromatography using ethyl acetate/hexane (1:1) and then ethyl acetate as the eluants gave the title compound **25** (320 mg, 23% yield): mp 130−135 °C; ^{1}H NMR ($CDCl_3$) δ 8.23 (d, J = 4.3, Hz, 1H), 8.17 (s, 1H), 7.51 (d, J = 7.8 Hz, 1H), 7.18 (d, J = 8.1 Hz, 2H), 7.13 (m, 1H), 7.08 (d, J = 8.1 Hz, 2H), 6.89 (s, 1H), 6.64 (s, 1H), 5.81 (d, J = 3.0 Hz, 2H), 5.80 (s, 1H), 4.5 (br s, 1H, OH), 2.45 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 147.8, 147.7, 147.4, 146.8, 140.0, 137.6, 137.1, 134.5, 134.4, 134.2, 129.7, 126.2, 123.1, 109.8, 107.3, 101.2, 60.3, 15.6; LRMS (APIMS) *m/z* 352 $(M + H)^+$.

1-(6-(Hydroxy-3-pyridylmethyl)(2*H*-benzo[3,4-d]1,3-dioxolan-5-yl))-4-(methylsulfonyl)benzene (26). The product of the above example, **25** (501 mg, 1.45 mmol), was dissolved in MeOH (35 mL). To this solution was added Oxone (1.9 g, 2.9 mmol) in water (12 mL) dropwise. The reaction mixture was stirred at room temperature for 2 h and diluted with water, and ammonium hydroxide was added until the solution was basic. The solvent was evaporated under reduced pressure. The resulting product was extracted with ethyl acetate (3 × 50 mL), washed with brine (1 × 50 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was evaporated under reduced pressure to give the title compound **26** that was used without further purification (550 mg, 99% yield): mp 165−185 °C; ^{1}H NMR ($CDCl_3$) δ 8.32 (br s, 1H), 8.19 (s, 1H), 7.88 (d, J = 8.0 Hz, 2H), 7.50 (d, J = 7.7 Hz, 1H), 7.41 (d, J = 8.0 Hz, 2H), 7.18 (m, 1H), 6.91 (s, 1H), 6.65 (s, 1H), 5.99 (d, J = 3.0 Hz, 2H), 5.71 (s, 1H), 3.95 (br s, 1H, OH), 3.07 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 148.3, 148.2, 147.8, 147.3, 146.3, 139.5, 134.3, 134.1, 133.0, 130.5 (2 × C), 127.4 (2 × C), 123.3, 109.5, 107.8, 101.6, 69.9, 44.5; LRMS (APIMS) *m/z* 384 $(M + H)^+$.

4-(Methylsulfonyl)-1-(6-(3-pyridylmethyl)(2*H*-benzo-[3,4-d]1,3-dioxolan-5-yl))benzene (27). The hydroxyl compound **26** (540 mg, 1.41 mmol) was dissolved in anhydrous dichloromethane (5 mL), and under nitrogen atmosphere trifluoroacetic acid (10 mL) was added followed by triethylsilane (5 mL). The reaction mixture was stirred at room temperature overnight. The solvent and trifluoroacetic acid were evaporated under reduced pressure, and the residue was extracted with dichloromethane. The combined organic extracts were washed with water and brine, dried over sodium sulfate, and filtered. The filtrate was evaporated under reduced pressure to give the crude product that was purified by silica gel column chromatography using 5% methanol in dichloromethane as the eluant to give the title compound as a white solid **27** (255 mg, 41% yield): mp 121−137 °C; ^{1}H NMR ($CDCl_3$) δ 8.38 (d, J = 4.0 Hz, 1H), 8.17 (s, 1H), 7.90 (d, J = 8.2 Hz, 2H), 7.37 (d, J = 8.2 Hz, 2H), 7.21 (d, J = 7.9 Hz, 1H), 7.12 (dd, J = 7.8 and 4.5 Hz, 1H), 6.7 (s, 1H), 6.68 (s, 1H), 5.99 (s, 2H), 3.81 (s, 2H), 3.08 (s, 3H); LRMS (APIMS) *m/z* 368 $(M + H)^+$. Anal. ($C_{20}H_{17}SNO_4$) C, H.

6-(4-(Methylsulfonyl)phenyl)(2*H*-benzo[d]1,3-dioxolan-5-yl) 3-Pyridyl Ketone (28). A suspension of the hydroxyl compound **26** (80 mg, 0.209 mmol) and alumina (1 g) in anhydrous CH_2Cl_2 (10 mL) was stirred at room temperature. To this mixture was added pyridinium chlorochromate (48 mg, 0.21 mmol), and the mixture was stirred at room temperature for 15 min. The reaction mixture was diluted with CH_2Cl_2, and the alumina was removed by filtration. The filtrate was washed with water (3 × 25 mL), saturated aqueous sodium bicarbonate (2 × 25 mL), and brine (1 × 25 mL) and then dried over anhydrous sodium sulfate and filtered. The filtrate was evaporated under reduced pressure. Purification by flash column chromatography using ethyl acetate as the eluant gave the title compound **28** as a white solid (110 mg, 96.5% yield): mp 186−190 °C; ^{1}H NMR ($CDCl_3$) δ 8.70 (br s, 1H), 8.59 (br s, 1H), 7.91 (d, J = 7.5 Hz, 1H), 7.75 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.0 Hz, 2H), 7.25 (br s, 1H), 7.09 (s, 1H), 6.98 (s, 1H), 6.14 (s, 2H), 2.94 (s, 3H); LRMS (APIMS) *m/z* 382 $(M + H)^+$.

4-Methyl-3-pyridyl 6-[4-(methylsulfonyl)phenyl](2*H*-benzo[d]1,3-dioxolan-5-yl) ketone (31): white solid; mp 192−194 °C; ^{1}H NMR ($CDCl_3$) δ 8.23 (d, J = 3.9 Hz, 1H), 7.70 (d, J = 7.9 Hz, 2H), 7.35 (d, J = 7.8 Hz, 2H), 7.16 (s, 1H), 7.07 (m, 1H), 6.78 (s, 1H), 6.08 (s, 2H), 2.95 (s, 3H). 2.37 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 196.6, 154.0, 150.3, 147.8, 146.7, 145.8, 138.9, 136.3, 134.2, 133.3, 129.7 (2 × C), 128.2, 126.7 (2 × C), 125.1, 110.4, 110.0, 102.2, 44.4, 19.0; LRMS (APIMS) *m/z* 396 $(M + H)^+$. Anal. ($C_{21}H_{17}SNO_5$) C, H.

4-Bromo-3-pyridyl 6-[4-(methylsulfonyl)phenyl](2*H*-benzo[d]1,3-dioxolan-5-yl) ketone (35): white solid; mp 180−190 °C; ^{1}H NMR ($CDCl_3$) δ 8.10 (m, 2H), 7.76 (d, J = 7.8 Hz, 2H), 7.36 (d, J = 7.8 Hz, 2H), 7.3−7.2 (m, 1H), 7.2 (s, 1H), 6.81 (s, 1H), 6.15 (s, 2H), 3.10 (s, 3H); LRMS (APIMS) m/z 460 $(M + H)^+$, 462 $(M + 2 + H)^+$. Anal. ($C_{20}H_{14}BrSNO_5$) C, H.

4-(Methylsulfonyl)-1-[6-(piperidylmethyl)(2*H*-benzo-[3,4-d]1,3-dioxolan-5-yl)]benzene (38a). Compound **38a** was prepared by alkylation of piperidine **37a** with chloromethyl compound **16** using method H. Pure product **38a** was obtained as white solid in 69% yield: mp 138−141 °C; ^{1}H NMR ($CDCl_3$) δ 7.93 (d, J = 8.3 Hz, 2H), 7.58 (d, J = 8.4 Hz, 2H), 7.25 (s, 1H), 7.03 (s, 1H), 5.98 (s, 2H), 3.17 (s, 2H). 3.10 (s, 3H), 2.23 (m, 4H), 1.47 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 147.4, 147.3, 146.4, 138.7, 133.9, 130.6, 130.5, 130.5, 126.8, 110.3, 109.6, 101.2, 60.4, 54.0, 45.5, 26.0, 24.3; LRMS (APIMS) m/z 374 $(M + H)^+$. Anal. ($C_{20}H_{23}SNO_4$) C, H.

Ethyl 1-({6-[4-(Methylsulfonyl)phenyl]-2*H*-benzo[d]1,3-dioxolan-5-yl}methyl)piperidine-3-carboxylate (38b). Compound **38b** was prepared by alkylation of 3-(carboxyethyl)-piperidine **37b** with chloromethyl compound **16** using method H. Pure product **38b** was obtained as white solid in 93% yield: mp 144−145 °C; ^{1}H NMR ($CDCl_3$) δ 7.93 (d, J = 8.3 Hz, 2H), 7.54 (d, J = 8.3 Hz, 2H), 7.01 (s, 1H), 6.67 (s, 1H), 5.98 (s, 2H), 4.05 (q, J = 7.2 Hz, 2H), 3.22 (s, 2H), 3.09 (s, 3H), 2.74 (m, 1H), 2.53 (m, 2H), 2.2 (m, 1H), 1.95 (m, 2H), 1.80 (m, 1H), 1.65 (m, 2H), 1.18 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 174.1, 147.5, 147.2, 146.5, 138.8, 133.8, 130.5, 129.9, 126.9, 110.1, 109.6, 101.2, 60.2, 59.9, 54.8, 53.3, 45.5, 41.8, 26.8, 24.5. 14.1; LRMS (APIMS) m/z 446 $(M + H)^+$. Anal. ($C_{23}H_{27}SNO_6$) C, H.

Ethyl 1-({6-[4-(Methylsulfonyl)phenyl]-2*H*-benzo[d]1,3-dioxolan-5-yl}methyl)piperidine-4-carboxylate (38c). Compound **38c** was prepared by alkylation of 4-(carboxyethyl)-piperidine **37c** with chloromethyl compound **16** using method H. Pure product **38c** was obtained as white solid in 94% yield: mp 121−122 °C; ^{1}H NMR ($CDCl_3$) δ 7.92 (d, J = 8.3 Hz, 2H), 7.55 (d, J = 8.3 Hz, 2H), 7.0 (s, 1H), 6.67 (s, 1H), 5.98 (s, 2H), 4.09 (q, J = 7.1 Hz, 2H), 3.19 (s, 2H), 3.09 (s, 3H), 2.69 (m, 2H), 2.1 (m, 1H), 1.8−1.5 (m, 6H), 1.21 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 175.1, 147.5, 147.2, 146.5, 138.8, 133.9, 130.5 (2 × C), 130.1, 126.9 (2 × C), 110.2, 109.6, 101.2, 60.2, 58.9, 52.4 (2 × C), 44.5, 41.0, 28.3 (2 × C), 14.2; LRMS (APIMS) m/z 446 $(M + H)^+$. Anal. ($C_{23}H_{27}SNO_6$) C, H.

1-{6-[(4-Hydroxypiperidyl)methyl](2*H*-benzo[3,4-d]1,3-dioxolan-5-yl)}-4-(methylsulfonyl)benzene (38d). Compound **38d** was prepared by alkylation of 4-hydroxypiperidine **37d** with chloromethyl compound **16** using method H. Pure product **38d** was obtained as white solid in 90% yield: mp 76−82 °C; ^{1}H NMR ($CDCl_3$) δ 7.92 (d, J = 7.0 Hz, 2H), 7.55 (d, J = 7.1 Hz, 2H), 7.01 (s, 1H), 6.67 (s, 1H), 5.98 (s, 2H), 3.62 (m, 1H), 3.20 (s, 2H). 3.09 (s, 3H), 2.59 (m, 2H), 1.99 (m, 2H), 1.8−1.4 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 147.5, 147.3, 146.5, 138.8, 133.9, 130.6, 130.2, 126.9, 110.2, 109.7, 101.3, 67.9, 59.5, 50.5, 44.5, 34.5; LRMS (APIMS) m/z 390 $(M + H)^+$. Anal. ($C_{20}H_{23}SNO_5$) C, H.

1-(6-{[2-(Hydroxymethyl)piperidyl]methyl}(2*H*-benzo-[3,4-d]1,3-dioxolan-5-yl))-4-(methylsulfonyl)benzene (38e). Compound **38e** was prepared by alkylation of 2-(hydroxymethyl)piperidine **37e** with chloromethyl compound **16** using method H. Pure product **38e** was obtained as white solid in 81% yield: mp 127−137 °C; ^{1}H NMR ($CDCl_3$) δ 7.93 (d, J = 6.5 Hz, 2H), 7.53 (d, J = 6.5 Hz, 2H), 7.00 (s, 1H), 6.67 (s, 1H), 5.98 (s, 2H), 3.85 (d, J = 13.6 Hz, 1H), 3.57 (dd, J = 11 and 4.1 Hz, 1H), 3.37 (dd, J = 11 and 4.1 Hz, 1H), 3.18 (d, J = 13.6 Hz, 1H), 3.1 (s, 3H), 2.63 (m, 1H), 2.42 (m, 1H), 2.00−1.20 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 147.6, 147.4, 146.5, 138.8, 133.9, 130.5, 130.1, 126.9, 110.2, 109.7, 101.3, 66.6, 60.4, 56.9, 53.8, 44.5, 38.2, 27.2, 24.6; LRMS (APIMS) m/z 404 $(M + H)^+$. Anal. ($C_{21}H_{25}SNO_5$) C, H.

1-(6-((3-(Hydroxymethyl)piperidyl)methyl)(2*H*-benzo-[3,4-d]1,3-dioxolan-5-yl))-4-(methylsulfonyl)benzene (38f). The chloromethyl compound **16** (410 mg, 1.2 mmol) and 2-piperidine methanol **37f** (138 mg, 1.2 mmol) were dissolved in anhydrous DMF (5 mL). Potassium carbonate (830 mg, 6 mmol) was added, and reaction mixture was stirred at room temperature overnight. The reaction mixture was then treated with ice-cold water and extracted with ethyl acetate (2 × 75 mL). The combined organic extracts were washed with water (1 × 50 mL) and brine (1 × 50 mL), dried over sodium sulfate, and filtered. The filtrate was evaporated under reduced pressure to give the crude product that was purified by flash column chromatography using methanol:dichloromethane (5:95) as an eluent to give the title compound **38f** as a white solid (410 mg, 80% yield): mp 127−137 °C; ^{1}H NMR ($CDCl_3$) δ 7.92 (d, J = 6.4 Hz, 2H), 7.56 (d, J = 6.4 Hz, 2H), 7.26 (s, 1H), 6.67 (s, 1H), 5.98 (s, 2H), 3.45 (m, 2H), 3.21 (s, 2H). 3.10 (s, 3H), 2.63 (m, 1H), 2.42 (m, 1H), 1.90−1.07 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 147.5, 147.4, 146.6, 138.8, 134.0, 130.5, 130.2, (2 × C), 127.0 (2 × C), 110.2, 109.7, 101.3, 66.7, 60.4, 56.9, 53.8, 44.6, 38.2, 27.3, 24.6; LRMS (APIMS) m/z 404 $(M + H)^+$. Anal. ($C_{21}H_{25}SNO_5$) C, H.

(6-(4-Methylthiophenyl)-2*H*-benzo[d]1,3-dioxolan-5-yl)-methylamine (39). To a stirred mixture of carbaldehyde **4** (2.72 g, 10 mmol), 4 A molecular sieves (6 g), and NH_4OAc (11.6 g, 150 mmol) in MeOH (80 mL) was added sodium cyanoborohydride (0.95 g, 15 mmol). The reaction mixture was stirred at room temperature for 4 days and filtered, and the filtrate was evaporated under reduced pressure. The resulting residue was dissolved in EtOAc (200 mL), washed with 2 M aqueous sodium carbonate, dried over sodium sulfate, and filtered. The filtrate was evaporated under reduced pressure. The crude product obtained was purified by flash chromatography using MeOH:CH_2Cl_2 (1:9) with a trace amount of NH_4OH as the eluant to give the title compound **39** as a viscous oil which solidified on standing (1.70 g, 62% yield): mp 42 °C; ^{1}H NMR ($CDCl_3$) δ 7.28 (dd, J = 6.5, 1.8 Hz, 2H), 7.20 (dd, J = 6.5, 1.8 Hz, 2H), 6.94 (s, 1H), 6.69 (s, 1H), 5.96 (s, 2H), 3.67 (s, 2H), 2.51 (s, 3H), 1.53 (br, 2H); LRMS (APIMS) m/z 274 $(M + H)^+$.

1-((6-(4-Methylsulfonyl)phenyl)-2*H*-benzo[d]1,3-dioxolan-5-yl)methyl)piperidin-2-one (42). Lactam **41** was prepared by alkylation of **39** with bromo ester **40**, and subsequently **41** was oxidized to give **42** using method C. Pure product **42** was obtained as white prisms (108 mg, 70% yield): mp 156−157 °C; ^{1}H NMR ($CDCl_3$) δ 7.97 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.4 Hz, 2H), 6.81 (s, 1H), 6.68 (s, 1H), 6.01 (s, 2H), 4.47 (s, 2H), 3.11 (s, 3H), 2.95 (t, J = 6.0 Hz, 2H), 2.38 (t, J = 6 0 Hz, 2H), 1.75−1.71 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 169.9, 148.2, 146.8, 146.4, 139.3, 133.4, 130.4, 128.4, 127.4, 109.6, 107.9, 101.4, 47.1, 44.5, 32.3, 23.1, 21.3; LRMS (APIMS) m/z 388 $(M + H)^+$. Anal. ($C_{20}H_{21}SNO_5$) C, H, N, S.

6-[4-(Methylsulfonyl)phenyl](2*H*-benzo[d]1,3-dioxolen-5-yl) Pyrrolidinyl Ketone (45a). Acid chloride **43b** was prepared from 6-[4-(methylsulfonyl)phenyl]-2*H*-benzo[*d*]1,3-dioxolene-5-carboxylic acid **43a** and it was reacted with pyrrolidine using method H to yield pure product **45a** in 57% yield as a white solid: mp 189−192 °C; ^{1}H NMR ($CDCl_3$) δ 7.94 (d, J = 8.5 Hz, 2H), 7.65 (d, J = 8.5 Hz, 2H), 6.91 (s, 1H), 6.87 (s, 1H), 6.06 (s, 2H), 3.37 (t, J = 7.0 Hz, 2H), 3.08 (s, 3H), 2.79 (t, J = 7.0 Hz, 2H), 1.67 (quin., J = 7.0 Hz, 2H), 1.54 (quin., J = 7.0 Hz, 2H); LRMS (APIMS) m/z 374 $(M + H)^+$. Anal. ($C_{19}H_{19}SNO_5$) C, H.

6-[4-(Methylsulfonyl)phenyl](2*H*-benzo[d]1,3-dioxolen-5-yl) Piperidyl Ketone (45b). Acid chloride **43b** was prepared from 6-[4-(methylsulfonyl)phenyl]-2*H*-benzo[*d*]1,3-dioxolene-5-carboxylic acid **43a** and it was reacted with piperidine using method H to yield pure product **45b** in 55% yield as a white solid: mp 152−154 °C; ^{1}H NMR ($CDCl_3$) δ 7.95 (d, J = 8.5 Hz, 2H), 7.64 (d, J = 8.5 Hz, 2H), 6.87 (s, 1H), 6.86 (s, 1H), 6.06 (d, J = 3.9 Hz, 2H), 3.56 (m, 1H), 3.36 (m, 1H), 3.07 (s, 3H), 3.03 (m, 1H), 2.71 (m, 1H), 1.48−1.23 (m, 5H), 0.77 (m, 1H); LRMS (APIMS) m/z 388 $(M + H)^+$. Anal. ($C_{20}H_{21}SNO_5$) C, H.

4-Methylpiperazinyl 6-[4-(Methylsulfonyl)phenyl](2*H*-benzo[d]1,3-dioxolen-5-yl) Ketone (46a). Acid chloride **43b** was prepared from 6-[4-(methylsulfonyl)phenyl]-2*H*-benzo[*d*]-1,3-dioxolene-5-carboxylic acid **43a** and it was reacted with

N-methylpiperazine using method H to yield pure product **46a** in 80% yield as a white solid: mp 204−206 °C.; ^{1}H NMR ($CDCl_3$) δ 7.96 (d, J = 8.3 Hz, 2H), 7.63 (d, J = 8.3 Hz, 2H), 6.88 (s, 1H), 6.86 (s, 1H), 6.06 (s, 2H), 3.55 (t, J = 5.0 Hz, 2H), 3.09 (s, 3H), 3.04 (m, 1H), 2.82 (m, 1H), 2.32 (m, 1H), 2.11 (s, 3H), 2.04 (m, 1H), 1.97 (m, 1H), 1.41 (m, 1H); LRMS (APIMS) m/z 403 $(M + H)^+$.

6-[4-(Methylsulfonyl)phenyl](2*H*-benzo[d]1,3-dioxolen-5-yl) Morpholin-4-yl Ketone (46b). Acid chloride **43b** was prepared from 6-[4-(methylsulfonyl)phenyl]-2*H*-benzo[*d*]1,3-dioxolene-5-carboxylic acid **43a** and it was reacted with morpholine using method H to yield pure product **46b** in 92% yield as a white solid: mp 203−205 °C; ^{1}H NMR ($CDCl_3$) δ 7.98 (d, J = 8.5 Hz, 2H), 7.63 (d, J = 8.5 Hz, 2H), 6.89 (s, 1H), 6.86 (s, 1H), 6.07 (s, 2H), 3.59 (m, 2H), 3.45 (m, 1H), 3.32 (m, 2H), 3.09 (s, 3H), 3.04 (m, 1H), 2.76 (m, 2H); LRMS (APIMS) m/z 390 $(M + H)^+$. Anal. ($C_{19}H_{19}SNO_6$) C, H.

5-[4-(Aminosulfonyl)phenyl]-4-benzyl-1,2-methylenedioxybenzene (47). 4-Benzyl-1,2-methylenedioxy-5-(4-methylsulfonylphenyl)benzene **21a** (152 mg, 0.419 mmol) was dissolved in dry THF (0.7 mL) in an oven-dried 25 mL single necked round-bottom flask which had been cooled to ambient temperature under argon. The flask was placed in a water bath and *n*-BuLi (1.2 equiv, 0.503 mmol, 0.3 mL of a 1.6 M solution in hexanes) was added, generating a dark yellow solution. The reaction mixture was stirred at ambient temperature for 0.5 h and then to the solution was added chloromethyltrimethylsilane (78 mg, 1.5 equiv, 0.635 mmol, 0.09 mL) in one portion. The orange reaction mixture was stirred at ambient temperature for 4 h, at which point TLC (3:7 EtOAc:hexanes) indicated the reaction to be complete. Tetrabutylammonium fluoride (5.4 equiv, 2.27 mmol, 2.27 mL of a 1 M solution in THF) was then added, generating a clear dark solution. The reaction flask was fitted with a reflux condenser and heated to the reflux temperature for 0.5 h. The reaction was cooled to ambient temperature and to the reaction mixture was added sequentially NaOAc (189 mg, 5.5 equiv, 2.31 mmol), H_2O (7 mL), and hydroxylamine-*O*-sulfonic acid (269 mg, 5.7 equiv, 2.38 mmol). The reaction mixture was stirred at ambient temperature overnight at which point TLC (3:7 EtOAc:hexanes) showed the reaction to be complete. The reaction mixture was poured into a separatory funnel and diluted with 15 mL of EtOAc, and the aqueous layer was removed. The organic layer was sequentially washed with saturated aqueous $NaHCO_3$ (2 × 7 mL), water (1 × 7 mL), and brine (1 × 7 mL). The organic layer was dried over Na_2SO_4, the reaction mixture filtered, and the solvent removed in vacuo, affording a brown oil. The oil was chromatographed on two 20 × 20 cm, 1 mm thick Alltech silica gel plates eluting once with methylene chloride and then once with 3:97 EtOAc:CH_2Cl_2. The desired band was scraped from the plates and extracted into CH_2Cl_2, affording 65 mg (43% yield) of the sulfonamide **47** as a white solid: mp 165−167 °C; ^{1}H NMR ($CDCl_3$) δ 7.89 (m, 2H), 7.36 (m, 2H), 7.20 (m, 3H), 6.95 (m, 2H), 6.70 (m, 2H), 5.98 (s, 2H), 4.79 (br s, 2H), 3.82 (s, 2H); LRMS (APIMS) m/z 385 $(M + NH_4)^+$. Anal. ($C_{20}H_{17}SNO_4$) C, H.

7-Methylthio-5-phenyl-2*H*-fluoreno[2,3-d]1,3-dioxolane (48). Treatment of compound **19a** under the conditions described in method F resulted in the formation of **48** in nearly quantitative yield: white solid; mp 173−175 °C; ^{1}H NMR ($CDCl_3$) δ 7.50 (d, J = 8.0 Hz, 2H), 7.30−7.00 (m, 7H), 6.70 (s, 1H), 5.96 (s, 2H), 4.80 (s, 1H), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 148.8, 147.7, 147.5, 141.7, 141.2, 138.8, 136.0, 134.4, 128.8 (2 × C), 128.3 (2 × C), 127.0, 126.3, 123.9, 119.2, 106.1, 101.3, 100.3, 54.1, 16.6.

4-Methylthio-1-[6-benzyl(2*H*-benzo[3,4-d]1,3-dioxolan-5-yl)]benzene (49a). Compound **19a** was hydrogenated overnight at 40 psi using method E to furnish **49a** as a white solid in 71% yield: mp 86−87 °C; ^{1}H NMR ($CDCl_3$) δ 7.25 (m, 7H), 7.00 (d, J = 8.5 Hz, 2H), 6.73 (s, 1H), 6.67 (s, 1H), 5.95 (s, 2H), 3.85 (s, 2H), 2.53 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 147.1, 145.9, 141.7, 138.4, 137.1, 135.0, 131.8, 130.0 (2 × C), 128.8 (2 × C), 128.4 (2 × C) 126.4 (2 × C), 126.3, 125.9, 110.3, 101.1, 38.9, 16.0.

Fluoro({4-[6-benzyl(2*H*-benzo[3,4-d]1,3-dioxolan-5-yl)]-phenyl}sulfonyl)methane (50). (Fluoromethyl) sulfone **50** was prepared in a two-step procedure. In a 25 mL two-neck round-bottom flask, to a solution of [bis(2-methoxyethyl)amino] sulfur trifluoride (130 μL) in anhydrous dichloromethane (2 mL) was added solution of **49a** (134 mg, 0.4 mmol) in dichloromethane (1 mL), followed by catalytic amount of $SbCl_3$ (5 mg). The reaction mixture was stirred at room temperature overnight. It was then diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The organic layer was separated and concentrated to approximately 10 mL, to this solution was added 98% *m*-chloroperbenzoic acid (178 mg) (1 mmol), and the mixture stirred at room temperature for 2 h. The resulting mixture was diluted with CH_2Cl_2 (50 mL), washed with 2 M aqueous sodium bicarbonate, dried over sodium sulfate, and filtered. The filtrate was evaporated under reduced pressure. The crude product obtained was purified by flash chromatography using EtOAc:hexanes (1:1) as the eluant to give the title compound **50** as a white solid (52 mg, 36% yield): mp 142−143 °C; ^{1}H NMR ($CDCl_3$) δ 7.64 (d, J = 8.1 Hz, 2H), 7.40 (d, J = 8.1 Hz, 2H), 7.20 (m, 2H), 6.94 (d, J = 7.0 Hz, 2H), 6.71 (s, 2H), 5.98 (s, 2H), 5.2 (dd, J = 9.0 and 4.0 Hz, 1H), 5.0 (dd, J = 9.0 and 4.0 Hz, 1H), 3.82 (s, 2H); LRMS (APIMS) m/z 385 $(M + H)^+$.

2-(4-Methylthiophenyl)benzaldehyde (52). Compound **52** was prepared using **51** and **3** by method A. The title compound **52** was obtained as colorless thick oil in 96% yield: ^{1}H NMR ($CDCl_3$) δ 9.98 (s, 1H), 8.01 (dd, J = 7.8 and 1.2 Hz, 1H), 7.60 (dt, J = 7.5 and 1.4 Hz, 2H), 7.62−7.40 (m, 2H), 7.30−7.25 (m, 3H), 2.53 (s, 3H); LRMS (APIMS) m/z 229 $(M + H)^+$.

(2-(4-Methylthiophenyl)phenyl)methan-1-ol (53). The product of the above example was converted to **53** by method I. The title compound was obtained as a white solid in 97% yield: mp 81−85 °C; ^{1}H NMR ($CDCl_3$) δ 7.55 (m, 1H), 7.40−7.20 (m, 7H), 4.61 (s, 2H), 2.50 (s, 3H), 1.63 (br s, 1H, OH); LRMS (APIMS) m/z 248 $(M + NH_4)^+$.

1-(2-(Hydroxymethyl)phenyl)-4-(methylsulfonyl)benzene (54). Compound **54** was prepared by method C in 89% yield: mp 123−124 °C; ^{1}H NMR ($CDCl_3$) δ 8.02 (d, J = 8.2 Hz, 2H), 7.65 (d, J = 8.2 Hz, 2H), 7.62 (s, 1H), 7.52−7.41 (m, 2H), 7.31 (d, J = 8.2 Hz, 1H), 4.60 (s, 2H), 3.15 (s, 3H), 2.10 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 146.5, 139.4, 139.2, 137.8, 130.2 (2 × C), 129.8, 129.0, 128.7, 127.9, 127.2 (2 × C), 62.7, 44.5; LRMS (APIMS) m/z 280 $(M + NH_4)^+$.

2-(4-(Methylsulfonyl)phenyl)benzaldehyde (55). The product of the above example **54** was oxidized to **55** by method G. The title compound **55** was obtained as a white solid in 64% yield: mp 115−116 °C; ^{1}H NMR ($CDCl_3$) δ 9.99 (s, 1H), 8.09 (m, 3H), 7.73 (t, J = 7.3 Hz, 1H), 7.63 (m, 3H), 7.46 (d, J = 7.4 Hz, 1H), 3.17 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 191.1, 143.7, 143.3, 140.2, 133.8, 133.6, 130.8 (2 × C), 130,6, 129.8, 128.5, 127.4 (2 × C) 44.5; LRMS (APIMS) m/z 278 $(M + NH_4)^+$.

1-(2-(Cyclohexylidenemethyl)phenyl)-4-(methylsulfonyl)benzene (56). Compound **56** was prepared by method B using cyclohexyltriphenylphosphonium bromide **5b** and **55**. The title compound was obtained as a white powder 35% yield: mp 83 °C; ^{1}H NMR ($CDCl_3$) δ 8.00 (d, J = 7.9 Hz, 2H), 7.63 (d, J = 7.9 Hz, 2H), 7.33 (m, 4H), 6.01 (s, 1H), 3.15 (s, 3H), 2.21 (m, 4H), 1.60−1.46 (m, 6H); LRMS (APIMS) m/z 344 $(M + NH_4)^+$. Anal. ($C_{20}H_{22}SO_2$) C, H.

(3-Fluorophenyl)(2-(4-methylthiophenyl)phenyl)-methan-1-ol (57). The Grignard reagent was prepared by refluxing 1-bromo-3-fluorobenzene and was reacted with carbaldehyde **4** by method D to give the title compound **57** as colorless thick oil in 98% yield: ^{1}H NMR ($CDCl_3$) δ 7.47 (d, J = 7.1 Hz, 1H), 7.40−7.18 (m, 8H), 6.90 (m, 3H), 5.91 (d, J = 3.6 Hz, 1H), 2.52 (s, 3H), 2.25 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 164.4, 161.1, 146.4, 140.7, 140.6, 137.7, 137.3, 130.1, 129.7 (2 × C), 129.6, 128.0, 127.7, 127.3, 126.3 (2 × C), 122.1, 114.0 (d, J = 21 Hz), 113.5 (d, J = 22 Hz), 71.8, 15.8; LRMS (APIMS) m/z 342 $(M + NH_4)^+$.

1-(2-((3-Fluorophenyl)hydroxymethyl)phenyl)-4-(methylsulfonyl)benzene (58). The (methylthio) compound

57 (220 mg, 0.679 mmol) was dissolved in dichloromethane (20 mL). Saturated aqueous sodium bicarbonate (5 mL) was added, followed by recrystallized *m*-chlorobenzoic acid (302 mg, 1.69 mmol, 98% yield), and the reaction mixture was stirred at room temperature for 2 h. The organic layer was separated. The aqueous layer was extracted with dichloromethane, and the combined organic layers were washed with 10% sodium bicarbonate (3 × 25 mL), water (1 × 25 mL), and brine (1 × 25 mL), dried over sodium sulfate, and filtered. The filtrate was evaporated under reduced pressure to give the crude product. Trituration with 10% ethyl acetate in hexane gave the title compound as a white solid that was recrystallized from hexane (190 mg, 79% yield): mp 117−119 °C; ^{1}H NMR ($CDCl_3$) δ 7.99 (d, J = 8.2 Hz, 2H), 7.62 (d, J = 7.6 Hz, 1H), 7.51 (d, J = 8.2 Hz, 2H), 7.44 (m, 2H), 7.31−7.20 (m, 2H), 7.00−6.70 (m, 3H), 5.86 (s, 2H), 3.15 (s, 3H), 2.35 (br s, 1H, OH); LRMS (APIMS) m/z 374 $(M + NH_4)^+$.

1-(2-((3-Fluorophenyl)methyl)phenyl)-4-(methylsulfonyl)benzene (59a). Compound **59a** was prepared from **58** by method F. The title compound **59a** was obtained as a white solid in 83% yield: mp 97−98 °C; ^{1}H NMR ($CDCl_3$) δ 7.97 (d, J = 8.3 Hz, 2H), 7.45 (d, J = 8.3 Hz, 2H), 7.45−7.15 (m, 5H), 6.98 (dt, J = 8.4 and 2.2 Hz, 1H), 6.75 (d, J = 7.6 Hz, 1H), 6.63 (d, J = 10 Hz, 1H), 3.97 (s, 2H), 3.15 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 164.4, 161.2, 147.2, 143.3 (d, J = 7 Hz), 140.3, 139.2, 137.2, 130.7, 130.1 (2 × C), 129.9, 129.7 (d, J = 2.5 Hz), 128.6, 127.1 (2 × C), 126.9, 124.3 (d, J = 2.5 Hz), 115.4 (d, J = 21 Hz), 112.9 (d, J = 21 Hz), 44.5, 38.9; LRMS (APIMS) m/z 358 $(M + NH_4)^+$. Anal. ($C_{20}H_{17}SFO_2$) C, H.

3-Fluorophenyl 2-(4-(Methylsulfonyl)phenyl)phenyl Ketone (60a). Compound **58** was converted to **60a** by method G to give the title compound **60a** as a white crystalline solid in 79% yield: mp 105−106 °C; ^{1}H NMR ($CDCl_3$) δ 7.79 (d, J = 8.1 Hz, 2H), 7.35−7.15 (m, 10H), 2.83 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 196.4, 164.0, 160.7, 145.7, 139.3, 138.2, 131.0, 130.2, 130.1, 130.0, 129.8 (2 × C), 129.1, 128.2, 127.7 (2 × C), 125.7 (d, J = 12 Hz), 120.1 (d, J = 22 Hz), 116.3 (d, J = 22 Hz), 44.4; LRMS (APIMS) m/z 372 $(M + NH_4)^+$. Anal. ($C_{20}H_{15}SFO_3$) C, H.

1-[6-(3,5-Difluorophenyl)(2*H*-benzo[3,4-d]1,3-dioxolan-5-yl)]-4-(methylsulfonyl)benzene (65). Compound **65** was prepared from carbaldehyde **61** in three steps. Suzuki coupling reaction of **61** with 4-(methylthio)phenylboronic acid **3** using standard conditions as described in method A gave the product **62** after purification by column chromatography. Another Suzuki coupling reaction of **62** with 3,5-difluoro-4-(methylthio)-phenylboronic acid **63** using method A gave the methylthio compound **64**, which was oxidized with Oxone using method C to afford the desired product **65** as a white solid (three steps overall 26% yield): mp 195−198 °C; ^{1}H NMR ($CDCl_3$) δ 7.79 (d, J = 8.3 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H), 6.86 (m, 2H), 6.7−6.5 (m, 3H), 6.02 (s, 2H), 3.05 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 164.2, 160.9, 148.0, 146.5, 143.9, 138.7, 132.4, 130.6, 127.2, 113.0 (d, J = 8 Hz), 112.8, 110.4, 102.4 (t, J = 25.2 Hz), 101.8, 44.5; LRMS (APIMS) m/z 406 $(M + NH_4)^+$. Anal. ($C_{20}H_{23}SNO_4$) C, H.

4-(Methylsulfonyl)-1-[6-(3-phenylpropyl)(2*H*-benzo[3,4-d]1,3-dioxolan-5-yl)]benzene (67). Compound **67** was prepared from carbaldehyde **4** in three steps. First, carbaldehyde **4** was treated with (phenethyl)magnesium chloride according to method D, the product obtained was oxidized with Oxone using method C, and then deoxygenation was performed using method E to give the desired product as a white solid: mp 110−114 °C; ^{1}H NMR ($CDCl_3$) δ 7.9 (d, J = 8.1 Hz, 2H), 7.40 (d, J = 8.1 Hz, 2H), 7.25 (m, 3H), 7.00 (d, J = 6.8 Hz, 2H), 6.80 (s, 1H), 6.63 (s, 1H), 5.97, (s, 2H), 3.1 (s, 3H), 2.47 (m, 4H), 1.76 (m, 2H); LRMS (APIMS) m/z 412 $(M + NH_4)^+$. Anal. ($C_{23}H_{22}SO_4$) C, H.

4,5-Dimethoxy-2-(4-methylthiophenyl)benzaldehyde (69). Compound **69** was prepared by the reaction of 2-bromoveratraldehyde **68** (25 g, 103.3 mmol) and 4-(methylthio)-benzeneboronic acid **3** (19.66 g, 118.5 mmol) in toluene (550 mL) and sodium carbonate (2 M, 103 mL, 206 mmol) using standard conditions for Suzuki cross-coupling reaction as described in method A. The product was purified by trituration with ethyl acetate:hexane to give the title compound as a white solid (21.3 g, 85% yield): mp 114−115 °C; ^{1}H NMR ($CDCl_3$) δ 9.83 (s, 1H), 7.64 (s, 1H), 7.43−7.23 (m, 4H), 6.83 (s, 1H), 3.98 (d, J = 2.4 Hz, 6H), 2.55 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 190.9, 153.4, 148.7, 140.8, 138.9, 134.1, 130.5, 126.9, 126.1, 112.5, 108.7, 56.2, 56.1, 15.6; LRMS (APIMS) m/z 289 $(M + H)^+$.

4-(1-(3′,5′-Difluorophenyl)-1-hydroxymethyl)-1,2-dimethoxy-5-(4-methylthiophenyl)benzene (70). Grignard reagent **17h** was prepared by refluxing magnesium metal (2.21 g, 91.06 mmol), dry THF (200 mL), and 3,5-difluorobromobenzene (11.04 mL, 95.85 mmol) and reacted with carbaldehyde **69** (91 mmol) using method D. The crude product obtained was oxidized using method C to afford the desired product **70** that was used without further purification.

5-(1-(3′,5′-Difluorophenyl)methyl)-1,2-dimethoxy-4-(4-methylsulfonylphenyl)benzene (72). Product **70** was oxidized using Oxone by method C to give methyl sulfone **71**, and the crude product **71** obtained was subsequently deoxygenated using method F to yield the title compound **72** as a white solid (18.74 g, 93.4% overall yield for the three steps from **70**): mp 157−159°C; ^{1}H NMR ($CDCl_3$) δ 7.92 (m, 2H), 7.40 (m, 2H), 6.75 (s, 1H), 6.73 (s, 1H), 6.59 (m, 1H), 6.44 (m, 2H), 3.89 (s, 6H), 3.86 (s, 2H), 3.09 (s, 3H); LRMS (APIMS) m/z 436 $(M + NH_4)^+$. Anal. ($C_{22}H_{20}SF_2O_4$) C, H.

5-(1-(3′,5′-Difluorophenyl)methyl)-1,2-dihydroxy-4-(4-methylsulfonylphenyl)benzene (73). Dimethoxy compound **72** (18.74 g, 44.78 mmol) was dissolved in dry CH_2Cl_2 (500 mL) and cooled to 0 °C, and boron tribromide (0.112 mol, 10.6 mL) was added over a period of 2−3 min. The resulting solution was stirred at 0 °C for 45 min. The reaction was quenched at 0 °C by the addition of MeOH (70 mL) followed a minute later by the addition of water (70 mL). The reaction mixture was warmed to room temperature. The solvent (CH_2Cl_2 and MeOH) was evaporated under reduced pressure to give a solid. The solid was removed by filtration, washed with water, and then dried under high vacuum overnight to give the title compound **73** as a pale yellow solid (17.0 g, 97.2% yield): mp 214°C (dec): ^{1}H NMR (DMSO-d_6) δ 9.15 (s, 1H), 9.13 (s, 1H), 7.90 (m, 2H), 7.47 (m, 2H), 6.99 (m, 1H), 6.64 (s, 1H), 6.62 (s, 1H), 6.60 (m, 2H), 3.81 (s, 2H), 3.24 (s, 3H); LRMS (APIMS) m/z 408 $(M + NH_4)^+$.

1-(7-((3,5-Difluorophenyl)methyl)(2*H*,3*H*-benzo[3,4-e]1,4-dioxin-6-yl))-4-(methylsulfonyl)benzene (74). To a stirred mixture of **73** (0.400 g, 1.02 mmol) and 1,2-dibromoethane (0.21 g, 0.140 mL, 1.13 mmol) in dry acetone (50 mL) was added powdered potassium carbonate (2.96 mmol, 0.409 g). The mixture was heated at reflux for 4 h, then additional 1,2-dibromoethane (0.105 g, 0.070 mL) and potassium carbonate (0.205 g) were added, and the mixture refluxed overnight. The reaction mixture was cooled, filtered through Celite, and washed with acetone. The filtrate was evaporated under reduced pressure, and the resulting residue was partitioned between ethyl acetate and water. The organic layer was separated, washed with brine, dried over magnesium sulfate, and filtered, and the filtrate was evaporated to near dryness. Addition of ether resulted in the formation of off-white crystals of the title compound **74** (0.308 g, 73% yield): mp 160−162 °C; ^{1}H NMR ($CDCl_3$) δ 7.93 (td, J = 1.9, 8.4 Hz, 2H), 7.39 (td, J = 1.9, 8.4 Hz, 2H), 6.80 (s, 1H), 6.78 (s, 1H), 6.61 (tt, J = 2.3, 9.0 Hz, 1H), 6.45 (m, 2H), 4.34 (s, 4H), 3.82 (s, 2H), 3.12 (s, 3H); MS (APIMS) m/e 434 $(M + NH_4)^+$. Anal. ($C_{22}H_{18}SF_2O_4$) C, H.

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