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Potent, Long-Acting Cyclopentane-1,3-Dione Thromboxane (A_2)-Receptor Antagonists

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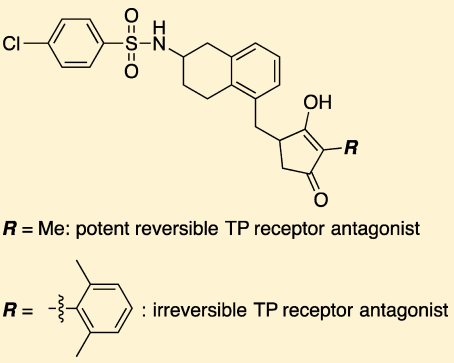
Supporting Information

ABSTRACT: A series of derivatives of the known thromboxane A_2 prostanoid (TP) receptor antagonists, 3-(6-((4-chlorophenyl)sulfonamido)-5,6,7,8-tetrahydronaphthalen-1-yl)propanoic acid and 3-(3-(2-((4-chlorophenyl)sulfonamido)-ethyl)phenyl) propanoic acid, were synthesized in which the carboxylic acid functional group was replaced with substituted cyclopentane-1,3-dione (CPD) bioisosteres. Characterization of these molecules led to the discovery of remarkably potent new analogues, some of which were considerably more active than the corresponding parent carboxylic acid compounds. Depending on the choice of the C2 substituent of the CPD unit, these new derivatives can produce either a reversible or an apparent irreversible inhibition of the human TP receptor. Given the potency and the long-lasting inhibition of TP receptor signaling, these novel antagonists may comprise promising leads for the development of antithromboxane therapies.



KEYWORDS: *Cyclopentane-1,3-dione, carboxylic acid bioisostere, thromboxane A_2, thromboxane receptor antagonists*

Thromboxane A_2[1] and the corresponding thromboxane A_2 prostanoid (TP) receptor have long been recognized as important players in the pathophysiology of a range of cardiovascular diseases due to the direct involvement of the thromboxane signaling pathway in platelet aggregation and vasoconstriction.[2,3] Several classes of TP receptor antagonists have been identified;[4] however, the clinical development of these compounds for cardiovascular indications has thus far been challenging,[5] in part due to the fact that relatively effective, safe, and inexpensive treatments are already available to treat these diseases (e.g., aspirin).[6] For example, the tetrahydronaphthalene S-18886 (**1**, Figure 1),[7] one of the most potent and selective TP receptor antagonists reported to date, has not advanced beyond phase III clinical testing as this drug candidate, although effective, failed to show superiority compared to low dose aspirin regimens in preventing adverse cardiovascular events.[6,8] Despite these setbacks, the investigation of this class of candidate therapeutics remains an area of interest for both cardiovascular diseases,[6] as well as for other indications, including cancer[9] and Alzheimer's disease (AD).[10]

Recently, we reported on a series of TP receptor antagonist derivatives of known compound **3**[11] (Figure 1) in which the carboxylic acid moiety, believed to be an essential pharmacophore constituent, was replaced with variously substituted cyclopentane-1,3-diones (CPDs).[12] We now report the synthesis and biological activity of a new series of related analogues in which CPDs bearing different substituents at the C2 position were employed to substitute for the carboxylic acid moiety of the TP receptor antagonists **2**[7] and **3** (Figure 1). Notably, most compounds within this series were found to be highly potent

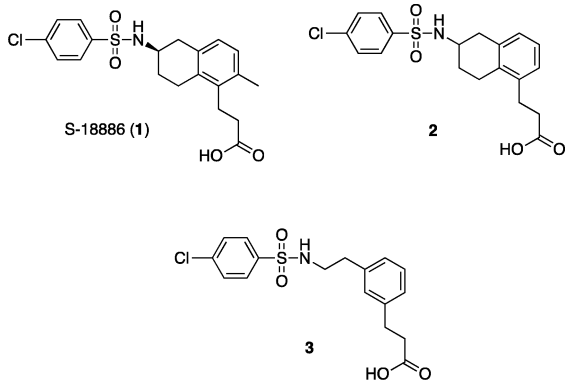


Figure 1. Structures of S-18886 and two other related TP receptor antagonists.

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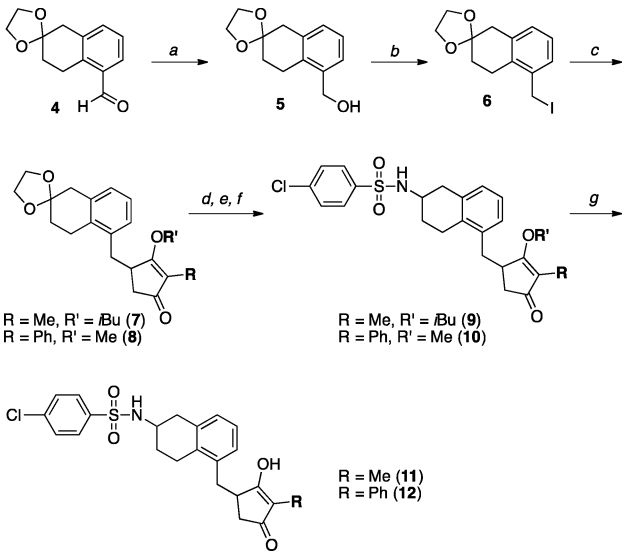
antagonists of the TP receptor, with selected examples being remarkably more potent than the corresponding carboxylic acids. Moreover, analogues bearing aromatic groups at the C2 position of the CPD unit, such as phenyl, substituted phenyl or benzyl substituents, were found to produce long-lasting inhibition of TP receptor signaling *in vitro*, as evidenced by the fact that receptor activity could not be fully recovered after repeated washes of compound-treated cells. The inability to readily dissociate these compounds from the TP receptor is suggestive of a covalent modification of the receptor. However, the data presented herein indicate that the interaction of these CPD derivatives with the TP receptor is specific. Thus, given the potency and the long-lasting inhibition of the TP receptor signaling, these novel antagonists may be promising leads in the development of antithromboxane therapies.

The synthesis of CPD derivatives of **2** was achieved as highlighted in Schemes 1 and 2, starting from known aldehyde

Scheme 1[a]

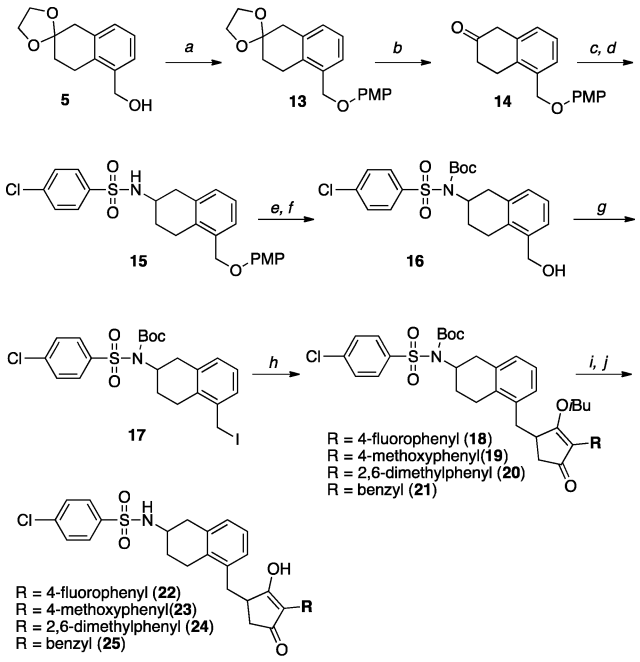


[a]Reagents and reaction conditions: (a) $NaBH_4$, MeOH, r.t., 30 min, 92%; (b) PPh_3, imidazole, I_2, CH_2Cl_2, 0 °C to r.t., 20 min, 90%; (c) KHMDS, appropriately substituted 3-methoxy- or 3-isobutoxycyclopent-2-en-1-one, THF, −78°C, 2 h, 62−73%; (d) TFA, acetone, r.t., 5 h;(e) ammonium acetate, $NaBH_3CN$, CH_2Cl_2, r.t., 4 h; (f) 4-chlorophenyl-sulphonyl chloride, TEA, CH_2Cl_2, r.t., 1 h, 12% over three steps; (g) 2 N HCl/acetone, r.t. or 50°C, 2−16 h, 62%.

4.[13] Thus, reduction of **4** to the corresponding alcohol (**5**), followed by an iodination reaction, provided benzyl iodide **6** (Scheme 1). Next, treatment of **6** with the appropriately substituted 3-methoxy- or 3-isobutoxycyclopent-2-en-1-one in the presence of potassium bis(trimethylsilyl)amide (KHMDS) furnished the C4 alkylated products **7** and **8** as racemic mixtures (see Supporting Information). Acid-catalyzed removal of the ketal, followed by reductive amination of the resulting tetralones with ammonium acetate, led to the primary amine intermediates, which were directly converted to the corresponding sulfonamides (**9** and **10**, Scheme 1). Lastly, acid hydrolysis of the vinylogous esters yielded the CPD derivatives **11** and **12** as mixtures of two enantiomers and two diastereoisomers (Scheme 1).

An alternative, more efficient synthesis of these CPD derivatives, highlighted in Scheme 2, was employed for the synthesis of derivatives **22**−**25**. In this case all compounds were

Scheme 2[a]



[a]Reagents and reaction conditions: (a) 4-methoxyphenol, PPh_3, DEAD, THF, r.t., 25 min, >95%; (b) *p*-toluenesulfonic acid monohydrate, acetone, r.t., 5 h, 87%; (c) ammonium acetate, $NaBH_3CN$, MeOH, r.t., 16 h; (d) 4-chlorobenzenesulfonyl chloride, TEA, CH_2Cl_2, 0 °C to r.t., 30 min, 41% over two steps; (e) di-*tert*-butyl pyrocarbonate, DMAP, CH_2Cl_2, 0 °C, 40 min, 79%; (f) CAN, THF, 0 °C, 30 min, 87%; (g) imidazole, PPh_3, I_2, CH_2Cl_2, 0 °C to r.t., 2 h, 75%; (h) KHMDS, appropriately substituted 3-isobutoxycyclopent-2-en-1-one, THF, −78°C; (i) TFA, CH_2Cl_2, r.t., 1 h; (j) acetone, 2 N HCl acid, 50 °C, 16 h, 21−53% over three steps.

obtained from the common intermediate, benzyl iodide **17** (see Supporting Information). Finally, CPD derivatives of **3** (**27** and **28**, Table 1) were synthesized following the same synthetic strategy described for closely related analogues.[12]

All test compounds were evaluated for inhibition of TP receptor activation, as determined by a functional assay that measures the formation of inositol monophosphate (IP_1), which is a metabolite of the second messenger inositol triphosphate (IP_3), in stably transfected HEK-293 cells expressing human TP receptor α. Typical assay conditions involved the coincubation of cells with different concentrations of test compounds for 15 min prior to the addition of the known TP receptor agonist, I-BOP (0.2 or 0.8 nM, as indicated in the figure legend). After an additional hour of incubation time, TP receptor activation was determined by assessing relative IP_1 levels (see Supporting Information). Under these assay conditions, carboxylic acids **1**−**3** exhibited IC_{50} values in the low (**1** and **2**) to high nanomolar range (**3**, Table 1). These values are approximately ∼10−100 times above the reported K_d values for these compounds, likely due to receptor reserve resulting from high levels of TP receptor expression in the transfected cells. As shown in Figure 2 and Table 1, with the notable exception of the isobutyl-protected CPD derivative **31**, truncated analogue **26**, and analogue **28**, several compounds exhibited IC_{50} values in the low to sub nanomolar range. Of particular interest were compounds **23** and **24**, which exhibited a marked leftward shift of the dose−response curve relative to the corresponding acid, **2** (Figure 2 and Table 1).

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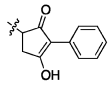
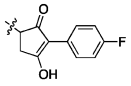
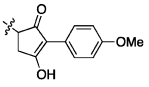
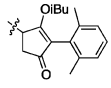
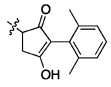
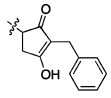
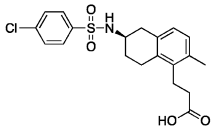
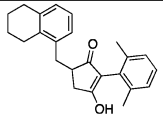
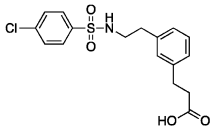
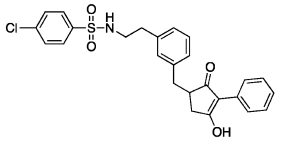
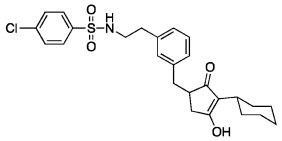
Table 1. IC_{50} Values of Test Compounds in the IP_1 TP Receptor Assay[a]

Cpd		IC_{50} (nM)
2	-CH_2COOH	10.7 +/- 1.1
11		11.2 +/- 5.5
12		3.9 +/- 4.9
22		6.5 +/- 2.6
23		0.052 +/- 0.880
31		2760 +/- 1506
24		0.015 +/- 0.060
25		29.2 +/- 14.5
Cpd	**Structure**	**IC_{50} (nM)**
1		16.4 +/- 1.3
26		891 +/-758
3		523 +/- 380
27		59 +/- 35
28		892 +/- 592

[a]Values represent the average and SD of one or more assays run in triplicate, utilizing 0.2 nM I-BOP as agonist.

Compound **2**, and related congener and clinical candidate **1**, are among the most potent TP receptor antagonists reported to date with K_d values in the high-picomolar range.[7,14−16] Thus, the observation that CPD derivatives **23** and **24** are considerably more potent than **1** and **2** in a functional assay would suggest that the K_d values of these CPD derivatives may be in the low to sub picomolar range. Such extremely low binding constants, however, are generally indicative of covalent binding, as the binding affinities of optimized noncovalent ligands typically fall within the low nanomolar to picomolar range.[17] Thus, to investigate further the mode of action of these CPD derivatives, we evaluated whether the TP receptor signaling could be recovered after repeated washes of compound-treated cells, under the presumption that if these CPD derivatives were to exhibit slow off-rates consistent with the formation of relatively stable covalent complexes, then a long-lasting inhibition of the receptor should be observed.

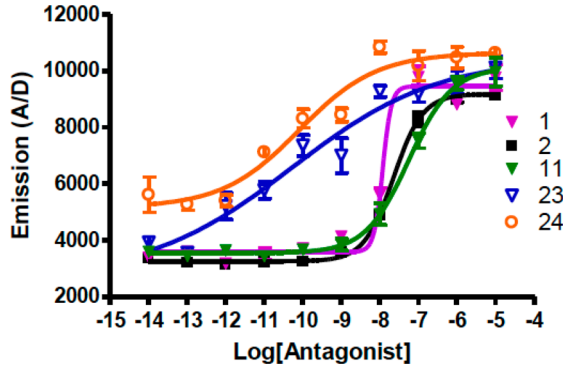


Figure 2. Concentration−response curves in the TP receptor IP_1 assay, utilizing 0.2 nM I-BOP as agonist.

For these experiments, TP receptor-expressing cells were initially incubated with 1 μM of test compound or control acid. As shown in Figure 2, at this compound concentration the CPD derivatives (**11**, **23**, and **24**) and carboxylic acid compound (**2**) produce a maximal inhibition of the TP receptor signaling. After an incubation time of either 15 or 60 min, compound-treated cells were subjected to four consecutive wash cycles, with each cell-wash cycle resulting in an approximately 50-fold dilution of test compounds. After a total of 4 consecutive wash-cycles, each separated by a 15 min equilibration time, cells were treated with the agonist I-BOP and TP receptor activity was determined using the IP_1 assay. As four consecutive 50-fold dilutions produce a theoretical dilution factor of 6,250,000, the compound concentration in the system would be expected to drop well below the IC_{50} values of all these compounds (see Figure 2), thereby allowing the cells to regain at least partial responsiveness to I-BOP-mediated activation of the TP receptor. Indeed, four repeated washes of cells treated with carboxylic acids **2**, or CPD derivative **11**, resulted in a recovery of TP receptor signaling (i.e., reduction of signal in the fluorescence assay) regardless of preincubation time, confirming that these compounds are readily reversible antagonists (Figure 3). In stark contrast, cells that were treated with **23** and **24** remained completely insensitive to I-BOP stimulation after the repeated dilutions. Also of note, the irreversible inhibition of the TP receptor caused by **23** and **24** was found to be complete within the first 15 min of incubation time (Figure 3), indicating that these compounds may be relatively fast acting irreversible antagonists when added at concentrations that would saturate the receptor binding sites (e.g., 1 μM). Following these results, the reversibility of a larger set of CPD derivatives was evaluated in a similar cell-wash study where test compounds were incubated with the TP receptor-expressing cells for 15 min, followed by 6 repeat

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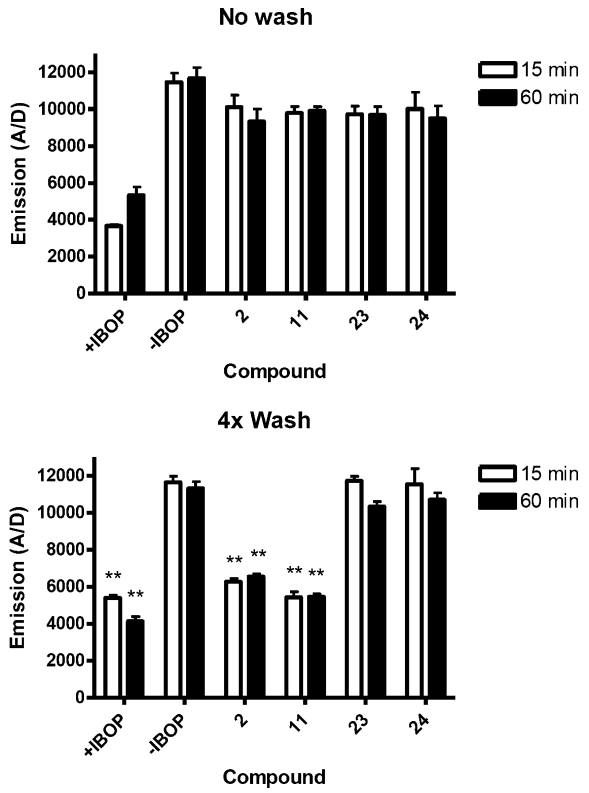

Figure 3. hTP-expressing cells were treated with antagonists (1 μM) for 15 or 60 min, followed by the addition of 0.8 nM I-BOP (top). Control cells received either I-BOP alone (+IBOP) or no treatment (−IBOP). A similar analysis was conducted in which the antagonist-treated and control cells underwent four consecutive wash cycles, each producing a 50-fold dilution, prior to the addition of I-BOP (bottom). For the 4× washed cells, data were analyzed by ANOVA with a Dunnett's posthoc test to determine differences from the −IBOP control at each time, $^{**}p < 0.01$.

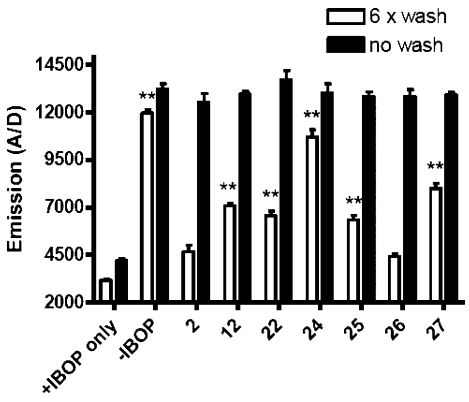

Figure 4. hTP-expressing cells were treated with antagonists (1 μM of **2**−**25** and **27**; 10 μM of **26**) for 15 min, followed by the addition of 0.8 nM I-BOP and determination of relative IP_1 levels ("no wash"). Control cells received either I-BOP alone (+IBOP) or no treatment (−IBOP). A similar analysis was conducted in which the antagonist-treated and control cells underwent 6 consecutive wash cycles, each producing a 50-fold dilution, prior to the addition of I-BOP (6×wash). $^{**}p = 0.01$ as determined by ANOVA analysis of the 6× wash data and comparison to the +I-BOP condition, using a Dunnett's test.

washes (i.e., theoretical dilution factor of 15,625,000,000) before the addition of I-BOP as described above. Again, while acids **2** (Figure 4) and **3** (Figure S1, Supporting Information) were found to have reversible receptor binding, as revealed by the full recovery of I-BOP-triggered TP receptor signaling after repeated cell-washes, treatment with CPD derivatives resulted in either full (**24**) or partial (e.g., **12**, **22**, **25**, and **27**) inhibition of TP receptor sensitivity to agonist (Figure 4). The results from these studies thus suggest that the nature of the substituent at the C2 position of the CPD unit may be critical to determine the degree of reversibility of inhibition. In particular, whereas analogues bearing aliphatic substituents at C2 (e.g., **11** and **28**) appeared to be readily reversible antagonists like acids **2** and **3** (see Figures 3 and S1, Supporting Information), the presence of aromatic substituents at C2 may be necessary for long-lasting receptor inhibition, with electron-rich systems, as in **23** and **24**, leading to an apparently unrecoverable inhibition. However, the observation that derivative **26**, a truncated analogue of **24**, is a relatively weak and reversible antagonist of the TP receptor suggests that the simultaneous contribution of a complex set of interactions taking place within the receptor binding site may ultimately be required for an irreversible inhibition.

To investigate whether the observed long-lasting inhibition of the TP receptor signaling caused by these CPD derivatives was in fact due to prolonged receptor occupancy, and not to compound-induced receptor internalization, compound **24** was evaluated in the extensive 6 cell-washes experiment, as described above, at a temperature that suppresses endocytosis and thus receptor trafficking (i.e., 4 °C). These experiments confirmed that **24** leads to a full inactivation of the TP receptor under conditions of impaired receptor internalization (see Figure S2, Supporting Information), suggesting that the observed activity of this compound, and likely the related antagonists **12**, **22**, **23**, **25**, and **27**, is due to prolonged receptor occupancy rather than compound-induced receptor internalization.

Next, an evaluation of the separated enantiomers of the slowly reversible antagonist, **27**, in the TP receptor functional assay under standard assay conditions revealed that the IC_{50} values were similar to that of racemic **27** (see Figure S3, Supporting Information), although it is possible that the (+)-isomer has a slightly lower IC_{50} value in the IP_1 assay relative to the (−)-enantiomer. When the enantiomers were evaluated in the six repeated cell-wash experiment, as described above, only the (+)-enantiomer was found to produce a significant level of long-lasting inhibition (Figure S4, Supporting Information), indicating that the (+)-isomer may exhibit a relatively slower off rate than the corresponding enantiomer.

Previous docking studies typically suggest that the carboxylic acid moiety of TP receptor antagonists is important for receptor binding due to the formation of a relatively stable salt bridge with the guanidine side-chain of Arg295.[18] A similar binding pose and set of interactions are also believed to take place in the case of CPD derivatives, with the acidic moiety being in close proximity to Arg295.[12] This raises the possibility that the side-chain of Arg295 may be potentially involved in the formation of a covalent adduct with the neighboring substituted CPD. To investigate this possibility, the ligand−receptor interactions were examined by docking irreversible antagonist **24**. These studies indicate that in addition to the expected ionic and H-bond interaction between the enolate and the guanidinium moiety (Figure 5A), the aromatic substituent at C2 may be contributing significantly to receptor binding by forming a π−cation interaction with the guanidinium of Arg295.[19,20] At the same time, this interaction is also likely to

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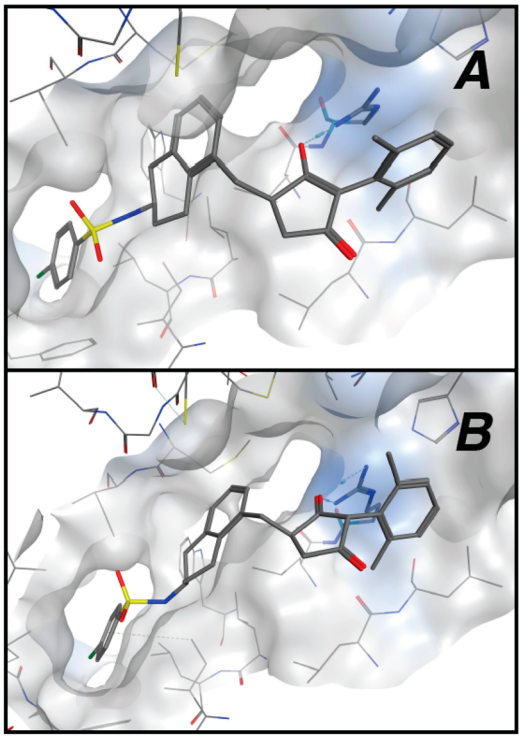

Figure 5. Docking of **24** within the TP receptor indicate that a π-stacking between the aromatic substituent at C2 and the guanidinium of Arg295 may increase the proximity of the guanidine and the CPD (A) and/or stabilize the 1,3-dicarbonyl tautomer (B).

position the guanidine residue orthogonal to the plane of the CPD, thus potentially predisposing the guanidine nitrogens for a nucleophilic attack to the enol-ketone of the CPD from either above or below the plane (Figure 5A). This π-stacking may also stabilize and thus possibly favor the formation of the nonconjugated 1,3-diketone tautomer of the CPD unit (Figure 5B) that would result in greater electrophilic character at the two carbonyl centers. Furthermore, the inductive effect of electron-rich aromatic substituents at C2, as in **23** and **24**, may further increase the potential for nucleophilic attacks to the carbonyl groups of the CPD by suppressing the intrinsic acidity of the vinylogous acid, thereby allowing for a relatively higher proportion of the neutral form of the CPD, at physiological pH. In this regard, it is known that the presence of an unsubstituted phenyl ring at C2 of the CPD increases the pK_a of the CPD from 4.4 to 5.4.[21] Finally, it should be noted that although our docking studies highlight the role of Arg295 in the binding of CPD derivatives, the possible involvement of other amino acid residues (e.g., Lys288) in the putative alkylation event cannot be ruled out.

To investigate whether CPD derivatives bearing aromatic substituents at the C2 position could spontaneously react with nucleophiles under physiological conditions, we monitored the stability of 2-(2,6-dimethylphenyl)cyclopentane-1,3-dione upon incubation with an equimolar amount (10 mM concentration) of glutathione in aqueous buffer (pH 7). These *in vitro* studies revealed that there was no consumption of the starting CPD derivative after 3 h of incubation (data not shown). Next, the plasma stability of irreversible antagonist **24** was evaluated. Plasma contains >4000 proteins, with albumin being present at concentrations of approximately 600 μM.[22] Relatively reactive and nonspecific carbonyl compounds such as 4-hydroxy-*trans*-2-nonenal have been reported to readily modify plasma proteins with an observable drop in free compound concentration, indicating that plasma stability studies may be useful to identify chemically reactive, nonspecific compounds. Our results showed that the free compound concentration of **24** remains unchanged after 1 h of incubation in plasma (Figure S5, Supporting Information), confirming that this compound does not covalently modify plasma proteins. Finally, we tested whether **24** could act as an antagonist of another prostanoid receptor, the prostaglandin E2 receptor (EP_1). These studies revealed that 1 μM of **24**, which causes a rapid, complete, and irreversible inhibition of the TP receptor, did not antagonize 17-PGE2-mediated activation of the EP_1 receptor, whereas the known EP_1 antagonist SC51089 blocked the effect of 17-PGE2 (Figure S6, Supporting Information).

Thus, collectively, the data presented above suggest that the CPD derivative **24** and possibly related congener **23** are potent, irreversible, and specific antagonists of the TP receptor. Our results indicate that the insurmountable inhibition caused by **23** and **24** and the partially recoverable inhibition caused by related analogues **12**, **22**, **25**, and **27** is likely to involve a specific alkylation event catalyzed by the proximity effect attainable within the receptor binding-site. Further studies are clearly needed to provide direct evidence of covalent modification.

Importantly, with the partial exception of benextramine,[23] a tetraamine disulfide reported to act irreversibly both on the TP receptor as well as on the α_1- and α_2-adrenoceptors; all other TP receptor antagonists developed to date are reversible antagonists. Given that some of the most successful antiplatelet therapeutics, such as aspirin and clopidogrel (Plavix), are irreversible inhibitors of their respective targets on platelets, an irreversible mode of action may be desirable, particularly in the context of antiplatelet therapies. Thus, the observation that an appropriate selection of substituent in the C2 position of the CPD can effectively modulate the mode of action of these TP receptor antagonists from a readily reversible to an irreversible or near irreversible inhibition suggests that the CPD bioisostere may provide a unique opportunity to design novel, potentially improved antithromboxane candidate drugs.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details concerning the synthesis and evaluation of test compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

The manuscript was written by C.B., K.R.B., and A.B.S. and was reviewed by all authors. X.W., K.H.R., L.H., L.L., A.S.C., S.S., A.B., M.B., M.J.J., and C.B. made experimental contributions; C.B. and K.R.B. directed research; V.M.Y.L. and J.Q.T. provided resources. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

CPD, cyclopentane-1,3-dione; TP, thromboxane A2 prostanoid; IP_1, inositol monophosphate; I-BOP, [1*S*-1α,2β(5*Z*),3α-(1*E*,3*R**),4α)]-7-[-3-(3-hydroxy-4-(4″-iodophenoxy)-1-butenyl)-7-oxabicyclo-[2.2.1]-heptan-2-yl]-5-heptenoic acid; EP_1, prostaglandin E2 receptor; 17-PGE2, 17-phenyl trinor Prostaglandin E2

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