Synthesis of 2(1*H*)-Quinolinone Derivatives and Their Inhibitory Activity on the Release of 12(*S*)-Hydroxyeicosatetraenoic Acid (12-HETE) from Platelets

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A search for potent inhibitors of release of 12(*S*)-hydroxyeicosatetraenoic acid (12-HETE), which plays an important role in the pathogenesis of various circulatory disorders and arteriosclerosis, led us to 6-[4-(1-cyclohexyl-5-tetrazolyl)butoxy]-3,4-dihydro-2(1*H*)-quinolinone (cilostazol) and 2(1*H*)-quinolinone derivatives having an azole group in the side chain. Many 2(1*H*)-quinolinone derivatives were synthesized and tested *in vitro* for the inhibitory activity in human platelets. 3,4-Dihydro-6-[3-(1-*o*-tolylimidazol-2-yl)sulfinylpropoxy]-2(1*H*)-quinolinone (5k) was found to be one of the most potent inhibitors of 12-HETE release, being more potent than esculetin. In addition, the sulfoxide 5k showed *in vivo* inhibitory activity on platelet adhesion in rats. Since 5k is racemic, the enantiomers were prepared and their potencies were compared *in vitro* and *in vivo*. (*S*)-(+)-5k had the best pharmacological profile and was selected as a candidate drug for further development. The structure–activity relationships are discussed.

Key words 12-HETE; platelet adhesion; 2(1*H*)-quinolinone; tolylimidazole; structure–activity relationship

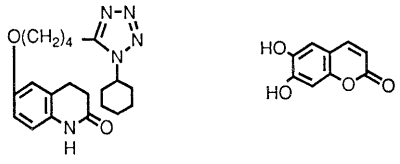
In platelets, thromboxane A_2 (TXA_2) and 12(*S*)-hydroxyeicosatetraenoic acid (12-HETE) are major arachidonic acid metabolites. Although the physiological role of TXA_2 is well established, that of 12-HETE has not been fully elucidated. It is known that platelets play a significant role in the early phase of arteriosclerosis through the release of 12-HETE, which is one of the most potent inducers of platelet adhesion,[1] and platelet adhesion plays an important role in thrombus formation in the throat of a stenosis.[2] Therefore an inhibitor of 12-HETE release is expected to be effective for the treatment of these diseases.

We have been investigating 2(1*H*)-quinolinone derivatives as potential novel drugs, and have developed a *β*-adrenergic blocker,[3] a stimulant,[4] a blood platelet aggregation inhibitor[5] and a gastric antiulcer agent.[6]

During modification of cilostazol (a blood platelet aggregation inhibitor), we found that cilostazol and 3,4-dihydro-2(1*H*)-quinolinone derivatives having an azole group in the side chain showed inhibitory activity on 12-HETE release from platelets. We synthesized many 2(1*H*)-quinolinone derivatives and tested their activity. In this paper, we report the synthesis of 2(1*H*)-quinolinone derivatives having an azole group and their biological activity.

Chemistry

N-Alkylated azole compounds **2a**—**g** were prepared by the reaction of *ω*-haloalkoxy-2(1*H*)-quinolinone **1a** with the corresponding azole[7] in the presence of a base (Chart 1). Reaction of **1a** with 1*H*-1,2,4-triazole afforded **2c** as a major product, and alkylation of **1a** with 1*H*-tetrazole in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in 2-propanol gave **2d** and **2e** in 34% and 31% yields, respectively. The structural assignment of these regio isomers was based on their ^{1}H-NMR spectra. The signals of two protons of the 1,2,4-triazole group of **2c** appear at δ 7.97 and δ 8.06, indicating that the two protons are non-equivalent. Therefore **2c** is a 1-substituted-1,2,4-tetrazole.[8] It is known that the signal due to the 5-position of a 1-alkyltetrazole appears at a higher field than that of a 2-alkyltetrazole.[9] Those of **2d** and **2e** appear at δ 8.99



Cilostazol Esculetin

Fig. 1. Structures of Cilostazol and Esculetin

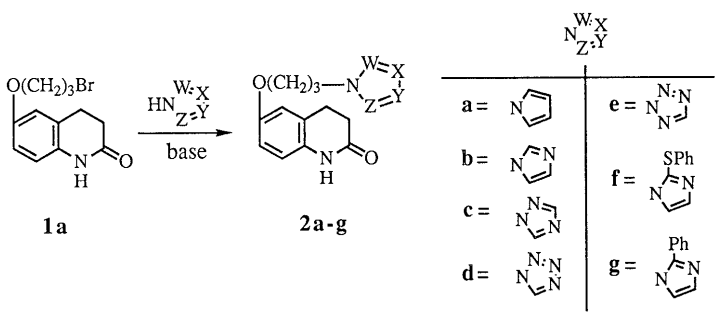


Chart 1

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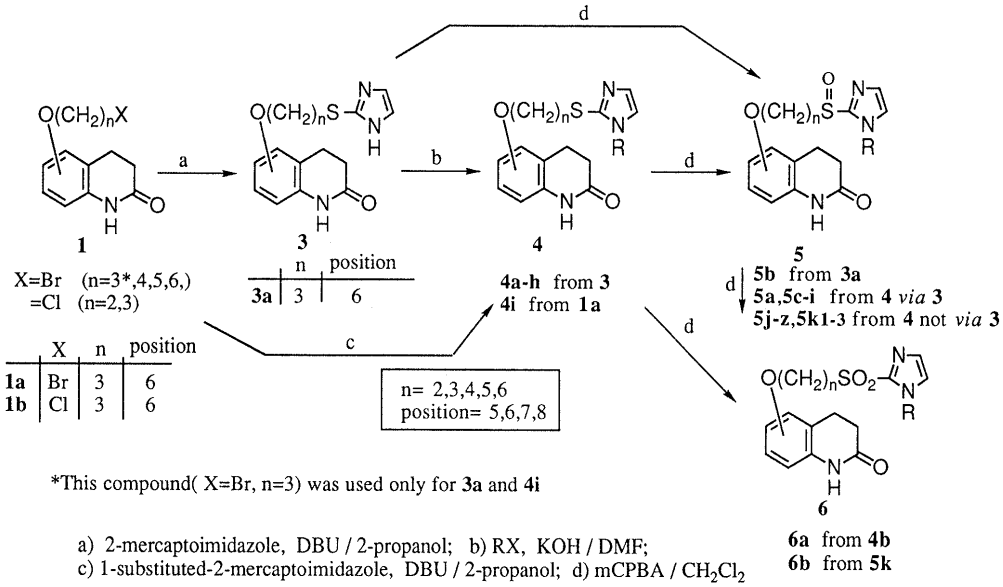
and δ 9.44, respectively. Therefore **2d** and **2e** are 1- and 2-substituted tetrazoles, respectively (Chart 1).

Sulfide derivatives (**3** and **4**), sulfoxide derivatives (**5**) and sulfone derivatives (**6**) were prepared as shown in Chart 2. Alkylation of **1** with 2-mercaptoimidazole gave the sulfide **3** in good yield. N-Alkylation of **3** with various alkyl halides gave the sulfide **4**. S-Alkylation of **1** with 1-substituted-2-mercaptoimidazole[10] gave the corresponding sulfide **4**. Oxidation of **4** with *m*-chloroperbenzoic acid (mCPBA) in dichloromethane (CH_2Cl_2) gave the corresponding sulfoxide **5** and sulfone **6**. 2(1*H*)-Quinolinone derivatives (**4A**,**5A**) were prepared from a 3,4-dehydro derivative of **1** by the same method.

N-Allylated triazole **8** and tetrazole **10** were prepared by the route shown in Chart 3. Alkylation of **1b** with 1*H*-1,2,4-triazole-3-thiol in the presence of DBU gave **7**, and reaction of **7** with allyl bromide in the presence of potassium hydroxide (KOH) in *N*,*N*-dimethylformamide (DMF) gave **8** and **9** in 24% and 7.5% yields, respectively. The proton signals of **8** and **9** appear at δ 7.87 and δ 8.01, respectively. Therefore **8** and **9** are 5- and 3-substituted, respectively.[11] Reaction of **1b** with 1-allyltetrazole-5-thiol in the presence of DBU afforded **10**.

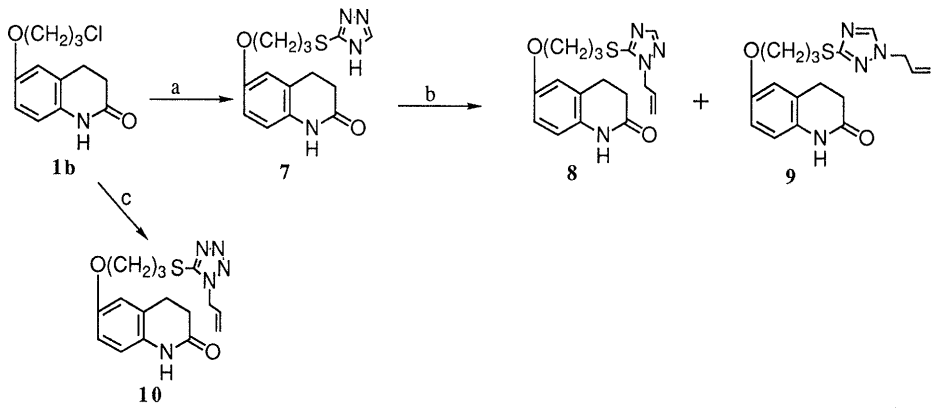
2-Alkylated imidazole **15** was prepared by the route shown in Chart 4. Reaction of **1c** with sodium cyanide gave the nitrile **11**, followed by treatment with anhydrous hydrogen chloride and methanol to afford the imidate **12** in good yield. Treatment of **12** with ammonium chloride (NH_4Cl) in ethanol gave the amidine **13** in good yield, followed by cyclization with chloroacetaldehyde in the presence of potassium carbonate (K_2CO_3) to give 2-alkylimidazole **14**. Allylation of **14** with allyl bromide afforded **15**.

The sulfoxide **5k** possessed good activity, and was selected for further evaluation. Since **5k** is racemic, we attempted to prepare the enantiomers, as shown in Charts 5 and 6. Modified Sharpless asymmetric oxidation[12] of the sulfide **4i** with cumene hydroperoxide in the presence of (+)- or (−)-diethyl tartrate and titanium tetraisopropoxide afforded **5k** (43—55% ee by HPLC with a chiral stationary phase column). Recrystallization of **5k** (43—55% ee) gave enantiomerically poor crystals (20—30% ee) and an enantiomerically rich mother liquor (70—80% ee). Therefore it was found to be difficult to



a) 2-mercaptoimidazole, DBU / 2-propanol; b) RX, KOH / DMF;
c) 1-substituted-2-mercaptoimidazole, DBU / 2-propanol; d) mCPBA / CH_2Cl_2

Chart 2



a) 1*H*-1,2,4-triazole-3-thiol, DBU/ 2-propanol; b) allyl bromide, KOH / DMF;
c) 1-allyltetrazole-5-thiol, DBU / 2-propanol

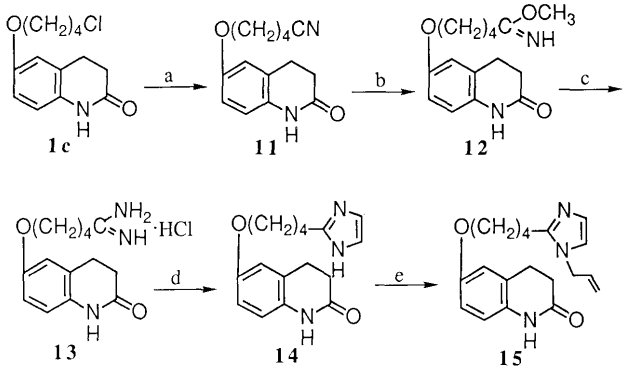
Chart 3

obtain enantiomerically pure **5k** by this method.

Enantiomerically pure **5k** were prepared by using (2*S*)-(+)-glycidyltosylate as a chiral source. Reaction of 3,4-dihydro-6-hydroxy-2(1*H*)-quinolinone **16** with (2*S*)-(+)-glycidyltosylate in the presence of sodium hydride (NaH) in dry DMF afforded the epoxide **17** in 62% yield, followed by ring opening with 2-mercapto-1-*o*-tolylimidazole to give (+)-**18** (83% ee, 76% yield) which was recrystallized 3 times from ethanol to give (+)-**18** (99.6% ee) in 46% yield. It is known that the configuration at the 2-position of glycidyl tosylate is retained in the reaction with various nucleophiles in the presence of NaH.[13] Therefore the *S* configuration of (2*S*)-(+)-glycidyl tosylate was retained to afford the *R* configuration of (*R*)-(+)-**18**. Oxidation of (*R*)-(+)-**18** with mCPBA afforded **19** and **20** as a diastereo mixture. These two products were separated by silica gel column chromatography. The first eluates gave **19** in 40% yield. Further elution gave **20** in 33% yield. The configuration of **20** was determined as *R*-sulfoxide by X-ray crystallographic analysis, based on the stereochemistry of the 2(*R*)-hydroxy group, as shown in Fig. 2.

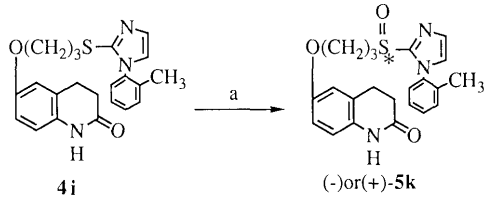
Therefore **19** was determined to be the *S*-sulfoxide. The removal of the hydroxy group was achieved in a usual manner. Namely, methanesulfonylation of **19** or **20** with methanesulfonyl chloride in the presence of triethylamine (Et_3N), followed by reduction with lithium triethylborohydride ($LiEt_3BH$)[14] in tetrahydrofuran (THF) afforded (*S*)-(+)-**5k** or (*R*)-(−)-**5k** (Chart 6).

Structure–Activity Relationships The compounds prepared in this paper were evaluated for *in vitro* inhibitory activity on 12-HETE release from human platelets. During our search to find novel inhibitors of 12-HETE release, we found that cilostazol having a tetrazole group in the side chain showed inhibitory activity. We focused our attention upon the tetrazole group and synthesized simple N-alkylated azoles (**2a**—**g**) to see how the azole group influences the activity. Compounds **2d** and **2e** with a tetrazole group on the side chain retained the potency, but replacement of tetrazole by other azoles [pyrrole (**2a**), imidazole (**2b**) and 1,2,4-triazole (**2c**)] resulted in loss of the potency. Compound **2f**, containing a 2-phenylthioimi-



a) NaCN /DMF; b) anhydrous HCl, methanol /CH_2Cl_2; c) NH_4Cl /ethanol; d) 40% aq. $ClCH_2CHO$, K_2CO_3 / DMF; e) allyl bromide, KOH / DMF

Chart 4



a) i: cumene hydroperoxide, $Ti(O\text{-}i\text{-}Pr)_4$, (-) or (+)-diethyl tartrate / $ClCH_2CH_2Cl$, ii: recrystallization

Chart 5

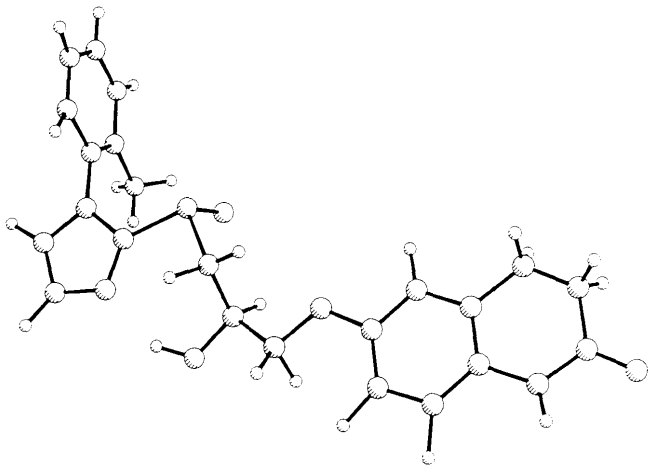
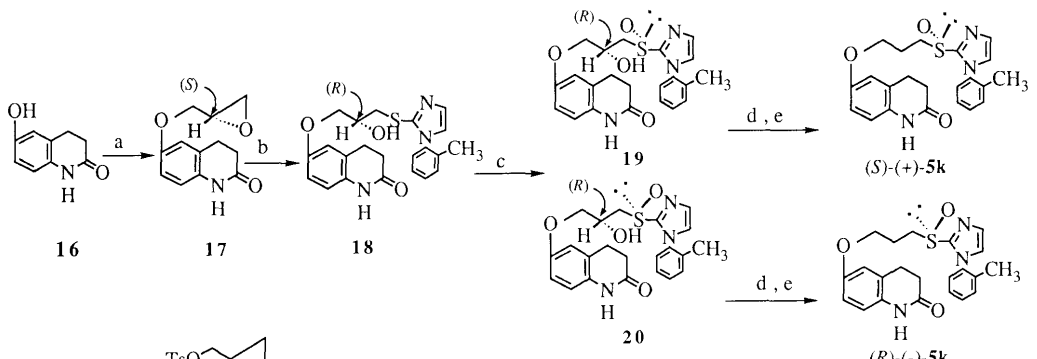


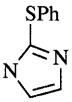
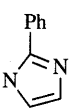
Fig. 2. A Perspective View of **20**



a) TsO, H, O, NaH / DMF;
b) i: 1-*o*-tolyl-2-mercaptoimidazole, DBu / 2-propanol, ii: recrystallization; c) i: mCPBA /CH_2Cl_2, ii: separation;
d) MsCl, Et_3N / CH_2Cl_2; e) $LiEt_3BH$ / THF

Chart 6

Table 1. Physical and Biological Properties of 2(1*H*)-Quinolinones

Compd. No.	R	Yield (%)	mp (°C) (Recryst. solvent)	Formula	Analysis (%) Calcd (Found) C	H	N	Inhibition of 12-HETE release IC_{50} (μM)
2a		17	127.5—130 ($CHCl_3$–Et_2O)	$C_{16}H_{18}N_2O_2$	71.09 (69.95	6.71 6.59	10.36 10.05)	>100
2b		42	102—103.5 (CH_2Cl_2–hexane)	$C_{15}H_{17}N_3O_2$	66.40 (66.31	6.32 6.30	15.49 15.49)	>100
2c		37	120.5—122 (EtOH–hexane)	$C_{14}H_{16}N_4O_2$	61.75 (61.57	5.92 5.81	20.58 20.37)	>100
2d		34	129.5—130 (EtOH–Et_2O)	$C_{13}H_{15}N_5O_2$	57.13 (57.33	5.53 5.61	25.63 25.79)	31
2e		31	151—152 (EtOH–Et_2O)	$C_{13}H_{15}N_5O_2$	57.13 (56.91	5.53 5.41	25.63 25.79)	6.4
2f		72	150.5—151.5 (EtOH–hexane)	$C_{21}H_{21}N_3O_2S$	66.46 (66.45	5.58 5.50	11.07 10.71)	9.0
2g		52	161—162 (AcOEt)	$C_{21}H_{21}N_3O_2$	72.60 (72.66	6.09 6.09	12.10 12.15)	>100
Cilostazol								25

dazole moiety, was more potent than cilostazol. But **2g**, in which the phenylthio group on the imidazole ring was replaced by a phenyl group, showed dramatically lower activity (Table 1).

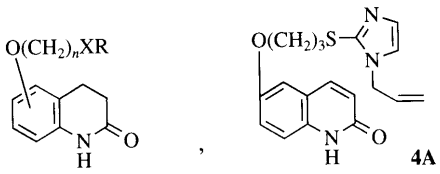
We focused our attention upon the 2-thioimidazole group. We found first a potent 1-allyl-2-thioimidazole (**4b**), and selected this as a lead compound. Then several N-allyl derivatives were synthesized and their activities were evaluated. The results are shown in Table 2. Their structure–activity relationships may be summarized as follows.

The 3,4-dihydro-2(1*H*)-quinolinone derivative (**4b**) was more active than the 2(1*H*)-quinolinone derivative (**4A**). The 6-substituted isomer (**4b**) showed stronger activity than the positional isomers (**4f—h**) when the side chain was retained. Therefore further comparisons of the effects of various substituents were made within the 6-substituted isomer. The effect of methylene chain length (n) was examined. The highest activity appeared at $n=3$ (**4b**). Shortening or lengthening of the chain resulted in reduction of the activity (**4c—e**). The order as regards the azole was 2-imidazolyl (**4b**) > 1,2,4-triazol-3-yl (**8**) ≫ 5-tetrazolyl (**10**). The order for the linking group between the side chain and the azole was S(O) (**5a**) ≧ CH_2 (**15**) ≧ S(**4b**) > SO_2 (**6a**).

We selected the sulfoxide **5a** for further study to improve the activity and tried to modify the substituent at the 1-position of imidazole. The results are shown in Table 3. The introduction of a phenyl group (**5j**) instead of the allyl group (**5a**) reduced the activity, but the introduction of an *o*-tolyl group (**5k**) increased the potency. The introduction of a 2-pyridyl (**5l**) or a 1-naphthyl (**5n**) group retained high potency. A 2-(3-methyl)pyridyl group (**5m**), however, resulted in reduction of the potency.

We next focused our attention upon the substituent on the benzene ring of **5k**. The *ortho*-substituted compound **5k** had higher activity than *para*-substituted **5p**, while *meta*-substituted **5o** exhibited loss of the potency. Therefore, further comparisons of the effect of various substituents were made within the *ortho*-substituted isomer. We introduced various substituents at the *ortho* position on the benzene ring to optimize the 1-phenylimidazole system. The introduction of a nitro group (**5x**) instead of the methyl group (**5k**) retained high potency, and the introduction of various other groups [ethyl (**5r**), halogen (**5u—w**), trifluoromethyl (**5q**), hydroxy (**5s**), methoxy (**5t**) and amino (**5y**)] decreased the potency. This indicates that an *ortho*-methyl group is necessary for the 1-phenylimidazole system to show high activity. Compound **5z**, with one more methyl group at the *para* position on the benzene ring of **5k**, was weak. Further modification of the benzene ring was not attempted. Compound **5k** was more active than its dehydro derivative **5A**, sulfide **4i**, sulfone **6b** or **5k1—3** ($n=2$, 4 and 6). These results indicated that **5k** might be optimum for the inhibitory activity. Since **5k** is racemic, the potency of the two enantiomers was compared. The order of the potency was found to be (*R*)-(−)-**5k** ≧ (±)-**5k** ≒ (*S*)-(+)-**5k**.

Table 2. Physical and Biological Properties of 2(1*H*)-Quinolinones



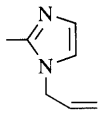
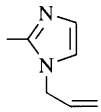
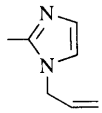
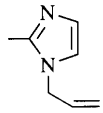
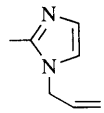
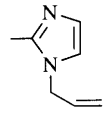
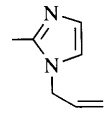
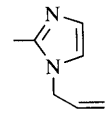
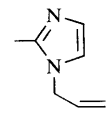
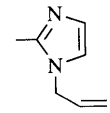
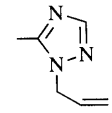
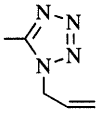
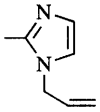
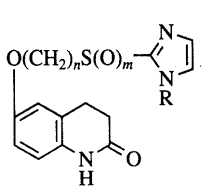
Compd. No.	Position	*n*	X	R	Yield[a] (%)	mp (°C) (Recryst. solvent)	Formula	Analysis (%) Calcd (Found) C	H	N	Inhibition of 12-HETE release IC_{50} (μM)
3a	6	3	S		61	189.0—190.0 ($CHCl_3$–MeOH–hexane)	$C_{15}H_{17}N_3O_2S$	59.38 (59.42	5.65 5.60	13.85 13.75)	60
4a	6	3	S		34	120.5—121.0 (EtOH–hexane)	$C_{17}H_{21}N_3O_2S$	61.60 (61.59	6.39 6.38	12.68 12.55)	>100
4b	6	3	S		21	92—93 (EtOH–hexane)	$C_{18}H_{21}N_3O_2S$	62.95 (62.56	6.16 6.23	12.24 12.26)	2.3
4c	6	2	S		57	108—109 (CH_2Cl_2–Et_2O)	$C_{17}H_{19}N_3O_2S$	61.98 (62.09	5.81 5.74	12.76 12.51)	>100
4d	6	4	S		31	78—79 (CH_2Cl_2–Et_2O)	$C_{19}H_{23}N_3O_2S$	63.84 (63.69	6.49 6.36	11.75 11.57)	>100
4e	6	5	S		46	90—91 (CH_2Cl_2–Et_2O)	$C_{20}H_{25}N_3O_2S$	64.66 (64.63	6.78 6.73	11.31 11.01)	>100
4f	5	3	S		41	102—103 (CH_2Cl_2–Et_2O)	$C_{18}H_{21}N_3O_2S$	62.95 (62.88	6.16 6.15	12.24 12.03)	31
4g	7	3	S		51	75.5—76.5 (EtOH–hexane)	$C_{18}H_{21}N_3O_2S$	62.95 (62.88	6.16 6.12	12.24 12.16)	55
4h	8	3	S		10	75—76 (iso-Pr_2O)	$C_{18}H_{21}N_3O_2S$	62.95 (62.77	6.16 5.96	12.23 12.13)	>100
4A	6	3	S		13	182—183 (EtOH–hexane)	$C_{18}H_{19}N_3O_3$	63.32 (60.46	5.61 5.32	12.31 11.72)	15
5a	6	3	S(O)		4.2	146.5—147.5 (EtOH–hexane)	$C_{18}H_{21}N_3O_3S$	60.15 (60.04	5.89 6.02	11.69 11.58)	1.1
6a	6	3	$S(O)_2$		7.6	106.5—107.5 (EtOH–hexane)	$C_{18}H_{21}N_3O_4S$	57.59 (57.45	5.64 5.65	11.19 11.21)	3.6
8	6	3	S		17	75—76.5 (EtOH–Et_2O)	$C_{17}H_{20}N_4O_2S$	59.28 (59.14	5.85 5.83	16.27 16.19)	8.4

Table 2. (continued)

Compd. No.	Position	*n*	X	R	Yield[a] (%)	mp (°C) (Recryst. solvent)	Formula	Analysis (%) Calcd (Found) C	H	N	Inhibition of 12-HETE release IC_{50} (μM)
10	6	3	S		35	120—122 (CH_2Cl_2–Et_2O)	$C_{16}H_{19}N_5O_2S$	55.64 (55.48	5.54 5.55	20.27 20.22)	>100
15	6	4	—		3.7	105—106.5 (EtOH–hexane)	$C_{19}H_{23}N_3O_2S$	63.13 (63.13	5.30 5.29	14.72 14.81)	1.5

a) Overall yield from **1b** or **1c**.

Table 3. Physical and Biological Properties of 3,4-Dihydro-2(1*H*)-quinolinones



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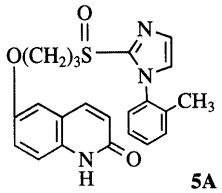


5A

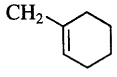
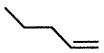
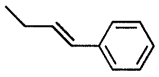
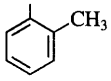
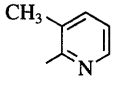
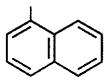
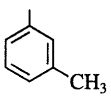
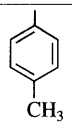
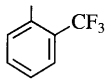
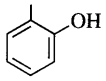
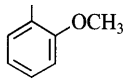
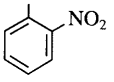
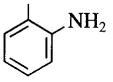
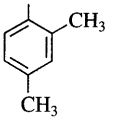
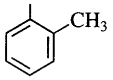
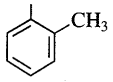
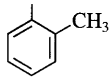
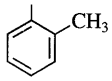
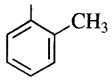
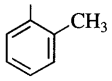
Compd. No.	*n*	*m*	R	Yield[a] (%)	mp (°C) (Recryst. solvent)	Formula	Analysis (%) Calcd (Found) C	H	N	Inhibition of 12-HETE release IC_{50} (μM)
5b	3	1	H	18	173.5—175 (CH_2Cl_2–hexane–MeOH)	$C_{15}H_{17}N_3O_3S$	55.63 (55.33	5.45 5.27	12.97 12.66)	7.0
5c	3	1	Et	77	152—153 (EtOH–hexane)	$C_{17}H_{21}N_3O_3S$	58.77 (58.75	6.09 6.06	12.09 11.99)	>100
5d	3	1		22	143—144 (CH_2Cl_2–Et_2O)	$C_{19}H_{23}N_3O_3S$	61.10 (60.89	6.21 6.38	11.25 10.99)	>100
5e	3	1		31	141.5—143 (EtOH–hexane)	$C_{18}H_{19}N_3O_3S$	60.49 (60.17	5.36 5.01	11.76 11.50)	5.0
5f	3	1		28	88—89 (iso-Pr_2O–EtOH)	$C_{22}H_{27}N_3O_3S$	63.90 (63.72	6.58 6.60	10.16 10.00)	4.0
5g	3	1		27	100.5—101.5 (iso-Pr_2O–EtOH)	$C_{19}H_{23}N_3O_3S$	61.10 (60.93	6.21 6.05	11.25 11.16)	3.4
5h	3	1	CH_2CONEt_2	27	159.5—161 (iso-Pr_2O–EtOH)	$C_{21}H_{28}N_4O_2S$	58.31 (58.17	6.52 6.33	12.95 12.85)	>100
5i	3	1		26	148–149 (EtOH–hexane)	$C_{24}H_{25}N_3O_3S$	66.18 (66.14	5.79 5.71	9.65 9.39)	2.6
5j	3	1		59	192.5—193.5 (CH_2Cl_2–hexane)	$C_{21}H_{21}N_3O_3S$	63.78 (63.52	5.35 5.24	10.62 10.49)	26
5k	3	1		50	141.5—142.5 (EtOH–hexane)	$C_{22}H_{23}N_3O_3S$	64.52 (64.62	5.66 5.57	10.26 10.13)	0.73
5l	3	1		41	172—173 (CH_2Cl_2–Et_2O)	$C_{20}H_{20}N_4O_3S$	60.59 (60.24	5.08 4.80	14.13 14.04)	1.3
5m	3	1		36	125–126 (CH_2Cl_2–Et_2O)	$C_{21}H_{22}N_4O_3S$	60.78 (60.78	5.47 5.08	13.50 13.43)	4.0
5n	3	1		38	197—198 (CH_2Cl_2–Et_2O)	$C_{25}H_{23}N_3O_3S$	66.72 (66.96	5.26 5.18	9.34 9.47)	1.6
5o	3	1		43	129–131 (EtOH–hexane)	$C_{22}H_{23}N_3O_3S$	64.53 (64.28	5.66 5.65	10.26 10.16)	>100

Table 3. (continued)

Compd. No.	*n*	*m*	R	Yield[a] (%)	mp (°C) (Recryst. solvent)	Formula	Analysis (%) Calcd (Found) C	H	N	Inhibition of 12-HETE release IC_{50} (μM)
5p	3	1		59	165—166 (iso-Pr_2O)	$C_{22}H_{23}N_3O_3S$	64.53 (64.13	5.66 5.57	10.26 10.06)	3.2
5q	3	1		30	141—143 (CH_2Cl_2–hexane)	$C_{22}H_{20}N_3O_3S$	57.01	4.35	9.07	22
5r	3	1		20	138—139 (EtOH–hexane)	$C_{23}H_{25}N_3O_3S$	65.23 (65.13	5.95 5.78	9.92 9.88)	6.4
5s	3	1		44	177—178 (CH_2Cl_2–Et_2O)	$C_{21}H_{21}N_3O_4S$	60.64 (60.44	5.21 4.91	10.10 9.92)	12
5t	3	1		37	165—166 (iso-Pr_2O)	$C_{22}H_{23}N_3O_3S$	62.10 (61.82	5.45 5.53	9.88 9.88)	29
5u	3	1		47	163.5—164.5 (EtOH–hexane)	$C_{21}H_{20}N_3O_3S$	61.00 (61.13	4.88 4.73	10.16 10.17)	8.5
5v	3	1		51	132—134 (iso-Pr_2O–EtOH)	$C_{21}H_{20}N_3O_3S$	58.67 (58.41	4.69 4.56	9.77 9.63)	5.2
5w	3	1		41	168—170 (EtOH–hexane)	$C_{21}H_{20}N_3O_3$	53.17 (53.26	4.25 4.29	8.86 8.78)	6.8
5x	3	1		62	135 (dec.) (iso-Pr_2O–EtOH)	$C_{21}H_{20}N_4O_5$	57.26 (56.97	4.58 4.61	12.72 12.78)	1.3
5y	3	1		56	165—167 (iso-Pr_2O–EtOH)	$C_{21}H_{22}N_4O_3S$	61.45 (61.07	5.40 5.09	13.65 13.48)	25
5z	3	1		33	111—112.5 (iso-Pr_2O–EtOH)	$C_{23}H_{25}N_3O_3S \cdot 1/4H_2O$	64.54 (64.61	6.00 6.01	9.82 9.68)	13
4i	3	0		58	136.5—137 (EtOH–hexane)	$C_{22}H_{23}N_3O_2S$	67.15 (67.41	5.89 5.98	10.68 10.82)	1.3
6b	3	2		17	138—142 (EtOH–hexane)	$C_{22}H_{23}N_3O_4S$	62.10 (62.01	5.45 5.37	9.88 9.82)	>100
5k1	2	1		41	141.5—142.5 (EtOH–hexane)	$C_{21}H_{21}N_3O_3S$	63.78 (63.61	5.35 5.31	10.62 10.65)	64
5k2	4	1		35	141.5—142.5 (EtOH–hexane)	$C_{23}H_{25}N_3O_3S$	65.23 (64.96	5.95 5.76	9.92 9.77)	>100
5k3	6	1		58	118—120 (EtOH–hexane)	$C_{25}H_{29}N_3O_3S$	66.49 (66.48	6.47 6.40	9.30 9.24)	>100
5A	3	1		36	141.5—142.5 (EtOH–hexane)	$C_{21}H_{21}N_3O_3S$	63.78 (63.61	5.35 5.31	10.62 10.65)	12
(*S*)-(+)-**5k**										0.80
(*R*)-(−)-**5k**										0.48
Esculetin										5.4

a) Overall yield from **1**.

Table 4. Inhibitory Activity on Platelet Adhesion *in Vivo* in Rats[a)]

Compound No.	Dose (mg/kg, *p.o.*)	Inhibition (%)
5a	30	63
(±)-**5k**	30	76
S-(+)-**5k**	30	70
R-(−)-**5k**	30	70
Cilostazol	100	8
Esculetin	60	43

a) Each value is the mean from three or more animals.

These four highly active compounds [(*S*)-(+)-**5k**, (*R*)-(−)-**5k**, (±)-**5k** and **5a**)], together with cilostazol and esculetin,[15] were tested for *in vivo* inhibitory activity on platelet adhesion in rats. The data are listed in Table 4. Cilostazol showed no effect, while (*S*)-(+)-**5k**, (*R*)-(−)-**5k** and (±)-**5k** showed higher potency than esculetin or **5a**. In addition, (*S*)-(+)-**5k** induced weaker changes of the blood pressure and heart rate than (*R*)-(−)-**5k** and (±)-**5k** when administered orally in dogs. Overall, (*S*)-(+)-**5k** had the best pharmacological profile and it was selected for further testing as a candidate drug.

Experimental

Melting points were determined with a Yamato MP-21 apparatus and are uncorrected. NMR spectra were recorded in $CDCl_3$ or deuteriodimethyl sulfoxide (DMSO-d_6) on a Bruker AC-250 spectrometer with tetramethylsilane (TMS) as an internal standard. Optical rotations were measured on a DIP-360 digital polarimeter (Japan Spectroscopic Co., Ltd.). Elemental analyses were determined on a Yanaco MT-5 CHN Corder. HPLC was performed with a Shimadzu LC-6A liquid chromatograph and an SPD-6A ultraviolet spectrophotometric detector. Column chromatography on silica gel was performed with Kieselgel 60 (E. Merck, No. 7734).

3,4-Dihydro-6-[3-(imidazo-1-yl)propoxy]-2(1*H*)-quinolinone (2b) A mixture of 6-(3-bromopropoxy)-3,4-dihydro-2(1*H*)-quinolinone[16] (**1a**) (2.0 g, 17 mmol), imidazole (0.62 g, 9.4 mmol) and 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU, 1.2 ml, 7.7 mmol) in 2-propanol (50 ml) was stirred under reflux for 15 h. The mixture was concentrated *in vacuo* and the residue was extracted with $CHCl_3$. The extract was washed with water, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, CH_2Cl_2 : MeOH = 50 : 1) and the product was recrystallized from CH_2Cl_2–hexane to give **2b** (0.80 g, 42%) as colorless prisms. ^{1}H-NMR ($CDCl_3$) δ: 2.12—2.32 (2H, m), 2.57—2.68 (2H, m), 2.82—3.00 (2H, m), 3.86 (2H, t, J = 6.0 Hz), 4.18 (2H, t, J = 7.0 Hz), 6.63—6.80 (3H, m), 6.92 (1H, s), 7.07 (1H, s), 7.48 (1H, s), 8.79 (1H, br s). Compounds **2a** and **2c—g** were similarly prepared.

3,4-Dihydro-6-[3-(2-imidazolyl)thiopropoxy]-2(1*H*)-quinolinone (3a) A mixture of **1b** (2.0 g, 7.0 mmol), 2-mercaptoimidazole (0.85 g, 8.5 mmol) and DBU (1.3 ml, 19 mmol) in 2-propanol (50 ml) was stirred under reflux for 3 h and concentrated *in vacuo*. The residue was poured into water. The precipitate was collected by filtration, washed with $CHCl_3$, and purified by column chromatography (silica gel; eluent, $CHCl_3$: MeOH = 30 : 1), followed by recrystallization from $CHCl_3$–MeOH–hexane to give **3a** (1.3 g, 61%) as colorless needles. ^{1}H-NMR (DMSO-d_6) δ: 1.90—2.05 (2H, m), 2.35—2.47 (2H, m), 2.80—2.90 (2H, m), 3.08 (2H, t, J = 7.0 Hz), 3.98 (2H, t, J = 6.2 Hz), 6.71—6.83 (3H, m), 7.05 (2H, br s), 9.90 (1H, br s), 12.27 (1H, br s). Compound **7** was similarly prepared.

3,4-Dihydro-6-[3-(1-allyl-2-imidazolyl)thiopropoxy]-2(1*H*)-quinolinone (4b) A mixture of **3a** (2.0 g, 6.6 mmol), allyl bromide (0.80 g, 6.6 mmol) and KOH (0.44 g, 6.6 mmol) in DMF (60 ml) was stirred at 80 °C for 3 h. After cooling, the reaction mixture was filtered through a Celite pad, and the filtrate was concentrated *in vacuo*. The residue was extracted with $CHCl_3$–AcOEt. The extract was washed with water, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, CH_2Cl_2 : MeOH = 30 : 1) and recrystallized from EtOH–hexane to give **4b** (0.80 g, 35%) as colorless needles. ^{1}H-NMR ($CDCl_3$) δ: 2.08—2.22 (2H, m), 2.57—2.67 (2H, m), 2.88—2.98 (2H, m), 3.21 (2H, t, J = 7.0 Hz), 4.03 (2H, t, J = 6.0 Hz), 4.52—4.62 (2H, m), 5.08 (1H, dd, J = 1.0, 17.0 Hz), 5.24 (1H, dd, J = 1.0, 10.3 Hz), 5.89 (1H, s), 6.65—6.77 (3H, m), 6.95 (1H, d, J = 1.3 Hz), 7.10 (1H, d, J = 1.3 Hz), 8.33 (1H, br s). Compounds **4a**, **4c—h**, **4A** and **15** were similarly prepared.

3,4-Dihydro-6-[3-(1-*o*-tolyl-2-imidazolyl)thiopropoxy]-2(1*H*)-quinolinone (4i) A mixture of **1a** (2.0 g, 8.4 mmol), 1-*o*-tolyl-2-mercaptoimidazole (1.9 g, 10 mmol) and DBU (1.4 ml, 10 mmol) in 2-propanol (50 ml) was stirred under reflux for 5 h and concentrated *in vacuo*. The residue was extracted with $CHCl_3$. The extract was washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, $CHCl_3$: MeOH = 30 : 1) and recrystallized from EtOH–hexane to give **4i** (1.9 g, 58%) as colorless prisms. ^{1}H-NMR ($CDCl_3$) δ: 1.92—2.30 (2H, m), 2.06 (3H, s), 2.62—2.72 (2H, m), 2.75—3.02 (2H, m), 3.20 (2H, t, J = 7 Hz), 3.95 (2H, t, J = 6 Hz), 6.50—6.90 (3H, m), 6.96 (1H, d, J = 1.0 Hz), 7.06—7.43 (5H, m), 9.62 (1H, br s). Compound **10** was similarly prepared.

3,4-Dihydro-6-[3-(1-*o*-tolyl-2-imidazolyl)sulfinylpropoxy]-2(1*H*)-quinolinone (5k) mCPBA (70%, 0.49 g, 2.5 mmol) was added portionwise to a solution of **4i** (1.0 g, 2.5 mmol) in $CHCl_3$ (50 ml) at 0 °C. The resulting mixture was stirred at room temperature overnight. The mixture was washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, CH_2Cl_2 : MeOH : AcOEt = 60 : 1 : 20) and the product was recrystallized from EtOH–hexane to give **5k** (0.88 g, 86%) as a white powder. ^{1}H-NMR ($CDCl_3$) δ: 2.10 (3H, br s), 2.10—2.30 (2H, m), 2.55—2.70 (2H, m), 2.88—3.02 (2H, m), 3.50 (1H, m), 3.68 (1H, m), 3.98—4.15 (2H, m), 6.60—6.73 (3H, m), 7.15 (1H, d, J = 1.1 Hz), 7.22—7.52 (5H, m), 8.37 (1H, br s). Other compounds **5** were similarly prepared.

3,4-Dihydro-6-[3-(1-*o*-tolyl-2-imidazolyl)sulfonylpropoxy]-2(1*H*)-quinolinone (6b) mCPBA (70%, 0.56 g, 2.7 mmol) was added portionwise to a solution of **5k** (1.0 g, 2.44 mmol) in $CHCl_3$ (50 ml) under ice cooling. The resulting mixture was stirred at room temperature overnight. The mixture was washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, CH_2Cl_2 : MeOH : AcOEt = 30 : 1 : 10) and the product was recrystallized from EtOH–2-propanol to give **6b** (0.88 g, 86%) as a white powder. ^{1}H-NMR ($CDCl_3$) δ: 2.12 (3H, s), 2.25—2.40 (2H, m), 2.57—2.67 (2H, m), 2.88—2.98 (2H, m), 3.57—3.67 (2H, m), 4.02 (2H, t, J = 5.9 Hz), 6.60—6.73 (3H, m), 7.09 (1H, d, J = 1.1 Hz), 7.30—7.50 (5H, m), 7.69 (1H, br s). Other compound **6a** was similarly prepared.

6-[3-(1-Allyl-1,2,4-triazol-5-yl)thiopropoxy]-3,4-dihydro-2(1*H*)-quinolinone (8) and 6-[3-(1-Allyl-1,2,4-triazol-3-yl)thiopropoxy]-3,4-dihydro-2(1*H*)-quinolinone (9) A mixture of **7** (5.8 g, 19 mmol), allyl bromide (1.65 ml, 19 mmol) and KOH (1.28 g, 19 mmol) in DMF (100 ml) was stirred at 0 °C for 3 h. Saturated aqueous NH_4Cl was added to the mixture. The mixture was concentrated *in vacuo* and the residue was extracted with $CHCl_3$–AcOEt. The extract was washed with water, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, AcOEt), and then by HPLC [column, TSK-80TM (21.5 mm × 300 mm); mobile phase, acetonitrile–water (30 : 70)]. The product from the first eluates was recrystallized from EtOH–ether to give **9** (1.58 g, 24%) as a white powder, mp 110—111 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.15—2.38 (2H, m), 2.57—2.68 (2H, m), 2.88—2.98 (2H, m), 3.29 (2H, t, J = 6.9 Hz), 4.06 (2H, t, J = 6.0 Hz), 4.71 (2H, t, J = 6.1 Hz), 5.83 (1H, d, J = 16.9 Hz), 5.88 (1H, d, J = 10.1 Hz), 5.99 (1H, m), 6.67—6.88 (3H, m), 8.01 (1H, s), 8.63 (1H, br s). *Anal.* Calcd for $C_{17}H_{20}N_4O_2S$: C, 59.28; H, 5.85; N, 16.27. Found: C, 59.00; H, 5.73; N, 16.25. Further elution gave another product, which was recrystallized from EtOH–ether to give **8** (0.49 g, 7.5%). ^{1}H-NMR ($CDCl_3$) δ: 2.15—2.38 (2H, m), 2.57—2.68 (2H, m), 2.90—3.00 (2H, m), 3.40 (2H, t, J = 7.0 Hz), 4.04 (2H, t, J = 5.9 Hz), 4.65—4.75 (2H, m), 5.16 (1H, dd, J = 17.1, 1.0 Hz), 5.28 (1H, dd, J = 1.0, 10.3 Hz), 5.93 (1H, m), 6.67—6.88 (3H, m), 7.87 (1H, s), 8.43 (1H, br s).

6-(4-Cyanobutoxy)-3,4-dihydro-2(1*H*)-quinolinone (11) A mixture of 6-(4-chlorobutoxy)-3,4-dihydro-2(1*H*)-quinolinone (**1c**) (28.6 g, 95.7 mmol) and NaCN (5.7 g, 115 mmol) in dimethyl sulfoxide (DMSO, 270 ml) was stirred at 70 °C for 2 h, then diluted with brine (700 ml). The precipitate was collected by filtration, washed with water and ether, and dried to give crude **11** (20.5 g, 88%) as a white powder. This was used

in the following reaction without further purification.

Methyl 4-[3,4-Dihydro-6-2(1*H*)-quinolinolyloxy]butyrimidate (12) Anhydrous HCl was bubbled into a solution of **11** (10 g, 43 mmol) and MeOH (30 ml) in CH_2Cl_2 (300 ml) until it was saturated. The mixture was allowed to stand at room temperature for 8 h and diluted in ether. The precipitate was collected by filtration and dissolved in CH_2Cl_2. The solution was washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was recrystallized from CH_2Cl_2–ether to give **12** (8.8 g, 73%) as a white powder, mp 107—108 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.70—1.88 (4H, m), 2.33 (2H, t, J=7.1 Hz), 2.57—2.67 (2H, m), 2.90—3.00 (2H, m), 3.71 (3H, s), 3.93 (2H, t, J=5.7 Hz), 6.68—6.78 (3H, m), 8.58 (1H, br s).

4-[3,4-Dihydro-6-2(1*H*)-quinolinolyloxy]butyramidine Hydrochloride (13) NH_4Cl (10.5 g, 10 mmol) was added to a solution of **12** (2.8 g, 10 mmol) in EtOH (75 ml). The mixture was stirred at room temperature overnight and diluted with ether. The precipitate was collected by filtration to give **13** (2.9 g, quant) as a white powder, mp 190—191 °C (EtOH–ether). ^{1}H-NMR ($CDCl_3$) δ: 1.65—1.88 (4H, m), 2.40—2.57 (4H, m), 2.80—2.90 (2H, m), 6.70—6.88 (3H, m), 8.78 (2H, br s), 9.11 (2H, br s), 9.97 (1H, br s).

3,4-Dihydro-6-[4-(2-imidazolyl)butoxy]-2(1*H*)-quinolinone (14) K_2CO_3 (1.4 g, 10 mmol) was added to a suspension of **13** (3.9 g, 61 mmol) in DMF (30 ml) and the mixture was stirred at room temperature for 0.5 h. A 40% aqueous solution of $ClCH_2CHO$ (0.55 ml, 4.0 mmol) was added to the mixture. The whole was stirred at 60 °C for 1 h, then concentrated *in vacuo*, and the residue was extracted with CH_2Cl_2. The extract was washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, CH_2Cl_2 : MeOH = 8 : 1) and recrystallized from EtOH–hexane to give **14** (0.10 g, 10%) as a colorless solid. ^{1}H-NMR (DMSO-d_6) δ: 1.60—1.80 (4H, m), 2.32—2.40 (2H, m), 2.62—2.70 (2H, m), 2.75—2.87 (2H, m), 3.88 (2H, d, J=6.0 Hz), 6.65—6.78 (3H, m), 6.88 (2H, s), 9.91 (1H, br s).

3,4-Dihydro-6-(2,3-epoxypropoxy)-2(1*H*)-quinolinone (17) 3,4-Dihydro-6-hydroxy-2(1*H*)-quinolinone (**16**) (10 g, 61 mmol) was added in small portions to a suspension of NaH (60%, 2.5 g, 61 mmol) in dry DMF (200 ml) with stirring at room temperature. The mixture was stirred for 1 h. A solution of (2*S*)-(+)-glycidyl tosylate (14 g, 61 mmol, *ca.* 91% ee) in DMF (100 ml) was then added dropwise over a period of 15 min and the whole was stirred at room temperature for 96 h. It was poured into ice-water (600 ml) and extracted with AcOEt (600 ml × 3). The extracts were combined, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, CH_2Cl_2 : MeOH = 20 : 1) to give **17** (8.3 g, 62%) as an amorphous powder. ^{1}H-NMR ($CDCl_3$) δ: 2.60—2.68 (2H, m), 2.74 (1H, dd, J=2.7, 4.9 Hz), 2.88—3.00 (3H, m), 3.35 (1H, m), 3.91 (1H, dd, J=5.7, 11.1 Hz), 4.21 (1H, dd, J=3.1, 11.1 Hz), 6.65—6.80 (3H, m), 7.92 (1H, br s). Unreacted **16** (3.0 g, 30%) was recovered.

(*R*)-(+)-3,4-Dihydro-6-[2-hydroxy-3-(1-*o*-tolyl-2-imidazolyl)thiopropoxy]-2(1*H*)-quinolinone [(*R*)-(+)-18] A mixture of **17** (7.8 g, 36 mmol) and 2-mercapto-1-*o*-tolylimidazole (6.8 g, 36 mmol) in DMF (80 ml) was stirred at 80 °C for 8 h. The reaction mixture was concentrated *in vacuo* to dryness. The residue was purified by column chromatography (silica gel; eluent, CH_2Cl_2 : MeOH = 20 : 1) to give (*R*)-(+)-**18** (11 g, 76%), optical purity (by HPLC): 83% ee. The crystalline material was recrystallized 3 times from EtOH to give (*R*)-(+)-**18** (6.8 g, 46%), optical purity (by HPLC): 99.6% ee. $[\alpha]_D^{25}$ +8.2° (c=1.0, MeOH). ^{1}H-NMR ($CDCl_3$) δ: 2.10 (3H, s), 2.58—2.70 (2H, m), 2.88—3.00 (2H, m), 3.30 (1H, m), 3.43 (1H, m), 4.01 (1H, m), 4.10 (1H, m), 4.40 (1H, m), 6.65—6.83 (3H, m), 6.98 (1H, d, J=1.4 Hz), 7.12 (1H, d, J=1.4 Hz), 7.15—7.50 (4H, m), 8.11 (1H, br s). *Anal.* Calcd for $C_{22}H_{23}N_3O_3S \cdot 1/4H_2O$: C, 63.82; H, 5.72; N, 10.15. Found: C, 64.09; H, 5.62; N, 9.94.

HPLC Analysis Chromatographic conditions were as follows: column, ULTRON ES-OVM (4.6 mm × 150 mm); mobile phase, acetonitrile–20 mM potassium dihydrogen phosphate (KH_2PO_4) aq. (10 : 90); flow rate, 1.0 ml/min; detection, UV at 254 nm; retention time, (*S*)-(−)-**18**, 10.2 min; (*R*)-(+)-**18**, 11.5 min.

3,4-Dihydro-6-{2-hydroxy-3-[1-(2-methylphenyl)-2-imidazolyl]sulfinylpropoxy}-2(1*H*)-quinolinone (19 and 20) mCPBA (70%, 3.2 g, 13 mmol) was added portionwise to a solution of (*R*)-(+)-**18** (5.3 g, 13 mmol) in CH_2Cl_2 (160 ml) at 0 °C and the mixture was stirred at 0 °C for 10 min. It was washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography [silica gel (mesh 230—400); eluent, CH_2Cl_2 : MeOH = 50 : 1]. The product from the first eluate was recrystallized from EtOH to give **19** (2.2 g, 40%), mp 132—133 °C. $[\alpha]_D^{25}$ −16.1° (c=1.0, MeOH). Diastereomeric purity (by HPLC): 99.8% de. ^{1}H-NMR ($CDCl_3$) δ: 2.11 (3H, br s), 2.55—2.65 (2H, m), 2.88—2.98 (2H, m), 3.53—3.72 (2H, m), 4.02—4.15 (2H, m), 4.82 (1H, m), 5.57 (1H, m, OH), 6.65 (1H, d, J=8.7 Hz), 6.70—6.80 (2H, m), 7.17 (1H, d, J=1.4 Hz), 7.30—7.55 (4H, m), 7.38 (1H, d, J=1.4 Hz), 7.68 (1H, br s). *Anal.* Calcd for $C_{22}H_{23}N_3O_4S$: C, 62.10; H, 5.45; N, 9.88. Found: C, 61.81; H, 5.43; N, 9.81. Further elution gave another product, which was recrystallized from EtOH to give **20** (1.8 g, 33%), mp 168—169 °C. $[\alpha]_D^{25}$ −31.6° (c=1.0, MeOH). Diastereomeric purity (by HPLC): 99.5% de. ^{1}H-NMR ($CDCl_3$) δ 2.11 (3H, br s), 2.55—2.65 (2H, m), 2.88—2.98 (2H, m), 3.41 (1H, dd, J=9.9, 13.4 Hz), 3.95—4.15 (4H, m), 4.63 (1H, m), 6.65—6.75 (3H, m), 7.18 (1H, d, J=1.1 Hz), 7.23—7.50 (4H, m), 7.38 (1H, d, J=1.1 Hz), 8.34 (1H, br s). *Anal.* Calcd for $C_{22}H_{23}N_3O_4S \cdot 1/4H_2O$: C, 61.45; H, 5.51; N, 9.77. Found: C, 61.51; H, 5.47; N, 9.75.

HPLC Analysis Chromatographic conditions were as follows: column, TSK-80TM (4.6 mm × 150 mm); mobile phase, acetonitrile–water (25 : 75); flow rate, 1.0 ml/min; detection, UV at 254 nm; retention time, **20**, 12.2 min; **19**, 14.0 min.

X-Ray Analysis of 20 Crystal data: $C_{22}H_{23}N_3O_4S$, M_r=425.50, monoclinic, space group $P2_1$, a=8.098(2) Å, b=101.13(2) Å, c=17.907(3) Å, b=101.13(2)°, V=1052.8(6) Å^3, Z=2, D_c=1.342 g/cm^3, $F(000)$=448 and m (MoK_α)=1.78 cm^{-1}. The data were collected using the ω–2θ scan technique to a maximum 2θ value of 45°. Of the 1514 independent reflections which were collected, 1130 reflections (I>3s(I)) were used for the structure determination and refinement. The structure was solved using the program package TEXSAN.[17] Refinement by the full-matrix least-squares method with isotropic temperature factors was carried out for non-H atoms. At final convergence, R=0.042, R_w=0.049. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.17 and −0.18 eÅ^{-3}, respectively. Atomic coordinates for non-H atoms of **20** are given in Table 5.[18] Atomic scattering factors were taken from "International Tables for X-ray Crystallography."[19]

(*S*)-(+)-5k Methanesulfonyl chloride (0.40 ml, 5.2 mmol) was added

Table 5. Atomic Coordinates for the Non-H Atoms of **20**

Atom	x	y	z	B_{eq}
S(1)	0.3602 (2)	0.7217	0.3045 (1)	4.23 (9)
O(1)	−1.0264 (7)	1.001 (1)	0.0109 (4)	6.5 (3)
O(2)	−0.1487 (6)	0.6752 (8)	0.1842 (3)	5.2 (3)
O(3)	0.1289 (8)	0.318 (1)	0.2555 (4)	6.4 (4)
O(4)	0.2742 (6)	0.736 (1)	0.3698 (3)	5.7 (3)
N(1)	−0.7992 (7)	0.824 (1)	0.0379 (4)	3.7 (3)
N(2)	0.4701 (7)	0.367 (1)	0.2948 (4)	4.7 (3)
N(3)	0.6554 (7)	0.5500 (9)	0.3642 (3)	3.7 (3)
C(2)	−0.879 (1)	0.980 (1)	0.0426 (5)	4.4 (4)
C(3)	−0.776 (2)	1.124 (2)	0.086 (2)	10.5 (9)
C(4)	−0.616 (2)	1.094 (1)	0.124 (1)	8.7 (7)
C(5)	−0.375 (1)	0.873 (1)	0.1506 (5)	3.9 (4)
C(6)	−0.3103 (8)	0.702 (1)	0.1447 (4)	3.5 (3)
C(7)	−0.406 (1)	0.573 (1)	0.1020 (4)	3.3 (3)
C(8)	−0.568 (1)	0.616 (1)	0.0653 (5)	3.5 (4)
C(9)	−0.537 (1)	0.915 (1)	0.1152 (5)	3.6 (3)
C(10)	−0.6325 (8)	0.785 (1)	0.0723 (4)	2.9 (3)
C(11)	−0.081 (1)	0.500 (1)	0.1886 (6)	4.6 (4)
C(12)	0.081 (1)	0.497 (1)	0.2475 (5)	4.0 (4)
C(13)	0.206 (1)	0.627 (1)	0.2256 (5)	4.1 (4)
C(14)	0.4994 (9)	0.532 (1)	0.3205 (4)	3.6 (3)
C(15)	0.614 (1)	0.275 (1)	0.3241 (6)	5.2 (5)
C(16)	0.726 (1)	0.384 (1)	0.3667 (6)	4.9 (4)
C(17)	0.7321 (8)	0.706 (1)	0.4042 (4)	3.5 (3)
C(18)	0.7098 (8)	0.736 (1)	0.4754 (5)	4.4 (4)
C(19)	0.793 (1)	0.889 (1)	0.5163 (6)	4.9 (4)
C(20)	0.890 (1)	0.997 (2)	0.4770 (7)	5.8 (5)
C(21)	0.916 (1)	0.961 (1)	0.4076 (6)	5.0 (5)
C(22)	0.835 (1)	0.817 (1)	0.3683 (6)	4.3 (4)
C(23)	0.608 (2)	0.617 (2)	0.5176 (8)	6.6 (6)

The equivalent isotropic parameters B_{eq} (Å^2) are as follows: $B_{eq}=(8/3)\pi^2\Sigma_i\Sigma_j U_{ij}a_i^*a_j^*a_ia_j$.

dropwise to a solution of **19** (1.0 g, 2.4 mmol) and triethylamine (0.80 ml, 5.6 mmol) in CH_2Cl_2 (20 ml) at 0 °C. The mixture was stirred at room temperature for 0.5 h, then washed with saturated aqueous $NaHCO_3$ and water, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, CH_2Cl_2 : MeOH = 20 : 1) to give the methanesulfonate of **19** (1.1 g, 100%). ^{1}H-NMR ($CDCl_3$) δ: 2.12 (3H, br s), 2.55—2.65 (2H, m), 2.88—2.98 (2H, m), 3.07 (3H, s), 3.90 (1H, m), 4.05 (1H, m), 4.28—4.37 (2H, m), 5.32 (1H, m), 6.68—6.78 (3H, m), 7.20 (1H, d, J = 0.9 Hz), 7.25—7.50 (4H, m), 7.39 (1H, d, J = 0.9 Hz), 8.45 (1H, br s). This was employed for the next step without further purification. Lithium triethylborohydride ($LiEt_3BH$) (1 M solution in THF, 4.9 ml, 4.9 mmol) was added dropwise to a solution of methanesulfonate of **19** (1.1 g, 2.4 mmol) in dry THF (40 ml) at 0 °C. The reaction mixture was stirred at room temperature for 0.5 h, then cooled with an ice-bath, and the reaction was quenched by adding water. The THF solution was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, CH_2Cl_2 : AcOEt : MeOH = 3 : 1 : 0—30 : 10 : 1) and the product was recrystallized from AcOEt to give (*S*)-(+)-**5k** (0.76 g, 80%), mp 124.5—126.5 °C. $[\alpha]_D^{25}$ +16.9° (c = 1.0, MeOH). Optical purity (by HPLC): 98.8% ee. *Anal.* Calcd for $C_{22}H_{23}N_3O_3S$: C, 64.52; H, 5.66; N, 10.26. Found: C, 64.44; H, 5.70; N, 10.03.

(*R*)-(−)-5k In the same manner as described above. 1.2 g of **20** gave 1.3 g of methanesulfonate of **20** (90%). ^{1}H-NMR ($CDCl_3$) δ: 2.11 (3H, br s), 2.55—2.67 (2H, m), 2.88—3.00 (2H, m), 3.11 (3H, s), 3.57 (1H, m), 4.20—4.38 (2H, m), 4.43 (1H, dd, J = 4.0, 10.8 Hz), 5.38 (1H, m), 6.68—6.80 (3H, m), 7.20 (1H, d, J = 1.0 Hz), 7.25—7.55 (4H, m), 7.40 (1H, d, J = 1.0 Hz), 8.18 (1H, br s). 1.3 g of methanesulfonate of **20** gave 0.78 g (71%) of (*R*)-(−)-**5k**, mp 124—126 °C. $[\alpha]_D^{25}$ −16.6° (c = 1.0, MeOH). Optical purity (by HPLC): 98.9% ee. *Anal.* Calcd for $C_{22}H_{23}N_3O_3S$: C, 64.52; H, 5.66; N, 10.26. Found: C, 64.44; H, 5.66; N, 10.05.

HPLC Analysis Chromatographic conditions were as follows: column, ULTRON ES-OVM (4.6 mm × 150 mm); mobile phase, acetonitrile–20 mM aqueous KH_2PO_4 (8 : 92); flow rate, 1.0 ml/min; detection, UV at 254 nm; retention time, (*S*)-(+)-**5k**, 16.5 min; (*R*)-(−)-**5k**, 24.5 min.

Inhibition of 12(*S*)-HETE Release (*in Vitro* Assay) Blood from healthy volunteers was collected into plastic tubes containing ethylenediaminetetraacetic acid (EDTA, final concentration 0.1%). Platelet-rich plasma (PRP) was obtained by centrifugation of blood at 1100 × *g* for 10 min. Washed platelets were prepared from PRP and resuspended in Tris–Tyrode buffer (pH 7.4) containing EDTA (final concentration 0.1%) at a final concentration of 3×10^5 platelets/μl. The platelet suspension was preincubated with a solution of a test compound in DMF (final concentration 0.5%) for 2 min at 37 °C and the reaction was started by the addition of collagen (final concentration 30 μg/ml). The incubation lasted 5 min, then the reaction was terminated by cooling on ice. The solution was extracted by the method reported by Raghunath *et al.*[20] The concentration of 12(*S*)-HETE was measured by using the Titer Zyme 12(*S*)-HETE Enzyme Immunoassay Kit (PerSeptive Diagnostics, Inc.). Inhibition (percent) of 12(*S*)-HETE release was calculated as follows:

$$\text{inhibition (\%)} = [1-(X-S)/(Y-S)] \times 100$$

X: release with collagen and test compound
Y: release with collagen alone
S: spontaneous release

Inhibition of Platelet Adhesion in Rats (*in Vivo* Assay) Compounds were tested according to the reported procedures.[21] Male Wistar rats (6 weeks of age) were anesthetized with pentobarbital-Na. The thoracic aorta of rats was injured with a Forgarty 2F balloon catheter (Baxter Health Care Corporation). Test compound was administered orally 1 h before the ballooning. The interaction of platelets with the surface was measured by the reported method.[22] Percent coverage and inhibition (%) were calculated by using the following formulae:

$$\text{percent coverage} = [(C)+(A)+(T)/(N)+(C)+(A)+(T)] \times 100$$

(C): contact, (A): adhesion, (T): thrombus, (N): naked

$$\text{inhibition (\%)} = (1-X/Y) \times 100$$

X: percent coverage with test compound
Y: spontaneous percent coverage

References and Notes

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