Azole Phenoxy Hydroxyureas as Selective and Orally Active Inhibitors of 5-Lipoxygenase

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Azole phenoxy hydroxyureas are a new class of 5-lipoxygenase (5-LO) inhibitors. Structure−activity relationship studies have demonstrated that electronegative substituents on the 2-phenyl portion of the oxazole tail increased the *ex vivo* potency of these inhibitors. Similar substitutions on the thiazole analogs had only minor contribution to the *ex vivo* activity. The trifluoromethyl-substituted oxazole **24** was the best compound of the oxazole series in both the *ex vivo* (6 h pretreated rats) and *in vivo* (3 h pretreated rats) RPAR assay with ED_{50} values of approximately 1 and 3.6 mg/kg, respectively, but was weakly active in the allergic guinea pig assay. Oxazole **50** was equally active in both the RPAR and guinea pig *in vivo* models and was similar to zileuton. The unsubstituted thiazole **52** was the best compound of the thiazole series, by inhibiting the leukotriene B_4 biosynthesis in the RPAR assay (3 h pretreated rats) by 99%, at an oral dose of 10 mg/kg, and the bronchoconstriction in the allergic guinea pig by 50%, at an intravenous dose of 10 mg/kg. Oxazole **24** demonstrated high and selective 5-LO inhibitory activity in the *in vitro* assays, with IC_{50} values ranging from 0.08 μM in mouse macrophages to 0.8 μM in human peripheral monocytes to 1.2 μM in human whole blood. This activity was selective for 5-LO, as concentrations up to 15 μM in mouse macrophages did not affect prostaglandin formation. Oxazole **59** was the most active inhibitor in the human monocyte assay with an IC_{50} value of 7 nM.

Introduction

Leukotrienes (LTs) are a class of arachidonic acid metabolites, synthesized by leukocytes in response to a variety of inflammatory and immunological stimuli. 5-Lipoxygenase (5-LO), present in cells of the myeloid lineage (e.g., polymorphonuclear leukocytes (PMNs), eosinophils, macrophages, etc.), is the first enzyme in the metabolism of arachidonic acid to leukotriene A_4 (LTA_4).[1,2] Further metabolism of LTA_4, produces LTB_4,[3] a potent chemotactic agent for leukocytes that was thought to be a key component in a variety of inflammatory diseases,[4] including inflammatory bowel disease, rheumatoid arthritis, and psoriasis, and the peptidoleukotrienes LTC_4, LTD_4, and LTE_4,[3] which are implicated in allergic hyperreactivity disorders,[4] such as asthma.

Elevated levels of these LTs, associated with several inflammatory and allergic disorders, have been found in various pathologic tissues. Thus, compounds that restrict LT synthesis by inhibition of 5-LO will have therapeutic utility in such pathological conditions. Encouraging preliminary clinical results for some of these pathological conditions have been reported for zileuton,[5−7] the most clinically studied 5-LO inhibitor.

Numerous patents and publications on 5-LO inhibitors have appeared in the last several years. Pioneered by Abbott and Borroughs Wellcome scientists, structure−activity relationship (SAR) studies on the initial findings of Corey et al.[8] that hydroxamic acid analogs of arachidonic acid competitively inhibited 5-LO of rat basophilic leukemia cell line (RBL-1) led to the identification of the first potent and selective orally active 5-LO inhibitors.[9−15] To date, inhibitors of 5-LO can be separated into four distinct classes based on their putative mechanisms. Three of these classes of inhibitors interact with the 5-LO enzyme via a redox, a nonredox, or an iron ligand mechanism,[16] while the fourth class blocks the association of the enzyme to the cellular membrane (FLAP inhibitors).[17,18] Representative inhibitors of these four classes are shown in Chart 1 (BW755C (redox), ICID2138 (nonredox), zileuton (iron ligand), and MK886 (FLAP inhibitor)).

Utilizing common structural features found in the hydroxamic acid and its derivative 5-LO inhibitors, a new series of azole phenoxy hydroxyureas was identified. The synthesis, SAR studies, and 5-LO inhibition of these compounds are described in this paper.

Chemistry

The azole phenoxy hydroxyureas described in this paper were prepared according to the synthetic Schemes 1−3. The ethoxy-linked azole phenoxy hydroxyureas (Table 1) were prepared according to Scheme 1. Refluxing benzamide **5a** or thiobenzamide **5b** with 4-chloroacetoacetate or 4-bromopropionyl acetate produced esters **6a,b**.[19] Reduction of esters **6a,b** with lithium aluminum hydride afforded alcohols **7a**,**b**. Coupling of compounds **7a,b** with phenol **8**, using the Mitsunobu protocol,[20] produced phenoxy azoles **9a,b**. Azoles **9a,b** were treated with hydroxylamine hydrochloride in the presence of sodium acetate to produce oximes **10a,b**. Reduction of **10a**,**b** with sodium cyanoborohydride under acidic conditions afforded hydroxylamines **11a,b**. Intermediates **11a,b** were converted to hydroxyureas **12a,b** upon treatment with trimethylsilyl isocyanate.

The methoxy-linked azole phenoxy hydroxyureas (Table 2) were prepared according to Scheme 2. Treat-

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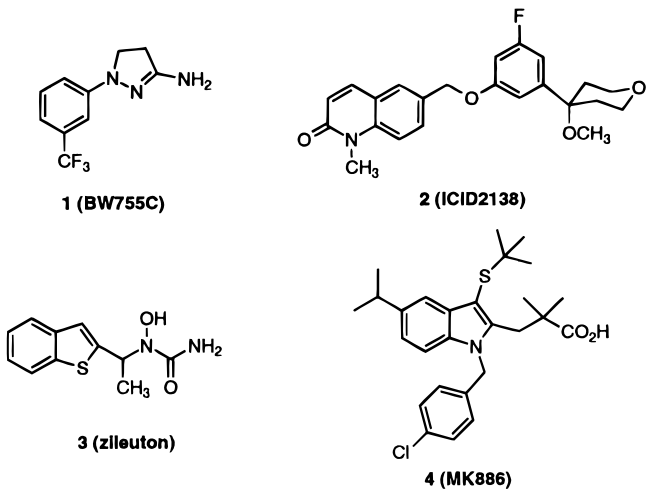
Chart 1



ment of benzaldehyde **13** with 2,3-butanedione monoxime produced oxazole *N*-oxide **14**. Deoxygenation of **14** with phosphorus oxychloride afforded oxazole **15**.[21] Desmethyl oxazole **17a** and thiazole **17b** were prepared from the appropriately substituted amide **16a** or thioamide **16b** upon condensation with 1,3-dichloroacetone and subsequent dehydration with thionyl chloride.[22] Alkylation of phenol **8** with either oxazole **15** or **17a** or thiazole **17b** in the presence of potassium carbonate produced phenoxy azoles **18a**−**c**. Intermediates **18a**−**c** were converted to the final products **19a**−**c**, in a similar manner as described in Scheme 1. The thiourea analog (**56**) (Table 2) of **54** was prepared in a similar manner by using trimethylsilyl thioisocyanate in the last step.

Oxadiazole hydroxyurea **40** (Table 1) was prepared according to Scheme 3. Treatment of 3-hydroxypropionitrile with hydroxylamine hydrochloride in the presence of sodium carbonate afforded amidoxime **20**. Condensation of **20** with benzoyl chloride in the presence of potassium carbonate and subsequent dehydration under acidic conditions produced alcohol **21**.[23] Intermediate **21** was converted to hydroxyurea **40** in a similar manner as described in Scheme 1.

Biological Testing

In Vitro. (a) The test compounds were evaluated *in vitro* for their ability to inhibit LTB_4 biosynthesis in the calcium ionophore (A-23187, 30 μM)-stimulated human whole blood leukocyte (HBL) assay.[24] Their *in vitro* activity was expressed as the percentage of inhibition from control values of LTB_4 biosynthesis, at specified inhibitor concentrations. Each compound was run in one donor at two concentrations (1 and 10 μM) in triplicate. To ensure reproducibility between donors, zileuton (5 μM; ~80% inhibition of LTB_4 biosynthesis) was used as the reference standard for each donor. (b) The intrinsic inhibitory activity in protein free media, as well as the selectivity for the 5-LO enzyme of selected compounds, was evaluated in zymosan-stimulated mouse resident peritoneal macrophages and A-23187-challenged purified human PMNs and monocytes.[25]

Ex Vivo. The oral bioavailability of the active compounds (≥50% inhibition of LTB_4 biosynthesis at 1 μM) in the HBL assay was assessed *ex vivo* in the rat whole blood leukocyte (RBL) assay.[26] After a single oral administration of the test compound, blood samples were collected at selected times and treated with A-23187 (30 μM). The *ex vivo* activity of the test drug was expressed as the percentage of inhibition from control values of LTB_4 biosynthesis at specified oral doses.

In Vivo. The *ex vivo* active compounds (≥50% inhibition of LTB_4 biosynthesis at oral doses of ≤10 mg/kg and predosing periods of ≥3 h) were further evaluated *in vivo* in the rat reverse passive Arthus-induced pleurisy (RPAR) and allergic guinea pig bronchospasm models.[25d,27] In the RPAR assay, the test compounds were evaluated for their ability to inhibit inflammatory mediator synthesis or release to an inflammatory response (anti-BSA IgG challenge). The oral potency of the tested drugs was expressed as the percentage of inhibition from control values of LTB_4 biosynthesis, at a specified drug oral dose. In the allergic guinea pig assay, the compounds were evaluated for their ability to inhibit bronchoconstriction, resulting from iv ovalbumin antigen challenge. The potency of the tested drugs was expressed as the percentage of inhibition from control values of bronchoconstriction, at a specified drug oral or intravenous dose.

Results and Discussion

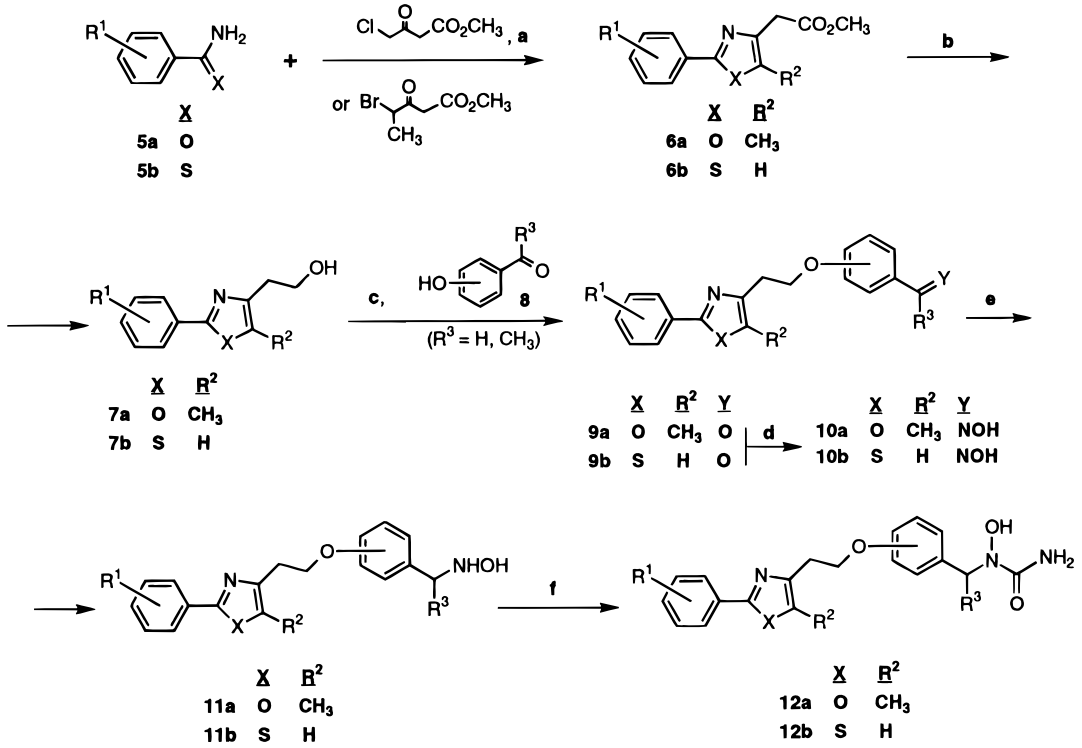
All prepared compounds were initially evaluated *in vitro* in the HBL and *ex vivo* in the RBL assays to determine their 5-LO inhibitory activity and assess their initial bioavailability properties, i.e., absorption and metabolism. Zileuton (**3**) was the reference standard in both assays.

SAR studies encompassed substituents on the azole (oxazole, thiazole) and phenoxy moieties, spacer variations between the azole, phenoxy, and hydroxyurea groups, and modifications of the hydroxyurea pharmacophore portion of the molecule. Results are discussed with respect to initial *in vitro* human blood and *ex vivo* rat blood evaluation of the prepared compounds followed by their inhibitory effects in the RPAR and allergic guinea pig bronchoconstriction models.

***In Vitro* and *ex Vivo* Studies. Ethoxy Spacer Analogs.** In the ethoxy spacer-linked, para-substituted analogs (Table 1), substitution of the oxazole ring at position 2 (Table 1, X = O) with either aromatic, heteroaromatic, or cycloalkyl groups produced inhibitors with similar *in vitro* activities (**22**, **33**−**36**). Introduction of electron-withdrawing groups (i.e., halogen, CF_3) on the 2-phenyl moiety of analogs **24**−**27** produced ca. a 2-fold increase of their *ex vivo* potency while their *in vitro* activity remained unchanged. Compound **24** was the most potent *ex vivo* inhibitor of this group, with an ED_{50} value of ca. 1.0 mg/kg, after a 6 h predosing period. In contrast, electron-donating groups (i.e., alkoxy) produced less active *ex vivo* compounds, without any significant loss of *in vitro* activity (**28**, **29** vs **24**). The reduction of *ex vivo* activity of these analogs may be due to either poor absorption, rapid elimination, and/or high degree of plasma protein binding. Fluorine substitution on the phenoxy moiety of compounds **30** and **31** appeared to favor the unsubstituted 2-phenyl analog **30**. While analog **30** maintained both *in vitro* and *ex vivo* activities, the trifluoromethyl-substituted analog **31** was less active *in vitro*. The meta-analog **41** was similarly active *in vitro* to the para-analog **42** but was inactive in the *ex vivo* assay (**41** vs **22**).

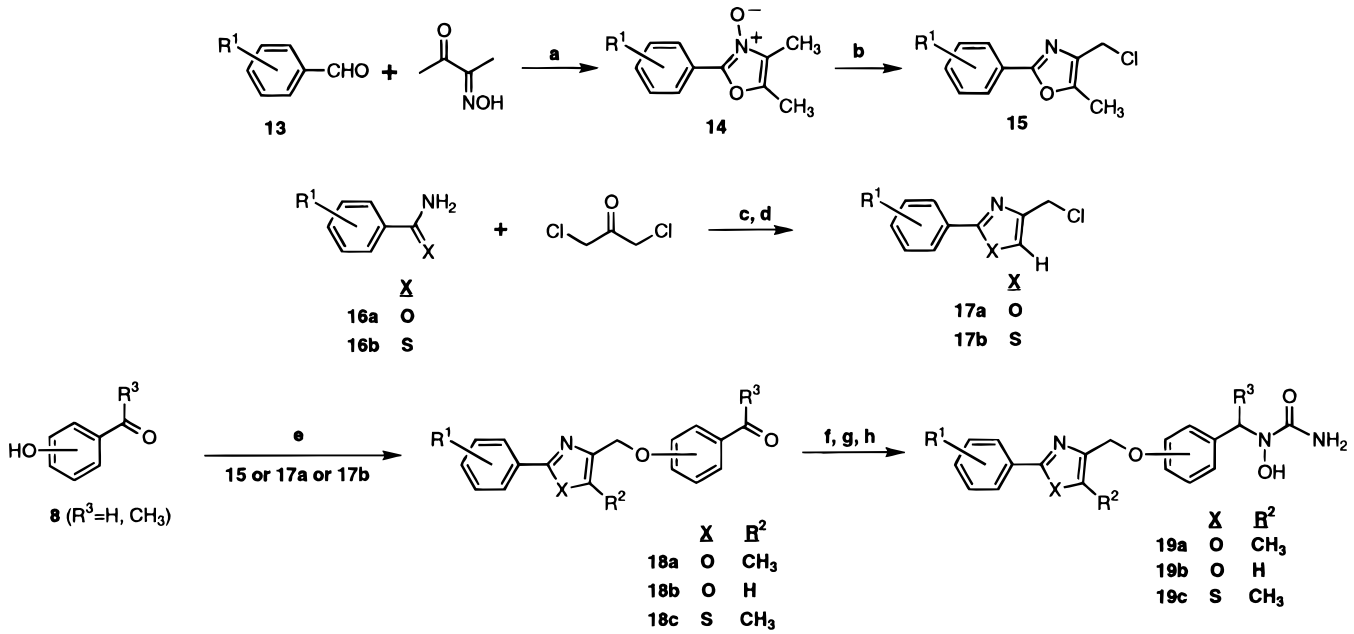
Thiazole **38** was found to be inferior *in vitro* to the analogous oxazole **37**. However, introduction of the

Scheme 1[a]



[a] Reagents: (a) $C_6H_5CH_3$, dioxane, reflux; (b) $LiAlH_4$, Et_2O; (c) diethyl azodicarboxylate, Ph_3P, THF; (d) $HONH_2$·HCl, NaOAc, EtOH, H_2O; (e) $NaCNBH_3$, HCl, MeOH, THF; (f) Me_3SiNCO, dioxane, THF.

Scheme 2[a]



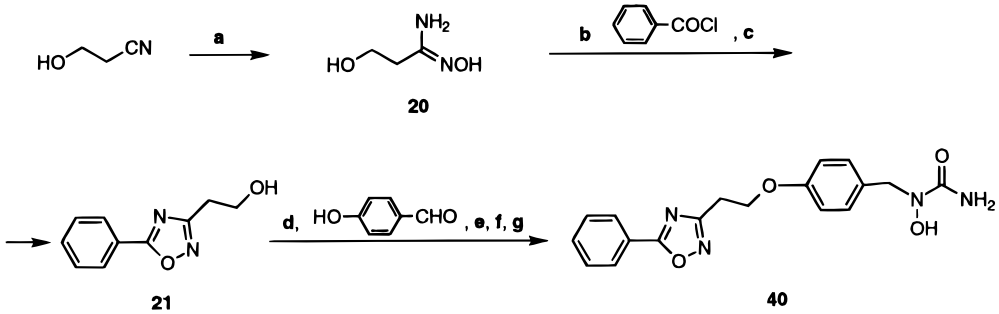
[a] Reagents: (a) HCl, EtOAc; (b) $POCl_3$, $CHCl_3$; (c) $NaHCO_3$, $ClCH_2CH_2Cl$; (d) $SOCl_2$; (e) K_2CO_2, DMF; (f) $HONH_2$·HCl, NaOAc, EtOH, H_2O; (g) $NaCNBH_3$, HCl, MeOH, THF; (h) Me_3SiNCO, dioxane, THF.

trifluoromethyl group on the 2-phenyl moiety of **38** resulted in an enhancement of the *in vitro* activity (**38** vs **39**). A smaller increase of activity was observed for the meta-substituted analog **43**. Both thiazoles **39** and **43** were devoid of any *ex vivo* activity at the tested doses. Replacement of the oxazole ring of **37** with an oxadiazole moiety produced analog **40** with enhanced inhibitory activity in both the *in vitro* and *ex vivo* assays (**40** vs **37**).

Methoxy Spacer Analogs. In the methoxy spacer-linked oxazoles (entries **44**, **46**, **51**, **57**, and **59**−**62**, Tables 2 and 3), similar electronegative substituents (i.e., halogen, CF_3) at position 4 of the 2-phenyl group caused only incremental changes of the *in vitro* activity, while increased *ex vivo* activity was observed (i.e., **44** vs **46**). The meta-substituted (trifluoromethyl)phenyl analog **65** was devoid of any *ex vivo* activity at the tested dose (**59** vs **65**), and the bis-trifluoromethyl analog **66** showed marked reduction in the *in vitro* activity (**66** vs **57**).

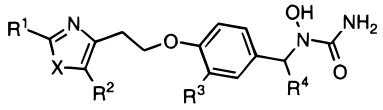
Substitutions on the phenoxy moiety of the para-isomeric oxazoles (Table 2) favored electron-withdraw-

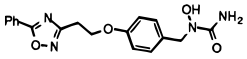
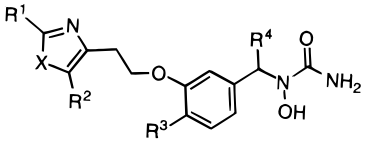
Scheme 3[a]



[a] Reagents: (a) $HONH_2 \cdot HCl$, Na_2CO_3, H_2O; (b) K_2CO_3, dioxane; (c) AcOH, reflux; (d) diethyl azodicarboxylate, Ph_3P, THF; (e) $HONH_2 \cdot HCl$, NaOAc, EtOH, H_2O; (f) $NaCNBH_3$, HCl, MeOH, THF; (g) Me_3SiNCO, dioxane, THF.

Table 1. Chemical and Biological Data of Azole Ethoxyphenyl *N*-Hydroxyureas[d]



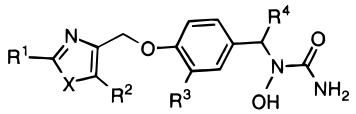
							inhibition of LTB_4 biosynthesis			
							in vitro[a] human blood	*ex vivo*[b] rat blood		
compd	R^1	R^2	R^3	R^4	X	mp, °C	inhibition, %, at 1 μM	dose, mg/kg, po	pretreatment period, h	inhibition, %
22	Ph	CH_3	H	H	O	128−129	55	25	3	79 ± 3.6*
								10	3	0
23	Ph	CH_3	H	CH_3	O	136−138	0	25	3	57 ± 18*
							60 (10 μM)			
24	4-CF_3-Ph	CH_3	H	H	O	156−157	IC_{50} = 1.24 μM	10	3	67 ± 12*
								1	6	57 ± 8.1*
25	4-F-Ph	CH_3	H	H	O	159−160	70	10	3	66 ± 9.7*
26	3-F-Ph	CH_3	H	H	O	142−143	63	10	3	80 ± 4.9*
27	2-F-Ph	CH_3	H	H	O	151−152	54	10	3	71 ± 5.5*
28	4-OCH_3-Ph	CH_3	H	H	O	160−161	57	25	3	32 ± 11
29	4-CH_3-Ph	CH_3	H	H	O	145−146	40	5	6	0
30	Ph	CH_3	F	H	O	135−136	71	10	3	52 ± 17*
31	4-CF_3-Ph	CH_3	F	H	O	144−146	36	ND[c]	ND	ND
32	4-CF_3S-Ph	CH_3	H	H	O	157−159	50	10	6	0
33	naphthyl	CH_3	H	H	O	163−165	42	ND	ND	ND
34	hexyl	CH_3	H	H	O	135−136	44	ND	ND	ND
35	thienyl	CH3	H	H	O	155−156	64	10	3	24 ± 2
36	furyl	CH_3	H	H	O	156−157	64	10	3	41 ± 7.2*
37	Ph	H	H	H	O	150−151	47	5	6	0
38	Ph	H	H	H	S	137−139	19	ND	ND	ND
39	4-CF_3-Ph	H	H	H	S	146−147	57	5	6	0
40						135−136	70	5	6	59 ± 9.7*
										
41	Ph	CH_3	H	H	O	152−153	51	10	3	0
42	Ph	CH3	H	CH3	O	153−154	34	ND	ND	ND
43	4-CF_3-Ph	H	H	H	S	118−120	30	10	6	0
zileuton							IC_{50} = 3.0 μM	ED_{50} = 10.2 mg/kg, 3 h pretreatment		

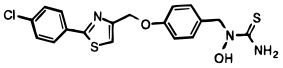
[a] Inhibition of LTB_4 biosynthesis was determined in triplicate at 1 and 10 μM drug concentration in human blood from the same donor; 10 μM produced ≥90% inhibition (data not included in the table), except where indicated in the table. To ensure reproducibility between donors, zileuton (5 μM; ~80% inhibition of LTB_4 biosynthesis) was used as the reference standard for each donor. [b] Drug administered orally (by gavage) at selected times prior to blood collection; values are mean ±SE, mean of four tested animals. Significance was determined by one-way analysis of variance with LSD comparisons to control (*$p < 0.05$). [c] ND = not determined. [d] Compounds **22**−**39** and **41**−**43** were prepared according to the synthetic Scheme 1, and compound **40** was prepared according to the synthetic Scheme 3.

ing groups rather than electron-donating groups (**47** vs **49**). In the analogous meta-isomeric compounds **63** and **64** (Table 3), a similar reduction of the *in vitro* activity was observed for both the electron-donating and electron-withdrawing groups (Table 3, **59** vs **63**, **64**).

The methoxy spacer-linked, para- or meta-substituted thiazoles **52**−**55** and **68**−**70** (Tables 2 and 3) were quite different. While all thiazoles were similar *in vitro*, the electronic nature of the substituents on the 2-phenyl moiety greatly influenced their *ex vivo* potency. Electronegative groups produced less active *ex vivo* compounds of the para-substituted analogs (**53**, **54** vs **52**), while electron-donating groups maintained their *ex vivo* inhibitory activity (**55** vs **52**). The findings with the

Table 2. Chemical and Biological Data of Azole Methoxy-*p*-phenyl *N*-Hydroxyureas[d]



							inhibition of LTB_4 biosynthesis			
							in vitro[a] human blood	*ex vivo*[b] rat blood		
compound	R^1	R^2	R^3	R^4	X	mp, °C	inhibition, %, at 1 μM	dose, mg/kg, po	pretreatment period, h	inhibition, %
44	Ph	CH_3	H	H	O	157−159	50	10	3	84 ± 4.8*
								10	6	0
45	Ph	CH_3	H	CH_3	O	123−124	17	ND[c]	ND	ND
							57 (10 μM)			
46	4-CF_3-Ph	CH_3	H	H	O	146−147	34	5	6	69 ± 17*
47	Ph	CH_3	F	H	O	143−144	47	10	3	66 ± 58*
48	Ph	CH_3	Cl	H	O	180−182	31	10	3	69 ± 15
49	Ph	CH_3	OCH_3	H	O	138−139	19	ND	ND	ND
							81 (10 μM)			
50	Ph	H	H	H	O	162−163	58	5	6	60 ± 8.9
51	4-CF_3-Ph	H	H	H	O	181−183	32	10	6	68 ± 15
52	Ph	H	H	H	S	161−164	44	10	6	67 ± 11*
53	4-CF_3-Ph	H	H	H	S	169−170	56	10	6	0
54	4-Cl-Ph	H	H	H	S	180−184	71	10	6	0
55	4-CH_3O-Ph	H	H	H	S	154−156	56	10	6	69 ± 7.1*
56						163−166	57	5	6	0

[a] Inhibition of LTB_4 biosynthesis was determined in triplicate at 1 and 10 μM drug concentration in human blood from the same donor; 10 μM produced ≥90% inhibition (data not included in the table), except where indicated in the table. To ensure reproducibility between donors, zileuton (5 μM; ∼80% inhibition of LTB_4 biosynthesis) was used as the reference standard for each donor. [b] Drug administered orally (by gavage) at selected times prior to blood collection; values are mean ±SE, mean of four tested animals. Significance was determined by one-way analysis of variance with LSD comparisons to control (*$p < 0.05$). [c] ND = not determined. [d] Compounds **44**−**55** were prepared according to the synthetic Scheme 2.

meta-substituted thiazoles were quite the opposite. Electron-withdrawing groups maintained their *ex vivo* inhibitory activity (**69** vs **68**), while electron-donating groups produced less active *ex vivo* compounds (**70** vs **68**). These findings may be due to undesirable pharmacokinetic parameters (poor absorption, rapid elimination) and/or to the different extent of binding to plasma proteins.

Introduction of a methyl group in the vicinity of the hydroxyurea moiety resulted in significant loss of the *in vitro* activity (entries **23**, **45**, and **58**). The thiourea analogs **56** and **71** were active only *in vitro*.

***In Vitro* Cellular Studies.** The intrinsic activity in protein free media, as well as the selectivity for the 5-LO enzyme, was assessed in cellular assays. Zileuton (**3**) was the reference standard in all assays.

In murine macrophage, compound **24** selectively inhibited zymosan-stimulated LTC_4 production with an IC_{50} value of 0.08 μM, while no effect was observed on PGE_2 production at 15 μM inhibitor concentration. Similar or slightly enhanced inhibitory activities were found for analogs **22** (IC_{50} = 0.06 μM), **57** (IC_{50} = 0.05 μM), and **59** (IC_{50} = 0.02 μM). Zileuton (**3**) blocked production of LTC_4 with an IC_{50} value of 0.05 μM.

Against the exogenous metabolism of arachidonic acid in murine macrophage, compound **24** demonstrated no effect on cellular cyclooxygenase at 1.0 μM concentration while inhibiting 5-LO activity with an IC_{50} value of 0.08 μM. In the human PMNs, compound **24** inhibited LTB_4 production with an IC_{50} value of 0.8 μM, while no inhibition of PAF production was noted at inhibitor concentrations up to 10 μM. Similar results were obtained for zileuton (**3**) in this assay.

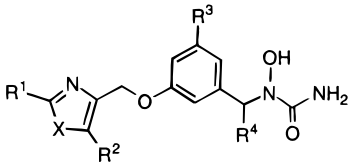
In the human monocytes, compound **24** was 80-fold more potent in blocking the production of LTB_4 (IC_{50} = 0.1 μM) than PGE_2 (IC_{50} = 8.0 μM). Zileuton inhibited LTB_4 production with an IC_{50} value of 0.6 μM. No effect was noted against PAF production. The methoxy spacer-linked oxazoles **57** and **59** exhibited enhanced inhibition of LTB_4 production, with IC_{50} values of 10 and 7 nM, respectively, in human monocytes.

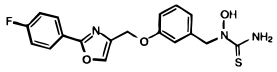
***In Vivo* Studies.** Compounds which showed ≥50% inhibition of LTB_4 biosynthesis in both the HBL *in vitro* assay at a concentration of 1 μM and the RBL *ex vivo* assay at oral doses of ≤10 mg/kg and predosing periods of ≥3 h were evaluated in the RPAR rat and allergic guinea pig *in vivo* assays (Table 4). WY-50295[25d] and zileuton (**3**) were the reference standards in both assays.

Among the 2-phenyl-substituted oxazoles **22**, **44**, **50**, and **57**, compound **50** exhibited the most appropriate profile *in vivo*, being equally effective in both animal models. The other analogs were only moderately active at the tested doses. In relatively good agreement with the *ex vivo* SAR data, where electron-withdrawing groups increased the *ex vivo* inhibitory activity of the tested compounds, similar enhancement in the inhibition of the LTB_4 biosynthesis was observed in the RPAR assay, i.e., **24** vs **22**. However, in the allergic guinea pig model, no correlation was observed. While the trifluoromethyl analog **24** was found to be the most potent LTB_4 biosynthesis inhibitor in the rat RPAR model, it was markedly less active in the guinea pig after either oral or intravenous administration.

The desmethyl 4-fluorophenyl analog **62** exhibited an increase in potency in the allergic guinea pig model but only after intravenous administration (**62** vs **60**). Com-

Table 3. Chemical and Biological Data of Azole Methoxy-*m*-phenyl *N*-Hydroxyureas[d]



							inhibition of LTB_4 biosynthesis			
							in vitro[a] human blood	*ex vivo*[b] rat blood		
compd	R^1	R^2	R^3	R^4	X	mp, °C	inhibition, %, at 1 μM	dose, mg/kg, po	pretreatment period, h	inhibiton, %
57	Ph	CH_3	H	H	O	151−152	52	25	3	78 ± 9.7*
								10	6	0
58	Ph	CH_3	H	CH_3	O	172−173	10	ND[c]	ND	ND
							80 (10 μM)			
59	4-CF_3-Ph	CH_3	H	H	O	142−143	48	5	6	55 ± 15
60	4-F-Ph	CH_3	H	H	O	156−157	74	10	6	49 ± 22
61	4-Cl-Ph	CH_3	H	H	O	166−167	77	10	6	38 ± 23
62	4-F-Ph	CH_3	H	H	O	176−177	74	10	6	85 ± 3*
63	4-CF_3-Ph	CH_3	F	H	O	155−157	15	ND	ND	ND
							85 (10 μM)			
64	4-CF_3-Ph	CH_3	OCH_3	H	O	156−158	0	ND	ND	ND
							59 (10 μM)			
65	3-CF_3-Ph	CH_3	H	H	O	160−161	51	10	6	0
66	3,5-$(CF_3)_2$-Ph	CH_3	H	H	O	150−151	15	ND	ND	ND
							57 (10 μM)			
67	Ph	CH_3	F	H	O	157−158	70	5	6	52 ± 10
68	Ph	H	H	H	S	158−160	66	10	6	80 ± 3*
69	4-Cl-Ph	H	H	H	S	164−167	68	10	6	63 ± 10*
70	4-OCH_3-Ph	H	H	H	S	179−181	50	10	6	0
71						188−189	61	10	6	0

[a] Inhibition of LTB_4 biosynthesis was determined in triplicate at 1 and 10 μM drug concentration in human blood from the same donor; 10 μM produced ≥90% inhibition (data not included in the table), except where indicated in the table. To ensure reproducibility between donors, zileuton (5 μM; ~80% inhibition of LTB_4 biosynthesis) was used as the reference standard for each donor. [b] Drug administered orally (by gavage) at selected times prior to blood collection; values are mean ±SE, mean of four tested animals. Significance was determined by one-way analysis of variance with LSD comparisons to control (*$p < 0.05$). [c] ND = not determined. [d] All compounds were prepared according to the synthetic Scheme 2.

pound **62** was only marginally active after oral administration. These findings may be due to either poor absorption or rapid elimination of the orally administered drug.

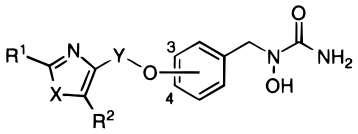
Among the thiazole analogs **52**−**54** and **68**−**70**, only **52** exhibited high potency in the RPAR assay by inhibiting the LTB_4 biosynthesis by 99%, at an oral dose of 10 mg/kg. However, **52** was less potent in the guinea pig after intravenous administration and only marginally active after oral administration. The meta-substituted thiazole **68** exhibited a loss of potency in the RPAR assay, while it was more potent in the guinea pig after intravenous administration (**68** vs **52**). The remaining thiazoles were active only after intravenous administration in the guinea pig assay. Poor pharmacokinetic parameters (poor absorption, rapid elimination) may explain the loss of inhibitory activity after oral administration of the tested thiazoles.

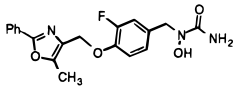
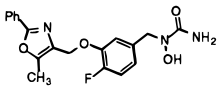
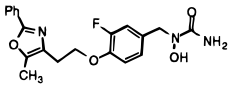
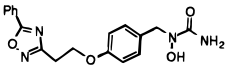
Compound **30**, where a fluorine group was introduced on the phenoxy moiety, exhibited an enhancement of oral potency in the rat RPAR assay (**30** vs **22**). The analogous fluorine-substituted compounds **47** and **67** were weakly active in the *in vivo* assays at the tested doses. Oxadiazole **40** exhibited good inhibitory activity in the guinea pig assay after intravenous administration but was less active after oral administration. Compound **40** was weakly active in the RPAR assay.

In conclusion, a new series of azole-substituted phenoxy hydroxyureas has been identified with potent *in vitro* and *ex vivo* inhibitory activity for the 5-LO enzyme. Electronegative substituents on the 2-phenyl portion of the oxazole tail significantly increased the *ex vivo* potency of the inhibitors. Similar substitutions on the thiazole analogs had only minor contribution to the *ex vivo* activity. Relatively similar findings were observed in their *in vivo* evaluation, in the rat RPAR model. The trifluoromethyl-substituted oxazole **24** was the best compound of the oxazole series in both the *ex vivo* and *in vivo* RPAR assay with ED_{50} values of ca. 1 and 3.6 mg/kg, respectively. The unsubstituted thiazole **52** was the best compound of the thiazole series, by inhibiting the LTB_4 biosynthesis in the RPAR assay by 99%, at an oral dose of 10 mg/kg, and the bronchoconstriction in the allergic guinea pig by 50%, at an intravenous dose of 10 mg/kg. The findings in the allergic guinea pig model were less consistent in relation to the electronic nature of the substiutents on the 2-phenyl group of the oxa(thia)zole moieties. Most of the orally active compounds in the RPAR model were active in the guinea pig after intravenous administration, and only a small fraction among them were active after oral administration. These discrepancies between intravenous and oral administration routes in the guinea pig may be attributed to the low bioavailability of these drugs in the guinea pig.

Compound **50** was similar to zileuton in the RPAR and guinea pig *in vivo* models. Compounds **24** and **52** were similar to zileuton and WY-50295 in the RPAR

Table 4. *In Vivo* Data of Selected Compounds in Rat and Guinea Pig



								bronchoconstriction in the allergic guinea pig			
								iv (10 mg/kg)[b]		po (25 mg/kg)[c]	
compd	R^1	R^2	X	Y	Y−O−	n[d]	LTB_4 synthesis in the rat RPAR pleurisy model[a] po (10 mg/kg), inhibition, %	n	inhibition, %	n	inhibition, %
44	Ph	CH_3	O	CH_2	4	3	69 ± 5.7* (25 mg/kg)	4	38 ± 12*	6	13 ± 4.9
						5	36 ± 4.3*				
57	Ph	CH_3	O	CH_2	3	5	79 ± 7.2* (25 mg/kg)		ND[e]	4	6.3 ± 3.5
						4	33 ± 12.5				
50	Ph	H	O	CH_2	4	3	60 ± 6.8**	6	54 ± 6**	5	44 ± 11*[f]
22	Ph	CH_3	O	$(CH_2)_2$	4	3	49 ± 14 (25 mg/kg)		ED_{50} = 15 mg/kg[g]	6	25 ± 9
						3	23 ± 8.3				
46	4-CF_3-Ph	CH_3	O	CH_2	4	5	45 ± 18.7	4	27 ± 5*	6	27 ± 10
59	4-CF_3-Ph	CH_3	O	CH_2	3	5	59 ± 22.1	5	14 ± 6.1	ND	
60	4-F-Ph	CH_3	O	CH_2	3	6	37 ± 7.8*	4	65 ± 10**	4	7.1 ± 1.3
61	4-Cl-Ph	CH_3	O	CH_2	3	3	47 ± 3.8*	5	41 ± 11*		ND
62	4-F-Ph	H	O	CH_2	3		ND		ED_{50} = 5 mg/kg	4	26 ± 6
24	4-CF_3-Ph	CH_3	O	$(CH_2)_2$	4		ED_{50} = 5 mg/kg	4	23 ± 4 (20 mg/kg)		11
28	3-F-Ph	CH_3	O	$(CH_2)_2$	4	4	38 ± 3.4* (25 mg/kg)		ND		ND
29	2-F-Ph	CH_3	O	$(CH_2)_2$	4	4	48 ± 1.2 (25 mg/kg)		ND		ND
52	Ph	H	S	CH_2	4	4	99 ± 0.1**	4	50 ± 4.3*	6	24 ± 12
68	Ph	H	S	CH_2	3	3	40 ± 9.1		ED_{50} = 6 mg/kg		0
53	4-CF_3-Ph	H	S	CH_2	4		ND	4	30 ± 3.4*		0
69	4-Cl-Ph	H	S	CH_2	3	3	0	3	59 ± 12*	4	11 ± 7.8
54	4-CH_3O-Ph	H	S	CH_2	4		ND	4	50 ± 7.4*	4	8 ± 7.7
70	4-CH_3O-Ph	H	S	CH_2	3		ND	6	58 ± 6**	4	18 ± 4.8
47						2	27 ± 0.2 (25 mg/kg)		ND		ND
67						3	16 ± 15	5	29 ± 5*		ND
30						3	58 ± 8.2* (25 mg/kg)		ND		ND
40						4	19 ± 18 (25 mg/kg)	5	85 ± 5*	5	34 ± 9*
zileuton							ED_{50} = 7.8 mg/kg		ED_{50} = 19 mg/kg		ED_{50} = 46 mg/kg
WY-50295							ED_{50} = 2.7 mg/kg		ED_{50} = 14 mg/kg		ED_{50} = 16 mg/kg

[a] Drug was administered orally (by gavage) 3 h prior to induction of RPAR; values are a mean ± SEM, mean of n tested animals. Significance was determined by one-way analysis of variance with LSD comparisons to control (*p < 0.05). [b] Drug was administered intravenously 5 min prior to iv antigen challenge; values are mean ± SE, mean of n tested animals. Significance was determined by one-way analysis of variance with LSD comparisons to control (*p < 0.05, **p < 0.01). [c] Drug was administered orally (by gavage) 4 h prior to iv antigen challenge; values are mean ± SE, mean of n tested animals. Significance was determined by one-way analysis of variance with LSD comparisons to control (*p < 0.05). [d] Number of animals. [e] ND = not determined. [f] Tested at 50 mg/kg. [g] ED_{50} values have 95% CL (calculated by the method of Litchfield and Wilcoxon).[31]

assay, but they were weaker in the guinea pig assay. Compounds **62** and **68** demonstrated the highest inhibitory activity in the guinea pig assay among all tested compounds after intravenous administration, but they were either weakly active or inactive after oral administration. *In vitro* cellular studies for selected compounds demonstrated that the azole phenoxy hydroxyureas are selective inhibitors of LTB_4 biosynthesis for the 5-LO vs CO enzyme systems.

Experimental Section

Chemistry. Melting points were determined in open capillary tubes on a Thomas-Hoover apparatus and are reported uncorrected. ^1H NMR spectra were determined in the cited solvent on a Bruker AM 400 (400 MHz), a Varian XL-300 (300 MHz), or a Varian XL-200 (200 MHz) instrument, with tetramethylsilane as an internal standard. Chemical shifts are given in ppm and coupling constants are in hertz. Splitting patterns are designated as follows: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet. The infrared spectra were recorded on a Perkin-Elmer 781 spectrophotometer as KBr pellets or as solutions in chloroform. Mass spectra were recorded on either a Finnigan model 8230 or a Hewlett-Packard model 5995A spectrometer. Elemental analyses (C, H, N) were performed on a Perkin-Elmer 240 analyzer, and all compounds are within ±0.4% of theory unless otherwise indicated. Optical rotations were determined in the cited solvent on a Perkin-Elmer model 241 MC polarimeter. All products, unless otherwise noted, were purified by "flash chromatography"[28] with use of 220−400 mesh silica gel. Thin-layer chromatography was done on silica gel 60 F-254 (0.25 mm thickness) plates. Visualization was accomplished with UV light and/or 10% phosphomolybdic acid in ethanol. Unless otherwise noted, all materials were obtained commercially and used without further purification. All reactions were carried out under an atmosphere of dried nitrogen.

General Procedure for the Synthesis of Azole Ethoxyphenyl *N*-Hydroxyureas (Table 1). Compounds of the

general structure **12a,b** (Scheme 1) were synthesized from alcohols **7a,b** by the representative procedure illustrated for analog **22** (Table 1). Alcohols **7a,b** were obtained from commercially available benzamide **5a** or thiobenzamide **5b** according to literature methods.[19]

4-[2-(5-Methyl-2-phenyloxazol-4-yl)ethoxy]benzaldehyde (9a, R^1,R^3 = H, R^2 = CH_3, X = O, Para-Substituted). Diethyl azodicarboxylate (3.87 mL, 24.63 mmol) was added dropwise into a cold (0 °C) solution of 4-(2′-hydroxyethyl)-5-methyl-2-phenyloxazole[19] (5.0 g, 24.63 mmol), triphenylphosphine (6.45 g, 24.63 mmol), and 4-hydroxybenzaldehyde (3.0 g, 24.63 mmol) in anhydrous THF (100 mL). The reaction temperature was allowed to come to room temperature, and the mixture was stirred for 48 h, poured into H_2O, and extracted with EtOAc. The organic extracts were dried over $MgSO_4$. Evaporation and purification by flash chromatography on silica gel (hexane/EtOAc, 4/1) gave a yellow solid (5.9 g, 78% yield): mp 77−78 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.35 (s, 3H, CH_3), 2.96 (t, J = 6.64 Hz, 2H, CH_2), 4.33 (t, J = 6.64 Hz, 2H, CH_2), 7.1 (d, J = 8.7 Hz, 2H, Ar-*H*), 7.46 (m, 3H, Ar-*H*), 7.84 (d, J = 8.7 Hz, 2H, Ar-*H*), 7.89 (m, 2H, Ar-*H*), 9.85 (s, 1H, C*H*O); IR (KBr, cm^{-1}) 1690 (CO); MS *m*/*e* 308 (M + H)$^+$. Anal. ($C_{19}H_{12}NO_3$) C, H, N.

4-[2-(5-Methyl-2-phenyloxazol-4-yl)ethoxy]benzaldehyde Oxime (10a, R^1,R^3 = H, R^2 = CH_3, X = O, Para-Substituted). Hydroxylamine hydrochloride (3.67 g, 52.76 mmol) and sodium acetate (5.77 g, 70.36 mmol) in H_2O (50 mL) were added into a solution of 4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]benzaldehyde (5.4 g, 17.59 mmol) in EtOH (300 mL). The mixture was stirred at room temperature for 24 h, poured into H_2O, and extracted with EtOAc. The organic extracts were dried over $MgSO_4$. Evaporation and crystallization from acetone/ethyl ether (after cooling to 0 °C) gave a white solid (5.1 g, 90% yield): mp 153−155 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.35 (s, 3H, CH_3), 2.93 (t, J = 6.64 Hz, 2H, CH_2), 4.23 (t, J = 6.64 Hz, 2H, CH_2), 6.95 (d, J = 8.7 Hz, 2H, Ar-*H*), 7.49 (m, 5H, Ar-*H*), 7.89 (m, 2H, Ar-*H*), 8.04 (s, 1H, C*H*), 10.94 (s, 1H, O*H*); IR (KBr, cm^{-1}) 3200 (OH); MS *m*/*e* 322 (M$^+$). Anal. ($C_{19}H_{18}N_2O_3$) C, H, N.

***N*-[4-[2-(5-Methyl-2-phenyloxazol-4-yl)ethoxy]benzyl]-hydroxylamine (11a, R^1,R^3 = H, R^2 = CH_3, X = O, Para-Substituted).** Sodium cyanoborohydride (3.87 g, 62.11 mmol) was added into a solution of 4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]benzaldehyde oxime (4.0 g, 19.42 mmol) and methyl orange (indicator, 10 mg) in MeOH (300 mL) in THF (50 mL). After 5 min, a solution of HCl (4 N) in dioxane was added dropwise in order to maintain the pH solution in the range of 3−4. When a steady red color was obtained, the mixture was poured into H_2O, basified with NaOH (1 N), and extracted with EtOAc. The organic extracts were dried over $MgSO_4$. Evaporation and purification by flash chromatography, on silica gel (EtOAc/MeOH, 10/1), gave a white solid (3.4 g, 85% yield): mp 95−96 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.35 (s, 3H, CH_3), 2.91 (t, J = 6.64 Hz, 2H, CH_2), 3.77 (s, 2H, CH_2), 4.18 (t, J = 6.64 Hz, 2H, CH_2), 5.9 (br s, 1H, N*H*), 6.87 (d, J = 8.7 Hz, 2H, Ar-*H*), 7.23 (m, 3H, Ar-*H*), 7.48 (m, 3H, O*H*, Ar-*H*), 7.91 (m, 2H, Ar-*H*); IR (KBr, cm^{-1}) 3400 (NH), 3200 (OH); MS *m*/*e* 325 (M + H)$^+$. Anal. ($C_{19}H_{20}N_2O_3$) C, H, N.

1-Hydroxy-1-[4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]-benzyl]urea (22 or 12a, R^1,R^3 = H, R^2 = CH_3, X = O, Para-substituted). Trimethylsilyl isocyanate (1.4 mL, 10.0 mmol) was added into a solution of *N*-[4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]benzyl]hydroxylamine (2.5 g, 7.71 mmol) in dioxane (30 mL). After being stirred for 2 h, the mixture was poured into H_2O, acidified with HCl (2 N), and extracted with EtOAc. The organic extracts were dried over $MgSO_4$. Evaporation and crystallization from acetone/ethyl ether (after cooling to 0 °C) gave a white solid (1.96 g, 69% yield): mp 128−129 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.35 (s, 3H, CH_3), 2.91 (t, J = 6.64 Hz, 2H, CH_2), 4.18 (t, J = 6.64 Hz, 2H, CH_2), 4.4 (s, 2H, CH_2), 6.28 (s, 2H, NH_2), 6.87 (d, J = 8.7 Hz, 2H, Ar-*H*), 7.18 (d, J = 8.7 Hz, 2H, Ar-*H*), 7.51 (m, 3H, Ar-*H*), 7.91 (m, 2H, Ar-*H*), 9.24 (s, 1H, O*H*); IR (KBr, cm^{-1}) 3450 (NH), 3200 (OH), 1670 (CO); MS *m*/*e* 368 (M + H)$^+$. Anal. ($C_{20}H_{21}N_3O_4$) C, H, N.

The oxadiazole hydroxyurea **40** (Table 1) was prepared according to the procedure described for compound **22**, using 3-(2′-hydroxyethyl)-5-phenyl-1,2,4-oxadiazole (**21**), which was prepared as follows.

3-(2′-Hydroxyethyl)-5-phenyl-1,2,4-oxadiazole (21). Benzoyl chloride (24.3 g, 173 mmol) in dioxane (50 mL) was added dropwise into a suspension of 2′-hydroxyethylamidoxime[29] (36 g, 346 mmol) and potassium carbonate (23.9 g, 173 mmol) in dioxane (400 mL). The mixture was stirred for 4 h, poured into water, and extracted with EtOAc. The organic extracts were dried over $MgSO_4$. Evaporation gave an off-white solid (40.0 g), which was taken in AcOH (275 mL) and refluxed for 2 h. The mixture was poured into water and extracted with EtOAc. The organic extracts were dried over $MgSO_4$. Evaporation and purification by flash chromatography, on silica gel (hexane/EtOAc, 3/2), gave a white solid (18.3 g, 28% yield): mp 58−59 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.9 (t, J = 6.64 Hz, 2H, CH_2), 3.81 (m, 2H, CH_2), 4.82 (t, J = 5.6 Hz, 1H, O*H*), 7.6−7.68 (m, 3H, Ar-*H*), 8.1 (m, 2H, Ar-*H*); IR (KBr, cm^{-1}) 3200 (OH); MS *m*/*e* 190 (M$^+$). Anal. ($C_{10}H_{20}N_2O_2$) C, H, N.

1-Hydroxy-1-[4-[2-(5-phenyl-1,2,4-oxadiazol-3-yl)ethoxy]-benzyl]urea (40): mp 135−136 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.25 (t, J = 6.22 Hz, 2H, CH_2), 4.39 (t, J = 6.22 Hz, 2H, CH_2), 4.41 (s, 2H, CH_2), 6.28 (s, 2H, NH_2), 6.88 (d, J = 8.7 Hz, 2H, Ar-*H*), 7.18 (d, J = 8.7 Hz, 2H, Ar-*H*), 7.6−7.7 (m, 3H, Ar-*H*), 8.01 (m, 2H, Ar-*H*), 9.25 (s, 1H, O*H*); IR (KBr, cm^{-1}) 3450 (NH), 3200 (OH), 1620 (CO); MS *m*/*e* 355 (M + H)$^+$. Anal. ($C_{18}H_{18}N_4O_4$) C, H, N.

General Procedure for the Synthesis of Azole Methoxyphenyl *N*-Hydroxyureas (Table 2). Compounds of the general structure **19a**−**c** (Scheme 2) were synthesized from chlorides 1**7a,b** and phenol **8**. Chlorides **17a,b** were obtained from commercially available benzaldehyde **13** or benzamide **16a**/thioamide **16b** according to literature methods.[21,22] After coupling of **8** with **17a,b** in the presence of potassium carbonate, a similar experimental process as described for compounds of Table 1 was followed.

4-[(5-Methyl-2-phenyloxazol-4-yl)methoxy]benzaldehyde (18a, R^1,R^3 = H, R^2 = CH_3, X = O, Para-Substituted). A mixture of 4-(chloromethyl)-5-methyl-2-phenyloxazole[30] (5.5 g, 26.5 mmol), 4-hydroxybenzaldehyde (3.23 g, 26.5 mmol), potassium carbonate (3.66 g, 26.5 mL), and DMF (80 mL) was stirred at 80 °C for 8 h. The mixture was poured into H_2O and extracted with EtOAc. The organic extracts were dried over $MgSO_4$. Evaporation and purification by flash chromatography on silica gel (hexane/EtOAc, 4/1) gave a yellow solid (6.8 g, 86% yield): mp 103−105° C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.46 (s, 3H, CH_3), 5.14 (s, 2H, CH_2), 7.24 (d, J = 8.7 Hz, 2H, Ar-*H*), 7.9 (d, J = 8.7 Hz, 2H, Ar-*H*), 7.94 (m, 2H, Ar-*H*), 9.88 (s, 1H, C*H*O); IR (KBr, cm^{-1}) 1690 (CO); MS *m*/*e* 294 (M + H)$^+$. Anal. ($C_{18}H_{15}NO_3$) C, H, N.

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