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Heme Oxygenase Inhibition by 1-Aryl-2-(1*H*-imidazol-1-yl/1*H*-1,2,4-triazol-1-yl)ethanones and Their Derivatives

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Previous studies by our research group have been concerned with the design of selective inhibitors of heme oxygenases (HO-1 and HO-2). The majority of these were based on a four-carbon linkage of an azole, usually an imidazole, and an aromatic moiety. In the present study, we designed and synthesized a series of inhibition candidates containing a shorter linkage between these groups, specifically, a series of 1-aryl-2-(1*H*-imidazol-1-yl/1*H*-1,2,4-triazol-1-yl)ethanones and their derivatives. As regards HO-1 inhibition, the aromatic moieties yielding best results were found to be halogen-substituted residues such as 3-bromophenyl, 4-bromophenyl, and 3,4-dichlorophenyl, or hydrocarbon residues such as 2-naphthyl, 4-biphenyl, 4-benzylphenyl, and 4-(2-phenethyl)phenyl. Among the imidazole-ketones, five (**36**–**39**, and **44**) were found to be very potent ($IC_{50} < 5$ μM) toward both isozymes. Relative to the imidazole-ketones, the series of corresponding triazole-ketones showed four compounds (**54**, **55**, **61**, and **62**) having a selectivity index > 50 in favor of HO-1. In the case of the azole-dioxolanes, two of them (**80** and **85**), each possessing a 2-naphthyl moiety, were found to be particularly potent and selective HO-1 inhibitors. Three non-carbonyl analogues (**87**, **89**, and **91**) of 1-(4-chlorophenyl)-2-(1*H*-imidazol-1-yl)ethanone were found to be good inhibitors of HO-1. For the first time in our studies, two azole-based inhibitors (**37** and **39**) were found to exhibit a modest selectivity index in favor of HO-2. The present study has revealed additional candidates based on inhibition of heme oxygenases for potentially useful pharmacological and therapeutic applications.

Introduction

The degradation of heme to biliverdin, ferrous iron, and carbon monoxide (CO) is catalyzed in mammals by two heme oxygenase (HO) isozymes, namely, HO-1 (inducible) and HO-2 (constitutive). Under physiological conditions, this process accounts for the majority of the CO produced.[1,2] Although the molecular targets of CO have not been fully identified, the role of this gasotransmitter as a regulator of cellular processes in the brain, and in circulatory, respiratory, and immune systems has been acknowledged increasingly,[3,4] and its anti-inflammatory, antiproliferative, and anti-apoptotic effects have been demonstrated.[5] In addition, the growing body of evidence concerning the direct relationship between HO overexpression and the survival rate of tumor cells[6–9] makes the inhibition of HO an attractive strategy for cancer therapy.[10,11] Many investigations of the HO/CO system have relied on the use of metalloporphyrin-based inhibitors, which also inhibit other heme-dependent enzymes such as soluble guanylyl cyclase,[12] nitric oxide synthase,[13] and various members of the cytochrome P450 (CYP) superfamily. As a result, some research groups have questioned the validity of observations and concepts related to HO activity.[14]

A large number of novel, potent imidazole-based inhibitors that are both specific for HO and selective toward HO-1 have been recently designed and synthesized by our group.[15–19] The majority of these inhibitors preserve the skeleton of the initial hit, azalanstat,[20,21] in which the imidazole is separated from the hydrophobic 4-chlorophenyl moiety by a four-carbon spacer in the central region (Figure 1).

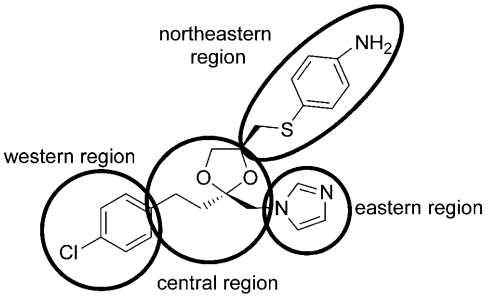

Figure 1. Topological representation of azalanstat. Biological activity: $IC_{50} = 6 \pm 1$ μM (HO-1, rat spleen microsomes); $IC_{50} = 28 \pm 18$ μM (HO-2, rat brain microsomes).[15]

Earlier we observed that a compound with a two-carbon linker instead of a four-carbon linker, namely, 1-(adamantan-1-yl)-2-(1*H*-imidazol-1-yl)ethanone, is a good HO-1 inhibitor.[22] This result provided the impetus for the present study of compounds possessing an aryl moiety in the western region and an azole group (an imidazole or 1,2,4-triazole ring) in the east-

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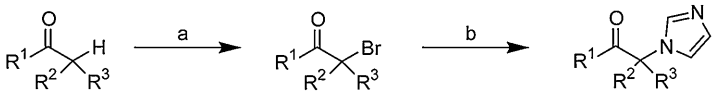
ern region joined by a two-carbon linker, namely, an ethanone moiety or derivatives thereof.

Results and Discussion

Synthesis

The first series of target compounds, namely, 1-aryl-2-(1*H*-imidazol-1-yl)ethanones **27**–**52**, were prepared by reaction of the 1-aryl-2-bromoethanones **1**–**26**, respectively, with imidazole (Scheme 1). Most of the required 1-aryl-2-bromoethanones are commercially available; those that were not available (compounds **8**, **11**–**16**, **20**, **21**, and **26**) were obtained by brominating the commercially available acetophenones using copper(II) bromide in chloroform/ethyl acetate at reflux. The reaction yielded preponderantly the desired 1-aryl-2-bromoethanones together with 5–10% of the starting material and the by-product, namely, the corresponding 1-aryl-2,2-dibromoethanone; the 1-aryl-2-bromoethanones could be separated by column chromatography using mostly toluene/hexanes.



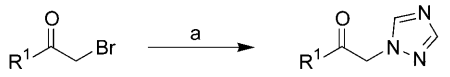
1	$R^1 = C_6H_5$	**27**	$R^1 = C_6H_5$
2	$R^1 = 4\text{-}CH_3C_6H_4$	**28**	$R^1 = 4\text{-}CH_3C_6H_4$
3	$R^1 = 4\text{-}CH_3OC_6H_4$	**29**	$R^1 = 4\text{-}CH_3OC_6H_4$
4	$R^1 = 4\text{-}FC_6H_4$	**30**	$R^1 = 4\text{-}FC_6H_4$
5	$R^1 = 4\text{-}ClC_6H_4$	**31**	$R^1 = 4\text{-}ClC_6H_4$
6	$R^1 = 3\text{-}BrC_6H_4$	**32**	$R^1 = 3\text{-}BrC_6H_4$
7	$R^1 = 4\text{-}BrC_6H_4$	**33**	$R^1 = 4\text{-}BrC_6H_4$
8	$R^1 = 4\text{-}IC_6H_4$	**34**	$R^1 = 4\text{-}IC_6H_4$
9	$R^1 = 4\text{-}O_2NC_6H_4$	**35**	$R^1 = 4\text{-}O_2NC_6H_4$
10	$R^1 = 4\text{-}(C_6H_5)C_6H_4$	**36**	$R^1 = 4\text{-}(C_6H_5)C_6H_4$
11	$R^1 = 4\text{-}(4'\text{-}BrC_6H_4)C_6H_4$	**37**	$R^1 = 4\text{-}(4'\text{-}BrC_6H_4)C_6H_4$
12	$R^1 = 4\text{-}(C_6H_5CH_2)C_6H_4$	**38**	$R^1 = 4\text{-}(C_6H_5CH_2)C_6H_4$
13	$R^1 = 4\text{-}(C_6H_5CH_2CH_2)C_6H_4$	**39**	$R^1 = 4\text{-}(C_6H_5CH_2CH_2)C_6H_4$
14	$R^1 = 4\text{-}(C_6H_5CH_2O)C_6H_4$	**40**	$R^1 = 4\text{-}(C_6H_5CH_2O)C_6H_4$
15	$R^1 = 4\text{-}(c\text{-}C_6H_{11})C_6H_4$	**41**	$R^1 = 4\text{-}(c\text{-}C_6H_{11})C_6H_4$
16	R^1 = naphthalen-1-yl	**42**	R^1 = naphthalen-1-yl
17	R^1 = naphthalen-2-yl	**43**	R^1 = naphthalen-2-yl
18	$R^1 = 3,4\text{-}Cl_2C_6H_3$	**44**	$R^1 = 3,4\text{-}Cl_2C_6H_3$
19	$R^1 = 2,4\text{-}Cl_2C_6H_3$	**45**	$R^1 = 2,4\text{-}Cl_2C_6H_3$
20	$R^1 = 2,5\text{-}Cl_2C_6H_3$	**46**	$R^1 = 2,5\text{-}Cl_2C_6H_3$
21	$R^1 = 2,3,4\text{-}Cl_3C_6H_2$	**47**	$R^1 = 2,3,4\text{-}Cl_3C_6H_2$
22	$R^1 = C_6H_5$; $R^2 = CH_3$; $R^3 = H$	**48**	$R^1 = C_6H_5$; $R^2 = CH_3$; $R^3 = H$
23	$R^1 = C_6H_5$; $R^2 = R^3 = CH_3$	**49**	$R^1 = C_6H_5$; $R^2 = R^3 = CH_3$
24	$R^1 = C_6H_5$; $R^2 = C_6H_5$; $R^3 = H$	**50**	$R^1 = C_6H_5$; $R^2 = C_6H_5$; $R^3 = H$
25	$(\text{-}R^2)R^1\text{-} = 2\text{-}(\text{-}CH_2)C_6H_4\text{-}$; $R^3 = H$	**51**	$(\text{-}R^2)R^1\text{-} = 2\text{-}(\text{-}CH_2)C_6H_4\text{-}$; $R^3 = H$
26	R^1 = thiophen-2-yl	**52**	R^1 = thiophen-2-yl

Scheme 1. Synthesis of imidazole-ketones **27**–**52**. Reagents and conditions: a) $CuBr_2$, EtOAc/$CHCl_3$, reflux, 5 h; b) imidazole, DMF, w/wo K_2CO_3, RT, 2–3 h; or imidazole, acetone, Et_3N, reflux, 6–8 h. In all cases except for **22**–**25** and **48**–**51**, $R^2 = H$ and $R^3 = H$. Compounds **1**–**7**, **9**, **10**, **17**–**19**, and **22**–**25** are commercially available.

The numerous variations reported for the synthesis of 1-aryl-2-(1*H*-imidazol-1-yl)ethanones from the corresponding 1-aryl-2-bromoethanones differ mainly with respect to the solvent used. Although *N*,*N*-dimethylformamide (DMF) appears to be the solvent of choice,[23–25] there are several reports of the use of acetone,[26,27] acetonitrile,[28] or tetrahydrofuran.[29] Despite the use of a three- to fivefold excess of imidazole, 1,3-bis(aroylmethyl)imidazolium halides have been frequently reported as by-products in this process. The formation of this type of by-product appears to be either suppressed if a previously formed imidazolide is employed as nucleophile,[30] or at least diminished by the addition of a base.[27] In the present work, it was found that the reaction proceeded smoothly at room temperature; however, 2-bromoisobutyrophenone afforded the imidazole-ketone **49** only at higher temperatures, presumably owing to the restricted access of imidazole to the sterically hindered reaction center. In some cases, NMR spectroscopy indicated the presence of only the desired product, whereas in other cases the presence of 1-aryl-2-(1*H*-imidazol-1-yl)ethanones and the corresponding 1,3-bis(aroylmethyl)imidazolium bromides, sometimes in a 1:1 ratio, was indicated. For the biological assay, most of the 1-aryl-2-(1*H*-imidazol-1-yl)ethanones were transformed into the corresponding water-soluble hydrochlorides. Many of the compounds have been reported previously as free bases or salts, but they have not been characterized fully.

The 1-aryl-2-(1,2,4-1*H*-triazol-1-yl)ethanones **53**–**64** were synthesized also by treatment of the corresponding 1-aryl-2-bromoethanones with a small excess of 1,2,4-1*H*-triazole in the presence of triethylamine in acetone at reflux (Scheme 2). In this case, one of the by-products of the reaction is the isomeric 1-aryl-2-(1,2,4-4*H*-triazol-4-yl)ethanone that resulted from the alkylation of the azole at N4. The formation of this isomer is controlled thermodynamically;[31] only the presence of small proportions were indicated by NMR spectroscopy. In the case of 2-bromo-4′-chloroacetophenone, a larger proportion of the isomer (**54a**, Scheme 3) resulting from the alkylation at N4 was observed. The structures of the regioisomers **54** and **54a** were assigned by ^{1}H NMR spectroscopy (two singlets, each corresponding in intensity to one magnetically non-equivalent triazole proton in **54**; one singlet corresponding in intensity to two magnetically equivalent triazole protons in **54a**).

The third series of target candidate compounds comprises imidazole- and 1,2,4-triazole-dioxolanes. Because of a report[23] of the low yields obtained in the direct conversions of 1-aryl-2-(1*H*-imidazol-1-yl)ethanones into the corresponding azole-dioxolanes, the azole-dioxolanes in the present study were prepared from 1-aryl-2-bromoethanones by way of the corresponding bromomethyl-dioxolanes (Scheme 4). In the case of the bromomethyl-dioxolane **65**, following a reported procedure[32] on acetophenone using trimethylphenylammonium tribromide, afforded **65** in low yield together with 2-

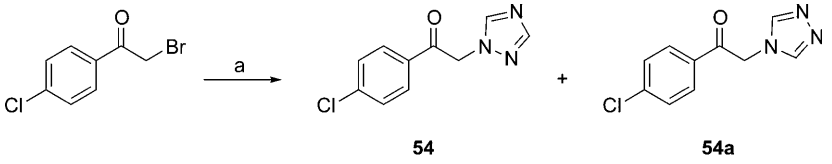


1 $R^1 = C_6H_5$ **53** $R^1 = C_6H_5$
5 $R^1 = 4\text{-}ClC_6H_4$ **54** $R^1 = 4\text{-}ClC_6H_4$
6 $R^1 = 3\text{-}BrC_6H_4$ **55** $R^1 = 3\text{-}BrC_6H_4$
7 $R^1 = 4\text{-}BrC_6H_4$ **56** $R^1 = 4\text{-}BrC_6H_4$
9 $R^1 = 4\text{-}O_2NC_6H_4$ **57** $R^1 = 4\text{-}O_2NC_6H_4$
10 $R^1 = 4\text{-}(C_6H_5)C_6H_4$ **58** $R^1 = 4\text{-}(C_6H_5)C_6H_4$
12 $R^1 = 4\text{-}(C_6H_5CH_2)C_6H_4$ **59** $R^1 = 4\text{-}(C_6H_5CH_2)C_6H_4$
16 R^1 = naphthalen-1-yl **60** R^1 = naphthalen-1-yl
17 R^1 = naphthalen-2-yl **61** R^1 = naphthalen-2-yl
18 $R^1 = 3,4\text{-}Cl_2C_6H_3$ **62** $R^1 = 3,4\text{-}Cl_2C_6H_3$
19 $R^1 = 2,4\text{-}Cl_2C_6H_3$ **63** $R^1 = 2,4\text{-}Cl_2C_6H_3$
20 $R^1 = 2,5\text{-}Cl_2C_6H_3$ **64** $R^1 = 2,5\text{-}Cl_2C_6H_3$

Scheme 2. Synthesis of 1,2,4-1*H*-triazole-ketones **53**–**64**. Reagents and conditions: a) 1,2,4-triazole, acetone, Et_3N, reflux, 8 h.

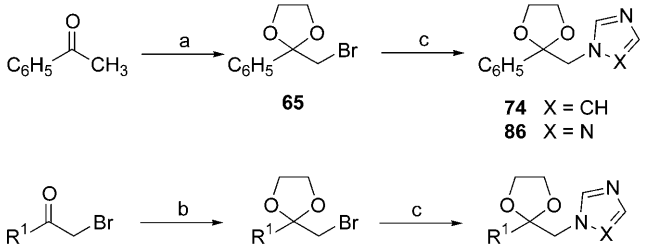
bromo-1-phenylethanone. The remaining bromomethyl-dioxolanes (**66**–**73**) shown in Scheme 4 were obtained in quantitative yields from the corresponding 1-aryl-2-bromoethanones by acid-catalyzed ketalization using ethylene glycol. The target azole-dioxolanes **75**–**85** were obtained by treatment of the corresponding bromomethyl-dioxolanes with the sodium salt of either imidazole or 1,2,4-triazole in DMF. As anticipated, the use of 1,2,4-triazole led to mixtures of N1- and N4-alkylated triazoles; the former isomer, which was always the major component, could be obtained in pure form by repeated crystallizations from 2-propanol.

Finally, the synthesis of candidate inhibitors involving the derivatization of the carbonyl function in 1-(4-chlorophenyl)-2-(1*H*-imidazol-1-yl)ethanone (**31**) was explored, and the conversions are summarized in Scheme 5. In the case of the reaction of **31** with hydroxylamine, the *Z* isomer of oxime **88** was obtained preponderantly; the assignment of configuration was based on a previous report.[33]



54 **54a**

Scheme 3. Synthesis of regioisomeric 1-(4-chlorophenyl)-2-(1,2,4-triazolyl)ethanones **54** and **54a**. Reagents and conditions: a) 1,2,4-triazole, acetone, Et_3N, reflux, 8 h.



65

74 X = CH
86 X = N

66 $R^1 = 4\text{-}ClC_6H_4$ **75** $R^1 = 4\text{-}ClC_6H_4$; X = CH
67 $R^1 = 3\text{-}BrC_6H_4$ **76** $R^1 = 3\text{-}BrC_6H_4$; X = CH
68 $R^1 = 4\text{-}BrC_6H_4$ **77** $R^1 = 4\text{-}BrC_6H_4$; X = CH
69 R^1 = biphenyl-4-yl **78** R^1 = biphenyl-4-yl; X = CH
70 $R^1 = 4\text{-}(C_6H_5CH_2)C_6H_4$ **79** $R^1 = 4\text{-}(C_6H_5CH_2)C_6H_4$; X = CH
71 R^1 = naphthalen-2-yl **80** R^1 = naphthalen-2-yl; X = CH
72 $R^1 = 3,4\text{-}Cl_2C_6H_3$ **81** $R^1 = 3,4\text{-}Cl_2C_6H_3$; X = CH
73 $R^1 = 2,4\text{-}Cl_2C_6H_3$ **82** $R^1 = 2,4\text{-}Cl_2C_6H_3$; X = CH

66 $R^1 = 4\text{-}ClC_6H_4$ **83** $R^1 = 4\text{-}ClC_6H_4$; X = N
68 $R^1 = 4\text{-}BrC_6H_4$ **84** $R^1 = 4\text{-}BrC_6H_4$; X = N
71 R^1 = naphthalen-2-yl **85** R^1 = naphthalen-2-yl; X = N

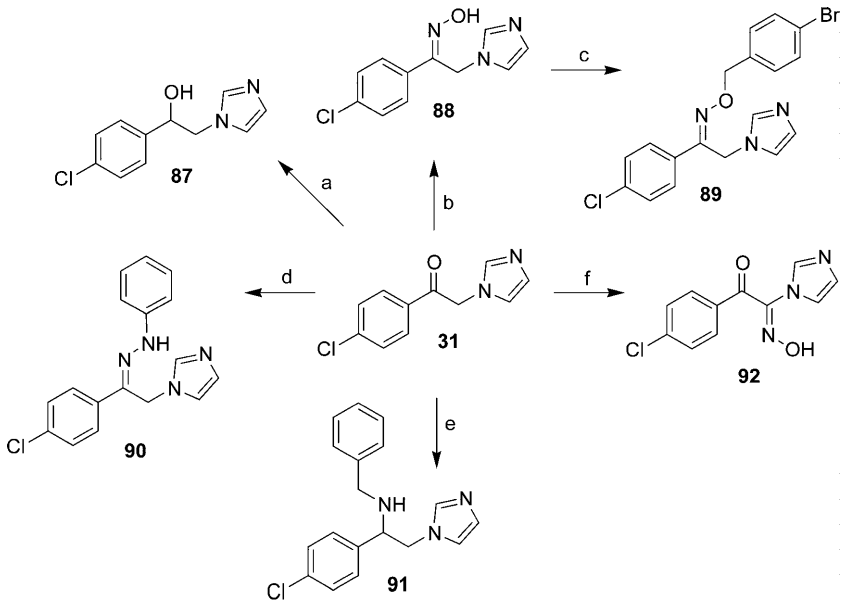
Scheme 4. Synthesis of imidazole-dioxolanes **74**–**82** and 1,2,4-triazole-dioxolanes **83**–**86**. Reagents and conditions: a) $(CH_3)_3NPhBr_3$, THF/ethylene glycol, RT, 22 h; b) ethylene glycol, benzene, *p*-toluenesulfonic acid monohydrate, reflux, 16 h; c) imidazole or 1,2,4-triazole, NaOH, DMSO, 70–80 °C, overnight.

Biological evaluation

Our previous studies[17,19,22] have explored the effect of structure on the inhibitory activities and selectivities of the heme oxygenase isozymes based on the topological analysis shown in Figure 1. Thus, for example, it was found that the presence of a carbonyl group in the linker afforded potent inhibitors of HOs. Also, in addition to imidazole, 1,2,4-triazole analogues led to potent inhibitors that were selective for HOs but not for CYPs.[34] As indicated above in the Introduction, the focus of the study presented herein was on compounds having a two-carbon linker instead of a four-carbon linker. In addition, the plethora of variously substituted aryl groups produced in this study has provided further insight into the influence of the hydrophobic aryl moiety on the inhibitory activities.[17,22,35] Table 1 summarizes the inhibitory potencies and selectivities of the compounds studied in this work toward HO-1 and HO-2. The candidate compounds have been classified in accordance with Schemes 1, 2, 4, and 5. Only the salient structure–activity features are discussed.

1-Aryl-2-(1*H*-imidazol-1-yl)ethanones: see Scheme 1

In the series of 1-aryl-2-(1*H*-imidazol-1-yl)ethanones, good inhibitors of HO-1, namely, those having IC_{50} values ≤ 5 μM, were found to be compounds **31**–**39**, **41**–**45**, and **47**. These compounds differ only in the nature of the aryl group in the western region. Of these, compounds **31**–**34**, **37**, **44**, **45**, and **47** contain one, two, or three halogen atoms, the dichloro analogue **44** being the most potent ($IC_{50} = 1.24 \pm 0.05$ μM). In the case of the phenyl-containing compounds bearing hydrocarbon groups, compounds **36**, **38**, **39**, and **41** were also found to be good inhibitors, the most potent being the 4-benzylphenyl compound **38** ($IC_{50} = 1.99 \pm 0.04$ μM). Notably, replacement of the cyclohexyl ring in compound **41** by a phenyl ring to afford the biphenyl compound **36** results in a doubling of the potency; this result substantiates the privileged status of biphenyl[36] and suggests that aromatic rings make better contact with the



Scheme 5. Synthesis of derivatives of 1-(4-chlorophenyl)-2-(1*H*-imidazol-1-yl)ethanone (**31**). Reagents and conditions: a) $NaBH_4$, MeOH, RT, overnight; b) $NH_2OH{\cdot}HCl$, Na_2CO_3, $EtOH/H_2O$, reflux, 4 h; c) 4-bromobenzyl bromide, NaH, RT for 4.5 h, then 50–60 °C for 10 min; d) $PhNHNH_2{\cdot}HCl$, EtOH, reflux, 2 h; e) benzylamine, *p*-toluenesulfonic acid monohydrate, benzene, reflux, overnight, then $NaBH_4$, MeOH, RT, 6 h; f) $NaNO_2$, $AcOH/H_2O$, RT, overnight.

hydrophobic pocket of the enzyme than saturated rings. Interestingly, the 4-nitrophenyl compound **35** was found to be both a potent ($IC_{50} = 2.5 \pm 0.2$ μM) and highly selective (selectivity index >40) HO-1 inhibitor. Both regioisomeric naphthalene derivatives **42** and **43** were found to be potent HO-1 inhibitors.

Regarding HO-2 inhibitory activity, only compounds **36**–**39** and **44** had IC_{50} values ≤ 5 μM, the most potent being the 4-bromobiphenyl compound **37** ($IC_{50} = 0.43 \pm 0.07$ μM). Significantly, two of the compounds, namely, the 4-bromobiphenyl compound **37** and the phenylethylphenyl compound **39** were found to be selective toward HO-2 inhibition; the compounds are potential leads for the development of HO-2-selective inhibitors. All of the other potent compounds were selective for HO-1. These two compounds are the first examples of azole-based inhibitors that are slightly selective for HO-2; selectivity toward HO-2 has been observed previously only in the case of metalloporphyrin-based HO inhibitors, such as chromium mesoporphyrin IX chloride.[37]

1-Aryl-2-(1,2,4-1*H*-triazol-1-yl)ethanones: see Scheme 2

For the most part, the 1,2,4-1*H*-triazole-ketones synthesized in the present study were those having the aryl groups which were in the imidazole-ketones that were potent against HO-1 ($IC_{50} \leq 5$ μM). On the basis of this criterion, compounds **54**–**56** and **58**–**63** were concluded to be potent inhibitors. Within the limited comparisons possible for the series of imidazole-ketones and 1,2,4-triazole-ketones, for the most part, the latter were found to be more potent inhibitors of HO-1 than their corresponding imidazole-containing analogues; the converse was observed in the case of HO-2. Accordingly, the selectivity indices of the triazole-ketones are greater than those of the corresponding imidazole-ketones. The same behavior was observed in the previous comparison of the imidazole- and 1,2,4-triazole-containing 1-azol-1-yl-4-phenyl-2-butanones, and the increased inhibitory activity of the triazole-based compounds may be attributed to the additional point of stabilization provided by the potential hydrogen bond between N2 of the triazole moiety with the amide group of Gly143 (see Ref. [19] for biological data and X-ray crystal structure).

The halogen-substituted compounds in this series also include some potent inhibitors; however, a drawback that could restrain their use in various applications is the lack of water solubility for both the free bases and the hydrochlorides. Interestingly, although the N1-alkylated 1,2,4-triazole **54** was found to be a potent HO-1 inhibitor, the N4-alkylated 1,2,4-triazole **54a**, which had been isolated as a by-product from the reaction shown in Scheme 3, showed very low inhibition of HO-1 and was completely inactive toward HO-2. In a previous report,[19] a comparative analysis of the structures and inhibitory potencies of several variously substituted N-alkylated azoles led to the conclusion that the presence of two carbon atoms adjacent to the nitrogen atom that binds to the heme iron in an azole group ensures a pharmacophore with optimal binding. Compound **54a** could potentially bind to the heme iron through both N1 and N2 atoms; however, each of these nitrogen atoms has only one adjacent carbon atom and one adjacent nitrogen atom. A structural analogue of the N4-alkylated 1,2,4-triazole **54a** is the previously reported[19] N1-alkylated 1,2,3-triazole derivative **93** (Figure 2). Compound **93**, which binds to the heme iron using the N3 atom, which is also adjacent to one carbon atom and one nitrogen atom, was found to be a very weak inhibitor of HO-1 ($IC_{50} = 89$ μM) and inactive toward HO-2 ($IC_{50} > 100$ μM). Notably, compound **93** has a four-carbon linker, which enables the inhibitor to reach all the way back and anchor to the distal pocket of HO-1; this is presumably the structural feature that contributes to the IC_{50}

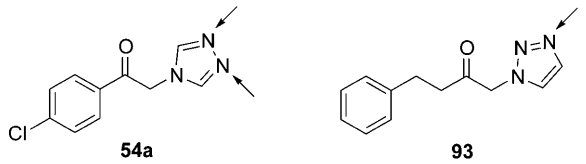


Figure 2. Nitrogen atoms potentially involved in binding to iron heme in compounds **54a** and **93**.

Table 1. In vitro inhibitory potency and selectivity of compounds toward HO-1 and HO-2.

Compd	IC_{50} [μM] HO-1 (rat spleen)	HO-2 (rat brain)	SI[a]
1-Aryl-2-(1*H*-imidazol-1-yl)ethanones (see Scheme 1):			
27	28 ± 3	> 100	> 3.6
28	17 ± 3	69 ± 11	4.1
29	39 ± 7	62 ± 3	1.6
30	25 ± 4	> 100	> 4
31	4 ± 1	20 ± 6	5
32	2.06 ± 0.09	35 ± 2	17
33	3.2 ± 0.6	14 ± 1	4.4
34	4.0 ± 0.6	25 ± 11	6.3
35	2.5 ± 0.2	> 100	> 40
36	2.1 ± 0.5	3.0 ± 0.5	1.4
37	1.5 ± 0.3	0.43 ± 0.07	0.29
38	1.99 ± 0.04	2.3 ± 0.2	1.2
39	4 ± 1	0.9 ± 0.1	0.2
40	11 ± 2	> 100	> 9
41	5 ± 1	6 ± 2	1
42	2.24 ± 0.07	10 ± 2	4.5
43	1.9 ± 0.1	12.05 ± 0.04	6.3
44	1.24 ± 0.05	4.7 ± 0.5	3.8
45	2.2 ± 0.3	15 ± 1	6.8
46	6.6 ± 0.1	58 ± 7	8.8
47	2.103 ± 0.002	6 ± 1	3
48	49 ± 1	> 100	> 2
49	> 100	≫ 100	–
50	24 ± 5	> 100	> 4
51	> 100	> 100	–
52	> 100	≫ 100	–
1-Aryl-2-(1,2,4-1*H*-triazol-1-yl)ethanones (see Scheme 2):			
53	11.9 ± 0.7	> 100	> 8
54	2.2 ± 0.4	121.56 ± 0.08	55
54a	> 100	≫ 100	–
55	1.8 ± 0.5	> 100	> 55
56	2.7 ± 0.4	50 ± 17	19
57	19.2 ± 0.4	> 100	> 5
58	0.74 ± 0.04	7 ± 3	10
59	2.7 ± 0.4	7 ± 2	3
60	0.79 ± 0.02	16 ± 4	20
61	0.7 ± 0.1	42 ± 7	60
62	1.3 ± 0.3	> 100	> 77
63	4.1 ± 0.6	> 100	> 24
64	18.4 ± 0.3	> 100	> 5
Imidazole-dioxolanes (see Scheme 4):			
74	31 ± 2	≫ 100	> 3
75	19 ± 2	> 100	> 5
76	4.0 ± 0.5	> 100	> 25
77	12 ± 1	> 100	> 8
78	16.2 ± 0.3	> 100	> 6
79	4.98 ± 0.05	> 100	> 20
80	2.63 ± 0.04	> 100	> 38
81	8 ± 1	> 100	> 13
82	29 ± 10	> 100	> 3
1,2,4-Triazole-dioxolanes (see Scheme 4):			
83	68.7 ± 0.4	≫ 100	> 1.5
84	38 ± 5	≫ 100	> 3
85	3.58 ± 0.06	> 100	> 28
86	144 ± 11	≫ 100	–
Derivatives of 1-(4-chlorophenyl)-2-(1*H*-imidazol-1-yl)ethanone (**31**) (see Scheme 5):			
87	1.19 ± 0.02	16 ± 6	13
88	46 ± 5	> 100	> 2
89	8.3 ± 0.6	51 ± 19	6.1
90	> 100	≫ 100	–
91	3.39 ± 0.05	22 ± 3	6.5
92	> 100	> 100	–

[a] Selectivity index: $(IC_{50\ HO\text{-}2})/(IC_{50\ HO\text{-}1})$.

value being lower than 100 μM; in contrast, the shorter linker in compound **54a** presumably prevents the inhibitor from making contact with the distal pocket of the enzyme.

As was observed in the imidazole-ketone series, the triazole-ketones **58**–**61**, with two isolated or fused phenyl rings in the western region, are amongst the most potent inhibitors of HO-1 in the triazole-ketone series. The water-soluble 2-naphthyl derivative **61**, having an IC_{50} value of 0.7 ± 0.1 μM for HO-1, and a selectivity index of 60, was found to be the best inhibitor in the series of triazole-ketones. The inhibitors **54**, **55**, **61**, and **62**, being both potent and selective toward HO-1, represent new and potentially useful pharmacological tools and therapeutics.[38]

Imidazole-dioxolanes: see Scheme 4

Based on the most promising candidates in the library of the azole-ketones, a series of corresponding azole-dioxolanes were examined. None of the compounds in this series showed an inhibition of HO-2 below 50% of the control activity, even at 100 μM. Relative to the results obtained with the imidazole-ketones, the inhibition of HO-1 by the corresponding imidazole-dioxolanes **74**–**82** was less pronounced. Again, the inhibitor with a 3-bromophenyl moiety, namely, compound **76** was the most potent of the monohalogenated imidazole-dioxolanes. In the cases of the inhibitors **78**–**80**, with a hydrocarbon residue in the western region, the 2-naphthyl derivative **80** was found to be the most potent and the most selective of these three, and indeed of all the imidazole-dioxolanes synthesized; its HO-1 inhibitory activity was actually similar to that of the parent imidazole-ketone **43**. Although the biphenyl- and 4-benzylphenyl-containing imidazole-ketones **36** and **38** were essentially equipotent, the imidazole-dioxolane **79** featuring a 4-benzylphenyl moiety was threefold more potent toward HO-1 than the biphenyl-based inhibitor **78**. It is possible that the replacement of the carbonyl function in imidazole-ketones by a bulkier 1,3-dioxolane moiety results in additional steric hindrance that forces the inhibitor to adopt a novel conformation, and that this conformation results either in a suboptimal binding of the pharmacophore to heme iron, or in a diminished number of contact points that the hydrophobic part of the inhibitor molecule uses to stabilize its binding within the enzyme pocket. As in the case of the previously studied imidazole-dioxolanes having a four-carbon linker, the incorporation of the dioxolane ring in an inhibitor having a two-carbon linker appeared to be responsible for the enhanced selectivity

toward HO-1. In summary, the water-soluble 2-naphthyl analogue imidazole-dioxolane **80** has emerged as another potentially valuable isozyme-selective HO-1 inhibitor ($IC_{50} = 2.63 \pm 0.04$ μM, selectivity index >38) for pharmacological applications.[39]

1,2,4-Triazole-dioxolanes: see Scheme 4

Only four candidate compounds in this series, namely, **83**–**86** were synthesized and examined. All of the compounds were essentially devoid of inhibitory activity toward HO-2 and were only weak inhibitors of HO-1. The 4-chlorophenyl triazole-dioxolane **83** and its 4-bromophenyl analogue **84** were found to be approximately threefold less potent than the corresponding imidazole-dioxolanes **75** and **77**, and these triazole-dioxolanes were found to be 31- and 14-fold less potent than the corresponding triazole-ketones **54** and **56**, respectively. Again, the 2-naphthyl-containing triazole-dioxolane **85** emerged with an IC_{50} value and selectivity index roughly similar to the values for the corresponding imidazole-dioxolane **80**.

Derivatives of 1-(4-chlorophenyl)-2-(1*H*-imidazol-1-yl)ethanone (31): see Scheme **5**

While maintaining the focus on compounds having a two-carbon linker, a preliminary exploration of non-carbonyl derivatives other than 1,3-dioxolanes was undertaken. Of the five non-carbonyl derivatives shown in Scheme 5, the alcohol **87** and amine **91** were found to be more potent and selective inhibitors of HO-1 than the parent carbonyl compound **31**. It is recognized that the alcohol product **87** and amine product **91** were formed as mixtures of enantiomers. The enhanced activity of the imidazole-alcohol product relative to the imidazole-ketone was also exhibited in the four-carbon linker series;[17] the effect is presumably due to the increased hydrogen bonding of the hydroxy group with either the trapped water or with the amino acid residues of the enzymes. Neither of the classic carbonyl derivatives, namely, oxime **88** or phenylhydrazone **90** were good inhibitors; however, the 4-bromobenzyl ether derivative **89** of the oxime showed more potent HO-1 inhibition than did the oxime. Included in this preliminary study was the oximino ketone **92**; this compound did not show inhibitory activity against either isozyme, a result that may be rationalized on the basis of a steric argument, which could also be offered for the lack of activity of the branched compounds **48**–**51**. The preliminary data obtained from the series of compounds in Scheme 5 suggest that a more comprehensive study of related analogues would be valuable.

Conclusions

In the present study, four series of compounds were examined: 1-aryl-2-(1*H*-imidazol-1-yl)ethanones, 1-aryl-2-(1,2,4-1*H*-triazol-1-yl)ethanones, imidazole-dioxolanes, and 1,2,4-triazole-dioxolanes as inhibitors of HO-1 and HO-2. A common structural feature in this series is the two-carbon linker between the azole moiety and the aryl moiety. The study identified halogen-substituted residues such as 3-bromophenyl, 4-bromophenyl, and 3,4-dichlorophenyl, or hydrocarbon residues such as 2-naphthyl, 4-biphenyl, 4-benzylphenyl, and 4-(2-phenethyl)phenyl as hydrophobic groups yielding the most promising inhibitors. The study has provided new potentially useful pharmacological tools for the study of the HO/CO system and their application as therapeutics.

Experimental Section

Chemistry

Materials and methods: 4-Benzylacetophenone and 4-(2-phenylethyl)acetophenone were obtained from Trans World Chemicals Inc. (Rockville, MD, USA). 2-Bromoisobutyrophenone was obtained from Acros Organics (Belgium). 2-Bromo-2′,4′-dichloroacetophenone (**19**) was obtained from TCI America Laboratory Chemicals (Portland, OR, USA). 1-Acetylnaphthalene, 2-acetylthiophene, 4′-(benzyloxy)acetophenone, 2′,5′-dichloroacetophenone, 4′-(4-bromophenyl)acetophenone, 4′-iodoacetophenone, 2′,3′,4′-trichloroacetophenone, 4′-cyclohexylacetophenone, 4′-fluorophenacyl bromide (**4**), 3′-bromophenacyl bromide (**6**), 2-bromo-4′-phenylacetophenone (**10**), 1,2,4-triazole, and $CuBr_2$ were obtained from Alfa Aesar (Ward Hill, MA, USA). Other reagents were obtained from Sigma–Aldrich. Column chromatography was performed on silica gel (230–400 mesh, 60 Å) (Silicycle, Quebec City, QC, Canada). Analytical thin-layer chromatography was performed on glass-backed Silicycle pre-coated silica gel 60 F_{254} plates, and the compounds were visualized by UV illumination (254 nm). Melting points were recorded on a Mel-Temp II apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer. The signals due to residual protons in the deuterated solvents were used as internal standards for the ^{1}H NMR spectra. The chemical shifts for the carbon atoms are given relative to $CDCl_3$ ($\delta = 77.16$ ppm), CD_3OD ($\delta = 49.00$ ppm), or [D_6]DMSO ($\delta = 39.52$ ppm). High-resolution mass spectra were obtained either on a Waters/Micromass GCT mass spectrometer in EI mode or on an Applied Biosystems/MDS Sciex QSTAR XL spectrometer equipped with an Agilent HP1100 Cap-LC system in ESI mode. All of the compounds were deemed to be pure by analysis of the ^{1}H NMR spectroscopic data.

General procedure for the synthesis of α-bromoketones: The mixture of the ketone (10 mmol) and $CuBr_2$ (4.46 g, 20 mmol) was heated at reflux in $CHCl_3$/EtOAc (40 mL, 1:1) for 5 h; the inorganic precipitate was removed by filtration and washed with EtOAc (20 mL). The filtrate and washings were evaporated under reduced pressure to give a mixture of the starting ketone, the product bromoketone, and any dibromoketone formed; the mixture was resolved by column chromatography on silica gel.

2-Bromo-1-(4-iodophenyl)ethanone (8): Column chromatography (silica gel, toluene/hexanes 1:2) afforded the product as a white solid (2372 mg, 73%); $R_f = 0.17$ (toluene/hexanes 1:2); mp: 112–113 °C (lit.[40] mp: 110.5–111.0 °C, lit.[41] mp: 111–113 °C); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.39$ (s, 2H), 7.69 (d, $J = 8.4$ Hz, 2H), 7.87 ppm (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 30.3$, 102.3, 130.4, 133.4, 138.4, 190.9 ppm; HRMS-EI *m/z* $[M]^+$ calcd for C_8H_6BrIO: 323.8647, found: 323.8633.

2-Bromo-1-(4′-bromobiphenyl-4-yl)ethanone (11): Column chromatography (silica gel, toluene/hexanes 1:2) afforded the product as a white solid (2350 mg, 66%); $R_f = 0.20$ (toluene/hexanes 1:1); mp: 144–145 °C (lit.[42] mp: 138–140 °C); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.47$ (s, 2H), 7.50 (d, $J = 8.4$ Hz, 2H), 7.61 (d, $J = 8.4$ Hz, 2H), 7.68 (d, $J = 8.4$ Hz, 2H), 8.06 ppm (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (100 MHz,

$CDCl_3$): $\delta = 30.9$, 123.1, 127.4, 129.0, 129.8, 132.3, 133.1, 138.6, 145.5, 191.0 ppm; HRMS-EI *m/z* $[M]^+$ calcd for $C_{14}H_{10}Br_2O$: 351.9098, found: 351.9108.

1-(4-Benzylphenyl)-2-bromoethanone (12): Column chromatography (silica gel, toluene/hexanes 1:1) afforded the product as a white solid (2235 mg, 77%); $R_f = 0.24$ (toluene/hexanes 1:1); mp: 47–48 °C (lit.[43] mp: 47.6–49.5 °C, lit.[44] mp: 44–45 °C); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.05$ (s, 2H), 4.42 (s, 2H), 7.16–7.27 (m, 3H), 7.28–7.35 (m, 4H), 7.91 ppm (dd, $J = 1.2$ and 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 31.0$, 42.1, 126.7, 128.8, 129.1, 129.4, 129.5, 132.2, 148.0, 191.0 ppm; HRMS-EI *m/z* $[M]^+$ calcd for $C_{15}H_{13}BrO$ 288.0150, found: 288.0160.

2-Bromo-1-[4-(2-phenylethyl)phenyl]ethanone (13): Column chromatography (silica gel, toluene/hexanes 1:1) afforded the product as a white solid (2153 mg, 71%); $R_f = 0.20$ (toluene/hexanes 1:1); mp: 58–59 °C (lit.[45] mp: 61 °C); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.91$–3.04 (m, 4H), 4.44 (s, 2H), 7.13–7.25 (m, 3H), 7.26–7.32 (m, 4H), 7.90 ppm (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 31.0$, 37.4, 38.0, 126.3, 128.6, 129.2, 129.3, 132.1, 141.1, 148.7, 191.1 ppm; HRMS-EI *m/z* $[M]^+$ calcd for $C_{16}H_{15}BrO$: 302.0306, found: 302.0301.

2-Bromo-1-(4-benzyloxyphenyl)ethanone (14): Column chromatography (silica gel, hexanes/EtOAc 12:1) afforded the product as a white solid (1083 mg, 71%); $R_f = 0.33$ (hexanes/EtOAc 12:1); mp: 80–81 °C (lit.[46] mp: 83–84 °C); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.40$ (s, 2H), 5.15 (s, 2H), 7.00–7.07 (m, 2H), 7.32–7.46 (m, 5H), 7.93–8.00 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 30.8$, 70.4, 115.0, 127.2, 127.6, 128.5, 128.9, 131.5, 136.1, 163.4, 190.0 ppm; HRMS-EI *m/z* $[M]^+$ calcd for $C_{15}H_{13}BrO_2$: 304.0099, found: 304.0102.

2-Bromo-1-[4-(cyclohexyl)phenyl]ethanone (15): Column chromatography (silica gel, toluene/hexanes 1:1) afforded the product as a white solid (2057 mg, 73%); $R_f = 0.20$ (toluene/hexanes 1:1); mp: 44–45 °C (lit.[47] mp: 43–44 °C); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.19$–1.33 (m, 1H), 1.34–1.50 (m, 4H), 1.72–1.80 (m, 1H), 1.81–1.94 (m, 4H), 2.52–2.64 (m, 1H), 4.43 (s, 2H), 7.32 (d, $J = 8.4$ Hz, 2H), 7.91 ppm (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 26.1$, 26.8, 31.1, 34.2, 33.9, 127.5, 129.3, 131.9, 155.0, 191.1 ppm; HRMS-EI *m/z* $[M]^+$ calcd for $C_{14}H_{17}BrO$: 280.0463, found: 280.0465.

2-Bromo-1-(naphthalen-1-yl)ethanone (16): Column chromatography (silica gel, toluene/hexanes 1:1) afforded the product as a pale-yellow oil (1544 mg, 62%); $R_f = 0.35$ (toluene/hexanes 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.57$ (s, 2H), 7.48–7.67 (m, 3H), 7.86–7.95 (m, 2H), 8.04 (d, $J = 8.4$ Hz, 1H), 8.64 ppm (d, $J = 8.4$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 34.0$, 124.3, 125.8, 126.9, 128.6, 128.7 (2×C), 130.8, 132.5, 134.0, 134.2, 194.4 ppm; HRMS-EI *m/z* $[M]^+$ calcd for $C_{12}H_9BrO$: 247.9837, found: 247.9838.

2-Bromo-1-(2,5-dichlorophenyl)ethanone (20): Column chromatography (silica gel, toluene/hexanes 1:3 afforded the product as a white solid (1930 mg, 72%); $R_f = 0.29$ (toluene/hexanes 1:3); mp: 32–33 °C (lit.[40] mp: 34–35 °C); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.48$ (s, 2H), 7.35–7.44 (m, 2H), 7.54 ppm (d, $J = 2.4$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 34.1$, 129.6, 130.2, 131.9, 132.8, 133.6, 192.9 ppm; HRMS-EI *m/z* $[M]^+$ calcd for $C_8H_5BrCl_2O$: 265.8901, found: 265.8913.

2-Bromo-1-(2,3,4-trichlorophenyl)ethanone (21): Column chromatography (silica gel, toluene/hexanes 1:1) afforded the product as a white solid (1965 mg, 65%); $R_f = 0.44$ (toluene/hexanes 1:1); mp: 41–43 °C (lit.[48] mp: 44–46 °C); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.44$ (s, 2H), 7.35 (d, $J = 8.4$ Hz, 1H), 7.49 ppm (d, $J = 8.4$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 33.8$, 127.9, 129.0, 131.3, 133.4, 136.9, 137.7, 193.0 ppm; HRMS-EI *m/z* $[M]^+$ calcd for $C_8H_4BrCl_3O$: 299.8511, found: 299.8515.

2-Bromo-1-(thiophen-2-yl)ethanone (26): Column chromatography (silica gel, toluene/hexanes 1:1) afforded the product as a yellow solid (1333 mg, 65%); $R_f = 0.24$ (toluene/hexanes 1:1); mp: 29–30 °C (lit.[49] mp: 33–35 °C); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.36$ (s, 2H), 7.17 (dd, $J = 4.0$ and 5.0 Hz, 1H), 7.72 (dd, $J = 0.8$ and 5.0 Hz, 1H), 7.81 ppm (dd, $J = 0.8$ and 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 30.7$, 128.5, 133.7, 135.3, 141.0, 184.5 ppm; HRMS-EI *m/z* $[M]^+$ calcd for C_6H_5BrOS: 203.9244, found: 203.9244.

General procedures for the synthesis of imidazole-ketones: *Method A*. A mixture of the α-bromoketone (3 mmol), imidazole (612 mg, 9 mmol), and anhydrous K_2CO_3 (1242 mg, 9 mmol) in DMF (6 mL) was stirred at room temperature for 2–3 h, and then the reaction mixture was diluted with H_2O (100 mL). If the product separated as a solid, it was collected by filtration and washed with H_2O; if as an oil, the mixture was extracted with EtOAc (2×30 mL), and then the combined organic phase was washed sequentially with H_2O (100 mL) and brine (20 mL). The organic phase was dried (Na_2SO_4), and the solvent was evaporated under reduced pressure to afford a solid. If the ^{1}H NMR analysis of the solid revealed the presence of the 1,3-bis(aroylmethyl)imidazolium bromide as a by-product, the solid was heated at reflux in either benzene or toluene (50 mL) for 5–10 min; the suspension was filtered while hot, and the filtrate was evaporated under reduced pressure to afford the pure imidazole-ketone. The hydrochlorides of the imidazole-ketones were prepared by treating the solution of the free bases in 2-propanol or acetone with a twofold molar excess of 37% aqueous HCl. If crystallization did not ensue by keeping the mixture for 3–4 h in a refrigerator, the mixture was gradually diluted with Et_2O with stirring until further addition of Et_2O did not produce new precipitate. The solid was collected by filtration, washed with Et_2O, and recrystallized from the appropriate solvent.

In some cases, extensive coloration of the reaction mixture occurred, and a colorless, pure final product could be obtained only by using column chromatography. In some other cases, removal of the colored impurities was successful merely by treating the solution of 1-aryl-2-(1*H*-imidazol-1-yl)ethanone, free of the bis-imidazolium salt, with charcoal.

Method B: Method A, except that no K_2CO_3 was used.

2-(1*H*-Imidazol-1-yl)-1-phenylethanone hydrochloride (27·HCl): Method A afforded the product as a white solid (234 mg, 35%); mp: 177–178 °C (2-propanol) (lit.[26] mp: 142–143 °C, lit.[50] mp: 131–135 °C); ^{1}H NMR (400 MHz, CD_3OD): $\delta = 6.04$ (s, 2H), 7.55–7.68 (m, 4H), 7.69–7.78 (m, 1H), 8.05–8.15 (m, 2H), 8.98 ppm (s, 1H); ^{13}C NMR (100 MHz, CD_3OD): $\delta = 56.2$, 120.5, 125.0, 129.3, 130.2, 135.2, 135.7, 138.1, 192.0 ppm; HRMS-ESI *m/z* $[M-Cl]^+$ calcd for $C_{11}H_{11}N_2O$: 187.0871, found: 187.0873.

2-(1*H*-Imidazol-1-yl)-1-(4-methylphenyl)ethanone hydrochloride (28·HCl): Method B afforded the product as a white solid (525 mg, 74%); mp: 193–195 °C (2-propanol/Et_2O) (lit.[26] mp: 105–130 °C, dec.); ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta = 2.42$ (s, 3H), 6.07 (s, 2H), 7.44 (d, $J = 8.0$ Hz, 2H), 7.68–7.77 (m, 2H), 7.96 (d, $J = 8.0$ Hz, 2H), 9.14 ppm (s, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): $\delta = 21.3$, 54.9, 119.3, 123.6, 128.2, 129.6, 131.3, 136.5, 145.1, 191.0 ppm; HRMS-ESI *m/z* $[M-Cl]^+$ calcd for $C_{12}H_{13}N_2O$: 201.1027, found: 201.1023.

2-(1*H*-Imidazol-1-yl)-1-(4-methoxyphenyl)ethanone hydrochloride (29·HCl): Method B afforded the product as a white solid (409 mg, 54%); mp: 200–202 °C (2-propanol/Et_2O); ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta = 3.88$ (s, 3H), 6.04 (s, 2H), 7.15 (d, $J = 8.8$ Hz, 2H), 7.72–7.76 (m, 2H), 8.04 (d, $J = 8.8$ Hz, 2H), 9.15 ppm (s, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): $\delta = 54.7$, 55.8, 114.3, 119.2, 123.6, 126.6, 130.6, 136.5, 164.1, 189.8 ppm; HRMS-ESI *m/z* $[M-Cl]^+$ calcd for $C_{12}H_{13}N_2O_2$: 217.0972, found: 217.0973.

1-(4-Fluorophenyl)-2-(1*H*-imidazol-1-yl)ethanone hydrochloride (30·HCl): Method A afforded the product as a white solid (419 mg, 58%); mp: 199–200 °C (2-propanol/Et_2O); ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta = 6.11$ (s, 2H), 7.44–7.52 (m, 2H), 7.73 (t, $J = 1.6$ Hz, 2H), 8.12–8.20 (m, 2H), 9.15 ppm (s, 1H); ^{13}C NMR (100 MHz,

[D$_6$]DMSO): δ = 54.9, 116.2 (d, $J^2_{C,F}$ = 22 Hz), 119.3, 123.5, 130.6 (d, $J^4_{C,F}$ = 2.5 Hz), 131.2 (d, $J^3_{C,F}$ = 9.6 Hz), 136.5, 165.6 (d, $J^1_{C,F}$ = 252 Hz), 190.2 ppm; ^{19}F NMR (376 MHz, [D$_6$]DMSO): δ = 104.8 ppm (septet); HRMS-ESI *m/z* $[M-Cl]^+$ calcd for $C_{11}H_{10}FN_2O$: 205.0777, found: 205.0773.

1-(4-Chlorophenyl)-2-(1*H*-imidazol-1-yl)ethanone hydrochloride (31·HCl): The free base was prepared according to Method A in 56% yield; mp: 158–159 °C (2-propanol) (lit.[23] mp: 160–160.5 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.37 (s, 2H), 6.93 (s, 1H), 7.13 (s, 1H), 7.47–7.58 (m, 3H), 7.90 ppm (dd, *J* = 2.0 and 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.5, 120.3, 129.5, 129.6, 129.8, 132.6, 138.2, 141.1, 190.7 ppm. The free base **31** (221 mg, 1 mmol) was converted into the hydrochloride (**31·HCl**) in the usual manner, which was obtained as a white solid (140 mg, 54%); mp: 227–228 °C (2-propanol) (lit.[23] mp: 228–229 °C); ^{1}H NMR (400 MHz, CD_3OD): δ = 6.02 (s, 2H), 7.59–7.69 (m, 4H), 8.09 (dd, *J* = 8.8 and 2.4 Hz, 2H), 8.97 ppm (s, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ = 56.2, 120.6, 125.0, 130.5, 131.0, 133.8, 138.1, 141.9, 191.1 ppm; HRMS-ESI *m/z* $[M-Cl]^+$ calcd for $C_{11}H_{10}ClN_2O$: 221.0482, found: 221.0472.

1-(3-Bromophenyl)-2-(1*H*-imidazol-1-yl)ethanone hydrochloride (32·HCl): Method A afforded the product as a light-yellow solid (480 mg, 53%); mp: 217–218 °C (EtOH); ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 6.11 (s, 2H), 7.61 (t, *J* = 8.0 Hz, 1H), 7.70 (t, *J* = 1.4 Hz, 1H), 7.73 (t, *J* = 1.4 Hz, 1H), 7.97 (dd, *J* = 8.0 and 1.2 Hz, 1H), 8.05 (d, *J* = 8.0 Hz, 1H), 8.21 (t, *J* = 1.2 Hz, 1H), 9.12 ppm (s, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 55.1, 119.4, 122.3, 123.4, 127.1, 130.6, 131.3, 135.8, 136.5, 136.9, 190.7 ppm; HRMS-ESI *m/z* $[M-Cl]^+$ calcd for $C_{11}H_{10}BrN_2O$: 264.9976, found: 264.9968.

1-(4-Bromophenyl)-2-(1*H*-imidazol-1-yl)ethanone hydrochloride (33·HCl): Method B afforded the product as a white solid (398 mg, 44%); mp: 231–233 °C (EtOH); ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 6.08 (s, 2H), 7.70 (t, *J* = 1.4 Hz, 1H), 7.73 (t, *J* = 1.4 Hz, 1H), 7.83–7.90 (m, 2H), 7.95–8.03 (m, 2H), 9.12 ppm (s, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 55.0, 119.4, 123.5, 128.6, 130.1, 132.2, 132.8, 136.6, 190.9 ppm; HRMS-ESI *m/z* $[M-Cl]^+$ calcd for $C_{11}H_{10}BrN_2O$: 264.9976, found: 264.9968.

1-(4-Iodophenyl)-2-(1*H*-imidazol-1-yl)ethanone (34): Method B produced, after the processing of the reaction mixture, a solid that was extracted with boiling MeOH (50 mL). Evaporation of the solvent and recrystallization of the residue from MeOH afforded the product as a pale-pink solid (356 mg, 38%); mp: 214–216 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 5.70 (s, 2H), 6.94 (br s, 1H), 7.12 (br s, 1H), 7.59 (br s, 1H), 7.78 (d, *J* = 8.4 Hz, 2H), 7.99 ppm (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 52.4, 102.4, 120.9, 127.8, 129.5, 133.8, 137.8, 193.2 ppm; HRMS-EI *m/z* $[M]^+$ calcd for $C_{11}H_9IN_2O$: 311.9760, found: 311.9746.

2-(1*H*-Imidazol-1-yl)-1-(4-nitrophenyl)ethanone hydrochloride (35·HCl): Method A produced, after extraction with EtOAc, a dark-red solid that was subjected to chromatography twice (silica gel, EtOAc/MeOH 9:1) and finally recrystallized from 2-propanol to afford the free base as a light-orange solid (243 mg, 35%). The hydrochloride was obtained in the usual manner in acetone as a white solid (249 mg, 31% overall); mp: 243–245 °C (2-propanol) (lit.[26] mp: 211–216 °C, dec.); ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 6.20 (s, 2H), 7.73 (t, *J* = 1.4 Hz, 1H), 7.76 (t, *J* = 1.4 Hz, 1H), 8.30 (d, *J* = 8.8. Hz, 2H), 8.44 (d, *J* = 8.8 Hz, 2H), 9.16 ppm (s, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 55.4, 119.3, 123.5, 124.1, 129.6, 136.5, 138.4, 150.5, 191.0 ppm; HRMS-ESI *m/z* $[M-Cl]^+$ calcd for $C_{11}H_{10}N_3O_3$: 232.0722, found: 232.0719.

1-(Biphenyl-4-yl)-2-(1*H*-imidazol-1-yl)ethanone hydrochloride (36·HCl): Method B afforded the product as a white solid (412 mg, 46%); mp: 235–237 °C (EtOH); ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 6.14 (s, 2H), 7.42–7.50 (m, 1H), 7.50–7.58 (m, 2H), 7.71–7.77 (m, 2H), 7.78–7.85 (m, 2H), 7.95 (d, *J* = 8.8 Hz, 2H), 8.14 (d, *J* = 8.8 Hz, 2H), 9.16 ppm (br s, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 55.0, 119.3, 123.5, 127.0, 127.1, 128.6, 128.8, 129.1, 132.5, 136.5, 138.5, 145.6, 191.0 ppm; HRMS-ESI *m/z* $[M-Cl]^+$ calcd for $C_{17}H_{15}N_2O$: 263.1184, found: 263.1180.

1-(4′-Bromobiphenyl-4-yl)-2-(1*H*-imidazol-1-yl)ethanone (37): Method B gave a mixture from which the desired compound was separated using column chromatography (silica gel, EtOAc/MeOH 9:1). Recrystallization from EtOH afforded the product as a white solid (471 mg, 46%); mp: 223–225 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 5.77 (s, 2H), 6.94 (s, 1H), 7.14 (s, 1H), 7.61 (s, 1H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.91 (d, *J* = 8.4 Hz, 2H), 8.12 ppm (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 52.6, 120.9, 122.2, 127.0, 127.9, 128.8, 129.2, 132.0, 133.6, 137.9, 138.4, 143.8, 193.2 ppm; HRMS-EI *m/z* $[M]^+$ calcd for $C_{17}H_{13}BrN_2O$: 340.0211, found: 340.0212.

1-[4-(Benzyl)phenyl]-2-(1*H*-imidazol-1-yl)ethanone hydrochloride (38·HCl): Method B afforded the product as a light-tan solid (554 mg, 59%); mp: 185–186 °C (2-propanol); ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 4.07 (s, 2H), 6.06 (s, 2H), 7.18–7.34 (m, 5H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.70 (t, *J* = 1.6 Hz, 1H), 7.72 (t, *J* = 1.6 Hz, 1H), 7.99 (d, *J* = 8.4 Hz, 2H), 9.13 ppm (s, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 40.9, 54.9, 119.2, 123.5, 126.2, 128.4, 128.5, 128.7, 129.3, 131.7, 136.5, 140.3, 148.4, 191.0 ppm; HRMS-ESI *m/z* $[M-Cl]^+$ calcd for $C_{18}H_{17}N_2O$: 277.1335, found: 277.1330.

2-(1*H*-Imidazol-1-yl)-1-[4-(2-phenylethyl)phenyl]ethanone hydrochloride (39·HCl): Method B, using CH_2Cl_2 instead of EtOAc for the extraction process, afforded the product as a white solid (627 mg, 64%); mp: 238–240 °C (2-propanol); ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 2.90–2.98 (m, 2H), 2.98–3.06 (m, 2H), 6.01 (s, 2H), 7.15–7.31 (m, 5H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.68 (t, *J* = 1.6 Hz, 1H), 7.72 (t, *J* = 1.6 Hz, 1H), 7.96 (d, *J* = 8.4 Hz, 2H), 9.05 ppm (s, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 36.4, 36.8, 54.9, 119.3, 123.5, 125.9, 128.2, 128.3, 128.4, 129.1, 131.6, 136.5, 140.9, 148.8, 191.0 ppm; HRMS-ESI *m/z* $[M-Cl]^+$ calcd for $C_{19}H_{19}N_2O$: 291.1491, found: 291.1493.

1-[4-(Benzyloxy)phenyl]-2-(1*H*-imidazol-1-yl)ethanone (40): Method A gave a solid that was decolorized using charcoal and recrystallized to afford the product as a pale-yellow solid (290 mg, 33%); mp: 177–178 °C (EtOH); ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 5.25 (s, 2H), 5.67 (s, 2H), 6.91 (s, 1H), 7.10 (s, 1H), 7.19 (d, *J* = 8.8 Hz, 2H), 7.32–7.50 (m, 5H), 7.58 (s, 1H), 8.01 ppm (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 52.2, 69.6, 115.0, 120.9, 127.5, 127.7, 127.8, 128.1, 128.5, 130.3, 136.4, 138.3, 162.7, 191.8 ppm; HRMS-EI *m/z* $[M]^+$ calcd for $C_{18}H_{16}N_2O_2$: 292.1212, found: 292.1212.

1-(4-Cyclohexylphenyl)-2-(1*H*-imidazol-1-yl)ethanone hydrochloride (41·HCl): Method B afforded the product as a white solid (477 mg, 52%); mp: 242–244 °C (2-propanol); ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.18–1.53 (m, 5H), 1.72 (d, *J* = 12.4 Hz, 1H), 1.80 (d, *J* = 12.0 Hz, 4H), 2.61–2.69 (m, 1H), 6.07 (s, 2H), 7.48 (d, *J* = 8.0 Hz, 2H), 7.71 (s, 1H), 7.73 (s, 1H), 7.98 (d, *J* = 8.0 Hz, 2H), 9.14 ppm (s, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 25.4, 26.0, 33.4, 43.8, 54.8, 119.2, 123.4, 127.3, 128.3, 131.6, 136.5, 154.5, 190.9 ppm; HRMS-ESI *m/z* $[M-Cl]^+$ calcd for $C_{17}H_{21}N_2O$: 269.1648, found: 269.1651.

2-(1*H*-Imidazol-1-yl)-1-(naphthalen-1-yl)ethanone hydrochloride (42·HCl): Method A afforded the product as a white solid (376 mg, 46%); mp: 215–216 °C (2-propanol/Et_2O); ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 6.18 (s, 2H), 7.60–7.76 (m, 3H), 7.77 (s, 1H), 7.83 (s, 1H), 8.08 (d, *J* = 7.6 Hz, 1H), 8.29 (d, *J* = 8.0 Hz, 1H), 8.39 (d, *J* = 7.2 Hz, 1H), 8.65 (d, *J* = 8.4 Hz, 1H), 9.25 ppm (s, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 56.5, 119.3, 123.6, 124.8, 125.2, 126.6, 128.4, 128.7, 129.6 (2C), 130.9, 133.5, 134.2, 136.7, 194.3 ppm; HRMS-ESI *m/z* $[M-Cl]^+$ calcd for $C_{15}H_{13}N_2O$: 237.1027, found: 237.1033.

2-(1*H*-Imidazol-1-yl)-1-(naphthalen-2-yl)ethanone hydrochloride (43·HCl): A mixture of 2-bromo-1-(naphthalen-1-yl)ethanone

(1245 mg, 5 mmol), imidazole (340 mg, 5 mmol), and Et_3N (505 mg, 5 mmol) in acetone (20 mL) was heated at reflux for 8 h, and then was concentrated to dryness under reduced pressure. The residue was partitioned between EtOAc (30 mL) and H_2O (30 mL), the aqueous phase was further extracted with EtOAc (30 mL), and then the combined organic phases were washed with H_2O and dried (Na_2SO_4). Evaporation to dryness gave a solid that was extracted with hot benzene (100 mL); filtration and evaporation of benzene afforded 2-(1*H*-imidazol-1-yl)-1-(naphthalen-2-yl)ethanone (**43**), which was transformed in the usual manner into the hydrochloride, which was isolated as a white solid (311 mg, 38%); mp: 224–226 °C (EtOH) (lit.[51] mp: 226–228.5 °C); ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 6.24 (s, 2H), 7.64–7.82 (m, 4H), 7.98–8.10 (m, 2H), 8.13 (d, J = 8.4 Hz, 1H), 8.20 (d, J = 8.4 Hz, 1H), 8.85 (s, 1H), 9.19 ppm (s, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 55.1, 119.4, 123.2, 123.6, 127.4, 127.9, 128.8, 129.3, 129.7, 130.5, 131.1, 132.1, 135.5, 136.6, 191.5 ppm; HRMS-ESI m/z $[M-Cl]^+$ calcd for $C_{15}H_{13}N_2O$: 237.1027, found: 237.1033.

1-(3,4-Dichlorophenyl)-2-(1*H*-imidazol-1-yl)ethanone hydrochloride (44·HCl): Method B afforded the product as a white solid (315 mg, 36%); mp: 211–213 °C (2-propanol); ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 6.11 (s, 2H), 7.70 (t, J = 1.6 Hz, 1H), 7.74 (t, J = 1.6 Hz, 1H), 7.93 (d, J = 8.4 Hz, 1H), 8.02 (dd, J = 8.4 and 2.4 Hz, 1H), 8.29 (d, J = 2.4 Hz, 1H), 9.13 ppm (s, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 55.0, 119.4, 123.4, 128.1, 130.0, 131.4, 132.1, 134.0, 136.5, 137.1, 190.0 ppm; HRMS-ESI m/z $[M-Cl]^+$ calcd for $C_{11}H_9Cl_2N_2O$: 255.0091, found: 255.0098.

1-(2,4-Dichlorophenyl)-2-(1*H*-imidazol-1-yl)ethanone hydrochloride (45·HCl): Method B gave, after processing of the reaction mixture, a residue from which the title compound was separated as the free base (**45**) by column chromatography (silica gel, EtOAc/MeOH 9:1, R_f = 0.36). The hydrochloride was obtained in the usual manner as a white solid (414 mg, 47%); mp: 192–193 °C (2-propanol); ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 6.02 (s, 2H), 7.68–7.77 (m, 3H), 7.86 (d, J = 2.0 Hz, 1H), 8.12 (d, J = 8.4 Hz, 1H), 9.19 ppm (s, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 56.8, 119.4, 123.4, 127.8, 130.8, 132.2, 132.4, 132.6, 136.6, 138.0, 191.6 ppm; HRMS-ESI m/z $[M-Cl]^+$ calcd for $C_{11}H_9Cl_2N_2O$: 255.0091, found: 255.0095.

1-(2,5-Dichlorophenyl)-2-(1*H*-imidazol-1-yl)ethanone hydrochloride (46·HCl): Method B gave, after processing of the reaction mixture, a residue from which the title compound was separated as the free base (**46**) by column chromatography (silica gel, EtOAc/MeOH 9:1, R_f = 0.32). The hydrochloride was obtained in the usual manner as a white solid (490 mg, 56%); mp: 213–214 °C (2-propanol); ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 6.05 (s, 2H), 7.69 (d, J = 8.4 Hz, 1H), 7.72–7.79 (m, 3H), 8.19 (d, J = 2.4 Hz, 1H), 9.22 ppm (s, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 56.8, 119.5, 123.4, 129.8, 130.2, 132.2, 132.9, 133.5, 135.4, 136.6, 191.8 ppm; HRMS-ESI m/z $[M-Cl]^+$ calcd for $C_{11}H_9Cl_2N_2O$: 255.0091, found: 255.0091.

2-(1*H*-Imidazol-1-yl)-1-(2,3,4-trichlorophenyl)ethanone hydrochloride (47·HCl): Method B afforded the product as a pale-pink solid (440 mg, 45%); mp: 236–237 °C (2-propanol); ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 6.03 (s, 2H), 7.75 (t, J = 1.4 Hz, 1H), 7.77 (t, J = 1.4 Hz, 1H), 7.94 (d, J = 8.4 Hz, 1H), 8.07 (d, J = 8.4 Hz, 1H), 9.23 ppm (s, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 56.9, 119.5, 123.4, 129.0, 129.3, 130.9, 132.2, 135.0, 136.6, 192.1 ppm; HRMS-ESI m/z $[M-Cl]^+$ calcd for $C_{11}H_8Cl_3N_2O$: 288.9696, found: 288.9700.

(±)-2-(1*H*-Imidazol-1-yl)-1-phenylpropan-1-one hydrochloride (48·HCl): Method B afforded a white solid (554 mg, 78%); mp: 174–176 °C (2-propanol/Et_2O) (lit.[52] mp: 179–181 °C); ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.78 (d, J = 7.6 Hz, 3H), 6.72 (q, J = 7.6 Hz, 1H), 7.55–7.66 (m, 2H), 7.69–7.77 (m, 2H), 7.90 (d, J = 1.6 Hz, 1H), 8.09 (d, J = 8.0 Hz, 2H), 9.40 ppm (s, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 18.1, 59.5, 119.2, 122.1, 128.9, 129.1, 133.1, 134.4, 135.7, 195.0 ppm; HRMS-ESI m/z $[M-Cl]^+$ calcd for $C_{12}H_{13}N_2O$: 201.1027, found: 201.1018.

2-(1*H*-Imidazol-1-yl)-2-methyl-1-phenylpropan-1-one hydrochloride (49·HCl): Method B, with the reaction performed at 60–70 °C instead of room temperature, afforded the product as a white solid (338 mg, 45%); mp: 183–184 °C (2-propanol/Et_2O); ^{1}H NMR (400 MHz, CD_3OD): δ = 2.11 (s, 6H), 7.41–7.49 (m, 2H), 7.55–7.64 (m, 2H), 7.65–7.71 (m, 2H), 7.79 (brs, 1H), 9.27 ppm (brs, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ = 26.6, 70.8, 121.2, 122.5, 129.5, 129.9, 134.2, 135.8, 136.2, 199.2 ppm; HRMS-ESI m/z $[M-Cl]^+$ calcd for $C_{13}H_{15}N_2O$: 215.1178, found: 215.1174.

(±)-2-(1*H*-Imidazol-1-yl)-1,2-diphenylethanone hydrochloride (50·HCl): Method B produced, after processing of the reaction mixture, a brown oil from which the title compound was separated as the free base **50** by column chromatography (silica gel, EtOAc, R_f = 0.31). The hydrochloride was prepared in the usual manner; treatment with charcoal and recrystallization afforded the product as a white solid (538 mg, 60%); mp: 171–173 °C (2-propanol/Et_2O); ^{1}H NMR (400 MHz, CD_3OD): δ = 7.44–7.53 (m, 5H), 7.54–7.65 (m, 4H), 7.66–7.69 (m, 1H), 7.75–7.80 (m, 1H), 8.01–8.07 (m, 2H), 9.02 ppm (brs, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ = 69.3, 120.5, 123.8, 130.1, 130.4, 130.6, 131.3, 131.6, 133.9, 135.0, 135.6, 137.1, 193.0 ppm; HRMS-ESI m/z $[M-Cl]^+$ calcd for $C_{17}H_{15}N_2O$: 263.1184, found: 263.1187.

(±)-2,3-Dihydro-2-(1*H*-imidazol-1-yl)-1*H*-inden-1-one hydrochloride (51·HCl): Method B gave, after processing of the reaction mixture, a brown tar from which the title compound was separated as the free base **51** by column chromatography (silica gel, EtOAc/MeOH 9:1, R_f = 0.56). The hydrochloride was prepared in the usual manner; treatment with charcoal and recrystallization afforded the product as a white solid (183 mg, 26%); mp: 110–111 °C (2-propanol/Et_2O); ^{1}H NMR (400 MHz, CD_3OD): δ = 3.61 (dd, J = 16.8 and 6.0 Hz, 1H), 4.01 (dd, J = 16.8 and 8.8 Hz, 1H), 5.69 (dd, J = 8.8 and 6.0 Hz, 1H), 7.51–7.60 (m, 1H), 7.63–7.72 (m, 2H), 7.74–7.87 (m, 3H), 9.21 ppm (s, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ = 34.5, 64.4, 121.5, 122.5, 125.6, 128.1, 129.9, 134.7, 137.2, 137.9, 152.1, 199.1 ppm; HRMS-ESI m/z $[M-Cl]^+$ calcd for $C_{12}H_{11}N_2O$: 199.0871, found: 199.0876.

2-(1*H*-Imidazol-1-yl)-1-(thiophen-2-yl)ethanone hydrochloride (52·HCl): Method A gave, after processing of the reaction mixture, a brown solid that was turned into the hydrochloride in the usual manner using acetone as solvent. Acetone was removed using a pipette, the pale-red residue was dissolved in 2-propanol (3 mL), the solution was diluted with EtOAc, and a gum-like precipitate was formed. The mixture was kept in the refrigerator overnight, and the gum turned into a gray solid which was removed by filtration. The solid was dissolved in MeOH and the solution was treated with charcoal. Evaporation of the solvent afforded a residue that was recrystallized to give the product as a white solid (206 mg, 30%); mp: 183–184 °C (2-propanol/EtOAc); ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 6.03 (s, 2H), 7.38 (dd, J = 4.0 and 4.8 Hz, 1H), 7.70–7.78 (m, 2H), 8.17–8.23 (m, 2H), 9.16 ppm (s, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 54.5, 119.4, 123.5, 129.2, 134.6, 136.4, 136.6, 139.7, 184.6 ppm; HRMS-ESI m/z $[M-Cl]^+$ calcd for $C_9H_9N_2OS$: 193.0435, found: 193.0430.

Synthesis of 1,2,4-triazole-ketones: A mixture of α-bromoketone (5 mmol), 1,2,4-1*H*-triazole (483 mg, 7 mmol), and Et_3N (505 mg, 5 mmol) was heated at reflux in acetone (15 mL) for 6 h. The solvent was removed under reduced pressure, and the residue was partitioned between H_2O (50 mL) and EtOAc (30 mL). The aqueous phase was further extracted with EtOAc (30 mL), and then the combined organic phases were successively washed with H_2O (100 mL) and brine (20 mL), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to afford a residue that was

purified as described in each case. The hydrochlorides of the triazole-ketones were usually prepared by treating the solution of the free bases in acetone, acetone/Et_2O, or 2-propanol with a twofold molar excess of 37% aqueous HCl.

1-Phenyl-2-(1,2,4-1*H*-triazol-1-yl)ethanone hydrochloride (53·HCl): The residue resulting from the processing of the reaction mixture afforded the hydrochloride directly as a white solid (224 mg, 20%); mp: 201–203 °C (2-propanol); ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 6.02 (s, 2H), 7.56–7.64 (m, 2H), 7.70–7.77 (m, 1H), 8.02–8.09 (m, 2H), 8.12 (br s, 1H), 8.63 ppm (br s, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 56.0, 128.2, 129.0, 134.0, 134.3, 145.0, 149.1, 192.1 ppm; HRMS-ESI *m/z* $[M-Cl]^+$ calcd for $C_{10}H_{10}N_3O$: 188.0823, found: 188.0828.

1-(4-Chlorophenyl)-2-(1,2,4-1*H*-triazol-1-yl)ethanone hydrochloride (54·HCl) and 1-(4-chlorophenyl)-2-(1,2,4–4*H*-triazol-4-yl)-ethanone (54a): Column chromatography of the residue (silica gel, EtOAc) yielded 1-(4-chlorophenyl)-2-(1,2,4-1*H*-triazol-1-yl)ethanone (**54**) as a yellow solid, which was recrystallized from 2-propanol to give white crystals (523 mg, 47%); R_f = 0.35 (EtOAc); mp: 152–153 °C (lit.[53] mp: 147 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.63 (s, 2H), 7.50 (d, J = 8.8 Hz, 2H), 7.91 (d, J = 8.8 Hz, 2H), 7.99 (s, 1H), 8.22 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.0, 129.6, 129.7, 132.4, 141.3, 144.9, 152.1, 189.6 ppm. This free base **54** (222 mg, 1 mmol) was transformed into the corresponding hydrochloride in the usual manner to afford white crystals (219 mg, 85%); mp: 211–213 °C (EtOH); ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 6.08 (s, 2H), 7.64–7.72 (m, 2H), 8.02–8.11 (m, 2H), 8.31 (s, 1H), 8.89 ppm (s, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 55.8, 129.2, 130.1, 132.8, 139.2, 145.1, 149.6, 191.4 ppm; HRMS-ESI *m/z* $[M-Cl]^+$ calcd for $C_{10}H_9ClN_3O$: 222.0434, found: 222.0425. Further elution using EtOAc/MeOH (4:1) yielded a solid that was recrystallized from EtOH to give compound **54a** as white crystals (90 mg, 8%); R_f = 0.22 (EtOAc/MeOH, 9:1); mp: 244–245 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 5.84 (s, 2H), 7.70 (d, J = 8.8 Hz, 2H), 8.05 (d, J = 8.8 Hz, 2H), 8.43 ppm (s, 2H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 50.9, 129.1, 129.9, 132.8, 139.0, 144.1, 191.8 ppm; HRMS-EI *m/z* $[M]^+$ calcd for $C_{10}H_8ClN_3O$: 221.0356, found: 221.0346.

1-(3-Bromophenyl)-2-(1,2,4-1*H*-triazol-1-yl)ethanone (55): Column chromatography (silica gel, EtOAc) afforded the product as a pale-yellow solid (600 mg, 45%); R_f = 0.31 (EtOAc); mp: 91–92 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.64 (s, 2H), 7.42 (t, J = 8.0 Hz, 1H), 7.78 (ddd, J = 0.8, 1.6 and 8.0 Hz, 1H), 7.89 (ddd, J = 0.8, 2.0 and 8.0 Hz, 1H), 7.99 (s, 1H), 8.10 (t, J = 2.0 Hz, 1H), 8.22 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.1, 123.6, 126.7, 130.8, 131.3, 135.8, 137.5, 144.9, 152.2, 189.6 ppm; HRMS-EI *m/z* $[M]^+$ calcd for $C_{10}H_8BrN_3O$: 264.9851, found: 264.9852.

1-(4-Bromophenyl)-2-(1,2,4-1*H*-triazol-1-yl)ethanone (56): Column chromatography (silica gel, EtOAc/MeOH 14:1) afforded the free base as a pale-yellow solid that was recrystallized to an off-white solid (520 mg, 39%); R_f = 0.44 (EtOAc/MeOH 14:1); mp: 179–180 °C (2-propanol) (lit.[54] mp: 178–180 °C); ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 5.99 (s, 2H), 7.82 (d, J = 8.4 Hz, 2H), 7.98 (d, J = 8.4 Hz, 2H), 8.03 (s, 1H), 8.51 ppm (s, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 55.2, 128.3, 130.1, 132.1, 133.2, 145.6, 151.3, 192.0 ppm; HRMS-EI *m/z* $[M]^+$ calcd for $C_{10}H_8BrN_3O$: 264.9851, found: 264.9844.

1-(4-Nitrophenyl)-2-(1,2,4-1*H*-triazol-1-yl)ethanone hydrochloride (57·HCl): Column chromatography (silica gel, EtOAc/MeOH 14:1) afforded the free base **57** as a dark-brown solid (R_f = 0.47), which was treated with 37% aqueous HCl in 2-propanol to give the hydrochloride as a brown solid (119 mg, 9%); mp: 216–218 °C (EtOH); ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 6.16 (s, 2H), 8.24–8.32 (m, 3H), 8.37–8.44 (m, 2H), 8.82 ppm (s, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 56.1, 124.1, 129.7, 138.7, 145.2, 150.0, 150.5, 191.8 ppm; HRMS-ESI *m/z* $[M-Cl]^+$ calcd for $C_{10}H_9N_4O_3$: 233.0674, found: 233.0664.

1-(Biphenyl-4-yl)-2-(1,2,4-1*H*-triazol-1-yl)ethanone (58): Extraction of the residue with benzene (50 mL), followed by removal of the solvent under reduced pressure and recrystallization of the resulting residue from 2-propanol gave the product as a yellow solid (603 mg, 46%); mp: 172–173 °C (lit.[55] mp: 123–125 °C); ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 6.04 (s, 2H), 7.41–7.49 (m, 1H), 7.49–7.57 (m, 2H), 7.76–7.83 (m, 2H), 7.91 (d, J = 8.4 Hz, 2H), 8.04 (s, 1H), 8.14 (d, J = 8.4 Hz, 2H), 8.54 ppm (s, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 55.2, 127.1, 128.6, 128.9, 129.2, 133.0, 138.6, 145.4, 145.6, 151.3, 192.1 ppm; HRMS-EI *m/z* $[M]^+$ calcd for $C_{16}H_{13}N_3O$: 263.1059, found: 263.1047.

1-(4-Benzylphenyl)-2-(1,2,4-1*H*-triazol-1-yl)ethanone hydrochloride (59·HCl): Column chromatography (silica gel, EtOAc/hexanes 2:1) yielded the free base **59** as a pale-yellow solid (R_f = 0.34), which was treated with 37% HCl in acetone/Et_2O to give the hydrochloride as a white solid (284 mg, 30%); mp: 180–182 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 4.06 (s, 2H), 6.03 (s, 2H), 7.16–7.35 (m, 5H), 7.46 (d, J = 8.0 Hz, 2H), 7.98 (d, J = 8.0 Hz, 2H), 8.29 (s, 1H), 8.86 ppm (s, 2H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 41.0, 55.7, 126.3, 128.5, 128.6, 128.8, 129.3, 132.1, 140.4, 145.1, 148.3, 149.6, 191.7 ppm; HRMS-ESI *m/z* $[M-Cl]^+$ calcd for $C_{17}H_{16}N_3O$: 278.1287, found: 278.1284.

1-(Naphthalen-1-yl)-2-(1,2,4-1*H*-triazol-1-yl)ethanone hydrochloride (60·HCl): Column chromatography (silica gel, EtOAc/MeOH 14:1) yielded the free base **60** as a yellow solid (R_f = 0.60), which gave upon treatment with 37% aqueous HCl in acetone the hydrochloride as a white solid (688 mg, 50%); mp: 209–210 °C (EtOH); ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 6.16 (s, 2H), 7.57–7.74 (m, 3H), 8.06 (d, J = 8.0 Hz, 1H), 8.25 (d, J = 8.4 Hz, 1H), 8.37 (d, J = 7.2 Hz, 1H), 8.41 (s, 1H), 8.59 (d, J = 8.4 Hz, 1H), 9.11 ppm (s, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 57.5, 124.9, 125.1, 126.8, 128.4, 128.8, 129.6, 131.3, 133.6, 134.1, 145.1, 149.1, 195.1 ppm; HRMS-ESI *m/z* $[M-Cl]^+$ calcd for $C_{14}H_{12}N_3O$: 238.0974, found: 238.0973.

1-(Naphthalen-2-yl)-2-(1,2,4-1*H*-triazol-1-yl)ethanone hydrochloride (61·HCl): Recrystallization of the residue from 2-propanol afforded the free base **61** as a yellow solid, which was converted by treatment with 37% aqueous HCl in acetone into the hydrochloride, which was obtained as a white solid (236 mg, 17%); mp: 203–205 °C (EtOH) (lit.[56] mp: 196–197 °C); ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 6.22 (s, 2H), 7.64–7.76 (m, 2H), 7.99–8.07 (m, 2H), 8.10 (d, J = 8.8 Hz, 1H), 8.16 (d, J = 8.0 Hz, 1H), 8.34 (s, 1H), 8.85 (s, 1H), 8.96 ppm (s, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 55.8, 123.3, 127.3, 127.9, 128.7, 129.2, 129.7, 130.6, 131.3, 132.1, 135.5, 145.2, 149.6, 192.1 ppm HRMS-ESI *m/z* $[M-Cl]^+$ calcd for $C_{14}H_{12}N_3O$: 238.0980, found: 238.0985.

1-(3,4-Dichlorophenyl)-2-(1,2,4-1*H*-triazol-1-yl)ethanone hydrochloride (62·HCl): Column chromatography (silica gel, EtOAc/MeOH 14:1) yielded the free base **62** as a yellow solid (R_f = 0.53), which was treated with 37% aqueous HCl in acetone/Et_2O to give the hydrochloride as a white solid (214 mg, 16%); mp: 224–226 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 6.09 (s, 2H), 7.89 (d, J = 8.4 Hz, 1H), 8.00 (dd, J = 2.0 and 8.4 Hz, 1H), 8.26 (s, 1H), 8.29 (d, J = 2.0 Hz, 1H), 8.81 ppm (s, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 55.8, 128.2, 130.2, 131.4, 132.1, 134.3, 137.0, 145.2, 149.9, 190.8 ppm; HRMS-ESI *m/z* $[M-Cl]^+$ calcd for $C_{10}H_8Cl_2N_3O$: 256.0044, found: 256.0035.

1-(2,4-Dichlorophenyl)-2-(1,2,4-1*H*-triazol-1-yl)ethanone (63): Column chromatography (silica gel, EtOAc) yielded the free base as a pale-yellow solid (611 mg, 48%); R_f = 0.37 (EtOAc); mp: 76–77 °C (lit.[53] mp: 117 °C); ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 5.85 (s, 2H), 7.64 (dd, J = 2.0 and 8.4 Hz, 1H), 7.81 (d, J = 2.0 Hz, 1H), 7.95 (d, J = 8.4 Hz, 1H), 8.03 (s, 1H), 8.53 ppm (s, 1H); ^{13}C NMR (100 MHz,

[D_6]DMSO): $\delta = 57.1$, 127.7, 130.5, 131.4, 132.0, 133.6, 137.4, 145.6, 151.5, 193.4 ppm; HRMS-EI *m/z* $[M]^+$ calcd for $C_{10}H_7Cl_2N_3O$: 254.9966, found: 254.9968.

1-(2,5-Dichlorophenyl)-2-(1,2,4-1*H*-triazol-1-yl)ethanone (64): Column chromatography (silica gel, EtOAc) yielded the free base as a pale-yellow solid (515 mg, 40%); $R_f = 0.57$ (EtOAc); mp: 115–116 °C; ^{1}H NMR (400 MHz, [D_6]DMSO): $\delta = 5.86$ (s, 2H), 7.62–7.72 (m, 2H), 8.00–8.05 (m, 2H), 8.53 ppm (s, 1H); ^{13}C NMR (100 MHz, [D_6]DMSO): $\delta = 57.2$, 129.3, 129.4, 132.1, 132.6, 133.0, 136.4, 145.5, 151.6, 193.5 ppm; HRMS-EI *m/z* $[M]^+$ calcd for $C_{10}H_7Cl_2N_3O$: 254.9966, found: 254.9960.

General procedure for the synthesis of 2-aryl-2-bromomethyl-1,3-dioxolanes: A mixture of 1-aryl-2-bromoethanone (10 mmol), ethylene glycol (2.5 g, 40 mmol), and *p*-toluenesulfonic acid monohydrate (100 mg) in benzene (40 mL) was heated at reflux for 8 h with azeotropic removal of H_2O. The Dean–Stark trap was then emptied, fresh benzene (10–15 mL) was added in the flask, and the mixture was heated at reflux for another 8 h with azeotropic removal of H_2O. At the end of the reaction time, the solvent was partially removed under reduced pressure, EtOAc (40 mL) was added, and the organic phase was washed sequentially with saturated $NaHCO_3$ (2×25 mL), H_2O, brine, and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford the pure bromomethyl-dioxolane in almost quantitative yield.

2-(Bromomethyl)-2-phenyl-1,3-dioxolane (65): Acetophenone was converted into the 1,3-dioxolane **65** by a specific procedure[32] as follows. A mixture of acetophenone (1.2 g, 10 mmol), trimethylphenylammonium tribromide (5.64 g, 15 mmol), and ethylene glycol (12 mL) in THF (12 mL) was stirred at room temperature for 22 h. The reaction mixture was poured onto a mixture of 10% aqueous $NaHCO_3$ (250 mL) and 5% aqueous $Na_2S_2O_3$ (25 mL), and the mixture was extracted with EtOAc (2×100 mL). The organic phase was washed sequentially with H_2O (3×100 mL) and brine, dried (Na_2SO_4), and then the solvent was removed under reduced pressure to give an oily solid (2.4 g) that was recrystallized repeatedly from small volumes of MeOH. Compound **65** was obtained as a solid in 34% yield; mp: 58–59 °C (lit.[32] mp: 61 °C, lit.[57] mp: 59–60 °C); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.67$ (s, 2H), 3.85–3.95 (m, 2H), 4.14–4.24 (m, 2H), 7.33–7.40 (m, 3H), 7.49–7.54 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 38.4$, 66.0, 107.4, 126.1, 128.5, 128.9, 139.8 ppm.

2-Bromomethyl-2-(4-chlorophenyl)-1,3-dioxolane (66): The General Procedure gave the product as a clear oil (2.7 g, 97%) that did not solidify even when stored at −20 °C (lit.[23] mp: 61–62 °C); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.62$ (s, 2H), 3.83–3.94 (m, 2H), 4.13–4.23 (m, 2H), 7.34 (d, $J = 6.8$ Hz, 2H), 7.45 ppm (d, $J = 6.8$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 38.0$, 66.0, 107.1, 127.7, 128.7, 135.0, 138.4 ppm.

2-(Bromomethyl)-2-(3-bromophenyl)-1,3-dioxolane (67): The General Procedure gave the product as a white solid (3.09 g, 96%); mp: 54–55 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.62$ (s, 2H), 3.85–3.95 (m, 2H), 4.14–4.24 (m, 2H), 7.24 (t, $J = 8.0$ Hz, 1H), 7.43 (ddd, $J = 1.0$, 1.6 and 8.0 Hz, 1H), 7.47 (ddd, $J = 1.0$, 2.0, and 8.0 Hz, 1H), 7.67 ppm (t, $J = 2.0$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 38.0$, 66.1, 106.8, 122.6, 124.9, 129.4, 130.1, 132.1, 142.3 ppm.

2-Bromomethyl-2-(4-bromophenyl)-1,3-dioxolane (68): The General Procedure gave the product as a white solid (3.05 g, 95%); mp: 80–81 °C (lit.[57] mp: 82–83 °C); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.61$ (s, 2H), 3.83–3.94 (m, 2H), 4.13–4.23 (m, 2H), 7.38 (d, $J = 8.8$ Hz, 2H), 7.49 ppm (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 37.9$, 66.0, 107.1, 123.2, 128.0, 131.6, 138.9 ppm.

2-(Biphenyl-4-yl)-2-bromomethyl-1,3-dioxolane (69): The General Procedure gave a colorless oil that was triturated with EtOH to afford the product as white crystals (2.84 g, 89%); mp: 78–79 °C (lit.[57] mp: 79.5–80 °C); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.72$ (s, 2H), 3.90–4.00 (m, 2H), 4.17–4.27 (m, 2H), 7.34–7.40 (m, 1H), 7.42–7.49 (m, 2H), 7.57–7.64 ppm (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 38.3$, 66.0, 107.4, 126.6, 127.2, 127.3, 127.7, 129.0, 138.7, 140.7, 141.9 ppm; HRMS-EI *m/z* $[M]^+$ calcd for $C_{16}H_{15}BrO_2$: 318.0255, found: 318.0252.

2-(4-Benzylphenyl)-2-bromomethyl-1,3-dioxolane (70): The General Procedure gave the product as a light-yellow oil (3.3 g, 99%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.66$ (s, 2H), 3.85–3.94 (m, 2H), 3.99 (s, 2H), 4.13–4.23 (m, 2H), 7.16–7.25 (m, 5H), 7.27–7.34 (m, 2H), 7.43 ppm (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 38.4$, 41.8, 65.9, 107.3, 126.2, 126.3, 128.6, 128.9, 129.1, 137.5, 140.8, 142.0 ppm.

2-Bromomethyl-2-(naphthalen-2-yl)-1,3-dioxolane (71): The General Procedure gave the product as a white solid (2.9 g, 99%); mp: 53–54 °C (lit.[58] mp: 64 °C); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.76$ (s, 2H), 3.90–4.00 (m, 2H), 4.19–4.29 (m, 2H), 7.47–7.56 (m, 2H), 7.59 (dd, $J = 2.0$ and 8.8 Hz, 1H), 7.80–7.91 (m, 3H), 8.02 ppm (d, $J = 1.2$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 38.2$, 66.0, 107.6, 123.8, 125.5, 126.5, 126.7, 127.8, 128.4, 128.5, 133.0, 133.5, 137.1 ppm.

2-Bromomethyl-2-(3,4-dichlorophenyl)-1,3-dioxolane (72): The General Procedure gave the product as a pale-yellow oil (3.1 g, 99%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.60$ (s, 2H), 3.85–3.95 (m, 2H), 4.14–4.24 (m, 2H), 7.34 (dd, $J = 2.0$ and 8.4 Hz, 1H), 7.44 (d, $J = 8.4$ Hz, 1H), 7.61 ppm (d, $J = 2.0$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 37.6$, 66.1, 106.6, 125.7, 128.4, 130.5, 132.7, 133.2, 140.2 ppm.

2-(Bromomethyl)-2-(2,4-dichlorophenyl)-1,3-dioxolane (73): Following the General Procedure except that heating was conducted for 30 h instead of 16 h gave the product as a slightly yellow oil (3.0 g, 96%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.90$ (s, 2H), 3.89–3.95 (m, 2H), 4.16–4.24 (m, 2H), 7.25 (dd, $J = 2.0$ and 8.4 Hz, 1H), 7.41 (d, $J = 2.0$ Hz, 1H), 7.63 ppm (d, $J = 8.4$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 35.9$, 66.1, 107.2, 127.0, 130.0, 131.3, 133.1, 135.2, 135.6 ppm.

General procedure for the synthesis of imidazole-dioxolanes and 1,2,4-triazole-dioxolanes: A mixture of imidazole or 1*H*-1,2,4-triazole (6 mmol) and NaOH (6 mmol) in DMSO (6 mL) was stirred at 60–70 °C for 1 h, then the bromomethyl-dioxolane (2 mmol) was added in one portion. After the mixture had been stirred at 60–80 °C overnight, it was cooled to room temperature and diluted with H_2O (30 mL). If a solid separated at this stage, it was removed by filtration and washed thoroughly with H_2O. If dilution with H_2O produced an oil, the mixture was extracted with EtOAc (2×30 mL), the combined organic phase was washed sequentially with H_2O (50 mL) and brine, and dried (Na_2SO_4). The solvent was removed under reduced pressure to give a residue that was purified as described in each case.

1-[(2-Phenyl-1,3-dioxolan-2-yl)methyl]-1*H*-imidazole hydrochloride (74·HCl): Following the General Procedure using compound **65** and imidazole, the final residue was converted into the hydrochloride by treating its solution in 2-propanol with a twofold molar excess of 37% aqueous HCl. The solid was removed by filtration and recrystallized to give the product as white crystals (380 mg, 71%); mp: 258–259 °C (2-propanol); ^{1}H NMR (400 MHz, CD_3OD): $\delta = 3.77$–3.84 (m, 4H), 4.64 (s, 2H), 7.37–7.46 (m, 3H), 7.52–7.58 (m, 3H), 7.61 (t, $J = 1.6$ Hz, 1H), 8.93 ppm (t, $J = 1.2$ Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD): $\delta = 56.0$, 66.4, 108.2, 120.1, 125.3, 127.0, 129.7, 130.4, 137.8, 139.9 ppm; HRMS-ESI *m/z* $[M-Cl]^+$ calcd for $C_{13}H_{15}N_2O_2$: 231.1128, found: 231.1131.

1-{[2-(4-Chlorophenyl)-1,3-dioxolan-2-yl]methyl}-1*H*-imidazole hydrochloride (75·HCl): Following the General Procedure using compound **66** and imidazole, the final residue was converted into the hydrochloride by treating its solution in 2-propanol with a twofold molar excess of 37% aqueous HCl. The solid resulting from di-

lution with Et_2O was removed by filtration and washed with Et_2O to give the product as white crystals (514 mg, 85%); mp: 245–246 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 3.70–3.80 (m, 4H), 4.67 (s, 2H), 7.46–7.54 (m, 4H), 7.60 (t, J = 1.6 Hz, 1H), 7.65 (t, J = 1.6 Hz, 1H), 9.05 ppm (t, J = 1.6 Hz, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 53.4, 65.1, 106.2, 119.0, 123.5, 127.7, 128.5, 133.8, 136.4, 137.7 ppm; HRMS-ESI m/z $[M-Cl]^+$ calcd for $C_{13}H_{14}ClN_2O_2$: 265.0738, found: 265.0743.

1-{[2-(3-Bromophenyl)-1,3-dioxolan-2-yl]methyl}-1*H*-imidazole hydrochloride (76·HCl): Following the General Procedure using compound **67** and imidazole, the final residue was converted into the hydrochloride by treating its solution in 2-propanol with a twofold molar excess of 37% aqueous HCl. The solid resulting from dilution with Et_2O was removed by filtration, washed with Et_2O, and recrystallized to give the product as white crystals (356 mg, 51%); mp: 231–233 °C (2-propanol); ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ 3.67–3.81 (m, 4H), 4.70 (s, 2H), 7.42 (t, J = 8.0 Hz, 1H), 7.46–7.51 (m, 1H), 7.59–7.69 (m, 4H), 9.07 ppm (s, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 53.4, 65.2, 106.0, 119.1, 121.8, 123.6, 124.8, 128.6, 130.8, 132.0, 136.5, 141.5 ppm; HRMS-ESI m/z $[M-Cl]^+$ calcd for $C_{13}H_{14}BrN_2O_2$: 309.0233, found: 309.0235.

1-{[2-(4-Bromophenyl)-1,3-dioxolan-2-yl]methyl}-1*H*-imidazole hydrochloride (77·HCl): Following the General Procedure using compound **68** and imidazole, the final residue was converted into the hydrochloride by treating its solution in 2-propanol with a twofold molar excess of 37% aqueous HCl. The solid resulting from dilution with Et_2O was removed by filtration and washed with Et_2O to give the product as white crystals (584 mg, 84%); mp: 259–261 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ 3.70–3.80 (m, 4H), 4.66 (s, 2H), 7.42 (dd, J = 2.0 and 8.4 Hz, 2H), 7.60 (t, J = 1.6 Hz, 1H), 7.62–7.68 (m, 3H), 9.04 ppm (s, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 53.4, 65.0, 106.2, 118.9, 122.4, 123.4, 127.9, 131.3, 136.3, 138.0 ppm; HRMS-ESI m/z $[M-Cl]^+$ calcd for $C_{13}H_{14}BrN_2O_2$: 309.0233, found: 309.0232.

1-{[2-(Biphenyl-4-yl)-1,3-dioxolan-2-yl]methyl}-1*H*-imidazole hydrochloride (78·HCl): Following the General Procedure using compound **69** and imidazole, the final residue was converted into the hydrochloride by treating its solution in acetone with a twofold molar excess of 37% aqueous HCl. The precipitate was removed by filtration and recrystallized to give the product as off-white crystals (501 mg, 73%); mp: 277–279 °C (EtOH) (lit.[59] mp: 262–277 °C); ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 3.70–3.84 (m, 4H), 4.70 (s, 2H), 7.36–7.43 (m, 1H), 7.45–7.52 (m, 2H), 7.58 (d, J = 8.4 Hz, 2H), 7.63–7.71 (m, 4H), 7.74 (d, J = 8.4 Hz, 2H), 9.11 ppm (s, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 53.6, 65.1, 106.6, 119.0, 123.7, 126.4, 126.8, 127.8 (2×), 129.0, 136.5, 137.8, 139.4, 140.9 ppm; HRMS-ESI m/z $[M-Cl]^+$ calcd for $C_{19}H_{19}N_2O_2$: 307.1441, found: 307.1445.

1-{[2-(4-Benzylphenyl)-1,3-dioxolan-2-yl]methyl}-1*H*-imidazole hydrochloride (79·HCl): Following the General Procedure using compound **70** and imidazole, the final residue was converted into the hydrochloride by treating its solution in 2-propanol with a twofold molar excess of 37% aqueous HCl. The solid resulting from dilution with Et_2O was removed by filtration, washed with Et_2O, and recrystallized to give the product as white crystals (138 mg, 19%); mp: 265–267 °C (EtOH); ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 3.65–3.77 (m, 4H), 3.96 (s, 2H), 4.63 (s, 2H), 7.15–7.35 (m, 7H), 7.41 (d, J = 8.0 Hz, 2H), 7.60 (s, 1H), 7.64 (s, 1H), 9.05 ppm (s, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 40.7, 53.7, 64.9, 106.6, 119.0, 123.6, 125.8, 126.0, 128.5, 128.7, 136.4, 140.9, 142.2 ppm; HRMS-ESI m/z $[M-Cl]^+$ calcd for $C_{20}H_{21}N_2O_2$: 321.1597, found: 321.1593.

1-{[2-(Naphthalen-2-yl)-1,3-dioxolan-2-yl]methyl}-1*H*-imidazole hydrochloride (80·HCl): Following the General Procedure using compound **71** and imidazole, the final residue was converted into the hydrochloride by treating its solution in 2-propanol with a twofold molar excess of 37% aqueous HCl. The solid resulting from dilution with Et_2O was removed by filtration, washed with Et_2O, and recrystallized to give the product as pale-yellow crystals (485 mg, 77%); mp: 265–266 °C (EtOH) (lit.[51] mp: 269–270 °C); ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 3.75–3.85 (m, 4H), 4.78 (s, 2H), 7.53–7.69 (m, 5H), 7.93–8.05 (m, 4H), 9.11 ppm (s, 1H). ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 53.7, 65.0, 106.7, 118.9, 123.3, 123.5, 124.8, 126.5, 126.7, 127.5, 128.2, 132.3, 132.9, 136.0, 136.3 ppm; HRMS-ESI m/z $[M-Cl]^+$ calcd for $C_{17}H_{17}N_2O_2$: 281.1284, found: 281.1283.

1-{[2-(3,4-Dichlorophenyl)-1,3-dioxolan-2-yl]methyl}-1*H*-imidazole (81): Following the General Procedure using compound **72** and imidazole, the final residue was recrystallized from 2-propanol/hexanes to give the product as pale-yellow crystals (380 mg, 64%); mp: 122–123 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 3.68–3.79 (m, 4H), 4.38 (s, 2H), 6.83 (s, 1H), 7.02 (s, 1H), 7.37 (dd, J = 2.0 and 8.4 Hz, 1H), 7.45 (s, 1H), 7.59 (d, J = 2.0 Hz, 1H), 7.64 ppm (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 52.2, 65.2, 106.6, 120.8, 126.1, 127.6, 127.9, 130.5, 131.0, 131.3, 138.4, 140.9 ppm; HRMS-EI m/z $[M]^+$ calcd for $C_{13}H_{12}Cl_2N_2O_2$: 298.0276, found: 298.0267.

1-{[2-(2,4-Dichlorophenyl)-1,3-dioxolan-2-yl]methyl}-1*H*-imidazole hydrochloride (82·HCl): Following the General Procedure using compound **73** and imidazole, the final residue was converted into the hydrochloride by treating its solution in 2-propanol with a twofold molar excess of 37% aqueous HCl. The solid resulting from dilution with Et_2O was removed by filtration, washed with Et_2O, and recrystallized to give the product as white crystals (406 mg, 60%); mp: 230–231 °C (2-propanol/Et_2O); ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 3.70–3.82 (m, 4H), 4.77 (s, 2H), 7.50 (dd, J = 2.0 and 8.4 Hz, 1H), 7.58 (d, J = 8.8 Hz, 1H), 7.60 (t, J = 1.6 Hz, 1H), 7.66 (t, J = 1.6 Hz, 1H), 7.72 (d, J = 2.0 Hz, 1H), 9.09 ppm (s, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 52.2, 65.2, 105.9, 119.2, 123.7, 127.5, 130.1, 130.8, 132.5, 134.3, 134.9, 136.7 ppm; HRMS-ESI m/z $[M-Cl]^+$ calcd for $C_{13}H_{13}Cl_2N_2O_2$: 299.0348, found: 299.0345.

1-{[2-(4-Chlorophenyl)-1,3-dioxolan-2-yl]methyl}-1*H*-1,2,4-triazole (83): Following the General Procedure using compound **66** and 1,2,4-triazole, the final residue was recrystallized twice from 2-propanol to give the product as white crystals (210 mg, 39%); mp: 135–136 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.73–3.83 (m, 4H), 4.47 (s, 2H), 7.33 (d, J = 8.8 Hz, 2H), 7.41 (d, J = 8.8 Hz, 1H), 7.90 (s, 1H), 8.13 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.3, 65.5, 107.2, 127.4, 128.9, 135.2, 137.8, 144.6, 151.5 ppm; HRMS-ESI m/z $[M+H]^+$ calcd for $C_{12}H_{13}ClN_3O_2$: 266.0690, found: 266.0685.

1-{[2-(4-Bromophenyl)-1,3-dioxolan-2-yl]methyl}-1*H*-1,2,4-triazole (84): Following the General Procedure using compound **68** and 1,2,4-triazole, the final residue was recrystallized twice from 2-propanol to give the product as white crystals (435 mg, 70%); mp: 134–135 °C (lit.[60] mp: 136 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.74–3.82 (m, 4H), 4.47 (s, 2H), 7.34 (d, J = 8.8 Hz, 2H), 7.49 (d, J = 8.8 Hz, 2H), 7.90 (s, 1H), 8.13 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.3, 65.5, 107.2, 123.5, 127.7, 131.9, 138.3, 144.6, 151.5 ppm; HRMS-ESI m/z $[M+H]^+$ calcd for $C_{12}H_{13}BrN_3O_2$: 310.0185, found: 310.0190.

1-{[2-(Naphthalen-2-yl)-1,3-dioxolan-2-yl]methyl}-1*H*-1,2,4-triazole (85): Following the General Procedure using compound **71** and 1,2,4-triazole, the final residue was recrystallized three times from 2-propanol to give the product as white crystals (305 mg, 54%); mp: 105–106 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.78–3.89 (m, 4H), 4.60 (s, 2H), 7.48–7.55 (m, 2H), 7.58 (dd, J = 2.0 and 8.4 Hz, 1H), 7.82–7.90 (m, 3H), 7.93 (s, 1H), 7.99 (d, J = 1.2 Hz, 1H), 8.17 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.4, 65.5, 107.7, 123.3, 125.4, 126.6, 126.8, 127.8, 128.5, 128.7, 133.0, 133.6, 136.5, 144.7, 151.4 ppm; HRMS-ESI m/z $[M+H]^+$ calcd for $C_{16}H_{16}N_3O_2$: 282.1242, found: 282.1234.

1-[(2-Phenyl-1,3-dioxolan-2-yl)methyl]-1*H*-1,2,4-triazole hydrochloride (86·HCl): Following the General Procedure using compound **65** and 1,2,4-triazole, the final residue was converted into the hydrochloride by treating its solution in acetone with a twofold molar excess of 37% aqueous HCl. After 1 h at room temperature, the mixture was diluted with Et_2O, the solid was removed by filtration and recrystallized to give the product as white crystals (305 mg, 57%) mp: 217–219 °C (EtOH); ^{1}H NMR (400 MHz, CD_3OD): δ = 3.80–3.90 (m, 4H), 4.84 (s, 2H), 7.37–7.46 (m, 3H), 7.52–7.58 (m, 3H), 8.86 (s, 1H), 9.86 ppm (s, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ = 58.5, 66.4, 108.0, 127.0, 129.7, 130.4, 139.6, 144.1, 144.2 ppm; HRMS-ESI *m/z* $[M-Cl]^+$ calcd for $C_{12}H_{14}N_3O_2$: 232.1080, found: 232.1082.

Synthesis of derivatives of 1-(4-chlorophenyl)-2-(1*H*-imidazol-1-yl)ethanone (31):

(±)-1-(4-Chlorophenyl)-2-(1*H*-imidazol-1-yl)ethanol hydrochloride (87·HCl): $NaBH_4$ (456 mg, 12 mmol) was gradually added to a solution of 1-(4-chlorophenyl)-2-(1*H*-imidazol-1-yl)ethanone (**31**) (882 mg, 4 mmol) in MeOH (30 mL) at room temperature. The mixture was stirred overnight, and then evaporated to dryness under reduced pressure to give a residue that was partitioned between H_2O (50 mL) and EtOAc (30 mL). The aqueous layer was further extracted with EtOAc (20 mL), and then the combined organic phase was washed with H_2O and dried (Na_2SO_4). Evaporation under reduced pressure gave a solid that was recrystallized from EtOH to afford the free base **87** as a white solid (664 mg, 75%); mp: 178–179 °C (lit.[23] mp: 183–184 °C, lit.[25] mp: 188–190 °C); ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 4.03 (dd, *J* = 7.6 and 14.0 Hz, 1H), 4.13 (dd, *J* = 4.0 and 14.0 Hz, 1H), 4.80–4.88 (m, 1H), 5.81 (d, *J* = 4.4 Hz, 1H), 6.82 (s, 1H), 7.09 (s, 1H), 7.31–7.41 (m, 4H), 7.47 ppm (s, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 53.3, 71.3, 120.0, 127.8, 127.9, 128.0, 131.8, 137.7, 141.6 ppm; HRMS-EI *m/z* $[M]^+$ calcd for $C_{11}H_{11}ClN_2O$: 222.0560, found: 222.0565. The corresponding hydrochloride salt **87·HCl** was prepared by treating the solution of the free base **87** (223 mg, 1 mmol) in 2-propanol (5 mL) with 37% aqueous HCl (200 mg) in 2-propanol (1 mL). After 1 h at room temperature, the mixture was diluted with Et_2O (40 mL), and the precipitate was removed by filtration and recrystallized from 2-propanol to afford **87·HCl** as white crystals (176 mg, 68%); mp: 203–204 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 4.28 (dd, *J* = 8.0 and 9.6 Hz, 1H), 4.47 (dd, *J* = 3.6 and 9.6 Hz, 1H), 5.00 (dd, *J* = 3.6 and 8.0 Hz, 1H), 6.23 (br s, 1H), 7.43 (s, 4H), 7.64 (t, *J* = 1.2 Hz, 1H), 7.72 (t, *J* = 1.2 Hz, 1H), 9.11 ppm (s, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 55.0, 70.0, 119.2, 122.7, 127.9, 128.2, 132.2, 135.7, 140.4 ppm.

(*Z*)-1-(4-Chlorophenyl)-2-(1*H*-imidazol-1-yl)ethanone oxime (88): A solution of 1-(4-chlorophenyl)-2-(1*H*-imidazol-1-yl)ethanone (**31**) (441 mg, 2 mmol) and hydroxylamine hydrochloride (209 mg, 3 mmol) in EtOH (10 mL) was treated with a solution of anhydrous Na_2CO_3 (318 mg, 3 mmol) in H_2O (4 mL), and the mixture was heated at reflux for 4 h. The mixture was evaporated under reduced pressure, and the residue was stirred with H_2O (30 mL) for 1 h. The insoluble material was removed by filtration, washed with H_2O (30 mL), and recrystallized to give **88** as white crystals (305 mg, 65%); mp: 195–196 °C (2-propanol) (lit.[33] mp: 210 °C); ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 5.32 (s, 2H), 6.81 (s, 1H), 7.03 (s, 1H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.64 (s, 1H), 7.68 (d, *J* = 8.4 Hz, 2H), 12.18 ppm (s, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 38.9, 119.5, 127.8, 128.5, 128.6, 132.9, 133.9, 137.6, 151.2 ppm; HRMS-ESI *m/z* $[M+H]^+$ calcd for $C_{11}H_{11}ClN_3O$: 236.0585, found: 236.0580.

(*Z*)-1-(4-Chlorophenyl)-2-(1*H*-imidazol-1-yl)ethanone *O*-4-bromobenzyl oxime hydrochloride (89·HCl): (*Z*)-1-(4-Chlorophenyl)-2-(1*H*-imidazol-1-yl)ethanone oxime (**88**) (566 mg, 2.4 mmol) was gradually added to a suspension of NaH (58 mg, 2.4 mmol) in DMSO (5 mL). The mixture was stirred at room temperature for 30 min, and then 4-bromobenzyl bromide (600 mg, 2.4 mmol) was added. The solution was stirred at room temperature for 4 h, heated at 50–60 °C for 10 min, and then cooled to room temperature. The reaction mixture was partitioned between EtOAc (30 mL) and H_2O (100 mL), the aqueous layer was further extracted with EtOAc (20 mL), and then the combined organic phase was washed sequentially with H_2O and brine, and dried (Na_2SO_4). Evaporation yielded a residue that was purified by column chromatography (silica gel, EtOAc) to give the oxime-ether **89** as an off-white solid (R_f = 0.49, EtOAc), which was converted into the hydrochloride by treating its solution in 2-propanol with a twofold molar excess of 37% aqueous HCl. Addition of Et_2O and refrigeration of the solution overnight gave **89·HCl** as a white solid (295 mg, 28%); mp: 172–173 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 5.27 (s, 2H), 5.62 (s, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 8.8 Hz, 2H), 7.55–7.60 (m, 3H), 7.61 (t, *J* = 1.2 Hz, 1H), 7.71 (d, *J* = 8.8 Hz, 2H), 9.22 ppm (s, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 42.8, 75.6, 120.1, 121.2, 122.2, 128.5, 128.8, 130.3, 131.1, 131.3, 134.9, 136.1, 136.4, 151.2 ppm; HRMS-ESI *m/z* $[M-Cl]^+$ calcd for $C_{18}H_{16}BrClN_3O$: 404.0165, found: 404.0159.

1-(4-Chlorophenyl)-2-(1*H*-imidazol-1-yl)ethanone phenylhydrazone hydrochloride (90·HCl): A solution of phenylhydrazine (238 mg, 2.2 mmol) in EtOH (5 mL) was treated with 37% aqueous HCl (296 mg, 3 mmol), and then a solution of 1-(4-chlorophenyl)-2-(1*H*-imidazol-1-yl)ethanone (**31**) (441 mg, 2 mmol) in EtOH (5 mL) was added. The mixture was heated at reflux for 2 h, then evaporated under reduced pressure, and the residue was recrystallized twice to give **90·HCl** as a white solid (315 mg, 45%); mp: 209–210 °C (EtOH) (lit.[61] mp: 207–208 °C); ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 5.87 (s, 2H), 6.86 (t, *J* = 7.4 Hz, 1H), 7.27 (t, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.44 (d, *J* = 8.8 Hz, 2H), 7.61 (t, *J* = 1.6 Hz, 1H), 7.63 (t, *J* = 1.6 Hz, 1H), 7.83 (d, *J* = 8.8 Hz, 2H), 9.28 (s, 1H), 10.94 ppm (s, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 42.3, 113.5, 120.1, 120.3, 122.0, 127.0, 128.6, 128.9, 132.5, 132.7, 135.4, 135.5, 145.1 ppm; HRMS-ESI *m/z* $[M-Cl]^+$ calcd for $C_{17}H_{16}ClN_4$: 311.1058, found: 311.1063.

(±)-*N*-Benzyl-1-(4-chlorophenyl)-2-(1*H*-imidazol-1-yl)ethanamine dihydrochloride (91·2 HCl): A mixture of 1-(4-chlorophenyl)-2-(1*H*-imidazol-1-yl)ethanone (**31**) (441 mg, 2 mmol), benzylamine (214 mg, 2 mmol), and *p*-toluenesulfonic acid monohydrate (38 mg, 0.2 mmol) in benzene (30 mL) was heated at reflux overnight with the azeotropic removal of H_2O. Evaporation under reduced pressure afforded a residue which was dissolved in MeOH (20 mL), and the solution was treated gradually with $NaBH_4$ (228 mg, 6 mmol). The reaction mixture was stirred at room temperature for 6 h, and then the solvent was removed under reduced pressure to yield a residue that was partitioned between EtOAc (30 mL) and H_2O (100 mL). The aqueous layer was further extracted with EtOAc (20 mL), the combined organic phase was washed sequentially with H_2O and brine, and dried (Na_2SO_4). Evaporation under reduced pressure gave a residue that was subjected to chromatography (silica gel, EtOAc/MeOH 19:1) to yield the imidazoleamine **91** as a pale-yellow oil (250 mg, R_f = 0.45), which was converted into the dihydrochloride by treating its solution in Et_2O with excess HCl in the same solvent. Recrystallization of the precipitate yielded **91·2 HCl** as white crystals (145 mg, 19%); mp: 236–238 °C (EtOH/Et_2O); ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 3.84 (d, *J* = 13.2 Hz, 1H), 4.00 (d, *J* = 13.2 Hz, 1H), 4.81 (dd, *J* = 8.4 and 13.6 Hz, 1H), 4.92–5.04 (m, 1H), 5.20 (dd, *J* = 6.0 and 13.6 Hz, 1H), 7.35–7.41 (m, 3H), 7.47–7.53 (m, 2H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.61 (t, *J* = 1.6 Hz, 1H), 7.69 (t, *J* = 1.6 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 2H), 9.09 (s, 1H), 11.06 ppm (br s, 2H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 49.0, 49.7, 59.8, 120.0, 122.3, 128.5, 128.8, 129.2, 130.1, 130.9, 131.1, 131.6,

134.6, 136.1 ppm; HRMS-ESI *m/z* $[M-2Cl]^+$ calcd for $C_{18}H_{19}ClN_3$: 312.1267, found: 312.1265.

1-(4-Chlorophenyl)-2-(hydroxyimino)-2-(1*H*-imidazol-1-yl)ethanone (92): A solution of $NaNO_2$ (207 mg, 3 mmol) in H_2O (1 mL) was added dropwise to an ice-cold solution of 1-(4-chlorophenyl)-2-(1*H*-imidazol-1-yl)ethanone (**31**) (441 mg, 2 mmol) in AcOH (6 mL). The mixture was stirred at room temperature overnight, diluted with H_2O (30 mL), and the precipitate was removed by filtration and washed thoroughly with H_2O. The dried solid was heated at reflux in MeOH (30 mL) for 15 min; the mixture was allowed to cool to room temperature, and was then filtered to give **92** as a white solid (325 mg, 65%); mp: 197–198 °C (dec.); ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta = 7.05$ (s, 1H), 7.48 (s, 1H), 7.63 (d, $J =$ 8.4 Hz, 2H), 7.98 (d, $J = 8.4$ Hz, 1H), 8.02 (s, 1H), 13.31 ppm (br s, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): $\delta = 119.7$, 127.4, 128.3, 132.3, 134.7, 137.9, 138.1, 141.2, 185.4 ppm; HRMS-ESI *m/z* $[M+H]^+$ calcd for $C_{11}H_9ClN_3O_2$: 250.0377, found: 250.0370.

In vitro inhibition of HO activity

Brain and spleen tissue were obtained from adult male Sprague–Dawley rats (250–300 g) purchased from Charles River Inc. (Montreal, QC, Canada). Rats were maintained on 12 h light cycles and had ad libitum access to water and standard Ralston Purina Laboratory chow 5001 (Ren's Feed Supplies Ltd., Oakville, ON, Canada). All of the animals were maintained in accordance with the principles and guidelines of the Canadian Council on Animal Care and experimental protocols approved by the Queen's University Animal Care Committee.

HO activity in rat spleen and brain microsomal fractions was determined by the quantitation of CO formed from the degradation of methemalbumin (heme complexed with albumin).[62,63] Spleen and brain (Sprague–Dawley rats) microsomal fractions were prepared according to the procedure outlined by Appleton et al.[64] The protein concentration of microsomal fractions was determined by a modification of the biuret method.[63] Incubations for HO activity analyses were done under conditions for which the rate of CO formation [pmol min^{-1} (mg protein)$^{-1}$] was linear with respect to time and microsomal protein concentration. Briefly, reaction mixtures (150 μL) consisting of 100 mM phosphate buffer (pH 7.4), 50 μM methemalbumin, and 1 mg mL^{-1} protein were pre-incubated with the inhibitors at final concentrations ranging from 0.01 to 100 μM for 10 min at 37 °C. Reactions were initiated by adding NADPH at a final concentration of 1 mM, and incubations were performed for an additional 15 min at 37 °C. Reactions were stopped by instantly freezing the reaction mixture on dry ice, and CO formation was monitored by gas chromatography according to the method described by Vreman and Stevenson.[62] The data from all experiments were analyzed and processed as reported.[17] The results are reported as the mean value ± standard error of measurement (SEM).

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