Bioorganic & Medicinal Chemistry 17 (2009) 4221–4229

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Design, synthesis and herbicidal activity of new iron chelating motifs for HPPD-inhibitors

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ARTICLE INFO

Article history:
Received 7 October 2008
Revised 30 October 2008
Accepted 4 November 2008
Available online 8 November 2008

Keywords:
p-Hydroxyphenylpyruvate dioxygenase
Herbicide
Topramezone
N-Hydroxyimidazole

ABSTRACT

HPPD (*p*-hydroxyphenylpyruvate dioxygenase) is a herbicidal target that all major companies active in plant protection research have worked on intensely in the last decade. Several modern herbicides with this mode of action have been introduced recently, or are currently in development. The activity of all commercialized HPPD-inhibitors is based on a chelating functionality, which binds to the redoxactive iron center in the enzyme. In the course of our research, leading to the new broad spectrum corn herbicide topramezone by BASF, this chelating functionality has been examined thoroughly, and many new chelating motifs have been synthesized. The chelating motif N–O in combination with C=O, which is known for its iron-binding potential from many natural siderophores, was especially promising. Examination of several different motifs of this type resulted in the identification of benzoyl-*N*-hydroxyimidazoles, which inhibited the HPPD-enzyme with potency comparable to the best known systems. Significant herbicidal activity in the greenhouse could also be identified for some of these compounds, but this activity was weaker than for the analogous benzoylpyrazolones of the topramezone-type.

1. Introduction

In the early 1970s a group at Sankyo identified the herbicidal activity of benzoylpyrazoles. Based on these findings the first commercial product, pyrazolinate, was launched 1980 for the control of annual and perennial weeds in rice. Pyrazolinate, which is a prodrug for the active principle DTP (detosylpyrazolate), is used at rates of 3–4 kg/ha. In 1985 Ishihara Sangyo Kaisha commercialized a second representative of this class, pyrazoxyfen, which is a different prodrug of the same active principle DTP. In 1987 Mitsubishi Petrochemical Co. introduced benzofenap, which is closely related to pyrazoxyfen and is used in the same indication. By now more than 600 patents covering herbicidal benzoylpyrazoles from all major companies active in plant protection research have been published, but it took until 2006 before the next benzoylpyrazole, topramezone,[1] was commercialized by BASF. This compound is used as a postemergence herbicide with excellent selectivity in corn at use rates of 12–75 g/ha, controlling all major grasses and broadleaf weeds. A further new benzoylpyrazole, pyrasulfotole, is currently introduced by Bayer in combination with a safener, for post-emergence control of broadleaf weeds in cereals (Fig. 1).

Independent of this research a group at Stauffer Chemical Company (then Zeneca, now Syngenta) identified 2-benzoyl-cyclohexane-1,3-diones as a new herbicidal compound class, which showed a very similar structure–activity relationship (SAR) to the benzoylpyrazoles, exchanging the pyrazolone with a diketone substructure. In course of this research the herbicides sulcotrione (1991) and later mesotrione (2001) were identified and commercialized for the control of broadleaf weeds in corn. The prodrug benzobicyclon was developed by SDS Biotech/Sandoz mainly for the control of sedges and some broadleaf weeds in transplanted rice. Bayer has introduced tembotrione in combination with a safener in 2007 for postemergence weed control in corn. Isoxaflutole, which is a prodrug of the diketonitrile DKN, has been commercialized 1996 by Rhone-Poulenc Agro (now Bayer CropScience) as a pre-emergence herbicide in corn (Fig. 2).

At Zeneca[2] (now Syngenta), simultaneously with a group at Hoechst[3] (now Bayer CropScience), the herbicidal mode of action of the 2-benzoyl-cyclohexane-1,3-diones could be identified as inhibition of the enzyme *p*-hydroxyphenylpyruvate dioxygenase (HPPD). This was later shown to be the mode of action for the benzoylpyrazoles and isoxaflutole as well.

The conversion of *p*-hydroxyphenylpyruvate (HPP) to homogentisic acid (HGA) starts by chelation of HPP to an Fe(II)-ion in the active site of the enzyme HPPD.

A complex decarboxylation-oxidation-rearrangement sequence leads subsequently to the formation of homogentisate (HGA).[4] All commercialized HPPD-inhibitors block this enzyme by chelation of the iron in the active site by a 1,3-dicarbonyl motif, in a manner similar to HPP (Fig. 3).

The inhibition of HPPD has as its main herbicidal effect the reduction of the plastoquinone-level in plants, as HGA is a key intermediate in the biosynthesis of plastoquinone. Plastoquinone

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doi:10.1016/j.bmc.2008.11.006

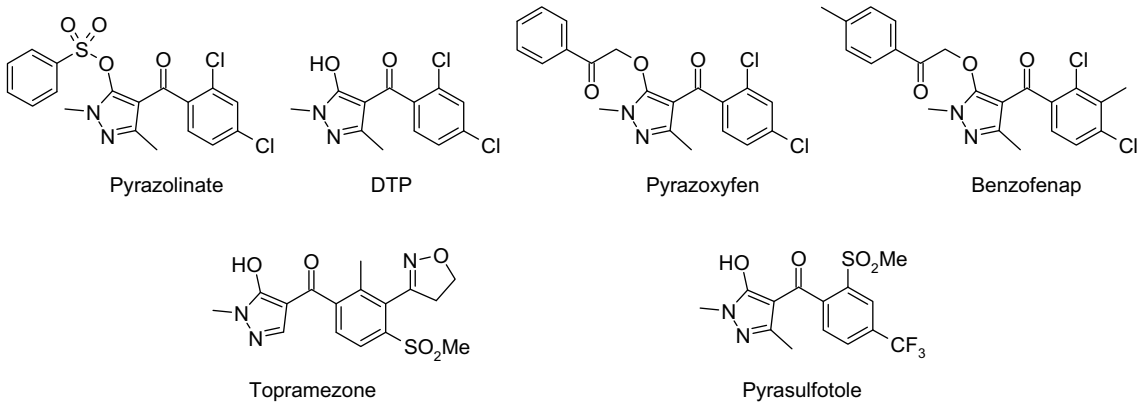


Figure 1. Chemical structures of benzoylpyrazole herbicides.

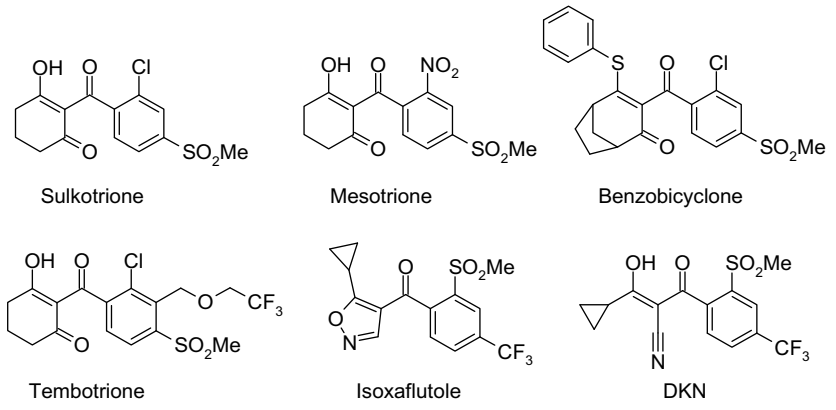


Figure 2. Chemical structures of benzoylcyclohexanedione- and benzoylisoxazole herbicides.

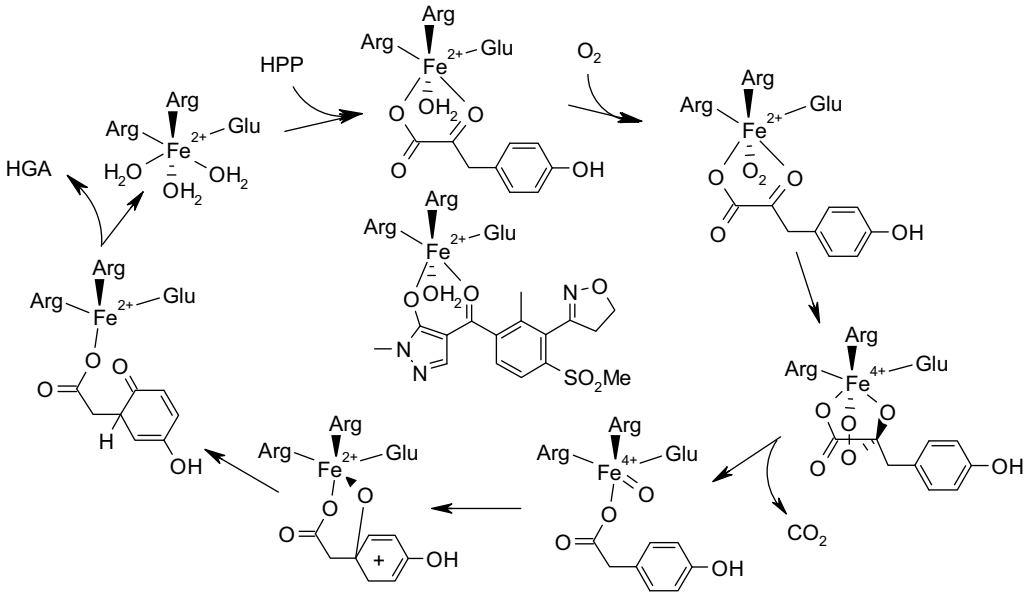


Figure 3. Reaction mechanism of HPPD and inhibition by topramezone.

is an essential cofactor for the enzyme phytoene-desaturase, so that a reduction in plastoquinone-levels results in a reduced production of phytoene, and thereby of the carotenoids. This in turn results in reduced protection of chlorophyll against photooxidation, which leads to bleaching and subsequent necrosis and death of the treated weeds. In addition to these effects, which are the main contributors to the herbicidal activity, the reduced level of homogentisate leads to a lower tocopherol production, for which it is also an intermediate (Fig. 4).

The strongest known iron-binding motifs in nature are those that chelate the iron ion between an N–O- and a carbonyl-functionality, used by many organisms, for example, in siderophores.[5–7] So

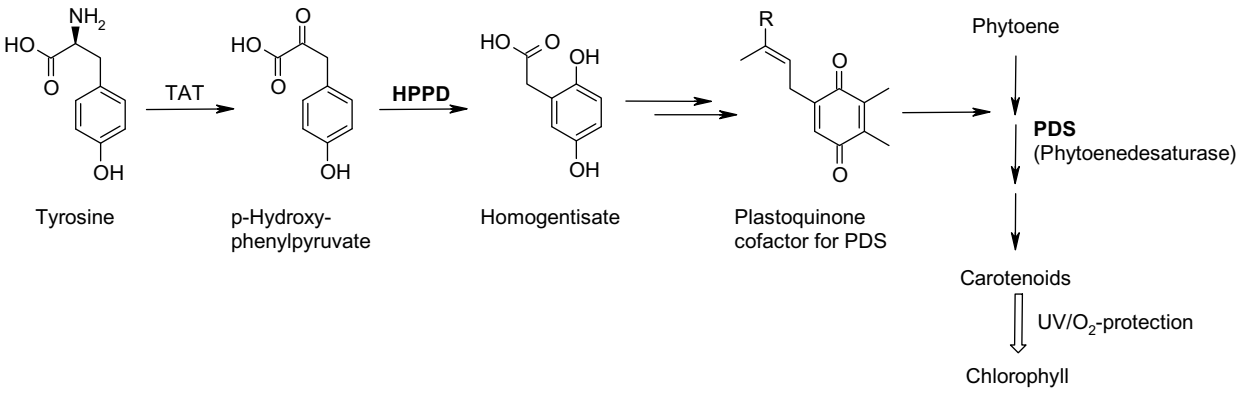


Figure 4. Role of HPPD in chlorophyll-protection (TAT, tyrosine aminotransferase).

far this concept has not been described for inhibitors of HPPD. Therefore we examined to what extent the 1,3-dicarbonyl-motif could be replaced by an isosteric N–O-carbonyl chelation.

2. Results and discussion

2.1. Replacement of a cyclohexane-1,3-dione by a pyridine *N*-oxide

It has been shown that substituted 2-benzoylcyclohexanones lacking the third carbonyl-group[8] present in sulcotrione do have target-activity on HPPD, only slightly lower than the 'trione'-systems like **1**. Therefore we set out to synthesize the isosteric 2-benzoylpyridine-*N*-oxide **2** (Fig. 5).

This compound was readily made by coupling 2-tributylstannylpyridine without catalysis[9] with the benzoylchloride **3**,[10] followed by oxidation with m-CPBA (Scheme 1).

Unfortunately **2** showed no significant activity on the HPPD enzyme at 2×10^{-5} M concentration, and consequently also no activity in the greenhouse. One explanation might be the neutral character of **2**, as all other known inhibitors of HPPD are weak acids and are binding in the deprotonated form.

2.2. Replacement of a cyclohexane-1,3-dione by a 1,2,3-trione-2-oxime

Chelation of the iron in HPPD by a 1,2,3-trione-2-oxime like **5** could result in a binding motif isosteric to that of 1,3-dicarbonyl-compounds like **1**: (Fig. 6).

Using a published method for the synthesis of 1-phenylbutane-1,3-diones **7**[11] from benzoylchlorides **3**, these could be oximated with butylnitrite,[12] resulting in inseparable *E*/*Z*-isomeric mixtures of the 1-phenylbutane-1,2,3-trione-2-oximes **5** (Scheme 2).

These oximes showed in combination with the most active phenyl substitution patterns some activity on the HPPD-target, but the activity level was significantly lower than for comparable butanedione systems (Table 1).

At the highest tested use rates in the greenhouse only low activity for the most active analogue **5d** could be detected in postemergence application on important weeds.

It has been described that acetylacetone gives stronger Fe(III)-complexes than their corresponding 2-oximated analogues.[13] For these oximes in solution the chelation can take the form of either a 5- or 6-membered ring, depending on the complexation conditions. These factors, together with the 2:1 predominance of the E-isomer of the oxime, which is not capable of a simultaneous chelation of the N–O-functionality with the benzylic carbonyl to the iron, might explain the relatively low target and greenhouse activity.

2.3. Replacement of a hydroxypyrazole by an *N*-hydroxy-imidazole

Reaction of the 1-phenylbutane-1,2,3-trione-2-oximes **5** with aldehydes and ammonium acetate resulted in a cyclization to the 5-benzoyl-*N*-hydroxy-imidazoles **8**[14,15] (Scheme 3 and Table 2).

For the various substitution patterns on the imidazole, the highest activity on the HPPD-enzyme was observed in the sequence Me = i-Pr > Et > H >> phenyl, 2-4-Cl_2-phenyl, thienyl, and 1-methyl-

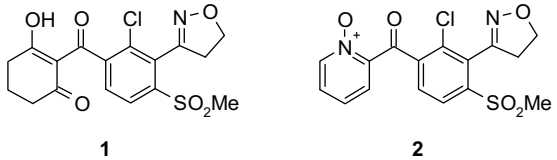


Figure 5. Analogy of 1,3-dicarbonyl- and 2-acylpyridine-*N*-oxide chelating motifs.

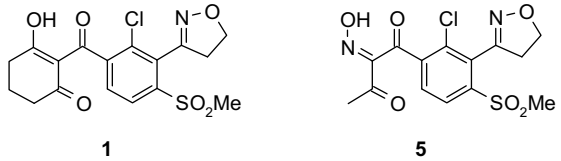
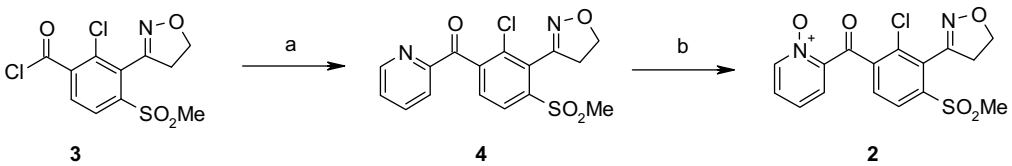
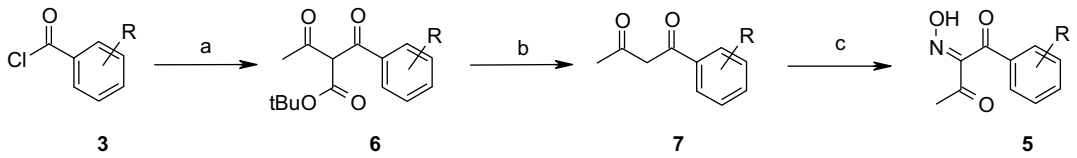


Figure 6. Analogy of 1,3-dicarbonyl and butanetrione-oxime chelating motifs.

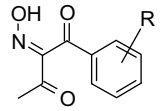


Scheme 1. Reagents and conditions: (a) 2-(tributylstannyl)pyridine, THF, 30 °C; (b) MCPBA, CH_2Cl_2, 40 °C.



Scheme 2. Reagents and conditions: (a) t-$BuO_2CCH_2COCH_3$, Mg, MeOH, CCl_4, 25 °C; MeCN; (b) p-TsOH, toluene, Δ; (c) n-BuONO, HCl/ether, toluene.

Table 1
HPPD-inhibition and herbicidal activity of **5a–d**



5a-d

Compound	Phenyl-substitution	HPPD IC_{50} (μM)	ECHCG GR_{50} (kg/ha)	SETIT GR_{50} (kg/ha)	CENCY GR_{50} (kg/ha)
5a	2-Cl-3-OEt-4-SO_2Et	20	>3	>3	>3
5b	2-Me-3-OMe-4-SO_2Me	>20	>3	>3	>3
5c	2-Me-3-Cl-4-SMe	>20	>3	>3	>3
5d	2-Cl-3-(3-isoxazolinyl)-4-SO2Me	13	2.5	>3	>3

GR_{50}: 50% growth reduction 21 days after postemergence spray application at given concentration in kg/ha.
ECHCG, *Echinochloa crus-galli*; SETIT, *Setaria italica*; CENCY, *Centaurea cyanus*.

2-pyrrolyl. This sequence of target activities corresponds very well with the SAR of the analogous pyrazole derivatives.

The 1-oxo-imidazole analogue **9**, which was prepared in a similar fashion by condensation of the 1-phenylbutane-1,2,3-trione-2-oxime **5a** with acetaldoxime,[14] gave a slightly weaker target activity compared to the imidazole analogues **8**, and showed no significant herbicidal effect (Scheme 4).

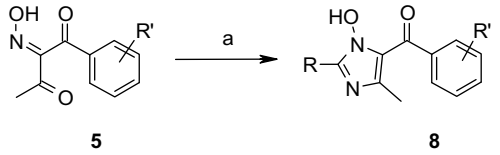
Next we studied the variation of the phenyl residue, keeping the methyl-substitution on the hydroxyimidazole as in **8b**, which showed the best herbicidal activity of the series (Table 3).

The highest target activity was identified for **8n**, which is closely related to topramezone, with an IC_{50} of 3.6×10^{-8} M. This activity on the HPPD target is even higher than for the isosteric dimethyl-hydroxypyrazole **10**,[16] which is one of the most active HPPD-inhibitors in the greenhouse in our experience. Again the SAR was very similar to the sequence found in the topramezone optimization program, giving much weaker activities for compounds not having a heterocyclic or alkoxy-residue in the 3-position of the benzoyl group.

In the greenhouse some herbicidal activity could be observed even below 100 g/ha for the most active derivatives, but this activity was still significantly lower than that observed for comparable hydroxypyrazole-derivatives like **10** or for topramezone. Potential reasons for this reduced activity could be either unfavorable physicochemical properties of the *N*-hydroxyimidazoles such as lower acidity and therefore reduced systemicity compared to the hydroxypyrazoles; or metabolic and/or UV-instability, which has not been examined so far.

3. Conclusions

We could show for the first time that the *p*-hydroxyphenylpyruvate dioxygenase enzyme (HPPD) can be inhibited with iron chelators, that do not have a 1,3-dicarbonyl substructure. Pyridine-*N*-oxides do not show activity on HPPD, so a charged interaction might be necessary. Substituted 1-phenylbutane-1,2,3-trione-2-oximes showed some activity on HPPD, but no significant activity in the greenhouse. Substituted benzoyl-*N*-hydroxyimidazoles showed very high activity in the HPPD assay, comparable to or even better than the activity of the isosteric benzoylpyrazoles. Herbicidal activity of these compounds in the greenhouse was on an interesting level, but significantly lower than for the benzoylpyrazoles like **10** or topramezone.



Scheme 3. Reagents and conditions: (a) RCHO, NH_4OAc, AcOH.

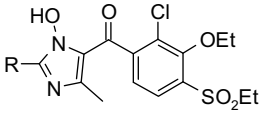
4. Experimental

4.1. Materials and methods

Melting points were recorded on a Büchi 530 apparatus and are uncorrected. TLC was carried out on precoated silica gel plates (F 254 Merck). ^1H and ^{13}C NMR spectra were recorded on a Bruker DRX 500 spectrometer. Chemical shifts are given in δ units (ppm) relative to the internal standard Me_4Si. HR-MS-ESI-spectra were recorded on a Micromass LCT, and the exact M−H-mass (M-1) was determined. Unless stated otherwise, all materials were obtained from commercial suppliers and used without further purification.

The synthesis of **7a**, **7b**, and **7c** has been described in the literature.[9] The other substituted phenyl butane-1,3-diones have been prepared from the corresponding substituted benzoic acids[10,17,18]

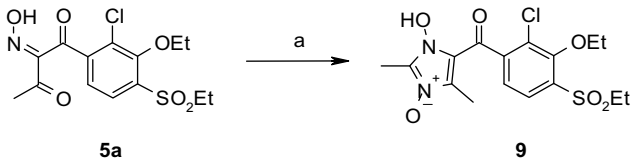
Table 2
HPPD-inhibition and herbicidal activity of **8a–h** and **9**



8a-h

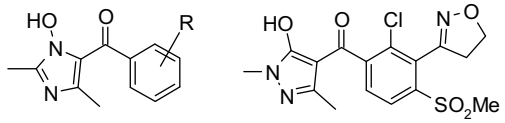
Compound	R	HPPD IC_{50} (μM)	ECHCG GR_{50} (kg/ha)	ABUTH GR_{50} (kg/ha)	CHEAL GR_{50} (kg/ha)
8a	H	20	>0.5	>0.5	0.4
8b	CH_3	0.048	0.5	0.1	0.05
8c	CH_2CH_3	0.071	>0.5	>0.5	0.2
8d	$CH(CH_3)_2$	0.043	>3	>3	1.5
8e	2-Thienyl	>20	>3	>3	>3
8f	2-(*N*-Methyl)-pyrrolyl	>20	>3	>3	>3
8g	Phenyl	>20	>0.5	>0.5	>0.5
8h	2,4-Cl_2-phenyl	>20	>0.5	>0.5	>0.5
9		0.19	>3	>3	>3

GR_{50}: 50% growth reduction 21 days after postemergence spray application at given concentration in kg/ha.
ECHCG, *Echinochloa crus-galli*; ABUTH, *Abutilon theophrasti*; CHEAL, *Chenopodium album*.



Scheme 4. Reagents and conditions: (a) CH_3CHNOH, NH_4OAc, AcOH.

Table 3
HPPD-inhibition and herbicidal activity of **8b**, **8i–n** and **10**



8i-n 10

Compound	Phenyl-substitution	HPPD IC_{50} (μM)	ECHCG GR_{50} (kg/ha)	ABUTH GR_{50} (kg/ha)	CHEAL GR_{50} (kg/ha)
8b	2-Cl-3-OEt-4-SO_2Et	0.048	0.5	0.1	0.05
8i	2-Me-3-OMe-4-SO_2Me	18	>1	0.7	0.06
8j	2-Me-3-Cl-4-SMe	>20	>0.5	>0.5	>0.5
8k	2- Cl-4-SO_2Me	>20	>0.5	>0.5	>0.5
8l	8-SO_2Me-5-quinolinoyl	>20	>1	>1	>1
8m	2,4,6-trimethyl	>20	>3	>3	>3
8n	2-Cl-3-(3-isoxazolinyl)-4-SO2Me	0.036	2	>3	0.3
10		0.19	<0.01	<0.01	<0.01

GR_{50}: 50% growth reduction 21 days after postemergence spray application at given concentration in kg/ha.
ECHCG, *Echinochloa crus-galli*; ABUTH, *Abutilon theophrasti*; CHEAL, *Chenopodium album*.

according to this literature, and were used crude without further purification.

The HPPD assay was performed with recombinant *Arabidopsis thaliana* enzyme as described by Grossmann et al.[1]

4.2. [2-Chloro-3-(4,5-dihydro-isoxazol-3-yl)-4-methanesulfonyl-phenyl]-pyridin-2-yl-methanone (4)

2-Tributylstannylpyridine (1.8 g, 5.0 mmol) was dissolved in 40 ml THF and 2-chloro-3-(4,5-dihydro-isoxazol-3-yl)-4-methanesulfonyl-benzoyl chloride **3** (1.6 g, 5.0 mmol) was added under cooling with an ice bath (internal temperature <30 °C). After the addition the solution was stirred for 14 h at room temperature. The solvents were evaporated, and the residue was triturated with *n*-hexane, dissolved with ethyl acetate (70 ml), and washed with saturated $NaHCO_3$ solution and water. The organic phase was dried with sodium sulphate and the solvents were evaporated, resulting in [2-chloro-3-(4,5-dihydro-isoxazol-3-yl)-4-methanesulfonyl-phenyl]-pyridin-2-yl-methanone **4** (1.25 g, 69%) as a colorless oil that still contained ca. 10% stannane-impurities and was used without further purification.

^{1}H NMR ($CDCl_3$): δ 3.27 (s, 3H); 3.42 (t, 2H); 4.50 (t, 2H); 7.57 (m, 1H); 7.69 (d, 1H); 7.94 (t, 1H); 8.18 (d, 1H); 8.28 (d, 1H); 8.65 (d, 1H).

HR-MS (M−H): 363.0244 (calc. for $C_{16}H_{12}ClN_2O_4$: 363.0206).

4.3. [2-Chloro-3-(4,5-dihydro-isoxazol-3-yl)-4-methanesulfonyl-phenyl]-(1-oxy-pyridin-2-yl)-methanone (2)

[2-Chloro-3-(4,5-dihydro-isoxazol-3-yl)-4-methanesulfonyl-phenyl]-pyridin-2-yl-methanone **4** (0.80 g, 2.2 mmol) was dissolved in methylene chloride (30 ml), and MCPBA (70%; 1.1 g, 4.4 mmol) was added at room temperature. The solution was heated 11 h to 35–40 °C, during which time further MCPBA (2× 0.2 g) was added. After cooling to room temperature the suspension was filtered and washed with methylene chloride, the organic phase was washed with saturated $NaHSO_3$ and $NaHCO_3$ solutions and water, dried with sodium sulphate and evaporated. The residue was chromatographed on silica with a methylene chloride/methanol gradient to give [2-chloro-3-(4,5-dihydro-isoxazol-3-yl)-4-methanesulfonyl-phenyl]-(1-oxy-pyridin-2-yl)-methanone **2** (0.4 g, 48%) as a colorless oil.

^{1}H NMR ($CDCl_3$): δ 4.23 (s, 3H); 3.42 (t, 2H); 4.48 (t, 2H); 7.47 (m, 2H); 7.78 (d, 1H); 7.84 (q, 1H); 8.10 (d, 1H); 8.18 (d, 1H).

HR-MS (M−H): 379.0193 (calc. for $C_{16}H_{12}ClN_2O_5$: 379.0155).

4.4. 1-(2-Chloro-4-ethanesulfonyl-3-ethoxy-phenyl)-butane-1,2,3-trione-2-oxime (5a)

1-(2-Chloro-4-ethanesulfonyl-3-ethoxy-phenyl)-butane-1,3-dione (7.6 g, 23 mmol) was dissolved in toluene (100 ml), HCl–saturated diethyl ether (19 ml) was added at −15 °C to −10 °C, and *n*-butylnitrite (3.5 g, 34 mmol) in 60 ml diethyl ether was added. After 16 h at room temperature the solution was added to ice water (200 ml) and extracted 3× with 10% NaOH. The aqueous phase was than acidified to pH 4 with 10% sulfuric acid and extracted 3× with ethyl acetate. This organic phase was dried with sodium sulfate and evaporated to give 1-(2-chloro-4-ethanesulfonyl-3-ethoxy-phenyl)-butane-1,2,3-trione-2-oxime **5a** (7.2 g; 87%) in a ca. 3:2 *E*/*Z* isomeric mixture as a colorless oil.

^{1}H NMR ($CDCl_3$, major isomer): δ 1.22 (t, 3H); 1.50 (t, 3H); 2.48 (s, 3H); 3.47 (q, 2H); 4.32 (q, 2H); 7.61 (d, 1H); 7.95 (d, 1H).

^{13}C NMR ($CDCl_3$): δ 7.0, 15.2, 25.9, 49.4, 72.0, 125.9, 128.7, 129.3, 137.3, 140.4, 154.5, 155.3, 189.4, 195.0.

HR-MS (M−H): 360.0335 (calc. for C14H17ClNO6S: 360.0309).

4.5. (2-Chloro-4-ethanesulfonyl-3-ethoxy-phenyl)-(3-hydroxy-5-methyl-3H-imidazol-4-yl)-methanone (8a)

1-(2-Chloro-4-ethanesulfonyl-3-ethoxy-phenyl)-butane-1,2,3-trione-2-oxime **5a** (0.8 g, 2.2 mmol) was dissolved in acetic acid (20 ml), ammonium acetate (0.25 g, 3.2 mmol) and paraformaldehyde (0.10 g, 3.3 mmol) were added, and the solution was stirred at room temperature for 16 h. The solvents were evaporated, and the residue was redissolved with MTBE and 5% NaOH and extracted. The aqueous phase was acidified with concentrated HCl, and extracted with ethyl acetate, the organic phase dried with sodium sulphate and evaporated. The residue was chromatographed on silica with a methylene chloride/methanol gradient, resulting in (2-chloro-4-ethanesulfonyl-3-ethoxy-phenyl)-(3-hydroxy-5-methyl-3H-imidazol-4-yl)-methanone **8a** (0.60 g, 73%) as colorless crystals.

Mp 155 °C (dec.).

^{1}H NMR ($CDCl_3$): δ 1.27 (t, 3H); 1.52 (t, 3H); 1.98 (s, 3H); 3.47 (q, 2H); 4.30 (q, 2H); 7.29 (d, 1H); 7.95 (d, 1H); 9.05 (s, 1H).

^{13}C NMR ($CDCl_3$): δ 7.2, 15.1, 15.3, 49.4, 72.1, 123.0, 123.7, 126.9, 129.5, 133.7, 135.6, 144.3, 144.4, 154.4, 183.7.

HR-MS (M−H): 371.0500 (calc. for $C_{15}H_{16}ClN_2O_5S$: 371.0468).

4.6. (2-Chloro-4-ethanesulfonyl-3-ethoxy-phenyl)-(3-hydroxy-2,5-dimethyl-3H-imidazol-4-yl)-methanone (8b)

1-(2-Chloro-4-ethanesulfonyl-3-ethoxy-phenyl)-butane-1,2,3-trione-2-oxime **5a** (1.3 g, 3.3 mmol) was dissolved in acetic acid (20 ml), ammonium acetate (0.35 g, 4.5 mmol) and acetaldehyde (0.15 g, 3.4 mmol) were added, and the solution was stirred at room temperature for 16 h. The solvents were evaporated, and

the residue was redissolved with MTBE and 5% NaOH and extracted. The aqueous phase was acidified with concentrated HCl, and extracted with ethyl acetate, the organic phase dried with sodium sulphate and evaporated. The residue was chromatographed on silica with a methylene chloride/methanol gradient, resulting in [2-chloro-3-(4,5-dihydro-isoxazol-3-yl)-4-methanesulfonyl-phenyl]-(3-hydroxy-2,5-dimethyl-3H-imidazol-4-yl)-methanone **8b** (0.70 g, 55%) as colorless crystals.

Mp 110–115 °C.

^{1}H NMR ($CDCl_3$): δ 1.25 (t, 3H); 1.52 (t, 3H); 1.93 (s, 3H); 2.44 (s, 3H); 3.48 (q, 2H); 4.32 (q, 2H); 7.40 (d, 1H); 7.90 (d, 1H).

^{13}C NMR ($CDCl_3$): δ 7.2, 10.7, 14.7, 15.3, 49.4, 72.1, 122.1, 123.0, 127.0, 129.5, 135.8, 142.4, 143.9, 144.3, 154.5, 183.2.

HR-MS (M−H): 387.0786 (calc. for $C_{16}H_{18}ClN_2O_5S$: 387.0781).

4.7. (2-Chloro-4-ethanesulfonyl-3-ethoxy-phenyl)-(2-ethyl-3-hydroxy-5-methy-3H-imidazol-4-yl)-methanone (8c)

1-(2-Chloro-4-ethanesulfonyl-3-ethoxy-phenyl)-butane-1,2,3-trione-2-oxime **5a** (0.5 g, 1.4 mmol) was dissolved in acetic acid (20 ml), ammonium acetate (0.16 g, 2.1 mmol) and propionaldehyde (0.12 g, 2.1 mmol) were added, and the solution was stirred at room temperature for 16 h. The solvents were evaporated, and the residue was redissolved with MTBE and 5% NaOH and extracted. The aqueous phase was acidified with concentrated HCl, and extracted with ethyl acetate, the organic phase dried with sodium sulphate and evaporated. The residue was chromatographed on silica with a methylene chloride/methanol gradient, resulting in [(2-chloro-4-ethanesulfonyl-3-ethoxy-phenyl)-(2-ethyl-3-hydroxy-5-methy-3H-imidazol-4-yl)-methanone **8c** (0.50 g, 89%) as colorless crystals.

Mp 105–108 °C.

^{1}H NMR ($CDCl_3$): δ 1.24 (t, 3H); 1.30 (t, 3H); 1.51 (d, 6H); 2.45 (q, 1H); 2.76 (s, 3H); 3.48 (q, 2H); 4.35 (q, 2H); 7.28 (d, 1H); 7.88 (d, 1H).

^{13}C NMR ($CDCl_3$): δ 7.2, 10.9, 15.1, 15.3, 19.3, 49.4, 71.9, 121.5, 123.0, 126.9, 129.3, 135.1, 142.0, 144.2, 145.4, 154.3, 182.0.

HR-MS (M−H): 399.0809 (calc. for $C_{16}H_{18}ClN_2O_5S$: 399.0781).

4.8. (2-Chloro-4-ethanesulfonyl-3-ethoxy-phenyl)-(3-hydroxy-2-isopropyl-5-methyl-3H-imidazol-4-yl)-methanone (8d)

1-(2-Chloro-4-ethanesulfonyl-3-ethoxy-phenyl)-butane-1,2,3-trione-2-oxime **5a** (1.0 g, 2.8 mmol) was dissolved in acetic acid (20 ml), ammonium acetate (0.21 g, 2.8 mmol) and isobutyraldehyde (0.20 g, 2.8 mmol) were added, and the solution was stirred at room temperature for 30 h. The solvents were evaporated, and the residue was redissolved with MTBE and 5% NaOH and extracted. The aqueous phase was acidified with concentrated HCl, and extracted with ethyl acetate, the organic phase dried with sodium sulphate and evaporated. The residue was chromatographed on silica with a methylene chloride/methanol gradient, resulting in (2-chloro-4-ethanesulfonyl-3-ethoxy-phenyl)-(3-hydroxy-2-isopropyl-5-methyl-3H-imidazol-4-yl)-methanone **8d** (0.85 g, 74%) as a colorless oil.

^{1}H NMR ($CDCl_3$): δ 1.24 (t, 3H); 1.35 (t, 3H); 1.50 (t, 3H); 2.66 (s, 3H); 2.80 (q, 2H); 3.48 (q, 2H); 4.35 (q, 2H); 7.28 (d, 1H); 7.88 (d, 1H).

^{13}C NMR ($CDCl_3$): δ 7.1, 15.2, 15.4, 19.9 (2C), 21.3, 49.5, 72.3, 121.3, 125.0, 128.1, 128.4, 137.3, 140.7, 144.2, 145.4, 150.7, 179.2.

HR-MS (M−H): 413.0924 (calc. for $C_{18}H_{22}N_2O_5SCl$: 413.0938).

4.9. (2-Chloro-4-ethanesulfonyl-3-ethoxy-phenyl)-(3-hydroxy-5-methyl-2-thiophen-2-yl-3H-imidazol-4-yl)-methanone (8e)

1-(2-Chloro-4-ethanesulfonyl-3-ethoxy-phenyl)-butane-1,2,3-trione-2-oxime **5a** (0.5 g, 1.4 mmol) was dissolved in acetic acid (20 ml), ammonium acetate (0.20 g, 2.6 mmol) and thiophene-2-carbaldehyde (0.30 g, 2.7 mmol) were added, and the solution was stirred at room temperature for 16 h. The solvents were evaporated, and the residue was chromatographed on silica with a cyclohexane/ethyl acetate gradient, resulting in (2-chloro-4-ethanesulfonyl-3-ethoxy-phenyl)-(3-hydroxy-5-methyl-2-thiophen-2-yl-3H-imidazol-4-yl)-methanone **8e** (0.60 g, 94%) as colorless crystals.

Mp 150–155 °C.

^{1}H NMR ($CDCl_3$): δ 1.26 (t, 3H); 1.53 (t, 3H); 2.03 (s, 3H); 3.48 (q, 2H); 4.32 (q, 2H); 7.4-7.5 (m, 3H); 7.50 (d, 1H); 7.99 (d, 1H).

^{13}C NMR ($CDCl_3$): δ 7.2, 15.2, 15.8, 49.3, 71.7, 123.1, 124.6, 126.8, 126.8, 127.0, 128.2, 128.7, 129.1, 134.8, 140.6, 145.7, 145.9, 181.0.

HR-MS (M−H): 453.0333 (calc. for $C_{19}H_{18}ClN_2O_5S_2$: 453.0346).

4.10. (2-Chloro-4-ethanesulfonyl-3-ethoxy-phenyl)-[3-hydroxy-5-methyl-2-(1-methyl-1H-pyrrol-2-yl)-3H-imidazol-4-yl]-methanone (8f)

1-(2-Chloro-4-ethanesulfonyl-3-ethoxy-phenyl)-butane-1,2,3-trione-2-oxime **5a** (0.50 g, 1.4 mmol) was dissolved in acetic acid (20 ml), ammonium acetate (0.20 g, 2.6 mmol) and 1-methyl-1H-pyrrol-2-carbaldehyde (0.23 g, 2.1 mmol) were added, and the solution was stirred at room temperature for 16 h. The solvents were evaporated, and the residue was chromatographed on silica with a cyclohexane/ethyl acetate gradient, resulting in (2-chloro-4-ethanesulfonyl-3-ethoxy-phenyl)-[3-hydroxy-5-methyl-2-(1-methyl-1H-pyrrol-2-yl)-3H-imidazol-4-yl]-methanone **8f** (0.35 g, 56%) as colorless crystals.

Mp. 85 °C (dec.).

^{1}H NMR ($CDCl_3$): δ 1.23 (t, 3H); 1.52 (t, 3H); 1.88 (s, 3H); 3.48 (q, 2H); 4.03 (s, 3H); 4.37 (q, 2H); 6.78 (s, 1H); 6.82 (s, 1H); 7.18 (s, 1H); 7.32 (d, 1H); 8.03 (d, 1H).

^{13}C NMR ($CDCl_3$): δ 7.3, 15.2, 15.8, 37.2, 49.4, 72.1, 109.0, 115.4, 118.9, 120.7, 123.1, 127.1, 127.8, 129.5, 135.6, 137.9, 143.9, 147.8, 54.5, 182.7.

HR-MS (M−H): 450.0925 (calc. for $C_{20}H_{21}ClN_3O_5S$: 450.0890).

4.11. (2-Chloro-4-ethanesulfonyl-3-ethoxy-phenyl)-(3-hydroxy-5-methyl-2-phenyl-3H-imidazol-4-yl)-methanone (8g)

1-(2-Chloro-4-ethanesulfonyl-3-ethoxy-phenyl)-butane-1,2,3-trione-2-oxime **5a** (0.5 g, 1.4 mmol) was dissolved in acetic acid (20 ml), ammonium acetate (0.12 g, 1.6 mmol) and benzaldehyde (0.16 g, 1.5 mmol) were added, and the solution was stirred at room temperature for 16 h. As the reaction was not complete by TLC further ammonium acetate (0.12 g, 1.6 mmol) and benzaldehyde (0.20 g, 1.89 mmol) were added, and the solution was stirred at room temperature for another 64 h. The solvents were evaporated, and the residue was chromatographed on silica with a cyclohexane/ethyl acetate gradient, resulting in (2-chloro-4-ethanesulfonyl-3-ethoxy-phenyl)-(3-hydroxy-5-methyl-2-phenyl-3H-imidazol-4-yl)-methanone **8g** (0.50 g, 80%) as colorless crystals.

Mp 135–140 °C.

^{1}H NMR ($CDCl_3$): δ 1.27 (t, 3H); 1.56 (t, 3H); 1.91 (s, 3H); 3.50 (q, 2H); 4.37 (q, 2H); 7.29 (d, 2H); 7.4-7.5 (m, 3H); 8.02 (d, 1H); 8.23 (dd, 2H).

^{13}C NMR ($CDCl_3$): δ 7.3, 15.3, 15.6, 49.4, 72.2, 121.9, 123.0, 126.6, 127.0, 128.3 (2C); 128.7 (2C); 129.6, 130.7, 135.9, 142.3, 143.6, 147.8, 154.6, 183.9.

HR-MS (M−H): 447.0824 (calc. for $C_{21}H_{20}ClN_2O_5S$: 447.0781).

4.12. (2-Chloro-4-ethanesulfonyl-3-ethoxy-phenyl)-[2-(2,4-dichloro-phenyl)-3-hydroxy-5-methyl-3H-imidazol-4-yl]-methanone (8h)

1-(2-Chloro-4-ethanesulfonyl-3-ethoxy-phenyl)-butane-1,2,3-trione-2-oxime **5a** (0.5 g, 1.4 mmol) was dissolved in acetic acid

(20 ml), ammonium acetate (0.20 g, 2.6 mmol) and 2,4-dichlorobenzaldehyde (0.41 g, 2.7 mmol) were added, and the solution was stirred at room temperature for 16 h. The solvents were evaporated, and the residue was chromatographed on silica with a cyclohexane/ethyl acetate gradient, resulting in (2-chloro-4-ethanesulfonyl-3-ethoxy-phenyl)-[2-(2,4-dichloro-phenyl)-3-hydroxy-5-methyl-3H-imidazol-4-yl]-methanone **8h** (0.44 g, 61%) as colorless crystals.

Mp 158–160 °C.

^{1}H NMR ($CDCl_3$): δ 1.28 (t, 3H); 1.55 (t, 3H); 1.90 (s, 3H); 3.48 (q, 2H); 4.35 (q, 2H); 7.30 (d, 1H); 7.38 (d, 1H); 7.49 (d, 1H); 7.52 (s, 1H); 8.03 (d, 1H).

^{13}C NMR ($CDCl_3$): δ 7.2, 15.3, 15.5, 49.4, 72.2, 122.1, 123.0, 124.6, 127.0, 128.5, 129.6, 130.2, 132.6, 135.0, 136.0, 137.4, 140.5, 143.7, 146.7, 154.6, 184.3.

HR-MS (M−H): 515.0032 (calc. for $C_{21}H_{18}Cl_3N_2O_5S$: 515.0002).

4.13. (2-Chloro-4-ethanesulfonyl-3-ethoxy-phenyl)-(3-hydroxy-2,5-dimethyl-1-oxy-3H-imidazol-4-yl)-methanone (9)

1-(2-Chloro-4-ethanesulfonyl-3-ethoxy-phenyl)-butane-1,2,3-trione-2-oxime **5a** (1.0 g, 2.8 mmol) was dissolved in methanol (20 ml), acetaldoxime (0.33 g, 9.5 mmol) and concentrated aqueous HCl (1.0 ml) were added, and the solution was stirred at room temperature for 60 h. As the reaction was not complete by TLC, further acetaldoxime (0.10 g, 1.7 mmol) was added, and the solution was refluxed for 3 h. After cooling Na_2CO_3 (0.30 g) was added, the suspension was filtered, the solvents were evaporated, and the residue was chromatographed on silica with a methylene chloride/methanol gradient, resulting in (2-chloro-4-ethanesulfonyl-3-ethoxy-phenyl)-(3-hydroxy-2,5-dimethyl-1-oxy-3H-imidazol-4-yl)-methanone **9** (0.70 g, 62%) as a colorless oil.

^{1}H NMR ($CDCl_3$): δ 1.24 (t, 3H); 1.55 (t, 3H); 2.4 (br, 6H); 3.47 (q, 2H); 4.35 (q, 2H); 7.41 (d, 1H); 7.99 (d, 1H).

^{13}C NMR ($CDCl_3$): δ 7.3, 9.1, 9.3, 15.3, 49.5, 72.2, 124.5, 124.6, 127.1, 129.5, 134.7, 136.1, 144.6, 144.9, 154.0, 181.1.

HR-MS (M−H): 401.0574 (calc. for $C_{16}H_{18}ClN_2O_6S$: 401.0574).

4.14. 2-[2-Chloro-3-(4,5-dihydro-isoxazol-3-yl)-4-methanesulfonyl-benzoyl]-3-oxo-butyric acid *tert*-butylester (6d)

Mg-turnings (1.0 g, 42 mmol) were suspended in methanol (100 ml) and *tert*-butyl-acetoacetate (5.2 g, 33 mmol) was added. Under cooling to 20–25 °C carbon tetrachloride (6 ml) was added. After 3 h at room temperature, the suspension was evaporated, the residue was dissolved in acetonitrile (70 ml), and 2-chloro-3-(4,5-dihydro-isoxazol-3-yl)-4-methanesulfonyl-benzoylchloride **3** (11 g, 33 mmol) in acetonitrile (30 ml) was added dropwise. After stirring for 16 h, 3% aqueous HCl (100 ml) was added. This mixture was extracted with ethyl acetate and the organic phase was evaporated to give 2-[2-chloro-3-(4,5-dihydro-isoxazol-3-yl)-4-methanesulfonyl-benzoyl]-3-oxo-butyric acid *tert*-butylester **6d** (16 g, 86%) as colorless crystals.

Mp 129–130 °C.

^{1}H NMR (enol-tautomer, $CDCl_3$): δ 1.13 (s, 9H); 2.58 (s, 3H); 3.22 (s, 3H); 3.42 (t, 2H); 4.63 (t, 2H); 7.56 (d, 1H); 8.15 (d, 1H), 15.0 (enol, 1H).

^{13}C NMR (enol-tautomer, $CDCl_3$): δ 23.0, 25.4, 27.5 (3C); 39.0, 45.7, 69.9, 81.8, 128.2, 129.1, 130.4, 131.9, 142.3, 144.2, 155.2, 164.2, 189.9, 197.7.

HR-MS (M−H): 442.0706 (calc. for $C_{19}H_{21}ClNO_7S$: 442.0727).

4.15. 1-[2-Chloro-3-(4,5-dihydro-isoxazol-3-yl)-4-methanesulfonyl-phenyl]-butane-1,3-dione (7d)

2-[2-Chloro-3-(4,5-dihydro-isoxazol-3-yl)-4-methanesulfonyl-benzoyl]-3-oxo-butyric acid *tert*-butylester **6d** (16 g, 36 mmol) was dissolved in toluene (250 ml), and *p*-toluensulfonicacid (2.0 g, 12 mmol) was added. The solution was heated for 5 h under reflux, cooled, extracted with water, dried with sodium sulphate and evaporated to give 1-[2-chloro-3-(4,5-dihydro-isoxazol-3-yl)-4-methanesulfonyl-phenyl]-butane-1,3-dione **7d** (9.5 g, 77%) as colorless crystals.

Mp: 130–132 °C.

^{1}H NMR (enol-tautomer, $CDCl_3$): δ 2.22 (s, 3H); 3.22 (s, 3H); 3.47 (t, 2H); 4.63 (t, 2H); 7.78 (d, 1H); 8.13 (d, 1H); 15.5 (OH, 1H).

^{13}C NMR (enol-tautomer, $CDCl_3$): δ 25.3, 39.1, 45.6, 70.0, 102.0, 128.2, 130.6, 131.1, 133.0, 141.5, 143.2, 155.5, 183.4, 192.9.

HR-MS (M−H): 342.0217 (calc. for $C_{14}H_{13}ClNO_5S$: 342.0203).

4.16. 1-[2-Chloro-3-(4,5-dihydro-isoxazol-3-yl)-4-methanesulfonyl-phenyl]-butane-1,2,3-trione-2-oxime (5d)

1-[2-Chloro-3-(4,5-dihydro-isoxazol-3-yl)-4-methanesulfonyl-phenyl]-butane-1,3-dione **7d** (9.8 g, 28 mmol) was dissolved in toluene (100 ml), HCl–saturated diethyl ether (23 ml) was added at −15 °C to −10 °C and *n*-butylnitrite (4.4 g, 43 mmol) in 60 ml diethyl ether was added. After 16 h at room temperature further *n*-butylnitrite (1.5 g, 14 mmol) was added, and stirring was continued for 2 h. The solution was than added to 400 ml ice water and extracted 3× with 10% NaOH. The aqueous phase was acidified to pH 4 with 10% sulfuric acid and extracted 3× with ethyl acetate. This organic phase was dried with sodium sulfate and evaporated. The residue was chromatographed on silica with a cyclohexane/ethyl acetate gradient, to give 1-[2-chloro-3-(4,5-dihydro-isoxazol-3-yl)-4-methanesulfonyl-phenyl]-butane-1,2,3-trione-2-oxime **5d** (3.9 g; 36%) in a ca. 2:1 *E*/*Z* isomeric mixture as a colorless oil.

^{1}H NMR ($CDCl_3$, major isomer): δ 2.45 (s, 3H); 3.20 (s, 3H); 3.40 (t, 2H); 4.58 (t, 2H); 7.95 (d, 1H); 8.18 (d, 1H); 9.4 (br s, 1H).

HR-MS (M−H): 371.0118 (calc. for $C_{14}H_{12}ClN_2O_6S$: 371.0105).

4.17. [2-Chloro-3-(4,5-dihydro-isoxazol-3-yl)-4-methanesulfonyl-phenyl]-(3-hydroxy-2,5-dimethyl-3H-imidazol-4-yl)-methanone (8n)

1-[2-Chloro-3-(4,5-dihydro-isoxazol-3-yl)-4-methanesulfonyl-phenyl]-butane-1,2,3-trione-2-oxime **5d** (1.0 g, 2.68 mmol) was dissolved in acetic acid (20 ml), ammonium acetate (0.2 g, 2.68 mmol) and acetaldehyde (0.12 g, 2.73 mmol) were added, and the solution was stirred at room temperature for 16 h. The solvents were evaporated, and the residue was redissolved with MTBE and 5% NaOH and extracted. The aqueous phase was acidified with concentrated HCl and extracted with ethyl acetate, and the organic phase dried with sodium sulphate and evaporated, resulting in [2-chloro-3-(4,5-dihydro-isoxazol-3-yl)-4-methanesulfonyl-phenyl]-(3-hydroxy-2,5-dimethyl-3H-imidazol-4-yl)-methanone **8n** (0.9 g, 84%) as a colorless oil.

^{1}H NMR ($CDCl_3$): δ 1.82 (s, 3H); 2.45 (s, 3H); 3.26 (s, 3H); 3.43 (t, 2H); 4.62 (t, 2H); 7.62 (d, 1H); 8.21 (d, 1H).

HR-MS (M−H): 396.0449 (calc. for $C_{16}H_{15}ClN_3O_5S$: 396.0419).

4.18. 1-(2-Chloro-4-methanesulfonyl-phenyl)-butane-1,2,3-trione-2-oxime

1-(2-Chloro-4-methanesulfonyl-phenyl)-butane-1,3-dione (10 g, 36 mmol) was dissolved in toluene (100 ml), HCl–saturated diethyl ether (10 ml) was added at −15 °C to −10 °C and *n*-butylnitrite (6.0 g, 55 mmol) in diethyl ether (20 ml) was added. After 16 h at room temperature, the solution was added to ice water (200 ml) and extracted 3× with 10% NaOH. The aqueous phase was acidified to pH 2.3 with 10% sulfuric acid and extracted 3× with ethyl acetate. This organic phase was dried with sodium sulfate and evaporated. The residue was chromatographed on silica with a

methylene chloride/methanol gradient, to give 1-(2-chloro-4-methanesulfonyl-phenyl)-butane-1,2,3-trione-2-oxime (5.8 g; 36%) as a colorless oil, that was used without further purification.

4.19. (2-Chloro-4-methanesulfonyl-phenyl)-(3-hydroxy-2,5-dimethyl-3H-imidazol-4-yl)-methanone (8k)

1-(2-Chloro-4-methanesulfonyl-phenyl)-butane-1,2,3-trione-2-oxime (0.5 g, 1.6 mmol) was dissolved in acetic acid (20 ml), ammonium acetate (0.19 g, 2.5 mmol) and acetaldehyde (0.10 g, 2.3 mmol) were added, and the solution was stirred at room temperature for 62 h. The solvents were evaporated, and the residue chromatographed on silica with a methylene chloride/methanol gradient to give (2-chloro-4-methanesulfonyl-phenyl)-(3-hydroxy-2,5-dimethyl-3H-imidazol-4-yl)-methanone **8k** (0.47 g, 89%) as colorless crystals.

Mp: 175–180 °C.

^{1}H NMR ($CDCl_3$): δ 2.31 (s, 3H); 2.66 (s, 3H); 3.20 (s, 3H); 7.60 (d, 1H); 8.00 (s, 1H); 8.39 (d, 1H).

^{13}C NMR ($CDCl_3$): δ 11.5, 15.1, 44.0, 122.6, 126.0, 128.7, 129.9, 132.0, 137.4, 143.1, 143.3, 146.2, 181.4.

HR-MS (M−H): 327.0236 (calc. for $C_{13}H_{12}ClN_2O_4S$: 327.0206).

4.20. 1-(4-Methanesulfonyl-3-methoxy-2-methyl-phenyl)-butane-1,2,3-trione-2-oxime (5b)

1-(4-Methanesulfonyl-3-methoxy-2-methyl-phenyl)-butane-1,3-dione (5.0 g, 18 mmol) was dissolved in toluene (80 ml), HCl–saturated diethyl ether (12 ml) was added at −15 °C to −10 °C and *n*-butylnitrite (2.7 g, 26 mmol) in diethyl ether (20 ml) was added. After 16 h at room temperature the solution was added to ice water (250 ml) and extracted 3× with 10% NaOH. The aqueous phase was acidified to pH 3 with 10% sulfuric acid and extracted 3× with ethyl acetate. This organic phase was dried with sodium sulfate and evaporated. The residue was chromatographed on silica with a methylene chloride/methanol gradient, to give 1-(4-methanesulfonyl-3-methoxy-2-methyl-phenyl)-butane-1,2,3-trione-2-oxime **5b.**

(1.9 g; 34%) in a ca. 2:1 *E*/*Z* isomeric mixture as colorless crystals.

Mp: 145–147 °C.

^{1}H NMR ($CDCl_3$, major isomer): δ 2.49 (s, 3H); 2.54 (s, 3H), 3.26 (s, 3H); 3.97 (s, 3H); 7.38 (d, 1H); 7.86 (d, 1H).

^{13}C NMR ($CDCl_3$, major isomer): 13.1, 25.8, 43.4, 62.8, 126.0, 126.5, 134.9, 137.5, 140.9, 155.9, 157.4, 194.4, 195.7.

HR-MS (M−H): 312.0508 (calc. for $C_{13}H_{14}NO_6S$: 312.0542).

4.21. (4-Methanesulfonyl-3-methoxy-2-methyl-phenyl)-(3-hydroxy-2,5-dimethyl-3H-imidazol-4-yl)-methanone (8i)

1-(4-methanesulfonyl-3-methoxy-2-methyl-phenyl)-butane-1,2,3-trione-2-oxime **5b** (0.60 g, 1.9 mmol) was dissolved in acetic acid (15 ml), ammonium acetate (0.15 g, 1.9 mmol) and acetaldehyde (0.10 g, 2.3 mmol) were added, and the solution was stirred at room temperature for 62 h. The solvents were evaporated, and the residue chromatographed on silica with a methylene chloride/methanol gradient to give (4-methanesulfonyl-3-methoxy-2-methyl-phenyl)-(3-hydroxy-2,5-dimethyl-3H-imidazol-4-yl)-methanone **8i** (0.40 g, 62%) as colorless crystals.

Mp: 150–153 °C.

^{1}H NMR ($CDCl_3$): δ 1.88 (s, 3H); 2.31 (s, 3H); 2.38 (s, 3H); 3.27 (s, 3H); 3.98 (s, 3H); 7.22 (d, 1H); 7.87 (d, 1H).

^{13}C NMR ($CDCl_3$): δ 11.2, 12.7, 15.7, 43.5, 62.6, 122.5, 124.0, 127.0, 131.1 135.5, 144.0, 144.8, 146.8, 157.1, 185.3.

HR-MS (M−H): 337.0854 (calc. for $C_{15}H_{17}N_2O_5S$: 337.0858).

4.22. 1-(3-Chloro-2-methyl-4-methylsulfanyl-phenyl)-butane-1,2,3-trione-2-oxime (5c)

1-(3-Chloro-2-methyl-4-methylsulfanyl-phenyl)-butane-1,3-dione (5.0 g, 19 mmol) was dissolved in toluene (80 ml), HCl–saturated diethyl ether (15 ml) was added at −15 °C to −10 °C and *n*-butylnitrite (3.0 g, 29 mmol) in diethyl ether (20 ml) was added. After 16 h at room temperature the solution was added to ice water (250 ml) and extracted 3× with 10% NaOH. The aqueous phase was acidified to pH 3 with 10% sulfuric acid and extracted 3× with ethyl acetate. This organic phase was dried with sodium sulfate and evaporated. The residue was chromatographed on silica with a methylene chloride/methanol gradient to give 1-(3-chloro-2-methyl-4-methylsulfanyl-phenyl)-butane-1,2,3-trione-2-oxime **5c** (2.5 g; 46%) in a ca. 2:1 *E*/*Z* isomeric mixture as colorless crystals.

Mp: 150–151 °C.

^{1}H NMR ($CDCl_3$, major isomer): δ 2.47 (s, 3H); 2,48 (s, 3H); 2.74 (s, 3H); 7.01 (d, 1H); 7.32 (d, 1H).

^{13}C NMR ($CDCl_3$, major isomer): δ 17.2, 15.1, 25.9, 120.9, 130.1, 131.0, 133.2, 138.3, 146.5, 157.0, 191.9, 195.1.

HR-MS (M−H): 284.0127 (calc. for $C_{12}H_{11}ClNO_3S$: 284.0148).

4.23. (3-Chloro-2-methyl-4-methylsulfanyl-phenyl)-(3-hydroxy-2,5-dimethyl-3H-imidazol-4-yl)-methanone (8j)

1-(3-Chloro-2-methyl-4-methylsulfanyl-phenyl)-butane-1,2,3-trione-2-oxime **5c** (0.70 g, 1.9 mmol) was dissolved in acetic acid (15 ml), ammonium acetate (0.20 g, 2.6 mmol) and acetaldehyde (0.12 g, 2.6 mmol) were added, and the solution was stirred at room temperature for 16 h. The solvents were evaporated, and the residue chromatographed on silica with a methylene chloride/methanol gradient to give (3-chloro-2-methyl-4-methylsulfanyl-phenyl)-(3-hydroxy-2,5-dimethyl-3H-imidazol-4-yl)-methanone **8j** (0.74 g, 97%) as colorless crystals.

Mp: 118 °C (dec.).

^{1}H NMR ($CDCl_3$): δ 1.78 (s, 3H); 2.32 (s, 6H); 2.48 (s, 3H); 6.97 (d, 1H); 7.13 (d, 1H).

^{13}C NMR ($CDCl_3$): δ 10.1, 15.2, 16.0, 17.1, 121.6, 123.2, 126.0, 132.3, 134.4, 135.4, 142.3 (2C); 145.4, 187.6.

HR-MS (M−H): 309.0468 (calc. for $C_{14}H_{14}ClN_2O_2S$: 309.0465).

4.24. 1-(8-Methanesulfonyl-quinolin-5-yl)-butane-1,2,3-trione-2-oxime

1-(8-Methanesulfonyl-quinolin-5-yl)-butane-1,3-dione (5.0 g, 17 mmol) was dissolved in toluene (80 ml), HCl–saturated diethyl ether (12 ml) was added at −15 °C to −10 °C and *n*-butylnitrite (2.7 g, 26 mmol) in diethyl ether (20 ml) was added. After 16 h at room temperature the solution was added to ice water (250 ml) and extracted 3× with 10% NaOH. The aqueous phase was acidified to pH 3 with 10% sulfuric acid and extracted 3× with ethyl acetate. This organic phase was dried with sodium sulfate and evaporated to give 1-(8-methanesulfonyl-quinolin-5-yl)-butane-1,2,3-trione-2-oxime (3.5 g) as an oil, which was used in the next step without further purification.

4.25. (3-Hydroxy-2,5-dimethyl-3H-imidazol-4-yl)-(8-methanesulfonyl-quinolin-5-yl)-methanone (8l)

1-(8-Methanesulfonyl-quinolin-5-yl)-butane-1,2,3-trione-2-oxime (1.0 g, 3.1 mmol) was dissolved in acetic acid (20 ml), ammonium acetate (0.24 g, 3.1 mmol) and acetaldehyde (0.10 g, 2.3 mmol) were added, and the solution was stirred at room temperature for 16 h. The solvents were evaporated, and the residue chromatographed on silica with a methylene chloride/methanol gradient to give (3-hydroxy-2,5-dimethyl-3H-imidazol-4-yl)-(8-methane-

sulfonyl-quinolin-5-yl)-methanone **8l** (0.62 g, 58%) as colorless crystals.

Mp: >210 °C.

^{1}H NMR ($CDCl_3$): δ 1.97, (s, 3H); 2.39 (s, 3H); 3.67 (s, 3H); 7.64 (q, 1H); 7.80 (d, 1H); 8.48 (d, 1H); 8.56 (d, 1H); 9.17 (d, 1H).

^{13}C NMR ($CDCl_3$): δ 11.4, 16.1, 44.3, 123.0, 125.1, 125.2, 125.3, 130.1, 134.3, 139.0, 143.4, 144.0, 145.0, 145.2, 151.7, 183.4.

HR-MS (M−H): 344.0703 (calc. for C16H14N3O4S: 344.0705).

4.26. 1-(2,4,6-Trimethyl-phenyl)-butane-1,2,3-trione-2-oxime

1-(2,4,6-Trimethyl-phenyl)-butane-1,3-dione (5.0 g, 25 mmol) was dissolved in toluene (50 ml), HCl–saturated diethyl ether (10 ml) was added at −15 °C to −10 °C and *n*-butylnitrite (4.0 g, 37 mmol) in diethyl ether (10 ml) was added. After 16 h at room temperature the solution was added to ice water (200 ml) and extracted 3× with 10% NaOH. The aqueous phase was acidified to pH 4 with 10% sulfuric acid and extracted 3× with ethyl acetate. This organic phase was dried with sodium sulfate and evaporated to give 1-(2,4,6-trimethyl-phenyl)-butane-1,2,3-trione 2-oxime (2.2 g) as a colorless oil, that was used in the next step without further purification.

4.27. (3-Hydroxy-2,5-dimethyl-3H-imidazol-4-yl)-(2,4,6-trimethyl-phenyl)-methanone (8m)

1-(2,4,6-Trimethyl-phenyl)-butane-1,2,3-trione-2-oxime (0.50 g, 2.1 mmol) was dissolved in acetic acid (20 ml), ammonium acetate (0.25 g, 3.2 mmol) and acetaldehyde (0.14 g, 3.2 mmol) were added, and the solution was stirred at room temperature for 16 h. The solvents were evaporated, and the residue chromatographed on silica with a cyclohexane/ethyl acetate gradient to give (3-hydroxy-2,5-dimethyl-3H-imidazol-4-yl)-(2,4,6-trimethyl-phenyl)-methanone **8m** (0.36 g, 66%) as colorless crystals.

Mp: 113–115 °C.

^{1}H NMR ($CDCl_3$): δ 1.67 (s, 3H); 2.18 (s, 6H); 2.32 (s, 3H); 2.42 (s, 3H); 6.91 (s, 2H).

^{13}C NMR ($CDCl_3$): δ 11.0, 14.6, 18.9 (2C), 21.2, 122.1, 128.7 (2C); 133.7 (2C); 135.3, 139.5, 141.5, 145.9, 191.6.

HR-MS (M−H): 257.1271 (calc. for $C_{15}H_{19}N_2O_2$: 257.1290).

Acknowledgments

The author thanks Dr. Thomas Ehrhardt, Peter Seiler, Dr. Ricarda Niggeweg and Yvonne Wunder for measurement of the enzymatic activity, and Sandra Schläger and Manfred Schmidt for technical assistance in the laboratory.

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