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ORIGINAL PAPER

Synthesis, crystal structure, and in vitro antiprotozoal activity of some 5-phenyl(methyl)sulfonyl-substituted dihydroisoxazoles

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Abstract 4,5-Dihydroisoxazole derivatives are interesting synthetic targets that exhibit various biological activities, including anti-infective. Taking account of the principle of bioisosterism, a number of 4,5-dihydroisoxazoles carrying a phenyl- (or methyl-)sulfonyl group at position 5 were designed and synthesized by 1,3-dipolar cycloaddition of nitrolic acid-generated nitrile oxides with electron-deficient phenyl (or methyl) vinyl sulfones. The structures of all the cycloadducts were elucidated by means of spectroscopic methods (NMR, MS), X-ray diffraction, and physical characteristics. The in vitro antiprotozoal and cytotoxic activities of these heterocyclic compounds were investigated.

Keywords 1,3-Dipolar cycloaddition · Nitrile oxide · Nitrolic acid · Bioacitivity · Toxicity

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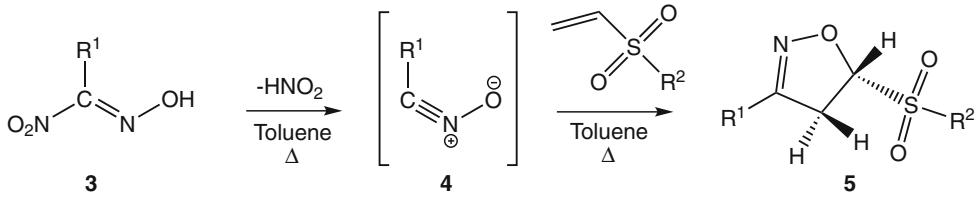
Introduction

Protozoal diseases such as malaria, trypanosomiasis, and leishmaniasis are responsible for significant morbidity and mortality in underdeveloped regions of the world. These diseases are caused by single cell parasites and transmitted to humans by different types of insects. With around 300 million new cases worldwide each year, and around one million deaths [1], malaria is by far the most important parasitic infection. Particularly falciparum malaria caused by *Plasmodium falciparum* and spread from person to person by *Anopheles* mosquitoes poses a high risk for young children and pregnant women in Africa. American trypanosomiasis (also known as Chagas' disease) is caused by *Trypanosoma cruzi* and transmitted to humans by triatomine bugs. It is endemic in South America and has an acute phase and a chronic stage resulting in heart or gastrointestinal complications. It is estimated that 10 million people are infected with American trypanosomiasis worldwide [2]. Human African trypanosomiasis (sleeping sickness, HAT) is transmitted by the bite of the tsetse fly. *Trypanosoma brucei rhodesiense* and *T. b. gambiense* are responsible for East and West African trypanosomiasis, respectively. The number of actual HAT cases estimated by the World Health Organization (WHO) is 30,000, and the number of new cases reported in 2009 is around 10,000 [3]. If left untreated, HAT is usually fatal. Human visceral leishmaniasis (HVL), a potentially fatal parasitic disease caused by *Leishmania donovani*, *L. infantum*, and *L. chagasi*, occurs via the bite of phlebotomine sandflies. HVL accounts for more than 50,000 deaths every year [4]. In the absence of a protective vaccine, antiparasitic drugs are essential to addressing the health and economic burdens caused by these diseases. Unfortunately, most current medications are generally very old with limited effectiveness or

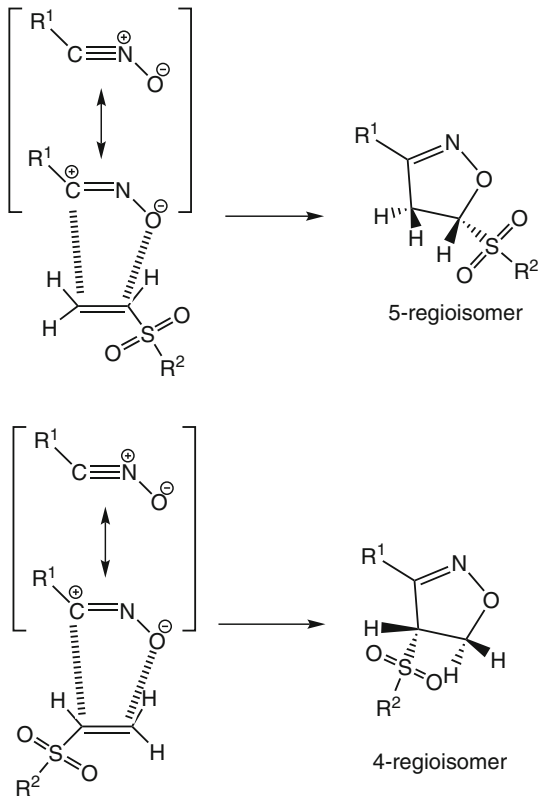
Scheme 1



serious adverse reactions. Moreover, parasite resistance to existing drugs has become a serious problem, indicating the need for new drugs in this field. Owing to lack of financial returns, however, antiprotozoal drug discovery and development largely depends on funding by public authorities and universities.

4,5-Dihydroisoxazoles are an interesting class of heterocycles that are stable toward nucleophiles such as thiols and are easily derived from 1,3-dipolar cycloaddition of nitrile oxides with an acrylate or a substituted ethylene via an inter- or intramolecular pathway [5–7]. 4,5-Dihydroisoxazoles are often used as intermediates in the preparation of or as protecting groups for a wide variety of difunctionalized compounds. For example, cleavage of the 4,5-dihydroisoxazole can give rise to β-hydroxyketones, α,β-unsaturated ketones, and γ-aminoalcohols [8–14]. The dihydroisoxazole moiety is also found as the end product in many pharmaceutically active compounds. Diverse biological activities have been reported for this class of compounds. Antibacterial, antitrypanosomal, and antitrichomoniasis activities of isoxazole-substituted nitroimidazoles have been known for a long time [15, 16]. Dihydroisoxazoles, particularly 4,5-dihydroisoxazole derivatives, also display calcium channel blocking, estrogen receptor agonist, anticancer, herbicidal, neuroprotective, human transglutaminase 2 inhibitory activity, and binding affinity at glutamic acid receptors [17–25]. *N*-Hydroxy- or *N*-oxy-benzamidino-isoxazoles and dihydroisoxazolyl-oxadiazoles have been shown to exhibit insecticidal, acaricidal, nematicidal, or molluscicidal potential [26–28]. Recent studies were devoted to the assessment of the anti-inflammatory [29] and anti-infective (such as antiviral [30], antiprotozoal, antifungal [17, 28, 31], and antibacterial [17]) properties of 4,5-dihydroisoxazole and other isoxazoles. For example, 3-bromoacivicin ((α*S*,5*S*)-α-amino-3-bromo-4,5-dihydroisoxazol-5-acetic acid) shows very potent in vitro trypanocidal and in vivo trypanostatic activity and inhibits CTP synthetase [32]. Dihydroisoxazolyl-6-chloropurine and adenine are effective against HIV-1 in acutely infected human lymphocytes [33], whereas phosphonated dihydroisoxazoles inhibit the herpes simplex virus (HSV) [34]. Owing to their wide range of biological activities, dihydroisoxazoles have been constructed by numerous synthetic approaches [35–42].

In continuation of our interest in the synthesis of novel synthetic antiprotozoal agents [43] plus our ongoing



Scheme 2

interest in 1,3-dipolar cycloaddition chemistry [44], a number of 4,5-dihydroisoxazoles carrying phenyl(methyl)-sulfonyl group at position 5 (**5a**–**5p**, Scheme 1) were designed. Since there is no report on the synthesis of dihydroisoxazoles by using nitrolic acid as the precursor of the nitrile oxide, we focused on the 1,3-dipolar cycloaddition reaction of **4**, which are generated in situ from nitrolic acids **3** (Schemes 1, 2). The nitrile oxides reacted regioselectively with phenyl or methyl vinyl sulfones to afford 3,5-disubstituted 4,5-dihydroisoxazoles **5a**–**5p**. Nitrolic acids (α-nitro oximes), some of which show biological activities [45], were first reported by Meyer [46]. Since then, a limited number of studies on their synthesis, stability, and use were reported in the literature [47–52]. Nitrolic acids are well known to undergo 1,3-dipolar cycloadditions; however, to the best of our knowledge, synthetic applications of this process are rarely found in the literature in contrast to the functionally equivalent

Table 1 Synthesis of dihydroisoxazoles **5a–5p** (Scheme 1)

Comp.	R^1	R^2	Yield/%	Solvent	Time/h
5a	2-Pyridyl	Ph	55	Toluene	2
5b	3-Pyridyl	Ph	71	Toluene	2
5c	4-Pyridyl	Ph	49	Toluene	2
5d	6-Cl-3-pyridyl	Ph	72	Toluene	2
5e	2-Pyridyl	Me	88	THF	0.5
5f	3-Pyridyl	Me	80	THF	0.5
5g	6-Cl-3-pyridyl	Me	92	THF	0.5
5h	4-NO_2-C_6H_4	Ph	70	Toluene	2
5i	2-NO_2-C_6H_4	Ph	69	Toluene	2
5j	3-NO_2-C_6H_4	Ph	65	Toluene	2
5k	4-Cl-C_6H_4	Ph	60	Toluene	2
5l	4-MeO-C_6H_4	Ph	69	DCM	2
5m	4-MeO-C_6H_4	Me	75	DCM	2
5n	4-F-C_6H_4	Ph	58	DCM	2
5o	4-F-C_6H_4	Me	78	DCM	2
5p	2-Furanyl	Ph	58	Toluene	2

cycloadditions of nitrile oxides [53–57]. This report deals with their synthetic methodology and antiprotozoal activities evaluated against a small panel of protozoan parasites, *T. b. rhodesiense*, *T. cruzi*, *L. donovani*, and *P. falciparum*. Selective toxicity of all compounds was also determined against L6 cells, a primary cell line derived from rat skeletal myoblasts.

Results and discussion

*Synthesis of nitrolic acids **3a–3g** and **3h–3p***

Pyridine-substituted nitrolic acids **3a–3g** were prepared from the reaction of aromatic aldoximes, which are easily obtained from the corresponding aromatic aldehyde and hydroxyl amine [47] with fuming nitric acid in acetic acid, whereas aryl-substituted nitrolic acids **3h–3p** were prepared from the interaction of aryl aldoximes with dinitrogen tetraoxide gas in diethyl ether. All nitrolic acids were obtained as a single isomer and kept in a refrigerator without decomposition over months.

*Synthesis and structure determination of dihydroisoxazoles **5a–5p***

Reaction of nitrolic acid with the dipolarophiles phenyl vinyl sulfone and methyl vinyl sulfone to yield dihydroisoxazoles **5a–5p** (Scheme 1; Table 1) was carried out under neutral conditions, and in this regard, this synthetic route can be regarded as one of the main advantages of using nitrolic acids in comparison to the other nitrile oxide precursors.

The structure elucidations of the new cycloadducts, namely phenyl (or methyl) sulfonyl-substituted dihydroisoxazoles, were performed by ^{1}H NMR, ^{13}C NMR, MS (low and high resolution), X-ray diffraction, and physical characteristics. On the basis of the relative positions of the peaks and coupling constants of the relevant protons in the ^{1}H NMR spectra, the 5-regioisomers were the major isomers formed, in all but one instance. In the case of *p*-nitrophenyl-substituted **5h** (Fig. 1), a mixture of the 5- and 4-regioisomers was found in a 3.46:1 ratio, calculated from the ^{1}H NMR spectrum of the crude reaction mixture. Attempts to separate the regioisomers failed owing to their very close physical characteristics.

Synthesis of methyl sulfonyl-substituted dihydroisoxazoles required less severe reaction conditions than phenyl sulfonyl-substituted derivatives and yields were also found to be relatively higher than those of phenyl sulfonyl-substituted products. This may be attributed to the electron-releasing and less bulky nature of the methyl group.

Theoretically, the 1,3-dipolar nitrile oxide species may approach the unsymmetrical alkene with the phenyl (or methyl) vinyl sulfone oriented in two different ways leading to the formation of 5-regioisomer or 4-regioisomer regioselectively, depending on the transition state energy of the 1,3-dipolar cycloaddition reaction as a result of the nature of the groups existing both in the 1,3-dipole and dipolarophile as depicted in Scheme 2 [52]. The regioselectivity and configurations of the stereocenters for the compounds **5a** and **5b** were also confirmed by single-crystal X-ray diffraction data (Fig. 2).

As for the representative spectral characteristics of the cycloaddition products phenyl (methyl) sulfonyl-substituted 4,5-dihydroisoxazoles, in the IR spectra of these

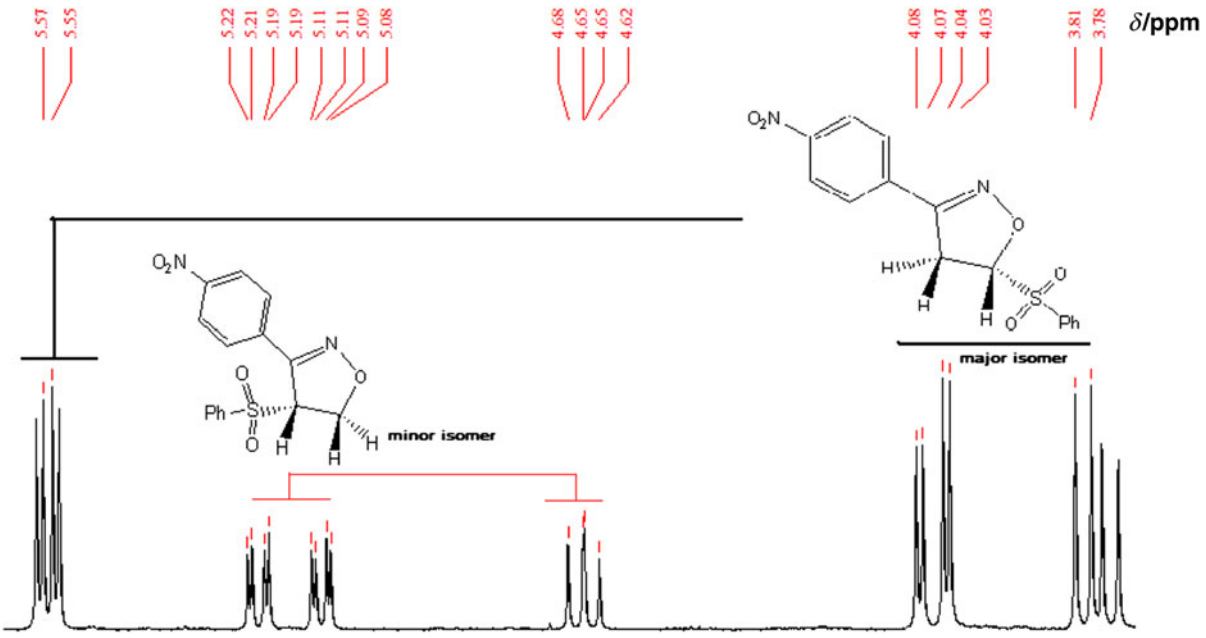


Fig. 1 Expanded partial ^{1}H NMR spectrum of compound **5h** showing proton signals related to both regioisomers

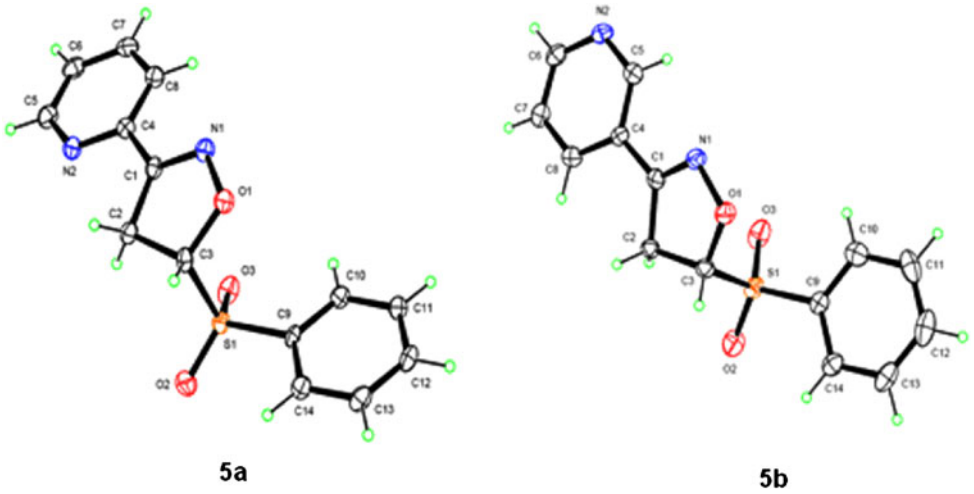


Fig. 2 X-ray crystal structures of compounds **5a** and **5b**

heterocycles, the C=N stretching vibration arises at around 1,602–1,541 cm^{-1} and the stretching vibration for the SO_2 group is found between 1,155 and 1,126 cm^{-1} indicating asymmetric and symmetric stretching of the sulfonyl group, respectively. In the ^{1}H NMR spectra, the hydrogen (Ha) on the sp^3 carbon attached to the sulfonyl group is most deshielded and resonates at around 5.60 ppm as a doublet of doublets. Methylene protons in the isoxazoline ring, in most cases, show a separate doublet of doublets splitting pattern at around 4.10 and 3.80 ppm (Fig. 3).

The interrelationship between the Ha proton and adjacent CH_2 hydrogens is clearly seen by COSY and also by DEPT-135 and DEPT-90 spectra. The DEPT spectra allowed the assignment of the number 4 and 5 carbons in the isoxazole ring. In addition to the aforementioned 1D and 2D NMR measurements, heteronuclear 2D NMR experiments, i.e., HMBC and HSQC, were also performed to establish the exact positions of the carbon atoms in the isoxazole ring.

In the EI mass spectra of the isoxazolines, the base peaks were found to be due to ionic species, $M-PhSO_2$, as would be predicted because extrusion of $PhSO_2$ from the molecule produces an aromatic stabilized species, i.e., an isoxazole (Scheme 3).

Bioactivity assessments

Table 2 displays the in vitro antiprotozoal activity of synthesized compounds against *T. b. rhodesiense* (bloodstream forms), *T. cruzi* (intracellular amastigotes in L6 rat skeletal

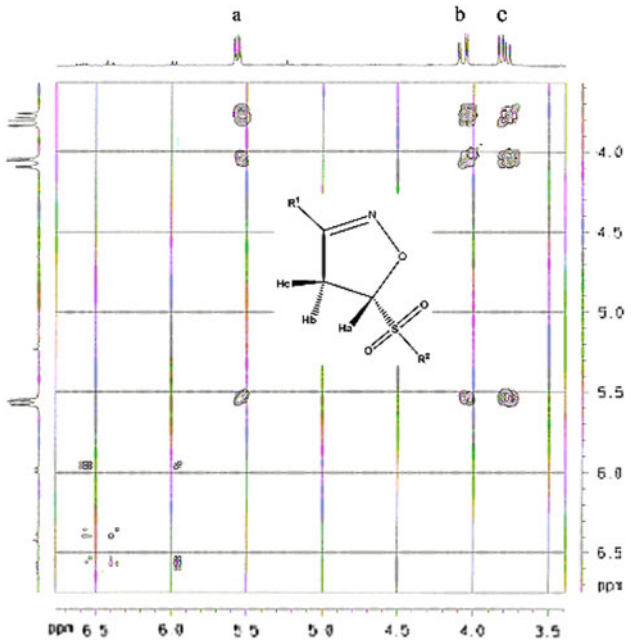
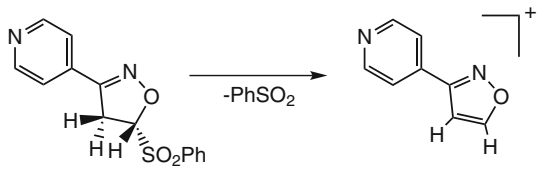


Fig. 3 COSY spectrum of **5j** indicating the couplings of C-4 (Hb, Hc) and C-5 (Ha) hydrogens in the isoxazoline ring



Scheme 3

myoblasts), *L. donovani* (axenic amastigotes), and *P. falciparum* (blood stage forms of multi-drug resistant K1 strain). Compounds **5h** and **5i** were the most potent against the *T. b. rhodesiense* parasite (IC_{50} values 6.9 and 9.0 μg cm^{-3}). All remaining compounds also possessed some activity with IC_{50} values ranging between 27.2 and 53.1 μg cm^{-3}.

Towards the American trypanosomes (*T. cruzi*), low activity was observed for all compounds (IC_{50} values 40.0–87.8 μg cm^{-3}). Among ten compounds that showed antileishmanial potential, **5i**, **5h**, **5l**, and **5d** were the most active ones with IC_{50} values between 3.4 and 9.9 μg cm^{-3}. A moderate leishmanicidal activity was exhibited by **5k** and **5n** with IC_{50} values below 20 μg cm^{-3}. The growth inhibitory potential was modest towards the malaria parasite (*P. falciparum*) and again **5h** and **5i** appeared to have the lowest IC_{50} values (9.3 and 13.9 μg cm^{-3}, respectively). The IC_{50} values of the remaining eight active molecules were within the range of 20.8–49.8 μg cm^{-3}. When tested for toxicity against L6 cells, a primary cell line derived from rat skeletal myoblasts, only **5h**, **5i**, **5l**, and **5m** showed some toxic potential whereas the others were nontoxic even at the highest test concentrations (100 μg cm^{-3}). These results indicate that a nitro substituent in either *ortho* or *para* positions of R^1, as found in compounds **5h** and **5i**, is favorable for antiprotozoal activity, although this is associated with some toxicity. Interestingly, a nitro substituent in the *meta* position of the phenyl ring is not favored, as the antiprotozoal potency of **5j** is much lower than that of **5h** and **5i**. As seen in compound **5l**, the combination of a *p*-methoxy substituent on the phenyl ring (R^1) and an aromatic substituent (phenyl) at R^2 results in a relatively good activity against *L. donovani*. However, when the substituent at R^2 is replaced by a methyl group (**5m**), leishmanicidal activity drops significantly. This tendency is clear for all other antiprotozoal activity for this entry (**5m**). Among those compounds with a pyridyl substituent at R^1, the most significant activity was obtained against *L. donovani* by **5d**. This compound bears a 3-pyridyl substituent with a chlorine atom at the 6-position at R^1. The pyridyl- and fluorine-substituted compounds with a methyl group at R^2 generally display low or no antiprotozoal potential, indicating the necessity of an aromatic function at R^2 in general. The only furanyl-substituted dihydroisoxazole, **5p**, showed some activity against *Trypanosoma* species, but was inactive towards other remaining parasites.

Conclusions

We have demonstrated a simple and practical new synthetic route for the preparation of a series of aryl- and phenyl(methyl)sulfonyl-substituted dihydroisoxazoles, some of which were previously reported through oxime-generated nitrile oxide cycloadditions, by 1,3-dipolar cycloaddition of nitrolic acid-generated nitrile oxides to phenyl (or methyl) vinyl sulfones and determined their structures by means of spectroscopic methods including X-ray crystallography.

Owing to the reported diverse biological activities such as antibacterial, antitrypanosomal, and antitrichomoniasis for this class of compounds [15, 16] and the fact that they also display calcium channel blocking, estrogen receptor agonist, anticancer, herbicidal, neuroprotective, and human transglutaminase 2 inhibitory activity and binding affinity at glutamic acid receptors [17–25], isoxazole derivatives **5a–5p** were efficiently designed, prepared, and assayed for their antiprotozoal activity as well as for general cytotoxicity. Among ten compounds that showed antileishmanial potential, **5i**, **5h**, **5l**, and **5d** were found to be the most active ones with IC_{50} values between 3.4 and 9.9 μg cm^{-3}. Nitro substitution in the *ortho* or *para* positions of R^1, as found in compounds **5h** and **5i**, is favorable for antiprotozoal activity, but associated with some toxicity. However,

Table 2 Antiprotozoal activities of compounds **5a–5p**

Comp.	*T. b. rhodesiense*	*T. cruzi*	*L. donovani*	*P. falciparum*	Cytotoxicity L6 cells
Standard[a]	0.005[b]	0.464[c]	0.171[d]	0.073[e]	0.007[f]
5a	42.0	44.6	91.5	49.8	>100
5b	41.7	50.7	97.5	36.3	>100
5c	42.9	43.4	>100	41.7	>100
5d	48.3	48.2	**9.9**	>50	>100
5e	42.4	50.0	>100	>50	>100
5f	36.9	53.2	>100	33.3	>100
5g	36.6	50.4	>100	44.6	>100
5h	**6.9**	42.3	**4.2**	**9.3**	**28.5**
5i	**9.0**	44.2	**3.4**	**13.9**	**42.3**
5j	28.7	55.4	53.3	43.1	>100
5k	29.3	48.1	15.7	28.9	>100
5l	27.2	40.0	**8.8**	20.8	**52.9**
5m	43.4	87.8	91.2	38.6	**83.0**
5n	27.4	50.3	16.6	>50	>100
5o	41.8	73.3	>100	>50	>100
5p	53.1	58.0	>100	>50	>100

IC_{50} values are in μg cm^{-3}. The significant activities are shown in bold

[a] Standard compounds (control drugs): [b] melarsoprol, [c] benznidazole, [d] miltefosine, [e] chloroquine, [f] podophyllotoxin

a nitro substituent in the *meta* position of the phenyl ring is not favored, interestingly, as the antiprotozoal potency of **5j** is much lower than that of **5h** and **5i**. In summary, although the observed bioactivity of the synthesized molecules is low in comparison to the reference compounds, this study still indicates the antiprotozoal potential of 4,5-dihydroisoxazoles, particularly when their toxic potential is reduced after further medicinal chemistry efforts.

Experimental

Melting points were determined on an Electro Thermal melting point apparatus. Infrared spectra were recorded on Shimadzu FTIR spectrophotometer. Mass spectra (low and high resolution) were recorded on a Fisons VG Platform II spectrometer and on a Micromass Q-TOF Micro spectrometer (ESI-interface). NMR spectra were recorded on a Bruker DPX 400 spectrometer operating at 400 MHz for ^{1}H and at 100 MHz for ^{13}C at 25 °C. All chemical shifts are reported in ppm downfield from TMS. Coupling constants (*J*) are reported in Hz. Multiplicity in ^{1}H NMR is reported as singlet (s), doublet (d), doublet doublet (dd), double triplet (dt), double triple doublet (dtd), double quartet (dq), triplet (t), and multiplet (m).

Pyridyl- (**3a–3g**) and other aryl-substituted (**3h–3p**) nitrolic acids were prepared according to the procedures described previously and used without further purification. Their structural characteristics were checked and compared with the data in the literature [47, 58, 59].

General procedure for synthesis of dihydroisoxazoles ***5a–5p***

Nitrolic acid **3a–3p** (1.0 mmol) was added to phenyl (or methyl) vinyl sulfone (1 mmol) in 5 cm^3 dry toluene and the mixture was heated to reflux for 30 min. The reaction mixture was concentrated in vacuo, and the crude residue was purified by flash column chromatography (eluent petroleum ether/ethyl acetate 2:1) to give the title compounds as yellow solids.

(R)-4,5-Dihydro-5-(phenylsulfonyl)-3-(pyridin-2-yl)-isoxazole (**5a**, $C_{14}H_{12}N_2O_3S$)
Recrystallized from ethylacetate/*n*-hexane to afford crystals suitable for single-crystal X-ray diffraction. Yield 158 mg (55 %); m.p.: 127–129 °C (Ref. [54] 126–127 °C).

Crystal data: $C_{14}H_{12}N_2O_3S$, $M_r = 288.32$; monoclinic, $P2_1/n$; $a = 5.3810(10)$ Å, $b = 8.2117(7)$ Å, $c = 29.564(7)$ Å, $\beta = 92.742(9)°$, $V = 1304.9(5)$ $Å^3$; $Z = 4$, $Dx = 1.468$ Mg m^{-3}, *Dm* not measured; Mo K_α radiation, $\lambda = 0.71073$ Å; cell parameters from 3,214 reflections, $\theta = 2.5–28.3°$, $\mu = 0.257$ mm^{-1}; $T = 90$ K; colorless needle, 0.37 × 0.07 × 0.03 mm.

(R)-4,5-Dihydro-5-(phenylsulfonyl)-3-(pyridin-3-yl)-isoxazole (**5b**, $C_{14}H_{12}N_2O_3S$)
Obtained as a colorless solid which was recrystallized from ethylacetate/*n*-hexane to afford suitable crystals for single-crystal X-ray diffraction. Yield 205 mg (71 %); m.p.: 154–155 °C; $R_f = 0.59$ (ethyl acetate/*n*-hexane 1:2); IR (KBr): $\bar{\nu} = 1{,}580, 1{,}451, 1{,}311, 1{,}306, 1{,}155, 851, 770, 735$ cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.75$ (s, 1H), 8.60

(s, 1H), 7.91 (t, 3H), 7.61 (t, 1H), 7.50 (t, 2H), 7.30 (m, 1H), 5.56 (dd, $J = 10.9$, 4.6 Hz, 1H), 4.00 (dd, $J = 8.3$, 4.5 Hz, 1H), 3.75 (q, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 154.7$ (C=N, isoxazole), 151.8 (C=N, pyridine), 147.8, 135.1, 134.7, 134.2, 129.7, 129.3, 128.3, 123.7, 93.5, 36.3 ppm; MS: *m/z* (%) = 146 (100, $[M-PhSO_2]^+$), 78 (46), 51 (25); HRMS-TOF–MS (ES^+): found 289.0633, calculated for $C_{14}H_{12}N_2O_3S + H$ 289.0647.

Crystal data: $C_{14}H_{12}N_2O_3S$, $M_r = 288.32$; orthorhombic, $P2_12_12_1$; $a = 5.2052(10)$ Å, $b = 9.894(2)$ Å, $c = 25.166(7)$ Å, $V = 1296.1(5)$ Å^3; $Z = 4$, $Dx = 1.478$ Mg m^{-3}, *Dm* not measured; Mo K_α radiation, $\lambda = 0.71073$ Å; cell parameters from 1,779 reflections, $\theta = 2.5$–$28.7°$, $\mu = 0.258$ mm^{-1}; $T = 90$ K; colorless plate, 0.37 × 0.22 × 0.03 mm.

(R)-4,5-Dihydro-5-(phenylsulfonyl)-3-(pyridin-4-yl)-isoxazole (**5c**, $C_{14}H_{12}N_2O_3S$)
Yellow solid; yield 170 mg (49 %); m.p.: 151–152 °C; $R_f = 0.50$ (ethyl acetate/*n*-hexane 1:2); IR (KBr): $\bar{\nu} =$ 1,595, 1,444, 1,408, 1,363, 1,309, 1,146, 862, 824, 735 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.72$ (d, $J = 5.8$ Hz, 2H), 8.02 (d, $J = 7.6$ Hz, 2H), 7.73 (t, 1H), 7.61 (t, 1H), 7.50 (d, $J = 5.9$ Hz, 2H), 5.56 (dd, $J = 10.9$, 4.6 Hz, 1H), 4.10 (dd, $J = 8.3$, 4.6 Hz, 1H), 3.80 (q, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 155.5$ (C=N, isoxazole), 150.3 (C=N, pyridine), 137.2, 135.0, 134.8, 129.7, 129.4, 120.9, 93.6, 35.9 ppm; MS: *m/z* (%) = 146 (100, $[M-PhSO_2]^+$), 78 (44), 51 (28); HRMS-TOF–MS (ES^+): found 289.0633, calculated for $C_{14}H_{12}N_2O_3S + H$ 289.0647.

(R)-3-(6-Chloropyridin-3-yl)-4,5-dihydro-5-(phenylsulfonyl)isoxazole (**5d**, $C_{14}H_{11}ClN_2O_3S$)
Yellow solid; yield 268 mg (72 %); m.p.: 142–144 °C; $R_f = 0.47$ (ethyl acetate/*n*-hexane 1:2); IR (KBr): $\bar{\nu} =$ 1,584, 1,480, 1,408, 1,369, 1,308, 1,151, 1,110, 859, 765, 729 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.56$ (d, $J = 2.0$ Hz, 1H), 7.98 (m, 3H), 7.70 (m, 1H), 7.58 (t, 3H), 7.37 (d, $J = 5.9$ Hz, 2H), 5.60 (dd, $J = 10.9$, 4.5 Hz, 1H), 4.10 (dd, $J = 18.3$, 4.5 Hz, 1H), 3.80 (q, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 153.9$ (C=N, isoxazole), 148.5 (C=N, pyridine), 136.6, 135.1, 129.7, 129.4, 124.7, 122.7, 93.3, 36.1 ppm; MS: *m/z* (%) = 180 (100, $[M-PhSO_2]^+$), 152 (19), 112 (28), 76 (44), 50 (28); HRMS-TOF–MS (ES^+): found 323.0267, calculated for $C_{14}H_{11}ClN_2O_3S + H$ 323.0257.

(R)-4,5-Dihydro-5-(methylsulfonyl)-3-(pyridin-2-yl)-isoxazole (**5e**, $C_9H_{11}N_2O_3S$)
Yellow solid; yield 199 mg (88 %); m.p.: 140 °C (dec.); $R_f = 0.45$ (ethyl acetate/*n*-hexane 1:2); IR (KBr): $\bar{\nu} =$ 1,581, 1,469, 1,444, 1,367, 1,305, 1,126, 945, 862, 786 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.55$ (d, $J = 4.0$ Hz, 1H), 7.90 (d, $J = 7.9$ Hz, 1H), 7.65 (t, 1H), 7.30 (t, 1H), 5.50 (dd, $J = 11.0$, 4.8 Hz, 1H), 4.15 (dd, $J = 19.2$, 4.9 Hz, 1H), 3.85 (q, 1H), 2.90 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 156.9$ (C=N, isoxazole), 150.0 (C=N, pyridine), 135.2, 134.5, 132.8, 131.7, 130.8, 130.6, 129.9, 129.2, 128.9, 128.7, 127.0, 93.9, 39.1, 33.9 ppm; HRMS-TOF–MS (ES^+): found 227.0480, calculated for $C_9H_{11}N_2O_3S + H$ 227.0490.

(R)-4,5-Dihydro-5-(methylsulfonyl)-3-(pyridin-3-yl)-isoxazole (**5f**, $C_9H_{11}N_2O_3S$)
Orange solid; yield 182 mg (80 %); m.p.: 144–146 °C; $R_f = 0.33$ (ethyl acetate/*n*-hexane 1:2); IR (KBr): $\bar{\nu} =$ 1,411, 1,365, 1,305, 1,263, 1,130, 1,028, 979, 939, 858, 804, 773 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.90$ (d, $J = 1.7$ Hz, 1H), 8.70 (dd, $J = 4.8$, 1.4 Hz, 1H), 8.05 (d, $J = 8.1$ Hz, 1H), 7.40 (t, 1H), 5.60 (dd, $J = 10.8$, 4.7 Hz, 1H), 4.05 (dd, $J = 18.2$, 4.7 Hz, 1H), 3.80 (dd, $J = 18.2$, 7.3 Hz, 1H), 3.09 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 156.9$ (C=N, isoxazole), 152.0 (C=N, pyridine), 148.1, 135.2, 134.5, 132.8, 131.7, 130.8, 130.6, 129.9, 129.2, 128.9, 128.7, 127.0, 93.9 ($CHSO_2Ph$), 37.0 (CH_3SO_2Ph), 35.4 (CH_2) ppm; HRMS-TOF–MS (ES^+): found 227.0484, calculated for $C_9H_{11}N_2O_3S$ 227.0490.

(R)-3-(6-Chloropyridin-3-yl)-4,5-dihydro-5-(methylsulfonyl)isoxazole (**5g**, $C_9H_{10}ClN_2O_3S$)
White solid; yield 239 mg (92 %); m.p.: 159–160 °C; $R_f = 0.39$ (ethyl acetate/*n*-hexane 1:2); IR (KBr): $\bar{\nu} =$ 1,602, 1,552, 1,433, 1,379, 1,305, 1,139, 1,109, 1,010, 933, 864, 765 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.56$ (d, $J = 2.4$ Hz, 1H), 7.95 (dd, $J = 8.4$, 2.4 Hz, 1H), 7.35 (d, $J = 8.3$ Hz, 1H), 5.50 (dd, $J = 10.8$, 4.7 Hz, 1H), 3.90 (dd, $J = 18.2$, 4.9 Hz, 1H), 3.75 (dd, $J = 18.1$, 10.8 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 156.6$ (C=N, isoxazole), 155.6 (Cl–C, pyridine), 152.1 (C=N, pyridine), 148.1, 135.2, 134.5, 132.8, 131.7, 130.8, 130.6, 129.9, 129.2, 128.9, 128.7, 127.0, 94.7 ($CHSO_2Ph$), 37.2 (CH_3SO_2Ph), 35.8 (CH_2, isoxazole) ppm; HRMS-TOF–MS (ES^+): found 261.0095, calculated for $C_9H_{10}ClN_2O_3S$ 261.0101.

*(R)-4,5-Dihydro-3-(4-nitrophenyl)-5-(phenylsulfonyl)-isoxazole (*5-regioisomer, **5h**, $C_{15}H_{12}N_2O_5S$*)*
and (R)-4,5-dihydro-3-(4-nitrophenyl)-4-(phenylsulfonyl)isoxazole (4-regioisomer, $C_{15}H_{12}N_2O_5S$)
It was deduced from ^{1}H NMR spectra that the ratio between 5-regioisomer and 4-regioisomer was 3.46:1. The mixed compound was obtained as a yellow solid. Yield 232 mg (70 %); m.p.: 143–145 °C (Ref. [53] 187–189 °C for the 5-regioisomer); $R_f = 0.35$ (ethyl acetate/*n*-hexane 1:2); IR (KBr): $\bar{\nu} =$ 1,600, 1,585, 1,521, 1,446, 1,348, 1,151, 848, 732 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.20$ (m, 4H), 7.98–7.40 (m, 5H), 5.55 (dd,

J = 10.9, 4.6 Hz, 1H), 5.20 (dd, J = 11.2, 2.9 Hz, 1H, 4-regioisomer), 5.10 (dd, J = 10.1, 2.9 Hz, 1H, 4-regioisomer), 4.60 (t, 1H, 4-regioisomer), 4.05 (dd, J = 18.3, 4.6 Hz, 1H, 5-regioisomer), 3.75 (dd, J = 18.3, 10.9 Hz, 1H, 5-regioisomer) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.5 (C=N), 149.1, 135.1, 135.0, 134.8, 133.3, 129.7, 129.4, 129.2, 129.1, 128.5, 127.9, 124.1, 123.9, 93.6 (C-5 of 5-regioisomer), 73.0 (C-4 of 4-regioisomer), 71.2 (C-5 of 4-regioisomer), 36.2 (C-4 of 5-regioisomer) ppm; MS: m/z (%) = 180 (100, $[M-PhSO_2]^+$), 152 (19), 112 (28), 76 (44), 50 (28); HRMS-TOF–MS (ES^+): found 333.0531, calculated for $C_{15}H_{12}N_2O_5S$ + H 333.0545.

(R)-4,5-Dihydro-3-(2-nitrophenyl)-5-(phenylsulfonyl)-isoxazole (**5i**, $C_{15}H_{12}N_2O_5S$)
Yellow solid; yield 179 mg (69 %); m.p.: 159–160 °C; R_f = 0.41 (ethyl acetate/*n*-hexane 1:2); IR (KBr): $\bar{\nu}$ = 1,599, 1,579, 1,512, 1,348, 1,317, 1,143, 1,085, 846, 729 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30 (d, J = 2.0 Hz, 2H), 8.00 (d, J = 2.0 Hz, 2H), 7.85 (d, J = 2.0 Hz, 2H), 7.70 (t, 1H), 7.60 (t, 2H), 5.60 (dd, J = 10.9, 4.5 Hz, 1H), 4.15 (dd, J = 18.3, 4.5 Hz, 1H), 3.85 (dd, J = 18.3, 10.9 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.9 (C=N, isoxazole), 148.5 (C=N, pyridine), 136.6, 135.1, 129.7, 129.4, 124.7, 122.7, 93.3, 36.1 ppm; MS: m/z (%) = 190 (100, $[M-PhSO_2]^+$), 143 (29), 89 (80); HRMS-TOF–MS (ES^+): found 333.0539, calculated for $C_{15}H_{12}N_2O_5S$ + H 333.0545.

(R)-4,5-Dihydro-3-(3-nitrophenyl)-5-(phenylsulfonyl)-isoxazole (**5j**, $C_{15}H_{12}N_2O_5S$)
Yellow solid; yield 216 mg (65 %); m.p.: 162–163 °C; R_f = 0.31 (ethyl acetate/*n*-hexane 1:2); IR (KBr): $\bar{\nu}$ = 1,531, 1,352, 1,311, 1,149, 720 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.48 (t, 1H), 8.35 (dd, J = 8.2, 1.2 Hz, 1H), 8.03 (t, 2H),7.75 (t, 1H), 7.70–7.60 (m, 5H), 5.65 (dd, J = 11.5, 4.4 Hz, 1H), 4.15 (dd, J = 18.3, 4.5 Hz, 1H), 3.80 (dd, 18.3, 7.4 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.9 (C=N, isoxazole), 148.4 (C=N, pyridine), 135.5, 135.2, 133.7, 131.1, 129.9, 129.8, 129.2, 125.9, 121.9, 93.7, 36.8 ppm; MS: m/z (%) = 189 (100, $[M-PhSO_2]^+$), 143 (20), 116 (21), 89 (74), 76 (44), 50 (29); HRMS-TOF–MS (ES^+): found 333.0541, calculated for $C_{15}H_{12}N_2O_5S$ + H 333.0545.

(R)-3-(4-Chlorophenyl)-4,5-dihydro-5-(phenylsulfonyl)-isoxazole (**5k**, $C_{15}H_{12}ClNO_3S$)
Yellow solid; yield 247 mg (60 %); m.p.: 136–138 °C; R_f = 0.44 (ethyl acetate/*n*-hexane 1:2); IR (KBr): $\bar{\nu}$ = 1,591, 1,477, 1,446, 1,321, 1,151, 1,084, 852, 759, 732 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (d, J = 7.4 Hz, 1H), 7.72 (t, 1H), 7.60 (m, 2H), 7.46–7.25 (m, 5H), 5.63 (t, 1H), 4.10 (dd, J = 11.3, 7.4 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.9 (C=N, isoxazole), 148.2 (C=N, pyridine), 135.2, 134.5, 132.8, 131.7, 130.8, 130.6, 129.9, 129.2, 128.9, 128.7, 127.0, 93.9, 39.1 ppm; MS: m/z (%) = 178 (100, $[M-PhSO_2]^+$), 150 (19), 111 (28), 89 (32), 75 (44), 50 (28); HRMS-TOF–MS (ES^+): found 322.0291, calculated for $C_{15}H_{12}ClNO_3S$ + H 322.0305.

(R)-4,5-Dihydro-3-(4-methoxyphenyl)-5-(phenylsulfonyl)isoxazole (**5l**)
Yellow solid; yield 91 mg (69 %); m.p.: 125.5–127 °C (Ref. [57] 128–130 °C, Ref. [54] 129–130 °C).

(R)-4,5-Dihydro-3-(4-methoxyphenyl)-5-(methylsulfonyl)isoxazole (**5m**)
Yellow solid; yield 96 mg (75 %); m.p.: 167.5–169 °C (Ref. [56] 167–168 °C).

(R)-4,5-Dihydro-3-(4-fluorophenyl)-5-(phenylsulfonyl)-isoxazole (**5n**, $C_{15}H_{12}FNO_3S$)
Yellow solid; yield 88 mg (58 %); m.p.: 135–136 °C; R_f = 0.43 (ethyl acetate/*n*-hexane 1:2); IR (KBr): $\bar{\nu}$ = 1,596, 1,514, 1,307, 1,236, 1,142, 856 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) : δ = 8.03 (d, 2H), 7.74–7.70 (m, 1H), 7.66–7.59 (m, 4H), 7.13 (dd, J = 11.5, 6.6 Hz, 2H), 5.58 (dd, J = 15.3, 6.3 Hz, 1H), 4.48 (dd, J = 18.2, 13.7 Hz, 1H), 3.81 (dd, J = 18.2, 10.8 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.0, 155.9, 134.6, 129.7, 129.2, 129.1, 123.6, 116.3, 116.0, 93.3, 36.8 ppm; HRMS-TOF–MS (ES^+): found 328.0430, calculated for $C_{15}H_{12}FNO_3S$ + Na 328.0420.

(R)-4,5-Dihydro-3-(4-fluorophenyl)-5-(methylsulfonyl)-isoxazole (**5o**, $C_{10}H_{10}FNO_3S$)
Yellow solid; yield 95 mg (78 %); m.p.: 155–157 °C; R_f = 0.29 (ethyl acetate/*n*-hexane 1:2); IR (KBr): $\bar{\nu}$ = 1,601, 1,559, 1,516, 1,306, 1,227, 1,134, 842 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) : δ = 7.77–7.63 (m, 2H), 7.15 (t, J = 8.5 Hz, 2H), 5.55 (dd, J = 10.8, 4.7 Hz, 1H), 4.02 (dd, J = 18.1, 4.6 Hz, 1H), 3.79 (dd, J = 18.1, 10.8 Hz, 1H), 3.06 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.7 (F–C), 156.2 (C=N, isoxazole), 129.4, 123.4, 116.3, 91.9, 37.0 (CH_3SO_2), 36.1 (CH_2, isoxazole) ppm; HRMS-TOF–MS (ES^+): found 266.0261, calculated for $C_{10}H_{10}FNO_3S$ + Na 266.0263.

(R)-3-(Furan-2-yl)-4,5-dihydro-5-(phenylsulfonyl)-isoxazole (**5p**, $C_{13}H_{11}NO_4S$)
Yellow oil; yield 161 mg (58 %); R_f = 0.36 (ethyl acetate/*n*-hexane 1:2); IR (neat): $\bar{\nu}$ = 1,583, 1,483, 1,446, 1,319, 1,309, 1,151, 1,085, 840, 783 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (t, 2H), 7.60 (t, 1H), 7.45 (m, 4H), 6.70 (d, J = 4.0 Hz, 1H), 6.40 (dd, J = 3.4, 1.7 Hz, 1H), 5.45 (dd, J = 10.8, 4.4 Hz, 1H), 4.00 (dd, J = 18.3, 4.4 Hz, 1H), 3.85 (dd, J = 18.2, 10.8 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.0 (C=N, isoxazole), 149.4,

147.0, 136.6, 135.4, 134.5, 129.7, 125.1, 122.1, 93.7, 36.8 ppm; HRMS-TOF–MS (ES^+): found 278.0489, calculated for $C_{13}H_{11}NO_4S$ 278.0442.

In vitro antiprotozoal and cytotoxic activity studies

The bioassays were carried out as described elsewhere [43].

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