Synthesis and in Vitro Antiprotozoal Activities of Dicationic 3,5-Diphenylisoxazoles

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3,5-Bis(4-amidinophenyl)isoxazole (**3**)—an analogue of 2,5-bis(4-amidinophenyl)furan (furamidine) in which the central furan ring is replaced by isoxazole—and 42 novel analogues were prepared by two general synthetic pathways. The 43 isoxazole derivatives were assayed against *Trypanosoma brucei rhodesiense* (*T. brucei rhodesiense*) STIB900, *Plasmodium falciparum* (*P. falciparum*) K1, and rat myoblast L6 cells (for cytotoxicity) in vitro. Eleven compounds (**3**, **13**, **16**−**18**, **22**, **26**, **29**, **31**, **37**, and **41**) exhibited antitrypanosomal IC_{50} values less than 10 nM, five of which displayed cytotoxic indices (ratios of cytotoxic IC_{50} to antiprotozoal IC_{50} values) at least 10 times higher than that of furamidine. Eighteen compounds (**4**−**8**, **12**, **14**, **18**−**22**, **25**, **26**, **28**, **29**, **32**, and **43**) were more active against *P. falciparum* than furamidine, with IC_{50} values less than 15 nM. Fourteen of these compounds had cytotoxic indices ranging between 10 and 120 times higher than that of furamidine, and five analogues exhibited high selectivity for *P. falciparum* over *T. brucei rhodesiense*.

Introduction

The protozoan parasites *Trypansoma brucei* (*T. brucei*) and *Plasmodium falciparum* (*P. falciparum*) cause considerable morbidity and mortality in some of the poorest areas on the planet.[1−3] The World Health Organization (WHO) estimated that a half-million cases of human African trypanosomiasis (HAT)[a] or "sleeping sickness" resulting from infections with *T. brucei rhodesiense* and *T. brucei gambiense* existed in 2002 and attributed 50 000 deaths annually to the disease.[4] By more recent estimates, up to 25 000 new cases occur per year, and 50 million people are at risk.[2, 5] At least 300 million acute cases of malaria lead to more than a million deaths annually, 90% of which occur in Africa. Most of these deaths are among young children, with malaria being Africa's leading cause of under-five mortality (20%). Malaria accounts for 10% of the continent's overall disease burden and 40% of public health expenditure.[6]

The few drugs currently available for treatment of HAT have problems with toxicity and efficacy, require parenteral administration, and/or lack assurance of future supplies. Since 1950, no new drug has been developed for treatment of early-stage HAT, and only one drug has been developed for late-stage HAT.[1,4,5] The need is great for new orally active drugs for the control and eradication of this disease. The major concern with regard to malaria caused by *P. falciparum* infections is not the lack of effective drugs but the emergence of resistance to many of the current therapies.[6] Because many of the antimalarial compounds under development are structurally related to existing drugs, the likelihood of cross-resistance is high. Thus, the search for new therapies for these potentially fatal diseases has intensified in recent years.

Since the middle of the past century there have been a number of reports on the antiprotozoal activity of pentamidine-related compounds.[7−11] 1,5-Bis(4-amidinophenoxy)pentane (pentamidine, Figure 1) has been used since the 1950s as the drug of choice for treating early-stage *T. brucei gambiense* HAT. Problems associated with the clinical use of pentamidine and the potential use of analogues of 2,5-bis(4-amidinophenyl)furan (furamidine) as alternatives to pentamidine have been summarized.[12] Recently a prodrug of furamidine, 2,5-bis[4-(*N*-methoxy)amidinophenyl]furan (pafuramidine), has shown promising results in clinical trials against both malaria and HAT.[13,14] Oral administration of pafuramidine cured 22 of 23 patients with uncomplicated *P. falciparum* infections.[13] In addition, pafuramidine has also been shown to be effective in phase 2 trials against early-stage HAT. A pivotal phase 3 clinical trial is currently under way. One approach to enhance the activity of furamidine has been the replacement of the central furan ring with other heterocyclic systems, including thiophene, pyrrole, oxazole, oxadiazole, thiadiazole, pyridazine, methylpyrimidine, and triazine.[15−19]

The present investigation involves 3,5-diphenylisoxazole analogues **1**−**43** (Table 1), in which the central ring of furamidine is replaced by isoxazole. 3,5-Bis(4-amidinophenyl)-isoxazole (**3**), the lead compound of the series and the most structurally similar to furamidine, was reported to have high activity against a murine *T. brucei rhodesiense* model,[20] but has received very little attention since. In a recent report on the structure−activity relationship of a series of diamidines against *T. brucei rhodesiense*, isoxazole analogue **3** retained the excellent in vitro antiprotozoal activity of furamidine but showed lower in vitro toxicity and had a more favorable solubility profile.[21] The current paper describes the synthesis of a series of 42 novel isoxazole linked amidines and diamidines and their in vitro activities against *T. brucei rhodesiense* and *P. falciparum* and their toxicities against L6 cells.

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[a] Abbreviations: DCC, 1,3-dicylohexylcarbodiimide; DMAP, 4-dimethylaminopyridine; DMF-DMA, *N*,*N*-dimethyllformamide dimethyl acetal; HAT, human African trypanosomiasis; IC_{50}, inhibition constant; MTBE, *tert*-butyl methyl ether; NCS, *N*-chlorosuccinimide; TMSA, (trimethylsilyl)-acetylene.

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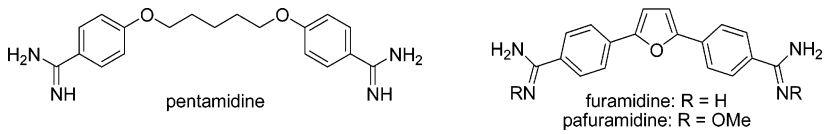
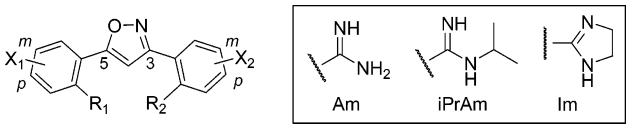


Figure 1. Structures of 1,5-bis(4-amidinophenoxy)pentane (pentamidine), 2,5-bis(4-amidinophenyl)furan (furamidine), and 2,5-bis[4-(*N*-methoxy)-amidinophenyl]furan (pafuramidine).

Table 1. Structures of Cationic Diphenylisoxazole Derivatives and Their in Vitro Antiprotozoal Activities and Cytotoxicities



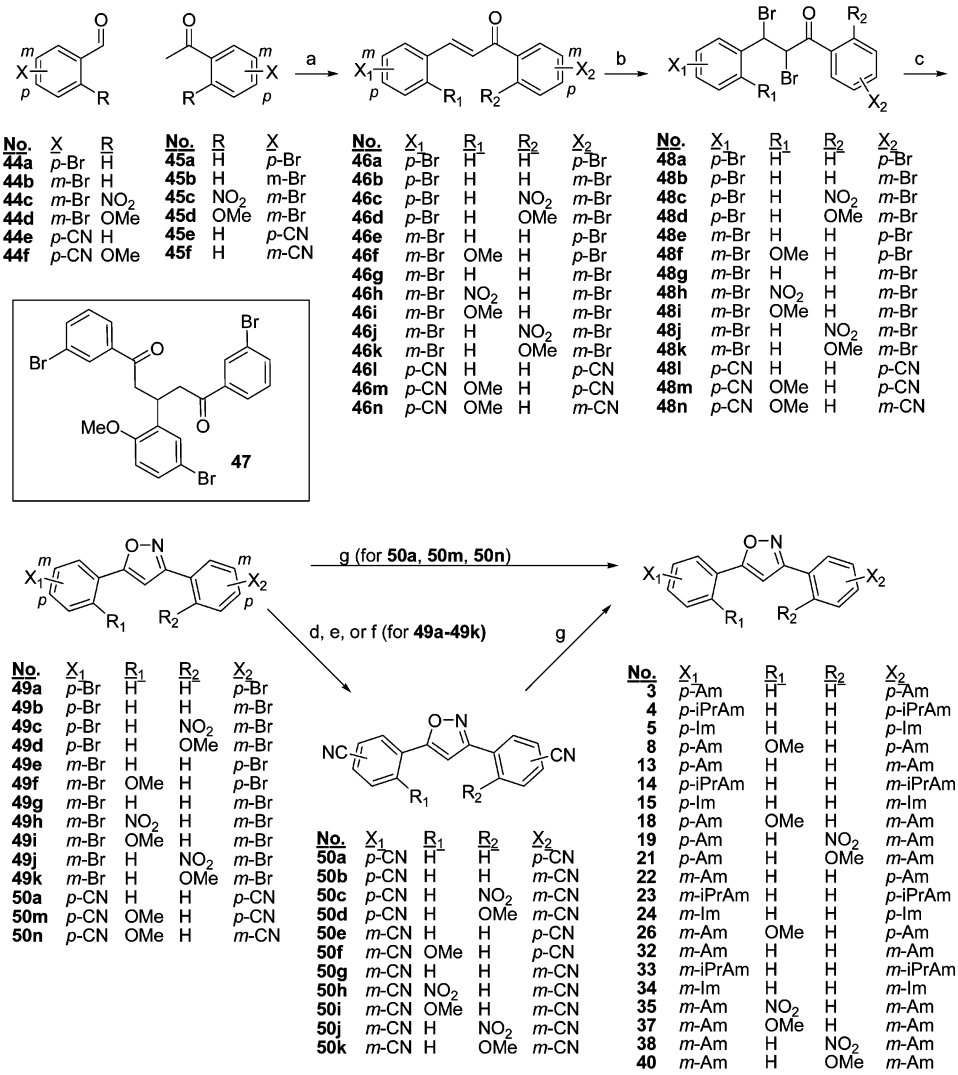
compd	X_1	R_1	R_2	X_2	IC_{50} (nM) T. brucei rhodesiense[a]	IC_{50} (nM) P. falciparum[b]	IC_{50} (μM) L6 cells[c]
1	*p*-Am	H	H	H	1719.1	>3296.4	19.1
2	H	H	H	*p*-Am	1120.8	>3296.4	18.5
3	*p*-Am	H	H	*p*-Am	5.1	22.6	2.1
4	*p*-iPrAm	H	H	*p*-iPrAm	196.3	6.6	>175.8
5	*p*-Im	H	H	*p*-Im	87.2	4.1	1.8
6	*p*-Am	NO_2	H	*p*-Am	13.9	14.9	15.8
7	*p*-Am	Cl	H	*p*-Am	15.5	7.9	41.0
8	*p*-Am	OMe	H	*p*-Am	10.6	6.0	122.2
9	*p*-Am	H	NO_2	*p*-Am	32.4	40.1	22.2
10	*p*-Am	H	Cl	*p*-Am	23.2	55.5	5.7
11	*p*-Am	H	OMe	*p*-Am	16.4	66.3	92.6
12	*p*-Am	OMe	OMe	*p*-Am	13.0	6.1	84.8
13	*p*-Am	H	H	*m*-Am	6.3	57.8	24.1
14	*p*-iPrAm	H	H	*m*-iPrAm	488.1	10.6	>187.3
15	*p*-Im	H	H	*m*-Im	1554.4	51.2	65.0
16	*p*-Am	NO_2	H	*m*-Am	9.0	25.9	48.0
17	*p*-Am	Cl	H	*m*-Am	6.3	18.7	82.7
18	*p*-Am	OMe	H	*m*-Am	6.5	3.5	177.0
19	*p*-Am	H	NO_2	*m*-Am	51.2	2.1	5.1
20	*p*-Am	H	Cl	*m*-Am	21.2	7.1	5.7
21	*p*-Am	H	OMe	*m*-Am	11.8	2.6	>212.9
22	*m*-Am	H	H	*p*-Am	3.5	2.5	31.2
23	*m*-iPrAm	H	H	*p*-iPrAm	316.1	34.7	>185.9
24	*m*-Im	H	H	*p*-Im	973.5	77.0	30.2
25	*m*-Am	Cl	H	*p*-Am	20.9	3.5	71.4
26	*m*-Am	OMe	H	*p*-Am	4.3	11.6	52.8
27	*m*-Am	H	NO_2	*p*-Am	19.4	30.4	>205.8
28	*m*-Am	H	Cl	*p*-Am	11.6	14.1	87.4
29	*m*-Am	H	OMe	*p*-Am	5.9	8.9	136.0
30	*m*-Am	OMe	NO_2	*p*-Am	34.2	19.5	116.2
31	*m*-Am	OMe	OMe	*p*-Am	5.7	29.7	191.2
32	*m*-Am	H	H	*m*-Am	29.0	9.2	153.0
33	*m*-iPrAm	H	H	*m*-iPrAm	4983.4	43.1	>180.5
34	*m*-Im	H	H	*m*-Im	18453.9	227.2	26.2
35	*m*-Am	NO_2	H	*m*-Am	1628.3	334.3	9.8
36	*m*-Am	Cl	H	*m*-Am	25.1	16.3	109.4
37	*m*-Am	OMe	H	*m*-Am	7.4	19.2	124.5
38	*m*-Am	H	NO_2	*m*-Am	85.0	104.5	177.0
39	*m*-Am	H	Cl	*m*-Am	46.3	30.6	55.5
40	*m*-Am	H	OMe	*m*-Am	27.0	17.4	>214.8
41	*m*-Am	OMe	OMe	*m*-Am	4.2	21.1	79.9
42	*m*-iPrAm	OMe	OMe	*m*-iPrAm	373.8	93.2	21.7
43	*m*-Im	OMe	OMe	*m*-Im	44.8	11.4	>164.4
melarsoprol					6.4		
chloroquine						103.5	
artemisinin						6.7	
Podophyllotoxin							0.0186
furamidine					4.3	15.5	6.4

[a] Average of duplicate determinations from refs 65 and 67. [b] Average of duplicate determinations from ref 66. [c] Average of duplicate determinations from ref 64.

Chemistry

3,5-Bis(4-amidinophenyl)isoxazole (**3**)[20] and a series of 42 novel analogues (Table 1) were prepared in our laboratory. Amidines **1** and **2** differ structurally from **3** by having only one amidino group. Diamidines **13**, **22**, and **32** are regioisomers of **3**, having different orientations of the two amidine moieties. Modification of these four "parent" structures by variation of the cationic group (*N*-isopropylamidine or imidazoline analogues) or the introduction of electron-withdrawing or -donating substituents (nitro, chloro, or methoxy) on either aromatic ring gave rise to four subgroups of compounds (**3**−**12**, **13**−**21**, **22**−**31**, and **32**−**43**) based upon the orientation of the two cationic

Scheme 1. Synthesis of Diphenylisoxaole Diamidines Using Claisen−Schmidt Strategy[a]



No.	X	R
44a	*p*-Br	H
44b	*m*-Br	H
44c	*m*-Br	NO_2
44d	*m*-Br	OMe
44e	*p*-CN	H
44f	*p*-CN	OMe

No.	R	X
45a	H	*p*-Br
45b	H	m-Br
45c	NO_2	*m*-Br
45d	OMe	*m*-Br
45e	H	*p*-CN
45f	H	*m*-CN

No.	X_1	R_1	R_2	X_2
46a	*p*-Br	H	H	*p*-Br
46b	*p*-Br	H	H	*m*-Br
46c	*p*-Br	H	NO_2	*m*-Br
46d	*p*-Br	H	OMe	*m*-Br
46e	*m*-Br	H	H	*p*-Br
46f	*m*-Br	OMe	H	*p*-Br
46g	*m*-Br	H	H	*m*-Br
46h	*m*-Br	NO_2	H	*m*-Br
46i	*m*-Br	OMe	H	*m*-Br
46j	*m*-Br	H	NO_2	*m*-Br
46k	*m*-Br	H	OMe	*m*-Br
46l	*p*-CN	H	H	*p*-CN
46m	*p*-CN	OMe	H	*p*-CN
46n	*p*-CN	OMe	H	*m*-CN

No.	X_1	R_1	R_2	X_2
48a	*p*-Br	H	H	*p*-Br
48b	*p*-Br	H	H	*m*-Br
48c	*p*-Br	H	NO_2	*m*-Br
48d	*p*-Br	H	OMe	*m*-Br
48e	*m*-Br	H	H	*p*-Br
48f	*m*-Br	OMe	H	*p*-Br
48g	*m*-Br	H	H	*m*-Br
48h	*m*-Br	NO_2	H	*m*-Br
48i	*m*-Br	OMe	H	*m*-Br
48j	*m*-Br	H	NO_2	*m*-Br
48k	*m*-Br	H	OMe	*m*-Br
48l	*p*-CN	H	H	*p*-CN
48m	*p*-CN	OMe	H	*p*-CN
48n	*p*-CN	OMe	H	*m*-CN

No.	X_1	R_1	R_2	X_2
49a	*p*-Br	H	H	*p*-Br
49b	*p*-Br	H	H	*m*-Br
49c	*p*-Br	H	NO_2	*m*-Br
49d	*p*-Br	H	OMe	*m*-Br
49e	*m*-Br	H	H	*p*-Br
49f	*m*-Br	OMe	H	*p*-Br
49g	*m*-Br	H	H	*m*-Br
49h	*m*-Br	NO_2	H	*m*-Br
49i	*m*-Br	OMe	H	*m*-Br
49j	*m*-Br	H	NO_2	*m*-Br
49k	*m*-Br	H	OMe	*m*-Br
50a	*p*-CN	H	H	*p*-CN
50m	*p*-CN	OMe	H	*p*-CN
50n	*p*-CN	OMe	H	*m*-CN

No.	X_1	R_1	R_2	X_2
50a	*p*-CN	H	H	*p*-CN
50b	*p*-CN	H	H	*m*-CN
50c	*p*-CN	H	NO_2	*m*-CN
50d	*p*-CN	H	OMe	*m*-CN
50e	*m*-CN	H	H	*p*-CN
50f	*m*-CN	OMe	H	*p*-CN
50g	*m*-CN	H	H	*m*-CN
50h	*m*-CN	NO_2	H	*m*-CN
50i	*m*-CN	OMe	H	*m*-CN
50j	*m*-CN	H	NO_2	*m*-CN
50k	*m*-CN	H	OMe	*m*-CN

No.	X_1	R_1	R_2	X_2
3	*p*-Am	H	H	*p*-Am
4	*p*-iPrAm	H	H	*p*-iPrAm
5	*p*-Im	H	H	*p*-Im
8	*p*-Am	OMe	H	*p*-Am
13	*p*-Am	H	H	*m*-Am
14	*p*-iPrAm	H	H	*m*-iPrAm
15	*p*-Im	H	H	*m*-Im
18	*p*-Am	OMe	H	*m*-Am
19	*p*-Am	H	NO_2	*m*-Am
21	*p*-Am	H	OMe	*m*-Am
22	*m*-Am	H	H	*p*-Am
23	*m*-iPrAm	H	H	*p*-iPrAm
24	*m*-Im	H	H	*p*-Im
26	*m*-Am	OMe	H	*p*-Am
32	*m*-Am	H	H	*m*-Am
33	*m*-iPrAm	H	H	*m*-iPrAm
34	*m*-Im	H	H	*m*-Im
35	*m*-Am	NO_2	H	*m*-Am
37	*m*-Am	OMe	H	*m*-Am
38	*m*-Am	H	NO_2	*m*-Am
40	*m*-Am	H	OMe	*m*-Am

[a] Key: (a) aq NaOH, EtOH or MeOH or CH_3CN; (b) Br_2, $CHCl_3$; (c) $NH_2OH{\cdot}HCl$, aq NaOH, EtOH or MeOH; (d) CuCN, DMF; (e) $Zn(CN)_2$, $Pd(PPh_3)_4$, DMF; (f) t-BuLi, THF, then tosyl cyanide, THF; (g) EtOH, dry HCl, 1,4-dioxane, then appropriate amine, EtOH.

groups. These types of structural modifications were based upon previous studies in this laboratory.[9,22,23]

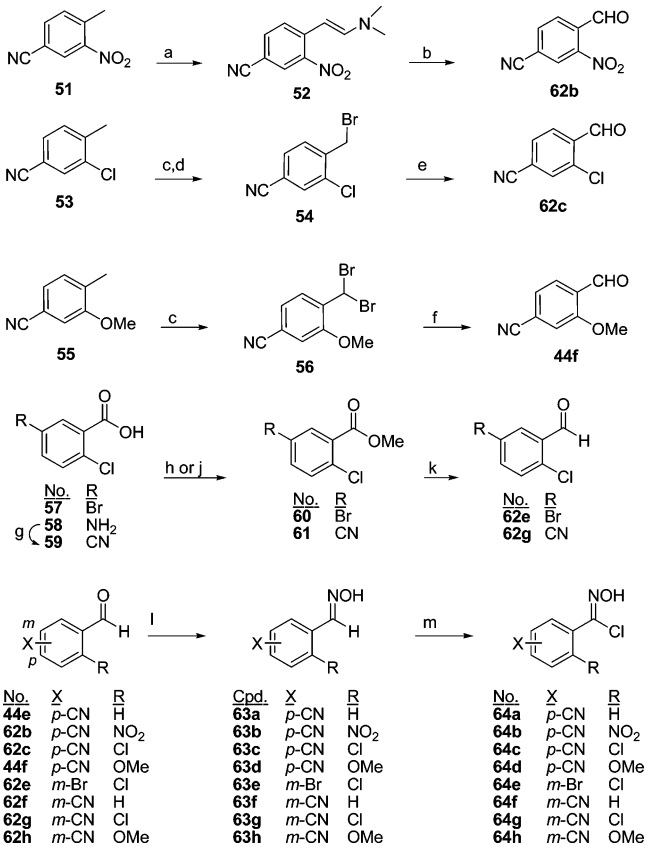
Compounds **1**−**43** were prepared from the corresponding nitriles. The nitrile precursors of monoamidines **1** and **2** were prepared as reported,[24,25] using methodology similar to that employed by the first of two general methods to prepare dicationic compounds **3**−**43**.

The first method is based upon a Claisen−Schmidt condensation and is shown in Scheme 1. Starting benzaldehydes **44a**,**b**,**d**,**e** and acetophenones **45a**,**b**,**e**,**f** were commercially available. Aldehyde **44f** was prepared as shown in Scheme 2 (vide infra). Aldehyde **44c** and ketone **45c** were prepared by nitration of **44b** and **45b**, respectively.[26,27] Methoxyketone **45d** was prepared from the corresponding phenol.[28] Condensations between benzaldehydes **44** and acetophenones **45** gave dibromochalcones **46a**−**k** and dicyanochalcones **46l**−**n**, of which **46a**,**g**,**l** had been reported previously.[29−31] The outcome of the Claisen−Schmidt reaction proved to be quite sensitive to the nature and position of substituents on the starting materials, especially the aldehydes. Chalcones **46a**−**d** were prepared from aldehyde **44a** and the appropriate ketone in ethanol at ambient temperature. The successful preparation of other analogues required the use of other solvents or lower temperatures. For example, a reaction between methoxyaldehyde **44d** and ketone **45b** in ethanol gave a 1:9 mixture (by HPLC) of chalcone **46i** and side-product **47** (a 1,4-addition product of **45b** and **46i**). The substitution of acetonitrile for ethanol as solvent resulted in the selective formation of chalcone **46i**.

Bromination of chalcone **46a** gave α,*β*-dibromoketone **48a** as reported.[32] Similar treatment of chalcones **46b**−**n** gave ketones **48b**−**n** in good yields in all cases except for analogue **48i**. Ethanolic solutions or suspensions of intermediates **48a**−**n** were treated with hydroxylamine hydrochloride, followed by sodium hydroxide[25] to effect the ring closure to dibromoisoxazoles **49a**−**k** (of which **49a**[20] and **49e**[33] had been reported previously) and dicyanoisoxazoles **50a,m,n**. Increased yields were obtained by allowing refluxing reaction mixtures to cool to ambient temperature immediately after the addition of the base or by performing the entire reactions at lower temperatures.

The dibromoisoxazoles **49a**−**k** were converted to their dicyano analogues **50a**−**k.** Treatment of **49a** using copper(I) cyanide in refluxing DMF gave dinitrile **50a** as reported. [20] Similar methodology was used to prepare analogues **50b**,**d**−**h**,**j**,**k**. Other reaction conditions were required in certain cases. Dibromonitroisoxazole **49c** was reacted with zinc cyanide and tetrakis(triphenylphosphine)palladium(0) in DMF[34] to give dinitrile **50c**. Dibromomethoxyisoxazole **49i** was treated with

Scheme 2. Synthesis of Benzaldehyde Chlorooxime Prescursors[a]



[a] Key: (a) DMF-DMA, DMF; (b) $NaIO_4$; aq THF; (c) NBS, benzoyl peroxide, CCl_4; (d) diethyl phosphite, $(i\text{-}Pr)_2NEt$, THF; (e) 2-nitropropane, NaOEt, EtOH; (f) $AgNO_3$, aq EtOH; (g) $NaNO_2$, aq HCl, then CuCN, KCN; (h) MeOH, H_2SO_4; (j) DCC, DMAP, MeOH, CH_2Cl_2; (k) Red-Al, *t*-BuOK, pyrrolidine, MTBE; (l) $NH_2OH{\cdot}HCl$, aq EtOH or Py, EtOH; (m) NCS, DMF.

tert-butyllithium in tetrahyrdrofuran (THF) followed by tosyl cyanide[35] to give dintrile **50i**.

The second general synthetic method involved benzaldehyde chlorooxime and phenylacetylene synthons (Schemes 2 and 3), which underwent cycloaddition reactions to give diphenylisoxazole nitriles (Scheme 4).

The synthesis of benzaldehyde chlorooxime precursors **64a**−**h** is depicted in Scheme 2. Aldehydes **44e** and **62f** were commercially available. The reaction of the *o*-nitrotoluene **51**[36] with *N*,*N*-dimethylformamide dimethyl acetal in DMF[37] gave the enamine **52**, which underwent oxidative cleavage using sodium periodate in THF to give aldehyde **62b** via a more facile preparation than previously reported.[38] A more expedient synthesis of aldehyde **62c**[39] is also reported. Commercially available chlorotoluene **53** underwent α-bromination to **54**[40] by a modification[41] of the original procedure. The reaction of **54** with 2-nitropropane and sodium ethoxide in ethanol[42] gave aldehyde **62c.** Methoxytolunitrile **55** was prepared in three steps from **51**.[36] α-Bromination of **55** using 1 equiv of *N*-bromosuccinimide gave little selectivity between the mono- and dibromo adducts, but the analogous reaction using 2.5 equiv gave dibromide **56** almost exclusively. Silver nitrate oxidation[43] of dibromide **56** gave aldehyde **44f**. Commercially available carboxylic acid **57** and analogue **59**[44] (prepared via a Sandmeyer reaction from commercially available **58**) were converted to methyl esters **60** and **61**, respectively. The esters were converted to aldehydes **62e** and **62g**, respectively, using sodium bis(2-methoxyethoxy)aluminum hydride, pyrrolidine, and potassium

Table 2. In Vitro Activities and Cytotoxicty Data of Cationic Diphenylisoxazoles Highly Active against *T. brucei rhodesiense*

compd	IC_{50} (nM) T. brucei rhodesiense[a]	IC_{50} (μM) L6 cells[b]	cytotoxic index[c]	ratio[d]
22	3.5	31.2	8 923	6.0
41	4.2	79.9	19 033	*12.8*
26	4.3	52.8	12 277	8.3
3	5.1	2.1	418	0.3
31	5.7	191.2	3 3542	*22.5*
29	5.9	136.0	23 047	*15.5*
13	6.3	24.1	3 822	2.6
17	6.3	82.7	13 130	8.8
18	6.5	177.0	27 226	*18.3*
37	7.4	124.5	16 824	*11.3*
16	9.0	48.0	5 334	3.6
8	10.6	122.2	11 527	7.8
28	11.6	87.4	7 534	5.1
21	11.8	>212.9	>18 044	*>12.1*
12	13.0	84.8	6 522	4.4
6	13.9	15.8	1 139	0.8
7	15.5	41.0	2 645	1.8
11	16.4	92.6	5 646	3.8
27	19.4	205.8	10 608	7.1
furamidine	4.3	6.4	1 488	1.0

[a] Average of duplicate determinations from refs 65 and 67. [b] Average of duplicate determinations from ref 64. [c] Ratio of cytotoxic IC_{50} to antitrypanosomal IC_{50} values. [d] Ratio of cytotoxic index of isoxazole compound to cytotoxic index of furamidine. Values in italics reflect cytotoxic indices at least 10 times higher than that of furamidine.

tert-butoxide in *tert*-butyl methyl ether.[45] Cyanoaldehyde **62h** was prepared by debromocyanation of **44d**.[46] Aldehydes **44e**,**f** and **62b**,**c**,**e**−**h** were converted to oxime derivatives **63a,**[47] **63b**−**e,f,**[47] and **63g,h** using hydroxylamine hydrochloride in either water/ethanol or pyridine/ethanol. The oximes **63a**−**h** were treated with *N*-chlorosuccinimide in DMF (following the procedure reported for **64e**)[48] to give chlorooximes **64a**−**h**, which were reacted immediately with the phenylacetylenes without further purification.

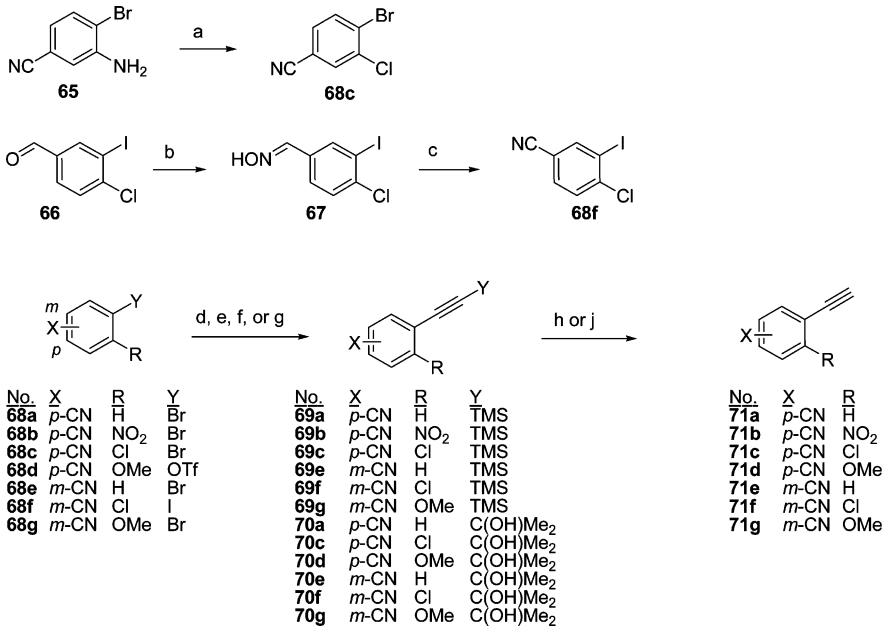
The phenylacetylenes **71a**−**g** were prepared as shown in Scheme 3. Aryl bromides **68a**,**e,g** were commercially available. The nitration of bromobenzonitrile **68a** to **68b**[49] and its subsequent reduction to aniline **65** have been reported previously.[49,50] Diazotization of **65** followed by treatment with copper(I) chloride gave chlorobenzene **68c**. Methoxy triflate **68d** was prepared by treatment of 4-bromo-3-hydroxybenzonitrile with triflic anhydride. Chloroiodobenazldehyde **66** was prepared from 4-chlorobenzaldehyde.[51] Treatment of **66** with hydroxylamine hydrochloride in pyridine and ethanol gave aldoxime **67**, which was dehydrated to nitrile **68f** using acetic anhydride.

The phenylacetylenes **71a**−**g** were prepared from intermediates **68a**−**g** either by treatment with (trimethylsilyl)acetylene[52] to give silyl acetylenes **69a**−**c,e**−**g** followed by deprotection with cesium carbonate or by reaction with 2-methyl-3-butyn-2-ol to give protected acetylenes **70a,c**−**g** followed by treatment with sodium hydride.[53] The latter procedure provided more economical preparations of all the phenylacetylenes except nitro analogue **71b.** Preparations of acetylenes **69a**,**d,**[54], **70a**[53] and **71a**,**e**,[53,55,56] have been reported previously.

Cycloaddition reactions of phenylacetylenes **71a**−**g** and benzaldehyde chlorooximes **64a**−**h** in the presence of bis-(tributyltin) oxide[57,58] or triethylamine[59] in nonpolar solvents are shown in Scheme 4. The 3,5-diphenylisoxazole nitrile products included dinitriles **72a**−**h,k**−**s** and bromonitrile **72i**, which was treated with copper(I) cyanide[60] to give dinitrile **72j**. This method also provided alternate routes to dinitriles **50a**,**f**,**i**,**m** prepared by the first method (Scheme 1).

Monoamidines **1**, **2** and dicationic compounds **3**−**11**, **13**−**43** (Schemes 1 and 4) were prepared from the corresponding

Scheme 3. Synthesis of Phenylacetylene Precursors[a]



No.	X	R	Y
68a	*p*-CN	H	Br
68b	*p*-CN	NO_2	Br
68c	*p*-CN	Cl	Br
68d	*p*-CN	OMe	OTf
68e	*m*-CN	H	Br
68f	*m*-CN	Cl	I
68g	*m*-CN	OMe	Br

No.	X	R	Y
69a	*p*-CN	H	TMS
69b	*p*-CN	NO_2	TMS
69c	*p*-CN	Cl	TMS
69e	*m*-CN	H	TMS
69f	*m*-CN	Cl	TMS
69g	*m*-CN	OMe	TMS
70a	*p*-CN	H	$C(OH)Me_2$
70c	*p*-CN	Cl	$C(OH)Me_2$
70d	*p*-CN	OMe	$C(OH)Me_2$
70e	*m*-CN	H	$C(OH)Me_2$
70f	*m*-CN	Cl	$C(OH)Me_2$
70g	*m*-CN	OMe	$C(OH)Me_2$

No.	X	R
71a	*p*-CN	H
71b	*p*-CN	NO_2
71c	*p*-CN	Cl
71d	*p*-CN	OMe
71e	*m*-CN	H
71f	*m*-CN	Cl
71g	*m*-CN	OMe

[a] Key: (a) $NaNO_2$, aq HCl, then CuCl; (b) $NH_2OH{\cdot}HCl$, Py, EtOH (c) Ac_2O; (d) TMSA, $Pd_2Cl_2(PPh_3)_2$, CuI, Et_3N; (e) TMSA, PPh_3, $Pd(PPh_3)_4$, CuI, piperidine; (f) 2-methyl-3-butyn-2-ol, $Pd_2Cl_2(PPh_3)_2$, CuI, Et_3N; (g) 2-methyl-3-butyn-2-ol, 10% Pd/C, PPh_3, CuI, aq K_2CO_3, DME; (h) Cs_2CO_3, aq CH_3CN or MeOH; (j) NaH, toluene.

nitriles by modified Pinner syntheses.[9,22] The imidate intermediates were treated with ammonia, isopropylamine, or ethylenediamine to give the respective amidine, *N*-isopropylamidine, and imidazoline target compounds. The attempted preparation of diamidine **12** under similar conditions was unsuccessful, presumably due to the extremely low solubility of dintrile **72f** in the reaction medium. Compound **12** was successfully prepared from **72f** via amidoxime **73**, which underwent *O*-acetylation to **74,** followed by catalytic hydrogenation in acetic acid/ethanol.[61] All compounds **1**−**43** were isolated as their hydrochloride salts.

Antiprotozoal Activities and Cytotoxicity

The activities of compounds **1**−**43** against *T. brucei rhodesiense* (STIB900) and chloroquine resistant *P. falciparum* (K1) in vitro, as well as their toxicities to L6 cells (rat myoblasts), are shown in Table 1. These values were compared to those of furamidine. Other controls employed were melarsoprol (against *T. brucei rhodesiense*), chloroquine and artemisinin (against *P. falciparum*), and podophyllotoxin (against L6 cells).

The dicationic isoxazole derivatives **3**−**43** displayed varying degrees of activity against *T. brucei rhodesiense* and *P. falciparum*, but monoamidines **1** and **2** were inactive against either parasite. In general, the isoxazole compounds were less toxic to L6 cells than furamidine.

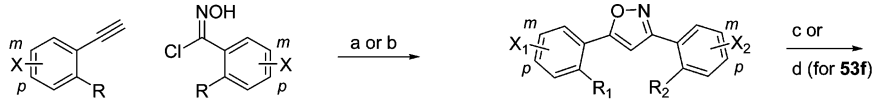
Eleven compounds were highly active against *T. brucei rhodesiense,* with IC_{50} values less than 10 nM (Table 2). Diamidine **22** was the most active, with an IC_{50} value of 3.5 nM. Methoxy analogues **26** and **41** also displayed IC_{50} values less than 5 nM, comparable to that of furamidine (4.3 nM). Diamidines **3** and **13**, methoxy analogues **18**, **29**, **31**, and **37**, chloro analogue **17**, and nitro analogue **16** exhibited IC_{50} values between 5 and 10 nM. Eight compounds (methoxy analogues **8**, **11**, **12**, and **21**, chloro analogues **7** and **28**, and nitro analogues **6** and **28)** displayed IC_{50} values between 10 and 20 nM. Another 10 compounds (**9**, **10**, **20**, **25**, **30**, **32**, **36**, **39**, **40,** and **43**) exhibited IC_{50} values between 20 and 50 nM. Among the 19 compounds with IC_{50} values less than 20 nM, all but compounds **3** and **6** displayed cytotoxic indices (ratios of cytotoxic IC_{50} to antitrypanosomal IC_{50} values) equal to or greater than that of furamidine. Methoxy analogues **18**, **29**, **31**, **37**, and **41** displayed antitrypanosomal IC_{50} values less than 10 nM as well as cytotoxic indices between 10 and 25 times higher than that of furamidine.

The in vitro antiplasmodial activities of these compounds were even more promising. Eighteen compounds exhibited were more active than furamidine, with IC_{50} values less than 15 nM (Table 3). The most active was nitro analogue **19**, with an IC_{50} value of 2.1 nM. Diamidine **22**, methoxy analogues **18** and **21**, chloro analogue **25**, and imidazoline **5** also displayed IC_{50} values under 5 nM. Compounds with IC_{50} values between 5 and 15 nM included isopropylamidines **4** and **14**, nitro analogue **6**, chloro analogues **7**, **20**, and **28**, methoxy compounds **8**, **12**, **26**, **29**, and **43**, and diamidine **32**. Fourteen other compounds were less active against *P. falciparum*, with IC_{50} values between 15 and 50 nM. This group included chloro analogues **17**, **36**, and **19**, methoxy analogues **31**, **37**, **40**, and **41**, methoxy−nitro analogue **30**, diamidine **3**, nitro analogues **9**, **16**, and **27**, and isopropylamidines **23** and **33**.

All of the compounds with antiplasmodial IC_{50} values less than 50 nM except for **3** exhibited cytotoxic indices (ratios of cytotoxic IC_{50} to antiplasmodial IC_{50} values) higher than that of furamidine. Twenty-three compounds (including 14 of the 18 compounds with IC_{50} values less than 15 nM) exhibited cytotoxic indices at least 10 times higher than that of furamidine. The most noteworthy in this regard were methoxy analogues **18** and **21**, with IC_{50} values less than 5 nM and cytotoxic indices between 120 and 200 times higher than that of furamidine. Compounds **4**, **8**, **12**, **14**, **22**, **25**, **32**, **39**, and **43** exhibited antiplasmodial IC_{50} values less than 15 nM in addition to cytotoxic indices between 30 and 65 times higher than that of furamidine.

A high selectivity for *P. falciparum* over *T. brucei* may be desirable for treating patients with mixed infections. Five compounds displayed selectivity (ratio of antitrypansomal IC_{50} to antiplasmodial IC_{50} values) greater than 20-fold. Isopropylamidine **33,** which showed selectivity greater than 100-fold,

Scheme 4. Synthesis of Diphenylisoxaole Diamidines Using Acetylene−Aldehyde Chlorooxime Cycloaddition Strategy[a]

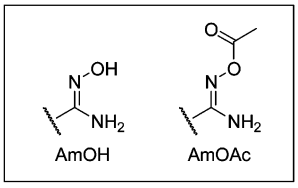


No.	X	R
71a	*p*-CN	H
71b	*p*-CN	NO_2
71c	*p*-CN	Cl
71d	*p*-CN	OMe
71e	*m*-CN	H
71f	*m*-CN	Cl
71g	*m*-CN	OMe

No.	R	X
64a	H	*p*-CN
64b	NO_2	*p*-CN
64c	Cl	*p*-CN
64d	OMe	*p*-CN
64e	H	*m*-CN
64f	Cl	*m*-Br
64g	Cl	*m*-CN
64h	OMe	*m*-CN

No.	X_1	R_1	R_2	X_2
72a	*p*-CN	NO_2	H	*p*-CN
72b	*p*-CN	Cl	H	*p*-CN
72c	*p*-CN	H	NO_2	*p*-CN
72d	*p*-CN	H	Cl	*p*-CN
72e	*p*-CN	H	OMe	*p*-CN
72f	*p*-CN	OMe	OMe	*p*-CN
72g	*p*-CN	NO_2	H	*m*-CN
72h	*p*-CN	Cl	H	*m*-CN
72i	*p*-CN	H	Cl	*m*-Br
e 72j	*p*-CN	H	Cl	*m*-CN
72k	*m*-CN	Cl	H	*p*-CN
72l	*m*-CN	H	NO_2	*p*-CN
72m	*m*-CN	H	Cl	*p*-CN
72n	*m*-CN	H	OMe	*p*-CN
72o	*m*-CN	OMe	NO_2	*p*-CN
72p	*m*-CN	OMe	OMe	*p*-CN
72q	*m*-CN	Cl	H	*m*-CN
72r	*m*-CN	H	Cl	*m*-CN
72s	*m*-CN	OMe	OMe	*m*-CN
50a	*p*-CN	H	H	*p*-CN
50m	*p*-CN	OMe	H	*p*-CN
50f	*m*-CN	OMe	H	*p*-CN
50i	*m*-CN	OMe	H	*m*-CN

No.	X_1	R_1	R_2	X_2
6	*p*-Am	NO_2	H	*p*-Am
7	*p*-Am	Cl	H	*p*-Am
9	*p*-Am	H	NO_2	*p*-Am
10	*p*-Am	H	Cl	*p*-Am
11	*p*-Am	H	OMe	*p*-Am
f 73	*p*-AmOH	OMe	OMe	*p*-AmOH
74	*p*-AmOAc	OMe	OMe	*p*-AmOAc
g 12	*p*-Am	OMe	OMe	*p*-Am
16	*p*-Am	NO_2	H	*m*-Am
17	*p*-Am	Cl	H	*m*-Am
20	*p*-Am	H	Cl	*m*-Am
25	*m*-Am	Cl	H	*p*-Am
27	*m*-Am	H	NO_2	*p*-Am
28	*m*-Am	H	Cl	*p*-Am
29	*m*-Am	H	OMe	*p*-Am
30	*m*-Am	OMe	NO_2	*p*-Am
31	*m*-Am	OMe	OMe	*p*-Am
36	*m*-Am	Cl	H	*m*-Am
39	*m*-Am	H	Cl	*m*-Am
41	*m*-Am	OMe	OMe	*m*-Am
42	*m*-iPrAm	OMe	OMe	*m*-iPrAm
43	*m*-Im	OMe	OMe	*m*-Im



[a] Key: (a) $(Bu_3Sn)_2O$, CH_2Cl_2 or C_6H_6; (b) Et_3N, $CHCl_3$; (c) EtOH, dry HCl, 1,4-dioxane, then appropriate amine, EtOH; (d) $NH_2OH{\cdot}HCl$, *t*-BuOK, DMSO; (e) CuCN, DMF, (f) Ac_2O, AcOH; (g) H_2, 10% Pd/C, AcOH, EtOH.

was the least active of the five compounds. Regioisomers **4** and **14**, with selectivity between 25- and 50-fold, offered the best compromise of high selectivity, high activity, and low cytotoxicity. Compounds **5** and **19**, the most active of the five compounds, were the least selective as well as the most cytotoxic.

Structure−Activity Relationships

The monoamidines **1** and **2** were inactive against both *T. brucei rhodesiense* and *P. falciparum*. Thus, two cationic groups are required for antimicrobial activity, consistent with previous findings in this laboratory.[23]

Diamidine **3**, in which both amidine moieties are para to the isoxazole ring, is most structurally similar to furamidine. Diamidines **13**, **22**, and **32** are regiosiomsers of **3**, having different orientations of the amidino groups. These four molecules are the parent structures for four subgroups of regioisomeric analogues (**3**−**12**, **13**−**21**, **22**−**31**, and **32**−**43**).

The orientation of the cationic groups proved to be critical to antitrypanosomal activity. Parent molecules **3**, **13**, and **22**, which have at least one *p*-amidine moiety, displayed IC_{50} values of 5.1, 6.3, and 3.5 nM, respectively, which were similar to that of furamidine (4.3 nM). Optimal activity was observed in compound **22**, which has *m*- and *p*-amidine functions near the isoxazole oxygen and nitrogen atoms, respectively. Parent molecule **32,** which has two *m*-amidino groups, was nearly 10 times less active than **22**, with an IC_{50} value of 29 nM.

All of the *N*-isopropylamidine (**4**, **13**, **23**, **33**, and **42**) and imidazoline derivatives (**5**, **15**, **24**, **34**, and **43**) were substantially less active against *T. brucei rhodesiense* than the corresponding diamidines, consistent with previous reports of pentamidine analogues.[62,63] The imidazolines were less active than the corresponding *N*-isopropylamidines except for **5** and **43**.

In general, the introduction of nitro, chloro, or methoxy substituents on either aromatic ring resulted in decreased antitrypanosomal activity. However, 16 of 27 diamidines with additional aromatic substituents displayed antitrypanosomal IC_{50} values less than 20 nM, and 15 of these analogues displayed lower cytotoxic indices than the corresponding parent molecules.

Of the three aromatic substituents, the methoxy group had the greatest effect upon retention of antitrypansomal activity and decreased cytotoxicity. Methoxy analogues accounted for 10 of the 19 most active compounds. Seven of the eight monomethoxy analogues prepared (**8**, **11**, **18**, **21**, **26**, **29**, and **37**), as well as the three dimethoxy diamidines (**12**, **31**, and **41**), displayed IC_{50} values less than 20 nM. Of these 10 compounds, all except **11**, **12**, and **26** exhibited cytotoxic indices at least times 10 higher than that of furamidine. Only the methoxy derivatives of **32** (**37**, **40**, and **41**) were more active than the parent molecule; of these, only **37** and **41** were highly active against the trypanosome. The methoxy−nitro analogue **30** was less active than either corresponding monosubstituted analogue **26** or **27**.

Table 3. In Vitro Activities, Cytotoxicity Data, and Selectivity of Cationic Diphenylisoxazoles Active against *P. falciparum*

compd	IC_{50} (nM) P. falciparum[a]	IC_{50} (μM) L6 cells[b]	cytotoxic index[c]	ratio[d]	selectivity[e]
19	2.1	5.1	2 414	5.9	*24.4*
22	2.5	31.2	12 492	30.3	1.4
21	2.6	>212.9	>81 892	*>198.3*	4.5
25	3.5	71.4	20 397	*49.4*	6.0
18	3.5	177.0	50 563	*122.5*	1.9
5	4.1	1.8	441	1.1	*21.3*
8	6.0	122.2	20 365	*49.3*	1.8
12	6.1	84.8	13 898	*33.7*	2.1
4	6.6	>175.8	>26 636	*>64.5*	*29.7*
20	7.1	5.7	799	1.9	3.0
7	7.9	41.0	5 190	*12.6*	2.0
29	8.9	136.0	15 279	*37.0*	0.7
32	9.2	153.0	16 634	*40.3*	3.2
14	10.6	>187.3	>17 673	*>42.8*	*46.1*
43	11.4	>164.4	>14 421	*>34.9*	3.9
26	11.6	52.8	4 551	*11.0*	0.4
28	14.1	87.4	6 199	*15.0*	0.8
6	14.9	15.8	1 062	2.6	0.9
36	16.3	109.4	6 713	*16.3*	1.5
40	17.4	>214.8	>12 342	*>29.9*	1.6
17	18.7	82.7	4 424	*10.7*	0.3
37	19.2	124.5	6 484	*15.7*	0.4
30	19.5	116.2	5 959	*14.4*	1.8
41	21.1	79.9	3 789	9.2	0.2
3	22.6	2.1	94	0.2	0.2
16	25.9	48.0	1 854	4.5	0.4
31	29.7	191.2	6 437	*15.6*	0.2
27	30.4	>205.8	>6 770	*>16.4*	0.6
39	30.6	55.5	1 812	4.4	1.5
23	34.7	>185.9	>5 359	*>13.0*	9.1
9	40.1	22.2	554	1.3	0.8
33	43.1	>180.5	>4 188	*>10.1*	*115.6*
furamidine	15.5	6.4	413	1.0	0.3

[a] Average of duplicate determinations from ref 66. [b] Average of duplicate determinations from ref 64. [c] Ratio of cytotoxic IC_{50} to antiplasmodial IC_{50} values. [d] Ratio of cytotoxic index of isoxazole compound to cytotoxic index of furamidine. Values in italics reflect cytotoxic indices at least 10 times higher than that of furamidine. [e] Ratio of antitrypanosomal IC_{50} to antiplasmodial IC_{50} values. Values in italics reflect greater than 20-fold selectivity for *P. falciparum* over *T. brucei rhodesiense*.

The effect of nitro and chloro substituents upon antitrypanosomal activity was less pronounced. Nitro analogues **6**, **16**, and **27** and the corresponding chloro analogues **7**, **17**, and **28** displayed IC_{50} values less than 20 nM. In these six analogues, the substituents are on an aromatic ring bearing a *p*-amidine function. All of these analogues except chloro analogue **28** displayed higher cytotoxic indices than the respective parent molecules. The remaining chloro analogues were less active, with IC_{50} values between 20 and 50 nM, while the remaining nitro analogues displayed IC_{50} values greater than 50 nM. Only the weakly active chloro analogue **36** was more active than the corresponding parent molecule.

Antiplasmodial activity was affected differently by structural variations. Parent compound **22**, which was the most active against *T. brucei rhodesiense*, was also the most active against *P. falciparum*, with an IC_{50} value of 2.5 nM. Antiplasmodial activities decreased with parent molecules **32** (9.2 nM), **3** (23 nM), and **13** (58 nM). Thus, activity was enhanced by a *m*-amidinophenyl group adjacent to the isoxazole oxygen atom but reduced by a *p*-amidino group on the same ring. The more highly active parents **22** and **32** also displayed cytotoxic indices more than 30 times greater than that of furamidine.

The antiplasmodial activities of the less active parent molecules **3** and **13** were more enhanced by the introduction of various substituents than were those of the more active molecules **22** and **32**. Isopropylamidines **4** and **14** were more active and had higher cytotoxic indices relative to the respective parent molecules. These molecules, as well as the less active analogue **33**, were highly selective for *P. falciparum* over *T. brucei rhodesiense*. Analogues **23** and **33** were less active than the respective parent molecules but had cytotoxic indices at least 10 times higher than that of furamidine. Imidazoline analogues **5** and **43** were more active and displayed higher cytotoxic indices than the corresponding amidines **3** and **41**. All derivatives of compound **13** having substituents on the aromatic rings (compounds **16**−**21**) were more active against *P. falciparum* and had higher cytotoxic indices than the parent molecule. Compounds **6**−**8** and **12**, all derivatives of diamidine **3** with substituents on the 5-phenyl ring, were more active than the parent molecule, and analogues **9**−**11** with substituents on the 3-phenyl ring were less active. The cytotoxic indices of all seven derivatives were higher than that of compound **3.** All aromatically substituted analogues of compound **22** were less active than the parent molecule, and all except analogues **25** and **29** displayed cytotoxic indices lower than that of **22**. However, IC_{50} values less than 15 nM and cytotoxic indices 10−50 times greater than those of furamidine were observed in chloro analogues **25** and **28** and methoxy analogues **26** and **29**. Nitro−methoxy and dimethoxy analogues **30** and **31** displayed IC_{50} values less than 30 nM and cytotoxic indices more than 10 times greater than that of furamidine. Similarly, all aromatically substituted derivatives of compound **32** were less active than the parent molecule; however, chloro analogue **36** and methoxy analogues **37** and **40** displayed IC_{50} values less than 20 nM and cytotoxic indices 15−30 times greater than that of furamidine.

With respect to antiplasmodial activity, the methoxy group had the greatest impact on retention of activity and decreased cytotoxicity. Of the 23 compounds with IC_{50} values less than 20 nM, ten analogues bear a methoxy group. Chloro analogues account for five members of this group of compounds. The introduction of an isopropyl group on the amidine nitrogen atoms was significant both with respect to decreased toxicity and selectivity for *P. falciparum* over *T. brucei rhodesiense*.

Conclusions

A number of the dicationic isoxazole compounds, with high activities in vitro against either *T. brucei rhodesiense* or *P. falciparum* along with low cytotoxicities relative to furamidine, are candidates for further evaluation against animal models of the diseases. Given the generally poor oral bioavailability of amidines,[10] the development of orally active prodrugs is highly desirable. The results of in vivo studies involving both active compounds and their amidoxime and methamidoxime prodrugs will be forthcoming.

Experimental Section

General Experimental Method. In vitro antiprotozoal activities and cytotoxicities against *T. brucei rhodesiense* (STIB900), chloroquine-resistant *P. falciparum* (K1), and L6 cells (rat myoblasts) were measured following established protocols.[12, 64−67] Uncorrected melting points were measured on a Thomas−Hoover capillary melting point apparatus. ^{1}H NMR spectra were recorded on a Varian Gemini 2000 (300 MHz) or a Varian 390 (90 MHz) spectrometer. Unless stated otherwise, spectra were recorded in dimethyl-d_6 sulfoxide (DMSO-d_6; with 0.05% tetramethylsilane (TMS)) at 300 MHz. Anhydrous EtOH was distilled over Mg/I_2 immediately prior to use. Other anhydrous solvents were purchased from Aldrich Chemical Co., Milwaukee, WI, in Sure/Seal containers and were used without further purification. Reaction mixtures were monitored by thin-layer chromatography (TLC) on silica gel or by reverse-phase high-performance liquid chromatography (HPLC). Organic layers of extraction mixtures were neutralized as necessary with

acidic or basic washes, washed with saturated NaCl solution, and dried over Na_2SO_4 or $MgSO_4$ before being evaporated under reduced pressure. Gravity and flash column chromatography were performed using Davisil grade 633, type 60A silica gel (200−425 mesh). Analytical HPLC chromatograms were recorded on a Hewlett−Packard 1090 Series II chromatograph using a Zorbax Rx C8 column (4.6 mm × 75 mm, 3.5 μm) and UV photodiode array detection at 230, 254, 265, 290, and 320 nm. Wavelengths reported are those at which the strongest signals of the major products were observed. Mobile phases consisted of mixtures of CH_3CN (0−75%) in water containing formic acid (80 mM), ammonium formate (20 mM), and triethylamine (15 mM). Flow rates were maintained at 1.5 mL/min at a column temperature of 40 °C. In method A, the concentration of CH_3CN was increased linearly from 0 to 22.5% over 6 min, then from 22.5 to 56.25% over 4 min, and then maintained for 1 min. In method B, the concentration of CH_3CN was increased linearly from 22.5 to 75% over 10 min and then maintained for 2 min. Preparative reverse-phase HPLC was performed on a Varian ProStar chromatography workstation configured with two PS-215 pumps fitted with 50 mL pump heads, a Dynamax Microsorb C18 (60 Å) column (41.4 mm × 25 cm, 8 μm), PS-320 variable wavelength UV−vis detector, and a PS-701 fraction collector. Mobile phases consisted of mixtures of CH_3CN (0−75%) in water containing formic acid (40 mM) and ammonium formate (10 mM). Flow rates were maintained at 40 mL/min. Detector wavelengths and mobile-phase gradients were optimized for the individual compounds. Select fractions were analyzed for purity using a Zorbax Rx C8 column (4.6 mm × 75 mm, 3.5 μm) and the latter mobile phases on an Agilent Technologies 1100 chromatograph. Pooled purified fractions were evaporated under reduced pressure, reconstituted in water, and lyophilized on a VirTis BenchTop 2K lyophilizer. Low-resolution electrospray ionization (ESI) mass spectra were recorded on an Agilent Technologies 1100 Series LC/MSD trap mass spectrometer. Elemental analyses were performed by Atlantic Microlab, Norcross, GA, and, unless stated otherwise, were within ±0.4% of calculated values.

General Procedure for Amidines 1−11 and 13−43. The nitrile was added to a mixture of anhydrous EtOH and 1,4-dioxane that had been saturated with hydrogen chloride at 0 °C in a dry three-neck flask equipped with a gas inlet tube, a thermometer, and a drying tube, and cooled in an ice−salt bath. The reaction mixture was then sealed, slowly warmed to ambient temperature, and stirred until the nitrile was no longer detectable. The reaction mixture was diluted with ether. The crude imidate was filtered off under inert gas and dried under high vacuum over KOH. The imidate (or an aliquot thereof) was then reacted immediately with the appropriate ammonia or the appropriate amine in EtOH. The reaction mixture was diluted with ether, and the crude amidine was filtered off. Compounds **3**−**9**, **11**, **13**−**18**, **20**, **21**, **23**, **24**, **27**, **29**, **31**, **33**, **35**, **36**, **38**, **42**, and **43** were purified by preparative HPLC and were converted to their dihydrochloride salts using aqueous or ethanol HCl. Other compounds were purified directly using similar solvents, or other sovlents as stated.

5-(4-Amidinophenyl)-3-phenylisoxazole hydrochloride (1) was prepared from 5-(4-cyanophenyl)-3-phenylisoxazole[24] (1.70 g, 6.90 mmol) following the general method in benzene, to give a solid (0.82 g, 40%): mp 262−265 °C; ^{1}H NMR (90 MHz) δ 9.63 (br s, 2H), 9.50 (br s, 2H), 8.08 (m, 6H), 7.82 (s, 1H), 7.60 (m, 3H). Anal. ($C_{16}H_{13}N_3O\cdot HCl\cdot 0.2H_2O$) C, H, N.

3-(4-Amidinophenyl)-5-phenylisoxazole (2) was prepared as above from 3-(4-cyanophenyl)-5-phenylisoxazole[24] (2.10 g, 8.50 mmol) to give a solid (0.87 g, 34%): mp 287−292 °C; ^{1}H NMR (90 MHz) δ 9.60 (br s, 3H), 8.13 (m, 6H), 7.94 (s, 1H), 7.60 (m, 3H). Anal. ($C_{16}H_{13}N_3O\cdot HCl\cdot 0.2H_2O$) C, H, N.

3,5-Bis(4-amidinophenyl)isoxazole dihydrochloride (3)[20] was prepared from nitrile **50a** (1.48 g, 5.47 mmol), EtOH (5 mL), and 1,4-dioxane (60 mL). The crude imidate (2.31 g, 97%) was filtered off and stirred overnight in EtOH/NH_3 (50 mL) to give a white solid (0.84 g, 41%): mp > 350 °C (dec, lit.[20] > 365°); ^{1}H NMR δ 9.55 (br s, 3H), 9.28 (br s, 3H), 8.17 (d, J = 8.7 Hz, 4H), 8.05 (d, J = 8.1 Hz, 2H), 8.04 (d, J = 8.7 Hz, 2H), 8.04 (s, 1H); MS m/z 306 (MH^+ of free base); HPLC (method A) t_R 3.96 min (100 area % at 265 nm). Anal. ($C_{17}H_{15}N_5O\cdot 2HCl$) C, H, N, Cl.

3,5-Bis[4-(*N*-isopropylamidino)phenyl]isoxazole dihydrochloride (4) was prepared from nitrile **50a** (2.18 g, 8.05 mmol). An aliquot of the crude imidate (1.20 g, 2.78 mmol) was reacted with isopropylamine (2.2 mL, 26 mmol) in EtOH (25 mL) overnight to give a white powder (0.51 g, 40%): mp 304−307 °C; ^{1}H NMR δ 9.78 (m, 2H), 9.62 (br s, 2H), 9.28 (br s, 2H), 8.16 (d, J = 8.3 Hz, 4H), 8.04 (s, 1H), 7.96 (d, J = 8.6 Hz, 2H), 7.94 (d, J = 8.5 Hz, 2H), 4.12 (m, 2H), 1.30 (d, J = 6.5 Hz, 2H); MS m/z 390 (MH^+ of free base); HPLC (method A) t_R 6.06 min (100 area % at 265 nm). Anal. ($C_{23}H_{27}N_5O\cdot 2HCl\cdot 2.75H_2O$) C, H, N, Cl.

3,5-Bis[4-(2-imidazolinyl)phenyl]isoxazole dihydrochloride (5). An aliquot of the imidate above (1.25 g, 2.86 mmol) was stirred overnight in a mixture of ethylenediamine (3 mL, 45 mmol) and EtOH (25 mL) to give a cream colored solid: (0.66 g, 54%): mp > 350 °C (dec); ^{1}H NMR δ 7.97 (d, J = 8.5 Hz, 2H), 7.96 (d, J = 8.7 Hz, 2H), 7.85 (d, J = 8.7 Hz, 4H), 7.25 (s, 1H), 4.01 (s, 8H); MS m/z 358 (MH^+ of free base); HPLC (method A) t_R 4.96 min (100 area % at 290 nm). Anal. ($C_{21}H_{19}N_5O\cdot 2HCl\cdot 0.3H_2O$) C, H, N, Cl.

5-(4-Amidino-2-nitrophenyl)-3-(4-amidinophenyl)isoxazole dihydrochloride (6) was prepared from nitrile **72a** (1.57 g, 4.96 mmol) to give a white solid: (0.67 g, 32%): mp > 350 °C (dec); ^{1}H NMR δ 9.78 (br s, 2H), 9.60 (br s, 4H), 9.37 (br s, 2H), 8.63 (s, 1H), 8.37 (d, J = 8.2 Hz, 1H) 8.26 (d, J = 8.1 Hz, 1H), 8.20 (d, J = 8.4 Hz, 2H), 8.05 (d, J = 8.0 Hz, 2H), 7.95 (s, 1H); MS m/z 351 (MH^+ of free base); HPLC (method A) t_R 3.96 min (100 area % at 254 nm). Anal. ($C_{17}H_{14}N_6O_3\cdot 2HCl\cdot 0.5H_2O$) C, H, N, Cl.

5-(4-Amidino-2-chlorophenyl)-3-(4-amidinophenyl)isoxazole dihydrochloride (7) was prepared from nitrile **72b** (1.53 g, 5.01 mmol) to give a white solid: (0.78 g, 38%): mp > 350 °C (dec); ^{1}H NMR δ 9.71 (br s, 2H), 9.60 (br s, 2H), 9.49 (br s, 2H), 9.38 (br s, 2H), 8.25 (m, 4H), 8.04 (m, 3H), 7.94 (s, 1H); MS m/z 340 (MH^+ of free base); HPLC (method A) t_R 4.43 min (100 area % at 265 nm). Anal. ($C_{17}H_{14}ClN_5O\cdot 2HCl\cdot 0.4H_2O$) C, H, N, Cl.

5-(4-Amidino-2-methoxyphenyl)-3-(4-amidinophenyl)isoxazole dihydrochloride (8) was prepared from nitrile **50m** (0.55 g, 1.84 g). The crude imidate was then reacted with ammonium carbonate (2.20 g, 22.9 mmol) in EtOH (30 mL) overnight to give a pale yellow solid (0.27 g, 36%): mp 336−337 °C; ^{1}H NMR δ 9.40 (br s, 7H), 8.25 (d, J = 8.2 Hz, 2H), 8.14 (d, J = 8.0 Hz, 1H), 8.02 (d, J = 8.5 Hz, 2H), 7.76 (s, 1H), 7.75 (d, J = 0.7 Hz, 1H), 7.61 (dd, J = 7.6 and 1.0 Hz, 1H), 4.14 (s. 3H); MS m/z 336 (MH^+ of free base); HPLC (method A) t_R 4.64 min (100 area % at 265 nm). Anal. ($C_{18}H_{17}N_5O_2\cdot 2HCl\cdot 1.5H_2O$) C, H, N, Cl.

3-(4-Amidino-2-nitrophenyl)-5-(4-amidinophenyl)isoxazole dihydrochloride (9) was prepared from nitrile **72c** (1.00 g, 3.17 g) to give a white solid (0.32 g, 24%): mp 350 °C (dec); ^{1}H NMR δ 9.55 (br s, 7H), 8.62 (d, J = 1.8 Hz, 1H), 8.33 (dd, J = 8.1 and 1.9 Hz, 1H), 8.19 (d, J = 8.7 Hz, 2H), 8.15 (d, J = 8.1 Hz, 1H), 8.05 (d, J = 8.7 Hz, 2H), 7.79 (s, 1H); MS m/z 351 (MH^+ of free base); HPLC (method A) t_R 3.77 min (100 area % at 265 nm). Anal. ($C_{17}H_1N_6O_3\cdot 2HCl\cdot 0.5H_2O$) C, H, N, Cl.

3-(4-Amidino-2-chlorophenyl)-5-(4-amidinophenyl)isoxazole dihydrochloride (10) was prepared from nitrile **72d** (1.00 g, 3.28 mmol). The crude product was dissolved in isopropyl alcohol, and the solution was diluted with ether to give a white power (0.55 g, 41%): mp 350 °C (dec); ^{1}H NMR δ 9.71 (br s, 2H), 9.62 (br s, 2H), 9.49 (br s, 2H), 9.40 (br s, 2H), 8.24 (d, J = 8.5 Hz, 2H), 8.21 (s, 1H), 8.06 (d, J = 8.9 Hz, 2H), 8.03 (d, J = 8.4 Hz, 1H), 7.98 (d, J = 8.4 Hz, 1H), 7.85 (s, 1H); MS m/z 340 (MH^+ of free base); HPLC (method A) t_R 4.29 min (100 area % at 265 nm). Anal. ($C_{17}H_{14}ClN_5O\cdot 2HCl\cdot H_2O$) C, H, N, Cl.

3-(4-Amidino-2-methoxyphenyl)-5-(4-amidinophenyl)isoxazole dihydrochloride (11) was prepared by nitrile **72e** (0.94 g, 3.16 mmol) to give a white solid (0.35 g, 28%): mp 335−337 °C (dec); ^{1}H NMR δ 9.48 (br s, 8H), 8.22 (d, J = 8.5 Hz, 2H), 8.04 (d, J = 8.4 Hz, 2H), 8.03 (d, J = 8.0 Hz, 1H), 7.76 (s, 1H), 7.73 (br s, 1H), 7.58 (dd, J = 8.1 and 1.3 Hz, 1H), 4.06 (s, 3H); MS

m/*z* 336 (MH^+ of free base); HPLC (method A) t_R 4.25 min (100 area % at 290 nm). Anal. ($C_{18}H_{17}N_5O_2 \cdot 2HCl \cdot 1.1H_2O$) C, H, N, Cl.

3,5-Bis(4-amidino-2-methoxyphenyl)isoxazole dihydrochloride (12). A mixture of *N*-acetoxy intermediate **74** (1.11 g, 2.31 mmol) and 10% Pd/C (0.60 g, 0.56 mmol) in AcOH and EtOH (100 mL of each) was hydrogenated at 60 psi for 2.5 h. The reaction mixture was filtered through Celite, and the filtrate was evaporated to dryness. An aliquot of the crude product (0.20 g) was suspended in EtOH (50 mL) was treated with EtOH/HCl (2 mL). A yellow solid was filtered off (0.13 g, 73% from the aliquot, 13% overall): mp > 350 °C (dec); ^{1}H NMR δ 9.64 (br s, 2H), 9.62 (br s, 2H), 9.34 (br s, 4H), 8.14 (d, J = 8.1 Hz, 1H), 8.02 (d, J = 8.0 Hz, 1H), 7.74 (s, 1H), 7.71 (s, 1H), 7.62 (d, J = 8.4 Hz, 1H), 7.57 (d, J = 8.1 Hz, 1H), 7.56 (s, 1H), 4.12 (s, 3H), 4.05 (s, 3H); MS *m*/*z* 366 (MH^+ of free base); HPLC (method A) t_R 5.02 min (100 area % at 265 nm). Anal. ($C_{19}H_{19}N_5O_3 \cdot 2HCl \cdot 1.2H_2O$) C, H, N, Cl.

3-(3-Amidinophenyl)-5-(4-amidinophenyl)isoxazole dihydrochloride (13) was prepared from nitrile **50b** (2.62 g, 9.66 mmol). An aliquot (2.27 g, wet) of the imidate was treated with EtOH/NH_3 to give an off-white solid (0.19 g, 10%): mp 212−215 °C (dec); ^{1}H NMR δ 9.52 (br s, 4 H), 8.48 (m, 1H), 8.28 (d, J = 8.1 Hz, 1H), 8.16 (d, J = 8.7 Hz, 2H), 8.08 (s, 1H), 8.07 (d, J = 8.7 Hz, 2H), 8.02 (d, J = 8.0 Hz, 1H), 7.83 (t, J = 7.8 Hz, 1H); MS *m*/*z* 306 (MH^+ of free base); HPLC (method A) t_R 3.99 min (100 area % at 290 nm). Anal. ($C_{17}H_{15}N_5O \cdot 2HCl \cdot H_2O$) C, H, N, Cl.

3-[3-(*N*-Isopropylamidino)phenyl]-5-[4-(*N*-isopropyl)amidinophenyl]isoxazole dihydrochloride (14) was prepared by treatment of an aliquot (2.16 g, wet) of the above imidate with isopropylamine to give a pale yellow crystals (0.85 g, 37%): mp > 350 °C; ^{1}H NMR δ 9.75 (br s, 6H), 8.37 (s, 1H), 8.25 (d, J = 7.8 Hz, 1H), 8.13 (d, J = 8.4 Hz, 2H), 8.13 (s, 1H), 7.98 (d, J = 8.5 Hz, 2H), 7.94 (d, J = 8.0 Hz, 1H), 7.80 (t, J = 7.8 Hz, 1H), 4.19 (m, 2H), 1.32 (d, J = 6.2 Hz, 1H), 1.31 (d, J = 6.1 Hz, 1H); MS *m*/*z* 390 (MH^+ of free base); HPLC (method A) t_R 5.92 min (99.0 area % at 265 nm). Anal. ($C_{23}H_{27}N_5O \cdot 2HCl \cdot H_2O$) C, H, N, Cl.

3-[3-(2-Imidazolinyl)phenyl]-5-[4-(2-imidazolinyl)phenyl]isoxazole dihydrochloride (15) was prepared by treatment of an aliquot (1.80 g, wet) of the imidate used in the preparation of **13** with ethylenediamine to give a yellow solid (0.80 g, 45%). mp 248−251 °C (dec); ^{1}H NMR δ 8.85 (m, 1H), 8.27 (m, 4H), 8.15 (m, 3H), 7.86 (t, J = 8.0 Hz, 1H), 4.05 (s, 1H), 4.03 (s, 1H); MS *m*/*z* 358 (MH^+ of free base); HPLC (method A) t_R 4.96 min (100 area % at 290 nm). Anal. ($C_{21}H_{19}N_5O \cdot 2HCl \cdot 1.5H_2O$) C, H, N, Cl.

5-(4-Amidino-2-nitrophenyl)-3-(3-amidinophenyl)isoxazole dihydrochloride (16) was prepared from nitrile **72g** (0.50 g, 1.58 mmol) to give a white solid (0.14 g, 21%): mp 225−225 °C; ^{1}H NMR δ 9.84 (br s, 2H), 9.64 (br s, 2H), 9.59 (br s, 2H), 9.37 (br s, 2H), 8.63 (d, J = 1.8 Hz, 1H); 8.46 (m, 1H), 8.36 (dd, J = 8.1 and 1.8 Hz, 1H), 8.30 (dm, J = 8.1 Hz, 1H), 8.24 (d, J = 8.1 Hz, 1H), 8.02 (dm, J = 8.0 Hz, 1H), 7.92 (s, 1H), 7.84 (t, J = 7.8 Hz, 1H); MS *m*/*z* 351 (MH^+ of free base); HPLC (method A) t_R 4.11 min (100 area % at 230 nm). Anal. ($C_{17}H_1N_6O_3 \cdot 2HCl \cdot 1.2H_2O$) C, H, N, Cl.

5-(4-Amidino-2-chlorophenyl)-3-(3-amidinophenyl)isoxazole dihydrochloride (17) was prepared from nitrile **72h** to give a white solid (0.16 g, 23%): mp 242−245 °C; ^{1}H NMR δ 9.72 (br s, 2H), 9.67 (br s, 2H), 9.49 (br s, 2H), 9.40 (br s, 2H), 8.54 (m, 1H), 8.36 (dm, J = 8.0 Hz, 1H), 8.25 (d, J = 8.0 Hz, 1H), 8.24 (d, J = 8.0 Hz, 1H), 8.06 (s, 1H), 8.04 (m, 1H), 8.02 (m, 1H), 7.83 (t, J = 7.9 Hz, 1H); MS *m*/*z* 340 (MH^+ of free base); HPLC (method A) t_R 4.52 min (100 area % at 230 nm). Anal. ($C_{17}H_{14}ClN_5O \cdot 2HCl \cdot 0.2H_2O$) C, H, N, Cl.

5-(4-Amidino-2-methoxyphenyl)-3-(3-amidinophenyl)isoxazole dihydrochloride (18) was prepared from nitrile **50n** (0.67 g, 2.47 mmol) to give a white solid (0.12 g, 14%): mp 241−246 °C; ^{1}H NMR δ 9.67 (br s, 4H), 9.37 (br s, 4H), 8.50 (s, 1H), 8.34 (d, J = 8.0 Hz, 1H), 8.15 (d, J = 8.2 Hz, 1H), 8.01 (d, J = 7.8 Hz, 1H), 7.83 (s, 1H), 7.82 (t, J = 7.9 Hz, 1H), 7.76 (d, J = 1.8 Hz, 1H), 7.62 (dd, J = 8.2 and 1.8 Hz, 1H), 4.16 (s, 3H); MS *m*/*z* 336 (MH^+ of free base); HPLC (method A) t_R 3.92 min (100 area % at 230 nm). Anal. ($C_{18}H_{17}N_5O \cdot 2HCl \cdot 1.3H_2O$) C, H, N, Cl.

3-(5-Amidino-2-nitrophenyl)-5-(4-amidinophenyl)isoxazole dihydrochloride (19) was prepared from nitrile **50c** (1.18 g, 3.73 mmol) to give a white solid (0.15 g, 12%): mp 238−240 °C; ^{1}H NMR δ 9.85 (br s, 1H), 9.60 (br s, 3H), 9.35 (br s, 1H), 8.43 (d, J = 1.9 Hz, 1H), 8.37 (d, J = 8.4 Hz, 1H), 8.25 (dd, J = 8.5 and 2.0 Hz, 1H), 8.15 (d, J = 8.6 Hz, 2H), 8.06 (d, J = 8.7 Hz, 2H), 7.88 (s, 1H); MS *m*/*z* 351 (MH^+ of free base); HPLC (method A) t_R 4.05 min (100 area % at 265 nm). Anal. ($C_{17}H_1N_6O_2 \cdot 2HCl \cdot 1.45H_2O$) C, H, N, Cl.

3-(5-Amidino-2-chlorophenyl)-5-(4-amidinophenyl)isoxazole dihydrochloride (20) was prepared from nitrile **72j** (0.41 g, 1.35 mmol) to give a white solid (0.18 g, 33%): mp 348 °C; ^{1}H NMR δ 9.68 (br s, 2H), 9.61(br s, 2H), 9.40 (br s, 4H), 8.28 (br s, 1H), 8.21 (d, J = 8.5 Hz, 2H), 8.06 (d, J = 8.2 Hz, 2H), 8.05 (dd, J = 8.5 and 1.9 Hz, 1H), 7.99 (d, J = 8.5 Hz, 1H), 7.89 (s, 1H); MS *m*/*z* 40 (MH^+ of free base); HPLC (method A) t_R 4.55 min (100 area % at 265 nm). Anal. ($C_{17}H_{14}ClN_5O \cdot 2HCl \cdot 0.7H_2O$) C, H, N, Cl.

3-(5-Amidino-2-methoxyphenyl)-5-(4-amidinophenyl)isoxazole dihydrochloride (21) was prepared from nitrile **50d** (0.90 g, 2.99 mmol) to give a white solid (0.25 g, 22%): mp 272−275 °C; ^{1}H NMR δ 9.40 (br s, 7H), 8.34 (d, J = 2.6 Hz, 1H), 8.21 (d, J = 8.7 Hz, 2H), 8.08 (dd, J = 8.9 and 2.6 Hz, 1H), 8.05 (d, J = 8.1 Hz, 2H), 7.77 (s, 1H), 7.49 (d, J = 9.1 Hz, 1H), 4.05 (s, 3H); MS *m*/*z* 336 (MH^+ of free base); HPLC (method A) t_R 4.31 min (100 area % at 290 nm). Anal. ($C_{18}H_{17}N_5O_2 \cdot 2HCl \cdot 0.8H_2O$) C, H, N, Cl.

3-(4-Amidinophenyl)-5-(3-amidinophenyl)isoxazole dihydrochloride (22) was prepared from nitrile **50e** (1.25 g, 4.61 mmol) to give a white solid (1.02 g, 58%): mp 336−338 °C; ^{1}H NMR δ 9.53 (br s, 8H), 8.48 (br s, 1H), 8.26 (d, J = 7.7 Hz, 1H), 8.15 (d, J = 8.8 Hz, 2H), 8.05 (d, J = 8.8 Hz, 2H), 8.03 (d, J = 7.7 Hz, 1H), 8.01 (s, 1H), 7.85 (dd, J = 7.7 and 7.7 Hz, 1H); HPLC (method A) t_R 4.09 min (100 area % at 265 nm). Anal. ($C_{17}H_{15}N_5O \cdot 2HCl \cdot 2.3H_2O$) C, H, N, Cl.

3-[4-(*N*-Isopropylamidino)phenyl]-5-[3-(*N*-isopropyl)amidinophenyl]isoxazole dihydrochloride (23) was prepared from nitrile **50e** (0.35 g, 1.28 mmol) to give a white solid (0.22 g, 38%): mp 340−343 °C (dec); ^{1}H NMR δ 9.90 (d, J = 8.4 Hz, 1H), 9.82 (d, J = 7.9 Hz, 1H), 9.73 (br s, 1H), 9.66 (br s, 1H), 9.41 (br s, 1H), 9.35 (br s, 1H), 8.35 (br s, 1H), 8.25 (d, J = 7.8 Hz, 1H), 8.14 (d, J = 7.9 Hz, 2H), 8.03 (s, 1H), 7.95 (d, J = 7.9 Hz, 2H), 7.92 (d, J = 7.8 Hz, 1H), 7.82 (dd, J = 7.8 and 7.8 Hz, 1H), 4.15 (m, 2H), 1.31 (d, J = 6.6 Hz, 6H), 1.30 (d, J = 6.6 Hz, 6H); HPLC (method A) t_R 5.97 min (100 area % at 254 nm). Anal. ($C_{23}H_{27}N_5O \cdot 2HCl \cdot 1.2H_2O$) C, H, N, Cl.

3-[4-(2-Imidazolinyl)phenyl]-5-[3-(2-imidazolinyl)phenyl]isoxazole dihydrochloride (24) was prepared from nitrile **50e** (0.35 g, 1.28 mmol) to give a white solid (0.39 g, 70%): mp 315−317 °C (dec); ^{1}H NMR δ 10.92 (br s, 4H), 8.75 (br s, 1H), 8.30 (d, J = 7.7 Hz, 1H), 8.21 (s, 4H), 8.17 (d, J = 7.7 Hz, 1H), 7.99 (br s, 2H), 7.91 (dd, J = 7.7 and 7.7 Hz, 1H), 4.06 (m, 8H); HPLC (method A) t_R 5.01 min (100 area % at 265 nm). Anal. ($C_{21}H_{19}N_5O \cdot 2HCl \cdot 2H_2O$) C, H, N, Cl.

5-(5-Amidino-2-chlorophenyl)-3-(4-amidinophenyl)isoxazole dihydrochloride (25) was prepared from nitrile **72k** (0.72 g, 2.36 mmol) to give a white solid (0.48 g, 50%): mp 356−358 °C (dec); ^{1}H NMR δ 9.75 (br s, 2H), 9.63 (br s, 2H), 9.49 (br s, 2H), 9.41 (br s, 2H), 8.49 (br s, 1H), 8.25 (m, 2H), 8.10−7.95 (m, 5H); HPLC (method A) t_R 4.67 min (100 area % at 254 nm). Anal. ($C_{17}H_{14}ClN_5O \cdot 2HCl \cdot 1H_2O$) C, H, N, Cl.

5-(5-Amidino-2-methoxyphenyl)-3-(4-amidinophenyl)isoxazole dihydrochloride (26) was prepared from nitrile **50f** (0.85 g, 2.82 mmol) to give a white solid (0.85 g, 74%): mp 240−242 °C; ^{1}H NMR δ 9.46 (br s, 8H), 8.46 (d, J = 2.2 Hz, 1H), 8.24 (d, J = 8.8 Hz, 2H), 8.07 (dd, J = 8.8 and 2.2 Hz, 1H), 8.04 (d, J = 8.8 Hz, 2H), 7.73 (s, 1H), 7.52 (d, J = 8.8 Hz, 1H), 4.14 (s, 3H); HPLC (method A) t_R 4.50 min (100 area % at 265 nm). Anal. ($C_{18}H_{17}N_5O_2 \cdot 2HCl \cdot 3.1H_2O$) C, H, N, Cl.

3-(4-Amidino-2-nitrophenyl)-5-(3-amidinophenyl)isoxazole dihydrochloride (27) was prepared from nitrile **72l** (0.78 g, 2.47 mmol) to give a white solid (0.26 g, 25%): mp 236 °C (dec); ^{1}H NMR δ 10.0−9.20 (br s, 8H), 8.63 (s, 1H), 8.48 (s, 1H), 8.35 (d, J = 8.2 Hz, 1H), 8.28 (d, J = 7.7 Hz, 1H), 8.14 (d, J = 8.2 Hz, 1H), 8.02 (d, J = 7.7 Hz, 1H), 7.85 (dd, J = 8.2 and 8.2 Hz, 1H), 7.73 (s, 1H); HPLC (method A) t_R 3.92 min (100 area % at 254 nm). Anal. ($C_{17}H_{14}N_6O_3$·2HCl·0.8H_2O) C, H, N, Cl.

3-(4-Amidino-2-chlorophenyl)-5-(3-amidinophenyl)isoxazole dihydrochloride (28) was prepared from nitrile **72m** (0.77 g, 2.47 mmol) to give a white solid (0.34 g, 33%): mp 210 °C (dec); ^{1}H NMR δ 9.58 (br s, 8H), 8.54 (s, 1H), 8.32 (d, J = 7.7 Hz, 1H), 8.21 (s, 1H), 8.03 (d, J = 7.7 Hz, 1H), 8.02 (d, J = 8.2 Hz, 1H), 7.99 (d, J = 8.2 Hz, 1H), 7.85 (dd, J = 8.2 and 8.2 Hz, 1H), 7.80 (s, 1H); HPLC (method A) t_R 4.41 min (100 area % at 254 nm). Anal. ($C_{17}H_{14}ClN_5O$·2HCl·1.1H_2O) C, H, N, Cl.

3-(4-Amidino-2-methoxyphenyl)-5-(3-amidinophenyl)isoxazole dihydrochloride (29) was prepared from nitrile **72n** (1.00 g, 3.32 mmol) to give a white solid (0.29 g, 22%): mp 288 °C (dec); ^{1}H NMR δ 9.69 (br s, 4H), 9.43 (br s, 4H), 8.52 (s, 1H), 8.30 (d, J = 7.7 Hz, 1H), 8.03 (d, J = 8.2 Hz, 1H), 8.00 (d, J = 7.7 Hz, 1H), 7.82 (dd, J = 7.7 and 7.7 Hz, 1H), 7.74 (s, 2H), 7.59 (d, J = 8.2 Hz, 1H), 4.08 (s, 3H); HPLC (method A) t_R 4.42 min (100 area % at 265 nm). Anal. ($C_{18}H_{17}N_5O_2$·2HCl·H_2O) C, H, N, Cl.

5-(5-Amidino-2-methoxyphenyl)-3-(4-amidino-2-nitrophenyl)-isoxazole dihydrochloride (30) was prepared from nitrile **72o** (0.70 g, 2.03 mmol) to give a white solid (0.10 g, 11%): mp 260 °C (dec); ^{1}H NMR δ 9.70−9.20 (br s, 8H), 8.62 (s, 1H), 8.48 (d, J = 1.6 Hz, 1H), 8.34 (d, J = 8.2 Hz, 1H), 8.19 (d, J = 8.2 Hz, 1H), 8.10 (dd, J = 8.8 and 1.6 Hz, 1H), 7.52 (d, J = 8.8 Hz, 1H), 7.48 (s, 1H), 4.10 (s, 3H); HPLC (method A) t_R 4.51 min (100 area % at 254 nm). Anal. ($C_{18}H_{16}N_6O_4$·2HCl·0.8H_2O) C, H, N, Cl.

3-(4-Amidino-2-methoxyphenyl)-5-(5-amidino-2-methoxyphenyl)isoxazole dihydrochloride (31) was prepared from nitrile **72p** (0.78 g, 2.35 mmol) to give a white solid (0.36 g, 35%): mp 330 °C (dec); ^{1}H NMR δ 9.63 (br s, 2H), 9.48 (br s, 2H), 9.34 (br s, 2H), 9.18 (br s, 2H), 8.44 (d, J = 2.2 Hz, 1H), 8.06 (dd, J = 8.9 and 2.2 Hz, 1H), 8.02 (d, J = 8.1 Hz, 1H), 7.72 (d, J = 1.3 Hz, 1H), 7.57 (dd, J = 8.1 and 1.3 Hz, 1H), 7.52 (d, J = 8.9 Hz, 1H), 7.41 (s, 1H), 4.11 (s, 3H), 4.05 (s, 3H); HPLC (method A) t_R 5.01 min (100 area % at 254 nm). Anal. ($C_{19}H_{19}N_5O_3$·2HCl) C, H, N, Cl.

3,5-Bis(3-amidinophenyl)isoxazole dihydrochloride (32) was prepared from nitrile **50g** (0.58 g, 2.15 mmol) to give a white solid (0.40 g, 62%): mp 365−367 °C; ^{1}H NMR δ 9.60 (br s, 4H), 9.32 (d, J = 6.8 Hz, 4H), 8.42 (br s, 2H), 8.27 (d, J = 7.7 Hz, 2H), 7.99 (d, J = 7.7 Hz, 2H), 7.96 (s, 1H), 7.86 (t, J = 7.7 Hz, 1H), 7.85 (t, J = 7.7 Hz, 1H); HPLC (method A) t_R 3.92 min (98.8 area % at 254 nm). Anal. ($C_{17}H_{15}N_5O$·2HCl·2H_2O) C, H, N, Cl.

3,5-Bis[3-(*N*-isopropylamidino)phenyl]isoxazole dihydrochloride (33) was prepared from nitrile **50g** (0.58 g, 2.15 mmol) to give a white solid (0.33 g, 42%): mp 260 °C (dec); ^{1}H NMR δ 9.83 (br s, 2H), 9.65 (br s, 2H), 9.29 (d, J = 4.1 Hz, 2H), 8.29 (br s, 2H), 8.24 (d, J = 7.7 Hz, 2H), 7.98 (s, 1H), 7.86 (m, 4H), 4.09 (m, 2H), 1.31 (d, J = 6.6 Hz, 12H); MS m/z 390.5 (MH^+ of free base); HPLC (method A) t_R 5.83 min (100 area % at 254 nm). Anal. ($C_{23}H_{27}N_5O$·2HCl·1.5H_2O·0.2EtOH) C, H, N, Cl.

3,5-Bis[3-(2-imidazolinyl)phenyl]isoxazole dihydrochloride (34) was prepared from nitrile **50g** (0.58 g, 2.15 mmol) to give a white solid (0.37 g, 54%): mp 373−374 °C; ^{1}H NMR δ 11.02 (s, 4H), 8.74 (s, 2H), 8.28 (d, J = 7.1 Hz, 2H), 8.19 (d, J = 7.7 Hz, 2H), 8.01 (s, 1H), 7.91 (m, 2H), 4.06 (s, 8H); HPLC (method A) t_R 5.00 min (100 area % at 254 nm). Anal. ($C_{21}H_{19}N_5O$·2HCl·0.5H_2O) C, H, N, Cl.

5-(5-Amidino-2-nitrophenyl)-3-(3-amidinophenyl)isoxazole dihydrochloride (35) was prepared from nitrile **50h** (0.42 g, 1.33 mmol) to give a white solid (0.05 g, 9%): mp 222 °C (dec); ^{1}H NMR δ 9.83 (s, 2H), 9.60 (s, 2H), 9.55 (s, 2H), 9.30 (s, 2H), 8.48 (s, 1H), 8.40 (s, 1H), 8.39 (d, J = 8.2 Hz, 1H), 8.26 (m, 2H), 8.00 (d, J = 7.7 Hz, 1H), 7.84 (t, J = 7.7 Hz, 1H), 7.82 (s, 1H); MS m/z 351 (MH^+ of free base); HPLC (method A) t_R 4.35 min (100 area % at 254 nm). Anal. ($C_{17}H_{14}N_6O_3$·2HCl·H_2O) C, H, N, Cl.

5-(5-Amidino-2-chlorophenyl)-3-(3-amidinophenyl)isoxazole dihydrochloride (36) was prepared from nitrile **72q** (0.50 g, 1.64 mmol) to give a white solid (0.33 g, 58%): mp 347 °C (dec); ^{1}H NMR δ 9.67 (s, 2H), 9.62 (s, 2H), 9.38 (s, 2H), 9.32 (s, 2H), 8.48 (d, J = 8.8 Hz, 2H), 8.35 (d, J = 7.1 Hz, 1H), 7.99 (m, 4H), 7.83 (t, J = 7.7 Hz, 1H); HPLC (method A) t_R 4.68 min (100 area % at 254 nm). Anal. ($C_{17}H_{14}N_5OCl$·2HCl·0.3H_2O) C, H, N, Cl.

5-(5-Amidino-2-methoxyphenyl)-3-(3-amidinophenyl)isoxazole dihydrochloride (37) was prepared from nitrile **50i** (0.19 g, 0.64 mmol) to give a white solid (0.12 g, 46%): mp 240 °C (dec); ^{1}H NMR δ 9.66 (s, 2H), 9.47 (s, 2H), 9.34 (s, 2H), 9.18 (s, 2H), 8.47 (m, 2H), 8.34 (d, J = 8.2 Hz, 1H), 8.06 (d, J = 8.8 Hz, 1H), 8.00 (d, J = 7.7 Hz, 1H), 7.81 (t, J = 7.7 Hz, 1H), 7.77 (s, 1H), 7.52 (d, J = 8.8 Hz, 1H), 4.12 (s, 3H); HPLC (method A) t_R 4.63 min (100 area % at 254 nm). Anal. ($C_{18}H_{17}N_5O_2$·2HCl·0.7H_2O) C, H, N, Cl.

3-(5-Amidino-2-nitrophenyl)-5-(3-amidinophenyl)isoxazole dihydrochloride (38) was prepared by from nitrile **50j** (0.24 g, 0.76 mmol) to give a white solid (0.08 g, 25%): mp 220 °C (dec); ^{1}H NMR δ 9.81 (s, 2H), 9.61 (s, 2H), 9.52 (s, 2H), 9.33 (s, 2H), 8.39 (m, 3H), 8.25 (m, 2H), 8.00 (d, J = 8.2 Hz, 1H), 7.87 (t, J = 7.7 Hz, 1H), 7.72 (s, 1H); MS m/z 351 (MH^+ of free base); HPLC (method A) t_R 4.11 min (97.6 area % at 254 nm). Anal. ($C_{17}H_{14}N_6O_3$·2HCl·H_2O) C, H, N, Cl.

3-(5-Amidino-2-chlorophenyl)-5-(3-amidinophenyl)isoxazole dihydrochloride (39) was prepared from nitrile **72r** (0.60 g, 1.96 mmol) to give a light yellow solid (0.39 g, 48%): mp 239−140 °C; ^{1}H NMR δ 9.66 (s, 4H), 9.40 (s, 4H), 8.50 (s, 1H), 8.30 (d, J = 8.2 Hz, 1H), 8.26 (d, J = 2.2 Hz, 1H), 8.04 (dd, J = 8.2 and 2.2 Hz, 1H), 8.00 (m, 2H), 7.84 (dd, J = 8.7 and 7.7 Hz, 1H), 7.80 (s, 1H); HPLC (method A) t_R 4.69 min (100 area % at 254 nm). Anal. ($C_{17}H_{14}N_5O$·2HCl·1.5H_2O·0.3EtOH) C, H, N, Cl.

3-(5-Amidino-2-methoxyphenyl)-5-(3-amidinophenyl)isoxazole dihydrochloride (40) was prepared from nitrile **50k** (0.34 g, 1.13 mmol) to give a light yellow solid (0.15 g, 33%): mp 210 °C (dec); ^{1}H NMR δ 9.64 (s, 2H), 9.42 (s, 2H), 9.35 (s, 2H), 9.12 (s, 2H), 8.47 (s, 1H), 8.33 (d, J = 2.2 Hz, 1H), 8.30 (d, J = 8.8 Hz, 1H), 8.06 (dd, J = 8.2 and 2.2 Hz, 1H), 7.98 (d, J = 7.7, 2H), 7.83 (t, J = 7.7 Hz, 1H), 7.71 (s, 1H), 7.50 (d, J = 8.8 Hz, 1H), 4.05 (s, 3H); HPLC (method A) t_R 4.46 min (100 area % at 254 nm). Anal. ($C_{18}H_{17}N_5O_2$·2HCl·0.6H_2O) C, H, N, Cl.

3,5-Bis(5-amidino-2-methoxyphenyl)isoxazole dihydrochloride (41) was prepared from nitrile **72s** (0.70 g, 2.11 mmol) to give a light yellow solid (0.34 g, 44%): mp 240 °C (dec); ^{1}H NMR δ 9.54 (s, 2H), 9.50 (s, 2H), 9.28 (s, 2H), 9.23 (s, 2H), 8.45 (d, J = 2.2 Hz, 1H), 8.31 (d, J = 2.2 Hz, 1H), 8.09 (dd, J = 8.8 and 2.2 Hz, 2H), 7.50 (t, J = 8.8 Hz, 2H), 7.43 (s, 1H), 4.11 (s, 3H), 4.03 (s, 3H); HPLC (method A) t_R 5.19 min (96.0 area % at 254 nm). Anal. ($C_{19}H_{19}N_5O_3$·2.1HCl·2.2H_2O) C, H, N, Cl.

3,5-Bis[5-(*N*-isopropyl)amidino-2-methoxyphenyl]isoxazole dihydrochloride (42) was prepared from nitrile **72s** (0.70 g, 2.11 mmol) to give a white solid (0.33 g, 30%): mp 185 °C (dec); ^{1}H NMR δ 9.70 (m, 2H), 9.57 (d, J = 10.9 Hz 2H), 9.18 (d, J = 13.2 Hz, 2H), 8.31 (d, J = 2.2 Hz, 1H), 8.20 (d, J = 2.2 Hz, 1H), 7.95 (dd, J = 8.8 and 2.2 Hz, 2H), 7.47 (d, J = 8.8 Hz, 2H), 7.44 (s, 1H), 4.11 (m, 2H), 4.09 (s, 3H), 4.02 (s, 3H), 1.29 (m, 12H); HPLC (method A) t_R 7.07 min (100 area % at 254 nm). Anal. ($C_{25}H_{31}N_5O_3$·2.4HCl·1.6H_2O·0.2EtOH) C, H, N, Cl.

3,5-Bis[5-(2-imidazolinyl)-2-methoxyphenyl]isoxazole dihydrochloride (43) was prepared by from nitrile **72s** (0.70 g, 2.11 mmol) to give a white solid (0.44 g, 42%): mp 210 °C (dec); ^{1}H NMR δ 10.95 (s, 2H), 10.91 (s, 2H), 8.67 (d, J = 2.2 Hz, 1H), 8.54 (d, J = 2.2 Hz, 1H), 8.33 (dd, J = 8.8 and 2.2 Hz, 2H), 7.54 (t, J = 8.8 Hz, 2H), 7.47 (s, 1H), 4.12 (s, 3H), 4.04 (s, 3H), 4.01 (s, 4H), 4.00 (s, 4H); HPLC (method A) t_R 6.16 min (100 area % at 254 nm). Anal. ($C_{23}H_{23}N_5O_3$·2.2HCl·2.5H_2O·0.1EtOH) C, H, N, Cl.

4-Cyano-2-methoxybenzaldehyde (44f). A solution of silver nitrate (25.0 g, 147 mmol) in water (75 mL) was added dropwise to a solution of α,α-dibromotoluene **56** (18.22 g, 59.74 mmol) in refluxing EtOH (300 mL). The mixture was maintained at reflux for 30 min, filtered, and evaporated to dryness. The residue was diluted with water and extracted into EtOAc to give a white solid (9.55 g, 99%): mp 109−111 °C; ^{1}H NMR δ 10.37 (d, J = 0.8 Hz, 1H), 7.82 (d, J = 7.8 Hz, 1H), 7.80 (d, J = 1.0 Hz, 1H), 7.54 (dm, J = 7.8 Hz, 1H), 3.99 (s, 3H); HPLC (method B) t_R 3.56 min (100 area % at 254 nm). Anal. ($C_9H_7N_5O_2$) C, H, N.

General Procedure for Chalcones 46b−f,h−n and Compound 47. A stirred solution of equimolar amounts of a benzaldehyde **44** and an acetophenone **45** in the appropriate solvent (EtOH at 25 °C unless stated otherwise) was treated dropwise with an aqueous solution of NaOH (1.2−1.5 equiv).[32] The product, which precipitated directly or after dilution of the reaction mixture with water, was filtered off, and recrystallized if necessary.

1-(3-Bromophenyl)-3-(4-bromophenyl)-2-propen-1-one (46b) was prepared from aldehyde **44a** and ketone **45b** to give a white solid (61.2 g, 88%): mp 142−143 °C; ^{1}H NMR δ 8.36 (m, 1H), 8.17 (d, J = 7.9 Hz, 1H), 8.02 (d, J = 15.7 Hz, 1H), 7.91 (d, J = 8.6 Hz, 2H), 7.88 (m, 1H), 7.76 (d, J = 15.6 Hz, 1H), 7.69 (d, J = 8.4 Hz, 2H), 7.55 (t, J = 7.8 Hz, 1H); HPLC (method B) t_R 9.34 min (100 area % at 265 nm). Anal. ($C_{15}H_{10}Br_2O$) C, H, Br.

1-(5-Bromo-2-nitrophenyl)-3-(4-bromophenyl)-2-propen-1-one (46c) was prepared from aldehyde **44a** and ketone **45c** to give a cream colored solid, (37.1 g, 82%): mp 169−190 °C; ^{1}H NMR δ 8.16 (dm, J = 8.2 Hz, 1H), 8.03 (dd, J = 8.4 and 2.1 Hz, 1H), 8.01 (s, 1H), 7.74 (d, J = 8.5 Hz, 2H), 7.65 (d, J = 8.7 Hz, 2H), 7.45 (d, J = 16.3 Hz, 1H), 7.34 (d, J = 16.3 Hz, 1H); HPLC (method B) t_R 8.56 min (100 area % at 290 nm). Anal. ($C_{15}H_9Br_2NO_3$) C, H, N, Br.

1-(5-Bromo-2-methoxyphenyl)-3-(4-bromophenyl)-2-propen-1-one (46d) was prepared from aldehyde **44a** and ketone **45d** to give a yellow solid (14.1 g, 89%) mp 118−120 °C; ^{1}H NMR δ 7.71 (m, 3H), 7.64 (d, J = 8.1 Hz, 2H), 7.61 (d, J = 1.8 Hz, 1H), 7.51 (d, J = 15.8 Hz, 1H), 7.42 (d, J = 16.0 Hz, 1H), 7.18 (d, J = 8.4 Hz, 1H), 3.86 (s, 3H); HPLC (method B) t_R 9.16 min (100 area % at 290 nm). Anal. ($C_{16}H_{12}Br_2O_2$) C, H, Br.

1-(4-Bromophenyl)-3-(3-bromophenyl)-2-propen-1-one (46e) was prepared in CH_3CN from aldehyde **44a** and ketone **45a** to give a yellow solid (14.5 g, 79%): mp 113−115 °C; ^{1}H NMR ($CDCl_3$) δ 7.88 (d, J = 8.3 Hz, 2H), 7.79 (dd, J = 1.3 and 1.3 Hz, 1H), 7.72 (d, J = 15.5 Hz, 1H), 7.65 (d, J = 8.3 Hz, 2H), 7.54 (dd, J = 7.7 and 1.3 Hz, 2H), 7.46 (d, J = 15.5 Hz, 1H), 7.29 (dd, J = 7.7 and 7.7 Hz, 1H); HPLC (method B) t_R 9.25 min (100 area % at 290 nm). Anal. ($C_{15}H_{10}Br_2O$) C, H, Br.

3-(5-Bromo-2-methoxyphenyl)-1-(4-bromophenyl)-2-propen-1-one (46f) was prepared in CH_3CN from aldehyde **44d** and ketone **45a** to give a yellow solid (21.2 g, 54%): mp 116−118 °C; ^{1}H NMR δ 8.27(d, J = 2.2 Hz, 1H), 8.12 (d, J = 8.8 Hz, 2H), 7.98 (s, 2H), 7.79 (d, J = 8.8 Hz, 2H), 7.54 (dd, J = 8.8 and 2.2 Hz, 1H), 7.10 (d, J = 8.8 Hz, 1H), 3.90 (s, 3H); HPLC (method B) t_R 9.50 min (100 area % at 290 nm). Anal. ($C_{16}H_{12}Br_2O_2$) C, H, Br.

3-(5-Bromo-2-nitrophenyl)-1-(3-bromophenyl)-2-propen-1-one (46h) was prepared in CH_3CN from aldehyde **44c** and ketone **45a** to give a yellow solid (30.4 g, 60%): mp 155−156 °C; ^{1}H NMR δ 8.49 (s, 1H), 8.37 (s, 1H), 8.20 (d, J = 8.2 Hz, 1H), 8.02 (m, 3H), 7.92 (d, J = 7.7 Hz, 2H), 7.57 (t, J = 7.7 Hz, 1H); HPLC (method B) t_R 8.88 min (100 area % at 254 nm). Anal. ($C_{15}H_9Br_2NO_2$) C, H, N, Br.

3-(5-Bromo-2-methoxyphenyl)-1-(3-bromophenyl)-2-propen-1-one (46i) was prepared in CH_3CN from aldehyde **44d** and ketone **45a** to give a yellow solid (20.0 g, 51%): mp 122−124 °C; ^{1}H NMR ($CDCl_3$) δ 7.95 (s, 1H), 7.85 (d, J = 15.9 Hz, 1H), 7.74 (br s, 1H), 7.53 (m, 2H), 7.27 (m, 3H), 6.64 (d, J = 8.8 Hz, 1H), 3.72 (s, 3H); HPLC (method B) t_R 9.46 min (100 area % at 254 nm). Anal. ($C_{16}H_{12}Br_2O_2$) C, H, Br.

1-(5-Bromo-2-nitrophenyl)-3-(3-bromophenyl)-2-propen-1-one (46j) was prepared from aldehyde **44b** and ketone **45c** in CH_3CN to give a brown solid (19.5 g, 64%): mp 141−143 °C; ^{1}H NMR δ 8.17 (d, J = 8.2 Hz, 1H), 8.03 (m, 3H), 7.80 (d, J = 8.2 Hz, 1H), 7.64 (d, J = 8.8 Hz, 1H), 7.41 (m, 3H); HPLC (method B) t_R 8.56 min (98.6 area % at 254 nm). Anal. ($C_{15}H_9Br_2NO_3$) C, H, N, Br.

1-(5-Bromo-2-methoxyphenyl)-3-(3-bromophenyl)-2-propen-1-one (46k) was prepared at 0 °C from aldehyde **44b** and ketone **45d** to give a yellow solid (37.2 g, 94%): mp 109−111 °C; ^{1}H NMR δ 8.01(s, 1H), 7.78 (d, J = 7.7 Hz, 1H), 7.72 (dd, J = 7.7 and 2.2 Hz, 1H), 7.63 (m, 2H), 7.47 (d, J = 6.6 Hz, 2H), 7.40 (t, J = 7.7 Hz, 1H), 7.19 (s, J = 8.8 Hz, 1H), 3.86 (s, 3H); HPLC (method B) t_R 9.18 min (100 area % at 254 nm). Anal. ($C_{16}H_{12}Br_2O_2$) C, H, Br.

3-(4-Cyano-2-methoxyphenyl)-1-(4-cyanophenyl)-2-propen-1-one (46m) was prepared from aldehyde **44e** and ketone **44e** in MeOH at 0 °C to give pale yellow crystals (0.73 g, 49%): mp 188−190 °C (MeOH); ^{1}H NMR δ 8.30 (d, J = 8.8 Hz, 2H), 8.22 (d, J = 8.2 Hz, 1H), 8.08 (d, J = 8.5 Hz, 2H), 8.07(d, J = 15.4 Hz, 1H), 8.01 (d, J = 15.4 Hz, 1H), 7.64, (d, J = 1.4 Hz, 1H), 7.53 (dd, J = 8.0 and 1.4 Hz, 1H), 3.96 (s, 3H); HPLC (method B) t_R 7.20 min (96.0 area % at 290 nm). Anal. ($C_{18}H_{12}N_2O_2.0.5H_2O$) C, H, N.

3-(4-Cyano-2-methoxyphenyl)-1-(3-cyanophenyl)-2-propen-1-one (46n) was prepared in MeOH at 0 °C from adldehyde **44f** and ketone **45f** to give a white solid (2.97 g, 83%): mp 215−128 °C; ^{1}H NMR δ 8.96 (s, 1H), 8.40 (d, J = 8.1 Hz, 1H), 8.25 (d, J = 8.0 Hz, 1H), 8.09 (m, 3H), 7.80 (t, J = 7.9 Hz, 1H), 7.63 (2, 1H), 7.54 (d, J = 8.2 Hz, 1H), 3.97 (s, 3H). Anal. ($C_{18}H_{12}N_2O_2$·0.3H_2O) C, H, N.

3-(5-Bromo-2-methoxyphenyl)-1,5-bis(3-bromophenyl)pentane-1,5-dione (47) was prepared from aldehyde **44d** and ketone **45b**. An oil precipitated after the reaction mixture was cooled to 0 °C, and the solvent was decanted. Column chromatography [hexanes/EtOAc (9:1)] gave a solid (10.2 g, 36%): mp 91−93 °C (EtOH, ether); ^{1}H NMR δ 8.10 (s, 2H), 7.95 (d, J = 7.7 Hz, 2H), 7.84 (d, J = 7.7 Hz, 2H), 7.50 (m, 3H), 7.31 (d, J = 7.7 Hz, 1H), 6.87 (d, J = 7.7 Hz, 1H), 4.17 (s, 3H), 3.40 (m, 4H); HPLC (method B) t_R 10.71 min (100 area % at 230 nm). Anal. ($C_{24}H_{19}Br_3O_3$) C, H, Br.

General Procedure for 2,3-Dibromo-1,3-diphenylpropan-1-ones 48. A solution of bromine (ca. 1.1−1.3 equiv) in $CHCl_3$ was added dropwise to a solution or suspension of a chalcone **46** in $CHCl_3$ at 0 °C. The mixture was stirred at room temperature until the reaction was complete. Unless stated otherwise, the solvent was evaporated and the product was recrystallized from an appropriate solvent.

2,3-Dibromo-1-(3-bromophenyl)-3-(4-bromophenyl)propan-1-one (48b) was prepared, after washing with ether, as a white solid (69.5 g, 81%): mp 158 °C; ^{1}H NMR δ 8.53 (m, 1H), 8.27 (d, J = 8.0 Hz, 1H), 7.99 (dm, J = 7.9 Hz, 1H), 7.84 (d, J = 8.5 Hz, 2H), 7.67 (d, J = 8.5 Hz, 2H), 7.62 (t, J = 7.9 Hz, 1H), 6.78 (d, J = 11.3 Hz, 1H), 5.84 (d, J = 11.2 Hz, 1H); HPLC (method B) t_R 10.32 min (100 area % at 254 nm). Anal. ($C_{15}H_{10}Br_2O$) C, H, Br.

2,3-Dibromo-1-(5-bromo-2-nitrophenyl)-3-(4-bromophenyl)-propan-1-one (48c) was prepared as white crystals (15.8 g, 88%): mp 200−201 °C (EtOH); ^{1}H NMR δ 8.61 (d, J = 2.1 Hz, 1H), 8.17 (dd, J = 8.6 and 2.0 Hz, 1H), 8.06 (d, J = 8.6 Hz, 1H), 7.76 (d, J = 8.5 Hz, 2H), 7.66 (d, J = 8.6 Hz, 2H), 6.74 (d, J = 11.3 Hz, 1H), 5.78 (d, J = 11.2 Hz, 1H).

2,3-Dibromo-1-(5-bromo-2-methoxyphenyl)-3-(4-bromophenyl)propan-1-one (48d) was prepared, after washing with ether, as a white solid (14.8 g, 75%): mp 158−159 °C; ^{1}H NMR δ 7.91 (d, J = 1.6 Hz, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.69 (d, J = 8.4 Hz, 2H), 7.63 (d, J = 8.5 Hz, 2H), 7.27 (d, J = 8.7 Hz, 1H), 6.32 (d, J = 11.3 Hz, 1H), 5.77 (d, J = 11.3 Hz, 1H), 3.97 (s, 3H); HPLC (method B) t_R 10.38 min (100 area % at 230 nm). Anal. ($C_{16}H_{12}Br_2O_2$) C, H, Br.

2,3-Dibromo-1-(4-bromophenyl)-3-(3-bromophenyl)propan-1-one (48e) was prepared as a white solid (20.4 g, 98%): mp 150−152 °C; ^{1}H NMR ($CDCl_3$) δ 7.95 (d, J = 8.2 Hz, 2H), 7.70 (d, J = 8.2 Hz, 2H), 7.67 (dd, J = 1.6 and 1.6 Hz, 1H), 7.52 (dd, J = 7.7 and 1.6 Hz, 1H), 7.44 (dd, J = 7.7 and 1.6 Hz, 1H), 7.30 (dd,

J = 7.7 and 7.7 Hz, 1H), 5.66 (d, J = 11.3 Hz, 1H), 5.54 (d, J = 11.3 Hz, 1H); HPLC (method B) t_R 10.16 min (100 area % at 265 nm). Anal. ($C_{15}H_{10}Br_4O$) C, H, Br.

2,3-Dibromo-3-(5-bromo-2-methoxyphenyl)-1-(4-bromophen-yl)propan-1-one (48f) was prepared as a white solid (28.0 g, 95%): mp 182−184 °C (dec); ^{1}H NMR δ 8.24 (d, J = 2.2 Hz, 1H), 8.22 (d, J = 8.8 Hz, 2H), 7.89 (d, J = 8.8 Hz, 2H), 7.56 (dd, J = 8.8 and 2.2 Hz, 1H), 7.08 (d, J = 8.8 Hz, 1H), 6.77 (d, J = 11.5 Hz, 1H), 6.04 (d, J = 11.5 Hz, 1H), 3.92 (s, 3H); HPLC (method B) t_R 10.04 min (100 area % at 265 nm). Anal. ($C_{16}H_{12}Br_4O_2$) C, H, Br.

2,3-Dibromo-1,3-bis(3-bromophenyl)propan-1-one (48g) was prepared as a white solid (8.81 g, 98%): mp 159−160 °C; ^{1}H NMR δ 8.51 (s, 1H), 8.27 (d, J = 7.7 Hz, 1H), 8.17 (s, 1H), 7.99 (d, J = 8.2 Hz, 1H), 7.84 (d, J = 8.4, 1H), 7.61 (m, 2H), 7.43 (7, J = 7.7 Hz, 1H), 6.77 (d, J = 11.5 Hz, 1H), 5.83 (d, J = 11.5 Hz, 1H); HPLC (method B) t_R 10.18 min (100 area % at 254 nm). Anal. ($C_{15}H_{10}Br_4O$) C, H, Br.

2,3-Dibromo-3-(5-bromo-2-nitrophenyl)-1-(3-bromophenyl)-propan-1-one (48h) was prepared as a white solid (12.9 g, 93%): mp 187−188 °C; ^{1}H NMR δ 8.70 (s, 1H), 8.47 (s, 1H), 8.26 (d, J = 7.7 Hz, 1H), 8.00 (m, 3H), 7.64 (t, J = 7.7 Hz, 1H), 6.85 (d, J = 11.0 Hz, 1H), 6.07 (d, J = 11.0 Hz, 1H); HPLC (method B) t_R 9.95 min (100 area % at 254 nm). Anal. ($C_{15}H_9Br_4NO_3$) C, H, N, Br.

2,3-Dibromo-3-(5-bromo-2-methoxyphenyl)-1-(3-bromophenyl)propan-1-one (48i) was prepared as a white solid. Two recrystallizations from $CHCl_3$/EtOH (1:5) gave pure product (4.52 g, 16%): mp 135−137 °C; ^{1}H NMR δ 8.48 (s, 1H), 8.24 (br s, 1H), 7.99 (d, J = 7.7 Hz, 1H), 7.59 (m, 2H), 7.08 (d, J = 8.8 Hz, 1H), 6.79 (d, J = 11.0 Hz, 1H), 6.05 (d, J = 11.0 Hz, 1H), 3.92 (s, 1H); HPLC (method B) t_R 10.30 min (100 area % at 254 nm).

2,3-Dibromo-1-(5-bromo-2-nitrophenyl)-3-(3-bromophenyl)-propan-1-one (48j) was prepared as a white solid (25.1 g, 95%): mp 153−155 °C; ^{1}H NMR δ 8.61 (s, 1H), 8.09 (m, 3H), 7.78 (dd, J = 8.2 and 2.2 Hz, 1H), 7.57 (d, J = 7.7 Hz, 1H), 7.40 (dd, J = 8.2 and 7.7 Hz), 6.76 (d, J = 11.0 Hz, 1H), 5.80 (d, J = 11.0 Hz, 1H). Anal. ($C_{15}H_9Br_4NO_3$) C, H, N, Br.

2,3-Dibromo-1-(5-bromo-2-methoxyphenyl)-3-(3-bromophenyl)propan-1-one (48k) was prepared as a white solid (51.5 g, 100%): mp 124−126 °C; ^{1}H NMR δ 8.01 (s, 1H), 7.92 (s, 1H), 7.84 (d, J = 8.8 Hz, 1H), 7.73 (d, J = 7.7 Hz, 1H), 7.59 (d, J = 8.2 Hz, 1H), 7.40 (dd, J = 8.2 and 7.7 Hz, 1H), 7.26 (d, J = 8.8 Hz, 1H), 6.35 (d, J = 11.5 Hz, 1H), 5.77 (d, J = 11.5 Hz, 1H), 3.96 (s, 3H); HPLC (method B) t_R 10.27 min (100 area % at 254 nm). Anal. ($C_{16}H_{12}Br_4O_2$) C, H, Br.

2,3-Dibromo-1,3-bis(4-cyanophenyl)propan-1-one (48l) was prepared as a cream colored solid (5.75 g, 84%): mp 192−193 °C (EtOH, $CHCl_3$); ^{1}H NMR δ 8.45 (d, J = 8.7 Hz, 2H), 8.17 (d, J = 8.7 Hz, 2H), 8.08 (d, J = 8.5 Hz, 2H), 7.97 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 11.3 Hz, 1H), 5.95 (d, J = 11.3 Hz, 1H); HPLC (method B) t_R 7.88 min (100 area % at 254 nm). Anal. ($C_{17}H_{10}Br_2N_2O$) C, H, N, Br.

2,3-Dibromo-3-(4-cyano-2-methoxyphenyl)-1-(4-cyanophenyl) propan-1-one (48m) was prepared, after column chromatography ($CHCl_3$) as white crystals (3.20 g, 54%): mp 163−165 °C (EtOH); ^{1}H NMR δ 8.43 (d, J = 8.5 Hz, 2H), 8.18 (m, 3H), 7.63 (d, J = 7.0 Hz, 2H), 6.84 (d, J = 11.3 Hz, 1H), 6.06 (d, J = 11.4 Hz, 1H), 4.00 (s, 3H); HPLC (method B) t_R 7.88 min (94.2 area % at 254 nm).

2,3-Dibromo-3-(4-cyano-2-methoxyphenyl)-1-(3-cyanophenyl) propan-1-one (48n) was prepared, after washing in ether, as a white solid (4.54 g, 98%): mp 72−75 °C; ^{1}H NMR δ 8.85 (s, 1H), 8.52 (d, J = 8.1 Hz, 1H), 8.27 (d, J = 7.8 Hz, 1H), 8.18 (d, J = 8.3 Hz, 1H), 7.89 (t, J = 7.9 Hz, 1H), 7.65 (m, 2H), 6.83 (d, J = 11.5 Hz, 1H), 6.06 (d, J = 11.4 Hz, 1H), 4.00 (s, 3H).

General Procedure for Diphenylisoxazoles 49b−d,f−k and 50a,m,n. A mixture of a ketone **48** in EtOH (at reflux temperature unless stated otherwise) was treated with aqueous solutions of hydroxylamine hydrochloride (1.2−2 equiv) and sodium hydroxide (4−5 equiv). The mixture was immediately cooled to ambient temperature and was stirred until the reaction was complete. The crude product was filtered off and purified if necessary by column chromatography and/or recrystallization.

3-(3-Bromophenyl)-5-(4-bromophenyl)isoxazole (49b) was prepared as white crystals (9.65 g, 54%); mp 169 °C; ^{1}H NMR δ 8.10 (t, J = 1.9 Hz, 1H), 7.93 (dm, J = 8.7 Hz, 1H), 7.85 (d, J = 8.9 Hz, 2H), 7.79 (d, J = 8.8 Hz, 2H), 7.76 (s, 1H), 7.75 (dm, J = 8.7 Hz, 1H), 7.53 (t, J = 7.9 Hz, 1H); HPLC (method B) t_R 9.95 min (100 area % at 265 nm). Anal. ($C_{15}H_9Br_2NO$) C, H, N, Br.

3-(5-Bromo-2-nitrophenyl)-5-(4-bromophenyl)isoxazole (49c) was prepared at 0−25 °C as a white solid (1.95 g, 53%): mp 184−185 °C (EtOH); ^{1}H NMR δ 8.12 (d, J = 1.6 Hz, 1H), 8.11 (d, J = 8.8 Hz, 1H), 8.05 (dd, J = 8.8 and1.6 Hz, 1H), 7.87 (d, J = 8.8 Hz, 2H), 7.81 (d, J = 8.8 Hz, 2H), 7.54 (s, 1H); HPLC (method B) t_R 9.24 min (100 area % at 265 nm). Anal. ($C_{15}H_8Br_2N_2O_3$) C, H, N, Br.

3-(5-Bromo-2-methoxyphenyl)-5-(4-bromophenyl)isoxazole (49d) was prepared as a white solid (3.55 g, 33%): mp 126−128 °C; ^{1}H NMR δ 7.90 (m, 3H), 7.77 (d, J = 8.6 Hz, 2H), 7.69 (dm, J = 9.0 Hz, 1H), 7.50 (s, 1H), 7.21 (d, J = 8.2 Hz, 1H), 3.92 (s, 3H); HPLC (method B) t_R 8.89 min (100 area % at 265 nm). Anal. ($C_{16}H_{11}Br_2N_2O_2$) C, H, N, Br.

5-(5-Bromo-2-methoxyphenyl)-3-(4-bromophenyl)isoxazole (49f) was prepared at 25 °C as a white solid (9.20 g, 48%): mp 153−154 °C; ^{1}H NMR δ 7.97 (d, J = 2.2 Hz, 1H), 7.93 (d, J = 8.8 Hz, 2H), 7.75 (d, J = 8.8 Hz, 2H), 7.69 (dd, J = 8.8 and 2.2 Hz, 1H), 7.50 (s, 1H), 7.24 (d, J = 8.8 Hz, 1H), 4.00 (s, 3H); HPLC (method B) t_R 10.25 min (100 area % at 254 nm). Anal. ($C_{16}H_{11}Br_2NO_2$) C, H, N, Br.

3,5-Bis(3-bromophenyl)isoxazole (49g) was prepared as a white solid (2.71 g, 44%): mp 155−156 °C; ^{1}H NMR δ 8.11 (d, J = 7.1 Hz, 2H), 7.93 (m, 2H), 7.86 (s, 1H), 7.75 (d, J = 8.2 Hz, 2H), 7.56 (m, 2H); HPLC (method B) t_R 9.81 min (100 area % at 265 nm). Anal. ($C_{15}H_9Br_2NO$) C, H, N, Br.

5-(5-bromo-2-nitrophenyl)-3-(3-bromophenyl)isoxazole (49h) was prepared as a light brown solid (7.34 g, 33%): mp 179−180 °C; ^{1}H NMR δ 8.24 (s, 1H), 8.09 (m, 3H), 7.95 (d, J = 7.7 Hz, 1H), 7.77 (d, J = 8.8 Hz, 1H), 7.76 (s, 1H), 7.54 (t, J = 7.7 Hz, 2H); HPLC (method B) t_R 9.23 min (100 area % at 265 nm). Anal. ($C_{15}H_8Br_2N_2O_3$) C, H, N, Br.

5-(5-Bromo-2-methoxyphenyl)-3-(3-bromophenyl)isoxazole (49i) was prepared as a white solid (2.01 g, 60%): mp 156 °C; ^{1}H NMR δ 8.18 (s, 1H), 8.00 (d, J = 8.8 Hz, 1H), 7.99 (s, 1H), 7.73 (m, 2H), 7.57 (s, 1H), 7.51 (t, J = 8.2 Hz, 1H) 7.25 (d, J = 8.8 Hz, 1H), 4.01 (s, 3H); HPLC (method B) t_R 10.09 min (100 area % at 265 nm). Anal. ($C_{16}H_{11}Br_2NO_2$) C, H, N, Br.

3-(5-Bromo-2-nitrophenyl)-5-(3-bromophenyl)isoxazole (49j) was prepared as a yellow solid (1.01 g, 5%): mp 195−197 °C; ^{1}H NMR δ 8.13 (m, 2H), 8.08 (m, *2*H), 7.93 (d, J = 7.7 Hz, 1H), 7.77 (d, J = 7.7 Hz, 1H), 7.61 (s, 1H), 7.55 (t, J = 0.7.7 Hz, 1H); HPLC (method B) t_R 9.25 min (96.9 area % at 265 nm). Anal. ($C_{15}H_8Br_2N_2O_3$) C, H, N, Br.

3-(5-Bromo-2-methoxyphenyl)-5-(3-bromophenyl)isoxazole (49k) was prepared as a white solid (5.71 g, 35%): mp 149−150 °C; ^{1}H NMR δ 8.19 (s, 1H), 7.96 (d, J = 7.7 Hz, 1H), 7.91 (s, 1H), 7.72 (m, 2H), 7.59 (s, 1H), 7.53 (t, J = 8.8 Hz, 1H), 7.21 (d, J = 8.8 Hz, 1H), 3.93 (s, 1H); HPLC (method B) t_R 9.93 min (100 area % at 265 nm). Anal. ($C_{16}H_{11}Br_2NO_2$) C, H, N, Br.

1,3-Bis(4-cyanophenyl)isoxazole (50a) was prepared from ketone **48l** at 25 °C as a white solid (0.15 g, 56%), mp 247 °C) (lit.[20] 248−250°); ^{1}H NMR δ 8.09 (m, 8H), 7.96 (s, 1H); HPLC (method B) t_R 6.98 min (100 area % at 265 nm). Anal. ($C_{17}H_9N_3O$) C, H, N.

The compound was also prepared by the general method for compounds **72** below from phenylacetylene **71a** and chlorooxime **64a** as a white solid (3.60 g, 54%) whose NMR spectrum matches that above.

5-(4-Cyano-2-methoxyphenyl)-3-(4-cyanophenyl)isoxazole (50m) was prepared from ketone **48m** in MeOH at 0−5 °C. Column chromatography ($CHCl_3$) afforded white crystals (0.57 g, 20%): mp 254−255 °C (acetone); ^{1}H NMR δ 8.20 (d, J = 8.5 Hz, 2H),

8.08 (d, J = 8.1 Hz, 1H), 8.04 (d, J = 8.7 Hz, 2H), 7.79 (d, J = 1.1 Hz, 1H), 7.73 (s, 1H), 7.61 (dd, J = 8.1 and 1.2 Hz, 1H), 4.08 (s, 3H); HPLC (method B) t_R 7.78 min (95.5 area % at 265 nm). Anal. ($C_{18}H_{11}N_5O_2$) C, H, N.

The compound was also prepared from phenylacetylene **71dg** and chlorooxime **64a** by the general method for compounds **72** below as a white solid (4.86 g, 65%): mp 247−250 °C; HPLC (method A) t_R 7.75 min (94.7 area % at 265 nm).

5-(4-Cyano-2-methoxyphenyl)-1-(3-cyanophenyl)isoxazole (50n) was prepared from ketone **48n** in MeOH at 0 °C as a yellow solid (1.16 g, 58%): mp 242−244 °C (EtOH); ^{1}H NMR δ 8.50 (s, 1H), 8.34 (dm, J = 7.9 Hz, 1H), 8.08 (d, J = 8.1 Hz, 1H), 8.02 (d, J = 7.9 Hz, 1H), 7.77 (m, 3H), 7.61 (dd, J = 8.2 and 1.4 Hz, 1H), 4.09 (s, 3H). Anal. ($C_{18}H_{11}N_3O_2$) C, H, N.

General Procedure for Isoxazole Dinitriles 50b,d-h,j,k. A dibromoisoxazole **49** was reacted with an excess of CuCN in refluxing DMF[60] until the reaction was complete. The reaction mixture, after successive treatments with ethylenediamine and sodium cyanide solutions, was extracted into an appropriate solvent. The product was purified by column chromatography and then recrystallized if needed.

5-(4-Cyanophenyl)-3-(3-cyanophenyl)isoxazole (50b) was prepared by from bromoisoxaole **49b** to give yellow crystals (4.72 g, 69%): mp 218 °C (EtOH/toluene); ^{1}H NMR δ 8.38 (m, 1H) 8.26 (dm, J = 7.9 Hz, 1H), 8.08 (s, 4H), 8.04 (dm, J = 7.9 Hz, 1H), 7.92 (s, 1H), 7.80 (t, J = 7.8 Hz, 1H); HPLC (method B) t_R 6.99 min (100 area % at 265 nm). Anal. ($C_{17}H_9N_3O$) C, H, N.

3-(5-Cyano-2-nitrophenyl)-5-(4-cyanophenyl)isoxazole (50c) was prepared from bromoisoxazole **49c** using $Zn(CN)_2$ (1.0 equiv) and $Pd(PPh_3)_4$ (8 mol %)[34] to give a white solid (1.38 g, 37%): mp > 260 °C; ^{1}H NMR δ 8.49, (m, 1H), 8.35 (m, 2H), 8.10 (m, 4H), 7.77 (s, 1H); HPLC (method B) t_R 6.73 min (100 area % at 265 nm). Anal. ($C_{17}H_8N_4O_3 \cdot 0.25H_2O$) C, H, N.

3-(5-Cyano-2-methoxyphenyl)-5-(4-cyanophenyl)isoxazole (50d) was prepared from bromoisoxazole **49d** to give white crystals (1.06 g, 42%): mp 243−244 °C (EtOH); ^{1}H NMR δ 8.20 (m, 1H), 8.16 (d, J = 8.2 Hz, 2H), 8.06 (d, J = 8.0 Hz, 2H), 8.02 (m, 1H), 7.71 (s, 1H), 7.43 (d, J = 8.4 Hz, 1H), 4.02 (s, 3H); HPLC (method B) t_R 6.99 min (100 area % at 265 nm). Anal. ($C_{18}H_{11}N_3O_2$) C, H, N.

3-(4-Cyanophenyl)-5-(3-cyanophenyl)isoxazole (50e) was prepared from bromoisoxazole **49e** to give white crystals (1.40 g, 33%): mp 188−190 °C (EtOH/$CHCl_3$); ^{1}H NMR δ 8.42 (br s, 1H), 8.24 (d, J = 7.7 Hz, 1H), 8.09 (m, 4H), 8.03 (d, J = 7.7 Hz, 1H), 7.92 (s, 1H), 7.82 (dd, J = 7.7 and 7.7 Hz, 1H); HPLC (method B) t_R 7.16 min (100 area % at 254 nm). Anal. ($C_{17}H_9N_3O$) C, H, N.

5-(5-Cyano-2-methoxyphenyl)-3-(4-cyanophenyl)isoxazole (50f) was prepared from bromoisoxazole **49f** to give white crystals (1.00 g, 29%): mp 251−253 °C ($CHCl_3$); ^{1}H NMR δ 8.31 (br s, 1H), 8.18 (d, J = 8.2 Hz, 2H), 8.03 (d, J = 8.2 Hz, 2H), 8.01 (d, J = 8.8 Hz, 1H), 7.64 (s, 1H), 7.45 (d, J = 8.8 Hz, 1H), 4.10 (s, 3H); HPLC (method B) t_R 7.40 min (100 area % at 254 nm). Anal. ($C_{18}H_{11}N_3O_2$) C, H, N.

3,5-Bis(3-cyanophenyl)isoxazole (50g) was prepared from bromoisoxazole **49g** to give white crystals (1.94 g, 43%): mp 214−215 °C (hexane/$CHCl_2$); ^{1}H NMR δ 8.38 (s, 1H), 8.34 (s, 1H), 8.22 (m, 2H), 8.02 (d, J = 7.7 Hz, 2H), 7.91 (s, 1H), 7.80 (m, 2H); HPLC (method B) t_R 6.96 min (100 area % at 265 nm). Anal. ($C_{17}H_9N_3O$) C, H, N.

5-(5-Cyano-2-nitrophenyl)-3-(3-cyanophenyl)isoxazole (50h) was prepared from bromoisoxazole **49h** to give light yellow crystals (0.53 g, 21%): mp 184−185 °C ($CHCl_3$); ^{1}H NMR δ 8.58 (s, 1H), 8.41 (s, 1H), 8.36 (m, 2H), 8.27 (d, J = 7.7 Hz, 1H), 8.05 (d, J = 7.7 Hz, 1H), 7.83 (s, 1H), 7.80 (t, J = 7.7 Hz, 1H); HPLC (method B) t_R 6.78 min (96.3 area % at 265 nm). Anal. ($C_{17}H_8N_4O_3$) C, H, N.

5-(5-Cyano-2-methoxyphenyl)-3-(3-cyanophenyl)isoxazole (50i). *tert*-Butyllithium (1.7 M solution in hexane, 6 mL, 10 mmol) was added dropwise to a stirred solution of bromoisoxazole **49i** (1.00 g, 2.44 mmol) in dry THF (10 mL) maintained at −85 °C under Ar at such a rate that the reaction temperature did not exceed −75 °C. The reaction mixture was maintained for 5 h. A solution of *p*-toluenesulfonyl cyanide (1.8 g, 10 mmol) in dry THF (10 mL) at −85 °C was added to the reaction mixture. The mixture was warmed to 25 °C and after 15 min was quenched with sat. NH_4OH (7 mL). After 15 min the mixture was poured into 1 M NaOH (100 mL). The mixture was extracted with EtOAc. Column chromatography ($CHCl_3$) followed by recrystallization from hexanes/EtOAc (1:1) afforded light yellow crystals (0.25 g, 34%): mp 235−238 °C; ^{1}H NMR δ 8.50 (s, 1H), 8.34 (m, 2H), 8.03 (m, 2H), 7.77 (t, J = 7.7 Hz, 1H), 7.71 (s, 1H), 7.47 (d, J = 8.8 Hz, 1H), 4.11 (s, 3H); HPLC (method B) t_R 7.29 min (100 area % at 265 nm). Anal. ($C_{18}H_{11}N_3O_2$) C, H, N.

The compound was also prepared by the general method for compounds **72** below, from phenylacetylene **71g** and chlorooxime **64e** as a light yellow solid (1.05 g, 42%); mp 235−237 °C; HPLC (method B) t_R 7.31 min (98.1 area % at 254 nm).

3-(5-Cyano-2-nitrophenyl)-5-(3-cyanophenyl)isoxazole (50j) was prepared from bromoisoxazole **49j** as a light yellow crystals (0.18 g, 24%): mp 225−227 °C ($CHCl_3$); ^{1}H NMR δ 8.48 (s, 1H), 8.45 (s, 1H), 8.35 (m, 2H), 8.25 (d, J = 7.7 Hz, 1H), 8.05 (d, J = 7.7 Hz, 1H), 7.82 (t, J = 7.7 Hz, 1H), 7.70 (s, 1H); HPLC (method B) t_R 6.67 min (100 area % at 265 nm). Anal. ($C_{17}H_8N_4O_3$) C, H, N.

3-(5-Cyano-2-methoxyphenyl)-5-(3-cyanophenyl)isoxazole (50k) was prepared from bromoisoxazole **49k** as light yellow crystals (1.41 g, 43%): mp 241−243 °C (CH_2Cl_2); ^{1}H NMR δ 8.49 (s, 1H), 8.26 (m, 2H), 8.00 (br s, 2H), 7.78 (br s, 1H), 7.68 (br s, 1H), 7.42 (s, 1H); HPLC (method B) t_R 7.36 min (97.8 area % at 265 nm). Anal. ($C_{18}H_{11}N_3O_2$) C, H, N.

3-Nitro-4-[(2-*N*,*N*-dimethylamino)ethenyl]benzonitrile (52). *N*,*N*-Dimethylformamide dimethyl acetal (12.1 g, 101 mmol) was added to a solution of nitrotoluene **51** (16.3 g, 101 mmol) in dry DMF (60 mL). The mixture was refluxed overnight under N_2. The reaction mixture was poured into ice water to give a red solid (21.5 g, 99%): mp 122−126 °C; ^{1}H NMR δ 8.22 (d, J = 1.6 Hz, 1H), 7.84 (d, J = 13.2 Hz, 1H), 7.82 (d, J = 8.8 Hz, 1H), 7.65 (dd, J = 8.8 and 1.6 Hz, 1H), 5.67 (d, J = 13.2 Hz, 1H), 2.98 (s, 6H). Anal. ($C_{11}H_{11}N_3O_2$) C, H, N.

3-Methoxy-4-dibromomethylbenzonitrile (56). A mixture of tolunitrile **55** (11.4 g, 77.6 mmol), NBS (34.50 g, 193.8 mmol), benzoyl peroxide (1.01 g, 4.17 mmol) in CCl_4 was refluxed for 3 h. The reaction mixture was diluted with water and extracted with CH_2Cl_2. Column chromatography [hexane/EtOAc (19:1)] of the extracts afforded white crystals (18.3 g, 77%): mp 78−79 °C; ^{1}H NMR δ 7.88 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 1.4 Hz, 1H), 7.52 (dd, J = 8.0 and 1.5 Hz, 1H), 7.34 (s, 1H), 3.96 (s, 3H); HPLC (method B) t_R 7.03 min (100 area % at 254 nm). Anal. ($C_9H_7Br_2NO$) C, H, N, Br.

2-Chloro-5-bromobenzoic Acid Methyl Ester (60). A solution of benzoic acid **57** (30.0 g, 127 mmol) and H_2SO_4 (2 mL) in MeOH (2 L) was stirred at reflux for 3 days. The reaction mixture was concentrated to give white crystals (31.2 g, 98%): mp 43−44 °C; ^{1}H NMR δ 7.99 (d, J = 2.4 Hz, 1H), 7.80 (dd, J = 8.6 and 2.5 Hz, 1H), 7.56 (d, J = 8.6 Hz, 1H), 3.87 (s, 3H); HPLC (method B) t_R 6.34 min (100 area % at 230 nm).

2-Chloro-5-cyanobenzoic Acid Methyl Ester (61). DCC (11.4 g, 55.0 mmol) was added to a solution of benzoic acid **59**, (9.08 g, 50.0 mmol), DMAP (0.60 g, 5.00 mmol), and MeOH (5 mL) in CH_2Cl_2 (100 mL) at 0 °C. After 1 h the solution was warmed to 25 °C. The reaction mixture was filtered and evaporated. The residue was purified by column chromatography (CH_2Cl_2) to give a light solid (9.21 g, 94%): mp 100−103 °C; ^{1}H NMR δ 8.30 (d, J = 2.2 Hz, 1H), 8.07 (dd, J = 8.2 and 2.2 Hz, 1H), 7.84 (d, J = 8.2 Hz, 1H), 3.89 (s, 3H); HPLC (method B) t_R 4.57 min (100 area % at 254 nm).

4-Cyano-2-nitrobenzaldehyde (62b). $NaIO_4$ (65.0 g, 304 mmol) was added to a solution of intermediate **52** (21.0 g, 96.7 mmol) in THF and water (350 mL each). The mixture was stirred for 2.5 h, filtered, and extracted into EtOAc, and evaporated. Filtration of a suspension of the residue in $CHCl_3$ through a plug of silica gel followed by recrystallization from toluene (Norit) gave yellow

crystals (13.1 g, 77%): mp 109−111 °C; ^{1}H NMR δ 10.27 (s, 1H), 8.75 (d, J = 1.5 Hz, 1H), 8.40 (dd, J = 8.0 and 1.5 Hz, 1H), 8.05 (d, J = 8.0 Hz, 1H). Anal. ($C_8H_4N_2O_3$) C, H, N.

2-Chloro-4-cyanobenzaldehyde (62c). A solution of NaOEt was prepared from sodium (2.01 g, 87.4 mmol) and dry EtOH (150 mL). 2-Nitropropane (8 mL, 89 mmol) was added, followed after a few minutes by 3-chloro-4-bromomethylbenzonitrile (**54**, 13.5 g, 58.6 mmol). The mixture was stirred overnight, filtered, and evaporated. The residue was partitioned between water and EtOAc to give white solid (8.63 g, 89%). An analytical sample was recrystallized from aqueous EtOH to give white needles: mp 117−119 °C (lit.[39] 122−123°); ^{1}H NMR δ 10.34 (s, 1 H), 8.29 (m, 1H), 8.00 (m, 2H). Anal. (C_8H_4ClNO) C, H, N, Cl.

5-Bromo-2-chlorobenzaldehyde (62e). A solution of pyrroline (4.00 g, 56.0 mmol) in MTBE (12 mL) was added dropwise over 20 min to a solution of Red-Al (3.4 M solution in toluene, 16 mL, 54.4 mmol) in MTBE (33 mL) maintained at −20 °C. The mixture was stirred for 1 h at 25 °C. A solution of potassium *tert*-butoxide (0.60 g, 5.36 mmol) in THF (3 mL) was added. The resulting solution was added dropwise to a solution of 2-chloro-5-bromobenzoic acid methyl ester (**60**, 6.80 g, 27.3 mmol) in MTBE (15 mL) at 10 °C. After 15 min the mixture was quenched with 2 N HCl (300 mL). Repeated recystallizations (hexanes) of the recovered material gave a crude solid (3.22 g, 54%, mp 43−46 °C) which was used without further purification in the next step.

2-Chloro-5-cyanobenzaldehyde (62g)[68] was prepared from ester **61** as described above for **62e**. Column chromatography of the crude material (7.60 g, 100%) [hexane/EtOAc (7:3)], followed by recrystallization from hexane/EtOAc (2:1) gave a solid (3.15 g, 41%): mp 191−193 °C; ^{1}H NMR δ 10.28 (s, 1H), 8.28 (d, J = 2.2 Hz, 1H), 8.17 (dd, J = 8.2 and 2.2 Hz, 1H), 7.87 (d, J = 8.2 Hz, 1H); HPLC (method B) t_R 3.70 min (100 area % at 254 nm) Anal. (C_8H_4ClNO) C, H, N, Cl.

General Procedure for Oximes 63b−e,g,h. The aldehydes **44** or **62** were treated with hydroxylamine hydrochloride (1.1 equiv) in aqueous EtOH (for **63b−e**) or EtOH/ pyridine (for **63g,h**). Products were isolated as precipitates filtered from the reaction mixtures (**63b−d**) or by extraction from concentrated reaction mixtures (**63e,g,h**).

4-Cyano-2-nitrobenzaldoxime (63b) was prepared from aldehyde **62b** as a white solid (3.34 g, 90%): mp 162−163 °C; ^{1}H NMR δ 12.34 (s, 1 H), 8.61 (d, J = 1.6 Hz, 1H), 8.43 (s, 1H), 8.19 (dd, J = 8.1 and 1.7 Hz, 1H), 8.06 (d, J = 8.5 Hz, 1H). Anal. ($C_8H_5N_3O_3$) C, H, N.

2-Chloro-4-cyanobenzaldoxime (63c) was prepared from aldehyde **62c** as a white solid (3.32 g, 92%): mp 177−179 °C; ^{1}H NMR δ 12.18 (s, 1H), 8.39 (s, 1H), 8.15 (d, J = 1.5 Hz, 1H), 7.97 (d, J = 8.2 Hz, 1H), 7.83 (dd, J = 8.1 and 1.6 Hz, 1H). Anal. ($C_8H_5ClN_2O_2$) C, H.

4-Cyano-2-methoxybenzaldoxime (63d) was prepared from aldehdye **44f** as a white solid (19.6 g, 95%): mp 170−171 °C; ^{1}H NMR δ 11.73 (s, 1H), 8.29 (s, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.58 (s, 1H), 7.42 (d, J = 8.0 Hz, 1H), 3.89 (s, 3H); HPLC (method B) t_R 3.16 min (100 area % at 265 nm). Anal. ($C_9H_8N_2O_2$) C, H, N.

5-Bromo-2-chlorobenzaldoxime (63e) was prepared from crude aldehyde **62e** as a brown solid (1.52 g, 48%): mp 126−128 °C; ^{1}H NMR δ 11.93 (br s, 1H), 8.30 (s, 1H), 7.90 (d, J = 2.5 Hz, 1H), 7.62 (dd, J = 8.6 and 2.5 Hz, 1H), 7.49 (d, J = 8.6 Hz, 1H); HPLC (method B) t_R 5.47 min (99.0 area % at 230 nm). Anal. ($C_7H_5BrClNO\cdot0.05C_2H_5OH$) C, H, N, Br, Cl.

5-Cyano-2-chlorobenzaldoxime (63g) was prepared from aldehyde **62g** as a solid (3.10 g, 100%): mp 191−193 °C (EtOH); ^{1}H NMR δ 12.06 (s, 1H), 8.35 (s, 1H), 8.16 (d, J = 2.2 Hz, 1H), 7.89 (dd, J = 8.2 and 2.2 Hz, 1H), 7.76 (d, J = 8.2 Hz, 1H); HPLC (method B) t_R 3.69 min (96.0 area % at 230 nm). Anal. ($C_8H_5ClN_2O$) C, H, N, Cl.

5-Cyano-2-methoxybenzaldoxime (63h) was prepared from aldehyde **62h** as a yellow solid (4.92 g, 90%): mp 142−144 °C (EtOAc/hexane); ^{1}H NMR δ 11.61 (s, 1H), 8.25 (s, 1H), 7.96 (d, J = 2.2 Hz, 1H), 7.87 (dd, J = 8.8 and 2.2 Hz, 1H), 7.27 (d, J = 8.8 Hz, 1H), 3.92 (s, 3H); HPLC (Method B) t_R 2.84 min (95.2 area % at 230 nm). Anal. ($C_9H_8N_2O_2\cdot0.1$EtOAc) C, H, N, Cl.

General Procedure for Benzaldehyde Chlorooximes 64. *N*-Chlorosuccinimide (1.1 equiv) was added to a stirred solution of an aldoxime **63** in DMF at 0 °C.[48] The mixture was stirred overnight at 25 °C. The mixture poured into ice−water and extacted into ether or EtOAc. The recovered material was used immediately in the next step without further purification.

4-Cyanobenzaldehye chlorooxime (64a) was prepared from oxime **63a** as a cream colored solid (3.47 g, 96%): mp 146−148 °C; ^{1}H NMR δ 12.89 (s, 1H), 7.96 (s, 4H); HPLC (method B) t_R 3.25 min (100 area % at 254 nm). Anal. ($C_8H_5ClN_2O$) C, H, N, Cl.

4-Cyano-2-nitrobenzaldehye chlorooxime (64b) was prepared as an oily residue (2.96 g, 105% crude): ^{1}H NMR δ 13.09 (s, 1H), 8.66 (d, J = 1.6 Hz, 1H), 8.31 (dd, J = 8.1 and1.6 Hz, 1H), 8.04 (d, J = 8.2 Hz, 1H); HPLC (method B) t_R 3.68 min (100 area % at 265 nm).

2-Chloro-4-cyanobenzaldehye chlorooxime (64c) was prepared as an oily residue (3.11 g, 115% crude): ^{1}H NMR δ 12.85 (s, 1H), 8.25 (d, J = 1.6 Hz, 1H), 7.96 (dd, J = 8.1 and1.6 Hz, 1H), 7.82 (d, J = 8.1 Hz, 1H); HPLC (method B) t_R 4.73 min (100 area % at 265 nm).

4-Cyano-2-methoxybenzaldehye chlorooxime (64d) was prepared as a white solid (2.62 g, 99%): mp > 150 °C (dec); ^{1}H NMR δ 12.51 (s, 1H), 7.66 (d, J = 1.3 Hz, 1H), 7.57 (d, J = 7.7 Hz, 1H), 7.49 (dd, J = 8.1 and 1.6 Hz, 1H), 3.89 (s, 3H); HPLC (method B) t_R 4.27 min (100 area % at 265 nm). Anal. ($C_9H_7ClN_2O_2$) C, H, N.

5-Bromo-2-chlorobenzaldehye chlorooxime (64f) was prepared as white crystals (0.87 g, 69%): mp 80−83 °C; ^{1}H NMR δ 8.21 (d, J = 2.2 Hz, 1H), 7.82 (dd, J = 8.7 and 2.4 Hz, 1H), 7.64 (d, J = 8.8 Hz, 1H); HPLC (method B) t_R 6.53 min (100 area % at 230 nm).

2-Chloro-5-cyanobenzaldehye chlorooxime (64g) was prepared as a white solid (3.69 g, 100%): ^{1}H NMR δ 11.08 (s, 1H), 8.19 (d, J = 1.6 Hz, 1H), 8.03 (dd, J = 8.8 and 1.6 Hz, 1H), 7.85 (d, J = 8.8 Hz, 1H).

5-Cyano-2-methoxybenzaldehye chlorooxime (64h) was prepared as a white solid (3.52 g, 71%): ^{1}H NMR δ 12.46 (s, 1H), 7.98 (dd, J = 8.8 and 1.6 Hz, 1H), 7.89 (d, J = 1.6 Hz, 1H), 7.33 (d, J = 8.8, 1H), 3.92 (s, 3H); HPLC (method B) t_R 3.88 min (89.3 area % at 265 nm).

4-Chloro-3-iodobenzaldoxime (67). A solution of aldehyde **66** (15.0 g, 56.3 mmol) and hydroxylamine hydrochloride (4.86 g, 69.9 mmol) in pyridine (30 mL) and dry EtOH (30 mL) was stirred overnight under Ar. The reaction mixture was concentrated to half-volume and poured into ice−water to afford a white solid (12.1 g, 76%): mp 97−99 °C; ^{1}H NMR δ 11.52 (s, 1H), 8.15 (d, J = 1.6 Hz, 1H), 7.66 (dd, J = 8.2 and 1.6 Hz, 1H), 7.59 (d, J = 8.2, 1H). Anal. (C_7H_5ClINO) C, H, N, Cl, I.

4-Bromo-3-chlorobenzonitrile (68c). Aniline **65** (5.19 g, 26.4 mmol) was added to concentrated HCl maintained below 0 °C. A solution of sodium nitrite (3.67 g, 53.2 mmol) in water (10 mL) was added dropwise such that the temperature of the reaction mixture did not exceed 5 °C. The mixture was maintained for 1 h, then was added to a solution of CuCl (6.55 g, 66.2 mmol) in concentrated HCl (20 mL). Toluene (200 mL) was added, and the biphasic mixture was stirred at 60−80 °C for 1 h. Layers were separated, and the aqueous layer was extracted into toluene to afford a white solid (4.67 g, 82%); mp 80−81 °C (hexane); ^{1}H NMR δ 9.55 (d, J = 1.8 Hz, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.78 (d, J = 8.4 and 1.9 Hz, 1H); HPLC (method B) t_R 3.96 min (100 area % at 265 nm). Anal. (C_7H_3BrClN) C, H, N, Br, Cl.

3-methoxy-4-*O*-trifluoromethylsulfonylbenzonitrile (68d). Triethylamine (15.7 g, 155 mmol) was added to a stirred solution of 4-hdyroxy-3-methoxybenzonitrile (20.0 g, 134 mmol) in dry CH_2Cl_2 maintained below 0 °C. Triflic anhydride (47.4 g, 168 mmol) was added dropwise over 45 min such that the temperature of the reaction mixture did not exceed 5 °C. The reaction mixture was maintained for 1 h, poured into ice−water, and extracted into EtOAc. Column chromatography [hexane/EtOAc (9:1)], afforded

colorless crystals (33.4 g, 89%): mp 51−53 °C (hexanes/EtOAc); ^{1}H NMR δ 7.92 (d, J = 1.9 Hz, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.56 (dd, J = 8.4 and 1.9 Hz, 1H), 3.97 (s, 3H); HPLC (method B) t_R 6.89 min (100 area % at 230 nm). Anal. ($C_9H_6F_3NO_4S$) C, H, N, F, S.

4-Chloro-3-iodobenzonitrile (68f). A mixture of aldoxime **67** (5.65 g, 20.0 mmol) in acetic anhydride (10 mL) was refluxed for 4 h. The reaction mixture was poured into ice−water and stirred for 1 h. The product was filtered off as a light yellow solid (4.79 g, 91%): mp 91−93 °C; ^{1}H NMR δ 8.49 (d, J = 2.2 Hz, 1H), 7.90 (dd, J = 8.2 and 2.2 Hz, 1H), 7.79 (d, J = 8.2 Hz, 1H); HPLC (method B) t_R 6.24 min (91.8 area % at 254 nm). Anal. (C_7H_3ClIN) C, H, N, Cl, I.

General Procedure for Silyl Acetylenes 69b,f,g. CuI (2 mol %) was added to a stirred mixture of an aryl halide **68**, (trimethylsilyl)acetylene (minimum, 1.3 equiv), and $PdCl_2(PPh_3)_2$ (2 mol %) in triethylamine.[52] The mixture was heated at 60 °C until the reaction was complete (ca. 3 h). Salts were filtered off and washed with EtOAc. Combined filtrates were evaporated under reduced pressure, and the residue was purified by column chromatography eluting with hexane/EtOAc. The recovered material was recrystallized as necessary.

3-Nitro-4-[2-(trimethylsilyl)ethynyl]benzonitrile (69b) was prepared from aryl bromide **68b** as an off-white solid (1.61 g, 66%): mp 81−82 °C (toluene/hexane); ^{1}H NMR δ 8.69 (d, J = 1.6 Hz, 1H), 8.20 (dd, J = 8.0 and 1.6 Hz, 1H), 7.94 (d, J = 8.2 Hz, 1H), 0.27 (s, 9H); HPLC (method B) t_R 8.39 min (100 area % at 254 nm). Anal. ($C_{12}H_{12}N_2O_2Si$) C, H, N.

3-Chloro-4[(2-(trimethylsilyl)ethynyl]benzonitrile (69c). A mixture of aryl bromide **68c**, (3.96 g, 18.2 mmol), (trimethylsilyl)-acetylene (1.80 g, 18.23 mmol), PPh_3 (0.24 g, 0.91 mol), $Pd(PPh_3)_4$ (0.11 g, 0.09 mmol), and CuI (0.17g, 0.91 mmol) in piperidine was stirred at 90 °C for 1 h. The reaction mixture was poured into water and extracted into EtOAc. Column chromatography [hexanes/EtOAc (40:1)] gave a white solid (3.24 g, 37%); mp 82−83 °C; ^{1}H NMR δ 8.27 (d, J = 1.9 Hz, 1H), 8.02 (d, J = 8.4 Hz, 1H), 7.78 (dd, J = 8.3 and 1.9 Hz, 1H), 0.27 (s, 9H); HPLC (method B) t_R 9.41 min (100 area % at 265 nm). Anal. ($C_{12}H_{12}ClNSi$) C, H, N, Cl.

4-Chloro-3-[2-(trimethylsilyl)ethynyl]benzonitrile (69f) was prepared from aryl iodide **68f** to give a white solid (3.11 g, 88%): mp 72−73 °C (hexanes); ^{1}H NMR δ 8.12 (d, J = 1.6 Hz, 1H), 7.90 (dd, J = 8.2 and 1.6 Hz, 1H), 7.80 (d, J = 8.2 Hz, 1H), 0.27 (s, 9H); HPLC (method B) t_R 9.35 min (100 area % at 254 nm). Anal. ($C_{12}H_{12}ClNSi$) C, H, N, Cl.

4-Methoxy-3-[(trimethylsilyl)ethynyl]benzonitrile (69g) was prepared from aryl bromide **68g** to give a white solid (8.67 g, 80%): mp 63−64 °C (hexanes); ^{1}H NMR δ 7.87 (d, J = 2.2 Hz, 1H), 7.86 (dd, J = 9.7 and 2.2 Hz, 1H), 7.24 (d, J = 9.7 Hz, 1H), 3.91 (s, 3H), 0.27 (s, 9H); HPLC (method B) t_R 8.31 min (98.1 area % at 254 nm). Anal. ($C_{13}H_{15}NOSi$) C, H, N.

3-Chloro-4-(3-hydroxy-3-methylbut-1-ynyl)benzonitrile (70b). 2-Methyl-3-butyn-2-ol (2.5 equiv) was added to a mixture of an aryl bromide **68c**, K_2CO_3 (2.5 equiv), CuI (4 mol %), PPh_3 (8 mol %), and 10% Pd/C (2 mol %) in 1,2-dimethoxyethane (DME) and water. [53] The biphasic mixture was stirred at reflux under Ar overnight and was then filtered (Celite) and partitioned between water and EtOAc. Column chromatography gave a white solid (4.25 g, 77%): mp 63−65 °C (hexane); ^{1}H NMR δ 8.18 (d, J = 1.5 Hz, 1H), 7.83 (dd, J = 8.1 and 1.6 Hz, 1H), 7.69 (d, J = 8.1 Hz, 1H), 5.68 (s, 1H), 1.50 (s, 6H); HPLC (method B) t_R 5.00 min (100 area % at 265 nm). Anal. ($C_{12}H_{10}ClNO$) C, H, N, Cl.

General Procedure for Butynyl Benzenes 70d−g. Methodology was similar to that employed for **61b,f,g** except that 2-methyl-3-butyn-2-ol (2.5 equiv) was used in place of (trimethylsilyl)-acetylene.

4-(3-Hydroxy-3-methylbut-1-ynyl)-3-methoxy-benzonitrile (70d) was prepared from aryl triflate **68d** to give off-white crystals (19.1 g, 86%): mp 68−70 °C (hexanes/EtOAc); ^{1}H NMR δ 7.54 (d, J = 1.4 Hz, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.40 (dd, J = 7.8 and 1.5 Hz, 1H), 5.55 (s, 1H), 3.87 (s, 3H), 1.46 s, 6H); HPLC (method B) t_R 4.09 min (100 area % at 230 nm). Anal. ($C_{13}H_{13}NO_2 \cdot 0.4H_2O$) C, H.

3-(3-Hydroxy-3-methylbut-1-ynyl)benzonitrile (70e) was prepared from 3-bromobenzonitrile (**68e**) to give a light-brown oil (20.0 g, 100%): ^{1}H NMR δ 7.85 (dd, J = 1.5 and 1.5 Hz, 1H), 7.84 (ddd, J = 7.8, 1.5 and 1.5 Hz, 1H), 7.72 (ddd, J = 7.8, 1.5 and 1.5 Hz, 1H), 7.61 (dd, J = 7.8, and 7.8 Hz, 1H), 5.57 (s, 1H), 1.47 (s, 6H); HPLC (method B) t_R 3.99 min (100 area % at 254 nm). Anal. ($C_{12}H_{11}NO$) C, H, N.

4-Chloro-3-(3-hydroxy-3-methylbut-1-ynyl)benzonitrile (70f) was prepared from aryl iodide **60f** to give off-white crystals (3.40 g, 82%): mp 80−82 °C (hexanes/EtOAc); ^{1}H NMR δ 8.03 (dd, J = 2.0 and 0.7 Hz, 1H), 7.86 (ddd, J = 8.4, 2.0 and 0.7 Hz, 1H), 7.78 (dd, J = 8.4 and 0.7 Hz, 1H), 5.63 (s, 1H), 1.49 (s, 6H); HPLC (method B) t_R 4.86 min (100 area % at 254 nm). Anal. ($C_{12}H_{10}ClNO$) C, H, N, Cl.

3-(3-Hydroxy-3-methylbut-1-ynyl)-4-methoxy-benzonitrile (70g) was prepared from 3-bromo-4-methoxybenzonitrile (**68g**) to give off-white crystals (30.5 g, 99%): mp 63−65 °C (hexanes/EtOAc); ^{1}H NMR δ 7.82 (dd, J = 8.7 and 2.1 Hz, 1H), 7.77 (d, J = 2.1 Hz, 1H), 7.22 (d, J = 8.7 Hz, 1H), 5.51 (s, 1H), 3.90 (s, 3H), 1.46 (s, 6H); HPLC (method B) t_R 3.83 min (100 area % at 254 nm). Anal. ($C_{13}H_{13}NO_2$) C, H, N.

General Procedure for Cyanophenylacetylenes 71. In method A, a solution of a silyl acetylene **69** in CH_3CN maintained at 0 °C was treated with an aqueous solution of a catalytic amount (0.05 to 0.1 equiv) of cesium carbonate. The product precipitated directly or upon dilution of the reaction mixture with water. In method B, a mixture of a protected acetylene **70** and a catalytic amount (0.1 equiv) of sodium hydride (60% dispersion in mineral oil) in toluene was heated at reflux as some of the solvent was distilled off.[53] The reaction mixture was filtered and evaporated, and the crude product was recrystallized from hexane.

4-Ethynyl-3-nitrobenzonitrile (71b) was prepared by method A from **69b**. After 45 min, the reaction mixture was diluted with water to give a white granular solid (1.50 g, 95%): mp 131 °C; ^{1}H NMR δ 8.70 (d, J = 1.6 Hz, 1H), 8.23 (dd, J = 8.2 and 1.6 Hz, 1H), 7.99 (d, J = 8.2 Hz, 1H), 5.13, (s, 1H); HPLC (method B) t_R 4.34 min (100 area % at 254 nm). Anal. ($C_9H_4N_2O_3$) C, H, N.

3-Chloro-4-ethynylbenzonitrile (71c) was prepared by method B from **70c** to give a pale yellow solid (2.96 g, 97%): mp 138−140 °C; ^{1}H NMR δ 8.21 (d, J = 1.5 Hz, 1H), 7.86 (dd, J = 8.3 and 1.5 Hz, 1H), 7.81 (d, J = 8.3 Hz, 1H), 4.99 (s, 1H); HPLC (method B) t_R 5.55 min (100 area % at 254 nm). Anal. (C_9H_4ClN) C, H, N, Cl.

By method A (at 25 °C) from **69c** a white solid (1.82 g, 98.6%) was obtained, identical in physical properties to that above.

4-Ethynyl-3-methoxybenzonitrile (71d) was prepared by method B from **70d** to give, after column chromatography [hexanes/EtOAc (4:1)] white needles (9.62 g, 67%): mp 105−106 °C (hexanes); ^{1}H NMR δ 7.59 (d, J = 7.8 Hz, 1H), 7.57 (d, J = 1.4 Hz, 1H), 7.42 (dd, J = 7.8 and 1.4 Hz, 1H), 4.61 (s, 1H), 3.89 (s, 3H); HPLC (method B) t_R 4.58 min (100 area % at 254 nm). Anal. ($C_{10}H_7NO$) C, H, N.

4-Chloro-3-ethynyl-benzonitrile (71f) was prepared by method A from **69f**. After 5 days, reaction mixture was concentrated. Column chromatography [hexanes/EtOAc (9:1)] afforded a solid (1.07 g, 62%): mp 122−124 °C; ^{1}H NMR δ 8.18 (d, J = 1.6 Hz, 1H), 7.91 (dd, J = 8.2 and 1.6 Hz, 1H), 7.80 (d, J = 8.2 Hz, 1H), 4.83, (s, 1H); HPLC (method B) t_R 5.41 min (100 area % at 254 nm). Anal. (C_9H_4ClN) C, H, N, Cl.

By method B from **70f** (10g, 45.5 mmol) a white solid (6.20 g, 84%) was obtained, identical in physical properties to that above.

3-Ethynyl-4-methoxybenzonitrile (71g) was prepared by method A from **69g.** After 3 days the reaction mixture was concentrated, and the residue was extracted in EtOAc. Column chromatography [hexanes/EtOAc (7:3)] gave a solid (3.52 g, 64%): mp 103−105 °C; ^{1}H NMR δ 7.92 (d, J = 2.2 Hz, 1H), 7.87 (dd, J = 8.8 and 2.2

Hz, 1H), 7.25 (d, $J = 8.8$ Hz, 1H), 4.46 (s, 1H), 3.92 (s, 3H); HPLC (method B) t_R 4.35 min (100 area % at 254 nm). Anal. ($C_{10}H_7NO$) C, H, N.

By method B from **70g**, after column chromatography [hexanes/EtOAc (4:1)] a yellow solid (15.7 g, 72%) was obtained, mp 115−116 °C (hexane/EtOAc); ^{1}H NMR and HPLC identical to that above. Anal. ($C_{10}H_7NO$) C, H, N.

General Procedure for Isoxaole Nitriles 72a-g,k−s. Bis-(tributyltin) oxide (0.5 equiv) was added to a mixture of a benzaldehyde chlorooxime **64** (1 equiv) and a phenylacetylene **71** (minimum 1.2 equiv) in CH_2Cl_2 (or other solvent, if stated).[57, 58] Unless stated otherwise, any undissolved solids went into solution upon addition of the oxide, and product precipitated out of solution as the reaction progressed. The reaction mixture was diluted with ether. The solid was filtered off and was purified by recrystallization from acetonitrile unless stated otherwise.

3-(4-Cyanophenyl)-5-(4-cyano-2-nitrophenyl)isoxazole (72a) was prepared from phenylacetylene **71b** and chlorooxime **64a** as an off-white solid (1.69 g, 67%); mp 280−281 °C; ^{1}H NMR δ 8.78 (d, $J = 1.5$ Hz, 1H), 8.44 (dd, $J = 8.1$ and 1.5 Hz, 1H), 8.20 (d, $J = 8.1$ Hz, 1H), 8.15 (d, $J = 8.2$ Hz, 2H), 8.07 (d, $J = 8.1$ Hz, 2H), 7.88 (s, 1H); HPLC (method B) t_R 6.87 min (97.4 area % at 254 nm). Anal. ($C_{17}H_8N_4O_3$) C, H, N.

3-(4-Cyanophenyl)-5-(2-chloro-4-cyanophenyl)isoxazole (72b) was prepared from phenylacetylene **71c** and chlorooxime **64a** as a white solid (2.10 g, 71%): mp 260−262 °C; ^{1}H NMR δ 8.36 (d, $J = 1.6$ Hz, 1H), 8.22 36 (d, $J = 8.6$ Hz, 2H), 8.18 (d, $J = 8.2$ Hz, 1H), 8.06 (d, $J = 8.6$ Hz, 2H), 8.06 (d, $J = 8.2$ Hz, 1H), 7.98 (s, 1H); HPLC (method B) t_R 7.84 min (96.1 area % at 265 nm). Anal. ($C_{17}H_8ClN_3O$) C, H, N.

3-(4-Cyano-2-nitrophenyl)-5-(4-cyanophenyl)isoxazole (72c) was prepared from phenylacetylene **71a** and chlorooxime **64b** to give, after column chromatography (CH_2Cl_2), a cream colored solid (2.26 g, 57%): mp 264−265 °C (CH_3CN); ^{1}H NMR δ 8.77 (d, $J = 1.5$ Hz, 1H), 8.41 (dd, $J = 8.1$ and 1.6 Hz, 1H), 8.11 (m, 5H), 7.74 (s, 1H); HPLC (method B) t_R 6.81 min (96.1 area % at 265 nm). Anal. ($C_{17}H_8N_4O_3$) C, H, N.

3-(2-Chloro-4-cyanophenyl)-5-(4-cyanophenyl)isoxazole (72d) was from phenylacetylene **71a** and chlorooxime **64c** to give, by recrystallization of the precipitate and column chromatography (CH_2Cl_2) of the filtrate, a white solid (2.15 g, 56%): mp 247−248 °C; ^{1}H NMR δ 8.35 (d, $J = 1.5$ Hz, 1H), 8.17 (d, $J = 8.5$ Hz, 2H), 8.07 (d, $J = 8.7$ Hz, 2H), 8.03 (dd, $J = 8.1$ and 1.5 Hz, 1H), 7.97 (d, $J = 8.0$ Hz, 1H), 7.81 (s, 1H); HPLC (method B) t_R 7.66 min (98.8 area % at 265 nm). Anal. ($C_{17}H_8ClN_3O$) C, H, N.

3-(4-Cyano-2-methoxyphenyl)-5-(4-cyanophenyl)isoxazole (72e) was prepared phenylacetylene **71a** and chlorooxime **64d** to give, after column chromatography (CH_2Cl_2) white crystals (2.99 g, 80%): mp 243−244 °C; ^{1}H NMR δ 8.17 (d, $J = 8.8$ Hz, 2H), 8.05 (d, $J = 8.8$ Hz, 2H), 7.99 (d, $J = 8.0$ Hz, 1H), 7.76 (d, $J = 1.4$ Hz, 1H), 7.73 (s, 1H), 7.57 (dd, $J = 8.0$ and 1.5 Hz, 1H), 4.00 (s, 3H); HPLC (method B) t_R 7.48 min (100 area % at 265 nm). Anal. ($C_{18}H_{11}N_3O_2$) C, H, N.

3,5-Bis(4-cyano-2-methoxyphenyl)isoxazole (72f) was prepared from phenylacetylene **71d** and chlorooxime **64d** (5.28 g, 25.1 mmol). The precipitated product was recrystallized from $CHCl_3$ using a Soxhlet extractor to give a white solid (6.27 g, 76%); mp 347−348 °C; ^{1}H NMR δ 8.09 (d, $J = 8.1$ Hz, 1H), 7.98 (d, $J = 8.0$ Hz, 1H), 7.79 (d, $J = 1.4$ Hz, 1H), 7.76 (d, $J = 1.4$ Hz, 1H), 7.62 (dd, $J = 8.1$ and 1.4 Hz, 1H), 7.56 (dd, $J = 8.0$ and 1.4 Hz, 1H), 7.43 (s, 1H), 4.05 (s, 3H), 3.98 (s, 3H). Anal. ($C_{19}H_{13}N_3O_3$) C, H, N.

3-(3-Cyanophenyl)-5-(4-cyano-2-nitroxyphenyl)isoxazole (72g) was prepared from phenylacetylene **71b** and chlorooxime **64e** in benzene as a yellow solid (0.15 g, 83%): mp 198−199 °C (EtOH); ^{1}H NMR δ 8.78 (d, $J = 1.5$ Hz, 1H), 8.43 (m, 2H), 8.29 (dm, $J = 8.5$ Hz, 1H), 8.19 (d, $J = 8.1$ Hz, 1H), 8.06 (dm, $J = 7.9$ Hz, 1H), 7.86 (s, 1H), 7.80 (t, $J = 7.8$ Hz, 1H); HPLC (method B) t_R 6.95 min (100 area % at 230 nm). Anal. ($C_{17}H_8N_4O_3 \cdot 0.2H_2O$) C, H, N.

3-(3-Cyanophenyl)-5-(2-chloro-4-cyanophenyl)isoxazole (72h). Triethylamine (1.25 g, 12.37 mmol) was added to a mixture of phenylacetylene **71c** (1.00 g, 6.19 mmol) and chlorooxime **64e** (2.00 g, 11.06 mmol) in $CHCl_3$ under N_2 atmosphere.[59] The reaction mixture was stirred at reflux. Following aqueous workup of the reaction mixture, the product was purified by column chromatography ($CHCl_3$) to give a yellow solid (1.01 g, 54%): mp 146−148 °C; ^{1}H NMR δ 8.52 (s, 1H), 8.34 (m, 2H), 8.17 (d, $J = 8.1$ Hz, 1H), 8.04 (m, 2H), 8.00 (s, 1H), 7.76 (t, $J = 7.9$ Hz, 1H); HPLC (method B) t_R 7.94 min (100 area % at 265 nm). Anal. ($C_{17}H_8ClN_3O$) C, H, N.

3-(5-Bromo-2-chlorophenyl)-5-(4-cyanophenyl)isoxazole (72i) was prepared analogously to **72h** from phenylacetylene **71a** and chlorooxime **64e** as a yellow solid (1.78 g, 58%): mp 198−199 °C (EtOH); ^{1}H NMR δ 8.16 (d, $J = 8.8$ Hz, 2H), 8.07 (d, $J = 8.6$ Hz, 2H), 7.97 (d, $J = 2.3$ Hz, 1H), 7.80 (dd, $J = 8.6$ and 2.4 Hz, 1H), 7.78 (s, 1H), 7.66 (d, $J = 8.5$ Hz, 1H); HPLC (method B) t_R 9.05 min (100 area % at 265 nm). Anal. ($C_{16}H_8BrClN_2O$) C, H, N, Br, Cl.

3-(2-Chloro-5-cyanophenyl)-5-(4-cyanophenyl)isoxazole (**72j**) was prepared by the general method for nitriles **50** above from bromoisoxazole **53i** (1.90 g, 5.28 mmol). The crude product was purified by column chromatography ($CHCl_3$). Purified fractions were evaporated. The residue was suspended in ether and filtered off to give a pale yellow solid (0.44 g, 27%); mp 257−259 °C; ^{1}H NMR δ 8.29 (d, $J = 2.1$ Hz, 1H), 8.17 (d, $J = 8.4$ Hz, 2H), 8.08 (m, 3H), 7.95 (d, $J = 8.4$ Hz, 1H), 7.80 (s, 1H); HPLC (method B) t_R 7.55 min (92.3 area % at 265 nm). Anal. ($C_{17}H_8ClN_3O \cdot 0.2H_2O$) C, H, N.

3-(4-Cyanophenyl)-5-(2-chloro-5-cyanophenyl)isoxazole (72k) was prepared from phenylacetylene **71f** and chlorooxime **64a** as a white solid (1.46 g, 32%); mp 207−209 °C; ^{1}H NMR δ 8.46 (d, $J = 1.6$ Hz, 1H), 8.19 (d, $J = 8.2$ Hz, 2H), 8.07 (dd, $J = 8.8$ and 1.6 Hz, 1H), 8.06 (d, $J = 8.2$ Hz, 2H), 7.95 (d, $J = 8.8$ Hz, 1H), 7.90 (s, 1H); HPLC (method B) t_R 7.69 min (98.0 area % at 254 nm). Anal. ($C_{17}H_8ClN_3O$) C, H, N, Cl.

3-(4-Cyano-2-nitrophenyl)-5-(3-cyanophenyl)isoxazole (72l) was prepared from phenylacetylene **71e** and chlorooxime **64b** as a white solid (3.10 g, 69%); mp 235−238 °C; ^{1}H NMR δ 8.77 (d, $J = 1.1$ Hz, 1H), 8.47 (dd, $J = 1.6$ and 1.6 Hz, 1H), 8.41 (dd, $J = 7.7$ and 1.1 Hz, 1H), 8.26 (ddd, $J = 8.2$, 1.6 and 1.6 Hz, 1H), 8.09 (d, $J = 8.2$ Hz, 1H), 8.04 (ddd, $J = 7.7$, 1.6 and 1.6 Hz, 1H), 7.81 (dd, $J = 7.7$ and 7.7 Hz, 1H), 7.68 (s, 1H); HPLC (method B) t_R 6.84 min (96.6 area % at 254 nm). Anal. ($C_{17}H_8N_4O_3$) C, H, N.

3-(2-Chloro-4-cyanophenyl)-5-(3-cyanophenyl)isoxazole (72m) was prepared from phenylacetylene **71e** and chlorooxime **64c** as a white solid (1.16 g, 27%); mp 221−223 °C; ^{1}H NMR δ 8.51 (br s, 1H), 8.33 (br s, 1H), 8.29 (d, $J = 8.2$ Hz, 1H), 8.03 (d, $J = 8.2$ Hz, 1H), 8.01 (s, 1H), 7.97 (d, $J = 7.7$ Hz, 1H), 7.81 (d, $J = 7.7$ Hz, 1H), 7.77 (s, 1H); HPLC (method B) t_R 7.65 min (98.0 area % at 254 nm). Anal. ($C_{17}H_8ClN_3O$) C, H, N, Cl.

3-(4-Cyano-2-methoxyphenyl)-5-(3-cyanophenyl)isoxazole (72n) was prepared from phenylacetylene **71e** and chlorooxime **64d** as a white solid (2.66 g, 88%); mp 202−204 °C; ^{1}H NMR δ 8.46 (br s, 1H), 8.25 (d, $J = 7.7$ Hz, 1H), 7.97 (d, $J = 7.7$ Hz, 2H), 7.76 (dd, $J = 7.7$ and 7.7 Hz, 1H), 7.70 (br s, 1H), 7.66 (br s, 1H), 7.54 (d, $J = 7.7$ Hz, 1H), 3.97 (s, 3H); HPLC (method B) t_R 7.48 min (100 area % at 254 nm). Anal. ($C_{18}H_{11}N_3O_2$) C, H, N.

3-(4-Cyano-2-nitrophenyl)-5-(5-cyano-2-methoxyphenyl)isoxazole (72o) was prepared from phenylacetylene **71g** and chlorooxime **64b** as a white solid (1.44 g, 47%); mp 264−266 °C; ^{1}H NMR δ 8.75 (d, $J = 1.1$ Hz, 1H), 8.38 (dd, $J = 8.2$ and 1.1 Hz, 1H), 8.35 (d, $J = 2.2$ Hz, 1H), 8.15 (d, $J = 8.2$ Hz, 1H), 8.04 (dd, $J = 8.8$ and 2.2 Hz, 1H), 7.47 (d, $J = 8.8$ Hz, 1H), 7.46 (br s, 1H), 4.07 (s, 3H); HPLC (method B) t_R 7.00 min (98.4 area % at 254 nm). Anal. ($C_{18}H_{10}N_4O_4$) C, H, N.

3-(4-Cyano-2-methoxyphenyl)-5-(5-cyano-2-methoxyphenyl)-isoxazole (72p) was from phenylacetylene **71g** and chlorooxime **64d** as a white solid (1.65 g, 76%); mp 271−273 °C; ^{1}H NMR δ 8.29 (br s, 1H), 7.99 (d, $J = 7.7$ Hz, 1H), 7.96 (d, $J = 8.8$ Hz, 1H), 7.71 (br s, 1H), 7.55 (d, $J = 7.7$ Hz, 1H), 7.43 (d, $J = 8.8$ Hz, 1H), 7.34 (br s, 1H), 4.06 (s, 3H), 3.96 (s, 3H); HPLC (method B) t_R 7.58 min (100 area % at 254 nm). Anal. ($C_{19}H_{13}N_3O_3$) C, H, N.

3-(3-Cyanophenyl)-5-(2-chloro-5-cyanophenyl)isoxazole (72q) was prepared from phenylacetylene **71f** and chlorooxime **64e** in benzene. Column chromatography ($CHCl_3$) afforded a yellow solid (1.22 g, 74%): mp 201−203 °C; ^{1}H NMR δ 8.50 (s, 1H), 8.46 (d, J = 1.6 Hz, 1H), 8.33 (d, J = 7.7 Hz, 1H), 8.05 (m, 2H), 7.96 (d, J = 8.2 Hz, 1H), 7.93 (s, 1H), 7.78 (t, J = 7.7 Hz, 1H); HPLC (method B) t_R 7.76 min (100 area % at 254 nm). Anal. ($C_{17}H_8ClN_3O$) C, H, N, Cl.

3-(2-Chloro-5-cyanophenyl)-5-(3-cyanophenyl)isoxazole (72r) was prepared from phenylacetylene **71a** and chlorooxime **64g** in benzene. Column chromatography ($CHCl_3$) afforded a yellow solid (2.10 g, 49%): mp 124−125 °C; ^{1}H NMR δ 8.50 (s, 1H), 8.28 (d, J = 7.7 Hz, 1H), 8.27 (d, J = 1.6 Hz, 1H), 8.07 (dd, J = 8.2 and 1.6 Hz, 1H), 8.03 (d, J = 8.2 Hz, 1H), 7.94 (d, J = 8.2 Hz, 1H), 7.80 (t, J = 7.7 Hz, 1H), 7.75 (s, 1H); HPLC (method B) t_R 7.55 min (98.5 area % at 254 nm). Anal. ($C_{17}H_8ClN_3O$) C, H, N, Cl.

3,5-Bis(5-cyano-2-methoxyphenyl)isoxazole (72s) was prepared from phenylacetylene **71g** and chlorooxime **64h** in benzene. Column chromatography ($CHCl_3$) afforded a yellow solid (4.30 g, 79%): mp 268−270 °C; ^{1}H NMR δ 8.31 (d, J = 1.6 Hz, 1H), 8.18 (d, J = 1.6 Hz, 1H), 8.02 (dd, J = 8.8 and 1.6 Hz, 2H), 7.45 (d, J = 8.8 Hz, 1H), 7.42 (d, J = 8.8 Hz, 1H), 7.34 (s, 1H), 4.07 (s, 3H) 4.00 (s, 3H); HPLC (method B) t_R 7.27 min (100 area % at 254 nm). Anal. ($C_{19}H_{13}N_3O_3$) C, H, N.

3,5-Bis[4-(*N*-hydroxy)amidino-2-methoxyphenyl]isoxazole (73). Potassium *tert*-butoxide (11.2 g, 100 mmol) was added to a solution of hydroxylamine hydrochloride (7.01 g, 101 mmol) in dry DMSO (60 mL). Dinitrile **72f** (3.32 g, 10.0 mmol) was added. The mixture was stirred under Ar for 12 days, with more DMSO (60 mL) added after 6 days. The reaction mixture was filtered, and the filtrate was poured into ice−water to give a white precipitated solid (3.14 g, 79%): mp 203−204 °C; ^{1}H NMR δ 9.87 (br s, 1 H), 9.82 (br s, 1 H), 7.89 (d, J = 8.1 Hz, 1H), 7.79 (d, J = 8.1 Hz, 1H), 7.51 (d, J = 1.3 Hz, 1H), 7.47 (m, 2H), 7.42 (dd, J = 8.1 and 1.5 Hz, 1H), 7.27 (s, 1H), 6.00 (br s, 2 H), 5.98 (br s, 2 H), 4.02 (s, 3H), 3.95 (s, 3H); HPLC (method A) t_R 6.99 min (100 area % at 265 nm). Anal. ($C_{19}H_{19}N_5O_6 \cdot 0.6H_2O$) C, H, N.

3,5-Bis[4-(*N*-acetoxy)amidino-2-methoxyphenyl]isoxazole (74). Acetic anhydride (5 mL) was added to a suspension of diamidoxime **73** (1.00 g, 2.51 mmol) in glacial acetic acid (25 mL). The mixture was stirred overnight, then poured over ice to give a white solid (1.14 g, 94%): mp 238 °C (dec); ^{1}H NMR δ 7.97 (d, J = 8.1 Hz, 1H), 7.87 (d, J = 8.2 Hz, 1H), 7.51 (m, 3H), 7.46 (d, J = 8.1 Hz, 1H), 7.33 (s, 1H), 6.98 (br s, 4H), 4.05 (s, 3H), 3.98 (s, 3H), 2.17 (s, 6H); HPLC (method B) t_R 4.08 min (96.0 area % at 265 nm). Anal. ($C_{23}H_{23}N_5O_7$) C, H, N.

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