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Synthesis and evaluation of trypanocidal activity of derivatives of naturally occurring 2,5-diphenyloxazoles

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ABSTRACT

African trypanosomiasis is a zoonotic protozoan disease affecting the nervous system. Various natural products reportedly exhibit trypanocidal activity. Naturally occurring 2,5-diphenyloxazoles present in *Oxytropis lanata*, and their derivatives, were synthesized. The trypanocidal activities of the synthesized compounds were evaluated against *Trypanosoma brucei brucei*, *T. b. gambiense*, *T. b. rhodesiense*, *T. congolense*, and *T. evansi*. Natural product **1** exhibited trypanocidal activity against all the species/subspecies of trypanosomes, exhibiting half-maximal inhibitory concentrations (IC_{50}) of 1.1–13.5 μM. Modification of the oxazole core improved the trypanocidal activity. The 1,3,4-oxadiazole (**7**) and 2,4-diphenyloxazole (**9**) analogs exhibited potency superior to that of **1**. However, these compounds exhibited cytotoxicity in Madin-Darby bovine kidney cells. The *O*-methylated analog of **1** (**12**) was non-cytotoxic and exhibited selective trypanocidal activity against *T. congolense* (IC_{50} = 0.78 μM). Structure-activity relationship studies of the 2,5-diphenyloxazole analogs revealed aspects of the molecular structure critical for maintaining selective trypanocidal activity against *T. congolense*.

1. Introduction

African trypanosomiasis is a zoonotic protozoan disease caused by infection of a host mammal by trypanosomes. African trypanosomiasis can be classified based on the causative species/subspecies of trypanosome and the host mammals.[1] Human African trypanosomiasis (HAT), also known as sleeping sickness, is a human disease caused by *Trypanosoma brucei rhodesiense* and *T. b. gambiense*.[2] Animal African trypanosomosis (AAT), also known as Nagana, is caused by *T. b. brucei*, *T. congolense*, and *T. vivaxi* affecting domestic and wild animals.[3] AAT caused by *T. congolense* causes the most severe symptoms in infected animals. Surra is a livestock disease caused by *T. evansi*.[4] Dourine is a venereal disease in equine caused by *T. equiperdum*.[5] While HAT and AAT are prevalent only in Sub-Saharan Africa, cases of surra and dourine are seen around the world (surra: North-East Africa, Asia, Latin America; dourine: Africa, Asia, the Middle East, South-East Europe, and South America).

At an early stage of infection, trypanosomes proliferate in the host's bloodstream before crossing the blood-brain barrier and parasitizing the central nervous system and cerebrospinal fluid. During the early stages of parasitism, when the protozoa are present in the blood, non-specific symptoms such as anemia and intermittent fever are observed. As the disease progresses, trypanosomes invade and proliferate within the central nervous system, which causes neurological symptoms including ataxia, paralysis, coma, and eventually death.[2] Since trypanosomes frequently and randomly change the cell surface antigens, it is very difficult to develop a vaccine for the disease, and so far, none have been developed.[6] Treatment with trypanocidal drugs remains the main strategy for disease control. Pentamidine, melarsoprol, eflornithine, suramin, and a combination of nifurtimox and eflornithine are available to treat HAT.[7] In addition, diminazene, quinapyramine, and suramin are used to treat AAT and surra.[3] However, most existing drugs were developed over 50 years ago, and multidrug-resistant strains have emerged as a result of protozoal mutations partly caused by improper drug administration and abuse.[8] Fexinidazole, recently approved for use in the Democratic Republic of Congo, based on positive reviews from the European Medicines Agency, is the first oral drug to treat HAT caused by *T. b. gambiense*.[9] However, fexinidazole and nifurtimox act through similar mechanisms and cross-resistance between them has been reported.[10] Additionally, there has not been any significant progress in the

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development of new drugs for AAT. Therefore, there is a need to design and develop new, structurally diverse anti-trypanosomal drugs with different mechanisms of action and improved safety.

Tremendous efforts have been devoted to discovering naturally occurring compounds with trypanocidal activity and various active skeletons, including flavonoids, xanthones, quinones, alkaloids, sesquiterpenoids, macrocycles, and cyclic peptides, have been isolated.[11] In 2016, Banzragchgarav et al. reported the isolation and structure elucidation of eleven 2,5-diphenyloxazoles from the roots of *Oxytropis lanata,* which is found in Mongolia.[12] Some of these compounds exhibited trypanocidal activity against *T. congolense,* with a half-maximal inhibitory concentration (IC_{50}) of 1.0–14.8 μM (**1**–**5**, Figure 1). The IC_{50} values of these compounds were in the order: **1** > **5** > **3** ≈ **2** > **4**. These results indicate that both the number of hydroxy groups and their position in the phenyl ring are important for trypanocidal activity. Although several naturally occurring 2,5-diaryloxazoles have been isolated,[13–18] some of which are biologically active, **1**–**5** were the first naturally occurring trypanocidal 2,5-diphenyloxazoles to be reported. The synthesis and evaluation of the anti-inflammatory activity of **1** have been reported in the literature.[19] 2,5-Bis[4-*amidinophenyl*]oxazole (**A**) is a synthetic trypanocidal agent,[20] and the trypanocidal activities of 2,5-diaryfurans,[21] 2,4-disubstituted arylthiazoles,[22,23] and 3,5-diarylisoxazoles[24,25] have been investigated. However, the trypanocidal activities of 2,5-diphenyloxazoles possessing hydroxy groups on the phenyl ring have not been investigated. Therefore, **1**–**5** are attractive synthetic scaffolds for the design of new trypanocidal agents.

We designed analogs of compound **1**, the most potent of the five compounds, by modifying the oxazole core (thiazole **6**, 1,3,4-oxadiazole **7**, and 1,3,4-thiadiazole **8**) and changing the position of the hydroxyphenyl substituents (2,4-diphenyloxazole **9**). In this study, we describe the synthesis of various 2,5-diphenyloxazole analogs, including the naturally occurring compounds **1**–**4**, and the evaluation of their biological against various trypanosome species/subspecies, to move toward the discovery of new trypanocidal drug leads.

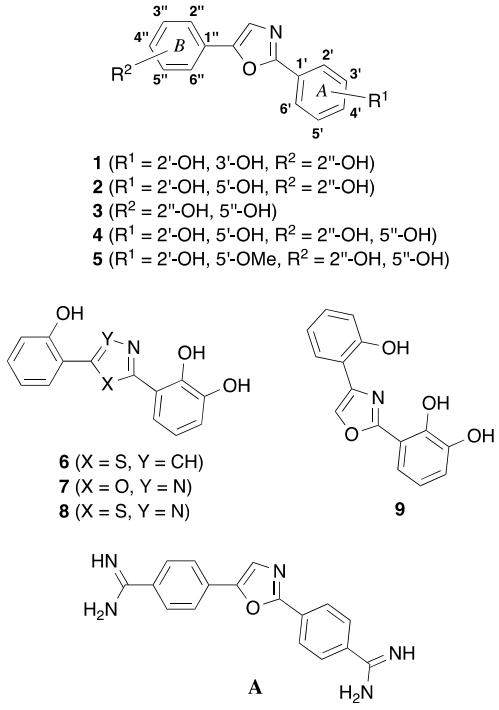


Fig. 1. Structures of naturally occurring 2,5-diphenyloxoazoles **1–5** with trypanocidal activity, compound **1**-analogs **6–9**, and synthetic trypanocidal agent 2,5-bis[4-*amidinophenyl*]oxazole (**A**).

2. Results and discussion

2.1. Chemistry

To date, several methods for the synthesis of 2,5-diaryloxazoles have been developed.[26–34] In 2013, Zhang et al. reported a highly practical method for synthesizing 2,5-diaryloxazoles from bromoketones and benzylamines using an I_2/K_2CO_3 system.[35] This method is noteworthy because the reaction can be performed under metal-free conditions, the reagents used are readily available and inexpensive, and a wide range of functional groups are tolerated. These features make the method suitable for the synthesis of **1**–**4**. The synthesis of compounds **1**–**4** is outlined in Scheme 1. The 2,5-diphenyloxazoles **12**[19]–**15** were synthesized using combinations of commercially available bromoacetophenones **10a**, **10b** and benzylamines **11 a**–**c** under Zhang's condition. The demethylation reaction using BBr_3 in CH_2Cl_2 afforded **1**–**4**; however, these compounds could not be separated from the borane residues at this step. Therefore, **1**–**4** were trapped as acetates **16**–**19**, and pure **1**–**4** were obtained via recrystallization after hydrolysis of the acetyl group using 3 M HCl. The mass spectrometry (MS) and ^1H and ^{13}C nuclear magnetic resonance spectroscopy (NMR) data of **1**–**4** was identical to those of compounds **1**–**4** isolated from natural sources.[12]

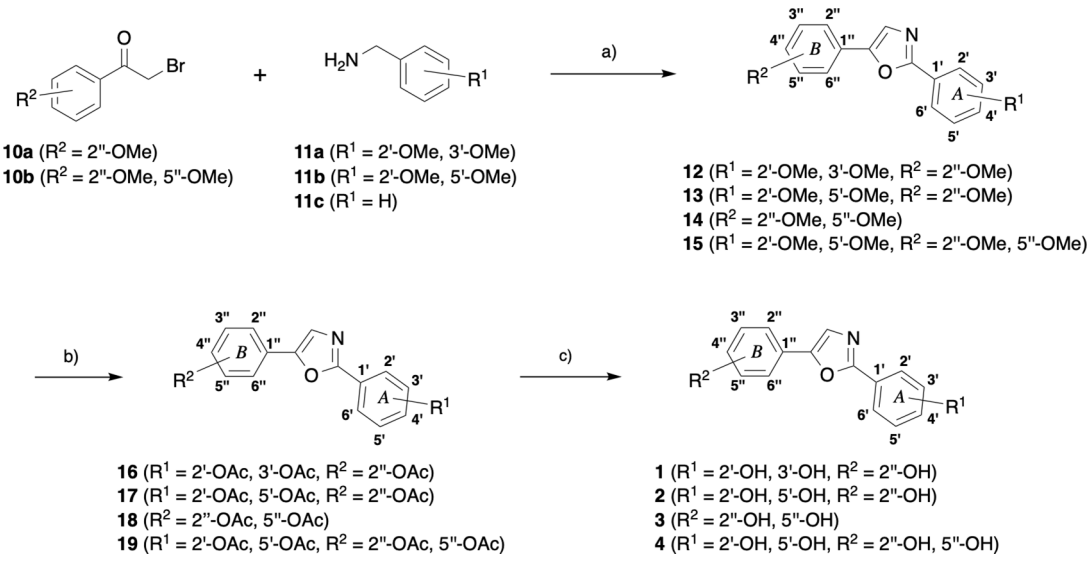
As shown in Scheme 2, heterocyclic analogs **6**–**9** were synthesized using Lawesson's reagent or acid-mediated cyclization reaction. The aminoketone **20** [36] was condensed with the carboxylic acid **21**, using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC·HCl) to afford the amide **22**. 2,5-Oxathiazole **6** was obtained by thionation, followed by cyclization of **22** using Lawesson's reagent,[37,38] and demethylation. 1,3,4-Oxadiazole **7** and 1,3,4-thiadiazole **8** were prepared from the common intermediate **25,** which was synthesized by the condensation of the hydrazide **24** [39] with **21**. Cyclization of **25** using $POCl_3$ afforded **26**, while cyclization of **25** using Lawesson's reagent afforded **27**.[40] Both were converted to the corresponding phenols, **7** and **8**, using BBr_3. Meanwhile, 2,4-diphenyloxazole **9** was synthesized via alkylation of **21** with **10a**, followed by cyclization using $BF_3{\cdot}OEt_2$ in the presence of acetamide,[41] and demethylation.

The initial evaluation of the trypanocidal activity of the synthesized analogs revealed the selective inhibitory activity of **12** against *T. congolense* (see below, Table 1). Therefore, we synthesized analogs **30**–**49** to investigate the effects of the number and position of methoxy groups. The bromoacetophenones **10a** − **l** and benzylamines **11a, b, d-i** were subjected to Zhang's conditions to afford analogs **30**–**49** (Scheme 3). Compounds **30**, **31**, **33**, **34** have been previously reported in the literature.[19,42]

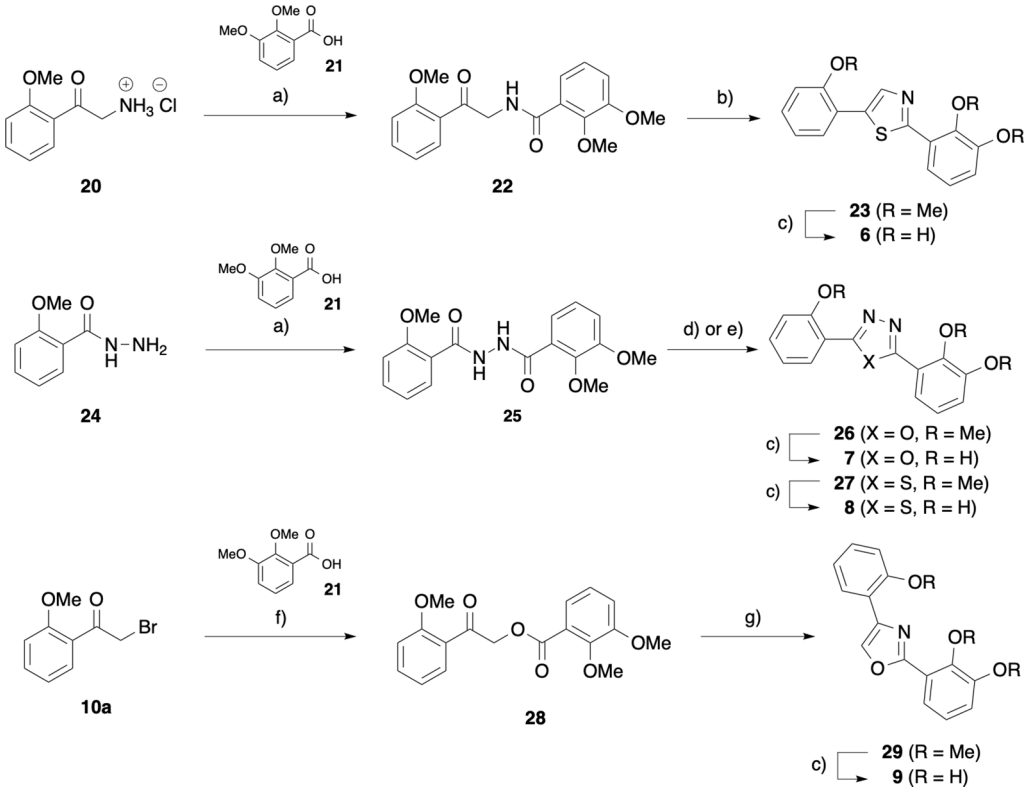
Additionally, the methoxy group at the 2″ position of **12** was modified to assess the steric and electronic effects of substitutions at this position. The benzyl group of **49** was removed by hydrogenolysis to afford **50**, which was then alkylated using alkyl halides, to afford compounds **51**–**53**, possessing alkoxy groups of different sizes at the 2″ position (Scheme 4). Compounds with nitrogen-containing groups substituted at the 2″ position **56**–**59** were also synthesized. The reaction of 2-bromo-2′-nitroacetophenone with **11a** under the same conditions produced a complex mixture and was found to be unsuitable for the synthesis of **56**. Therefore, the oxazole **56** was synthesized by acid-mediated cyclization of the amide **55**, which was obtained from the condensation of **54** [43] with **21**. Reduction of the nitro group in **56** afforded the aniline analog **57**, which was then converted to dimethylaniline **58** and acetamide **59**.

2.2. Biological evaluation

The trypanocidal activity of the synthesized compounds was evaluated against *T. b. brucei*, *T. b. gambiense*, *T. b. rhodesiense*, *T. congolense*, and *T. evansi.* Additionally, preliminary safety was evaluated by assessing the cytotoxic activity against normal Madin-Darby bovine kidney (MDBK) cells. The selectivity index (SI) against each trypanosome species was calculated.[44,45] These results are summarized in



Scheme 1. Synthesis of naturally occurring 2,5-diphenyloxazoles **1–4**. Reagents and conditions: a) I_2, K_2CO_3, *N,N*-dimethylformamide, 60 °C, 18 h, 60–74%. b) 1) BBr_3, CH_2Cl_2, 0 °C, 24 h. 2) acetic anhydride, 4-dimethylaminopyridine, pyridine, r.t., 5 h, 35–90% (2 steps). c) 3 M HCl, tetrahydrofuran, r.t., 3 d, 62–83%. OMe = methoxy, Ac = acetyl.



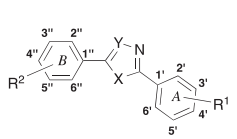
Scheme 2. Synthesis of analogs **6–9.** Reagents and conditions: a) **21**, EDC·HCl, HOBt, triethylamine, CH_2Cl_2, r.t., 12 h, 65% (**22**) or 83% (**25**). b) Lawesson's reagent, tetrahydrofuran, reflux, 3 h, 85%. c) BBr_3, CH_2Cl_2, 0 °C, 20 h, 79% (**6**) or 65% (**7**,8) or 92% (**9**). d) $POCl_3$, CH_3CN, reflux, 24 h, 85% (**26**). e) Lawesson's reagent, toluene, reflux, 2 d, 54% (**27**). f) **21**, DBU, dimethylformamide, 60 °C, 3 h, 82%. g) acetamide, BF_3·OEt_2, xylene, reflux, 2 d, 60%. EDC·HCl = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, HOBt = 1-hydroxybenzotriazole, DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene. Me = methyl.

Table 1.

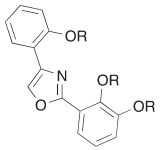
Among the synthesized natural products, compound **1** exhibited the most potent inhibitory activity in all the species/subspecies of trypanosomes against which its activity was evaluated. Similar to the trypanocidal activity against *T. congolense*,[12] these results suggest that the number and positions of the hydroxy groups in 2,5-diphenyloxazole significantly affect the trypanocidal activity of other trypanosome species as well, and the substitutional pattern of **1** is most favorable. Compound **1** showed the highest potency (lowest IC_{50} value) against *T. congolense* (1.1 μM), followed by *T. b. rhodesiense* (2.8 μM), *T. evansi* (4.7 μM), *T. b. brucei* (9.1 μM), and *T. b. gambiense* (13.5 μM). Compounds **2**–**4** also exhibited the lowest IC_{50} values against *T. congolense*. These findings suggest that hydroxy-substituted 2,5-diphenyloxazoles can effectively inhibit the growth of *T. congolense*.

Compounds **6**–**8**, compound **1** analogs with a modified oxazole core, exhibited activity comparable or superior to that of **1**. The 1,3,4-oxadiazole (**7**) exhibited better potency than the thiazole derivative (**6**) and the 1,3,4-thiadiazole derivative (**8**) against all species of trypanosomes and retained preferential inhibitory activity against *T. congolense* (IC_{50} = 0.85 μM). The positional isomer **9** exhibited inhibitory activity against

Table 1
Trypanocidal activities of 2,5-diphenyloxazoles **1–4** and their analogs **6–9, 12–19, 23, 26, 27, 29**.



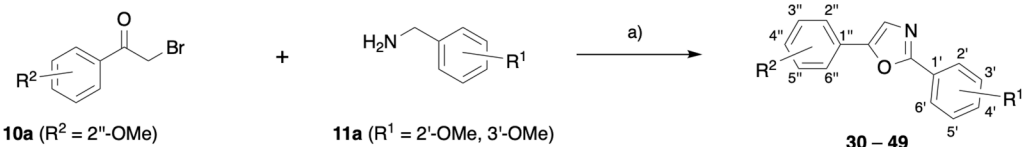
1-8, 12–19, 23, 26, 27



9 (R = H)
29 (R = Me)

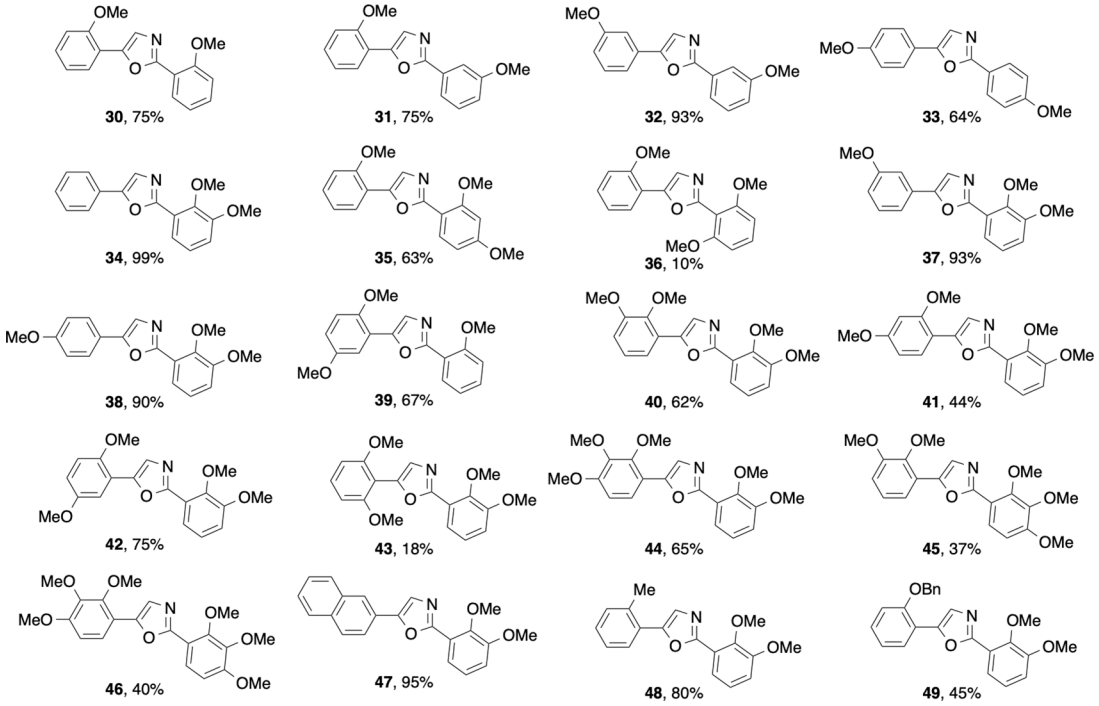
Compound	X	Y	R^1	R^2	Trypanosomes IC_{50} μM[a] ± SD (SI^c) *T. b. brucei*		*T. b. gambiense*		*T. b. rhodesiense*		*T. congolense*		*T. evansi*		Normal cell IC_{50} μM[b] MDBK
1	O	CH	2′, 3′-OH	2″-OH	9.1 ± 2.0	(0.77)	13.5 ± 0.7	(0.52)	2.8 ± 0.7	(2.5)	1.1 ± 0.1	(6.3)	4.7 ± 1.2	(1.5)	7.0 ± 0.8
2	O	CH	2′, 5′-OH	2″-OH	25.9 ± 4.1	(3.0)	80.9 ± 6.6	(0.96)	84.2 ± 0.2	(0.92)	9.5 ± 0.7	(8.2)	22.2 ± 5.3	(3.5)	77.4 ± 10.0
3	O	CH	—	2″, 5″-OH	20.6 ± 2.5	(0.36)	17.8 ± 1.1	(0.42)	18.1 ± 0.1	(0.42)	4.7 ± 0.5	(1.6)	12.2 ± 5.8	(0.61)	7.5 ± 2.9
4	O	CH	2′, 5′-OH	2″, 5″-OH	54.7 ± 22.1	(0.41)	78.3 ± 3.6	(0.29)	72.1 ± 10.4	(0.31)	8.6 ± 6.6	(2.6)	44.4 ± 26.9	(0.51)	22.7 ± 9.0
6	S	CH	2′, 3′-OH	2″-OH	7.7 ± 2.2	(2.6)	8.2 ± 1.7	(2.4)	7.8 ± 2.3	(2.6)	2.3 ± 0.1	(8.8)	4.0 ± 0.6	(5.0)	20.0 ± 0.3
7	O	N	2′, 3′-OH	2″-OH	1.9 ± 0.6	(3.1)	1.9 ± 0.5	(3.1)	1.9 ± 0.6	(3.1)	0.67 ± 0.10	(8.8)	0.81 ± 0.25	(7.2)	5.9 ± 0.6
8	S	N	2′, 3′-OH	2″-OH	3.9 ± 1.0	(3.5)	4.6 ± 0.4	(3.0)	4.4 ± 1.3	(3.1)	0.85 ± 0.19	(16)	2.1 ± 0.7	(6.3)	13.6 ± 0.1
9	See above				1.3 ± 0.6	(7.5)	1.6 ± 1.0	(6.1)	1.5 ± 0.8	(6.4)	0.85 ± 0.44	(11)	0.42 ± 0.07	(23)	9.7 ± 0.6
12	O	CH	2′, 3′-OMe	2″-OMe	> 80.3	ND	> 80.3	ND	> 80.3	ND	0.78 ± 0.27	(>414)	> 80.3	ND	> 321
13	O	CH	2′, 5′-OMe	2″-OMe	> 80.3	ND	> 80.3	ND	> 80.3	ND	> 80.3	ND	> 80.3	ND	> 321
14	O	CH	—	2″, 5″-OMe	> 88.9	ND	> 88.9	ND	> 88.9	ND	15.4 ± 2.9	(>23)	> 88.9	ND	> 355
15	O	CH	2′, 5′-OMe	2″, 5″-OMe	> 73.2	ND	> 73.2	ND	> 73.2	ND	2.9 ± 0.0	(>100)	> 73.2	ND	> 293
16	O	CH	2′, 3′-OAc	2″-OAc	4.6 ± 1.9	(1.2)	6.5 ± 1.1	(0.82)	2.5 ± 1.2	(2.1)	0.80 ± 0.13	(6.6)	5.6 ± 2.8	(0.96)	5.3 ± 0.8
17	O	CH	2′, 5′-OAc	2″-OAc	33.6 ± 19.4	(1.9)	55.3 ± 1.9	(1.2)	56.0 ± 2.7	(1.1)	14.4 ± 2.7	(4.4)	34.0 ± 16.3	(1.9)	64.2 ± 22.2
18	O	CH	—	2″, 5″-OAc	16.6 ± 0.1	(0.58)	41.9 ± 26.1	(0.23)	64.4 ± 4.9	(0.15)	3.9 ± 0.0	(2.4)	18.9 ± 1.8	(0.51)	9.6 ± 6.5
19	O	CH	2′, 5′-OAc	2″, 5″-OAc	35.2 ± 12.1	(0.85)	49.8 ± 2.7	(0.60)	47.4 ± 2.5	(0.63)	16.8 ± 4.4	(1.8)	44.7 ± 2.1	(0.67)	30.0 ± 1.8
23	S	CH	2′, 3′-OMe	2″-OMe	32.0 ± 2.5	(3.6)	31.4 ± 0.6	(3.6)	29.6 ± 5.7	(3.9)	5.7 ± 1.1	(20)	30.9 ± 4.1	(3.7)	114.5 ± 9.3
26	O	N	2′, 3′-OMe	2″-OMe	13.3 ± 4.1	(2.4)	13.3 ± 4.1	(2.4)	13.4 ± 4.3	(2.4)	2.7 ± 0.5	(12)	7.5 ± 2.9	(4.3)	32.3 ± 0.4
27	S	N	2′, 3′-OMe	2″-OMe	29.8 ± 4.3	(>10)	22.1 ± 0.6	(>14)	27.2 ± 7.7	(>11)	3.8 ± 0.9	(>80)	28.1 ± 5.7	(>11)	> 305
29	See above				38.1 ± 0.0	(>8.4)	38.7 ± 0.4	(>8.3)	31.6 ± 7.5	(>10)	9.4 ± 1.0	(>34)	37.9 ± 1.6	(>8.5)	> 321
Suramine[d]	—				0.066 ± 0.005	—	0.064 ± 0.002	—	0.076 ± 0.011	—	7.2 ± 0.9	—	0.38 ± 0.06	—	—
Nifrutimox[d]	—				4.7 ± 2.0	—	4.6 ± 2.4	—	4.4 ± 1.6	—	1.1 ± 0.2	—	2.6 ± 1.4	—	—

[a] Concentration that induces 50% inhibition of trypanosomatids. [b] Concentration that induces 50% inhibition of normal Madin-Darby bovine kidney (MDBK) cells. [c] SI: Selectivity index: IC_{50} in MDBK/IC_{50} in trypanosomatids. [d] Positive control. ND: not determined.

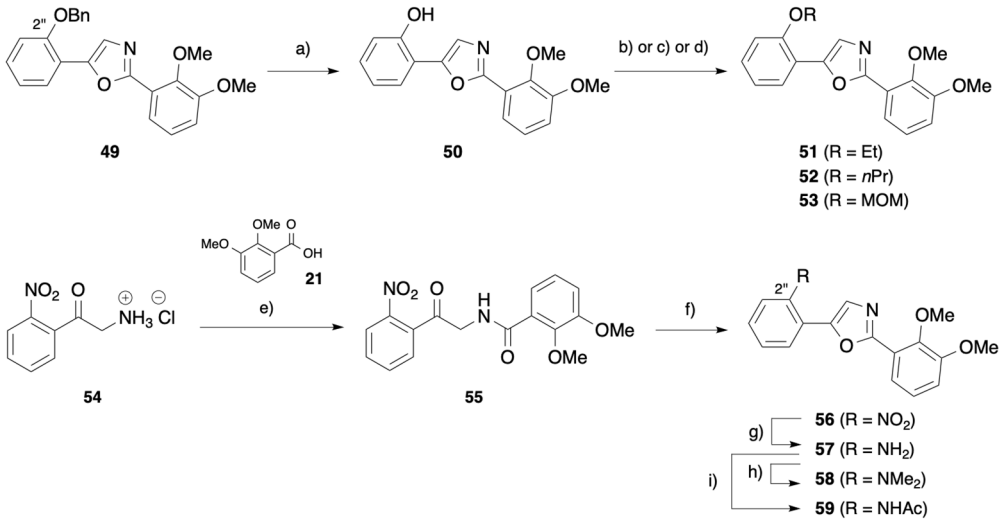


10a (R^2 = 2''-OMe)
10b (R^2 = 2''-OMe, 5''-OMe)
10c (R^2 = 3''-OMe)
10d (R^2 = 4''-OMe)
10e (R^2 = H)
10f (R^2 = 2''-OMe, 3''-OMe)
10g (R^2 = 2''-OMe, 4''-OMe)
10h (R^2 = 2''-OMe, 6''-OMe)
10i (R^2 = 2''-OMe, 3''-OMe, 4''-OMe)
10j (R^2 = 2-naphtyl)
10k (R^2 = 2''-Me)
10l (R^2 = 2''-OBn)

11a (R^1 = 2'-OMe, 3'-OMe)
11b (R^1 = 2'-OMe, 5'-OMe)
11d (R^1 = 2'-OMe)
11e (R^1 = 3'-OMe)
11f (R^1 = 4'-OMe)
11g (R^1 = 2'-OMe, 4'-OMe)
11h (R^1 = 2'-OMe, 6'-OMe)
11i (R^1 = 2'-OMe, 3'-OMe, 4'-OMe)

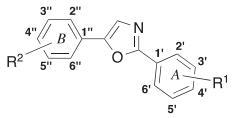


Scheme 3. Syntheses of compounds **30**–**49**. Reagents and conditions: a) I_2, K_2CO_3, dimethylformamide, 60 °C, 18 h. OMe = methoxy.



Scheme 4. Synthesis of the 2″-modified analogs **49**–**59**. Reagents and conditions: a) H_2 (balloon), Pd/C, tetrahydrofuran, r. t., 24 h, 87%. b) ethyl iodide, K_2CO_3, DMF, 60 °C, 2 h, 94% (**51**). c) *n*-propyl iodide, K_2CO_3, DMF, 60 °C, 2 h, 96% (**52**). d) MOMCl, NaH, DMF, r.t., 1 h, 90%. (**53**). e) **21**, EDC·HCl, HOBt, Et_3N, CH_2Cl_2, r.t., 12 h, 62%. f) $POCl_3$, reflux, 3 h, 71%. g) H_2 (balloon), Pd/C, methanol, rt, 1 h, 77%. h) methyl iodide, K_2CO_3, 60 °C, 24 h, 70%. i) AcCl, Et_3N, CH_2Cl_2, 0 °C, 3 h, 87%. Me = methyl, Ac = acetyl, MOM = methoxymethyl, DMF = dimethylformamide, Et_3N = trimethylamine, EDC·HCl = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, HOBt = 1-hydroxybenzotriazole.

Table 2
Trypanocidal activities of 2,5-diphenyloxazoles **30–53, 56–59**.



30-53, 56–59

Compound	R^1	R^2	Trypanosomes IC_{50} μM[a] ± SD (SI[c])										Normal cell IC_{50} μM[b]
			T. b. brucei		*T. b. gambiense*		*T. b. rhodesiense*		*T. congolense*		*T. evansi*		MDBK
30	2′-OMe	2″-OMe	> 88.9	ND	> 88.9	ND	> 88.9	ND	2.8 ± 0.6	(>128)	> 88.9	ND	> 355
31	3′-OMe	2″-OMe	> 88.9	(<1.8)	> 88.9	(<1.8)	> 88.9	(<1.8)	6.7 ± 0.6	(24)	> 88.9	(<1.8)	161.1 ± 0.2
32	3′-OMe	3″-OMe	62.2 ± 5.7	(>5.7)	66.9 ± 15.6	(>5.3)	66.5 ± 1.0	(>5.3)	21.4 ± 5.4	(>17)	53.9 ± 6.7	(>6.6)	> 355
33	4′-OMe	4″-OMe	> 88.9	(ND)	> 88.9	ND	> 88.9	ND	> 88.9	ND	> 88.9	ND	> 355
34	2′, 3′-OMe	—	86.6 ± 1.9	(0.47)	84.7 ± 0.4	(0.48)	84.1 ± 0.0	(0.48)	4.0 ± 0.0	(10)	59.3 ± 20.6	(0.68)	40.6 ± 11.2
35	2′, 4′-OMe	2″-OMe	75.3 ± 1.2	(0.79)	35.8 ± 0.1	(1.7)	59.2 ± 19.7	(1.0)	15.3 ± 1.9	(3.9)	65.1 ± 9.5	(0.91)	59.5 ± 14.6
36	2′, 6′-OMe	2″-OMe	19.7 ± 3.5	(1.9)	24.6 ± 0.3	(1.5)	18.4 ± 1.0	(2.0)	5.3 ± 0.0	(7.1)	21.7 ± 2.2	(1.7)	37.6 ± 5.1
37	2′, 3′-OMe	3″-OMe	76.0 ± 0.4	(1.3)	73.9 ± 0.9	(1.3)	76.1 ± 0.4	(1.3)	10.3 ± 0.3	(9.3)	68.2 ± 12.4	(1.4)	96.3 ± 20.7
38	2′, 3′-OMe	4″-OMe	76.4 ± 0.9	(0.30)	74.5 ± 0.4	(0.31)	77.0 ± 0.9	(0.30)	17.3 ± 1.2	(1.3)	64.5 ± 4.2	(0.35)	22.8 ± 0.5
39	2′-OMe	2″, 5″-OMe	> 80.3	ND	22.2 ± 1.0	(>14)	> 80.3	ND	4.3 ± 0.9	(>75)	> 80.3	ND	> 321
40	2′, 3′-OMe	2″, 3″-OMe	70.0 ± 0.3	(1.3)	69.2 ± 0.9	(1.3)	70.2 ± 0.1	(1.3)	26.4 ± 0.3	(3.4)	65.5 ± 2.8	(1.4)	90.8 ± 3.9
41	2′, 3′-OMe	2″, 4″-OMe	35.4 ± 0.2	(>8.3)	31.2 ± 0.9	(>9.4)	28.7 ± 7.0	(>10)	1.5 ± 0.4	(>190)	28.2 ± 4.5	(>10)	> 293
42	2′, 3′-OMe	2″, 5″-OMe	> 73.2	ND	> 73.2	ND	> 73.2	ND	1.6 ± 0.1	(>188)	> 73.2	ND	> 293
43	2′, 3′-OMe	2″, 6″-OMe	31.6 ± 1.0	(2.9)	25.8 ± 4.7	(3.5)	32.2 ± 0.1	(2.8)	7.7 ± 1.8	(12)	26.6 ± 5.6	(3.4)	91.6 ± 17.6
44	2′, 3′-OMe	2′, 3′, 4″-OMe	64.9 ± 0.1	(1.5)	63.4 ± 0.6	(1.6)	65.0 ± 0.2	(1.5)	23.6 ± 6.9	(4.2)	59.8 ± 3.1	(1.7)	99.1 ± 13.7
45	2′, 3′, 4′-OMe	2″, 3″-OMe	64.1 ± 0.2	(>4.2)	63.1 ± 0.1	(>4.3)	64.5 ± 0.1	(>4.2)	51.3 ± 9.5	(>5.3)	19.9 ± 8.7	(>14)	> 269
46	2′, 3′, 4′-OMe	2″, 3″, 4″-OMe	37.6 ± 15.0	(1.1)	40.5 ± 13.4	(0.98)	31.4 ± 0.8	(1.3)	16.4 ± 2.1	(2.4)	60.4 ± 0.5	(0.66)	39.7 ± 5.1
47	2′, 3′-OMe	2-naphthyl	71.5 ± 2.4	(0.60)	51.7 ± 4.4	(0.83)	71.7 ± 2.4	(0.60)	45.8 ± 1.0	(0.93)	71.2 ± 1.7	(0.60)	42.7 ± 0.2
48	2′, 3′-OMe	2″-Me	39.1 ± 0.1	(1.5)	40.0 ± 0.6	(1.4)	40.0 ± 0.5	(1.4)	3.0 ± 0.5	(19)	36.0 ± 0.7	(1.6)	56.9 ± 13.3
49	2′, 3′-OMe	2″-Obenzyl	15.5 ± 0.3	(6.3)	16.2 ± 0.4	(6.0)	15.8 ± 0.8	(6.2)	7.7 ± 2.3	(13)	16.7 ± 1.3	(5.8)	97.6 ± 48.8
50	2′, 3′-OMe	2″-OH	> 84.1	ND	> 84.1	ND	> 84.1	ND	> 84.1	ND	> 84.1	ND	> 336
51	2′, 3′-OMe	2″-OEt	> 76.8	ND	> 76.8	ND	> 76.8	ND	4.4 ± 0.8	(>69)	> 76.8	ND	> 307
52	2′, 3′-OMe	2″-O*n*Pr	20.3 ± 1.0	(>15)	28.2 ± 7.4	(>10)	27.1 ± 8.8	(>11)	7.6 ± 2.3	(>39)	28.4 ± 6.9	(>10)	> 295
53	2′, 3′-OMe	2″-OMOM	21.5 ± 2.4	(3.8)	19.6 ± 1.1	(4.2)	26.2 ± 7.9	(3.1)	3.9 ± 1.0	(21)	25.8 ± 0.3	(3.2)	82.2 ± 30.3
56	2′, 3′-OMe	2″-NO_2	49.6 ± 2.4	(>6.2)	63.4 ± 11.0	(>4.8)	56.4 ± 18.1	(>5.4)	8.4 ± 1.6	(>36)	49.0 ± 9.8	(>6.3)	> 306
57	2′, 3′-OMe	2″-NH_2	59.8 ± 18.9	(0.80)	46.2 ± 2.3	(1.0)	62.1 ± 20.5	(0.77)	9.1 ± 2.0	(5.2)	105.3 ± 60.7	(0.45)	47.6 ± 21.4
58	2′, 3′-OMe	2″-NMe_2	20.4 ± 0.9	(>15)	35.2 ± 0.9	(>8.8)	23.3 ± 4.6	(>13)	4.6 ± 0.9	(>66)	24.7 ± 0.7	(>12)	> 308
59	2′, 3′-OMe	2″-NHAc	> 73.9	ND	> 73.9	ND	> 73.9	ND	38.2 ± 6.9	(>7.8)	> 73.9	ND	> 296

[a] Concentration that induces 50% inhibition of trypanosomatids. [b] Concentration that induces 50% inhibition of normal Madin-Darby bovine kidney (MDBK) cells. [c] SI: Selectivity index: IC_{50} in MDBK / IC_{50} in trypanosomatids. ND: not determined.

T. congolense, equal to that of **7**. It was twice as active against *T. evansi* (IC_{50} = 0.42 μM) as against *T. congolense*. This indicates that the positions of the phenyl rings in the oxazole scaffold affect the spectrum of trypanocidal activity, and 2,4-diphenyloxazole skeleton may be suitable for developing *T. evansi* inhibitors. However, the potencies of **1**–**9** showed a positive correlation with their cytotoxicity against MDBK cells, and the compounds exhibited low SI values.

Fortunately, this drawback could be overcome by methylating the phenolic hydroxy groups. Compounds **12**–**15,** the methoxy-substituted synthetic precursors of **1**–**4,** exhibited very low cytotoxicity against MDBK cells. However, their trypanocidal activities against most strains were also dramatically reduced, except for the anti-*T. congolense* activities of **12** and **15.** The IC_{50} values of **12** and **15** against *T. congolense* were 0.78 μM and 2.9 μM, respectively, which were 1.4- and 3-fold lower than those of the corresponding OH derivatives, respectively (**1**: IC_{50} = 1.1 μM, **4**: IC_{50} = 8.6 μM). The SI values of **12** and **15** against *T. congolense* were also very high (**12**: SI > 414, **15**: SI > 100). Notably, the IC_{50} and SI values of **12** were comparable to the hit anti-trypanosomiasis activity criteria defined by the World Health Organization: Tropical Disease Research.[46] While the acetate derivatives **16**–**19** exhibited inhibitory profiles similar to those of the corresponding OH derivatives, there were no improvements in their SI values. They might have been converted to the corresponding phenols in culture conditions. On the other hand, the *O*-methylated hetero aromatics **23**, **26**, **27**, and **29** also exhibited reduced cytotoxicity but no improvements in the trypanocidal activities against *T. congolense*, as seen with **12** and **15**. These results suggest that methylation of the phenolic hydroxy group in 2,5-diphenyloxazoles and related compounds reduces the cytotoxicity against MDBK cells, and 2,5-diphenyloxazoles possessing methoxy groups are preferable structure structures that selectively inhibit *T. congolense* with low cellular toxicity.

The unique inhibitory profile of **12** prompted us to evaluate the trypanocidal activities of **30**–**53** and **56**–**59**; the results are summarized in Table 2. Generally, the properties of all the methoxy-substituted 2,5-diphenyloxazoles tested were similar to those of **12**; they exhibited low cytotoxicity and were selective toward *T. congolense*. While none of them were superior to **12**, this work revealed several aspects of the structure–activity relationships (SAR) of the scaffold.

Compounds **30**–**34** are dimethoxy-substituted analogs. Compound **30**, which lacks the 3′-methoxy group present in **12**, exhibited reduced potency compared to **12** but maintained the *T. congolense*-selective activity and high SI value (IC_{50} = 2.8 μM, SI = 128). On the other hand, compound **31**, which lacks the 2′-methoxy group of **12**, exhibited a higher IC_{50} (6.7 μM) and lower SI value (SI = 24). Compounds **32** (3′-OMe, 3″-OMe) and **33** (4′-OMe, 4″-OMe) exhibited much higher IC_{50} values (**32**: 21.4 μM, **33**: 88.9 μM). Meanwhile, compound **34** (2′-OMe, 3′-OMe) exhibited comparable trypanocidal activity to **31** but was less selective (IC_{50} = 4.0 μM, SI = 10). These results suggest that the methoxy groups on the A and B rings neighboring the oxazole core (2′ and 2′ positions) are essential for potent trypanocidal activity and high selectivity. The introduction of additional methoxy groups on the phenyl rings severely impacted the activity against *T. congolense*. Compounds **35**–**46**, possessing various substitutional patterns of three to six methoxy groups exhibited lower inhibitory activities than **12**, although **39** (2′-OMe, 2″,5″-OMe), **41** (2′,3′-OMe, 2″,4″-OMe), and **42** (2′,3′-OMe, 2″,5″-OMe) exhibited acceptable potencies and SI values. Therefore, the 4″ and/or 5″ positions on the B ring appear to tolerate the introduction of additional functional groups or carbon side chains.

The replacement of the 2″-OMe group on the B ring in **12**, with a methyl group, reduced its trypanocidal activity against *T. congolense* (**48**: IC_{50} = 3.0 μM), resulting in an inhibitory profile similar to that of **34** (2″-H). The replacement of the B ring with a 2-naphthyl group significantly reduced the trypanocidal activity of the scaffold (**47**: IC_{50} = 45.8 μM). Therefore, the phenyl ring with an oxygen atom at the 2″ position, as seen in **12**, was considered essential for its high potency and selectivity. However, the 2″–OH derivative (**50**) was found to be inactive. This result was unexpected since both **1** (2′,3′–OH, 2″–OH) and **12** (2′,3′-OMe, 2″-OMe) exhibited potent inhibitory activities. While the reason for this is unclear, one possible explanation is that **1** and **12** may engage with different targets, despite their structural similarity; the 2″-demethylation of **12** may have led to the loss of trypanocidal activity through both modes of action. Additionally, the steric size of the alkoxy group at the 2″ position in **12** also had a significant impact on the activity. The steric sizes were estimated to follow the order methoxy < ethoxy < methoxy-methoxy (OMOM) ≈ *O*-*n*-propyl < *O*-benzyl, while the trypanocidal activity against *T. congolense* was in the order **12** (2″-OMe, IC_{50} = 0.78 μM) > **51** (2″-ethoxy, IC_{50} = 4.4 μM) > **53** (2″-OMOM, IC_{50} = 5.1 μM) > **52** (2″-*O*-*n*-propyl, IC_{50} = 7.6 μM) ≈ **49** (2″-*O*-benzyl, IC_{50} = 7.7 μM). Therefore, the substitution of a small alkoxy group is preferable, suggesting that the 2″-methoxy group may act as a hydrogen bond acceptor and occupy a small hydrophobic pocket, explaining the restricted molecular size. Regarding the influence of the nitrogen-containing functional groups, the 2″-nitro- (**56**) and 2″-amino-substituted (**57**) analogs exhibited comparable anti-*T. congolense* activities, however, the cytotoxicity of **57** was found to be 6-fold higher than that of **56**. Compound **58**, the dimethylated form of **57**, exhibited a 2-fold higher trypanocidal activity and a 12-fold higher SI than **57**. On the other hand, the cytotoxicity of **57** was reduced by acetamidation, but the 2″-acetamide analog **59** also exhibited poor trypanocidal activity. As with the alkoxy group, it appears that small hydrogen bond acceptors are preferable at this position, and the electron density of the B ring does not affect the trypanocidal activity.

As described above, **12** and its analogs selectively inhibited *T. congolense* among the five species/subspecies evaluated, with low cellular toxicity. The mode of action of these compounds, why they are selective for *T. congolense*, and how *T. congolense* recognizes them, remains unclear but transporters or target enzymes specific to *T. congolense* may be responsible for this species-specific activity.

3. Conclusion

A total of 47 analogs of 2,5-diphenyloxazole (41 new compounds and six known compounds) were synthesized, and the trypanocidal activities of the synthesized compounds were evaluated against *T. b. brucei*, *T. b. gambiense*, *T. rhodesiense*, *T. congolense*, and *T. evansi.* Although the naturally occurring compound **1** exhibited high activity against all of these species/subspecies, its high cytotoxicity presented a challenge. The trypanocidal activities were improved by modifying the oxazole core into 1,3,4-oxadiazole and 2,4-diphenyloxazole. The cytotoxicity was reduced by replacing the hydroxy group with a methoxy group. Compound **12** exhibited selective trypanocidal activity against *T. congolense* with high potency and low cytotoxicity (IC_{50} = 0.78 μM, SI = 414). The SAR of **12** was further evaluated, but none of the analogs exhibited improved activity. However, the SAR studies of the 2,5-diphenyloxazole scaffold revealed the following about maintaining selective trypanocidal activity against *T. congolense*: i) the number and positions of methoxy groups in phenyl rings are important, and 2′,3′-OMe and 2″-OMe substituents are favorable for high potency and low cytotoxicity on the mammalian cell line used; and ii) the molecular size of the substituent at the 2″ position affects its trypanocidal activity, and the small methoxy group is most favorable. These findings may be useful in the design and development of new trypanocidal drugs to treat AAT and the design of biological tools to evaluate the species specificity of the molecules toward *T. congolense*. Further structural optimization of 2,5-diphenyloxazole to enhance its trypanocidal activity and investigation of its underlying mode of action are currently underway and will be reported in due course.

4. Experimental

4.1. Chemistry

All reactions involving air- and moisture-sensitive reagents were carried out using oven-dried glassware and standard syringe–septum cap techniques. Routine reaction monitoring was carried out using glass-supported Merck silica gel 60 F_{254} TLC plates. Flash column chromatography was performed on Kanto Chemical Silica Gel 60 N (spherical, neutral 40–50 nm) with the solvents indicated. Commercially available anhydrous solvent, tetrahydrofuran (THF), dichloromethane (CH_2Cl_2) were used. Other all solvents and reagents were used as supplied. ^{1}H and ^{13}C NMR spectroscopy was carried out on a JEOL AL-400 (400 MHz) spectrometer. Chemical shifts are expressed in ppm using Me_4Si ($\delta = 0$) as an internal standard or residual solvent peak [^{1}H NMR, $CDCl_3$ (7.26), acetone-d_6 (2.05), DMSO-d_6 (2.50), CD_3OD (3.31): ^{13}C NMR, $CDCl_3$ (77.2), acetone-d_6 (29.8, 206.3), DMSO-d_6 (39.5), CD_3OD (49.0)]. IR spectral measurements were carried out on a JASCO FT/IR-4100 spectrophotometer. HRMS spectra were measured on a JEOL JMS-700 high-resolution mass spectrometer.

4.1.1. 2-(2′,3′-Dimethoxyphenyl)-5-(2″-methoxyphenyl)oxazole (12)

Iodine (4.87 g, 19 mmol) was added to a stirred solution of 2-bromo-2′-methoxyacetophenone (**10a**) (2.00 g, 8.7 mmol), 2,3-dimethoxybenzylamine (**11a**) (1.6 mL, 11 mmol) and K_2CO_3 (4.83 g, 35 mmol) in DMF (87 mL). The mixture was stirred at 80 °C for 18 h. After cooling to room temperature, the reaction was quenched with 10% aqueous $Na_2S_2O_3$ (30 mL), and the resulting mixture was extracted with Et_2O (3 × 60 mL). The combined extracts were washed with brine (2 × 60 mL), then dried with Na_2SO_4. The mixture was concentrated in vacuo, and the residue was purified by recrystallization (hexane/ $CHCl_3$ 3:1) to give **12** (1.65 g, 60%) as off-white powders. Spectroscopic data for **12** were consistent with those previously reported for this compound.[19] M.p. 153–154 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.92$ (3H, s), 3.99 (3H, s), 4.01 (3H, s), 6.99–7.03 (2H, m), 7.07 (1H, t, $J = 7.6$ Hz), 7.16 (1H, t, $J = 8.0$ Hz), 7.28–7.33 (1H, m), 7.65 (1H, dd, $J = 8.0$, 1.5 Hz), 7.69 (1H, s), 7.90 ppm (1H, dd, $J = 8.0$, 1.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 55.4$, 56.1, 61.2, 110.8, 114.1, 117.4, 120.9, 121.4, 122.2, 124.2, 125.9, 127.5, 128.9, 147.7, 147.8, 153.8, 155.7, 158.3 ppm. FT-IR (KBr): 2940, 1566, 1529, 1493, 1474, 1421, 1344, 1303, 1261, 1185, 1165, 1128, 1082, 1043, 1021, 1002, 942, 837, 790, 750, 726 cm^{-1}. HRMS (EI): calcd for $C_{18}H_{17}NO_4$ 311.1158; found 311.1153. Anal. calcd for $C_{18}H_{17}NO_4$: C 69.44, H 5.50, N 4.50; found C 69.24, H 5.55, N 4.52.

4.1.2. 2-(2′,5′-Dimethoxyphenyl)-5-(2″-methoxyphenyl)oxazole (13)

Compound **13** was synthesized from 2-bromo-2′-methoxyacetophenone (**10a**) (1.00 g, 4.4 mmol), 2,5-dimethoxybenzylamine (**11b**) (0.78 mL, 5.2 mmol) in a manner similar to that described for the synthesis of **12**. Purification by column chromatography (hexane/EtOAc 3:1) gave **13** (1.01 g, 74%) as a pale yellow solid. Recrystallization from hexane/CH_2Cl_2 (2:1) gave an analytical sample of **13** as pale yellow needles. M.p. 85–87 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.85$ (3H, s), 3.96 (3H, s), 3.97 (3H, s), 6.97–6.99 (3H, m), 7.06 (1H, t, $J = 8.0$ Hz), 7.29 (1H, td, $J = 8.0$, 1.5 Hz), 7.60–7.61 (1H, m), 7.69 (1H, s), 7.88 ppm (1H, dd, $J = 8.0$, 1.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 55.4$, 55.8, 56.8, 110.8, 113.9, 114.4, 117.2, 117.27, 117.32, 120.8, 125.9, 127.5, 128.8, 147.3, 152.0, 153.4, 155.7, 158.2 ppm. FT-IR (KBr): 3398, 3005, 2934, 2834, 1568, 1536, 1509, 1459, 1309, 1281, 1258, 1209, 1182, 1161, 1129, 1117, 1054, 1020, 872, 831, 802, 744 cm^{-1}. HRMS (EI): calcd for $C_{18}H_{17}NO_4$ 311.1158; found 311.1145. Anal. calcd for $C_{18}H_{17}NO_4$: C 69.44, H 5.50, N 4.50; found C 69.37, H 5.54, N 4.49.

4.1.3. 2-Phenyl-5-(2″,5″-dimethoxyphenyl)oxazole (14)

Compound **14** was synthesized from 2-bromo-2′,5′-methoxyacetophenone (**10b**) (1.00 g, 3.9 mmol), benzylamine (**11c**) (0.51 mL, 4.6 mmol) in a manner similar to that described for the synthesis of **12**. Purification by recryatallization (hexane/CH_2Cl_2 3:1) gave **14** (810 mg, 74%) as pale yellow needles. M.p. 133–134 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.86$ (3H, s), 3.93 (3H, s), 6.84 (1H, dd, $J = 8.8$, 3.2 Hz), 6.91 (1H, d, $J = 8.8$ Hz), 7.42–7.51 (4H, m), 7.67 (1H, s), 8.10–8.13 ppm (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 55.87$, 55.89, 111.5, 111.9, 113.7, 117.9, 126.3 (2C), 127.5, 128.0, 128.7 (2C), 130.2, 147.6, 150.2, 153.7, 160.0 ppm. FT-IR (KBr): 2955, 2840, 1586, 1571, 1506, 1449, 1343, 1290, 1277, 1240, 1205, 1188, 1133, 1042, 1017, 965, 866, 836, 800, 793, 774, 737, 708 cm^{-1}. HRMS (EI): calcd for $C_{17}H_{15}NO_3$ 281.1052; found 281.1051. Anal. calcd for $C_{18}H_{17}NO_4$: C 72.58, H 5.37, N 4.98; found C 72.55, H 5.43, N 5.02.

4.1.4. 2-(2′,5′-Dimethoxyphenyl)-5-(2″,5″-dimethoxyphenyl)oxazole (15)

Compound **15** was synthesized from 2-bromo-2′,5′-methoxyacetophenone (**10b**) (1.00 g, 3.9 mmol), 2,5-dimethoxybenzylamine (**11b**) (0.65 mL, 4.3 mmol) in a manner similar to that described for the synthesis of **12**. Purification by recrystallization (hexane/CH_2Cl_2 1:1) gave **15** (840 mg, 64%) as pale yellow granules. M.p. 127–129 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.85$ (3H, s), 3.86 (3H, s), 3.94 (3H, s), 3.97 (3H, s), 6.84 (1H, dd, $J = 8.8$, 2.9 Hz), 6.92 (1H, d, $J = 8.8$ Hz), 6.99–7.02 (2H, m), 7.44 (1H, d, $J = 2.9$ Hz), 7.60–7.61 (1H, m), 7.71 ppm (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 55.8$, 55.9, 56.0, 56.9, 111.5, 112.0, 113.8, 113.9, 114.4, 117.2, 117.4, 118.0, 127.8, 147.2, 150.2, 152.0, 153.5, 153.7, 158.3 ppm. FT-IR (KBr): 3408, 3005, 2962, 2835, 1609, 1569, 1509, 1459, 1318, 1278, 1219, 1182, 1118, 1051, 1019, 974, 852, 807, 743 cm^{-1}. HRMS (EI): calcd for $C_{19}H_{19}NO_5$ 341.1263; found 341.1272. Anal. calcd for $C_{18}H_{17}NO_4$: C 66.85, H 5.61, N 4.10; found C 66.73, H 5.66, N 4.11.

4.1.5. 2-(2′,3′-Diacetoxyphenyl)-5-(2″-acetoxyphenyl)oxazole (16)

Boron tribromide (1 M in CH_2Cl_2; 16.1 mL, 16 mmol) was added to a stirred solution of **12** (1.00 g, 3.2 mmol) in CH_2Cl_2 (16 mL) at 0 °C under argon. After 24 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (30 mL), and the resulting mixture was extracted with EtOAc (3 × 60 mL). The combined extracts were washed with brine (2 × 60 mL), then dried with Na_2SO_4. Concentration of the solvent in vacuo afforded 2-(2′,3′-Dihydroxyphenyl)-5-(2″-hydroxyphenyl)oxazole (**1**) (865 mg), which was used for the next reaction without further purification.

Acetic anhydride (1.5 mL, 16 mmol) was added was added to a stirred solution of crude product **1** (862 mg) in pyridine (32 mL) containing 4-dimethylaminopyridine (DMAP) (39.2 mg, 0.32 mmol) at room temperature under argon. After 5 h, the reaction mixture was diluted with Et_2O (200 mL). The organic layer was washed successively with 3 M HCl (2 × 60 mL), saturated aqueous $NaHCO_3$ (2 × 60 mL) and brine (2 × 60 mL), then dried with Na_2SO_4. The mixture was concentrated in vacuo, and the residue was purified by column chromatography (hexane/EtOAc 2:1) to give **16** (611 mg, 48% for 2 steps) as a pale pink solid. Recrystallization from hexane/$CHCl_3$ (3:1) gave an analytical sample of **16** as pale pink needles. M.p. 130–131 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.32$ (3H, s), 2.39 (3H, s), 2.41 (3H, s), 7.21 (1H, dd, $J = 7.8$, 1.5 Hz), 7.30–7.40 (4H, m), 7.46 (1H, s), 7.79 (1H, dd, $J = 7.6$, 1.7 Hz), 8.00 ppm (1H, dd, $J = 7.8$, 1.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 20.6$, 20.8, 21.2, 120.7, 122.0, 123.4, 125.3, 126.2, 126.3, 126.6, 126.8, 126.9, 129.4, 140.2, 143.8, 146.7, 147.2, 157.3, 168.1, 168.5, 168.6 ppm. FT-IR (KBr): 3009, 2927, 1763, 1569, 1530, 1490, 1468, 1444, 1374, 1250, 1212, 1185, 1156, 1137, 1117, 1055, 1014, 949, 907, 858, 827, 796, 754, 727 cm^{-1}. HRMS (EI): calcd for $C_{21}H_{17}NO_7$ 395.1005; found 395.1007. Anal. calcd for $C_{21}H_{17}NO_7$: C 63.80, H 4.33, N 3.54; found C 63.69, H 4.37, N 3.57.

4.1.6. 2-(2′,5′-Diacetoxyphenyl)-5-(2″-acetoxyphenyl)oxazole (17)

Compound **17** was synthesized from **13** (200 mg, 0.64 mmol) in a manner similar to that described for the synthesis of **16**. Purification by column chromatography (hexane/EtOAc 2:1) gave **17** (154 mg, 76% for 2 steps) as a white solid. Recrystallization from hexane/CH_2Cl_2 (3:1)

gave an analytical sample of **17** as colorless powders. M.p. 144–145 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.33 (3H, s), 2.40 (3H, s), 2.41 (3H, s), 7.17–7.26 (3H, m), 7.31–7.40 (2H, m), 7.46 (1H, s), 7.81 (1H, dd, J = 7.3, 2.0 Hz), 7.85 ppm (1H, d, J = 2.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.0, 21.2, 21.3, 120.6, 121.2, 121.9, 123.4, 124.5, 125.0, 126.4, 126.8, 126.9, 129.4, 145.6, 146.7, 147.2, 148.3, 157.0, 168.6, 169.0, 169.7 ppm. FT-IR (KBr): 3422, 2925, 2851, 1763, 1655, 1560, 1543, 1498, 1372, 1220, 1175, 1125, 1051, 1015, 950, 928, 912, 890, 819, 756, 741 cm^{-1}. HRMS (EI): calcd for $C_{21}H_{17}NO_7$ 395.1005; found 395.1011. Anal. calcd for $C_{21}H_{17}NO_7$: C 63.80, H 4.33, N 3.54; found C 63.60, H 4.30, N 3.56.

4.1.7. 2-Phenyl-5-(2″,5″-diacetoxyphenyl)oxazole (18)

Compound **18** was synthesized from **14** (200 mg, 0.71 mmol) in a manner similar to that described for the synthesis of **16**. Purification by column chromatography (hexane/EtOAc 3:1) gave **18** (154 mg, 76% for 2 steps) as a pale yellow solid. Recrystallization from hexane/CH_2Cl_2 (5:1) gave an analytical sample of **18** as pale yellow needles. M.p. 126–127 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.34 (3H, s), 2.41 (3H, s), 7.10 (1H, dd, J = 8.8, 2.4 Hz), 7.23 (1H, d, J = 8.8 Hz), 7.46–7.48 (3H, m), 7.49 (1H, s), 7.60 (1H, d, J = 2.4 Hz), 8.08–8.10 ppm (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.0, 21.3, 119.4, 121.95, 121.98, 124.3, 126.4 (2C), 126.9, 127.3, 128.8 (2C), 130.7, 143.8, 146.2, 148.4, 161.2, 168.5, 169.1 ppm. FT-IR (KBr): 2922, 1762, 1618, 1542, 1498, 1448, 1376, 1342, 1201, 1170, 1142, 1054, 1016, 923, 887, 839, 778, 712 cm^{-1}. HRMS (EI): calcd for $C_{19}H_{15}NO_5$ 337.0950; found 337.0958. Anal. calcd for $C_{19}H_{15}NO_5$: C 67.65, H 4.48, N 4.15; found C 67.55, H 4.50, N 4.16.

4.1.8. 2-(2′,5′-Diacetoxyphenyl)-5-(2″,5″-diacetoxyphenyl)oxazole (19)

Compound **19** was synthesized from **15** (628 mg, 1.8 mmol) in a manner similar to that described for the synthesis of **16** (In the demethylation step, 15 equivalent of Boron Tribromide (27.6 mL, 28 mmol) was used. In the acetylation step, 6 equivalent of acetic anhydride (1.0 mL, 111 mmol) was used). Purification by column chromatography (hexane/$CHCl_3$ 2:1) gave **17** (154 mg, 76% for 2 steps) as a white solid. Recrystallization from hexane/ $CHCl_3$ (3:1) gave an analytical sample of **19** as colorless granules. M.p. 193–195 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.33 (3H, s), 2.34 (3H, s), 2.40 (3H, s), 2.41 (3H, s), 7.11 (1H, dd, J = 9.0, 2.9 Hz), 7.19 (1H, d, J = 9.0 Hz), 7.23–7.26 (3H, m), 7.49 (1H, s), 7.52 (1H, d, J = 2.9 Hz), 7.84 ppm (1H, d, J = 2.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.0 (2C), 21.1, 21.2, 119.6, 121.0, 121.5, 122.0, 122.4, 124.3, 124.7, 125.0, 127.50, 144.0, 145.6, 146.3, 148.30, 148.32, 157.2, 168.4, 169.0, 169.1, 169.7 ppm. FT-IR (KBr): 3504, 3083, 3019, 2940, 1766, 1572, 1500, 1429, 1369, 1208, 1172, 1052, 1015, 924, 891, 837, 783, 748 cm^{-1}. HRMS (EI): calcd for $C_{23}H_{19}NO_9$ 453.1060; found 453.1059. Anal. calcd for $C_{23}H_{19}NO_9$: C 60.93, H 4.22, N 3.09; found C 60.93, H 4.24, N 3.12.

4.1.9. 2-(2′,3′-Dihydroxyphenyl)-5-(2″-hydroxyphenyl)oxazole (1)

3 M aqueous HCl (10 mL) was added to a stirred solution of **16** (488 mg, 1.2 mmol) in THF/MeOH (2:1, 30 mL) at room temperature. After 3 days, the reaction mixture was diluted with water (30 mL), and the resulting mixture was extracted with EtOAc (3 × 60 mL). The combined extracts were washed with brine (2 × 60 mL), then dried with Na_2SO_4. The mixture was concentrated in vacuo, and the residue was purified by recrystallization (hexane/EtOAc 3:1) to give **1** (206 mg, 62%) as colorless powders. Spectroscopic data for **1** were consistent with those previously reported for this compound.[12,19] M.p. 196–197 °C. ^{1}H NMR (400 MHz, acetone-d_6): δ = 6.90 (1H, t, J = 8.0 Hz), 6.99–7.04 (2H, m), 7.07 (1H, dd, J = 7.8, 1.0 Hz), 7.22–7.26 (1H, m), 7.52 (1H, dd, J = 8.0, 1.7 Hz), 7.78 (1H, s), 7.89 ppm (1H, dd, J = 7.8, 1.5 Hz). ^{13}C NMR (100 MHz, acetone- d_6): δ = 111.8, 115.5, 116.7, 117.1, 118.5, 120.5, 120.8, 125.3, 126.5, 130.3, 146.3, 146.7, 148.1, 154.7, 160.6 ppm. FT-IR (KBr): 3588, 3567, 3531, 3483, 3365, 3253, 1499, 1484, 1456, 1427, 1388, 1375, 1281, 1243, 1225, 1152, 1116, 778, 751, 726 cm^{-1}. HRMS (EI): calcd for $C_{15}H_{11}NO_4$ 269.0688; found 269.0689. Anal. calcd for $C_{15}H_{11}NO_4{\cdot}H_2O$: C 62.72, H 4.62, N 4.88; found C 62.60, H 4.62, N 4.88.

4.1.10. 2-(2′,5′-Dihydroxyphenyl)-5-(2″-hydroxyphenyl)oxazole (2)

Compound **2** was synthesized from **17** (51.7 mg, 0.13 mmol) in a manner similar to that described for the synthesis of **1**. Purification by recrystallization (hexane/EtOAc 4:1) gave **2** (25.2 mg, 72%) as colorless powders. Spectroscopic data for **2** were consistent with those previously reported for this compound.[12] M.p. 269–271 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.85–6.90 (2H, m), 6.97 (1H, t, J = 7.6 Hz), 7.01 (1H, d, J = 8.3 Hz), 7.24 (1H, t, J = 7.8 Hz), 7.35 (1H, d, J = 2.4 Hz), 7.72 (1H, s), 7.78 (1H, d, J = 7.8 Hz), 9.22 (1H, s), 10.46 (1H, s), 10.57 ppm (1H, s). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 110.5, 110.9, 114.2, 115.9, 117.6, 119.5, 120.2, 124.5, 125.4, 129.7, 147.0, 149.4, 150.1, 154.1, 158.9 ppm. FT-IR (KBr): 3376, 1655, 1638, 1604, 1572, 1560, 1543, 1508, 1491, 1459, 1448, 1338, 1201, 1159, 1121, 945, 889, 869, 812, 786, 762 cm^{-1}. HRMS (EI): calcd for $C_{15}H_{11}NO_4$ 269.0688; found 269.0700. Anal. calcd for $C_{15}H_{11}NO_4$: C 66.91, H 4.12, N 5.20; found C 66.72, H 4.12, N 5.18.

4.1.11. 2-Phenyl-5-(2″,5″-dihydroxyphenyl)oxazole (3)

Compound **3** was synthesized from **18** (217 mg, 0.64 mmol) in a manner similar to that described for the synthesis of **1**. Purification by recrystallization (acetone) gave **3** (120 mg, 83%) as orange needles. Spectroscopic data for **3** were consistent with those previously reported for this compound.[12] M.p. 292–294 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.63 (1H, dd, J = 8.8, 2.9 Hz), 6.80 (1H, d, J = 8.8 Hz), 7.20 (1H, d, J = 2.9 Hz), 7.50–7.58 (3H, m), 7.61 (1H, s), 8.04–8.06 (2H, m), 8.98 (1H, s), 9.76 ppm (1H, s). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 111.0, 114.5, 116.3, 116.7, 125.7 (2C), 126.7, 127.0, 129.2 (2C), 130.4, 146.8, 148.3, 150.0, 158.7 ppm. FT-IR (KBr): 3245, 3033, 2745, 1520, 1491, 1480, 1446, 1396, 1357, 1282, 1241, 1198, 1135, 1122, 923, 866, 818, 774, 708 cm^{-1}. HRMS (EI): calcd for $C_{15}H_{11}NO_3$ 253.0739; found 253.0745. Anal. calcd for $C_{15}H_{11}NO_3$: C 71.14, H 4.38, N 5.63; found C 70.85, H 4.49, N 5.49.

4.1.12. 2-(2′,5′-Dihydroxyphenyl)-5-(2″,5″-dihydroxyphenyl)oxazole (4)

Compound **4** was synthesized from **19** (59.1 mg, 0.13 mmol) in a manner similar to that described for the synthesis of **1**. Purification by recrystallization (hexane/EtOAc 3:1) gave **4** (23.1 mg, 62%) as pale pink powders. Spectroscopic data for **4** were consistent with those previously reported for this compound.[12] M.p. 276–278 °C. ^{1}H NMR (400 MHz, DMSO- d_6): δ = 6.67 (1H, dd, J = 8.8, 2.4 Hz), 6.82 (1H, d, J = 8.8 Hz), 6.84–6.90 (2H, m), 7.17 (1H, d, J = 2.4 Hz), 7.30 (1H, d, J = 2.4 Hz), 7.68 (1H, s), 9.02 (1H, s), 9.24 (1H, s), 9.85 (1H, s), 10.44 ppm (1H, s). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 110.5, 110.8, 110.9, 114.2, 116.7, 116.8, 117.7, 120.2, 124.5, 146.9, 147.1, 149.4, 150.05, 150.10, 158.7 ppm. FT-IR (KBr): 3335, 1637, 1577, 1543, 1509, 1448, 1407, 1363, 1235, 1209, 1119, 1041, 972, 875, 827, 787, 754 cm^{-1}. HRMS (EI): calcd for $C_{15}H_{11}NO_5$ 285.0637; found 285.0650. Anal. calcd for $C_{15}H_{11}NO_5$: C 63.16, H 3.89, N 4.91; found C 63.02, H 3.85, N 4.85.

4.1.13. 2,3-Dimethoxy-N-(2-(2-methoxyphenyl)-2-oxoethyl)benzamide (22)

Et_3N (3.9 mL, 28 mmol) was added dropwise to a stirred solution of aminoketone **20** (1.88 g, 9.3 mmol) and carboxcylic acid **21** (1.70 g, 9.3 mmol) in CH_2Cl_2 (45 mL) containing EDC·HCl (2.32 g, 12 mmol) and HOBt (1.64 g, 12 mmol) at room temperature under argon. After 12 h, the reaction was quenched with 3 M aqueous HCl (30 mL), and the resulting mixture was extracted with EtOAc (3 × 100 mL). The combined extracts were washed successively with saturated aqueous $NaHCO_3$ (2 × 100 mL) and brine (2 × 100 mL), then dried with Na_2SO_4. The mixture was concentrated in vacuo, and the residue was purified by column chromatography (hexane/EtOAc 1:2) to give **22** (1.98 g, 65%) as a white solid. Recrystallization from hexane/CH_2Cl_2 (3:1) gave an analytical sample of **22** as colorless powders. M.p. 93–94 °C. ^{1}H NMR

(400 MHz, $CDCl_3$): $\delta = 3.92$ (3H, s), 3.99 (3H, s), 4.06 (3H, s), 4.96 (2H, d, $J = 4.4$ Hz), 7.01–7.08 (3H, m), 7.15 (1H, t, $J = 8.0$ Hz), 7.52–7.56 (1H, m), 7.75 (1H, dd, $J = 8.0$, 1.7 Hz), 7.98 (1H, dd, $J = 7.6$, 1.7 Hz), 9.19 ppm (1H, br s). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 51.7$, 55.6, 56.1, 61.5, 111.7, 115.6, 120.8, 122.8, 124.1, 124.7, 126.3, 131.0, 134.8, 148.1, 152.7, 159.7, 165.0, 195.1 ppm. FT-IR (KBr): 3369, 2939, 2837, 1650, 1597, 1577, 1518, 1464, 1437, 1356, 1285, 1264, 1207, 1163, 1059, 1020, 993, 808, 755, 641 cm^{-1}. HRMS (EI): calcd for $C_{18}H_{19}O_5$ 329.1263; found 329.1264. Anal. calcd for $C_{18}H_{19}O_5$: C 65.64, H 5.82, N 4.25; found C 65.61, H 5.83, N 4.25.

4.1.14. 2-(2′,5′-Dimethoxyphenyl)-5-(2″-methoxyphenyl)thiazole (23)

A solution of **22** (100 mg, 0.30 mmol) in THF (6 mL) containing Lawesson's reagent (243 mg, 0.60 mmol) was heated at reflux for 3 h. After cooling to room temperature, concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/EtOAc 1:2) to give **23** (83.4 mg, 85%) as a pale yellow solid. Recrystallization from hexane/CH_2Cl_2 (1:1) gave an analytical sample of **23** as pale yellow needles. M.p. 83–84 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.92$ (3H, s), 3.95 (3H, s), 3.99 (3H, s), 6.96 (1H, dd, $J = 7.8$, 1.5 Hz), 7.00–7.05 (2H, m), 7.16 (1H, t, $J = 7.8$ Hz), 7.31 (1H, td, $J = 7.8$, 1.5 Hz), 7.68 (1H, dd, $J = 7.8$, 1.5 Hz), 7.96 (1H, dd, $J = 7.8$, 1.5 Hz), 8.27 ppm (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 55.5$, 55.9, 60.1, 111.5, 113.0, 119.4, 120.9, 121.0, 124.2, 127.6, 128.7, 129.0, 135.5, 140.1, 146.5, 153.0, 155.7, 161.5 ppm. FT-IR (KBr): 2937, 2835, 1596, 1578, 1514, 1487, 1470, 1432, 1317, 1265, 1249, 1181, 1116, 1094, 1078, 1053, 1010, 994, 844, 788, 747 cm^{-1}. HRMS (EI): calcd for $C_{18}H_{17}NO_3S$ 327.0929; found 327.0932. Anal. calcd for $C_{18}H_{17}NO_3S$: C 66.03, H 5.23, N 4.28; found C 65.91, H 5.23, N 4.27.

4.1.15. 2-(2′,5′-Dihydroxyphenyl)-5-(2″-hydroxyphenyl)thiazole (6)

Boron tribromide (1 M in CH_2Cl_2; 1.6 mL, 1.6 mmol) was added to a stirred solution of **22** (100 mg, 0.31 mmol) in CH_2Cl_2 (3 mL) at 0 °C under argon. After 20 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (3 mL), and the resulting mixture was extracted with EtOAc (3 × 6 mL). The combined extracts were washed with brine (2 × 6 mL), then dried with Na_2SO_4. The mixture was concentrated in vacuo, and the residue was purified by column chromatography (hexane/EtOAc 1:2) to give **6** (68.6 mg, 79%) as a yellow solid. Recrystallization from hexane/CH_2Cl_2 (3:1) gave an analytical sample of **6** as yellow powders. M.p. 180–181 °C. ^{1}H NMR (400 MHz, acetone-d_6): $\delta = 6.78$ (1H, t, $J = 8.0$ Hz), 6.88 (1H, dd, $J = 7.8$, 1.5 Hz), 6.91–6.95 (1H, m), 7.04 (1H, d, $J = 8.3$ Hz), 7.19 (1H, td, $J = 3.9$, 1.5 Hz), 7.21 (1H, td, $J = 3.9$, 1.5 Hz), 7.71 (1H, dd, $J = 7.8$, 1.5 Hz), 8.34 ppm (1H, s). ^{13}C NMR (100 MHz, acetone-d_6): $\delta = 117.2$, 117.5, 117.7, 118.2, 118.7, 120.4, 121.2, 129.0, 130.5, 134.3, 139.0, 146.1, 147.2, 154.4, 168.9 ppm. FT-IR (KBr): 3855, 3751, 3736, 3713, 3691, 3677, 3650, 3630, 3407, 2922, 1603, 1489, 1470, 1352, 1269, 1195, 1162, 1101, 1060, 814, 774, 748, 721 cm^{-1}. HRMS (EI): calcd for $C_{15}H_{11}NO_3S$ 285.0460; found 285.0461. Anal. calcd for $C_{15}H_{11}NO_3S$: C 63.14, H 3.89, N 4.91; found C 63.14, H 3.89, N 4.91.

4.1.16. 2,3-Dimethoxy-N′-(2-methoxybenzoyl)benzohydrazide (25)

Et_3N (3.8 mL, 27 mmol) was added dropwise to a stirred solution of hydrazide **24** (1.50 g, 9.0 mmol) and carboxcylic acid **21** (1.64 g, 9.0 mmol) in CH_2Cl_2 (45 mL) containing EDC·HCl (2.25 g, 12 mmol) and HOBt (1.59 g, 12 mmol) at room temperature under argon. After 12 h, the reaction was quenched with 3 M aqueous HCl (30 mL), and the resulting mixture was extracted with EtOAc (3 × 100 mL). The combined extracts were washed successively with saturated aqueous $NaHCO_3$ (2 × 100 mL) and brine (2 × 100 mL), then dried with Na_2SO_4. The mixture was concentrated in vacuo, and the residue was purified by recrystallization (hexane/EtOAc 1:1) to give **25** (2.47 g, 83%) as colorless needles. M.p. 149 °C. ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 3.85$ (3H, s), 3.85 (3H, s), 3.92 (3H, s), 7.08 (1H, t, $J = 7.6$ Hz), 7.15–7.23 (4H, m), 7.51–7.55 (1H, m), 7.81 (1H, dd, $J = 7.6$, 1.7 Hz), 10.22 (1H, d, $J = 2.9$ Hz), 10.38 ppm (1H, d, $J = 2.9$ Hz). ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 55.96$, 55.98, 61.3, 112.1, 115.4, 120.6, 120.8, 121.0, 124.2, 127.7, 130.6, 133.0, 146.7, 152.6, 157,1, 163.4, 163.8 ppm. FT-IR (KBr): 3855, 3842, 3736, 3691, 3650, 3353 2956 1617, 1571, 1448, 1268, 1184, 1109, 1060, 1015, 978, 962, 877, 817, 760 cm^{-1}. HRMS (EI): calcd for $C_{17}H_{18}N_2O_5$ 330.1216; found 330.1219. Anal. calcd for $C_{17}H_{18}N_2O_5$: C 61.81, H 5.49, N 8.48; found C 61.84, H 5.47, N 8.48.

4.1.17. 2-(2′,5′-Dimethoxyphenyl)-5-(2″-methoxyphenyl)-1,3,4-oxadiazole (26)

A solution of **25** (1.12 g, 3.4 mmol) in MeCN (14 mL) containing phosphoryl chloride (1.4 mL, 15 mmol) was heated at reflux for 24 h. After cooling to room temperature, the reaction mixture was diluted with CH_2Cl_2 (100 mL). The organic layer was washed successively with saturated aqueous $NaHCO_3$ (2 × 30 mL) and brine (2 × 30 mL), then dried with $MgSO_4$. The mixture was concentrated in vacuo, and the residue was purified by recrystallization (hexane/$CHCl_3$ 2:1) to give **26** (805 mg, 85%) as pale red powders. M.p. 117–118 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.93$ (3H, s), 3.99 (3H, s), 4.01 (3H, s), 7.07–7.12 (3H, m), 7.19 (1H, t, $J = 7.8$ Hz), 7.49–7.54 (1H, m), 7.64 (1H, dd, $J = 7.8$, 1.0 Hz), 8.04 ppm (1H, dd, $J = 7.8$, 1.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 55.9$, 56.0, 61.4, 111.9, 113.2, 115.3, 119.0, 120.7, 121.6, 124.5, 130.5, 132.9, 148.0, 153.7, 157.9, 162.9, 163.6 ppm. FT-IR (KBr): 2940, 2843, 1604, 1580, 1534, 1497, 1456, 1366, 1283, 1265, 1234, 1170, 1132, 1086, 1042, 1019, 998, 844, 789, 775, 750, 722 cm^{-1}. HRMS (EI): calcd for $C_{17}H_{16}N_2O_4$ 312.1110; found 312.1102. Anal. calcd for $C_{17}H_{16}N_2O_4$: C 65.38, H 5.16, N 8.97; found C 65.10, H 5.24, N 8.93.

4.1.18. 2-(2′,5′-Dihydroxyphenyl)-5-(2″-hydroxyphenyl)-1,3,4-oxadiazole (7)

Boron tribromide (1 M in CH_2Cl_2; 3.2 mL, 3.2 mmol) was added to a stirred solution of **26** (200 mg, 0.64 mmol) in CH_2Cl_2 (6 mL) at 0 °C under argon. After 20 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL), and the resulting mixture was extracted with EtOAc (3 × 20 mL). The combined extracts were washed with brine (2 × 20 mL), then dried with Na_2SO_4. The mixture was concentrated in vacuo, and the residue was purified by recrystallization (hexane/EtOAc 1:2) to give **7** (112 mg, 65%) as off-white powders. M.p. 201–202 °C. ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 6.87$ (1H, td, $J = 8.0$, 1.0 Hz), 7.02–7.06 (2H, m), 7.10 (1H, d, $J = 8.0$ Hz), 7.32 (1H, d, $J = 8.0$ Hz), 7.47 (1H, td, $J = 8.0$, 1.0 Hz), 7.87 (1H, d, $J = 8.0$ Hz), 9.91 ppm (3H, br s). ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 109.4$, 109.6, 117.1, 118.2, 118.8, 119.8, 119.9, 128.8, 133.5, 145.4, 146.3, 156.4, 162.6, 163.1 ppm. FT-IR (KBr): 3650, 3498, 3185, 1624, 1586, 1542, 1487, 1407, 1231, 1147, 1066, 1043, 1028, 991, 967, 882, 823, 793, 751, 735, 701 cm^{-1}. HRMS (EI): calcd for $C_{14}H_{10}N_2O_4$ 270.0641; found 270.0634. Anal. calcd for $C_{14}H_{10}N_2O_4$: C 62.22, H 3.73, N 10.37; found C 61.96, H 3.77, N 10.28.

4.1.19. 2-(2′,5′-Dimethoxyphenyl)-5-(2″-methoxyphenyl)-1,3,4-thiadiazole (27)

A solution of **25** (400 mg, 1.2 mmol) in toluene (12 mL) containing Lawesson's reagent (785 mg, 1.9 mmol) was heated at reflux for 2 days. After cooling to room temperature, concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/EtOAc 2:1) to give **27** (215 mg, 54%) as a white solid. Recrystallization from hexane/$CHCl_3$ (2:1) gave an analytical sample of **27** as colorless needles. M.p. 150–151 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.94$ (3H, s), 3.98 (3H, s), 4.04 (3H, s), 7.03 (1H, dd, $J = 8.0$, 1.2 Hz), 7.07 (1H, d, $J = 8.0$ Hz), 7.14 (1H, t, $J = 8.0$ Hz), 7.20 (1H, t, $J = 8.0$ Hz), 7.45–7.49 (1H, m), 8.10 (1H, dd, $J = 8.0$, 1.2 Hz), 8.56 ppm (1H, dd, $J = 7.8$, 2.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 55.7$, 56.0, 60.4, 111.3, 114.0, 119.7, 120.0, 121.3, 124.5, 124.9, 128.7, 131.7, 146.4, 152.9, 156.0, 163.0, 163.7 ppm. FT-IR (KBr): 3073, 3005, 2945, 2836, 1921, 1597, 1581, 1471, 1409, 1267, 1160, 1101, 1053, 1013, 975, 885, 844, 786, 761 cm^{-1}. HRMS (EI): calcd for $C_{17}H_{16}N_2O_3S$ 328.0882; found 328.0888. Anal. calcd for $C_{17}H_{16}N_2O_3S$: C 62.18, H 4.91, N 8.53; found

C 62.18, H 4.92, N 8.50.

4.1.20. 2-(2′,5′-Dihydroxyphenyl)-5-(2″-hydroxyphenyl)-1,3,4-thiadiazole (8)

Boron Tribromide (1 M in CH_2Cl_2; 1.5 mL, 1.5 mmol) was added to a stirred solution of **27** (100 mg, 0.30 mmol) in CH_2Cl_2 (3 mL) at 0 °C under argon. After 20 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL), and the resulting mixture was extracted with EtOAc (3 × 10 mL). The combined extracts were washed with brine (2 × 10 mL), then dried with Na_2SO_4. The mixture was concentrated in vacuo, and the residue was purified by column chromatography (hexane/EtOAc 2:1) to give **8** (56.9 mg, 65%) as a yellow solid. Recrystallization from hexane/$CHCl_3$ (5:1) gave an analytical sample of **8** as yellow powders. M.p. 237–238 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.81 (1H, t, J = 7.8 Hz), 6.94 (1H, d, J = 7.8 Hz), 7.00 (1H, t, J = 7.8 Hz), 7.08 (1H, d, J = 7.8 Hz), 7.36–7.41 (1H, m), 7.67 (1H, d, J = 7.8 Hz), 8.24 (1H, d, J = 7.8 Hz), 9.87 (1H, br s), 10.28 (1H, br s), 11.13 ppm (1H, br s). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 109.4, 109.6, 117.1, 118.2, 118.8, 119.8, 119.9, 128.8, 133.5, 145.4, 146.3, 156.4, 162.6, 163.1 ppm. FT-IR (KBr): 3397, 1617, 1593, 1576, 1559, 1503, 1478, 1456, 1362, 1259, 1160, 1132, 1091, 1066, 973, 949, 878, 820, 788, 756, 739, 727 cm^{-1}. HRMS (EI): calcd for $C_{14}H_{10}N_2O_3S$ 286.0412; found 286.0411. Anal. calcd for $C_{14}H_{10}N_2O_3S$: C 58.73, H 3.52, N 9.78; found C 58.61, H 3.54, N 9.75.

4.1.21. 2-(2-Methoxyphenyl)-2-oxoethyl 2,3-dimethoxybenzoate (28)

DBU (1.6 mL, 11 mmol) was added dropwise to a stirred solution of 2-bromo-2′-methoxyacetophenone (**10a**) (2.00 g, 8.7 mmol) and carboxylic acid **21** (1.65 g, 9.1 mmol) in DMF (44 mL) at room temperature under argon, and the resulting mixture was stirred at 60 °C for 3 h. The reaction was quenched with water (20 mL), and the resulting mixture was extracted with Et_2O (3 × 20 mL). The combined extracts were washed with brine (2 × 20 mL), then dried with Na_2SO_4. The mixture was concentrated in vacuo, and the residue was purified by column chromatography (hexane/EtOAc 1:1) to give **28** (2.36 g, 82%) as a white solid. Recrystallization from hexane/CH_2Cl_2 (5:1) gave an analytical sample of **28** as colorless powders. M.p. 107–108 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.88 (3H, s), 3.93 (3H, s), 3.96 (3H, s), 5.47 (2H, s), 7.00 (1H, d, J = 8.3 Hz), 7.03–7.13 (3H, m), 7.50–7.55 (2H, m), 7.96 ppm (1H, dd, J = 7.8, 2.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.5, 56.0, 61.6, 70.4, 111.5, 116.0, 121.0, 122.7, 123.8, 124.4, 125.7, 131.0, 134.8, 149.3, 153.4, 159.5, 165.6, 192.9 ppm. FT-IR (KBr): 3369, 2939, 2837, 1650, 1597, 1577, 1518, 1464, 1437, 1356, 1285, 1264, 1207, 1163, 1059, 1020, 993, 808, 755, 641 cm^{-1}. HRMS (EI): calcd for $C_{18}H_{18}O_6$ 330.1103; found 330.1104. Anal. calcd for $C_{18}H_{18}O_6$: C 65.45, H 5.49; found C 65.45, H 5.45.

4.1.22. 2-(2′,3′-Dimethoxyphenyl)-4-(2″-methoxyphenyl)oxazole (29)

$BF_3{\cdot}OEt_2$ (1.1 mL, 8.6 mmol) was added to a stirred solution of **28** (2.36 g, 7.1 mmol) in xylene (36 mL) containing acetamide (2.11 g, 36 mmol) at room temperature under argon, and the resulting mixture was heated at reflux for 2 days. After cooling to room temperature, the reaction was quenched with water (20 mL), and the resulting mixture was extracted with EtOAc (3 × 20 mL). The combined extracts were washed with brine (2 × 20 mL), then dried with Na_2SO_4. The mixture was concentrated in vacuo, and the residue was purified by column chromatography (hexane/EtOAc 4:1) to give **29** (1.35 g, 60%) as a white solid. Recrystallization from hexane/CH_2Cl_2 (5:1) gave an analytical sample of **29** as colorless powders. M.p. 107–108 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.92 (3H, s), 3.98 (6H, s), 6.98 (1H, d, J = 8.0 Hz), 7.02 (1H, dd, J = 8.0, 1.5 Hz), 7.09 (1H, td, J = 8.0, 1.0 Hz), 7.15 (1H, t, J = 8.0 Hz), 7.28–7.32 (1H, m), 7.64 (1H, dd, J = 8.0, 1.5 Hz), 8.27–8.29 ppm (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.3, 56.1, 61.4, 110.4, 114.2, 120.2, 120.8, 121.8, 122.4, 124.2, 128.0, 128.4, 136.9, 137.4, 147.9, 153.7, 156.4, 158.7 ppm. FT-IR (KBr): 3000, 2941, 1565, 1492, 1311, 1264, 1244, 1167, 1128, 1099, 1064, 1034, 997, 939, 837, 793, 754, 725 cm^{-1}. HRMS (EI): calcd for $C_{18}H_{17}NO_4$ 311.1158; found 311.1149. Anal. calcd for $C_{18}H_{17}NO_4$: C 69.44, H 5.50, N 4.50; found C 69.31, H 5.60, N 4.50.

4.1.23. 2-(2′,3′-Dihydroxyphenyl)-4-(2″-hydroxyphenyl)oxazole (9)

Boron tribromide (1 M in CH_2Cl_2; 22 mL, 22 mmol) was added to a stirred solution of **29** (1.35 g, 4.3 mmol) in CH_2Cl_2 (22 mL) at 0 °C under argon. After 20 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (40 mL), and the resulting mixture was extracted with EtOAc (3 × 50 mL). The combined extracts were washed with brine (2 × 50 mL), then dried with Na_2SO_4. The mixture was concentrated in vacuo, and the residue was purified by column chromatography (hexane/EtOAc 2:1) to give **9** (1.07 g, 92%) as a white solid. Recrystallization from hexane/EtOAc (3:1) gave an analytical sample of **9** as yellow powders. M.p. 203–204 °C. ^{1}H NMR (400 MHz, CD_3OD): δ = 6.84 (1H, t, J = 8.0 Hz), 6.92–6.98 (3H, m), 7.18 (1H, td, J = 7.8, 1.5 Hz), 7.39 (1H, dd, J = 7.8, 1.5 Hz), 7.94 (1H, dd, J = 7.8, 1.5 Hz), 8.37 ppm (1H, s). ^{13}C NMR (100 MHz, CD_3OD): δ = 112.4, 116.4, 117.6, 118.3, 119.0, 120.6, 120.7, 128.1, 130.0, 137.2, 137.4, 146.9, 147.1, 156.3, 161.8 ppm. FT-IR (KBr): 3855, 3752, 3736, 3712, 3691, 3677, 3650, 3630, 3418, 1618, 1580, 1471, 1436, 1277, 1226, 1159, 1117, 1068, 814, 720 cm^{-1}. HRMS (EI): calcd for $C_{15}H_{11}NO_4$ 269.0688; found 269.0688. Anal. calcd for $C_{15}H_{11}NO_4$: C 66.91, H 4.12, N 5.20; found C 66.87, H 4.27, N 5.12.

4.1.24. 2-(2′-Methoxyphenyl)-5-(2″-methoxyphenyl)oxazole (30)

Compound **30** was synthesized from 2-bromo-2′-methoxyacetophenone (**10a**) (1.00 g, 4.4 mmol), 2-methoxybenzylamine (**11d**) (0.67 mL, 5.2 mmol) in a manner similar to that described for the synthesis of **12**. Purification by column chromatography (hexane/EtOAc 2:1) gave **30** (920 mg, 75%) as a white solid. Recrystallization from hexane/CH_2Cl_2 (4:1) gave an analytical sample of **30** as white powders. Spectroscopic data for **30** were consistent with those previously reported for this compound.[19] M.p. 117–119 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.99 (3H, s), 4.01 (3H, s), 7.00 (1H, d, J = 8.3 Hz), 7.05–7.09 (3H, m), 7.30 (1H, td, J = 7.8, 1.5 Hz), 7.43 (1H, td, J = 7.8, 1.5 Hz), 7.69 (1H, s), 7.89 (1H, dd, J = 7.8, 1.5 Hz), 8.06 ppm (1H, dd, J = 7.8, 1.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.5, 56.1, 110.9, 112.0, 116.7, 117.5, 120.6, 120.8, 125.9, 127.6, 128.8, 130.1, 131.4, 147.2, 155.7, 157.6, 158.4 ppm. FT-IR (KBr): 3398, 2967, 2838, 1603, 1563, 1496, 1451, 1429, 1282, 1260, 1189, 1159, 1110, 1059, 1022, 953, 828, 759, 740, 703 cm^{-1}. HRMS (EI): calcd for $C_{17}H_{15}NO_3$ 281.1052; found 281.1059. Anal. calcd for $C_{17}H_{15}NO_3$: C 72.59, H 5.37, N 4.98; found C 72.45, H 5.43, N 4.98.

4.1.25. 2-(3′-Methoxyphenyl)-5-(2″-methoxyphenyl)oxazole (31)

Compound **31** was synthesized from 2-bromo-2′-methoxyacetophenone (**10a**) (1.00 g, 4.4 mmol), 3-methoxybenzylamine (**11e**) (0.67 mL, 5.2 mmol) in a manner similar to that described for the synthesis of **12**. Purification by column chromatography (hexane/EtOAc 3:1) gave **31** (924 mg, 75%) as a pale yellow solid. Recrystallization from hexane/CH_2Cl_2 (2:1) gave an analytical sample of **31** as pale yellow needles. Spectroscopic data for **31** were consistent with those previously reported for this compound.[19] M.p. 128–129 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.90 (3H, s), 3.98 (3H, s), 6.99–7.01 (2H, m), 7.08 (1H, t, J = 7.8 Hz), 7.31 (1H, t, J = 7.8 Hz), 7.39 (1H, t, J = 7.8 Hz), 7.65–7.66 (2H, m), 7.72 (1H, d, J = 7.8 Hz), 7.89 ppm (1H, d, J = 7.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.4 (2C), 110.86, 110.91, 116.6, 117.2, 118.8, 120.8, 125.8, 127.6, 128.8, 129.0, 129.9, 147.8, 155.7, 159.85, 159.89 ppm. FT-IR (KBr): 2961, 2838, 1616, 1568, 1540, 1492, 1454, 1347, 1285, 1250, 1214, 1188, 1123, 1043, 1017, 940, 869, 836, 780, 749, 724 cm^{-1}. HRMS (EI): calcd for $C_{17}H_{15}NO_3$ 281.1052; found 281.1052. Anal. calcd for $C_{17}H_{15}NO_3$: C 72.59, H 5.37, N 4.98; found C 72.58, H 5.48, N 4.95.

4.1.26. 2-(3′-Methoxyphenyl)-5-(3″-methoxyphenyl)oxazole (32)

Compound **32** was synthesized from 2-bromo-3′-

methoxyacetophenone (**10c**) (1.00 g, 4.4 mmol), 3-methoxybenzylamine (**11f**) (0.68 mL, 5.2 mmol) in a manner similar to that described for the synthesis of **12**. Purification by column chromatography (benzene/EtOAc 6:1) gave **32** (1.14 g, 93%) as a pale yellow solid. Recrystallization from hexane/CH_2Cl_2 (8:1) gave an analytical sample of **32** as pale yellow columnar crystals. M.p. 78–79 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.87 (3H, s), 3.89 (3H, s), 6.89 (1H, ddd, J = 8.0, 2.4, 1.2 Hz), 7.01 (1H, ddd, J = 8.0, 2.4, 1.2 Hz), 7.24 (1H, dd, J = 2.4, 1.2 Hz), 7.30 (1H, dt, J = 8.0, 1.2 Hz), 7.35 (1H, t, J = 8.0 Hz), 7.39 (1H, t, J = 8.0 Hz), 7.43 (1H, s), 7.63 (1H, dd, J = 2.4, 1.2 Hz), 7.70 ppm (1H, dt, J = 7.8, 1.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.3, 55.4, 109.7, 110.9, 114.0, 116.7, 116.8, 118.7, 123.7, 128.6, 129.2, 129.9, 130.0, 151.1, 159.9, 160.0, 161.0 ppm. FT-IR (KBr): 3000, 2955, 2836, 1608, 1587, 1542, 1489, 1346, 1314, 1286, 1227, 1164, 1134, 1088, 1045, 994, 972, 865, 851, 775, 726 cm^{-1}. HRMS (EI): calcd for $C_{17}H_{15}NO_3$ 281.1052; found 281.1061. Anal. calcd for $C_{17}H_{15}NO_3$: C 72.59, H 5.37, N 4.98; found C 72.57, H 5.48, N 5.04.

4.1.27. 2-(4′-Methoxyphenyl)-5-(4″-methoxyphenyl)oxazole (33)

Compound **33** was synthesized from 2-bromo-4′-methoxyacetophenone (**10d**) (1.00 g, 4.4 mmol), 4-methoxybenzylamine (**11f**) (0.68 mL, 5.2 mmol) in a manner similar to that described for the synthesis of **12**. Purification by recrystallization (benzene/CH_2Cl_2 4:1) gave **33** (787 mg, 64%) as yellow plates. Spectroscopic data for **33** were consistent with those previously reported for this compound.[42] M.p. 136–138 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.85 (3H, s), 3.87 (3H, s), 6.95–7.00 (4H, m), 7.28 (1H, s), 7.61–7.65 (2H, m), 8.01–8.04 ppm (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.33, 55.35, 114.2 (2C), 114.3 (2C), 120.4, 121.0, 121.7, 125.6 (2C), 127.8 (2C), 150.7, 159.6, 160.6, 161.2 ppm. FT-IR (KBr): 2938, 2839, 1615, 1589, 1560, 1492, 1442, 1419, 1339, 1306, 1290, 1250, 1173, 1105, 1056, 1022, 950, 831, 740, 703 cm^{-1}. HRMS (EI): calcd for $C_{17}H_{15}NO_3$ 281.1052; found 281.1051. Anal. calcd for $C_{17}H_{15}NO_3$: C 72.59, H 5.37, N 4.98; found C 72.38, H 5.47, N 5.07.

4.1.28. 2-(2′,3′-Dimethoxyphenyl)-5-phenyloxazole (34)

Compound **34** was synthesized from 2-bromo-acetophenone (**10e**) (500 mg, 2.5 mmol), 2,3-dimethoxybenzylamine (**11a**) (0.45 mL, 3.0 mmol) in a manner similar to that described for the synthesis of **12**. Purification by column chromatography (hexane/EtOAc 3:1) gave **34** (633 mg, 99%) as a yellow solid. Recrystallization from hexane/Et_2O (10:1) gave an analytical sample of **34** as yellow columnar crystals. Spectroscopic data for **34** were consistent with those previously reported for this compound.[19] M.p. 61–62 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.90 (3H, s), 4.01 (3H, s), 7.01 (1H, dd, J = 8.0, 1.5 Hz), 7.15 (1H, td, J = 8.0, 5.4 Hz), 7.30–734 (1H, m), 7.42 (2H, t, J = 8.0 Hz), 7.49 (1H, s), 7.63 (1H, dd, J = 8.0, 1.5 Hz), 7.72 ppm (2H, d, J = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.0, 61.1, 114.2, 121.2, 121.9, 123.2, 124.1, 124.2 (2C), 128.0, 128.3, 128.8 (2C), 147.6, 151.1, 153.7, 159.3 ppm. FT-IR (KBr): 3000, 2936, 2836, 1583, 1530, 1480, 1424, 1347, 1313, 1264, 1235, 1173, 1131, 1086, 1045, 1005, 965, 942, 844, 790, 763, 748, 728 cm^{-1}. HRMS (EI): calcd for $C_{17}H_{15}NO_3$ 281.1052; found 281.1051. Anal. calcd for $C_{17}H_{15}NO_3$: C 72.59, H 5.37, N 4.98; found C 72.69, H 5.46, N 5.06.

4.1.29. 2-(2′,4′-Dimethoxyphenyl)-5-(2″-methoxyphenyl)oxazole (35)

Compound **35** was synthesized from 2-bromo-2′-methoxyacetophenone (**10a**) (1.00 g, 4.4 mmol), 2,4-dimethoxybenzylamine (**11 g**) (0.79 mL, 5.2 mmol) in a manner similar to that described for the synthesis of **12**. Purification by column chromatography (hexane/EtOAc 1:1) gave **35** (859 mg, 63%) as a pale yellow solid. Recrystallization from hexane/CH_2Cl_2 (10:1) gave an analytical sample of **35** as pale yellow columnar crystals. M.p. 72–73 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.88 (3H, s), 3.98 (3H, s), 3.99 (3H, s), 6.58–6.62 (2H, m), 6.99 (1H, d, J = 8.0 Hz), 7.06 (1H, t, J = 8.0 Hz), 7.26–7.31 (1H, m), 7.65 (1H, s), 7.87 (1H, dd, J = 8.0, 1.5 Hz), 8.00 ppm (1H, d, J = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.3, 55.4, 56.0, 99.0, 105.0, 109.9, 110.7, 117.5, 120.7, 125.7, 127.3, 128.5, 131.0, 146.5, 155.5, 158.5, 158.9, 162.4 ppm. FT-IR (KBr): 2942, 2838, 1614, 1494, 1458, 1402, 1345, 1301, 1249, 1215, 1174, 1142, 1114, 1056, 1033, 929, 841, 820, 801, 758, 741 cm^{-1}. HRMS (EI): calcd for $C_{18}H_{17}NO_4$ 311.1158; found 311.1165. Anal. calcd for $C_{18}H_{17}NO_4$: C 69.44, H 5.50, N 4.50; found C 69.17H 5.69, N 4.57.

4.1.30. 2-(2′,6′-Dimethoxyphenyl)-5-(2″-methoxyphenyl)oxazole (36)

Compound **36** was synthesized from 2-bromo-2′-methoxyacetophenone (**10a**) (1.00 g, 4.4 mmol), 2,6-dimethoxybenzylamine (**11 h**) [47] (876 mg, 5.2 mmol) in a manner similar to that described for the synthesis of **12**. Purification by column chromatography (hexane/EtOAc 2:1) gave **36** (137 mg, 10%) as a white solid. Recrystallization from hexane/Et_2O (2:1) gave an analytical sample of **36** as colorless plates. M.p. 158–159 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.78 (6H, s), 3.97 (3H, s), 6.62 (2H, d, J = 8.3 Hz), 6.97 (1H, d, J = 7.6 Hz), 7.01 (1H, t, J = 7.6 Hz), 7.25–7.29 (1H, m), 7.37 (1H, t, J = 8.3 Hz), 7.71 (1H, s), 7.81 ppm (1H, dd, J = 7.6, 1.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.4, 56.0 (2C), 103.9, 107.1 (2C), 110.7, 117.6, 120.6, 126.1, 126.9, 128.6, 131.9, 148.0, 155.4, 155.5, 159.9 (2C) ppm. FT-IR (KBr): 2959, 2838, 1613, 1586, 1492, 1472, 1432, 1250, 1182, 1110, 1054, 1024, 956, 836, 791, 765, 734 cm^{-1}. HRMS (EI): calcd for $C_{18}H_{17}NO_4$ 311.1158; found 311.1161. Anal. calcd for $C_{18}H_{17}NO_4$: C 69.44, H 5.50, N 4.50; found C 69.40H 5.61, N 4.57.

4.1.31. 2-(2′,3′-Dimethoxyphenyl)-5-(3″-methoxyphenyl)oxazole (37)

Compound **37** was synthesized from 2-bromo-3′-methoxyacetophenone (**10c**) (1.00 g, 4.4 mmol), 2,3-dimethoxybenzylamine (**11a**) (0.79 mL, 5.2 mmol) in a manner similar to that described for the synthesis of **12**. Purification by column chromatography (hexane/EtOAc 2:1) gave **37** (1.26 g, 93%) as a white solid. Recrystallization from hexane/CH_2Cl_2 (4:1) gave an analytical sample of **37** as colorless needles. M.p. 84–85 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.86 (3H, s), 3.92 (3H, s), 4.01 (3H, s), 6.87–6.90 (1H, m), 7.02 (1H, d, J = 8.0 Hz), 7.16 (1H, t, J = 8.0 Hz), 7.26–7.27 (1H, m), 7.30–7.37 (2H, m), 7.48 (1H, s), 7.61–7.64 ppm (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.3, 56.0, 61.2, 109.5, 114.0, 114.2, 116.7, 121.3, 122.0, 123.5, 124.3, 129.3, 130.0, 147.7, 151.0, 153.8, 159.3, 159.9 ppm. FT-IR (KBr): 2961, 2830, 1601, 1525, 1480, 1424, 1349, 1298, 1268, 1232, 1188, 1133, 1083, 1051, 1005, 972, 847, 782, 742, 724 cm^{-1}. HRMS (EI): calcd for $C_{18}H_{17}NO_4$ 311.1158; found 311.1156. Anal. calcd for $C_{18}H_{17}NO_4$: C 69.44, H 5.50, N 4.50; found C 69.28H 5.59, N 4.50.

4.1.32. 2-(2′,3′-Dimethoxyphenyl)-5-(4″-methoxyphenyl)oxazole (38)

Compound **38** was synthesized from 2-bromo-4′-methoxyacetophenone (**10d**) (1.00 g, 4.4 mmol), 2,3-dimethoxybenzylamine (**11a**) (0.79 mL, 5.2 mmol) in a manner similar to that described for the synthesis of **12**. Purification by column chromatography (hexane/EtOAc 3:1) gave **38** (1.22 g, 90%) as white solid. Recrystallization from hexane/Et_2O (5:1) gave an analytical sample of **38** as colorless needles. M.p. 61–63 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.86 (3H, s), 3.93 (3H, s), 4.00 (3H, s), 6.96–6.999 (2H, m), 7.02 (1H, dd, J = 7.8, 1.5 Hz), 7.16 (1H, t, J = 8.0 Hz), 7.37 (1H, s), 7.62 (1H, dd, J = 7.8, 1.5 Hz), 7.64–7.68 ppm (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.2, 55.9, 61.1, 113.9, 114.3 (2C), 120.9, 121.1, 121.7, 122.0, 124.2, 125.6 (2C), 147.5, 151.1, 153.7, 158.6, 159.6 ppm. FT-IR (KBr): 2935, 2836, 1614, 1570, 1532, 1500, 1480, 1465, 1421, 1318, 1302, 1257, 1177, 1129, 1082, 1048, 1027, 1004, 943, 833, 789, 744, 728 cm^{-1}. HRMS (EI): calcd for $C_{18}H_{17}NO_4$ 311.1158; found 311.1151. Anal. calcd for $C_{18}H_{17}NO_4$: C 69.44, H 5.50, N 4.50; found C 69.36H 5.65, N 4.51.

4.1.33. 2-(2′-Methoxyphenyl)-5-(2″,5″-dimethoxyphenyl)oxazole (39)

Compound **39** was synthesized from 2-bromo-2′,5′-dimethoxyacetophenone (**10b**) (1.00 g, 3.9 mmol), 2-methoxybenzylamine (**11d**) (0.59 mL, 4.6 mmol) in a manner similar to that described for the

synthesis of **12**. Purification by column chromatography (hexane/EtOAc 2:1) gave **39** (809 mg, 67%) as a yellow solid. Recrystallization from hexane/CH_2Cl_2 (10:1) gave an analytical sample of **39** as yellow granules. M.p. 102–103 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.85$ (3H, s), 3.93 (3H, s), 4.00 (3H, s), 6.84 (1H, dd, $J = 9.0$, 2.9 Hz), 6.91 (1H, d, $J = 9.0$ Hz), 7.04–7.09 (2H, m), 7.41–7.45 (2H, m), 7.71 (1H, s), 8.05 ppm (1H, dd, $J = 7.6$, 1.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 55.8$, 55.9, 56.1, 111.4, 112.0 (2C), 113.4, 116.6, 118.1, 120.6, 127.9, 130.0, 131.5, 147.0, 150.2, 153.7, 157.6, 158.4 ppm. FT-IR (KBr): 3005, 2947, 2834, 1569, 1507, 1456, 1316, 1288, 1258, 1178, 1109, 1053, 1011, 971, 867, 830, 798, 762, 745, 703 cm^{-1}. HRMS (EI): calcd for $C_{18}H_{17}NO_4$ 311.1158; found 311.1153. Anal. calcd for $C_{18}H_{17}NO_4$: C 69.44, H 5.50, N 4.50; found C 69.29H 5.57, N 4.59.

4.1.34. 2-(2′,3′-Dimethoxyphenyl)-5-(2″,3″-dimethoxyphenyl)oxazole (40)

Compound **40** was synthesized from 2-bromo-2′,3′-dimethoxyacetophenone (**10f**) [48] (1.00 g, 3.9 mmol), 2,3-dimethoxybenzylamine (**11a**) (0.70 mL, 4.6 mmol) in a manner similar to that described for the synthesis of **12**. Purification by column chromatography (hexane/EtOAc 2:1) gave **40** (822 mg, 62%) as a white solid. Recrystallization from hexane/Et_2O (10:1) gave an analytical sample of **40** as colorless needles. M.p. 55–56 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.91$ (3H, s), 3.92 (6H, s), 4.01 (3H, s), 6.90 (1H, dd, $J = 8.0$, 1.5 Hz), 7.02 (1H, dd, $J = 8.0$, 1.5 Hz), 7.14 (1H, t, $J = 8.0$ Hz), 7.16 (1H, t, $J = 8.0$ Hz), 7.47 (1H, dd, $J = 8.0$, 1.5 Hz), 7.65 (1H, dd, $J = 8.0$, 1.5 Hz), 7.77 ppm (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 55.9$, 56.0, 59.7, 61.2, 112.1, 114.1, 117.7, 121.3, 122.0, 122.5, 124.2, 124.5, 127.5, 145.6, 147.6, 147.7, 153.1, 153.8, 158.6 ppm. FT-IR (KBr): 2945, 2831, 1586, 1528, 1488, 1433, 1343, 1315, 1263, 1193, 1131, 1082, 1051, 999, 974, 837, 782, 741, 725 cm^{-1}. HRMS (EI): calcd for $C_{19}H_{19}NO_5$ 341.1263; found 341.1253. Anal. calcd for $C_{19}H_{19}NO_5$: C 66.85, H 5.61, N 4.10; found C 66.96, H 5.69, N 4.17.

4.1.35. 2-(2′,3′-Dimethoxyphenyl)-5-(2″,4″-dimethoxyphenyl)oxazole (41)

Compound **41** was synthesized from 2-bromo-2′,4′-dimethoxyacetophenone (**10 g**) (1.00 g, 3.9 mmol), 2,3-dimethoxybenzylamine (**11a**) (0.70 mL, 4.6 mmol) in a manner similar to that described for the synthesis of **12**. Purification by column chromatography (hexane/EtOAc 2:1) gave **41** (586 mg, 44%) as a pale yellow solid. Recrystallization from hexane/CH_2Cl_2 (10:1) gave an analytical sample of **41** as pale yellow needles. M.p. 122–124 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.83$ (3H, s), 3.90 (3H, s), 3.93 (3H, s), 3.99 (3H, s), 6.53 (1H, d, $J = 2.4$ Hz), 6.59 (1H, dd, $J = 8.3$, 2.4 Hz), 6.98 (1H, dd, $J = 8.0$, 1.5 Hz), 7.13 (1H, t, $J = 8.0$ Hz), 7.56 (1H, s), 7.63 (1H, dd, $J = 8.0$, 1.5 Hz), 7.79 ppm (1H, d, $J = 8.3$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 55.3$, 55.4, 55.9, 61.2, 98.5, 104.9, 110.6, 113.8, 121.2, 122.2, 124.1, 125.4, 126.6, 147.5, 147.8, 153.7, 156.9, 157.6, 160.6 ppm. FT-IR (KBr): 2941, 2837, 1612, 1569, 1531, 1499, 1466, 1321, 1268, 1232, 1207, 1127, 1083, 1046, 1026, 948, 822, 788, 744, 721 cm^{-1}. HRMS (EI): calcd for $C_{19}H_{19}NO_5$ 341.1263; found 341.1256. Anal. calcd for $C_{19}H_{19}NO_5$: C 66.85, H 5.61, N 4.10; found C 66.98, H 5.71, N 4.08.

4.1.36. 2-(2′,3′-Dimethoxyphenyl)-5-(2″,5″-dimethoxyphenyl)oxazole (42)

Compound **42** was synthesized from 2-bromo-2′,5′-dimethoxyacetophenone (**10b**) (1.00 g, 3.9 mmol), 2,3-dimethoxybenzylamine (**11a**) (0.78 mL, 5.2 mmol) in a manner similar to that described for the synthesis of **12**. Purification by recrystallization (hexane/CH_2Cl_2 4:1) gave **42** (987 mg, 75%) as pale yellow granules. M.p. 138–139 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.84$ (3H, s), 3.93 (3H, s), 3.94 (3H, s), 4.01 (3H, s), 6.85 (1H, dd, $J = 9.0$, 3.2 Hz), 6.92 (1H, d, $J = 9.0$ Hz), 7.02 (1H, dd, $J = 8.0$, 1.5 Hz), 7.16 (1H, t, $J = 8.0$ Hz), 7.46 (1H, d, $J = 3.2$ Hz), 7.66 (1H, dd, $J = 8.0$, 1.5 Hz), 7.71 ppm (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 55.8$, 55.9, 56.1, 61.2, 111.0, 112.1, 114.1, 114.2, 117.9, 121.4, 122.1, 124.3, 127.7, 147.66, 147.68, 150.2, 153.7, 153.8, 158.4 ppm. FT-IR (KBr): 2943, 2836, 1567, 1533, 1507, 1473, 1339, 1265, 1245, 1206, 1178, 1152, 1129, 1082, 1048, 1024, 1007, 971, 856, 837, 791, 750 cm^{-1}. HRMS (EI): calcd for $C_{19}H_{19}NO_5$ 341.1263; found 341.1263. Anal. calcd for $C_{19}H_{19}NO_5$: C 66.85, H 5.61, N 4.10; found C 66.71, H 5.72, N 4.14.

4.1.37. 2-(2′,3′-Dimethoxyphenyl)-5-(2″,6″-dimethoxyphenyl)oxazole (43)

Compound **43** was synthesized from 2-bromo-2′,6′-dimethoxyacetophenone (**10 h**) [49] (1.00 g, 3.9 mmol), 2,3-dimethoxybenzylamine (**11a**) (0.70 mL, 4.6 mmol) in a manner similar to that described for the synthesis of **12**. Purification by column chromatography (hexane/EtOAc 2:1) gave **43** (240 mg, 18%) as a pale yellow solid. Recrystallization from hexane/CH_2Cl_2 (10:1) gave an analytical sample of **43** as pale yellow needles. M.p. 137–138 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.87$ (6H, s), 3.91 (3H, s), 3.97 (3H, s), 6.65 (2H, d, $J = 8.8$ Hz), 6.99 (1H, dd, $J = 8.0$, 1.5 Hz), 7.13 (1H, t, $J = 8.0$ Hz), 7.30 (1H, t, $J = 8.8$ Hz), 7.48 (1H, s), 7.64 ppm (1H, dd, $J = 8.0$, 1.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 56.0$ (2C), 56.1, 61.2, 104.2 (2C), 106.7, 113.8, 121.5, 122.7, 124.1, 129.2, 130.1, 144.7, 147.7, 153.7, 158.2 (2C), 158.8 ppm. FT-IR (KBr): 3005, 2936, 2838, 1587, 1542, 1480, 1425, 1343, 1265, 1234, 1188, 1110, 1079, 1048, 992, 969, 944, 838, 782, 754, 729 cm^{-1}. HRMS (EI): calcd for $C_{19}H_{19}NO_5$ 341.1263; found 341.1263. Anal. calcd for $C_{19}H_{19}NO_5$: C 66.85, H 5.61, N 4.10; found C 66.81, H 5.81, N 4.15.

4.1.38. 2-(2′,3′-Dimethoxyphenyl)-5-(2″,3″,4″-trimethoxyphenyl)oxazole (44)

Compound **44** was synthesized from 2-bromo-2′,3′,4′-trimethoxyacetophenone (**10i**) [50] (1.00 g, 3.5 mmol), 2,3-dimethoxybenzylamine (**11a**) (0.62 mL, 4.2 mmol) in a manner similar to that described for the synthesis of **12**. Purification by column chromatography (hexane/EtOAc 2:1) gave **44** (836 mg, 65%) as a yellow solid. Recrystallization from hexane/CH_2Cl_2 (10:1) gave an analytical sample of **44** as yellow granules. M.p. 102–104 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.91$ (3H, s), 3.92 (3H, s), 3.93 (3H, s), 3.98 (3H, s), 4.00 (3H, s), 6.78 (1H, d, $J = 8.8$ Hz), 7.01 (1H, dd, $J = 8.0$, 1.5 Hz), 7.16 (1H, t, $J = 8.0$ Hz), 7.55 (1H, d, $J = 8.8$ Hz), 7.62–7.65 ppm (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 56.00$, 56.02, 60.2, 60.9, 61.2, 107.8, 114.0, 115.7, 120.5, 121.3, 122.1, 124.2, 125.6, 142.6, 147.59, 147.62, 150.5, 153.8 (2C), 158.1 ppm. FT-IR (KBr): 2971, 2841, 1605, 1561, 1534, 1487, 1337, 1287, 1268, 1229, 1209, 1130, 1087, 1045, 1011, 916, 849, 809, 788, 746 cm^{-1}. HRMS (EI): calcd for $C_{20}H_{21}NO_6$ 371.1369; found 371.1365. Anal. calcd for $C_{20}H_{21}NO_6$: C 64.68, H 5.70, N 3.77; found C 64.55, H 5.79, N 3.84.

4.1.39. 2-(2′,3′,4′-Trimethoxyphenyl)-5-(2″,3″-dimethoxyphenyl)oxazole (45)

Compound **45** was synthesized from 2-bromo-2′,3′-dimethoxyacetophenone (**10f**) (1.00 g, 3.9 mmol), 2,3,4-trimethoxybenzylamine (**11i**) [51] (0.84 mL, 4.6 mmol) in a manner similar to that described for the synthesis of **12**. Purification by recrystallization (hexane/EtOAc 3:1) gave **45** (535 mg, 37%) as yellow needles. M.p. 145–146 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.92$ (6H, s), 3.93 (3H, s), 3.94 (3H, s), 4.04 (3H, s), 6.80 (1H, d, $J = 8.8$ Hz), 6.90 (1H, dd, $J = 8.0$, 1.2 Hz), 7.15 (1H, t, $J = 8.0$ Hz), 7.45 (1H, dd, $J = 8.0$, 1.2 Hz), 7.73 (1H, s), 7.78 ppm (1H, d, $J = 8.8$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 55.9$, 56.1, 59.7, 61.0, 61.6, 107.7, 111.9, 115.1, 117.7, 122.7, 124.5, 124.6, 127.4, 143.1, 145.5, 147.0, 152.6, 153.1, 155.5, 158.6 ppm. FT-IR (KBr): 2938, 2834, 1597, 1486, 1459, 1410, 1341, 1268, 1248, 1211, 1131, 1092, 1025, 997, 972, 915, 854, 814, 784, 732, 701 cm^{-1}. HRMS (EI): calcd for $C_{20}H_{21}NO_6$ 371.1369; found 371.1365. Anal. calcd for $C_{20}H_{21}NO_6$: C 64.68, H 5.70, N 3.77; found C 64.62, H 5.77, N 3.84.

4.1.40. 2-(2′,3′,4′-Trimethoxyphenyl)-5-(2″,3″,4″-trimethoxyphenyl) oxazole (46)

Compound **46** was synthesized from 2-bromo-2′,3′,4′-

trimethoxyacetophenone (**10i**) (625 mg, 2.2 mmol), 2,3,4-trimethoxybenzylamine (**11i**) (512 mg, 2.6 mmol) in a manner similar to that described for the synthesis of **12**. Purification by column chromatography (benzene/EtOAc 5:1) gave **46** (344 mg, 40%) as a pale yellow solid. Recrystallization from hexane/CH_2Cl_2 (10:1) gave an analytical sample of **46** as pale yellow crystals. M.p. 84–85 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.92 (3H, s), 3.93 (3H, s), 3.93 (3H, s), 3.94 (3H, s), 3.97 (3H, s), 4.03 (3H, s), 6.77 (1H, d, J = 6.3 Hz), 6.80 (1H, d, J = 6.3 Hz), 7.52 (1H, d, J = 8.8 Hz), 7.58 (1H, s), 7.76 ppm (1H, d, J = 8.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.1 (2C), 60.2, 60.9, 61.1, 61.5, 107.7, 107.8, 115.2, 115.9, 120.4, 124.5, 125.5, 142.7, 143.1, 147.1, 150.5, 152.5, 153.7, 155.4, 158.1 ppm. FT-IR (KBr): 2987, 2938, 1599, 1489, 1468, 1431, 1415, 1292, 1245, 1210, 1191, 1173, 1130, 1090, 1015, 915, 849, 818, 728, 703 cm^{-1}. HRMS (EI): calcd for $C_{21}H_{23}NO_7$ 401.1475; found 401.1473. Anal. calcd for $C_{21}H_{23}NO_7$: C 62.84, H 5.78, N 3.49; found C 62.80, H 5.65, N 3.43.

4.1.41. 2-(2′,3′-Dimethoxyphenyl)-5-(naphthalen-2-yl)oxazole (47)

Compound **47** was synthesized from 2-Bromo-2′-acetonaphthone (**10j**) (1.00 g, 4.0 mmol), 2,3-dimethoxybenzylamine (**11a**) (0.73 mL, 4.8 mmol) in a manner similar to that described for the synthesis of **12**. Purification by column chromatography (hexane/EtOAc 3:1) gave **47** (1.26 g, 95%) as a pale yellow solid. Recrystallization from hexane/CH_2Cl_2 (5:1) gave an analytical sample of **47** as pale yellow needles. M.p. 105–107 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.93 (3H, s), 4.06 (3H, s), 7.04 (1H, dd, J = 8.0, 1.2 Hz), 7.19 (1H, t, J = 8.0 Hz), 7.54–7.47 (2H, m), 7.61 (1H, s), 7.68 (1H, dd, J = 8.0, 1.2 Hz), 7.79 (1H, dd, J = 8.0, 1.2 Hz), 7.82–7.85 (1H, m), 7.88–7.90 (2H, m), 8.20 ppm (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.0, 61.3, 114.3, 121.3, 122.0, 122.1, 122.9, 123.8, 124.3, 125.4, 126.4, 126.7, 127.8, 128.2, 128.7, 133.0, 133.4, 147.8, 151.3, 153.8, 159.5 ppm. FT-IR (KBr): 2940, 1528, 1477, 1422, 1330, 1264, 1229, 1190, 1130, 1084, 1041, 1001, 972, 932, 892, 862, 820, 790, 751, 726 cm^{-1}. HRMS (EI): calcd for $C_{21}H_{17}NO_3$ 331.1208; found 331.1216. Anal. calcd for $C_{21}H_{17}NO_3$: C 76.12, H 5.17, N 4.23; found C 75.92, H 5.22, N 4.24.

4.1.42. 2-(2′,3′-Dimethoxyphenyl)-5-(2″-methylphenyl)oxazole (48)

Compound **48** was synthesized from 2-bromo-2′-methylacetophenone (**10 k**) (1.00 g, 4.7 mmol), 2,3-dimethoxybenzylamine (**11a**) (0.85 mL, 5.6 mmol) in a manner similar to that described for the synthesis of **12**. Purification by column chromatography (hexane/EtOAc 2:1) gave **48** (1.11 g, 80%) as a yellow solid. Recrystallization from hexane/CH_2Cl_2 (10:1) gave an analytical sample of **48** as yellow needles. M.p. 97–98 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.55 (3H, s), 3.93 (3H, s), 3.99 (3H, s), 7.03 (1H, dd, J = 8.3, 1.5 Hz), 7.16 (1H, t, J = 8.3 Hz), 7.25–7.33 (3H, m), 7.40 (1H, s), 7.64 (1H, dd, J = 8.3, 1.5 Hz), 7.78–7.81 ppm (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.9, 56.1, 61.3, 114.2, 121.4, 122.0, 124.3, 126.1, 126.2, 126.8, 127.4, 128.3, 131.2, 134.9, 147.8, 150.7, 153.8, 159.0 ppm. FT-IR (KBr): 2941, 2842, 1561, 1527, 1458, 1421, 1380, 1347, 1309, 1263, 1233, 1154, 1132, 1086, 1049, 1005, 970, 940, 837, 791, 762, 748, 728 cm^{-1}. HRMS (EI): calcd for $C_{18}H_{17}NO_3$ 295.1208; found 295.1207. Anal. calcd for $C_{18}H_{17}NO_3$: C 73.20, H 5.80, N 4.74; found C 73.34, H 5.95, N 4.72.

4.1.43. 2-(2′,3′-Dimethoxyphenyl)-5-(2″-benzyloxyphenyl)oxazole (49)

Compound **49** was synthesized from 2-bromo-2′-benzyloxyacetophenone (**10 l**) [52] (2.00 g, 7.7 mmol), 2,3-dimethoxybenzylamine (**11a**) (1.2 mL, 9.3 mmol) in a manner similar to that described for the synthesis of **12**. Purification by column chromatography (hexane/EtOAc 4:1) gave **49** (1.36 g, 45%) as a white solid. Recrystallization from hexane/CH_2Cl_2 (5:1) gave an analytical sample of **49** as colorless granules. M.p. 131–132 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.91 (3H, s), 3.99 (3H, s), 5.21 (2H, s), 7.01 (1H, dd, J = 8.0, 1.2 Hz), 7.06–7.10 (2H, m), 7.14 (1H, t, J = 8.0 Hz), 7.29 (1H, td, J = 8.0, 1.5 Hz), 7.35–7.43 (3H, m), 7.49 (2H, d, J = 7.3 Hz), 7.62–7.64 (2H, m), 7.93 ppm (1H, dd, J = 8.0, 1.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.1, 61.2, 70.6, 111.9, 114.1, 117.6, 121.1, 121.3, 122.1, 124.2, 125.6, 127.8, 127.9 (2C), 128.3, 128.8 (2C), 128.9, 136.2, 147.68, 147.72, 153.8, 154.8, 158.2 ppm. FT-IR (KBr): 3004, 2934, 2878, 1567, 1530, 1493, 1468, 1420, 1388, 1345, 1259, 1133, 1087, 1046, 1003, 833, 787, 741, 701 cm^{-1}. HRMS (EI): calcd for $C_{24}H_{21}NO_4$ 387.1471; found 387.1473. Anal. calcd for $C_{24}H_{21}NO_4$: C 74.40, H 5.46, N 3.62; found C 74.52, H 5.63, N 3.64.

4.1.44. 2-(2′,3′-Dimethoxyphenyl)-5-(2″-hydroxyphenyl)oxazole (50)

10% Pd/C (235 mg) was added to a solution of **49** (911 mg, 2.4 mmol) in THF (24 mL) at room temperature. The mixture was stirred for 24 h under H_2 (1 atm) at room temperature. The reaction mixture was diluted with EtOAc (30 mL), and the catalyst was removed by filtration through a small pad of Celite. The filtrate was concentrated in vacuo to give a residue, which was purified by column chromatography ($CHCl_3$/MeOH 40:1) to give **50** (608 mg, 87%) as a white solid. Recrystallization from hexane/EtOAc (2:1) gave an analytical sample of **50** as colorless needles. M.p. 186–187 °C. ^{1}H NMR (400 MHz, acetone-d_6): δ = 3.92 (3H, s), 4.00 (3H, s), 6.99–7.03 (1H, m), 7.06 (1H, d, J = 7.8 Hz), 7.16–7.24 (3H, m), 7.62 (1H, dd, J = 6.8, 2.9 Hz), 7.72 (1H, s), 7.87 (1H, dd, J = 7.8, 1.5 Hz), 9.43 ppm (1H, br s). ^{13}C NMR (100 MHz, acetone-d_6): δ = 56.3, 61.3, 115.2, 116.5, 116.7, 120.9, 122.0, 123.0, 125.1, 126.4, 127.7, 129.9, 148.5, 149.2, 154.6, 155.0, 159.1 ppm. FT-IR (KBr): 3482, 3067, 1572, 1525, 1474, 1450, 1421, 1351, 1263, 1228, 1133, 1086, 1056, 1001, 945, 847, 786, 743, 719 cm^{-1}. HRMS (EI): calcd for $C_{17}H_{15}NO_4$ 297.1001; found 297.0995. Anal. calcd for $C_{17}H_{15}NO_4 \cdot H_2O$: C 64.75, H 5.43, N 4.44; found C 64.77, H 5.44, N 4.45.

4.1.45. 2-(2′,3′-Dimethoxyphenyl)-5-(2″-ethoxyphenyl)oxazole (51)

EtI (82.0 μL, 1.0 mmol) was added to a stirred solution of **50** (100 mg, 0.34 mmol) in DMF (3.4 mL) containing K_2CO_3 (139 mg, 1.0 mmol) at room temperature, and the mixture was stirred at 60 °C for 2 h. After this time, the mixture was cooled to room temperature, and H_2O (5 mL) was added. The resulting mixture was extracted with Et_2O (3 × 5 mL), and the combined extracts were washed with brine (2 × 5 mL), then dried with Na_2SO_4. The mixture was concentrated in vacuo, and the residue was purified by column chromatography (hexane/EtOAc 2:1) to give **51** (102 mg, 94%) as white solid. Recrystallization from hexane/CH_2Cl_2 (5:1) gave an analytical sample of **51** as colorless plates. M.p. 108–109 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.56 (3H, t, J = 7.0 Hz), 3.92 (3H, s), 4.01 (3H, s), 4.19 (2H, q, J = 7.0 Hz), 6.97 (1H, d, J = 8.0 Hz), 7.00–7.07 (2H, m), 7.16 (1H, t, J = 8.0 Hz), 7.25–7.30 (1H, m), 7.65 (1H, dd, J = 8.0, 2.0 Hz), 7.77 (1H, s), 7.90 ppm (1H, dd, J = 8.0, 2.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.9, 56.0, 61.2, 63.9, 111.5, 114.0, 117.3, 120.7, 121.4, 122.2, 124.2, 125.8, 127.5, 128.9, 147.7, 147.9, 153.8, 155.1, 158.2 ppm. FT-IR (KBr): 2940, 2835, 1561, 1528, 1475, 1420, 1342, 1303, 1261, 1244, 1166, 1129, 1081, 1045, 1000, 943, 839, 793, 747, 725 cm^{-1}. HRMS (EI): calcd for $C_{19}H_{19}NO_4$ 325.1314; found 325.1311. Anal. calcd for $C_{19}H_{19}NO_4$: C 70.14, H 5.89, N 4.31; found C 70.32, H 6.01, N 4.35.

4.1.46. 2-(2′,3′-Dimethoxyphenyl)-5-(2″-n-propoxyphenyl)oxazole (52)

*n*PrI (98.0 μL, 1.0 mmol) was added to a stirred solution of **50** (100 mg, 0.34 mmol) in DMF (3.4 mL) containing K_2CO_3 (139 mg, 1.0 mmol) at room temperature, and the mixture was stirred at 60 °C for 2 h. After this time, the mixture was cooled to room temperature, and H_2O (5 mL) was added. The resulting mixture was extracted with Et_2O (3 × 5 mL), and the combined extracts were washed with brine (2 × 5 mL), then dried with Na_2SO_4. The mixture was concentrated in vacuo, and the residue was purified by column chromatography (hexane/EtOAc 2:1) to give **52** (110 mg, 96%) as a white solid. Recrystallization from hexane/CH_2Cl_2 (5:1) gave an analytical sample of **52** as colorless needles. M.p. 82–83 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.13 (3H, t, J = 7.6 Hz), 1.91–2.00 (2H, m), 3.92 (3H, s), 4.01 (3H, s), 4.09 (2H, q, J = 6.3 Hz), 6.97 (1H, d, J = 7.8 Hz), 7.00–7.06 (2H, m), 7.16 (1H, t, J = 7.8 Hz), 7.25–7.30 (1H, m), 7.66 (1H, dd, J = 7.8, 1.5 Hz), 7.77 (1H, s), 7.90 ppm (1H, dd, J = 7.8, 1.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.9, 22.6,

56.0, 61.2, 70.0, 111.5, 114.0, 117.3, 120.6, 121.3, 122.1, 124.2, 125.8, 127.5, 128.9, 147.7, 147.9, 153.8, 155.2, 158.2 ppm. FT-IR (KBr): 2972, 2941, 2878, 1562, 1527, 1493, 1476, 1421, 1391, 1345, 1249, 1167, 1130, 1084, 1043, 1005, 841, 789, 748, 724 cm^{-1}. HRMS (EI): calcd for $C_{20}H_{21}NO_4$ 339.1471; found 339.1471. Anal. calcd for $C_{20}H_{21}NO_4$: C 70.78, H 6.24, N 4.13; found C 71.01, H 6.40, N 4.16.

4.1.47. 2-(2′,3′-Dimethoxyphenyl)-5-(2″-methoxymethoxyphenyl)oxazole (53)

NaH (55.7 mg, 1.4 mmol) was added portionwise to a stirred solution of **50** (276 mg, 0.93 mmol) in DMF (9 mL) at 0 °C under argon, and the mixture was stirred at 0 °C for 30 min. After this time, MOMCl (105 μL, 1.4 mmol) was added and the mixture was stirred at room temperature for a further 1 h. The reaction was then quenched with saturated aqueous NH_4Cl (5 mL), and the resulting mixture was extracted with Et_2O (3 × 10 mL). The combined extracts were washed with brine (2 × 10 mL), then dried with Na_2SO_4. The mixture was concentrated in vacuo, and the residue was purified by column chromatography (hexane/EtOAc, 2:1) to give **53** (286 mg, 90%) as a white solid. Recrystallization from hexane/CH_2Cl_2 (10:1) gave an analytical sample of **53** as colorless needles. M.p. 82–83 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.52 (3H, s), 3.91 (3H, s), 4.02 (3H, s), 5.36 (2H, s), 7.01 (1H, dd, J = 8.0, 1.2 Hz), 7.09–7.17 (2H, m), 7.18–7.22 (1H, m), 7.24–7.30 (1H, m), 7.65 (1H, dd, J = 8.0, 1.2 Hz), 7.73 (1H, s), 7.91 ppm (1H, dd, J = 8.0, 1.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.0, 56.3, 61.1, 94.1, 114.1 (2C), 117.9, 121.3, 121.9, 122.0, 124.2, 125.9, 127.4, 128.8, 147.60, 147.64, 153.1, 153.7, 158.4 ppm. FT-IR (KBr): 2940, 2903, 1561, 1527, 1491, 1349, 1263, 1229, 1196, 1158, 1126, 1083, 1045, 1003, 920, 838, 788, 754, 723 cm^{-1}. HRMS (EI): calcd for $C_{19}H_{19}NO_5$ 341.1263; found 341.1265. Anal. calcd for $C_{19}H_{19}NO_5$: C 66.85, H 5.61, N 4.10; found C 66.82, H 5.70, N 4.14.

4.1.48. 2,3-Dimethoxy-N-(2-(2-nitrophenyl)-2-oxoethyl)benzamide (55)

Et_3N (0.45 mL, 3.3 mmol) was added dropwise to a stirred solution of aminoketone **54** (236 mg, 1.1 mmol) and carboxcylic acid **21** (198 mg, 1.1 mmol) in CH_2Cl_2 (11 mL) containing EDC·HCl (272 mg, 1.4 mmol) and HOBt (191 mg, 1.4 mmol) at room temperature under argon. After 12 h, the reaction was quenched with 3 M aqueous HCl (10 mL), and the resulting mixture was extracted with EtOAc (3 × 20 mL). The combined extracts were washed successively with saturated aqueous $NaHCO_3$ (2 × 20 mL) and brine (2 × 20 mL), then dried with Na_2SO_4. The mixture was concentrated in vacuo, and the residue was purified by column chromatography (hexane/EtOAc, 2:1) to give **55** (231 mg, 62%) as a white solid. Recrystallization from hexane/CH_2Cl_2 (3:1) gave an analytical sample of **55** as colorless needles. M.p. 129–130 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.90 (3H, s), 3.98 (3H, s), 4.71 (2H, d, J = 5.0 Hz), 7.07 (1H, dd, J = 8.0, 1.0 Hz), 7.14 (1H, t, J = 8.0 Hz), 7.59–7.67 (3H, m), 7.77 (1H, td, J = 8.0, 1.0 Hz), 8.15 (1H, d, J = 8.0 Hz), 8.89 ppm (1H, br t, J = 5.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 49.5, 56.0, 61.4, 115.8, 122.6, 124.2, 124.3, 125.5, 127.8, 131.0, 134.4, 135.8, 145.7, 147.9, 152.6, 165.4, 198.4 ppm. FT-IR (KBr): 3364, 2978, 2945, 2843, 1709, 1646, 1577, 1514, 1458, 1426, 1372, 1267, 1227, 1078, 1052, 995, 849, 811, 768, 736 cm^{-1}. HRMS (EI): calcd for $C_{17}H_{16}N_2O_6$ 344.1008; found 344.1010. Anal. calcd for $C_{17}H_{16}N_2O_6$: C 59.30, H 4.68, N 8.14; found C 59.32, H 4.63, N 8.14.

4.1.49. 2-(2′,3′-Dimethoxyphenyl)-5-(2″-nitrophenyl)oxazole (56)

A solution of **55** (1.12 g, 3.4 mmol) in phosphoryl chloride (10 mL) was heated at reflux for 3 h. After cooling to room temperature, concentration of the solvent in vacuo afforded a residue, which was diluted with CH_2Cl_2 (200 mL). The organic layer was washed successively with water (2 × 50 mL), saturated aqueous $NaHCO_3$ (2 × 50 mL) and brine (2 × 50 mL), then dried with $MgSO_4$. The mixture was concentrated in vacuo, and the residue was purified by column chromatography (hexane/EtOAc, 1:2) to give **56** (490 mg, 71%) as a yellow solid. Recrystallization from hexane/EtOAc (3:1) gave an analytical sample of **56** as yellow plates. M.p. 112–113 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.91 (3H, s), 3.96 (3H, s), 7.04 (1H, d, J = 8.0 Hz), 7.15 (1H, t, J = 8.0 Hz), 7.50 (1H, t, J = 8.0 Hz), 7.56 (1H, s), 7.58 (1H, dd, J = 8.0, 1.2 Hz), 7.65 (1H, t, J = 7.3 Hz), 7.80 (1H, d, J = 7.3 Hz), 7.84 ppm (1H, d, J = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.0, 61.2, 114.8, 121.1, 121.4, 121.8, 124.3, 124.4, 127.5, 129.2, 129.3, 132.5, 146.0, 147.2, 147.9, 153.7, 160.8 ppm. FT-IR (KBr): 3168, 3094, 2936, 1607, 1531, 1477, 1458, 1424, 1359, 1308, 1268, 1234, 1192, 1160, 1133, 1087, 1044, 1003, 967, 847, 791, 776, 744, 726 cm^{-1}. HRMS (EI): calcd for $C_{17}H_{14}N_2O_5$ 326.0903; found 326.0906. Anal. calcd for $C_{17}H_{14}N_2O_5$: C 62.57, H 4.32, N 8.59; found C 62.76, H 4.48, N 8.60.

4.1.50. 2-(2′,3′-Dimethoxyphenyl)-5-(2″-aminophenyl)oxazole (57)

10% Pd/C (42.6 mg) was added to a solution of **56** (139 mg, 0.43 mmol) in MeOH (8 mL) at room temperature. The mixture was stirred for 1 h under H_2 (1 atm) at room temperature. The reaction mixture was diluted with EtOAc (10 mL), and the catalyst was removed by filtration through a small pad of Celite. The filtrate was concentrated in vacuo to give a residue, which was purified by column chromatography (hexane/EtOAc 2:1) to give **57** (96.6 mg, 77%) as yellow solid. Recrystallization from hexane/CH_2Cl_2 (10:1) gave an analytical sample of **57** as yellow granules. M.p. 130–131 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.92 (3H, s), 3.94 (3H, s), 4.56 (2H, br s), 6.77 (1H, d, J = 7.3 Hz), 6.81 (1H, d, J = 7.3 Hz), 7.01 (1H, dd, J = 8.0, 1.5 Hz), 7.13–7.18 (2H, m), 7.42 (1H, s), 7.53 (1H, dd, J = 8.0, 1.5 Hz), 7.66 ppm (1H, dd, J = 8.0, 1.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.0, 61.5, 112.7, 114.0, 116.9, 118.2, 121.1, 121.7, 123.6, 124.4, 127.1, 129.7, 143.5, 147.5, 150.8, 153.6, 158.4 ppm. FT-IR (KBr): 3471, 3380, 2934, 1607, 1559, 1530, 1475, 1422, 1345, 1320, 1266, 1127, 1084, 1046, 993, 941, 812, 789, 763, 743, 721 cm^{-1}. HRMS (EI): calcd for $C_{17}H_{16}N_2O_3$ 296.1161; found 296.1152. Anal. calcd for $C_{17}H_{16}N_2O_3$: C 68.91, H 5.44, N 9.45; found C 68.77, H 5.55, N 9.42.

4.1.51. 2-(2′,3′-Dimethoxyphenyl)-5-(2″-N,N-dimethylaminophenyl) oxazole (58)

MeI (0.13 mL, 2.0 mmol) was added to a stirred solution of **57** (100 mg, 0.34 mmol) in DMF (3.4 mL) containing K_2CO_3 (280 mg, 2.0 mmol) at room temperature, and the mixture was stirred at 60 °C for 24 h. After this time, the mixture was cooled to room temperature, and H_2O (5 mL) was added. The resulting mixture was extracted with Et_2O (3 × 5 mL), and the combined extracts were washed with brine (2 × 5 mL), then dried with Na_2SO_4. The mixture was concentrated in vacuo, and the residue was purified by column chromatography (hexane/EtOAc 2:1) to give **58** (76.0 mg, 70%) as a white solid. Recrystallization from hexane/CH_2Cl_2 (10:1) gave an analytical sample of **58** as colorless granules. M.p. 103–104 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.75 (6H, s), 3.92 (3H, s), 4.02 (3H, s), 7.02 (1H, dd, J = 8.0, 1.0 Hz), 7.11–7.15 (1H, m), 7.16 (1H, t, J = 8.0 Hz), 7.20 (1H, dd, J = 8.0, 1.0 Hz), 7.29 (1H, td, J = 8.0, 2.0 Hz), 7.66 (1H, dd, J = 8.0, 2.0 Hz), 7.81 (1H, s), 7.87 ppm (1H, dd, J = 8.0, 2.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.2 (2C), 56.1, 61.2, 114.1, 119.6, 121.4, 122.2, 122.8, 123.1, 124.3, 126.87, 126.91, 128.8, 147.7, 149.3, 151.1, 153.8, 158.3 ppm. FT-IR (KBr): 2941, 2831, 2784, 1561, 1527, 1457, 1342, 1303, 1260, 1230, 1183, 1127, 1083, 1044, 1002, 946, 841, 792, 744, 725 cm^{-1}. HRMS (EI): calcd for $C_{19}H_{20}N_2O_3$ 324.1474; found 324.1470. Anal. calcd for $C_{19}H_{20}N_2O_3$: C 70.35, H 6.21, N 8.64; found C 70.31, H 6.36, N 8.63.

4.1.52. 2-(2′,3′-Dimethoxyphenyl)-5-(2″-acetoamidophenyl)oxazole (59)

Acetyl chloride (0.13 mL, 1.9 mmol) was added dropwise to a stirred solution of **57** (288 mg, 0.97 mmol) in CH_2Cl_2 (10 mL) containing Et_3N (0.54 mL, 3.9 mmol) at 0 °C under argon. After 3 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL), and the resulting mixture was extracted with $CHCl_3$ (3 × 10 mL). The combined extracts were washed with brine (2 × 10 mL), then dried with Na_2SO_4. The mixture was concentrated in vacuo, and the residue was purified by column chromatography (hexane/EtOAc, 3:1) to give **59** (285 mg, 87%)

as a white solid. Recrystallization from hexane/$CHCl_3$ (3:1) gave an analytical sample of **59** as colorless needles. M.p. 179–180 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.28$ (3H, s), 3.93 (3H, s), 3.95 (3H, s), 7.05 (1H, d, $J = 8.0$ Hz), 7.16–7.20 (2H, m), 7.39 (1H, t, $J = 8.0$ Hz), 7.44 (1H, s), 7.61 (1H, d, $J = 8.0$ Hz), 7.68 (1H, d, $J = 8.0$ Hz), 8.35 (1H, d, $J = 8.0$ Hz), 8.60 ppm (1H, br s). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 24.6$, 56.0, 61.2, 114.6, 117.8, 121.1, 123.1, 124.4, 124.6, 125.2, 127.2, 129.7, 134.5, 147.6, 149.6, 153.7 (2C), 159.5, 168.9 ppm. FT-IR (KBr): 3264, 2939, 1656, 1584, 1568, 1524, 1476, 1351, 1302, 1262, 1150, 1134, 1088, 1045, 1006, 969, 844, 788, 768, 743, 722 cm^{-1}. HRMS (EI): calcd for $C_{19}H_{18}N_2O_4$ 338.1267; found 338.1269. Anal. calcd for $C_{19}H_{18}N_2O_4$: C 67.45, H 5.36, N 8.28; found C 67.41, H 5.36, N 8.23.

4.2. Biological evaluation

Trypanocidal activity of synthesized compounds against 5 trypanosome species and cytotoxicity of synthesized compounds against MDBK cell were evaluated *in vitro* using 96-well cell culture plate format as previously established with slight modification.[44,45] Briefly, for trypanocidal activity evaluation, each well contain 100 μL of trypanosomes as 5×10^3 cells/mL (*T. b. brucei, T. b. gambiense* and *T. b. rhodesiense*) or 1×10^4 cells/mL (*T. evansi*) or 2×10^5 cells/mL (*T. congolense*) were cultivated with compounds from 25 μg/mL to 1.6 ng/mL by 5 times serial dilution. After incubation for 72 h in 37 °C (*T. b. brucei, T. b. gambiense*, *T. b. rhodesiense* and *T. evansi*) or 33 °C (*T. congolense*), 25 μL of CellTiter-Glo™ Luminescent Cell Viability Assay reagent (Promega Japan, Tokyo, Japan) was added to evaluate intracellular ATP concentration according to the instruction. For cytotoxicity evaluation, each well contain 1×10^4 cells/mL of MDBK cell were cultivated with compounds from 100 μg/mL to 6.4 ng/mL by 5 times serial dilution. After incubation for 72 h in 37 °C, OD450 nm was measured at 0 and 4 h after adding 10 μL of Cell Counting Kit-8 (Dojindo laboratories, Kumamoto, Japan). The trypanocidal activity and cytotoxicity evaluations were replicated three times. The IC_{50}s were calculated using GraphPad Prism version 8 (GraphPad Software, San Diego, CA, USA).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bmc.2021.116253.

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