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Novel 2,4,5-trisubstituted oxazole derivatives: Synthesis and antiproliferative activity

Xin-Hua Liu [a,b], Peng-Cheng Lv [a], Jia-Yu Xue [a], Bao-An Song [c], Hai-Liang Zhu [a,b,*]

[a] State Key Laboratory of Pharmaceutical Biotechnology, Nanjing University, Nanjing 210093, PR China
[b] Key Laboratory of Anhui Educational Department, Anhui University of Technology, Maanshan 243002, PR China
[c] Key Laboratory of Green Pesticide and Agriculture Bioengineering, Ministry of Education, Guizhou University, Guiyang 550025, PR China

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ABSTRACT

Microwave irradiation promotes the rapid *O*,*N*-acylation–cyclodehydration cascade reaction of oximes and acid chloride. Twenty novel 2,4,5-trisubstituted oxazole derivatives containing heterocycle moiety were synthesized and evaluated for their antiproliferative activity. The twenty compounds are all first reported and their structures were established by elemental analysis, ^{1}H NMR and ^{13}C NMR spectra. The bioassay tests showed that compounds *2-(2-(2-fluorophenyl)-4-(2,3,4-trimethoxyphenyl)oxazol-5-ylthio)benzo[d]thiazole* (**6af**), *2-(2-(pyridin-3-yl)-4-(2,3,4-trimethoxyphenyl)oxazol-5-ylthio)pyrimidine* (**6bg**) and *2-(2-(2-fluorophenyl)-4-(2,3,4-trimethoxyphenyl)oxazol-5-ylthio)-5-methyl-1,3,4-thiadiazole* (**6cf**) displayed good antiproliferative activity *in vitro*, which were comparable to the positive control (5-fluorouracil).

1. Introduction

Oxazoles are one of the key building elements of natural products. Among the numerous heterocyclic moieties of biological and pharmacological interest, the oxazole ring is endowed with various activities [1], such as hypoglycemic [2], analgesic [3], anti-inflammatory [4], and antibacterial [5] activities. It is reported that new Δ^2-isoxazoline derivatives can be as β-adrenergic receptor antagonists [2]. A series of new carbapenems containing isoxazole moiety showed potent antibacterial activities [5]. Besides, Srivastava et al. reported that on evaluation of HIV-inhibitory activity of 5-(2,2-dibromoacetyl)-3-phenylisoxazole [6]. In this case, oxazole derivatives have raised considerable attention to medicinal research, and a large number of investigations on their synthesis and biological activities have been reported during the last ten years [7–10]. However, little attention has been paid to the synthesis of 2,4,5-trisubstituted oxazole bearing another heterocyclic moieties. Previous research showed that compounds containing trimethoxyphenyl and benzothiazol moieties had moderate antiproliferative activity [11–14].

In view of that, a series of pyrogallol derivatives which have the oxazole moiety were synthesized in order to improve the antiproliferative activity. We began with a leading natural compound pyrogallol, followed by etheration, acylation, bromination, and etherification, then 2-substituted 1-(2,3,4-trimethoxyphenyl)ethanone was condensed with hydroxylamine hydrochloride, eventually, through microwave irradiation over the oxime and acyl chloride, the target compounds were obtained. When we structurally modified an oxazole with diverse substitutes some of which actually had appeared in drugs and medicine, it was reasonable to believe that our new compounds would hold better bioactivity. Through the comparison of their activity, more structure–activity relationship (SAR) could be reflected.

In this paper, a series of 2,4,5-trisubstituted oxazole derivatives containing heterocyclic moiety were designed and synthesized. The structures of the compounds were verified by ^{1}H NMR, ^{13}C NMR and elemental analysis. Preliminary bioassays indicated that compounds **6af**, **6bg** and **6cf** displayed good antiproliferative activity *in vitro*, which were comparable to the positive control (5-fluorouracil).

2. Results and discussion

2.1. Chemistry

The synthetic route leading to **6** was based on the following sequence of reactions, as shown in Scheme 1. 1,2,3-trimethoxybenzene (**1**) was prepared from pyrogallol etheration [15],

* Corresponding author. State Key Laboratory of Pharmaceutical Biotechnology, Nanjing University, Nanjing 210093, PR China. Tel./fax: +86 25 8359 2672.
E-mail address: zhuhl@nju.edu.cn (H.-L. Zhu).

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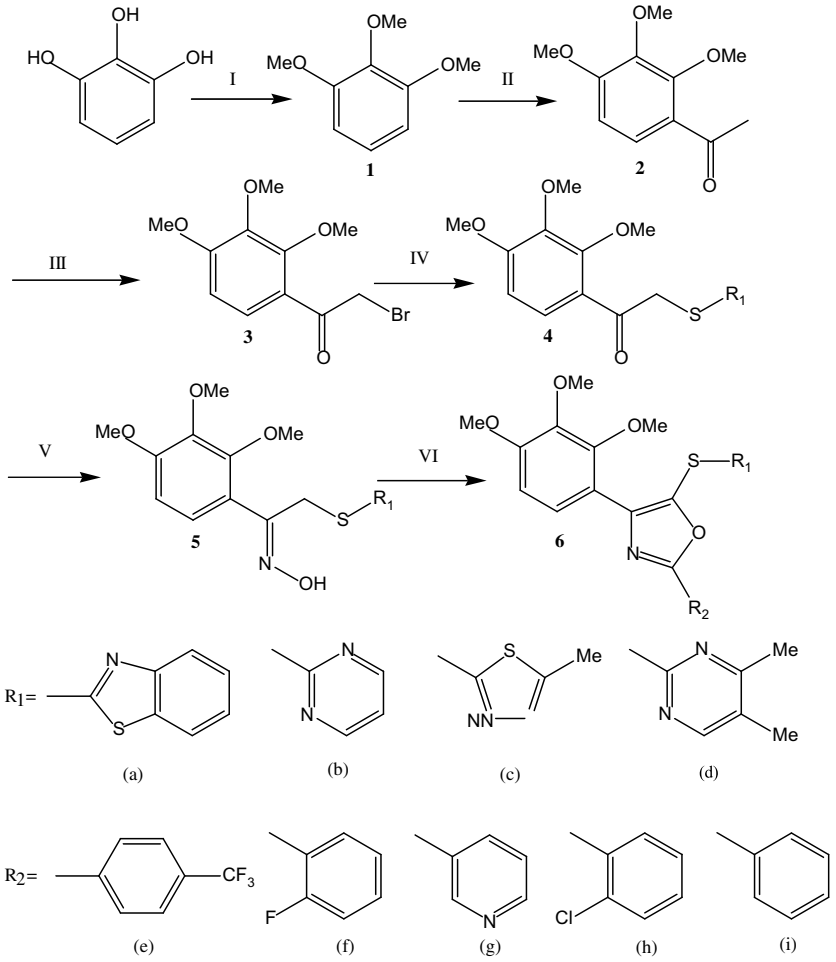

Scheme 1. Route for synthesis of oxazole. Reagents and conditions: I) Me_2SO_4, NaOH, 0 °C–r.t., 3–4 h, 82%; II) $(CH_3CO)_2O$, PPA, 80%; III) Br_2, benzene, 25–60 °C, 20–40 min, 78%; IV) R1–SH, Et_3N, 2–4 h, 74%; V) $NH_2OH{\cdot}HCl$, CH_3OH, pyridine, reflux, 5 h, 70%; VI) *N*-methylmorpholine, DMF, irradiation, 100 °C, 10 min, then, 5 °C, 10 h.

substituted acetophenone (**2**) was prepared from trimethoxybenzene and acetic anhydride via Friedel–Crafts acetylation reaction [16], while compound **3** was synthesized by bromination of substituted acetophenone (**2**). The ethanone **4a** was prepared by alkylation of thioles [17,18]. The reaction of compound **4** with hydroxylamine was carried out in methanol catalyzed by pyridine to produce compound **5**, and the reaction was completed within 5 h at refluxing temperature [19,20]. Using the literature method for converting oxime to oxazole under microwave irradiation at various temperatures in pyridine/toluene (5.6:1) actually did not lead to formation of oxazoles [21]. Then catalytic *N*-methylmorpholine in DMF was added to attempt to facilitate acyl transferring processes. In addition to a much faster conversion, the major advantage of microwave irradiation was a considerable increased yield [22]. Control reactions with oxime **5** and acid chloride under a range of thermal and optimized microwave conditions are shown in Table 1.

2.2. Biological activity

It is reported that oxazoles showed antiproliferative activity against many cancer cells, especially PC-3 (human prostate cancer) and A431 (human epidermoid carcinoma) [23–25]. In view of that, in order to search for new antiproliferative agents, all the twenty compounds were evaluated for their antiproliferative activity against the above two cell lines. The cells were allowed to proliferate in presence of tested material for 48 h, and the results were reported in terms of IC_{50} values (Table 2). From the IC_{50} values, it is obvious that compounds **6af**, **6bg** and **6cf** exhibited the strongest inhibitory activity against the two assayed cell lines with some of their IC_{50}s much lower than the positive control, while compounds **6ag**, **6ai**, **6bi**, **6ce**, **6cg**, **6ch**, **6de**, **6df**, **6dh** and **6di** demonstrated less potent cytotoxicity, and the others' inhibition was much weaker. From the molecular structures of **6af** and **6cf**, it can be clearly figured out that they have an identical substitute group R_2, which may be crucial. Based on the above facts, it can be concluded that the fluorophenyl group has an important effect on the antiproliferative activity. In addition, it was noted that both **6af** and **6cf** held S-containing groups, comparing them to **6bf** and **6df** without an S-containing group, it was found that the former two showed clearly higher inhibitory activity than the latter ones. By comparing the average IC_{50} values

Table 1
Microwave promoted oxazole formation reaction.

Entry	Solvent (v/v)	Conditions	Additive	**6ae** (Yield/%)
1	Pyridine/toluene (5.6:1)	120 °C, 18 h	–	–
2	Pyridine/toluene (5.6:1)	μW, 100 °C, 30 min	NMM[a]	–
3	DMF	μW, 120 °C, 15 min	NMM[a]	37.2
4	DMF	μW, 140 °C, 30 min	NMM[a]	22.3
5	DMF	μW, 100 °C, 10 min	NMM[a]	62.5

[a] 5 mol% of NMM was used.

Table 2
Antiproliferative activity of the synthesized compounds against PC-3 and A431cell lines.

Compound	IC_{50} (μM)		Compound	IC_{50} (μM)	
	PC-3	A431		PC-3	A431
6ae	0.036	0.047	**6ce**	0.022	0.025
6af	0.0030	0.0031	**6cf**	0.0035	0.0026
6ag	0.023	0.026	**6cg**	0.032	0.022
6ah	0.039	0.032	**6ch**	0.024	0.041
6ai	0.025	0.042	**6ci**	0.042	0.038
6be	0.066	0.059	**6de**	0.023	0.028
6bf	0.051	0.038	**6df**	0.020	0.020
6bg	0.0047	0.0076	**6dg**	0.035	0.081
6bh	0.047	0.109	**6dh**	0.018	0.021
6bi	0.023	0.032	**6di**	0.020	0.023
5-Fluorouracil[a]	0.016	0.018			

The data represented the mean of three experiments in triplicate.
The IC_{50} value was defined as the concentration at which 50% survival of cells was observed. The results are listed in the table.
[a] Used as a positive control.

of four groups of synthetic compounds (**6ae**–**6ai**, **6be**–**6bi**, **6ce**–**6ci** and **6de**–**6di**), it was found that the third group (**6ce**–**6ci**) exhibited the highest inhibition, indicating that thiadiazole may play an important role in antiproliferative activities against the two cancer cells.

3. Experimental section

3.1. General

Melting points (uncorrected) were determined on an XT4 MP apparatus (Taike Corp., Beijing, China). ESI mass spectra were obtained on a Mariner System 5304 mass spectrometer, and ^{1}H NMR spectra were recorded on a Bruker PX500 or DPX300 spectrometer at 25 °C with TMS and solvent signals allotted as internal standards. The ^{13}C NMR spectra were recorded on a Varian INOVA400 (100 MHz) pulse Fourier-transform NMR spectrometer. Chemical shifts were reported in ppm (δ). Elemental analysis was performed by a Vario-III CHN analyzer. The reagents were all analytical reagents or chemically pure.

3.2. General procedure for the synthesis of compounds **1**, **2**, **3**, **4**, **5**

1,2,3-trimethoxybenzene (**1**) was prepared from pyrogallol. Treating pyrogallol (1.26 g, 10 mmol) with dimethyl sulfate yielded compound **1** (1.34 g, 82%). Treating 1,2,3-trimethoxybenzene (**1**) (1.68 g, 10 mmol) with acetic anhydride via Friedel–Crafts acetylation reaction gave substituted acetophenone (**2**) (1.78 g, 80%). Compound **3** was synthesized by bromination of substituted acetophenone (**2**) with a yield of 78%, and compound **4a** was prepared by alkylation of thioles with a yield of 74%. Treating compound **4a** with hydroxylamine in methanol catalyzed by pyridine produced compound **5a**, and the reaction was completed within 5 h at refluxing temperature with a yield of 70%. Similarly, **4b**–**4d** were prepared according to the same method as **4a**, and **5b**–**5d** were prepared following the same method as **5a**.

Derivatives **5a**–**d** were obtained from the oxime formation reaction as a mixture of *E* and *Z* isomers, *E*/*Z* ratios depended on the reaction conditions and substituents. As in the *Z* isomers heterocyclic moieties and hydroxy group are situated on one side relative to the imino bond of oxime, the formation of the intramolecular hydrogen bond occurred, that led to the appearance of the shift corresponding to the signal of hydrogen from N–OH group at around 10.8 ppm.

3.3. Spectral properties of intermediate compounds **3**, **4a**–**d** and **5a**–**d**

3.3.1. 2-Bromo-1-(2,3,4-trimethoxyphenyl)ethanone (**3**)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.75–3.84 (3s, 9H), 4.69 (s, 2H), 6.52–7.38 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 31.5, 56.2, 56.5, 56.6, 108.3, 114.2, 122.6, 138.9, 153.0, 155.2, 192.3. ESI-MS: 289.1 ($C_{11}H_{14}BrO_4$, $[M+H]^+$). Anal. Calcd for $C_{11}H_{13}BrO_4$: C 45.70, H 4.53; Found C 45.71, H 4.51.

3.3.2. 2-(Benzo[d]thiazol-2-ylthio)-1-(2,3,4-trimethoxyphenyl) ethanone (**4a**)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.73–3.81 (3s, 9H), 4.59 (s, 2H), 6.48–8.41 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 39.4, 56.5, 56.7, 56.8, 108.1, 114.4, 121.2, 121.4, 122.9, 126.1, 127.0, 134.6, 139.6, 151.5, 153.0, 156.0, 165.3, 195.0. ESI-MS: 376.1 ($C_{18}H_{18}NO_4S_2$, $[M+H]^+$). Anal. Calcd for $C_{18}H_{17}NO_4S_2$: C 57.58, H 4.56; Found C 57.59, H 4.54.

3.3.3. 2-(Pyrimidin-2-ylthio)-1-(2,3,4-trimethoxyphenyl)ethanone (**4b**)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.75–3.80 (3s, 9H), 4.28 (s, 2H), 6.48–7.32 (m, 3H), 8.79 (d, $J = 5.1$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 40.2, 56.3, 56.5, 56.6, 108.4, 114.2, 117.5, 123.7, 140.0, 152.0, 155.9, 158.1, 172.8, 195.2. ESI-MS: 321.1 ($C_{15}H_{17}N_2O_4S_2$, $[M+H]^+$). Anal. Calcd for $C_{15}H_{16}N_2O_4S_2$: C 56.24, H 5.03; Found C 56.26, H 5.05.

3.3.4. 2-(5-Methyl-1,3,4-thiadiazol-2-ylthio)-1-(2,3,4-trimethoxyphenyl)ethanone (**4c**)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.32 (s, 3H), 3.73–3.79 (3s, 9H), 4.26 (s, 2H), 6.51–7.32 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 17.1, 38.9, 56.5, 56.6, 56.7, 108.3, 114.0, 123.3, 140.3, 152.1, 155.9, 165.0, 167.9, 194.7. ESI-MS: 341.1 ($C_{14}H_{17}N_2O_4S_2$, $[M+H]^+$). Anal. Calcd for $C_{14}H_{16}N_2O_4S_2$: C 49.40, H 4.74; Found C 49.42, H 4.73.

3.3.5. 2-(4,5-Dimethylpyrimidin-2-ylthio)-1-(2,3,4-trimethoxyphenyl)ethanone (**4d**)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.37–2.41 (2s, 6H), 3.73–3.78 (3s, 9H), 4.24 (s, 2H), 6.48–7.32 (m, 2H), 8.51 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 17.4, 17.5, 39.3, 56.4, 56.6, 56.7, 108.0, 114.2, 123.7, 12.9, 140.0, 152.1, 155.7, 158.2, 163.9, 169.9, 194.9. ESI-MS: 349.1 ($C_{17}H_{21}N_2O_4S$, $[M+H]^+$). Anal. Calcd for $C_{17}H_{20}N_2O_4S$: C 58.60, H 5.79; Found C 58.62, H 5.78.

3.3.6. (Z)-2-(Benzo[d]thiazol-2-ylthio)-1-(2,3,4-trimethoxyphenyl)ethanone oxime (**5a**)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.73–3.79 (3s, 9H), 4.76 (s, 2H), 6.68–8.42 (m, 6H), 10.92 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 36.2, 56.5, 56.6, 56.8, 108.4, 110.9, 122.8, 123.0, 123.9, 125.8, 126.1, 136.2, 140.5, 151.7, 154.1, 154.6, 164.9, 165.3. ESI-MS: 391.1 ($C_{18}H_{19}N_2O_4S_2$, $[M+H]^+$). Anal. Calcd for $C_{18}H_{18}N_2O_4S_2$: C 55.37, H 4.65; Found C 55.39, H 4.64.

3.3.7. (Z)-2-(Pyrimidin-2-ylthio)-1-(2,3,4-trimethoxyphenyl) ethanone oxime (**5b**)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.78–3.80 (3s, 9H), 4.39 (s, 2H), 6.57–7.39 (m, 3H), 8.82 (d, $J = 5.1$ Hz, 2H), 10.85 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 36.3, 56.4, 56.5, 56.7, 108.2, 111.1, 117.2, 124.3, 140.4, 152.4, 153.9, 157.8, 165.6, 172.8. ESI-MS: 336.1 ($C_{15}H_{18}N_3O_4S$, $[M+H]^+$). Anal. Calcd for $C_{15}H_{17}N_3O_4S$: C 53.72, H 5.11; Found C 53.74, H 5.13.

3.3.8. (Z)-2-(5-Methyl-1,3,4-thiadiazol-2-ylthio)-1-(2,3,4-trimethoxyphenyl)ethanone oxime (**5c**)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.38 (s, 3H), 3.77–3.79 (3s, 9H), 4.41 (s, 2H), 6.61–7.39 (m, 2H), 10.88 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 17.3, 36.6, 56.5, 56.6, 56.7, 108.5, 110.9, 124.2, 140.5, 152.5,

153.8, 165.0, 165.7, 168.2. ESI-MS: 356.1 ($C_{14}H_{18}N_3O_4S_2$, $[M+H]^+$). Anal. Calcd for $C_{14}H_{17}N_3O_4S_2$: C 47.31, H 4.82; Found C 47.32, H 4.80.

3.3.9. (Z)-2-(4,5-Dimethylpyrimidin-2-ylthio)-1-(2,3,4-trimethoxyphenyl)ethanone oxime (**5d**)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.67–2.70 (2s, 6H), 3.73–3.77 (3s, 9H), 4.69 (s, 2H), 6.61–7.41 (m, 2H), 8.68 (s, 1H), 10.86 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 17.2, 17.4, 36.4, 56.5, 56.7, 56.8, 108.2, 110.9, 124.1, 124.3, 140.3, 151.9, 154.2, 157.8, 164.1, 165.2, 170.1. ESI-MS: 364.1 ($C_{17}H_{22}N_3O_4S$, $[M+H]^+$). Anal. Calcd for $C_{17}H_{21}N_3O_4S$: C 56.18, H 5.82; Found C 56.16, H 5.81.

3.4. General procedure for the synthesis of compound **6**

3.4.1. 2-(2-(4-(Trifluoromethyl)phenyl)-4-(2,3,4-trimethoxyphenyl)oxazol-5-ylthio)benzo[d]thiazole (**6ae**)

To a solution of oxime **5a** (2 mmol) and *N*-methylmorpholine (0.010 mmol) in DMF (30 mL) at 1–5 °C was added dropwise 4-trifluoromethylbenzoyl chloride (2.5 mmol). The reaction mixture was heated in the microwave for 10 min at 100 °C and poured into water (50 mL), then the solution was maintained at 5 °C for 10 h. The product was collected by filtration, and the crude residue was purified by chromatography on SiO_2 (acetone/petroleum, 3:1) to give **6ae** (0.68 g, 62.5%) as a colorless solid. Mp: 171–172 °C. Other title compounds were prepared according to the same method. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.78–3.95 (3s, 9H), 6.34 (d, J = 8.8 Hz, 1H), 6.90 (d, J = 8.8 Hz, 1H), 7.39–7.50 (m, 4H), 7.58 (m, 2H), 8.16 (d, J = 8.2 Hz, 1H), 8.24 (d, J = 8.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 56.1, 56.3, 56.4, 108.2, 112.2, 121.5, 121.7, 121.9, 124.2, 125.5, 125.7, 125.8, 125.9, 127.8, 129.8, 131.3, 135.3, 138.3, 139.8, 149.5, 150.6, 153.5, 159.0, 167.6. ESI-MS: 545.1 ($C_{26}H_{20}F_3N_2O_4S_2$, $[M+H]^+$). Anal. Calcd for $C_{26}H_{19}F_3N_2O_4S_2$: C 57.34, H 3.52, N 5.14; Found: C 57.61, H 3.81, N 4.92.

3.4.2. 2-(2-(2-Fluorophenyl)-4-(2,3,4-trimethoxyphenyl)oxazol-5-ylthio)benzo[d]thiazole (**6af**)

Colorless crystals, yield 66.3%. Mp: 153–154 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.75–3.96 (3s, 9H), 6.32 (d, J = 8.8 Hz, 1H), 6.88 (d, J = 8.8 Hz, 1H), 7.00–7.48 (m, 4H), 7.58 (m, 2H), 8.11 (d, J = 8.2 Hz, 1H), 8.26 (d, J = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 56.3, 56.4, 56.5, 108.2, 112.4, 116.3, 121.6, 121.8, 122.1, 123.7, 125.0, 125.4, 125.6, 126.1, 129.4, 130.2, 135.3, 138.4, 139.7, 149.5, 150.9, 153.8, 155.5, 159.6, 167.9. ESI-MS: 495.1 ($C_{25}H_{20}FN_2O_4S_2$, $[M+H]^+$). Anal. Calcd for $C_{25}H_{19}FN_2O_4S_2$: C 60.71, H 3.87, N 5.66; Found C 60.88, H 3.61, N 5.91.

3.4.3. 2-(2-(Pyridin-3-yl)-4-(2,3,4-trimethoxyphenyl)oxazol-5-ylthio)benzo[d]thiazole (**6ag**)

Colorless crystals, yield 61.0%. Mp: 197–198 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.75–3.94 (3s, 9H), 6.30 (d, J = 8.8 Hz, 1H), 6.8 (d, J = 8.8 Hz, 1H), 7.48–7.59 (m, 3H), 7.93 (d, J = 7.9 Hz, 1H), 8.16 (d, J = 8.2 Hz, 1H), 8.31 (d, J = 8.2 Hz, 1H), 8.60 (d, J = 6.1 Hz, 1H), 8.84 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 56.3, 56.4, 56.6, 108.3, 112.5, 121.6, 121.8, 121.9, 124.2, 124.8, 125.5, 125.6, 126.3, 134.5, 135.5, 138.4, 139.6, 148.2, 149.5, 149.6, 150.9, 153.4, 159.5, 167.1. ESI-MS: 478.1 ($C_{24}H_{20}N_3O_4S_2$, $[M+H]^+$). Anal. Calcd for $C_{24}H_{19}N_3O_4S_2$: C 60.36, H 4.01, N 8.80; Found: C 60.11, H 3.64, N 8.46.

3.4.4. 2-(2-(2-Chlorophenyl)-4-(2,3,4-trimethoxyphenyl)oxazol-5-ylthio)benzo[d]thiazole (**6ah**)

Colorless crystals, yield 64.2%. Mp: 180–181 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.75–3.89 (3s, 9H), 6.26 (d, J = 8.8 Hz, 1H), 6.86 (d, J = 8.8 Hz, 1H), 7.18–7.45 (m, 4H), 7.59 (m, 2H), 8.10 (d, J = 8.2 Hz, 1H), 8.25 (d, J = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 56.2, 56.3, 56.6, 108.2, 112.4, 121.9, 122.2, 122.4, 125.4, 125.7, 126.2, 127.7, 128.9, 129.6, 130.5, 132.7, 135.4, 136.9, 138.4, 139.8, 149.5, 150.9, 153.6, 159.2, 167.2. ESI-MS: 511.0 ($C_{25}H_{20}ClN_2O_4S_2$, $[M+H]^+$). Anal. Calcd for $C_{25}H_{19}ClN_2O_4S_2$: C 58.76, H 3.75, N 5.48; Found: C 58.51, H 3.89, N 5.40.

3.4.5. 2-(2-Phenyl-4-(2,3,4-trimethoxyphenyl)oxazol-5-ylthio)benzo[d]thiazole (**6ai**)

Colorless crystals, yield 58.9%. Mp: 140–141 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.77–3.92 (3s, 9H), 6.30 (d, J = 8.8 Hz, 1H), 6.87 (d, J = 8.8 Hz, 1H), 7.20–7.45 (m, 5H), 7.52 (m, 2H), 8.15 (d, J = 8.2 Hz, 1H), 8.28 (d, J = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 56.2, 56.4, 56.5, 108.2, 112.5, 121.7, 121.8, 121.9, 125.3, 125.6, 125.9, 126.2, 127.8, 128.9, 129.7, 135.4, 138.3, 139.8, 149.4, 150.6, 153.8, 159.3, 167.0. ESI-MS: 477.9 ($C_{25}H_{21}N_2O_4S_2$, $[M+H]^+$). Anal. Calcd for $C_{25}H_{20}N_2O_4S_2$: C 63.01, H 4.23, N 5.88; Found: C 62.79, H 4.55, N 6.20.

3.4.6. 2-(2-(4-(Trifluoromethyl)phenyl)-4-(2,3,4-trimethoxyphenyl)oxazol-5-ylthio)pyrimidine (**6be**)

Colorless crystals, yield 63.1%. Mp: 91–92 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.76–3.92 (3s, 9H), 6.30 (d, J = 8.8 Hz, 1H), 6.90 (d, J = 8.8 Hz, 1H), 7.18 (m, 1H), 7.44–7.56 (m, 4H), 8.69 (d, J = 5.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 56.2, 56.3, 56.5, 108.3, 112.5, 118.9, 121.9, 124.4, 125.7, 126.1, 127.9, 129.7, 131.2, 138.5, 139.9, 149.4, 151.0, 157.9, 159.4, 172.2. ESI-MS: 490.1 ($C_{23}H_{19}F_3N_3O_4S$, $[M+H]^+$). Anal. Calcd for $C_{23}H_{18}F_3N_3O_4S$: C 56.44, H 3.71, N 8.58; Found: C 56.77, H 3.80, N 8.41.

3.4.7. 2-(2-(2-Fluorophenyl)-4-(2,3,4-trimethoxyphenyl)oxazol-5-ylthio)pyrimidine (**6bf**)

Colorless crystals, yield 56.9%. Mp: 87–88 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.75–3.89 (3s, 9H), 6.30 (d, J = 8.8 Hz, 1H), 6.86 (d, J = 8.8 Hz, 1H), 7.00–7.48 (m, 5H), 8.66 (d, J = 5.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 56.2, 56.5, 56.6, 108.2, 112.4, 116.2, 119.2, 122.1, 123.7, 125.2, 125.6, 129.4, 130.6, 138.5, 139.8, 149.4, 150.9, 157.9, 158.4, 159.5, 172.1. ESI-MS: 440.1 ($C_{22}H_{19}FN_3O_4S$, $[M+H]^+$). Anal. Calcd for $C_{22}H_{18}FN_3O_4S$: C 60.13, H 4.13, N 9.56; Found: C 60.22, H 3.91, N 9.79.

3.4.8. 2-(2-(Pyridin-3-yl)-4-(2,3,4-trimethoxyphenyl)oxazol-5-ylthio)pyrimidine (**6bg**)

Colorless crystals, yield 59.2%. Mp: 115–116 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.79–3.88 (3s, 9H), 6.33 (d, J = 8.8 Hz, 1H), 6.88 (d, J = 8.8 Hz, 1H), 7.12 (m, 1H), 7.48 (q, 1H), 7.97 (d, J = 7.7 Hz, 1H), 8.47 (d, J = 6.1 Hz, 1H), 8.68 (d, J = 5.2 Hz, 2H), 8.89 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 56.2, 56.3, 56.6, 108.3, 112.6, 118.9, 122.0, 124.2, 124.8, 125.6, 134.0, 138.7, 140.2, 148.4, 149.3, 149.5, 151.1, 158.0, 159.6, 172.0. ESI-MS: 423.1 ($C_{21}H_{19}N_4O_4S$, $[M+H]^+$). Anal. Calcd for $C_{21}H_{18}N_4O_4S$: C 59.70, H 4.29, N 13.26; Found: C 60.01, H 4.04, N 13.55.

3.4.9. 2-(2-(2-Chlorophenyl)-4-(2,3,4-trimethoxyphenyl)oxazol-5-ylthio)pyrimidine (**6bh**)

Colorless crystals, yield 57.1%. Mp: 100–101 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.75–3.89 (3s, 9H), 6.35 (d, J = 8.8, 1H), 6.90 (d, J = 8.8, 1H), 7.12 (m, 1H), 7.18–7.46 (m, 4H), 8.71 (d, J = 5.2, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 56.2, 56.4, 56.6, 108.5, 112.4, 119.2, 122.1, 125.7, 127.9, 129.3, 129.8, 130.4, 132.8, 137.3, 138.4, 140.2, 149.4, 151.0, 158.1, 159.3, 172.2. ESI-MS: 456.1 ($C_{22}H_{19}ClN_3O_4S$, $[M+H]^+$). Anal. Calcd for $C_{22}H_{18}ClN_3O_4S$: C 57.96, H 3.98, N 9.22; Found: C 58.05, H 4.17, N 9.01.

3.4.10. 2-(2-Phenyl-4-(2,3,4-trimethoxyphenyl)oxazol-5-ylthio)pyrimidine (**6bi**)

Colorless crystals, yield 69.2%. Mp: 89–91 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.79–3.94 (3s, 9H), 6.29 (d, J = 8.8 Hz, 1H), 6.88 (d, J = 8.8 Hz, 1H), 7.10 (m, 1H), 7.18–7.46 (m, 5H), 8.75 (d, J = 5.2 Hz,

2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 56.0, 56.4, 56.5, 108.3, 112.5, 119.0, 122.0, 125.6, 126.5, 127.8, 129.1, 129.6, 138.7, 140.4, 149.5, 151.3, 158.2, 159.4, 171.7. ESI-MS: 422.1 ($C_{22}H_{20}N_3O_4S$, $[M+H]^+$). Anal. Calcd for $C_{22}H_{19}N_3O_4S$: C, 62.69; H, 4.54; N, 9.97; Found: C, 62.77; H, 4.19; N, 10.12.

*3.4.11. 2-Methyl-5-(2-(4-(trifluoromethyl)phenyl)-4-(2,3,4-trimethoxyphenyl)oxazol-5-ylthio)-1,3,4-thiadiazole (**6ce**)*

Colorless crystals, yield 70.5%. Mp: 168–169 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.26 (s, 3H), 3.70–3.87 (3s, 9H), 6.38 (d, $J=8.8$ Hz, 1H), 6.97 (d, $J=8.8$ Hz, 1H), 7.32–7.58 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.9, 56.4, 56.5, 56.6, 108.0, 112.1, 122.2, 124.0, 125.5, 127.4, 128.1, 129.7, 131.3, 137.7, 140.2, 149.1, 151.4, 159.0, 161.5, 167.8. ESI-MS: 510.1 ($C_{22}H_{19}F_3N_3O_4S_2$, $[M+H]^+$). Anal. Calcd for $C_{22}H_{18}F_3N_3O_4S_2$: C 51.86, H 3.56, N 8.25; Found: C 52.07, H 3.44, N 8.11.

*3.4.12. 2-(2-(2-Fluorophenyl)-4-(2,3,4-trimethoxyphenyl)oxazol-5-ylthio)-5-methyl-1,3,4-thiadiazole (**6cf**)*

Colorless crystals, yield 71.3%. Mp: 154–155 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.32 (s, 3H), 3.73–3.88 (3s, 9H), 6.34 (d, $J=8.8$ Hz, 1H), 6.90 (d, $J=8.8$ Hz, 1H), 7.01–7.50 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.3, 56.2, 56.5, 56.6, 108.3, 112.5, 116.7, 121.9, 123.8, 125.2, 125.1, 128.7, 129.9, 138.3, 140.0, 149.4, 151.0, 158.0, 159.8, 161.7, 166.9. ESI-MS: 460.1 ($C_{21}H_{19}FN_3O_4S_2$, $[M+H]^+$). Anal. Calcd for $C_{21}H_{18}FN_3O_4S_2$: C 54.89, H 3.95, N 9.14; Found: C 55.08, H 3.74, N 8.89.

*3.4.13. 3-(5-(5-Methyl-1,3,4-thiadiazol-2-ylthio)-4-(2,3,4-trimethoxyphenyl)oxazol-2-yl)pyridine (**6cg**)*

Colorless crystals, yield 77.8%. Mp: 189–190 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.33 (s, 3H), 3.77–3.89 (3s, 9H), 6.32 (d, $J=8.8$ Hz, 1H), 6.90 (d, $J=8.8$ Hz, 1H), 7.38 (q, 1H), 8.01 (d, $J=7.7$ Hz, 1H), 8.51 (d, $J=6.2$ Hz, 1H), 8.89 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.4, 56.2, 56.3, 56.4, 108.4, 112.2, 122.0, 124.3, 124.5, 125.8, 134.3, 138.7, 140.1, 148.5, 149.4, 149.5, 150.6, 159.5, 161.4, 167.5. ESI-MS: 443.1 ($C_{20}H_{19}N_4O_4S_2$, $[M+H]^+$). Anal. Calcd for $C_{20}H_{18}N_4O_4S_2$: C 54.28, H 4.10, N 12.66; Found: C 54.55, H 4.36, N 12.30.

*3.4.14. 2-(2-(2-Chlorophenyl)-4-(2,3,4-trimethoxyphenyl)oxazol-5-ylthio)-5-methyl-1,3,4-thiadiazole (**6ch**)*

Colorless crystals, yield 70.8%. Mp: 178–179 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.38 (s, 3H), 3.75–3.87 (3s, 9H), 6.35 (d, $J=8.8$ Hz, 1H), 6.89 (d, $J=8.8$ Hz, 1H), 7.14–7.48 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.7, 56.2, 56.3, 56.5, 108.5, 112.5, 121.7, 125.6, 127.2, 129.2, 129.8, 130.3, 132.5, 137.2, 138.7, 139.1, 149.0, 150.9, 159.8, 161.2, 166.9. ESI-MS: 476.0 ($C_{21}H_{19}ClN_3O_4S_2$, $[M+H]^+$). Anal. Calcd for $C_{21}H_{18}ClN_3O_4S_2$: C 52.99, H 3.81, N 8.83; Found: C 52.81, H 4.10, N 9.07.

*3.4.15. 2-Methyl-5-(2-phenyl-4-(2,3,4-trimethoxyphenyl)oxazol-5-ylthio)-1,3,4-thiadiazole (**6ci**)*

Colorless crystals, yield 68.7%. Mp: 144–145 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.34 (s, 3H), 3.79–3.88 (3s, 9H), 6.32 (d, $J=8.8$, 1H), 6.88 (d, $J=8.8$ Hz, 1H), 7.28–7.55 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.8, 56.4, 56.5, 56.7, 108.0, 112.1, 121.9, 125.8, 126.8, 128.0, 129.2, 130.0, 138.8, 140.2, 149.5, 151.1, 159.6, 161.5, 167.4. ESI-MS: 442.1 ($C_{21}H_{20}N_3O_4S_2$, $[M+H]^+$). Anal. Calcd for $C_{21}H_{19}N_3O_4S_2$: C 57.13, H 4.34, N 9.52; Found: C 57.00, H 4.59, N 9.19.

*3.4.16. 4,5-Dimethyl-2-(2-(4-(trifluoromethyl)phenyl)-4-(2,3,4-trimethoxyphenyl)oxazol-5-ylthio)pyrimidine (**6de**)*

Colorless crystals, yield 52.5%. Mp: 131–132 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.32–2.39 (2s, 6H), 3.77–3.90 (3s, 9H), 6.26 (d, $J=8.8$ Hz, 1H), 6.91 (d, $J=8.8$ Hz, 1H), 7.46–7.56 (m, 4H), 8.31 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 17.9, 18.1, 56.1, 56.3, 56.4, 108.3, 112.5, 122.1, 124.6, 125.7, 126.0, 126.2, 127.2, 129.9, 131.5, 138.4, 140.0, 149.8, 150.2, 157.6, 159.8, 164.4, 169.9. ESI-MS: 518.1 ($C_{25}H_{23}F_3N_3O_4S$, $[M+H]^+$). Anal. Calcd for $C_{25}H_{22}F_3N_3O_4S$: C 58.02, H 4.28, N 8.12; Found: C 58.24, H 4.41, N 8.01.

*3.4.17. 2-(2-(2-Fluorophenyl)-4-(2,3,4-trimethoxyphenyl)oxazol-5-ylthio)-4,5-dimethylpyrimidine (**6df**)*

Colorless crystals, yield 56.0%. Mp: 116–117 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.31–2.36 (2s, 6H), 3.75–3.91 (3S, 9H), 6.30 (d, $J=8.8$ Hz, 1H), 6.93 (d, $J=8.8$ Hz, 1H), 7.05–7.50 (m, 4H), 8.36 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 17.9, 18.0, 56.2, 56.3, 56.5, 108.4, 112.6, 116.7, 121.9, 123.8, 124.6, 125.3, 126.5, 129.6, 131.0, 138.7, 140.2, 149.5, 150.9, 157.9, 159.0, 159.4, 164.8, 169.9. ESI-MS: 468.1 ($C_{24}H_{23}FN_3O_4S$, $[M+H]^+$). Anal. Calcd for $C_{24}H_{22}FN_3O_4S$: C 61.66, H 4.74, N 8.99; Found: C 61.47, H 5.02, N 9.21.

*3.4.18. 4,5-Dimethyl-2-(2-(pyridin-3-yl)-4-(2,3,4-trimethoxyphenyl)oxazol-5-ylthio)pyrimidine (**6dg**)*

Colorless crystals, yield 54.1%. Mp: 158–159 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.34–2.40 (2s, 6H), 3.77–3.90 (3s, 9H), 6.33 (d, $J=8.8$ Hz, 1H), 6.92 (d, $J=8.8$ Hz, 1H), 7.40 (q, 1H), 7.92 (d, $J=7.7$ Hz, 1H), 8.26 (s, 1H), 8.61 (d, $J=6.1$ Hz, 1H), 8.89 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 17.6, 17.7, 56.2, 56.3, 56.4, 108.1, 112.4, 122.1, 123.9, 124.4, 125.6, 126.3, 134.7, 138.4, 140.0, 148.3, 150.0, 150.2, 157.6, 159.0, 159.5, 164.4, 169.5. ESI-MS: 451.1 ($C_{23}H_{23}N_4O_4S$, $[M+H]^+$). Anal. Calcd for $C_{23}H_{22}N_4O_4S$: C 61.32, H 4.92, N 12.44; Found: C 61.41, H 5.09, N 12.17.

*3.4.19. 2-(2-(2-Chlorophenyl)-4-(2,3,4-trimethoxyphenyl)oxazol-5-ylthio)-4,5-dimethylpyrimidine (**6dh**)*

Colorless crystals, yield 61.1%. Mp: 136–137 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.30–2.36 (2s, 6H), 3.75–3.9 (3s, 9H), 6.28 (d, $J=8.8$ Hz, 1H), 6.90 (d, $J=8.8$ Hz, 1H), 7.18–7.47 (m, 4H), 8.26 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 17.8, 18.0, 56.2, 56.3, 56.5, 108.3, 112.3, 121.9, 125.7, 126.6, 127.8, 129.3, 129.8, 130.7, 132.8, 136.8, 138.3, 140.1, 149.6, 150.6, 158.1, 159.4, 164.2, 169.6. ESI-MS: 484.1 ($C_{24}H_{23}ClN_3O_4S$, $[M+H]^+$). Anal. Calcd for $C_{24}H_{22}ClN_3O_4S$: C 59.56, H 4.58, N 8.68; Found: C 59.69, H 4.30, N 9.02.

*3.4.20. 4,5-Dimethyl-2-(2-phenyl-4-(2,3,4-trimethoxyphenyl)oxazol-5-ylthio)pyrimidine (**6di**)*

Colorless crystals (yield 51.7%). Mp: 96–97 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.33–2.40 (2s, 6H), 3.77–3.91 (3s, 9H), 6.24 (d, $J=8.8$ Hz, 1H), 6.92 (d, $J=8.8$ Hz, 1H), 7.26–7.49 (m, 5H), 8.30 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 17.9, 18.0, 56.4, 56.5, 56.6, 108.3, 112.2, 122.0, 125.7, 126.3, 126.4, 127.9, 129.1, 129.7, 138.4, 140.0, 149.4, 151.1, 158.2, 159.6, 164.4, 169.8. ESI-MS: 450.1 ($C_{24}H_{24}N_3O_4S$, $[M+H]^+$). Anal. Calcd for $C_{24}H_{23}N_3O_4S$: C 64.13, H 5.16, N 9.35; Found: C 64.01, H 5.44, N 9.64.

3.5. Antiproliferative assay

The method for cytotoxicity evaluation was described elsewhere [26,27] with some modifications. Briefly, target tumor cells were grown to log phase in *RPMI 1640* medium supplemented with 10% fetal bovine serum. After diluting to 3×10^4 cells ml^{-1} with the complete medium, 100 μL of the obtained cell suspension was added to each well of 96-well culture plates. The subsequent incubation was permitted at 37 °C, 5% CO_2 atmosphere for 24 h before the cytotoxicity assessment. Tested samples at pre-set concentrations were added to 6 wells with 5-fluorouracil co-assayed as a positive reference. After 48-h exposure period, 25 μL of PBS containing 2.5 mg ml^{-1} of MTT (=3-(4,5-dimethylthiazol-2-yl)-2,

5-diphenyltetrazolium bromide) was added to each well. And 4 h later the medium was replaced by 150 μL DMSO to solubilize the purple formazan crystals produced. The absorbance at 570 nm of each well was measured on an ELISA plate reader. The data represented the mean of three experiments in triplicate. The IC_{50} value was defined as the concentration at which 50% survival of cells was observed. The results are listed in Table 2.

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References

[1] O.A. Spinelli, Ital. Soc. Chem. 3 (1999) 301.
[2] P. Conti, C. Dallanoce, M.D. Amici, C.D. Micheli, K.N. Klotz, Bioorg. Med. Chem. 6 (1998) 401.
[3] A. Mishra, S.K. Jain, J.G. Asthana, Orient. J. Chem. 14 (1998) 151.
[4] D.H. Ko, M.F. Maponya, M.A. Khalil, E.T. Oriaku, Z. You, J. Med. Chem. Res. 8 (1998) 313.
[5] Y.Y. Kang, K.J. Shin, K.H. Yoo, K.J. Seo, C.Y. Hong, C.S. Lee, S.Y. Park, D.J. Kim, S.W. Park, Bioorg. Med. Chem. Lett. 10 (2000) 95.
[6] S. Srivastava, L.K. Bajpai, S. Batra, A.P. Bhaduri, J.P. Maikhuri, G. Gupta, J.D. Dhar, Bioorg. Med. Chem. 7 (1999) 2607.
[7] P. Wipf, J.M. Fletcher, L. Scarone, Tetrahedron Lett. 46 (2005) 5463.
[8] H. Razavi, E.T. Powers, H.E. Purkey, S.L. Adamski-Werner, K.P. Chiang, M.T.A. Dendle, J.W. Kelly, Bioorg. Med. Chem. Lett. 15 (2005) 1075.
[9] P.C. Lv, H.Q. Li, J.Y. Xue, L. Shi, H.L. Zhu, Eur. J. Med. Chem. 44 (2009) 908–914.
[10] P. Cao, H. Ding, H.M. Ge, H.L. Zhu, Chem. Biodivers. 4 (2007) 881.
[11] M. Sriram, J.J. Hall, N.C. Grohmann, T.E. Strecker, T. Wootton, A. Franken, M.L. Trawick, K.G. Pinney, Bioorg. Med. Chem. 16 (2008) 8161–8171.
[12] R. Romagnoli, P.G. Baraldi, T. Sarkar, M.D. Carrion, O. Cruz-Lopez, C.L. Cara, M. Tolomeo, S. Grimaudo, A.D. Cristina, M.R. Pipitone, J. Balzarini, R. Gambari, L. Ilaria, R. Saletti, A. Brancale, E. Hamel, Bioorg. Med. Chem. 16 (2008) 8419–8426.
[13] K. Odlo, J. Hentzen, J.F. dit Chabert, S. Ducki, Osman A.B.S.M. Gani, I. Sylte, M. Skrede, V.A. Flørenes, T.V. Hansen, Bioorg. Med. Chem. 16 (2008) 4829–4838.
[14] N. Xue, X.C. Yang, R. Wu, J. Chen, Q.J. He, B. Yang, X.Y. Lu, Y.Z. Hu, Bioorg. Med. Chem. 16 (2008) 2550–2557.
[15] P.C. Lv, Z.P. Xiao, R.Q. Fang, H.Q. Li, H.L. Zhu, Eur. J. Med. Chem. 44 (2009) 1779–1787.
[16] X.F. Huang, B.F. Ruan, X.T. Wang, C. Xu, H.M. Ge, H.L. Zhu, R.X. Tan, Eur. J. Med. Chem. 42 (2007) 263.
[17] S. Yang, B.A. Song, H. Zhang, D.Y. Hu, L.-H. Jin, G. Liu, J. Heterocycl. Chem. 41 (2004) 617–619.
[18] G.F. Xu, B.A. Song, P.S. Bhadury, S. Yang, P.Q. Zhang, L.H. Jin, W. Xue, D.Y. Hu, P. Lu, Bioorg. Med. Chem. 15 (2007) 3768–3774.
[19] H. Liu, Z.B. Gao, Z.Y. Yao, S.X. Zheng, Y. Li, W.L. Zhu, X.J. Tan, X.M. Luo, J.H. Shen, K.X. Chen, G.Y. Hu, H.L. Jiang, J. Med. Chem. 50 (2007) 83–93.
[20] W. Xue, B.A. Song, W. He, H. Wang, S. Yang, L.H. Jin, D.Yu. Hu, G. Liu, P. Lu, J. Heterocycl. Chem. 43 (2006) 867–871.
[21] A.R. Katritzky, Z.Q. Wang, C.D. Hall, N.G. Akhmedov, A.A. Shestopalov, P.J. Steel, J. Org. Chem. 68 (2003) 9093–9099.
[22] A. Paola, C. Patricia, C. Riccardo, G. Lucedio, R. Corrado, S. Pierluigi, J. Heterocycl. Chem. 41 (6) (2004) 971–974.
[23] A.A. Mohamed, R.M. El-Sherbiny, Bioorg. Med. Chem. 15 (2007) 1206–1211.
[24] Patrick Dallemagne, Lan Pham Khanh, Abdellah Alsaïdi, Isabelle Varlet, Valérie Collot, Magalie Paillet, Ronan Bureau, Sylvain Rault, Bioorg. Med. Chem. 11 (2003) 1161–1167.
[25] D. Kumar, M.R. Jacob, M.B. Reynolds, S.M. Kerwin, Bioorg. Med. Chem. 10 (2002) 3997–4004.
[26] M.S. Malamas, J. Sredy, C. Moxham, A. Katz, W. Xu, R. McDevitt, F.O. Adebayo, D.R. Sawicki, L. Seestaller, D. Sullivan, J.R. Taylor, J. Med. Chem. 43 (2000) 1293.
[27] X. Chen, C. Plasencia, Y. Hou, N. Neamati, J. Med. Chem. 48 (2005) 1098.