

Identification of antitumor activity of pyrazole oxime ethers

Hyun-Ja Park, Kyung Lee, Su-Jin Park, Bangle Ahn, Jong-Cheol Lee,
HeeYeong Cho and Kee-In Lee*

*Bio-Organic Science Division, Korea Research Institute of Chemical Technology, PO Box 107,
Yusong, Taejeon 305-600, Republic of Korea*

Received 17 January 2005; revised 15 March 2005; accepted 22 March 2005

Available online 26 May 2005

Abstract—A series of pyrazole oxime ether derivatives were prepared and examined as cytotoxic agents. In particular, 5-phenoxy-pyrazole was comparable to doxorubicin, while exhibiting very potent cytotoxicity against XF 498 and HCT15.

© 2005 Elsevier Ltd. All rights reserved.

1. Introduction

The pyrazole ring is a prominent structural motif found in numerous pharmaceutically active compounds. Due to the easy preparation and rich biological activity, pyrazole framework plays an essential role in biologically active compounds and therefore represents an interesting template for combinatorial¹ as well as medicinal chemistry.^{2–4} Indeed, pyrazole-based derivatives have shown several biological activities as seen in COX-2,² p38 MAP kinase,³ and CDK2/Cyclin A inhibitors.⁴ Many of them are currently being tested and/or clinically evaluated for new drug discovery.

In the search for antitumor agents, a certain number of in-house-stock pyrazole oxime compounds exhibited promising antiproliferative properties against several kinds of human tumor cell lines. Our attention was focused on the pyrazole scaffold, which produces a number of compounds that are constrained to a limited

number of conformations by heterocyclic core and hindered rotation by substituents. This prompted us to synthesize pyrazole oxime ether derivatives and evaluate their inhibitory potential against tumor cell lines.

In order to find structural types, we needed a systematic replacement with a wide range of substituents within pyrazole moiety. We envisioned that the Vilsmeier–Haack chloroformylation of pyrazolone would offer a quite straightforward and easy access to a number of multi-functionalized pyrazole oxime ethers, as shown in Figure 1. Thus, the starting pyrazolone could be prepared by the condensation of the corresponding β -keto ester with hydrazines, according to the well-known procedure. The remaining synthesis included (a) Vilsmeier–Haack chloroformylation of pyrazolone **A**, (b) introduction of nucleophile into 5-chloropyrazole **B** to produce 5-substituted pyrazole **C** by nucleophilic aromatic substitution, and (c) oximation of 4-formylpyrazole **C** and (d) the subsequent Williamson synthesis to

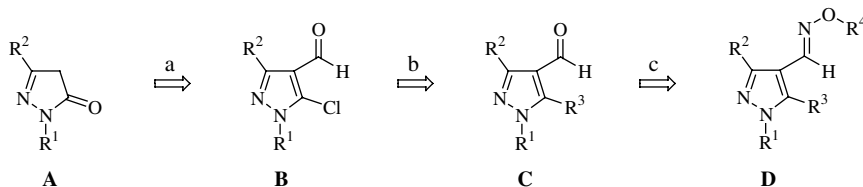


Figure 1. Easy access to a number of multi-functionalized pyrazole oxime ethers.

Keywords: Pyrazolone; Chloroformylation; Pyrazole oxime ether; Cytotoxicity.

* Corresponding author. Tel.: +82 42 860 7186; fax: +82 42 860 7160; e-mail: kilee@kRICT.re.kr

give pyrazole oxime ether **D**. Here, we would like to report the generation of multi-functionalized pyrazole oxime ethers and their preliminary biological results.

2. Results and discussion

2.1. Synthesis of pyrazole oxime ethers

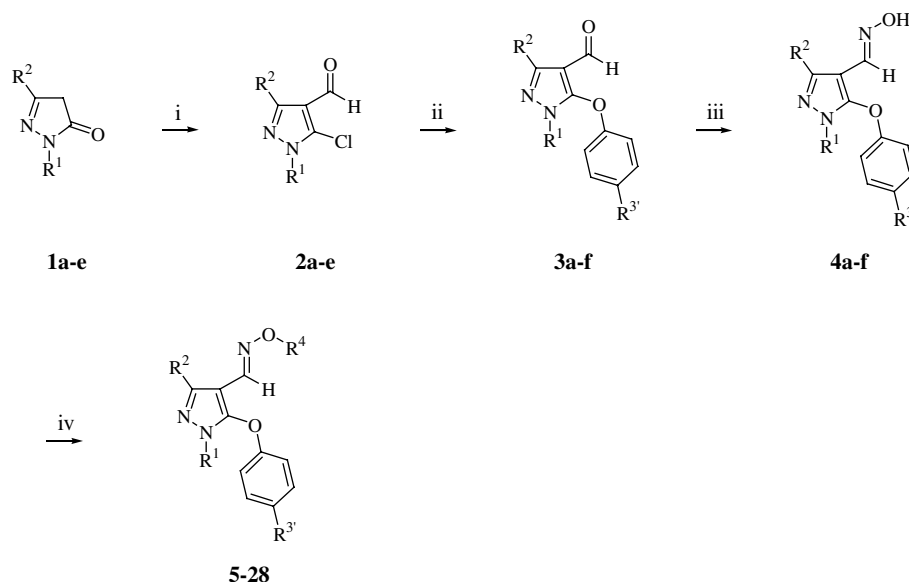
The starting pyrazolone **1a** ($R^1 = \text{Me}$, $R^2 = \text{Me}$) was easily synthesized by the condensation of ethyl acetoacetate with methylhydrazine in a quantitative yield. Also, the known pyrazolones **1b–e** were prepared from the corresponding two components, respectively.⁵ The pyrazolones **1a–e** were then subjected to the Vilsmeier–Haack chloroformylation using DMF and an excess POCl_3 to yield the corresponding 5-chloro-4-formylpyrazoles **2a–e**, according to the literature procedures.⁶ Previously, we studied the facile introduction of nucleophiles into 5-chloro-pyrazole, activated by the *ortho*-formyl group, by the nucleophilic aromatic substitution.⁷ Thus, the reaction was simply carried out by heating a

mixture of 5-chloropyrazole, phenol, and KOH in DMF and gave 5-phenoxy pyrazole derivatives **3a–f**, respectively, without any problem. Finally, many pyrazole oxime ethers were generated by the oximation of 4-formylpyrazoles with hydroxylamine and the subsequent Williamson synthesis of 5-phenoxy pyrazole oximes with various alkyl halides, as shown in Scheme 1.

2.2. Antitumor activities of pyrazole oxime ethers

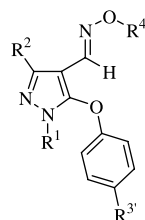
The antiproliferative potential of the synthesized compounds **5–28** was determined in vitro against several human tumor cell lines such as HepG2 (liver), MCF7 (breast), MKN45 (stomach), and A549 (lung) by sulforhodamine B (SBR) assay.⁸ The cytotoxicity values were obtained as % inhibition at 1 μM and are summarized in Table 1 showing different sub-class of structural types.

The table shows pyrazole oxime ether compounds **5–15** with random alkyl or aromatic groups at R^1 and R^2 positions, still commonly have phenoxy at the R^3 and benzyl group at the R^4 position. The results exhibit that



1/2	R^1	R^2	3/4	R^1	R^2	$R^{3'}$
a	Me	Me	a	Me	Me	H
b	Ph	Me	b	Me	Me	Cl
c	Ph	Pr^i	c	Ph	Me	Cl
d	Ph	Ph	d	Ph	Pr^i	Cl
e	2-Py ^a	Me	e	Ph	Ph	Cl
			f	2-Py	Me	H

Scheme 1. Reagents and conditions: (i) POCl_3 , DMF, 120 °C; (ii) HOPh (for **3a** and **3f**) or HOPh-*p*-Cl (for **3b–e**), KOH, DMF, 120 °C; (iii) NH_2OH , NaOH, MeOH, 60 °C; (iv) $\text{R}^4\text{-X}^b$ ($\text{X} = \text{Cl}$ or Br), KOH/DMSO/50 °C or NaH/THF/0 °C. ^a2-Py = 2-pyridinyl. ^bThe structures of R^4 are shown in Table 1.

Table 1. Cytotoxicity of pyrazole oxime ether

Compd.	4	R ⁴	% Inhibition at 1 μ M			
			HepG2	MCF7	MKN45	A549
5	4a	CH ₂ Ph-3-OMe	−41.2	8.4	−19.6	1.0
6		CH ₂ Ph-4-Me	8.4	38.2	17.9	29.1
7		CH ₂ Ph-4-CF ₃	5.8	30.5	11.0	34.7
8		CH ₂ Ph-4-NO ₂	−2.8	24.0	18.3	39.4
9		CH ₂ Ph-2-Me-3-Ph	−13.2	24.4	−12.1	5.0
10	4c	CH ₂ Ph-4-CO ₂ Et	−31.8	12.0	−17.8	−9.9
11		CH ₂ Ph-4-CO ₂ Bu ^t	−31.1	−8.4	−9.9	−6.5
12	4d	CH ₂ Ph-4-CO ₂ Bu ^t	−14.7	−4.9	−27.0	−10.6
13		CH ₂ Ph-4-CF ₃	−2.2	−1.9	−15.4	−12.1
14	4e	CH ₂ Ph-2-Me-3-Ph	−14.8	−17.5	−15.0	−10.1
15	4f	CH ₂ Ph-4-CO ₂ Bu ^t	−25.1	−14.8	−9.8	−9.1
16	4a	(CH ₂) ₂ NMe ₂	−36.1	8.9	−29.0	−5.9
17		(CH ₂) ₂ N	−25.0	7.7	−24.2	−8.2
18		(CH ₂) ₂ N	−29.0	3.2	−22.5	−9.9
19		(CH ₂) ₂ N	−40.5	5.4	−28.0	−19.4
20		(CH ₂) ₂ N	6.7	23.4	10.5	28.4
21		(CH ₂) ₂ N	14.4	37.7	15.4	39.7
22		(CH ₂) ₂ N	19.8	32.0	19.2	44.7
23	4b	CH ₂ Ph-4-Me	31.3	30.7	30.4	50.0
24		CH ₂ Ph-4-OMe	13.9	37.0	28.1	43.9
25		CH ₂ Ph-4-CF ₃	20.6	16.4	27.6	50.9
26		CH ₂ Ph-4-NO ₂	18.4	27.1	24.6	39.6
27		CH ₂ Ph-4-CO ₂ Me	20.3	33.6	26.1	49.9
28		CH ₂ Ph-4-CO ₂ Et	27.4	33.9	20.9	48.2

only three compounds **6–8** (R¹, R² = Me) have moderate potency of around 30% inhibition at 1 μ M against MCF7 and A549, even though weak cytotoxicity was observed for other analogues. It is interesting to note that the compounds (**6–7**) having electron-withdrawing groups at the R⁴ proved to be more active than the compound **5**. When the methyl groups on pyrazole had been replaced by a bigger group (**10–13**), the detrimental potency was observed even in the presence of the electron-withdrawing groups. This clearly suggests that next approach should narrow a scope into the structural pattern featuring small alkyl groups at R¹ and R² positions.

Thus, starting from **3a** and **3b**, wide ranges of compounds with benzyl or 2-aminoethyl group at the R⁴ position, in principle, possessing a hydrophobic or hydrophilic character were prepared in good to fair yield. The structures of the prepared compounds **16–28**

are also indicated in Table 1. The compounds with two carbon atoms between the oxime and the side-chain nitrogen atom (**16–19**) show a very weak potency comparing to those with benzyl group (**6–8**). Thus, introduction of flexible spacer or hydrophilic surrounding is not necessary, presumably, due to moderate out of plane in certain directions. Interestingly, the compounds with *N'*-substituted piperazine moiety (**20–22**) regained the potency reaching around 40% inhibition at 1 μ M against A549. We believed that, in those cases, electronic character could be diminished in a bulky hydrophobic environment.

The compounds with benzyl group at R⁴ position show the potent cytotoxic activities against broad range of tumor cell lines. The benzylic derivatives **23–28** are more potent than those of 2-aminoethyl derivatives (**16–19**). While all of the compounds exhibited moderate activity

against four cell lines, they were strongly effective against A549 with >40% inhibition at 1 μ M. The compounds **25–26** sustained a slightly higher potency than the parent compounds **7–8**, which led us to explore the modification of the R³ position of the pyrazole skeleton.

From the results in Table 1, we needed to design the molecular structures for further study. It is desirable that the pyrazole skeleton should have smaller groups at the R¹ and R², and bulky group at the R⁴ position. Generally, the results show that the introduction of benzyl group at R⁴ enhanced the cytotoxic activities and also suggest that the hydrophobic group is more favorable. From this point of view, we eventually chose the benzyl group hanging *tert*-butyl ester at *para* position of the phenyl ring. Next, we readily undertook a modification of the remaining R³ position of the pyrazole skeleton.

The compounds **29–38** were similarly prepared as depicted in Scheme 1. Starting from **2a**, we extended the nucleophilic aromatic substitution to the readily available heteroatom-containing nucleophiles such as dimethylamine, pyrrolidine, imidazole, indole, and thio-

phenol. The reaction generously allowed the introduction of a wide range of heterocycles into the pyrazole ring.⁷ The remaining steps included oximation of 4-formyl-pyrazole derivatives and the subsequent alkylation with the *tert*-butyl ester, respectively. The structures of R³ are depicted in Table 2.

The growth suppressing potential of pyrazol oxime ether derivatives was investigated by determining their IC₅₀ values by SBR assay against human solid tumor cell lines: A549 (non-small cell lung), SKOV-3 (ovarian), SKMEL-2 (melanoma), XF 498 (CNS), and HCT15 (colon). The cytotoxic activities of the compounds prepared including cisplatin and doxorubicin are summarized in Table 2. In general, the amine derivatives **29–35** commonly show decreased cytotoxicity compared to the oxygen derivatives, but are still comparable to cisplatin. The compounds **36–38** that contain phenyl residue at the R³ position show relatively potent activity. Interestingly, the compound **36** was known as fenpyroximate, one of the most important insecticides acting at proton-translocating NADH:ubiquinone oxidoreductase.⁹ The compounds **36** and **37** were proved to be less or more active than doxorubicin depending on the cell

Table 2. Antitumor activity of 3-substituted pyrazole oxime ether

Compound	R ³	Cytotoxicity IC ₅₀ (μ g/mL)				
		A549	SKOV-3	SKMEL-2	XF498	HCT15
29	NMe ₂	2.76	9.06	23.94	3.87	6.22
30		0.13	3.19	14.44	0.12	0.10
31		0.39	8.87	16.71	1.04	1.83
32		1.64	3.91	24.90	2.67	2.48
33		2.49	9.63	28.78	5.51	3.63
34		5.93	14.08	9.35	8.15	8.67
35		0.43	2.07	26.51	1.61	1.57
36		0.12	0.21	13.27	0.04	0.02
37		0.10	0.28	18.78	0.02	0.01
38		0.13	0.92	4.91	0.28	0.26
Cisplatin	—	3.09	3.42	3.28	3.47	6.91
Doxorubicin	—	0.05	0.09	0.07	0.09	0.28

lines, while exhibiting very potent cytotoxicity against XF 498 and HCT15. In this regard, the phenoxy derivative could be a promising lead candidate, although its molecular target remains to be determined by further studies.

In summary, a number of multi-functionalized pyrazole oxime ethers **5–38** were conveniently prepared from pyrazolones utilizing Vilsmeier–Haack chloroformylation. Investigation of structure–activity relationships has identified 5-phenoxy pyrazole as a promising scaffold showing potent cytotoxicity against various human tumor cell lines. The compounds **36** and **37** were proved to be less or more active than doxorubicin depending on the cell lines, while exhibiting very potent cytotoxicity against XF 498 and HCT15. Further modification of the structure and identification of its molecular target are under investigation.

3. Experimental

3.1. Preparation of 5-pyrazolones (1a–e)

The starting pyrazolones were readily prepared by the reactions of the appropriate hydrazines with β -ketoesters according to the literature procedures.⁵

3.2. Preparation of 5-chloro-4-formylpyrazoles (2a–e)

The known 5-chloro-4-formylpyrazoles were prepared from the 5-pyrazolones employing Vilsmeier–Haack chloroformylation.⁶ Thus, 5-pyrazolones were heated with an excess phosphorus oxychloride in DMF to afford the corresponding 5-chloro-4-formylpyrazoles.

3.3. Preparation of 5-substituted-4-formylpyrazoles (3a–f)

The nucleophilic aromatic substitution was conveniently carried out by heating a mixture of 5-chloro-4-formylpyrazole and the corresponding nucleophile with powdered KOH in DMF to give 5-substituted pyrazole according to the previously described procedure.⁷

3.4. Preparation of pyrazole oximes (4a–f)

The treatment of 4-formylpyrazole with hydroxylamine hydrochloride in NaOH/EtOH gave the corresponding pyrazole oxime in good yield. All pyrazole oximes were isolated as single isomers and assigned as *E*-geometry.^{6a}

3.5. General procedure for the synthesis of **6**

To an ice-cooled solution of **4a** (232 mg, 1.0 mmol) in THF (10 mL) were added NaH (31 mg, 1.3 mmol) and then 4-methylbenzyl chloride (169 mg, 1.2 mmol) under the nitrogen atmosphere. The solution was stirred for overnight at room temperature. The solvent was removed and the resulting residue was partitioned with EtOAc and water. The organic layer was washed successively with brine and water and dried over Na₂SO₄, then evaporated under reduced pressure to give a residue.

The residue was purified by flash chromatography on silica gel (hexane/EtOAc = 6:1) to give **6** (189 mg, 56%); ¹H NMR (DMSO-*d*₆) δ 7.71 (s, 1H), 7.41–7.36 (m, 2H), 7.18–7.08 (m, 5H), 6.96–6.93 (m, 2H), 4.85 (s, 2H), 3.54 (s, 3H), 2.27 (s, 3H), 2.23 (s, 3H); MS (70 eV) *m/z* (rel intensity) 335 (M⁺, 3), 227 (8), 128 (9), 105 (100), 77 (23); Anal. Calcd for C₂₀H₂₁N₃O₂: C, 71.62; H, 6.31; N, 12.53; O, 9.54. Found: C, 71.58; H, 6.78; N, 12.97; O, 9.75.

7. 53% (yield); ¹H NMR (DMSO-*d*₆) 7.80 (s, 1H), 7.66–7.63 (m, 2H), 7.45–7.34 (m, 4H), 7.16–7.11 (m, 1H), 6.94–6.92 (m, 2H), 5.00 (s, 2H), 3.54 (s, 3H), 2.21 (s, 3H); MS (70 eV) *m/z* (rel intensity) 389 (M⁺, 20), 214 (90), 199 (91), 144 (44), 77 (44).

8. 58% (yield); ¹H NMR (CDCl₃) 8.14–8.12 (m, 2H), 7.84 (s, 1H), 7.40–7.37 (m, 2H), 7.32–7.25 (m, 1H), 7.12–7.07 (m, 1H), 6.87–6.84 (m, 2H), 5.06 (s, 2H), 3.59 (s, 3H), 2.32 (s, 3H); MS (70 eV) *m/z* (rel intensity) 366 (M⁺, 40), 258 (15), 214 (38), 199 (58), 128 (42), 77 (100); Anal. Calcd for C₁₉H₁₈N₄O₄: C, 62.29; H, 4.95; N, 15.29; O, 17.47. Found: C, 62.10; H, 5.21; N, 16.00; O, 17.21.

20. 30% (yield); ¹H NMR (CDCl₃) 7.69 (s, 1H), 7.24–7.16 (m, 7H), 7.02–7.01 (m, 1H), 6.80 (d, 2H, *J* = 9.0 Hz), 4.02 (t, 2H, *J* = 6.0 Hz), 3.52 (s, 3H), 3.42 (s, 2H), 2.50 (t, 2H, *J* = 6.0 Hz), 2.29 (s, 3H); MS (70 eV) *m/z* (rel intensity) 433 (M⁺, 5), 216 (16), 203 (37), 189 (100), 91 (71); Anal. Calcd for C₂₅H₃₁N₅O₂: C, 69.26; H, 7.21; N, 16.15; O, 7.38. Found: C, 68.08; H, 7.91; N, 18.24; O, 9.06.

21. 44% (yield); ¹H NMR (CDCl₃) 7.78 (s, 1H), 7.58–7.56 (m, 2H), 7.46–7.43 (m, 2H), 7.34–7.28 (m, 2H), 7.11–7.06 (m, 1H), 6.91–6.88 (m, 2H), 4.14–4.09 (m, 2H), 3.55 (s, 2H), 2.59 (t, 2H, *J* = 3.0 Hz), 2.48 (s, 8H); MS (70 eV) *m/z* (rel intensity) 501 (M⁺, 8), 271 (15), 257 (100), 216 (22), 159 (33).

22. 58% (yield); oil; ¹H NMR (CDCl₃) 7.78 (d, 2H, *J* = 8.1 Hz), 7.62 (s, 1H), 7.23–7.12 (m, 4H), 6.96–6.91 (m, 1H), 6.75–6.72 (m, 2H), 4.01–3.94 (m, 2H), 2.47 (s, 4H), 2.36 (s, 4H), 3.39 (s, 2H), 1.49 (m, 2H), 1.44 (s, 9H); MS (70 eV) *m/z* (rel intensity) 533 (M⁺, 3), 342 (30), 233 (58), 135 (100), 57 (85); Anal. Calcd for C₃₀H₃₉N₅O₄: C, 67.52; H, 7.37; N, 13.12; O, 11.99. Found: C, 65.19; H, 6.90; N, 12.71; O, 11.88.

23. 52% (yield); ¹H NMR (CDCl₃) 7.70 (s, 1H), 7.25–7.01 (m, 6H), 6.75–6.70 (m, 2H), 5.36 (s, 2H), 3.53 (s, 3H), 3.42 (s, 3H), 2.19 (s, 3H); MS (70 eV) *m/z* (rel intensity) 369 (M⁺, 52), 242 (30), 105 (100), 77 (42), 65 (20); Anal. Calcd for C₂₀H₂₀ClN₃O₂: C, 64.95; H, 5.45; N, 11.36; O, 8.65. Found: C, 65.61; H, 5.51; N, 13.10; O, 8.63.

25. 88% (yield); ¹H NMR (CDCl₃) 7.83 (s, 1H), 7.31–7.23 (m, 2H), 7.56–7.41 (m, 2H), 7.31–7.23 (m, 2H), 6.84–6.79 (m, 2H), 5.13 (s, 2H), 3.61 (s, 3H), 2.34 (s, 3H); MS (70 eV) *m/z* (rel intensity) 423 (M⁺, 60), 248 (100), 233 (62), 159 (90), 123 (47).

28. 47% (yield); ^1H NMR (CDCl_3) 7.92–7.89 (s, 2H), 7.74 (s, 1H), 7.22–7.15 (m, 4H), 6.74–6.71 (m, 2H), 4.94 (s, 2H), 4.29 (q, 2H, $J = 7.2$ Hz), 1.32 (t, 3H, $J = 7.1$ Hz), 3.51 (s, 3H), 2.25 (s, 3H); MS (70 eV) m/z (rel intensity) 427 (M^+ , 47), 247 (100), 163 (87), 135 (60), 107 (40); Anal. Calcd for $\text{C}_{22}\text{H}_{22}\text{ClN}_3\text{O}_4$: C, 61.75; H, 5.18; N, 9.82; O, 14.96. Found: C, 59.43; H, 5.19; N, 10.54; O, 14.63.

30. 58% (yield); ^1H NMR (CDCl_3) 8.14 (s, 1H), 7.96–7.99 (d, 2H, $J = 8.1$ Hz), 7.41–7.44 (d, 2H, $J = 8.1$ Hz), 5.15 (s, 2H), 3.65 (s, 3H), 3.13–3.18 (t, 2H, $J = 6.6$ Hz), 2.26 (s, 3H), 1.87–1.91 (m, 2H), 1.60 (s, 9H); MS (70 eV) m/z (rel intensity) 398 (M^+ , 3), 325 (36), 191 (100), 174 (38), 134 (33); Anal. Calcd for $\text{C}_{22}\text{H}_{30}\text{N}_4\text{O}_3$: C, 66.31; H, 7.59; N, 14.06; O, 12.04. Found: C, 65.35; H, 8.11; N, 14.67; O, 12.95.

36. 79% (yield); ^1H NMR (CDCl_3) 7.93–7.90 (d, 2H, $J = 9.0$ Hz), 7.82 (s, 1H), 7.26–7.33 (m, 4H), 7.13–7.09 (t, 1H, $J = 12.0$ Hz), 6.88–6.86 (d, 2H, $J = 8.8$ Hz), 5.03 (s, 2H), 3.59 (s, 3H), 2.34 (s, 3H), 1.59 (s, 9H); ^{13}C NMR (CDCl_3) δ 16.0, 29.4, 35.4, 76.6, 82.2, 101.4, 116.5, 124.9, 129.1, 130.7, 131.2, 132.6, 142.3, 143.7, 148.2, 149.0, 158.0, 166.8; Anal. Calcd for $\text{C}_{24}\text{H}_{27}\text{N}_3\text{O}_4$: C, 68.39; H, 6.46; N, 9.97. Found: C, 68.10; H, 6.62; N, 9.56; HRMS (EI) calcd for $\text{C}_{24}\text{H}_{27}\text{N}_3\text{O}_4$: 421.2002 found: 421.2001.

38. 44% (yield); ^1H NMR (CDCl_3) 8.13 (s, 1H), 7.87–7.90 (d, 2H, $J = 8.1$ Hz), 7.32–7.35 (d, 2H, $J = 8.1$ Hz), 7.09–7.18 (m, 3H), 6.89–6.92 (m, 2H), 5.09 (s, 2H), 3.70 (s, 3H), 2.35 (s, 3H), 1.51 (s, 9H); MS (70 eV) m/z (rel intensity) 437 (M^+ , 27), 364 (35), 231 (51), 135 (100), 106 (80), 90 (58); Anal. Calcd for $\text{C}_{24}\text{H}_{27}\text{N}_3\text{O}_3\text{S}$: C, 65.88; H, 6.22; N, 9.60; O, 10.97; S, 7.33. Found: C, 65.23; H, 6.59; N, 10.42; O, 11.36; S, 7.63.

References and notes

- (a) Tietze, L. F.; Steinmetz, A.; Balkenhohl, F. *Bioorg. Med. Chem. Lett.* **1997**, 7, 1303; (b) Brooking, P.; Doran, A.; Grimsey, P.; Hird, N. W.; MacLachlan, W. S.; Vimil, M. *Tetrahedron Lett.* **1999**, 40, 1405; (c) Grosche, P.; Holtzel, A.; Walk, T. B.; Trautwein, A. W.; Jung, G. *Synthesis* **1999**, 1961; (d) Watson, S. P.; Wilson, R. D.; Judd, D. B.; Richards, S. A. *Tetrahedron Lett.* **1997**, 38, 9065.
- Penning, T. D.; Talley, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; Docter, S.; Graneto, M. J.; Lee, L. F.; Malecha, J. W.; Miyashiro, J. M.; Rogers, R. S.; Rogier, D. J.; Yu, S. S.; Anderson, G. D.; Burton, E. G.; Cogburn, J. N.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Veenhuizen, A. W.; Zhang, Y. Y.; Isakson, P. C. *J. Med. Chem.* **1997**, 40, 1347.
- Regan, J.; Breitfelder, S.; Cirillo, P.; Gilmore, T.; Graham, A. G.; Hickey, E.; Klaus, B.; Madwed, J.; Moriak, M.; Moss, N.; Pargellis, C.; Pav, S.; Proto, A.; Swinamer, A.; Tang, L.; Torcellini, C. *J. Med. Chem.* **2002**, 45, 2994.
- Pevarello, P.; Brasca, M. G.; Amici, R.; Orsini, P.; Traquandi, G.; Corti, L.; Piutti, C.; Sansonna, P.; Villa, M.; Pierce, B. S.; Pulici, M.; Giordano, P.; Martina, K.; Fritzen, E. L.; Nugent, R. A.; Casale, E.; Cameron, A.; Ciomei, M.; Roletto, F.; Isacchi, A.; Fogliatto, G.; Pesenti, E.; Pastori, W.; Marsiglio, A.; Leach, K. L.; Clare, P. M.; Fiorentini, F.; Varasi, M.; Vulpetti, A.; Warpehoski, M. A. *J. Med. Chem.* **2004**, 47, 3367.
- (a) Khan, M. A.; Ellis, G. P.; Pagotto, M. C. *J. Heterocycl. Chem.* **2001**, 38, 193; (b) Reiner, K.; Richter, R.; Hauptmann, S.; Becher, J.; Hennig, L. *Tetrahedron* **1995**, 51, 13291.
- (a) Holzer, W.; Hahn, K. *J. Heterocycl. Chem.* **2003**, 40, 303; (b) Abd El Latiff, F. M. *J. Heterocycl. Chem.* **2000**, 37, 1659; (c) Becher, J.; Toftlund, H.; Olesen, P. H. *J. Chem. Soc., Chem. Commun.* **1983**, 740; (d) Becher, J.; Jørgensen, P. L.; Pluta, K.; Krake, N. J.; Fält-Hansen, B. *J. Org. Chem.* **1992**, 57, 2127.
- Park, M.-S.; Park, H.-J.; Park, K. H.; Lee, K.-I. *Synth. Commun.* **2004**, 34, 1541.
- (a) Rubinstein, L. V.; Shoemaker, R. H.; Paull, K. D.; Simon, R. M.; Tosini, S.; Skehan, P.; Scudiero, D. A.; Monks, A.; Boyd, M. R. *J. Natl. Cancer Inst.* **1990**, 82, 1113; (b) Skehan, P.; Storeng, R.; Scudiero, D.; Monks, A.; McMahon, J.; Vistica, D.; Warren, J. T.; Bokesch, H.; Kenney, S.; Boyd, M. R. *J. Natl. Cancer Inst.* **1990**, 82, 1107.
- (a) Miyoshi, H. *Biochim. Biophys. Acta* **1998**, 1364, 236; (b) Lümmen, P. *Biochim. Biophys. Acta* **1998**, 1364, 287.