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Synthesis, Crystal Structure and Biological Activity of 2-[(Pyridin-2-yl)methylthio]-1H-benzimidazole Derivatives postprint

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Abstract

In order to discover the novel anti-tumor agents, a series of 2-[(pyridin-2-yl)methylthio]-1H-benzimidazole derivatives were designed and synthesized, and the structures were characterized by IR, MS, and proton NMR. 2-[(3,4-Dimethoxypyridin-2-yl)methylthio]-1H-benzimidazole was investigated with X-ray crystallography, and the molecule is in orthorhombic system, space group P212121, with a = 9.1828(16), b = 11.625(2), c = 13.463(2) Z = 4, R = 0.0231 and wR = 0.0596. The antitumor activities of target compounds were evaluated against human liver cancer cell line HepG2, and human liver normal cell line HL7702 using MTT assay. The target compounds have demonstrated weak or moderate anti-tumor activity against HepG2, while all the target compounds exhibit no cytotoxic effects on HL7702.

Full Text

Preamble

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Abstract

In order to discover novel anti-tumor agents, a series of 2-[(pyridin-2-yl)methylthio]-1H-benzimidazole derivatives were designed and synthesized, and their structures were characterized. The structure of 2-[(3,4-dimethoxypyridin-2-yl)methylthio]-1H-benzimidazole was investigated by X-ray crystallography, revealing that the molecule crystallizes in the orthorhombic system, space group P2 2 2 , with unit cell parameters a = 9.1828(16), b = 11.625(2), c = 13.463(2) Å, Z = 4, R = 0.0231 and wR = 0.0596. The antitumor activities of the target compounds were evaluated against human liver cancer cell line HepG2 and human liver normal cell line HL7702 using MTT assay. The target compounds demonstrated weak or moderate anti-tumor activity against HepG2, while all compounds exhibited no cytotoxic effects on HL7702.

Keywords: 2-[(pyridin-2-yl)methylthio]-1H-benzimidazole derivatives; synthesis; crystal structure; antitumor activity
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1. Introduction

Cancer affects a large number of populations worldwide. In 2012 alone, 14.2 million new cancer cases and 8.2 million deaths occurred, and this number is projected to increase to approximately 19 million by 2030 [1].

In recent decades, benzimidazole derivatives have been discovered to exhibit various biological activities, including antibacterial, antiviral, antiallergic, cardiovascular, antitumor, analgesic, anti-inflammatory, H /K -ATPase inhibitory, and antipyretic effects [2]. Benzimidazole derivatives containing a pyridyl group have been reported to demonstrate potent anticancer and antitumor activities. For example, benzimidazole derivatives with a 2-pyridylethyl moiety at the 2-position displayed inhibitory effects on the proliferation of murine leukemia cells (L1210/0) and human T-lymphocyte cells (Molt 4/C8 and CEM/0) with IC values in the low microgram range [3,4]. Some 2-[3-(pyridin-3-yl)styryl]-1H-benzimidazole derivatives have exhibited antiproliferative activity against HeLa, HepG2, A498, MCF-7, and U937 cell lines [5]. Hybrid compounds containing both benzimidazole ring and pyridine skeleton were designed and evaluated against NCI-60 cell lines, and screening results showed that some compounds exhibit very good antitumor activity against renal cancer A498 and breast cancer MDA-MB-468, as well as significant antitumor activity against leukemia (RPMI-8226, CCRF-CEM, K-562, SR), non-small cell lung cancer (NCI-H23, A549/ATCC), and breast cancer T-47D [6].

Based on the structure-activity relationship of antitumor benzimidazole derivatives, and applying principles of bioisosterism and hybridization, a series of 2-[(pyridin-2-yl)methylthio]-1H-benzimidazole derivatives were designed and synthesized as target compounds. The synthetic route is shown in Scheme 1, following reported procedures [7-11].

Scheme 1. Synthesis of the target compounds

The target compounds were characterized by IR, proton NMR, and ESI-MS. A single crystal of one target compound was successfully grown, and its structure was determined by X-ray diffraction analysis. Preliminary pharmacological testing showed that all target compounds exhibit weak or moderate cytotoxicity against human liver cancer cell line HepG2 and no cytotoxic effects on human liver normal cell line HL7702.

2. Experimental

2.1 Apparatus and Materials

Melting points were determined on a melting-point apparatus with microscope (Zhengzhou Mingyi Instrument Equipment Co., Ltd., Zhengzhou, China) and are uncorrected. ESI mass spectra were performed on a Waters spectrometer (Waters Corporation, USA). IR spectra were recorded on a Bruker IFS55 spectrometer (KBr pellets). ^{1}H NMR spectra were recorded on a Bruker (400 MHz) NMR spectrometer (Faellanden, Switzerland) with TMS as internal standard and CDCl as solvent. Chemical shifts (values) and coupling constants (J values) are given in ppm and Hz, respectively.

All starting materials were commercially available and used directly without further purification. Reaction progress was monitored by thin layer chromatography analysis using silica gel plates (Qingdao Jiyida silica reagent factory, Qingdao, China). 2-Chloromethyl-4-methoxy-3,5-dimethylpyridine hydrochloride, 2-chloromethyl-3,4-dimethoxypyridine hydrochloride, 2-chloromethyl-3-methyl-4-(2,2,2-trifluoroethoxyl)pyridine hydrochloride, and 2-chloromethyl-4-(3-methoxypropoxy)-3-methylpyridine hydrochloride were prepared according to previously reported procedures [7,8].

2.2 Synthesis and Characterization

A mixture of 2-chloromethyl-4-methoxy-3,5-dimethylpyridine hydrochloride (0.0040 mol), 1H-benzimidazole-2-thiol (0.0040 mol), 40% aqueous sodium hydroxide solution (20 mL), and dichloromethane (20 mL) was refluxed for 15 h. After cooling to room temperature, the mixture was partitioned between dichloromethane and water. The aqueous layer was extracted with dichloromethane (3 × 10 mL), the organic layers were combined and dried over anhydrous magnesium sulphate, filtered, and purified using column chromatography (V(petroleum ether):V(ethyl acetate) = 3:1) to afford 2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylthio]-1H-benzimidazole (3a, white solid, 99.1% purity) in 85.6% yield. m.p.: 124.0–126.6 °C. EI-MS(m/z): 300.1([M+H]), 322.1([M+Na]); IR(KBr): 3577.9, 3133.6, 3056.5, 1618.6, 1592.8, 1567.3, 1501.8, 1438.3, 1270.1, 1227.1, 875.1, 762.6, 734.6; ^{1}H NMR (400 MHz, Chloroform-d): 12.73 (s, 1H), 8.27 (s, 1H), 7.62 (d, J = 9.0 Hz, 1H), 7.45 (d, J = 9.0 Hz, 1H), 7.22–7.16 (m, 2H), 4.37 (s, 2H), 3.79 (s, 3H), 2.33 (s, 3H), 2.28 (s, 3H).

Similarly, 2-[(3,4-dimethoxy-2-pyridinyl)methylthio]-1H-benzimidazole (3b) was prepared as a white solid in 85.6% yield. m.p.: 117.9–120.0 °C. EI-MS(m/z): 302.1([M+H]); IR(KBr): 3421.3, 2971.7, 2881.1, 1640.5, 1585.6, 1489.0, 1302.8, 1266.2, 1232.4, 1067.5, 820.7, 746.6. ^{1}H NMR (400 MHz, Chloroform-d): 13.01 (s, 1H), 8.28 (d, J = 5.6 Hz, 1H), 7.62 (s, 1H), 7.49 (s, 1H), 7.19 (dd, J = 6.0, 3.2 Hz, 2H), 6.87 (d, J = 5.6 Hz, 1H), 4.40 (s, 2H), 3.95 (s, 3H), 3.94 (s, 3H).

2-{[(3-Methyl-4-(2,2,2-trifluoroethoxyl)-2-pyridinyl)]methylthio}-1H-benzimidazole (3c) was prepared as a white solid in 88.0% yield. m.p.: 149.3–150.5 °C (lit [7]: 149–150 °C). EI-MS(m/z): 354.1([M+H]); IR(KBr): 3135.1, 3052.5, 2976.3, 2896.6, 2844.4, 1618.5, 1589.8, 1577.9, 1444.2, 1269.1, 1163.6, 1174.2, 1110.4, 857.9, 746.0; ^{1}H NMR (400 MHz, Chloroform-d): 12.57 (s, 1H), 8.43 (d, J = 5.5 Hz, 1H), 7.62 (s, 1H), 7.46 (s, 1H), 7.19 (dd, J = 6.0, 3.1 Hz, 2H), 6.74 (d, J = 5.6 Hz, 1H), 4.45 (m, 1H), 4.42 (s, 2H), 2.33 (s, 3H).

2-{[(4-(3-Methoxypropoxy)-3-methyl-2-pyridinyl]methylthio}-1H-benzimidazole (3d) was prepared as a white solid in 77.0% yield. m.p.: 105.1–106.0 °C. EI-MS(m/z): 344.1([M+H]); IR(KBr): 3420.1, 3267.0, 3098.9, 2966.6, 2925.0, 2837.3, 1625.5, 1599.0, 1550.3, 1510.0, 1464.4, 1382.4, 1360.8, 1323.2, 1303.4, 1260.4, 1176.3, 1164.0, 1121.3; ^{1}H-NMR (400 MHz, chloroform-d): 8.12 (d, J = 8.9 Hz, 2H), 7.54 (d, J = 8.6 Hz, 1H), 7.09–6.90 (m, 4H), 4.14–4.00 (m, 3H), 3.90 (s, 3H), 2.95–2.88 (m, 1H), 2.84 (dt, J = 12.5, 6.3 Hz, 1H), 2.78–2.71 (m, 1H), 2.60 (s, 3H), 1.10 (d, J = 6.3 Hz, 6H).

2.3 Crystal Structure Determination

A portion of target compound 3b was placed in a conical flask and dissolved in a methanol/acetone mixture (V/V = 1/1). The flask was sealed with plastic film for slow evaporation. White single crystals of 3b (0.24 mm × 0.22 mm × 0.18 mm) suitable for X-ray crystallographic analysis were obtained after 7 days. Data for 3b were collected on a Rigaku 007HF XtaLAB P200 diffractometer equipped with graphite-monochromated MoK radiation (= 0.71073 Å) using scan mode at 113 K.

In the range of 3.0 27.5°, a total of 18516 reflections were collected, with 5388 unique ones (Rint = 0.0347), of which 3181 (-11 h 11, -15 k 15, -16 l 17) were observed with I > 2 (I) and used in subsequent refinements. The intensity data were corrected for Lp factors and empirical absorption. The structure was solved by direct methods and expanded by difference Fourier techniques using SHELXL and SHELXS programs [12-14]. All non-hydrogen atoms were located from successive difference Fourier syntheses. The structure was refined by full-matrix least-squares techniques on F^2 using anisotropic thermal parameters for all non-hydrogen atoms. Hydrogen atoms were added according to theoretical models. The final cycle of refinement converged to R = 0.0231, wR = 0.0596 (w = 1/[^{2}(Fo^2) + (0.0360P)^2 + 0.1411P], where P = (Fo^2 + 2Fc^2)/3), S = 1.073, (/)max = 0.035, ( )max = 0.191, and ( )min = -0.168 e • Å ^{3}.

2.4 Antitumor Activity

Human liver cancer cell line HepG2 and human liver normal cell line HL7702 were used to evaluate the antitumor activity of target compounds in vitro by MTT assay with 5-fluorouracil as positive control [15,16]. HepG2 and HL7702 cells were harvested in logarithmic growth phase and seeded in 96-well plates at a density of 8000 cells per well, then cultured at 37 °C in humidified atmosphere containing 5% CO in Dulbecco' s modified Eagle' s medium (DMEM or RPMI-1640) with 10% fetal bovine serum (FBS) for 24 h before treatment. Test compounds were dissolved in DMSO and diluted in culture medium to obtain various concentrations. Cells were treated with target compounds and incubated overnight.

Subsequently, 20 L of MTT (5 mg/mL) was added to each well. After 4 h incubation, the medium was removed and MTT formazan was solubilized in 150 L DMSO. Optical densities (OD) were measured with a microplate reader (Bio-Tek Instruments, Inc., USA) at 490 nm. Inhibitory effects were expressed as percentage inhibition. Each assay was performed in triplicate.

3. Results and Discussion

3.1 Molecular Structure

The crystal structure of target compound 3b (0.24 mm × 0.22 mm × 0.18 mm) was confirmed by X-ray diffraction analysis. Compound 3b crystallizes in the orthorhombic space group P2 2 2 with a = 9.1828(16), b = 11.625(2), c = 13.463(2) Å, V = 1437.2(5) Å³, Z = 4, C H O N S, Dc = 1.393 g • cm ³, = 0.233 mm ¹, F(000) = 632, S = 1.073, R = 0.0222 and wR = 0.0593 for 3181 independent reflections (Rint = 0.0347) with I > 2 (I). Selected bond distances and bond angles are listed in Table 1 .

Table 1. Selected Bond Lengths (Å) and Bond Angles (°) for Compound 3b

Dist.		Dist.		Dist.	
S(1)-C(1)	1.8091(16)	N(2)-C(9)	1.311(2)	C(5)-C(6)	1.386(3)
S(1)-C(9)	1.7489(16)	N(2)-C(15)	1.396(2)	C(10)-C(11)	1.394(2)
O(1)-C(3)	1.3740(18)	N(3)-C(2)	1.347(2)	C(10)-C(15)	1.404(2)
O(1)-C(7)	1.436(2)	N(3)-C(6)	1.337(2)	C(11)-C(12)	1.384(2)
O(2)-C(4)	1.3513(19)	C(1)-C(2)	1.512(2)	C(12)-C(13)	1.395(3)
O(2)-C(8)	1.437(2)	C(2)-C(3)	1.387(2)	C(13)-C(14)	1.385(3)
N(1)-C(9)	1.362(2)	C(3)-C(4)	1.400(2)	C(14)-C(15)	1.401(2)
N(1)-C(10)	1.385(2)	C(4)-C(5)	1.392(2)		

Angle		Angle		Angle	
C(9)-S(1)-C(1)	100.84(8)	C(2)-C(3)-C(4)	119.38(14)	N(1)-C(10)-C(15)	105.28(13)
C(4)-O(2)-C(8)	117.52(13)	O(2)-C(4)-C(3)	116.11(14)	C(11)-C(10)-C(15)	122.22(15)
C(9)-N(1)-C(10)	105.87(13)	O(2)-C(4)-C(5)	125.68(15)	C(12)-C(11)-C(10)	116.91(16)
C(9)-N(2)-C(15)	103.57(13)	C(5)-C(4)-C(3)	118.21(14)	C(11)-C(12)-C(13)	121.36(16)
C(6)-N(3)-C(2)	117.09(14)	C(6)-C(5)-C(4)	117.97(15)	C(14)-C(13)-C(12)	122.02(16)
C(2)-C(1)-S(1)	114.49(11)	N(3)-C(6)-C(5)	124.65(15)	C(13)-C(14)-C(15)	117.40(17)
N(3)-C(2)-C(1)	118.78(13)	C(3)-O(1)-C(7)	113.77(12)	N(2)-C(15)-C(10)	110.32(14)
N(3)-C(2)-C(3)	122.64(14)	N(1)-C(9)-S(1)	118.55(12)	N(2)-C(15)-C(14)	129.61(16)
C(3)-C(2)-C(1)	118.58(14)	N(2)-C(9)-S(1)	126.48(12)	C(14)-C(15)-C(10)	120.07(15)
O(1)-C(3)-C(2)	120.18(13)	N(2)-C(9)-N(1)	114.97(14)		
O(1)-C(3)-C(4)	120.35(14)	N(1)-C(10)-C(11)	132.50(16)		

Molecular structures and crystal packing diagrams were generated using the Diamond program [17]. One structural unit of 3b is shown in Fig. 1 [Figure 1: see original paper]. The molecular packing of 3b viewed along the a axis is depicted in Fig. 2 [Figure 2: see original paper].

Some weak interactions (donor–H $\cdots$ acceptor interactions, D–H $\cdots$ A interactions, including N–H $\cdots$ N, C–H $\cdots$ O, C–H $\cdots$ S, C–H $\cdots$ N, C–H $\cdots$ interactions) are observed in Fig. 3 [Figure 3: see original paper] (generated using the Mercury program [18]), with red dashed lines indicating the interactions. These weak interactions are listed in Table 2 .

Table 2. Weak D–H $\cdots$ A Interactions of 3b

D–H $\cdots$ A	d(D–H) (Å)	d(H $\cdots$ A) (Å)	d(D $\cdots$ A) (Å)	Angle(D–H $\cdots$ A) (º)	Symmetry codes
N(1)–H(1) $\cdots$ N(3)(i)	0.8330(215)	2.0911(216)	2.9192(20)	172.675(2066)	(i) -1/2+x, 1/2–y, 1–z
C(1)–H(1B) $\cdots$ O(1)	0.9900(16)	2.3447(11)	2.8046(20)	107.400(97)	

D-H ⋯ A	d(D-H) (Å)	d(H ⋯ A) (Å)	d(D ⋯ A) (Å)	Angle(D-H ⋯ A) (º)	Symmetry codes
C(6)-H(6)⋯S(1)(i)	0.9496(17)	2.8873(6)	3.6781(18)	141.471(104)	(i) -1/2+x, 1/2-y, 1-z
C(8)-H(8B)⋯O(1)(ii)	0.9797(19)	2.4740(11)	2.8660(22)	103.528(112)	(ii) -1/2+x, 1/2-y, -z
C(11)-H(11)⋯S(1)(iii)	0.9500(17)	2.8339(5)	3.4307(18)	121.782(105)	(iii) 1/2+x, 1/2-y, 1-z
C(12)-H(12)⋯N(2)(iv)	0.9499(18)	2.5018(13)	3.3565(22)	149.720(112)	(iv) 1-x, -1/2+y, 1/2-z
C(7)-H(7C)⋯C(9)(v)	0.9803(18)	2.8540(15)	3.4371(24)	118.935(109)	(v) 2-x, -1/2+y, 1/2-z

3.2 Antitumor Activity

Using 5-fluorouracil as positive control, the target compounds were evaluated for cytotoxic activity in vitro against human liver cancer cell line HepG2 and human liver normal cell line HL7702 by MTT colorimetric assay. The in vitro inhibitory activity results are summarized in Table 3 .

Table 3. Inhibitory Activity in vitro of the Target Compounds

Compound	Inhibition rate (%) (50 M)
	HepG2
5-Fluorouracil	

These results show that the target compounds exhibit weak or moderate cytotoxic activity against HepG2, while all target compounds display almost no cytotoxic effects on HL7702. These findings reveal that the target compounds possess excellent selective activity against the malignant tumor cell line.

4. Conclusion

A series of 2-[(pyridin-2-yl)methylthio]-1H-benzimidazole derivatives were designed, synthesized, and characterized by IR, MS, and proton NMR. The structure of target compound 2-[(3,4-dimethoxypyridin-2-yl)methylthio]-1H-benzimidazole (3b) was investigated by X-ray crystallography. The antitumor activities of the target compounds were evaluated for cytotoxic activity against human liver cancer cell line HepG2 and human liver normal cell line HL7702

using MTT assay. The cytotoxicity assay results showed that these target compounds exhibit weak or moderate anti-tumor activity against HepG2, while all target compounds show no cytotoxic effects on HL7702, which implies that the target compounds display excellent selective activity against the malignant tumor cell line.

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