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Synthesis and bioactivity of novel coumarin derivatives

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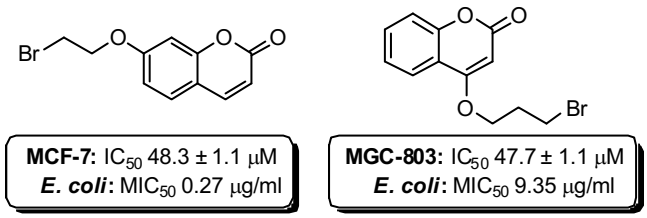


A series of novel coumarin derivatives were synthesized from commercially available chemical agents. All prepared compounds were evaluated for their *in vitro* antiproliferative activity against five selected human cancer cell lines (EC109, MGC-803, PC-3, MCF-7, and EC9706) and their *in vitro* antimicrobial activity against *E. coli* and *M. albicans*. 4-(3-Bromopropoxy)-2*H*-chromen-2-one exhibited the highest growth inhibition against MGC-803 cell line (IC_{50} 47.7 μM) and 7-(2-bromoethoxy)-2*H*-chromen-2-one exhibited the highest growth inhibition against MCF-7 cell line (IC_{50} 48.3 μM). The latter compound was also the most active against *E. coli* (MIC_{50} 0.27 μg/ml).

Keywords: coumarin, anticancer activity, antimicrobial activity.

Coumarins and their derivatives possess a wide range of biological activities such as antimicrobial[1], anti-inflammatory,[2] anticoagulant,[3] antiHIV,[4] antitumor,[5] and enzyme inhibitory (*E. coli* topoisomerase and DNA gyrase).[6] Furthermore, hydroxycoumarins, powerful chain-breaking antioxidants, can prevent free radical injury by scavenging reactive oxygen species.[7] For example, novobiocin, an antibiotic that acts through inhibition of DNA gyrase, has been structurally modified to develop a series of selective Hsp90 inhibitors (Fig. 1).[8]

In order to find novel coumarin derivatives with potential cytotoxic and antimicrobial activity, a series of novel coumarin derivatives was synthesized from 4-hydroxycoumarin (**1a**) and 7-hydroxycoumarin (**1b**). The Williamson etherification reaction of compounds **1a**,**b** with versatile alkyl halogenides gave the corresponding ethers **2a**–**f** in the presence of potassium carbonate (Scheme 1). To further investigate the structure–activity relationship for such coumarin ethers, compounds **3a**–**e** were designed containing another heterocyclic moiety connected to the coumarin system by means of a spacer. Thus, bromides **2c**,**d**,**f** underwent a nucleophilic substitution reaction with appropriate mercaptanes in the presence of potassium carbonate and catalytic amount of potassium iodide (Scheme 2). The synthesized products **2a**–**f**, **3a**–**e** were fully characterized by ^{1}H and ^{13}C NMR spectroscopy, as well as by high-resolution mass spectrometry.

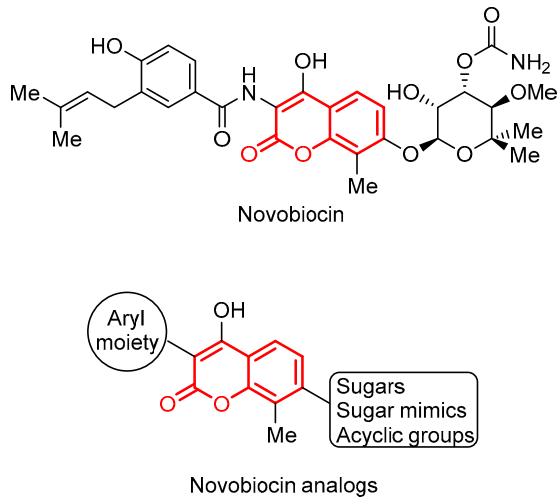
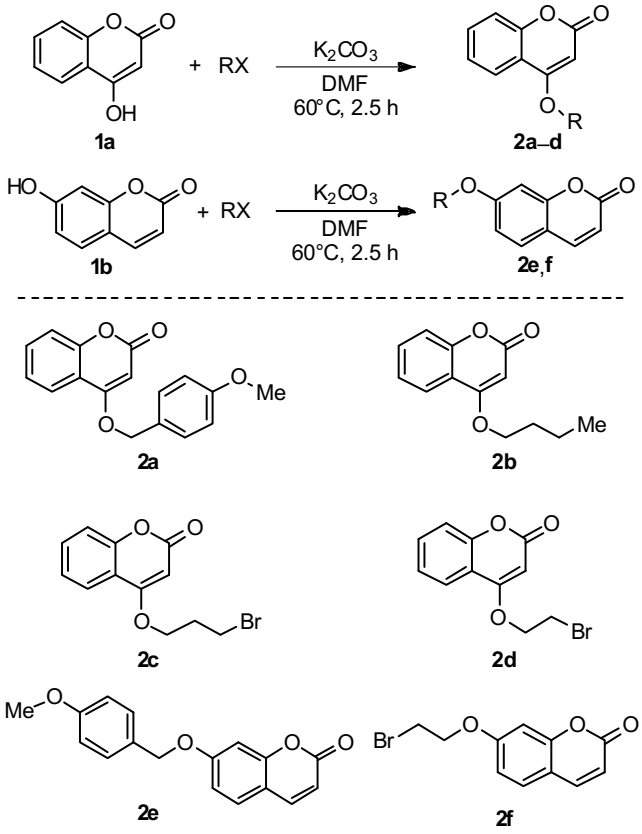
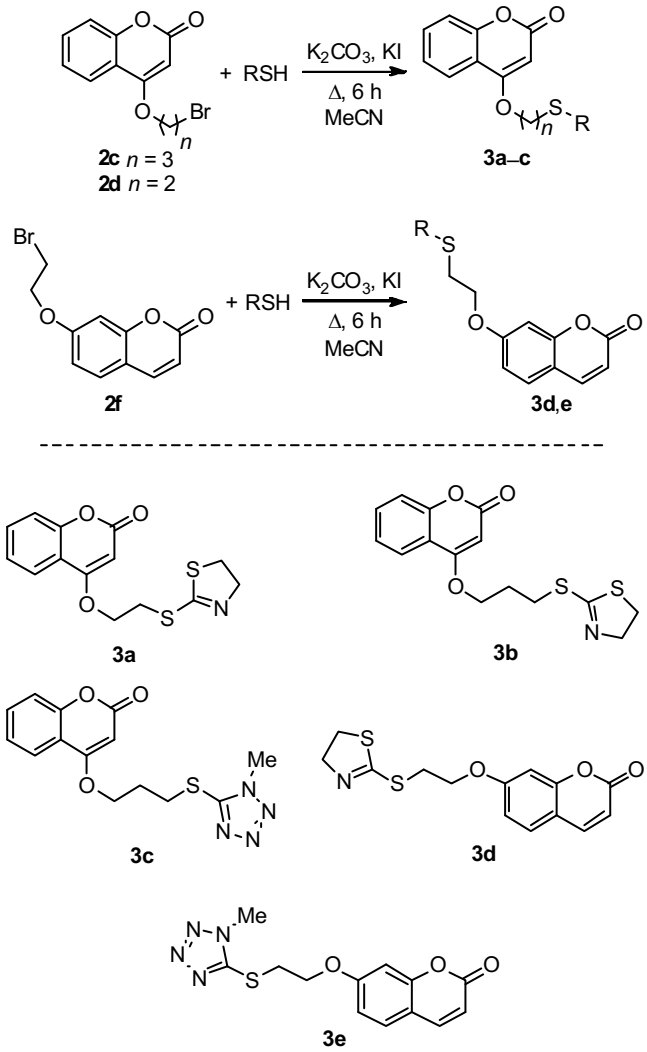


Figure 1. The structure motif of coumarin in the molecule of novobiocin and its analogs.

Scheme 1



Scheme 2



4(7)-Alkoxy-2*H*-chromen-2-ones **2a**–**f**, **3a**–**e** were evaluated for their cytotoxic activity *in vitro* against human esophageal carcinoma (EC109 and EC9706), human stomach cancer (MGC-803), human prostatic carcinoma (PC-3), and human breast carcinoma (MCF-7) cell lines (Table 1). A clinically used anticancer drug 5-fluorouracil was used as the positive control.

The cytotoxicity test results show that some of the synthesized compounds exhibited weak activity against all the cancer cell lines assayed. However, some of the tested compounds (**2a**,**d**,**e**, **3c**,**d**) exhibited no growth inhibition against any of the tested cancer cell lines. Compound **2c** with a bromopropyl group exhibited better cytotoxic activity than compound **2b** with a butyl group against MGC-803 cell line while compounds containing a bromoethyl group **2d**,**f** or methoxybenzyl group **2a**,**e** showed no activity. This result indicated that both the nature of substituent and its position on the coumarin ring influence the anticancer activity considerably.

The length of the carbon tether between the coumarin ring system and the terminal bromine atom can considerably affect the antiproliferative activity. In the case of compounds **2c** and **2d**, the shortening of the chain from 3 to 2 methylene groups lead to a complete loss of activity against MGC-803 and MCF-7 cell lines. An analogous effect on all five cell lines was observed when bromine atom was substituted by thiazolinylsulfanyl group (compounds **3b** and **3a**, respectively).

Regarding the position of the substituent at the coumarin ring system, while 2-bromoethyl group conferred no

Table 1. The *in vitro* anticancer activity of the synthesized compounds **2a**–**f** and **3a**–**e** (IC_{50}, μM)*

Compound	Human cancer cell line				
	EC109	EC9706	MGC-803	PC-3	MCF-7
2a	>128	>128	>128	>128	>128
2b	>128	>128	87.2±1.3	>128	>128
2c	>128	>128	47.7±1.1	>128	50.2±1.2
2d	>128	>128	>128	>128	>128
2e	>128	>128	>128	>128	>128
2f	>128	>128	>128	>128	48.3±1.1
3a	>128	>128	>128	48.2±1.2	>128
3b	>128	111.9±1.4	121.5±0.9	81.3±0.9	59.4±1.0
3c	>128	>128	>128	>128	>128
3d	>128	>128	>128	>128	>128
3e	>128	100.3±1.6	113.8±1.6	54.6±1.2	72.7±1.4
5-Fluorouracil	2.6±0.4	0.3±1.3	32.4±1.5	29.3±1.9	7.5±0.7

* Antiproliferative activity was assayed by exposure for 72 h to the tested substances and expressed as the concentration required to inhibit tumor cell proliferation by 50% (IC_{50}). The data are presented as the means with standard deviation from the dose–response curves of three independent experiments.

activity against MCF-7 cells when in position 4 (compound **2d**), compound **2f** with 2-bromoethyl group in position 7 was active against the same cell line. A similar observation could be made with compounds **3d** and **3a** with respect to PC-3 cells.

As to the choice of the heterocyclic end group, 4-substituted coumarin **3d** with oxazoline ring at the end of two-carbon spacer showed no cytotoxic activity, while compound **3e** with methyltetrazole at the same position was moderately active against four cell lines. Conversely, 4-substituted coumarin **3b** with oxazoline ring at the end of three-carbon spacer was moderately active against the same four cell lines, while compound **3c** with methyltetrazole at the same position showed no activity.

The test results show that both the end group and the length of the linker of the substituent, as well as its position at the coumarin ring system determine the cytotoxicity in this series of compounds. The cytotoxicity of the most active compounds against MGC-803 (compound **2c**) and PC-3 (compound **3e**) cell lines approached that of 5-fluorouracil.

The synthesized compounds **2a**–**f** and **3a**–**e** were also screened for their antimicrobial activities *in vitro* against *Escherichia coli* and *Monilia albicans* (Table 2). Clinically used antimicrobial drugs levofloxacin and fluconazole, respectively, were used as the positive controls. All prepared coumarin compounds could effectively inhibit the growth of Gram-negative bacteria *E. coli*, and compounds **2a**,**e**, **3a**,**c**,**d** displayed activity against fungi *M. albicans in vitro*. Especially, compounds **2d**,**f**, and **3a** had a high activity against *E. coli* approaching that of the standard drug.

In summary, a series of novel coumarin derivatives was synthesized and evaluated for their antiproliferative and antimicrobial activity. The nature (both the end group and the length of the linker) and position of the substituent group at the coumarin ring system influenced the biological activities considerably. Some of the synthesized compounds displayed either cytotoxic or antimicrobial activity approaching that of the commercial standard drugs. Further modifications and a SAR study are underway and will be reported elsewhere.

Table 2. The *in vitro* antibacterial activity of the synthesized compounds **2a**–**f** and **3a**–**e** (MIC_{50}, μg/ml)

Compound	*E. coli*	*M. albicans*
2a	32.87	20.38
2b	10.67	>128
2c	9.35	>128
2d	0.29	>128
2e	4.18	81.00
2f	0.27	>128
3a	0.41	30.97
3b	8.95	>128
3c	7.75	71.40
3d	3.32	9.93
3e	4.47	>128
Levofloxacin	<0.25	–
Fluconazole	–	<0.5

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-400 spectrometer (400 and 100 MHz, respectively) with TMS as internal standard. Mass spectra were recorded on a Bruker 3000 mass spectrometer using electrospray ionization. Melting points were determined on a Beijing Keyi XT4A apparatus. Thin-layer chromatography was carried out on glass plates coated with silica gel and visualized by UV light (254 nm). All reagents and solvents used were of analytical grade purchased from commercial sources.

Synthesis of 4(7)-alkoxy-2*H*-chromen-2-ones 2a–f (General method). Compound **1a** or **1b** (65 mg, 0.40 mmol) was dissolved in DMF (2 ml), followed by addition of anhydrous K_2CO_3 (138 mg, 1.00 mmol). Then an appropriate alkyl halide (0.40 mmol) was added dropwise to the stirred reaction mixture. The stirring was continued for 2.5 h at 60°C. The reaction mixture was extracted with CH_2Cl_2 (80 ml), the organic extracts were washed with water (100 ml), dried over Na_2SO_4, filtered, and the solvent was removed *in vacuo*. The residue was recrystallized from EtOH.

4-[(4-Methoxybenzyl)oxy]-2*H*-chromen-2-one (2a). Yield 92%, white powder, mp 137.2–138.2°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 7.85 (1H, dd, *J* = 7.9, *J* = 1.4, H Ar); 7.61–7.51 (1H, m, H Ar); 7.40 (2H, d, *J* = 8.6, H Ar); 7.34 (1H, d, *J* = 8.3, H Ar); 7.29–7.23 (1H, m, H Ar); 6.99 (2H, d, *J* = 8.6, H Ar); 5.81 (1H, s, H-3); 5.15 (2H, s, CH_2); 3.86 (3H, s, OCH_3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 165.4; 162.9; 160.1; 153.4; 132.4; 129.7; 126.4; 123.9; 123.2; 116.8; 115.8; 114.3; 91.1; 71.1; 55.4. Found, *m*/*z*: 283.0970 $[M+H]^+$. $C_{17}H_{15}O_4$. Calculated, *m*/*z*: 283.0965.

4-Butoxy-2*H*-chromen-2-one (2b). Yield 95%, white powder, mp 87.5–88.1°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 7.83 (1H, d, *J* = 7.8, H Ar); 7.55 (1H, t, *J* = 7.6, H Ar); 7.42–7.16 (2H, m, H Ar); 5.68 (1H, s, H-3); 4.14 (2H, t, *J* = 6.3, OCH_2); 2.01–1.80 (2H, m, CH_2); 1.68–1.45 (2H, m, CH_2); 1.03 (3H, t, *J* = 7.3, CH_3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 165.8; 163.1; 153.4; 132.3; 123.8; 123.0; 116.8; 115.8; 90.4; 69.1; 30.5; 19.2; 13.8. Found, *m*/*z*: 241.0840. $[M+Na]^+$. $C_{13}H_{14}NaO_4$. Calculated, *m*/*z*: 241.0835.

4-(3-Bromopropoxy)-2*H*-chromen-2-one (2c). Yield 91%, white powder, mp 104.9–111.7°C. ^{1}H NMR spectrum ($(CD_3)_2CO$), δ, ppm (*J*, Hz): 7.92 (1H, dd, *J* = 7.9, *J* = 1.4, H Ar); 7.73–7.55 (1H, m, H Ar); 7.37–7.28 (2H, m, H Ar); 5.81 (1H, s, H-3); 4.43 (2H, t, *J* = 5.9, OCH_2); 3.78 (2H, t, *J* = 6.6, CH_2Br); 2.51 (2H, quint, *J* = 6.2, CH_2). ^{13}C NMR spectrum ($(CD_3)_2CO$), δ, ppm: 165.9; 162.2; 154.4; 133.4; 124.8; 124.0; 117.3; 116.6; 91.5; 68.1; 32.5; 30.5. Found, *m*/*z*: 304.9789 $[M(^{79}Br)+Na]^+$. $C_{12}H_{11}BrNaO_3$. Calculated, *m*/*z*: 304.9784.

4-(2-Bromoethoxy)-2*H*-chromen-2-one (2d). Yield 92%, white powder, mp 142.8–146.2°C. ^{1}H NMR spectrum

($CDCl_3$), δ, ppm (*J*, Hz): 7.89 (1H, dd, *J* = 7.9, *J* = 1.4, H Ar); 7.64–7.54 (1H, m, H Ar); 7.40–7.27 (2H, m, H Ar); 5.70 (1H, s, H-3); 4.41 (2H, t, *J* = 5.4, OCH_2); 3.96 (2H, t, *J* = 5.4, CH_2Br). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 165.0; 162.5; 153.4; 132.7; 124.1; 123.1; 116.8; 115.3; 90.9; 68.8; 41.0. Found, *m/z*: 290.9633 $[M(^{79}Br)+Na]^+$. $C_{11}H_9BrNaO_3$. Calculated, *m/z*: 290.9628.

7-[(4-Methoxybenzyl)oxy]-2*H*-chromen-2-one (2e). Yield 95%, white flocculent solid, mp 156.4–158.4°C. ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 7.63 (1H, d, *J* = 9.5, H Ar); 7.40–7.33 (3H, m, H Ar); 6.99–6.84 (4H, m, H Ar); 6.24 (1H, d, *J* = 9.5, H Ar); 5.05 (2H, s, CH_2); 3.82 (3H, s, OCH_3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 162.0; 161.2; 159.8; 155.8; 143.4; 129.4; 128.8; 127.8; 114.2; 113.3; 113.2; 112.7; 101.9; 70.4; 55.3. Found, *m/z*: 283.0957 $[M+H]^+$. $C_{17}H_{15}O_4$. Calculated, *m/z*: 283.0965.

7-(2-Bromoethoxy)-2*H*-chromen-2-one (2f) was synthesized according to a literature procedure.[9] Yield 85%, white flocculent solid, mp 134–135°C (mp 134–135°C[9]). The spectral characteristics of compound **2f** were consistent with the literature data.[9]

Synthesis of 4(7)-alkoxy-2*H*-chromen-2-ones 3a–e (General method). Bromide **2c**,**d**,**f** (0.43 mmol) was completely dissolved in anhydrous MeCN (5 ml) followed by the addition of anhydrous K_2CO_3 (116 mg, 0.84 mmol) and a catalytic amount of KI (14.3 mg, 0.086 mmol). Then an appropriate thiol (0.43 mmol) was added, and the reaction mixture was refluxed for 6 h, filtered to remove K_2CO_3, and purified by silica gel chromatography with hexane–EtOAc, 6:1, as eluent.

4-{2-[(4,5-Dihydrothiazol-2-yl)sulfanyl]ethoxy}-2*H*-chromen-2-one (3a). Yield 96%, white powder, mp 126.7–127.8°C. ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 7.83 (1H, d, *J* = 7.9, H Ar); 7.57 (1H, t, *J* = 7.8, H Ar); 7.38–7.28 (2H, m, H Ar); 5.81 (1H, s, H-3); 4.43 (2H, t, *J* = 6.5, CH_2); 4.25 (2H, t, *J* = 8.0, CH_2); 3.58 (2H, t, *J* = 6.5, CH_2); 3.46 (2H, t, *J* = 8.0, CH_2). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 165.1; 164.3; 162.8; 153.4; 132.5; 123.9; 123.1; 116.8; 115.5; 91.0; 67.4; 64.0; 35.9; 30.5. Found, *m/z*: 330.0235 $[M+Na]^+$. $C_{14}H_{13}NNaO_3S_2$. Calculated, *m/z*: 330.0229.

4-{3-[(4,5-Dihydrothiazol-2-yl)sulfanyl]propoxy}-2*H*-chromen-2-one (3b). Yield 90%, white powder, mp 143.8–145.8°C. ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 7.85 (1H, dd, *J* = 7.9, *J* = 1.4, H Ar); 7.62–7.52 (1H, m, H Ar); 7.37–7.26 (2H, m, H Ar); 5.69 (1H, s, H-3); 4.25 (2H, t, *J* = 6.0, CH_2); 4.20 (2H, t, *J* = 8.0, CH_2); 3.41 (2H, t, *J* = 8.0, CH_2); 3.34 (2H, t, *J* = 6.9, CH_2); 2.36 (2H, quin, *J* = 6.4, CH_2). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 165.5; 164.8; 162.9; 153.3; 132.5; 123.9; 123.1; 116.8; 115.6; 90.6; 67.5; 64.2; 35.6; 28.9; 28.6. Found, *m/z*: 344.0391 $[M+Na]^+$. $C_{15}H_{15}NNaO_3S_2$. Calculated, *m/z*: 344.0386.

4-{3-[(1-Methyl-1*H*-tetrazol-5-yl)sulfanyl]propoxy}-2*H*-chromen-2-one (3c). Yield 92%, white powder, mp 117.5–118.5°C. ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 7.83 (1H, d, *J* = 7.8, H Ar); 7.57 (1H, t, *J* = 7.8, H Ar); 7.35–7.25 (2H, m, H Ar); 5.69 (1H, s, H-3); 4.30 (2H, t, *J* = 5.8, CH_2); 3.94 (3H, s, CH_3); 3.60 (2H, t, *J* = 7.0, CH_2); 2.56–2.45 (2H, m, CH_2). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 165.3; 162.7; 153.7; 153.3; 132.6; 124.0; 122.9; 116.8; 115.5; 90.8; 67.1; 33.4; 29.6; 28.3. Found, *m/z*: 341.0684 $[M+Na]^+$. $C_{14}H_{14}N_4NaO_3S$. Calculated, *m/z*: 344.0386.

7-{2-[(4,5-Dihydrothiazol-2-yl)sulfanyl]ethoxy}-2*H*-chromen-2-one (3d). Yield 96%, white powder, mp 141.7–146.7°C. ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 7.65 (1H, d, *J* = 9.5, H Ar); 7.39 (1H, d, *J* = 8.6, H Ar); 6.92 (1H, d, *J* = 2.1, H Ar); 6.88 (1H, dd, *J* = 8.6, *J* = 2.3, H Ar); 6.27 (1H, d, *J* = 9.5, H Ar); 4.32 (2H, t, *J* = 6.6, CH_2); 4.26 (2H, t, *J* = 8.0, CH_2); 3.50 (2H, t, *J* = 6.6, CH_2); 3.45 (2H, t, *J* = 8.0, CH_2). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 164.7; 161.6; 161.2; 155.9; 143.4; 128.8; 113.3; 113.0; 112.8; 101.7; 66.9; 64.1; 35.9; 31.0. Found, *m/z*: 330.0235 $[M+Na]^+$. $C_{14}H_{13}NNaO_3S_2$. Calculated, *m/z*: 330.0229.

7-{2-[(1-Methyl-1*H*-tetrazol-5-yl)sulfanyl]ethoxy}-2*H*-chromen-2-one (3e). Yield 95%, white powder, mp 73.4–76.6°C. ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 7.65 (1H, d, *J* = 9.5, H Ar); 7.40 (1H, d, *J* = 8.6, H Ar); 6.86 (1H, dd, *J* = 8.6, *J* = 2.2, H Ar); 6.82 (1H, br. s, H Ar); 6.26 (1H, d, *J* = 9.5, H Ar); 4.44 (2H, t, *J* = 5.9, CH_2); 3.95 (3H, s, CH_3); 3.77 (2H, t, *J* = 5.9, CH_2). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 161.2; 161.0; 155.7; 153.7; 143.3; 129.0; 113.6; 113.1; 112.3; 102.0; 66.4; 33.5; 32.1. Found, *m/z*: 327.0528 $[M+Na]^+$. $C_{13}H_{12}N_4NaO_3S$. Calculated, *m/z*: 327.0523.

Antiproliferative activity assay.[10] Cancer cell lines were purchased from the China Center for Type Culture Collection (CCTCC, Shanghai, China). All cancer cell lines were maintained in minimal essential medium supplemented with 10% fetal bovine serum and 1% penicillin–streptomycin in a humidified atmosphere (5% CO_2 and 95% air) at 37°C. Cancer cells were maintained in RPMI1640 medium. For pharmacological investigations, 10 mM stock solutions of the tested compounds were prepared with DMSO.

Antimicrobial activity assays. The microbial species were purchased from the China Center for Type Culture Collection (CCTCC, Shanghai, China). Antibacterial activity was determined using the broth microdilution method according to the National Committee for Clinical Laboratory Standards (NCCLS).[11] The bacterial species (*E. coli*) were grown in Luria broth medium, and the fungal species (*M. albicans*) were grown in RPMI 1640 medium until exponential growth was achieved. The tests were performed in a 96-well microtiter plates. All the compounds were dissolved in DMSO at an initial concentration of 10 mg/ml, and the stock solutions were diluted with the test medium. A series of concentrations ranging from 1 to 128 μg/ml to a final volume of 200 μl in plate was obtained by twofold dilutions. Each well, except for the blank well, was inoculated with the test bacteria and incubated for 24 h at 37°C. The plates were read using ELIASA at 492 nm. The MIC_{50} value is the lowest concentration of compound that inhibits growth to half the absorption value of the untreated control. The reported MIC_{50} was the mean value of three independent experiments.

Supplementary information file to this article containing the ^1H and ^{13}C NMR spectra of the synthesized compounds is available at http://link.springer.com/journal/10593.

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