Sorafenib 硫脲衍生物的合成及活性研究

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摘要: 在已上市的多靶点小分子靶向抗肿瘤药 sorafenib 的基础上, 设计合成了 16 个 4-[4-(2-甲胺酰基吡啶)]氧苯基芳香硫脲衍生物。16 个目标化合物的结构经 ^{1}H NMR、MS 及元素分析确证。采用四氮唑盐 (MTT) 法测试了所合成化合物的体外抗肿瘤活性, 结果表明所合成的化合物均具有一定的抗肿瘤活性, 其中化合物 **1a**、**1d**、**1i** 及 **1j** 的抗肿瘤活性优于或相当于阳性对照 sorafenib。

关键词: 抗肿瘤; sorafenib; 硫脲; 合成; 生物活性

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Synthesis and biological evaluation of sorafenib thiourea derivatives

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Abstract: Basing on the market multi-target antitumor agent sorafenib, a series of sixteen 4-[4-(2-methyl-aminoacyl-pyridyl)]oxylphenyl aryl thiourea derivatives were designed and synthesized. Their structures were identified by the spectra of ^{1}H NMR, MS and elemental analysis. The evaluation of antitumor bioactivities *in vitro* was done by MTT method. It was shown that the synthesized compounds had antitumor activities and compounds **1a**, **1d**, **1i** and **1j** showed better or equal antitumor activity on sorafenib.

Key words: antitumor; sorafenib; thiourea; synthesis; bioactivity

Sorafenib (图 1) 是由美国 Onyx 制药公司和德国 Bayer 公司开发的多靶点小分子靶向抗肿瘤药, 已于 2005 年首次在美国上市, 可有效抑制 VEGFR-2、VEGFR-3 及 PDGFR-β 等多种受体酪氨酸激酶[1], 同时抑制 RAF/MEK/ERK 等信号途径, 具有抑制肿瘤细胞和抑制血管生成双重作用, 对多种实体肿瘤表现出很好的潜在药效[2, 3]。多靶点的作用机制有利于协同药效、减少耐药性发生[4−6], 已成为目前抗肿瘤药物研究的热点。继 sorafenib 后, 芳香脲的结构受到人们关注, 近年来, 具有芳香脲结构且具有多靶点抑制作用的 tivozanib[7]、linifanib[8]、tandutinib[9]、lenvatinib[10]等表现出良好的抗肿瘤活性。考虑到硫脲基团比脲具有更强的亲脂性及组织渗透性, 且文献[11, 12]报道的一系列硫脲衍生物具有理想的潜在抗癌活性, 因此, 作者在 sorafenib 的基础上, 采用生物电子等排原理, 设计合成了 16 个类似于 sorafenib 结构的 4-[4-(2-甲胺酰基吡啶)]氧苯基芳香硫脲衍生物, 化合物结构经 ^{1}H NMR、MS (ESI) 及元素分析确证。

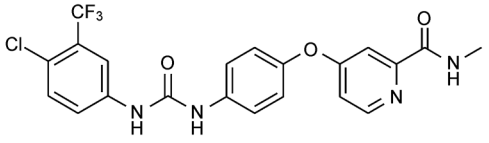

Figure 1 Structure of sorafenib

采用文献[13]方法, 将 2-吡啶甲酸经氯化亚砜制备得酰氯盐酸盐 **3** 后, 与甲胺溶液反应得酰胺化合物 **4**, 再于碱性条件下与对氨基苯酚反应得 4-[4-(2-甲胺

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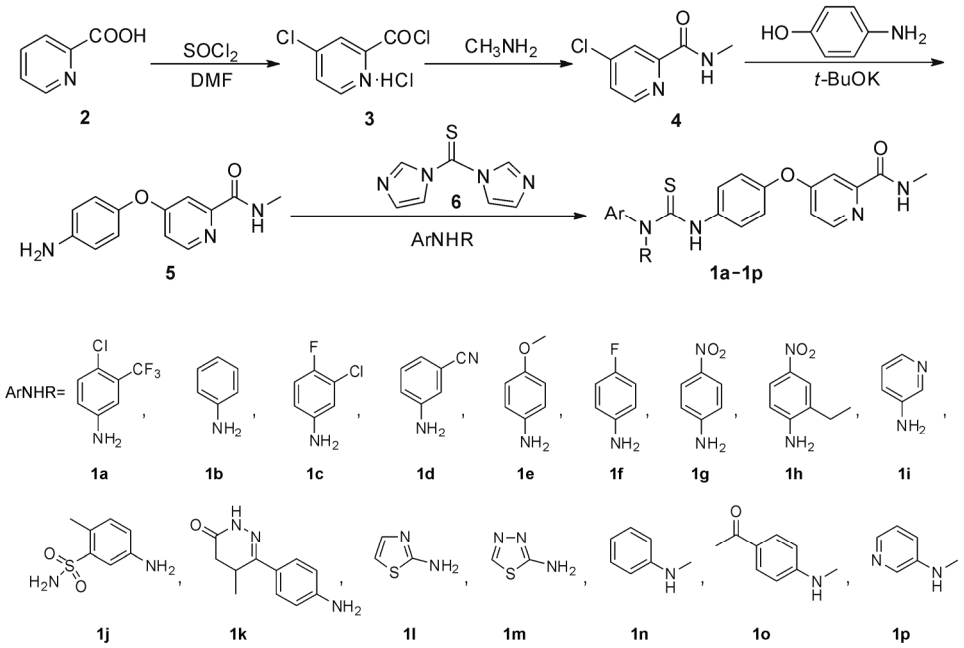
酰基吡啶)]氧基苯胺 (**5**)。最后, 将 1-三甲基硅基咪唑与硫光气反应所得的 *N*, *N*'-硫酰二咪唑 (**6**)、化合物 **5** 以及芳香胺经“一锅法”生成目标化合物 **1a**～**1p**。合成方法及化合物结构见合成路线 1。常见的合成硫脲的方法是采用胺与异硫氰酸酯进行反应, 但异硫氰酸酯不易购买且化学性质不稳定, 而采用本实验方法反应条件温和, 芳香胺化合物易得, 且后处理简便, 有利于合成一系列硫脲衍生物。

目标产物的生物活性测试采用四氮唑盐 (MTT) 还原法, 以 sorafenib 为阳性对照, 测试它们对肾癌 760-O、肝癌 HepG2、肺癌 A549、乳腺癌 MDA-MB-435、前列腺癌 PC3 和结肠癌细胞 HT-29 共 6 种肿瘤细胞的体外抗肿瘤活性。16 个芳香硫脲衍生物均表现出一定的抗癌活性, 其中, 化合物 **1a**、**1d**、**1i** 及 **1j** 表现出优于或相当于阳性对照的抗肿瘤效果。

结果与讨论

1　Sorafenib 硫脲衍生物 1a～1p 的合成

目标化合物结构经 ^{1}H NMR、MS (ESI) 及元素分析确证, 合成产率、理化常数及波谱数据见表 1 和表 2。



Scheme 1　Synthetic route of the target compounds **1a**−**1p**

Table 1　Physical properties of compounds **1a**−**1p**

Compd.	Formula	Yield /%	mp /℃	Elemental analysis/% Calcd. (Found)		
				C	H	N
1a	$C_{21}H_{16}ClF_3N_4O_2S$	64.2	193.5−195.6	52.45 (52.31)	3.35 (3.32)	11.65 (11.81)
1b	$C_{20}H_{18}N_4O_2S$	76.6	165.9−166.6	63.47 (63.56)	4.79 (4.61)	14.80 (14.77)
1c	$C_{20}H_{16}ClFN_4O_2S$	72.9	190.0−192.7	55.75 (55.54)	3.74 (3.80)	13.00 (13.12)
1d	$C_{21}H_{17}N_5O_2S$	59.4	227.5−230.6	62.52 (62.39)	4.25 (4.38)	17.36 (17.61)
1e	$C_{21}H_{20}N_4O_3S$	80.6	207.3−209.9	61.75 (61.67)	4.94 (5.09)	13.72 (13.93)
1f	$C_{20}H_{17}FN_4O_2S$	75.3	207.1−210.7	60.59 (60.77)	4.32 (4.32)	14.13 (13.99)
1g	$C_{20}H_{17}N_5O_3S$	60.1	220.0−221.7	56.73 (56.48)	4.05 (4.19)	16.54 (16.71)
1h	$C_{22}H_{21}N_5O_3S$	69.2	188.9−189.2	58.52 (58.31)	4.69 (4.65)	15.51 (15.69)
1i	$C_{19}H_{17}N_5O_2S$	66.8	153.6−155.0	60.14 (60.33)	4.52 (4.26)	18.46 (18.32)
1j	$C_{21}H_{21}N_5O_4S2$	58.9	186.9−190.3	53.49 (53.45)	4.49 (4.63)	14.85 (14.90)
1k	$C_{25}H_{24}N_6O_3S$	71.3	>250	61.46 (61.59)	4.95 (4.88)	17.20 (17.00)
1l	$C_{17}H_{15}N_5O_2S_2$	43.5	199.1−203.6	52.97 (52.68)	3.92 (3.97)	18.17 (18.35)
1m	$C_{16}H_{14}N_6O_2S_2$	49.0	231.5−232.8	49.73 (50.01)	3.65 (3.54)	21.75 (21.65)
1n	$C_{21}H_{20}N_4O_2S$	70.1	195.0−196.5	64.27 (64.33)	5.14 (5.12)	14.28 (14.27)
1o	$C_{23}H_{22}N_4O_3S$	62.8	222.9−223.6	63.58 (63.71)	5.10 (4.89)	12.89 (12.65)
1p	$C_{20}H_{19}N_5O_2S$	55.7	183.4−185.6	61.05 (60.87)	4.87 (4.98)	17.80 (17.99)

Table 2　Spectral data of compounds **1a**−**1p**.　*DMSO-d_6 for compound **1a**

Compd.	^{1}H NMR ($CDCl_3$)	MS (ESI)
1a*	2.86 (d, J = 4.8 Hz, 3H, $NHCH_3$), 7.06 (m, 1H, aromatic), 7.09 (d, J = 7.5 Hz, 2H, aromatic), 7.38 (m, 1H, aromatic), 7.57−7.58 (m, 4H, aromatic), 7.60 (m, 1H, aromatic), 7.90 (m, 1H, aromatic), 8.22 (br, H, $NHCH_3$), 8.47 (s, 1H, thiourea), 8.62 (s, 1H, thiourea)	481.1 $[M+H]^+$
1b	2.79 (d, J = 4.9 Hz, 3H, $NHCH_3$), 6.98 (m, 1H, aromatic), 7.15 (m, 3H, aromatic), 7.29 (m, 2H, aromatic), 7.39 (m, 1H, aromatic), 7.47 (m, 2H, aromatic), 7.58 (m, 2H, aromatic), 8.50 (br, 1H, $NHCH_3$), 8.69 (m, 1H, aromatic), 8.75 (s, 1H, thiourea), 8.81 (s, 1H, thiourea)	379.1 $[M+H]^+$
1c	2.79 (d, J = 4.7 Hz, 3H, $NHCH_3$), 7.16 (m, 3H, aromatic), 7.33 (m, 2H, aromatic), 7.39 (m, 1H, aromatic), 7.58 (m, 2H, aromatic), 7.80 (m, 1H, aromatic), 8.50 (m, 1H, aromatic), 8.73 (s, 1H, thiourea), 8.84 (br, 1H, $NHCH_3$), 8.89 (s, H, thiourea)	431.1 $[M+H]^+$
1d	2.83 (d, J = 4.8 Hz, 3H, $NHCH_3$), 7.13−7.18 (m, 5H, aromatic), 7.39 (m, 2H, aromatic), 7.58−5.60 (m, 3H, aromatic), 7.60−7.61 (m, 1H, aromatic), 8.50 (br, 1H, $NHCH_3$), 8.74 (s, 1H, thiourea), 8.86 (s, 1H, thiourea)	404.1 $[M+H]^+$
1e	2.79 (d, J = 4.9 Hz, 3H, $NHCH_3$), 3.72 (s, 3H, OCH_3), 6.87 (m, 2H, aromatic), 7.14 (m, 3H, aromatic), 7.37 (m, 3H, aromatic), 7.58 (m, 2H, aromatic), 8.49−8.50 (m, 2H, aromatic and $CONHCH_3$), 8.72 (s, 2H, thiourea)	409.1 $[M+H]^+$
1f	2.79 (d, J = 4.9 Hz, 3H, $NHCH_3$), 7.08−7.17 (m, 5H, aromatic), 7.38 (m, 1H, aromatic), 7.48 (m, 2H, aromatic), 7.57 (m, 2H, aromatic), 8.50 (m, 1H, aromatic), 8.73 (br, 1H, $NHCH_3$), 8.76 (s, 1H, thiourea), 8.80 (s, 1H, thiourea)	397.1 $[M+H]^+$
1g	2.79 (d, J = 4.7 Hz, 3H, $NHCH_3$), 7.16 (m, 3H, aromatic), 7.39 (m, 1H, aromatic), 7.61 (m, 2H, aromatic), 7.71 (m, 2H, aromatic), 8.20 (m, 2H, aromatic), 8.50 (m, 1H, aromatic), 8.74 (br, 1H, $NHCH_3$), 9.05 (s, 1H, thiourea), 9.47 (s, 1H, thiourea)	424.1 $[M+H]^+$
1h	1.24 (t, J = 7.4 Hz, 3H, CH_2CH_3), 2.71−2.78 (m, 5H, CH_2 and $NHCH_3$), 7.20 (m, 3H, aromatic), 7.40 (m, 1H, aromatic), 7.47 (m, 1H, aromatic), 7.62 (m, 2H, aromatic), 7.85 (m, 1H, aromatic), 8.31 (m, 1H, aromatic), 8.52 (m, 1H, aromatic), 8.72 (br, 1H, $NHCH_3$), 8.92 (s, 1H, thiourea), 9.36 (br, 1H, thiourea)	452.1 $[M+H]^+$
1i	2.80 (d, J = 4.5 Hz, 3H, $NHCH_3$), 7.18 (m, 3H, aromatic), 7.33 (m, 1H, aromatic), 7.40 (m, 1H, aromatic), 7.60 (m, 2H, aromatic), 7.95 (m, 1H, aromatic), 8.20 (m, 1H, aromatic), 8.50 (m, 1H, aromatic), 8.63 (br, 1H, $NHCH_3$), 8.75 (s, 1H, aromatic), 8.93 (s, 2H, thiourea)	380.1 $[M+H]^+$
1j	2.50 (s, 3H, CH_3), 2.82 (d, J = 4.7 Hz, 3H, $NHCH_3$), 7.14 (m, 3H, aromatic), 7.26 (m, 1H, aromatic), 7.35 (br, 2H, SO_2NH_2), 7.39 (m, 1H, aromatic), 7.56 (m, 3H, aromatic), 8.04 (m, 1H, aromatic), 8.50 (m, 1H, aromatic), 8.77 (q, J = 4.7 Hz, 1H, $NHCH_3$), 8.87 (s, 1H, thiourea), 8.95 (s, 1H, thiourea)	473.1 $[M+H]^+$
1k	1.03 (d, J = 7.0 Hz, 3H, CH_3), 2.17 (m, 1H, $COCH_2$), 2.58 (m, 1H, $COCH_2$), 2.82 (d, J = 4.9 Hz, 3H, $NHCH_3$), 3.27 (q, 1H, CH), 6.49 (m, 2H, aromatic), 6.86 (m, 2H, aromatic), 7.11−7.16 (m, 3H, aromatic), 7.37−7.41 (m, 3H, aromatic), 7.58−7.62 (m, 2H, aromatic and CONH), 8.50 (m, 1H, $NHCH_3$), 8.79 (s, 2H, thiourea)	489.2 $[M+H]^+$
1l	2.79 (d, J = 4.7 Hz, 3H, $NHCH_3$), 7.12 (m, 1H, aromatic), 7.15 (m, 1H, aromatic), 7.21 (m, 2H, aromatic), 7.39 (m, 2H, aromatic), 7.61 (m, 2H, aromatic), 8.51 (m, 1H, aromatic), 8.76 (br, 1H, $NHCH_3$), 9.10 (s, 1H, thiourea), 10.65 (br, 1H, thiourea)	386.1 $[M+H]^+$
1m	2.80 (d, J = 4.9 Hz, 3H, $NHCH_3$), 7.12−7.15 (m, 2H, aromatic), 7.29 (m, 2H, aromatic), 7.46 (m, 1H, aromatic), 7.59 (m, 1H, aromatic), 8.37 (m, 1H, aromatic), 8.70 (br, 1H, $NHCH_3$), 9.11 (s, 1H, aromatic), 9.20 (s, 1H, thiourea), 10.86 (br, 1H, thiourea)	387.1 $[M+H]^+$
1n	2.79 (d, J = 4.8 Hz, 3H, $NHCH_3$), 3.25 (s, 3H, NCH_3), 6.92−6.99 (m, 3H, aromatic), 7.15 (m, 1H, aromatic), 7.26 (m, 1H, aromatic), 7.30 (m, 1H, aromatic), 7.39 (m, 1H, aromatic), 7.46 (m, 2H, aromatic), 7.59 (m, 2H, aromatic), 8.51 (m, 1H, aromatic), 8.54 (br, 1H, $NHCH_3$), 8.76 (s, 1H, thiourea)	393.1 $[M+H]^+$
1o	2.41 (s, 3H, $COCH_3$), 2.79 (d, J = 4.8 Hz, 3H, $NHCH_3$), 3.30 (s, 3H, NCH_3), 7.11 (m, 1H, aromatic), 7.26 (m, 1H, aromatic), 7.45 (m, 2H, aromatic), 7.77 (m, 2H, aromatic), 7.92−7.95 (m, 2H, aromatic), 8.16−8.19 (m, 2H, aromatic), 8.26 (m, 1H, aromatic), 8.49 (br, 1H, $CONHCH_3$), 8.66 (s, 1H, thiourea)	435.2 $[M+H]^+$
1p	2.79 (d, J = 4.7 Hz, 3H, $NHCH_3$), 3.07 (s, 3H, NCH_3), 7.15−7.20 (m, 3H, aromatic), 7.28 (m, 1H, aromatic), 7.41−7.48 (m, 2H, aromatic), 7.59 (m, 1H, aromatic), 7.70 (m, 1H, aromatic), 7.95 (m, 1H, aromatic), 8.29 (m, 1H, aromatic), 8.53 (m, 1H, aromatic), 8.67 (m, 1H, $NHCH_3$), 8.86 (s, 1H, thiourea)	394.1 $[M+H]^+$

2　Sorafenib 硫脲衍生物 1a～1p 的体外抗癌活性研究

采用 MTT 还原法, 以 sorafenib 为阳性对照, 测试它们对肾癌 760-O、肝癌 HepG2、肺癌 A549、乳腺癌 MDA-MB-435、前列腺癌 PC3 和结肠癌细胞 HT-29 共 6 种肿瘤细胞的体外抗肿瘤活性。实验结果见表 3。结果显示: ① **1a** 是 sorafenib 结构中脲被硫脲替代的衍生物, 体外抗肿瘤活性优于对照, 说明硫脲的结构对抗肿瘤活性有益。② **1b** 为经苯胺合成的脲, 将其他苯环上有取代基的衍生物与其进行活性数据比较, 结果表明: 苯环上斥电子取代基不利于抗肿瘤活性, 而大多数具有吸电子取代基的衍生物抗肿瘤活性优于 **1b**。③ **1n**～**1p** 为硫脲基团上 N 被甲基取代的衍生物, 体外抗肿瘤活性均较弱, 可能原因是硫脲基团 N 上的氢与作用靶点存在一定的氢键作用, 因此, 采用芳香伯胺制备的硫脲化合物将会有利于抗癌活性。④ **1a**、**1d**、**1i** 及 **1j** 的抗肿瘤活性优于阳性对照或与阳性对照相当。

3　小结

以多靶点抗肿瘤药 sorafenib 为母核, 设计合成了一系列 4-[4-(2-甲胺酰基吡啶)]氧苯基芳香硫脲衍生物。初步的体外抗肿瘤活性筛选结果表明: 可能由于硫脲基团比脲具有更强的亲脂性及组织渗透性,因此表现出较好的抗癌活性。大多数具有吸电子取代基的芳香伯胺制备得到的 sorafenib 硫脲衍生物抗肿瘤活性较强。本研究结果对 sorafenib 硫脲衍生物的进一步优化设计具有一定的指导意义。

Table 3 Anti-tumor activities of compounds **1a**−**1p** *in vitro*

Compd.	IC_{50}/μmol·L^{-1}					
	760-O	HepG2	A549	MDA-MB-435	PC3	HT-29
1a	13.2	7.9	8.5	16.9	20.1	12.1
1b	45.6	49.8	55.4	>100	>100	55.9
1c	22.8	29.6	35.4	>100	26.0	21.9
1d	15.9	12.8	16.8	21.2	52.7	14.6
1e	65.6	67.9	79.0	>100	>100	>100
1f	33.5	28.0	25.9	49.3	52.8	38.6
1g	16.8	8.5	17.9	16.2	32.1	18.6
1h	40.0	58.6	>100	62.7	>100	79.6
1i	10.6	6.3	7.1	21.9	16.2	15.3
1j	4.5	3.1	5.9	11.6	8.7	9.8
1k	35.6	30.1	48.3	41.3	77.2	40.9
1l	18.6	16.2	15.7	40.1	29.7	18.9
1m	19.6	25.0	20.6	38.3	35.5	29.8
1n	>100	78.2	67.9	>100	>100	>100
1o	>100	82.5	76.1	96.8	>100	>100
1p	>100	>100	>100	>100	>100	>100
Sorafenib	16.7	9.6	10.6	17.8	33.2	13.6

实验部分

熔点用天津大学精密仪器厂 YRT-3 熔点仪测定; ^{1}H NMR 用 Bruker AV-500 或 AV-300 型核磁共振仪测定, MS (ESI) 由 Agilent 1100 LC/MS 质谱仪测定, 元素分析经 Elementa Vario EL III 型元素分析仪测定。体外活性测定所用的阳性对照 sorafenib 为实验室自制 (HPLC 纯度 > 99.0%)。硫光气纯度 95%以上, 反应溶剂 CCl_4 和 CH_2Cl_2 经无水处理, 其余均为分析纯或化学纯。

1 *N*, *N*'-硫酰二咪唑 (6) 的合成[14]

氮气保护下, 于 1-三甲基硅基咪唑 (14.6 mL, 0.1 mol) 的干燥 CCl_4 (80 mL) 溶液中, 保持 10 ℃以下慢慢滴加硫光气 (3.8 mL, 0.05 mol) 的干燥 CCl_4 (20 mL) 溶液, 加完后室温反应 6 h。搅拌下冷却至 0 ℃, 1.5 h 后过滤, 得黄色固体 6.8 g, 收率 76.4%, mp 104～106 ℃ (lit.105～106 ℃)。

2 化合物 1a～1p 的合成

氮气保护下, 将芳香胺 (10 mmol) 溶解于干燥 CH_2Cl_2 (20 mL) 中, 加入上步所得 **6** (2.10 g, 12 mmol), 室温搅拌 1 h 后, 慢慢滴加 **5** (2.4 g, 10 mmol) 的干燥 CH_2Cl_2 (20 mL) 溶液, 继续室温反应 4 h。适当减压浓缩母液, 冷却析出固体, 抽滤, 冷 CH_2Cl_2 洗涤。无水乙醇重结晶或打浆洗涤。抽滤, 真空干燥, 得 **1a**～**1p**。

3 体外抗癌活性测试

采用 MTT 法对目标化合物 (**1a**～**1p**) 进行肾癌 760-O、肝癌 HepG2、肺癌 A549、乳腺癌 MDA-MB-435、前列腺癌 PC3 和结肠癌细胞 HT-29 共 6 种肿瘤细胞的体外抗肿瘤活性测试, 阳性对照为 sorafenib。将处于细胞对数生长期的实验用肿瘤细胞按一定的细胞量接种于 96 孔培养板中, 培养 24 h 后加入目标物的 DMSO 溶液, 将细胞在 37 ℃、5% CO_2 条件下继续培养 72 h 后, 每孔加入 20 μL 溴化噻唑蓝四氮唑试液 (MTT, 5 mg·L^{-1}), 4 h 后向每孔中加入 100 μL DMSO, 溶解后于室温下振摇 15 min, 在酶标仪下用 570 nm 波长进行检测, 以化合物浓度对数值对抑制率作线性回归, 得直线方程, 从中求出抑制半数癌细胞的化合物浓度 (IC_{50})。

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由中国药学会主办、绿叶制药集团有限公司等协办的 2011 年中国药学大会暨第 11 届中国药师周大会, 定于 2011 年 11 月 5 日至 6 日在山东省烟台市 (具体地点详见第三轮通知) 举行。有关大会的征文范围和要求、论文评奖、壁报交流、会议学分、收费标准及报名方式等详情请登陆中国药学会网站 (http://www.cpa.org.cn) 或会议网站 (http://www.cpameeting.org.cn) 查询。

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