二茂铁杂环类化合物的合成及抗三阴性乳腺癌活性研究

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摘要:目的 设计、合成杂环二茂铁衍生物,并研究其抗三阴性乳腺癌活性。方法 以二茂铁查耳酮为先导化合物,对 其进行结构改造,合成了一系列含有杂环的二茂铁衍生物,并通过 CCK8 试剂盒测试化合物抗乳腺癌活性。结果 合成 了 28 个二茂铁衍生物,其结构均通过¹H-NMR 和 MS 加以确证。初步的生物活性测试结果表明,所合成的二茂铁衍生物 对三阴性乳腺癌 MDA-MB-231 细胞有较强的选择性和抑制活性,其中咪唑杂环化合物抗肿瘤活性强于相应的吡唑类和嘧 啶化合物。尤其是 **28a**[IC₅₀=(1.6±0.23)µmol·L⁻¹]对 MDA-MB-231 的抑制活性分别是先导化合物 **3**[IC₅₀=(10.7±1.41)µmol·L⁻¹] 和他莫昔芬[IC₅₀=(13.7±1.17)µmol·L⁻¹]的 6 和 10 倍,同时这些二茂铁衍生物对正常乳腺上皮细胞 MCF-10A 均没有毒性。 结论 本研究为开发具有抗三阴性乳腺癌活性的化合物提供了信息和依据。 关键词: 二茂铁衍生物; 合成; 抗三阴性乳腺癌

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Synthesis of Ferrocenyl Heterocyclic Derivatives and Anti-triple Negative Breast Cancer Screening

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ABSTRACT: OBJECTIVE To design and synthesis of ferrocenyl heterocyclic derivatives and investigate anti-triple negative breast cancer activity. **METHODS** A series of ferrocenyl derivatives were designed and synthesized from ferrocenyl chalcone, and their anti-breast cancer activities were evaluated by CCK8 assay. **RESULTS** Twenty-eight ferrocenyl heterocyclic derivatives were synthesized and the structures had been confirmed by ¹H-NMR and MS spectra. The preliminary biological results showed that all synthesized ferrocenyl derivatives showed selective anticancer activity that were more potent against MDA-MB-231 cells than MCF-7, which also showed moderate inhibitory activity, against MDA-MB-231 cell lines, and imidazole heterocyclic compounds had more potent anti-tumor than corresponding pyrazole and pyrimidine derivatives, specifically, compound **28a** $[IC_{50}=(1.6\pm0.23)\mu mol \cdot L^{-1}]$ showed about 6 and 10-fold potency than lead compound **3** $[IC_{50}=(10.7\pm$ 1.41) $\mu mol \cdot L^{-1}]$ and tamoxifen $[IC_{50}=(13.7\pm1.17)\mu mol \cdot L^{-1}]$, against MDA-MB-231 cell lines, and these ferrocenyl derivatives were not toxic to normal cells. **CONCLUSION** This study provides information and basis for development of ferrocenyl derivatives with anti-triple negative breast cancer activity.

KEY WORDS: ferrocenyl derivatives; synthesis; anti-triple negative breast cancer

三阴性乳腺癌(triple negative breast cancer, TNBC)是乳腺癌中恶性程度较高的类型,约占乳 腺癌病理类型的 10%~20%^[1]。在治疗上由于缺乏 TNBC 有效的特异性靶点,因此传统的靶向药物对 之无效。对 TNBC 来说,其复发率和转移率特别 高,这也是该种类型乳腺癌有较高死亡率的原因^[2]。 临床上对于 TNBC 的治疗,主要是以铂类、蒽环 类、紫杉醇类为基础的化疗^[3],但其全身药物的不 良反应严重,药物毒性大,严重影响了患者的生 活质量。因此,开发出新型、高效、低毒的抗 TNBC 药物已成为医疗界迫切的需要,同时也是当今学 术界和制药界的研究热点^[4]。 近年来研究发现,查耳酮作为一类重要的天 然产物也表现出了抗乳腺癌活性^[5],同时对正常细 胞没有毒性。本课题组设计、合成了一系列的查 耳酮,并对 TNBC 展现出了中等的抑制活性(图 1, 化合物 1, IC₅₀>29 μmol·L⁻¹)^[6];随后,笔者对该 类查耳酮化合物进行结构修饰,引入二茂铁(图 1, 化合物 2)基团构建了一系列的二茂铁查耳酮,显 著地提高对 TNBC 的抑制活性,其中化合物 3 [图 1, IC₅₀=(10.7±1.41)μmol·L⁻¹]展现出了最强活 性^[7],但与他莫昔芬相比,大部分二茂铁类查耳酮 抗乳腺癌活性仍然较低。因此,拟进一步对二茂 铁查耳酮进行结构优化,以期望得到抗 TNBC 活

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性更强、毒性更低的新型二茂铁查耳酮衍生物。

参考查耳酮的结构改造经验发现,将查耳酮 α,β-不饱和酮修饰成杂环后能提高抗肿瘤活性^[8-11]。 因此,笔者拟构建一系列杂环类二茂铁衍生物, 其合成过程见图 2~3。首先,以 1-二茂铁基-3-(4-氯苯基)-2-丙烯酮(化合物 3)为先导化合物,将其修 饰成嘧啶(化合物 4~10)杂环后能够显著提高其抗 乳腺癌活性;接着,将化合物 3 修饰成二氢吡咯 杂环化合物 11~17 后,其抗 TNBC 活性较嘧啶类 化合物进一步提高,其中 *N*-1 位为 4-F 苯基取代的 化合物 17a 活性强于其他取代基的化合物,而将 化合物 17a 的二氢吡咯环氧化成吡咯环(化合物 18) 后却降低了抗肿瘤活性;随后,保留了 N-1 位上 4-F 苯基,合成了 4-醛基二茂铁化合物 21,并通 过 Claisen-Schmidt 羟醛缩合反应合成了另一系列 具有咪唑杂环的二茂铁类查耳酮 22~28。通过生物 活性研究发现,这类咪唑杂环化合物对 TNBC 的 抑制活性强于二氢吡咯杂环类,其中化合物 28a [IC₅₀=(1.6±0.23)μmol·L⁻¹]展现出了最强的抑制活 性,是先导化合物 3 的 6 倍。



图 2 二茂铁类化合物 4~18 的合成路线 Fig. 2 Synthetic route of ferrocenyl compounds 4-18



- 图 3 二茂铁类化合物 22~28 的合成路线
- Fig. 3 Synthetic route of ferrocenyl compounds 22–28

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1 仪器和试剂

1.1 仪器

BrukerAM-400Hz 型核磁共振仪(TMS 内标); XR4 显微熔点测定仪(上海光学仪器厂); DF-101S 集热式恒温加热磁力搅拌器(河南巩义市予华仪器 有限责任公司); FA(N)/JA(N)系列 MINQI (○ 电子 天平(上海民桥精密科学仪器有限公司); 1106 型元 素分析仪(意大利 Carlo Erba 公司); HP1100 质谱 仪(美国 Agilent 公司); GF254 硅胶薄层板(青岛海 洋化工厂)。

1.2 试剂

乙酰基二茂铁(北京百灵威科技有限公司,纯度>98%);对氯苯甲醛(北京百灵威科技有限公司,纯度>98%);苯肼衍生物(阿拉丁试剂有限公司,纯度>95%);苯甲氰衍生物(阿拉丁试剂有限公司,纯度>95%);合成使用的其他试剂均为分析纯;水为蒸馏水。

2 合成方法

2.1 1-二茂铁基-3-(4-氯苯基)-2-丙烯酮(3)

称取单乙酰基二茂铁(4.347 g, 12.4 mmol)和 对氯苯甲醛(1.736 g, 12.4 mmol)溶解到 50 mL 甲 醇中,将反应瓶置于冰浴中,冷却后缓慢加入 KOH (3.484 g, 62.1 mmol),撤除冰浴后在室温下反应 12 h,用 10%盐酸调节溶液 pH 3,析出红色沉淀, 过滤,滤饼在真空干燥箱中干燥过夜即得到化合 物 3,产率:78%,m.p. 158~160 ℃;¹H-NMR (400 MHz, CDCl₃) δ 7.64 (d, J = 15.6 Hz, 1H), 7.49 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 6.99 (d, J = 16.0 Hz, 1H), 4.83 (s, 2H), 4.52 (s, 2H), 4.13 (s, 5H)。

2.2 嘧啶类化合物 4~10 的合成

称取二茂铁查耳酮(化合物 3,0.421g, 1.2 mmol)、苯甲氰衍生物(1.2 mmol)、羟胺 (0.041g,1.2 mmol)溶解到5 mL 醋酸中,室温反 应 2.5 h 后,将反应液在微波(600 W,180 ℃)中反 应 5 min,将反应液冷却至室温,加入15 mL 饱和 的 NaCl 溶液,用乙酸乙酯萃取(3×30 mL),有机 层用无水硫酸钠干燥,减压除去溶剂,经柱层析(石 油醚-乙酸乙酯,4:1)得到相应的嘧啶类化合物 4~10,其收率、理化常数及波谱数据见表1~2。

2.3 二氢吡唑类化合物 11~17 的合成

氩气保护下,将二茂铁查耳酮(化合物 3,0.386g,1.1 mmol)和苯肼衍生物(1.1 mmol)溶解到

无乙醇(10 mL)、醋酸(6 mL)与水(2 mL)的混合溶剂 中,加入回流反应 6 h,将反应液冷却至室温,倒 入 20 mL 冰水中,析出红色的沉淀,过滤,滤饼真 空干燥,甲醇重结晶得到相应的二氢吡唑类化合物 11~17,其收率、理化常数及波谱数据见表 1~2。

2.4 1-(4-氟苯基)-3-二茂铁基-5-(4-氟苯基)-1*H*-吡 唑(化合物 **18**)的合成

称取化合物 17a(0.279 g, 0.6 mmol)和二氯二 氰基苯醌(DDQ, 0.091 g, 0.4 mmol)溶解到苯 (20 mL)中,加热至回流反应4h,将反应液冷却至 室温,减压除去溶剂,经柱层析(石油醚-乙酸乙酯, 2:1)得到吡唑化合物18,其收率、理化常数及波 谱数据见表1~2。

2.5 1-(4-氟苯基)-2-(1-二茂铁亚乙基)肼(化合物 **20**)的合成

氩气保护下,称取乙酰二茂铁(化合物 1, 0.386 g, 1.1 mmol)和 4-氟苯肼(1.1 mmol)溶解到无 乙醇(20 mL)中,缓慢滴加 1 mL 浓硫酸,室温反应 12 h,用 10% NaOH 溶液调节 pH 8,析出红色的 沉淀,过滤,滤饼真空干燥,甲醇重结晶得到化 合物 20,产率为 84%,m.p. 184~186 ℃;⁻¹H-NMR (400 MHz, CDCl₃) δ 7.53 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 7.08 (d, J = 8.0 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 4.72 (s, 2H), 4.22 (s, 5H), 4.11 (s, 2H), 2.97 (s, 3H)。

2.6 1-(4-氟苯基)-3-苯基-1*H*-咪唑-4-苯甲醛(化合物 22)的合成

冰浴下,称取化合物 **19**(0.386 g, 4.1 mmol) 溶解到 POCl₃ (0.5 mL, 6.1 mmol)和 DMF(10 mL) 的溶液中,加热至 60 ℃反应 6 h,反应液冷却至 室温后倒入 50 mL 的冰水中,用 10% NaOH 溶液 调节 pH 7,析出红色的沉淀,过滤,滤饼真空干 燥,甲醇重结晶得到化合物 **21**,产率:71%,m.p. 169~172 ℃;¹H-NMR (400 MHz, CDCl₃) δ 7.61 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 6.84 (s, 1H), 4.71 (s, 2H), 4.24 (s, 5H), 4.13 (s, 2H). **2.7** 咪唑类化合物 **22~28** 的合成

称取化合物 20(0.598 g, 2.3 mmol)和相应的芳 乙酮(1.6 mmol)溶于 20 mL 无水甲醇中,室温搅拌 10 min 后,将反应液置于冰浴中冷却,缓慢加入 10 mL 20%的 KOH 溶液,反应液呈红色。在室温 下继续反应 12 h,用 20%的盐酸调节 pH 3 后,部 分产物以沉淀析出后过滤,滤饼在真空干燥箱中 干燥;如加盐酸调节 pH 后未能析出沉淀则用乙酸 乙酯(3×25 mL)萃取,合并有机层,无水硫酸钠干 燥,减压除去溶剂,经柱层析(石油醚-乙酸乙酯, 4:1~1:1)得到化合物 22~28,其收率、理化常数 及波谱数据见表 1~2。

3 结果与讨论

3.1 化合物的合成

在目标化合物 4~10 的合成中,该反应是经过

表1 目标化合物 4~18, 22~28 的理化常数和质谱数据

Tab. 1 Physical contants and MS of synthesized compounds 4–18, 22–28

两步反应进行,如图 4 所示,首先苯甲氰化合物 与羟胺反应生成胺肟中间体 I,接着在微波的环境 下与化合物 3 反应制得嘧啶类化合物 4~10。目标 化合物 18 是通过氧化相应的二氢吡唑类化合物 17 制备的;在合成咪唑类化合物 22~28 时,其中关 键中间体 21 是通过采用 POCl₃-DMF 试剂经过 Vilsmeier-Haack 反应制得的。

在构式		化스物	٨٣	立	m n /°C	柳珊桃	元素分析(%, Calcd)			MS(ESI) m/z
	知何式	11. 11. 11.	AI) 444/70	m.p./ C	初建付任	С	Н	Ν	$\left[M+H\right]^{+}(Calcd)$
Fe D		4	Ph	74.5	215~218	红色固体	69.74 (69.28)	4.17 (4.25)	5.91 (6.21)	451 (451.74)
		5	4-MePh	86.2	226~229	红色固体	69.91 (69.77)	4.39 (4.55)	5.87 (6.03)	465 (465.77)
	Ar	6	4-OMePh	79.7	208~210	红色固体	67.52 (67.45)	4.55 (4.40)	5.71 (5.83)	481 (481.77)
	4-10	7	4-OHPh	65.9	236~234	红色固体	67.15 (66.91)	4.23 (4.10)	5.72 (6.00)	467 (467.74)
		8	4-ClPh	73.3	241~244	红色固体	64.52 (64.36)	3.71 (3.74)	5.35 (5.77)	486 (486.19)
		9	4-BrPh	71.9	225~227	红色固体	59.03 (58.96)	3.66 (3.43)	5.07 (5.29)	530 (530.64)
		10a	4-FPh	75.6	218~223	红色固体	67.04 (66.62)	3.55 (3.87)	5.86 (5.98)	469 (469.73)
		10b	3-FPh	77.1	236~238	红色固体	66.87 (66.62)	3.93 (3.87)	5.74 (5.98)	469 (469.73)
		10c	2-FPh	80.2	225~227	红色固体	67.05 (66.62)	3.96 (3.87)	5.62 (5.98)	469 (469.73)
		11	Ph	76.5	186~188	红色固体	68.27 (68.13)	4.92 (4.80)	6.05 (6.36)	441 (441.75)
		12	4-MePh	84.3	179~181	红色固体	68.85 (68.67)	4.89 (5.10)	6.01 (6.16)	441 (455.78)
		13	4-OMePh	83.9	182~185	红色固体	66.62 (66.33)	4.78 (4.92)	5.83 (5.95)	471 (471.77)
	Ar N−N	14	4-OHPh	68.4	194~196	红色固体	65.89 (65.74)	4.74 (4.63)	6.02 (6.13)	457 (457.75)
\bigcirc		15	4-ClPh	75.5	190~192	红色固体	63.28 (63.19)	4.55 (4.24)	5.77 (5.90)	476 (476.19)
Fe	CI	16	4-BrPh	73.2	201~204	红色固体	57.93 (57.78)	3.72 (3.88)	5.15 (5.39)	520 (520.64)
	11-17	17a	4-FPh	70.8	207~209	红色固体	65.66 (65.46)	4.18 (4.39)	6.04 (6.11)	459 (459.74)
		17b	3-FPh	77.6	196~199	红色固体	65.72 (65.46)	4.06 (4.39)	6.09 (6.11)	459 (459.74)
		17c	2-FPh	71.7	194~197	红色固体	65.69 (65.46)	4.25 (4.39)	6.01 (6.11)	459 (459.74)
	Ar N-N	141	0.1							
\bigcirc	LAN (18	4-FPh	82.1	218~221	红色固体	65.71 (65.60)	4.22 (4.18)	6.04 (6.12)	457 (457.72)
Fe	CI									
	18	22	Dh	84.6	226,220	行布固体	70.84 (70.60)	1 36 (1 14)	5 62 (5 99)	ATT (ATT 22)
Ar Fe		22	T II 4-MePh	81.1	220~228	江口回座	71.35 (71.02)	4 50 (4.44)	5.58 (5.71)	401 (401 35)
		23	4-MePh	76.8	235~230	江口四座	68 93 (68 70)	4 42 (4 58)	5 36 (5 53)	507 (507 36)
		24 25		70.2	237~239	红白田体	68 52 (69 21)	4 47 (4 20)	5 45 (5.53)	A03 (A02 22)
		20 24		70.5 70.7	241~243	江口凹砕	65 08 (65 94)	+.+/ (4.50)	5 22 (5 49)	511 (511 77)
	N N F 22-28	20	4-CIFII	72.7	241~249	红色回冲	60.85 (60.57)	3.03(3.93)	<i>J.25</i> (<i>J.</i> 48)	511(511.77) 556(55622)
		27	4-DIPI	13.3	220~228	红色四种	(00.65 (00.57)	5.51 (5.05) 4.17 (4.09)	4.07 (3.03)	405 (405 22)
		288	4-rPn 2 EDh	/8.4 74.9	215~211	红色凹体	08.32 (08.03)	4.17 (4.08)	5.42 (5.07)	495 (495.52)
		280	3-FPN	/4.8	245~242	<u>红</u> 巴回体	08.45 (08.03)	4.11 (4.08)	5.20 (5.67)	495 (495.32)
		28c	2-FPh	/5./	218~220	红巴回怀	68.39 (68.03)	4.22 (4.08)	5.39 (5.67)	495 (495.32)

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表 2 目标化合物 4~18, 22~28 的核磁氢谱数

Tab. 2 The ¹H-NMR data of target compounds 4–18, 22–28

 4 S28 (2H, <i>Q</i>, =8,4 Hz), 822 (2H, <i>d</i>, <i>J</i>=8,0 Hz), 7.96 (1H, s), 7.50 (7.55 (3H, m), 747 (2H, <i>d</i>, <i>J</i>=8,4 Hz), 4.73 (s, 2H), 4.99 (s, 2H), 4.09 (s, 2H), 4.50 (s, 4.12 (s, 3H), 2.32 (3H), 9. 8 25 (2H, <i>d</i>, <i>J</i>=8,0 Hz), 8.21 (2H, <i>d</i>, <i>J</i>=8,0 Hz), 7.95 (1H, s), 7.55 (2H, <i>d</i>, <i>J</i>=8,4 Hz), 7.47 (2H, <i>d</i>, <i>J</i>=8,4 Hz), 4.71 (s, 2H), 4.54 (s, 4.17 (s, 5H), 3.84 (3H), s). 8 18 (2H, <i>d</i>, <i>J</i>=8,4 Hz), 8.21 (2H, <i>d</i>, <i>J</i>=8,0 Hz), 7.92 (1H, s), 7.55 (2H, <i>d</i>, <i>J</i>=8,4 Hz), 7.47 (2H, <i>d</i>, <i>J</i>=8,4 Hz), 4.71 (s, 2H), 4.54 (s, 4.17 (s, 5H), 3.84 (3H), s). 8 18 (2H, <i>d</i>, <i>J</i>=8,4 Hz), 8.21 (2H, <i>d</i>, <i>J</i>=8,4 Hz), 7.91 (1H, s), 7.57 (2H, <i>d</i>, <i>J</i>=8,4 Hz), 7.53 (2H, <i>d</i>, <i>J</i>=8,4 Hz), 4.74 (s, 2H), 4.48 (s, 4.14 (s, 5H). 8 23 (2H, <i>d</i>, <i>J</i>=8,4 Hz), 8.23 (2H, <i>d</i>, <i>J</i>=8,0 Hz), 7.95 (1H, s), 7.13 (2H, <i>d</i>, <i>J</i>=8,4 Hz), 7.53 (2H, <i>d</i>, <i>J</i>=8,4 Hz), 4.67 (s, 2H), 4.48 (s, 4.15 (s, 5H). 8 21 (2H, <i>d</i>, <i>J</i>=8,4 Hz), 8.17 (2H, <i>d</i>, <i>J</i>=8,0 Hz), 7.55 (1H, s), 7.57 (3H, m), 7.48 (2H, <i>d</i>, <i>J</i>=8,4 Hz), 4.67 (s, 2H), 4.46 (s, 2H), 4.48 (s, 4.11 (s, 5H). 8 22 (2H, <i>d</i>, <i>J</i>=8,4 Hz), 7.17 (2H, <i>d</i>, <i>J</i>=8,0 Hz), 7.55 (2H, <i>d</i>, <i>J</i>=8,1 Hz), 4.76 (s, 2H), 4.43 (s, 2H), 4.43 (s, 2H), 4.44 (s, 5H). 8 22 (2H, <i>d</i>, <i>J</i>=8,4 Hz), 7.17 (1H, s), 7.79 -738 (2H, <i>m</i>, 7.57 (3H, m), 7.37 (4H, <i>m</i>), 7.44 (s), 2.11, 4.46 (s, 2H), 4.41 (s, 5H). 8 22 (2H, <i>d</i>, <i>J</i>=8,4 Hz), 7.10 (1H, s), 7.107 (2H, <i>d</i>, <i>J</i>=84 Hz), 4.71 (6 kz), 2.49 (Hz), 4.26 (kz), 4.3 (s, 2H), 4.41 (s, 2H), 4.41 (s, 2H), 4.41 (s), 7.107 (2H, <i>d</i>, <i>J</i>=84 Hz), 4.55 (s) (1H), 4.47 (s, 1H), 4.47 (s) 1Hz, <i>J</i>=1.2 Hz), 3.00 (1H, <i>d</i>, <i>J</i>=1.6 Hz), <i>J</i>=0 (Hz), 4.55 (s) (H), 4.17 (s) 1H, 3.77 (2H, <i>d</i>, <i>J</i>=84 Hz), 4.55 (s) (H, <i>d</i>, <i>J</i>=1.2 Hz), 3.10 (1H, <i>d</i>, <i>J</i>=1.16 Hz), <i>J</i>=0 (Hz), 4.26 (Hz),	化合物	⁴ H-NMR (400 MHz, Acetone- d_6)			
 \$25 (211, d 4.80 (1z), 8.21 (211, d. J - 8.0 Hz), 7.94 (1H, s), 7.52 (211, d. J - 8.0 Hz), 7.42 (211, d. J - 8.0 Hz), 4.69 (s. 211), 4.50 (s. 4.12 (s. 511), 2.32 (211, s), \$26 (211, d. J - 8.0 Hz), 8.23 (211, d. J - 8.0 Hz), 7.92 (1H, s), 7.55 (211, d. J - 8.0 Hz), 7.47 (211, d. J - 8.4 Hz), 4.71 (s. 211), 4.24 (s. 4.17 (s. 511), 3.24 (211, s), \$81 (211, d. J - 8.4 Hz), 8.11 (211, d. J - 8.4 Hz), 7.91 (1H, s), 7.57 (211, d. J - 8.4 Hz), 7.30 (211, d. J - 8.4 Hz), 4.69 (s. 211), 4.41 (s. 4.14 (s. 511), \$81 (211, d. J - 8.4 Hz), 8.26 (211, d. J - 8.0 Hz), 7.96 (1H, s), 7.73 (211, d. J - 8.0 Hz), 7.55 (211, d. J - 8.4 Hz), 4.69 (s. 211), 4.41 (s. 4.11 (s. 511), \$82 (211, d. J - 8.4 Hz), 8.23 (211, d. J - 8.0 Hz), 7.95 (1H, s), 7.73 (211, d. J - 8.0 Hz), 7.55 (211, d. J - 8.4 Hz), 4.69 (s. 211), 4.49 (s. 511), \$82 (211, d. J - 8.4 Hz), 8.17 (211, d. J - 8.0 Hz), 7.95 (1H, s), 7.52 (211, d. J - 8.0 Hz), 7.28 (211, d. J - 8.4 Hz), 4.67 (s. 211), 4.49 (s. 511), \$82 (211, d. J - 8.4 Hz), 7.17 (211, d. J - 8.4 Hz), 5.71 (1H, d. J - 110, J - 110, J - 216 (s. 211), 4.46 (s. 211), 4.09 (s. 511), \$82 (211, d. J - 8.4 Hz), 7.17 (211, d. J - 8.4 Hz), 5.71 (1H, d. J - 110, J - 110, J - 246 (s. 211), 4.09 (s. 511), \$82 (211, d. J - 8.4 Hz), 7.17 (211, d. J - 8.4 Hz), 5.71 (1H, d. J - 110, J	4	8.28 (2H, d, <i>J</i> =8.4 Hz), 8.22 (2H, d, <i>J</i> =8.0 Hz), 7.96 (1H, s), 7.50-7.55 (3H, m), 7.47 (2H, d, <i>J</i> =8.4 Hz), 4.73 (s, 2H), 4.49 (s, 2H), 4.09 (s, 5H).			
 8 226 CH, d., ≠80 HB, 822 (2H, d., ≠8.0 Hz), 7.92 (1H, s), 7.55 (2H, d., ≠8.0 Hz), 7.47 (2H, d., ≠8.4 Hz), 4.71 (s, 2H), 4.54 (s, 417 (s, 5H), 384 (3H, 3). 8 18 (2H, d., ≠8.4 Hz), 8.11 (2H, d., ≠8.4 Hz), 7.91 (1H, s), 7.57 (2H, d., ≠8.4 Hz), 7.30 (2H, d., ≠8.4 Hz), 4.69 (s, 2H), 4.48 (s, 414 (s, 5H). 8 35 (2H, d., ≠8.0 Hz), 8.26 (2H, d., ≠8.0 Hz), 7.96 (1H, s), 7.91 (2H, d., ≠8.4 Hz), 7.33 (2H, d., ≠8.4 Hz), 4.70 (s, 2H), 4.45 (s, 419 (s, 5H). 8 23 (2H, d., ≠8.4 Hz), 8.12 (2H, d., ≠8.0 Hz), 7.95 (1H, s), 7.73 (2H, d., ≠8.0 Hz), 7.55 (2H, d., ≠8.4 Hz), 4.60 (s, 2H), 4.49 (s, 4H), 4.51 (s, 5H). 8 21 (2H, d., ≠8.4 Hz), 8.17 (2H, d., ≠8.0 Hz), 7.93 (1H, s), 7.32 (2H, d., ≠8.0 Hz), 7.28 (2H, d., ≠8.4 Hz), 4.67 (s, 2H), 4.49 (s, 4H), 4.5 (s, 5H). 8 02 (1H, s), 8.19 (2H, d., ≠8.0 Hz), 7.99 (1H, s), 7.44 (1H, d., ≠8.4 Hz), 7.47 (s, 2H), 4.43 (s, 2H), 4.49 (s, 5H), 4.10 (s, 5H). 8 02 (1H, s), 8.19 (2H, d., ≠8.0 Hz), 7.99 (1H, s), 7.97 7.34 (2H, m), 7.34 (2H, d., ±8.0 Hz), 7.28 (2H, d., ±8.4 Hz), 4.97 (s, 2H), 4.43 (s, 2H), 4.12 (s, 1H), (s, 5H), 3.87 (1H, d., ±1, 1H), 7.79 (73 Hz), 5.79 (1H, m), 7.74 (s, 2H), 4.43 (s, 2H), 4.12 (s, 1Z), 1.17 (2H, d., ±8.4 Hz), 5.17 (1H, d., ±18.0 Hz), ±4.4 Hz). 7 47 (2H, d., ±6.4 Hz), 7.20 (2H, d., ±6.4 Hz), 7.05 (2H, d., ±6.4 Hz), 5.53 (1H, d., ±1, =1.1 Hz), ±2.4 (s, 1H), (s, 2H), 4.21 (s, 5H), 3.87 (1H, d., ±1, 1H), 3.00 (1H, d., ±1, ±8.0 Hz), 5.53 (1H, d., ±1, =1.1 Hz), 5.20 (1H), 4.2 (s, 1H), 4.13 (s, 5H), 3.70 (1H, d., ±5.4 Hz), 5.53 (1H, d., ±1, ±1, ±1, ±1), 5.10 (1H, d., ±1, ±1, ±1), 5.25 (1H, d., ±1, ±1, ±1), 5.25 (1H, d., ±1, ±1, ±1, ±1), 5.21 (Hz), ±4.4 Hz). 7 43 (2H, d., ±6.8 Hz), 7.26 (2H, d., ±6.8 Hz), 7.53 (2H, d., ±5.8 Hz), 5.40 (1H, d., ±1, ±1, ±1, ±1), 5.11 (Hz), ±4.4 Hz), (s, 2H), 4.21 (s, 5H), 3.70 (Hz), ±5.8 (Hz), 4.70 (Hz), ±5.8 (Hz), 4.70 (Hz), ±5.8 (Hz), 4.70 (Hz), ±5.8 (Hz), 4.10 (Hz), ±5.8 (Hz), 4.10 (Hz), ±5.8 (Hz), 4.10 (Hz), ±5.8 (Hz), 4.10 (H	5	8.25 (2H, d, J=8.0 Hz), 8.21 (2H, d, J=8.0 Hz), 7.94 (1H, s), 7.52 (2H, d, J=8.4 Hz), 7.42 (2H, d, J=8.0 Hz), 4.69 (s, 2H), 4.50 (s, 2H), 4.12 (s, 5H), 2.32 (3H, s).			
7 8.18 (2H, d. J=8.4 Hz), 8.11 (2H, d. J=8.4 Hz), 7.91 (1H, s), 7.57 (2H, d. J=8.4 Hz), 7.00 (2H, d. J=8.4 Hz), 4.59 (s. 2H), 4.48 (s. 4.14 (s. 5H). 8 85.55 (2H, d. J=8.0 Hz), 8.26 (2H, d. J=8.0 Hz), 7.96 (1H, s), 7.91 (2H, d. J=8.4 Hz), 7.53 (2H, d. J=8.4 Hz), 4.74 (s. 2H), 4.41 (s. 4.19 (s. 5H). 9 82.8 (2H, d. J=8.4 Hz), 8.23 (2H, d. J=8.4 Hz), 7.95 (1H, s), 7.73 (2H, d. J=8.0 Hz), 7.55 (2H, d. J=8.4 Hz), 4.69 (s. 2H), 4.45 (s. 4.15 (s. 5H). 19 82.1 (2H, d. J=8.4 Hz), 8.17 (2H, d. J=8.0 Hz), 7.93 (1H, s), 7.32 (2H, d. J=8.0 Hz), 7.28 (2H, d. J=8.4 Hz), 4.69 (s. 2H), 4.49 (s. 5H). 10 8.02 (1H, s), 8.19 (2H, d. J=8.0 Hz), 7.95 (1H, s), 7.84 (1H, d. J=8.4 Hz), 7.51 (7.59 (4H, m), 4.74 (s. 2H), 4.46 (s. 2H), 4.49 (s. 5H). 11 7.42 (2H, d. J=8.1 T, 7.91 (2H, s), 7.29 (2H, m), 7.49 (7.57 (3H, m), 7.24 (1H, d. J=4.1 Hz), 4.29 (s. 1H), 4.43 (s. 2H), 4.10 (s. 5H). 12 7.47 (2H, d. J=8.1 Hz), 7.12 (7.36 (Hz), 7.10 (2H, d. J=8.4 Hz), 5.61 (H, d. J=1.6 Hz), 5.4 (Hz), 4.5 (s. 1H), 4.25 (s. 1H), 4.15 (s. 5H), 3.37 (2H, d. J=8.4 Hz), 7.50 (2H, d. J=8.8 Hz), 5.5 (2H, d. J=1.16 Hz), 3.5 (s. HI). 13 7.43 (2H, d. J=8.0 Hz), 7.22 (2H, d. J=8.4 Hz), 7.50 (2H, d. J=8.8 Hz), 5.5 (1H, d. J=1.16 Hz), J=4.4 Hz). (s, 2H), 4.25 (s, 2H), 4.11 (s, 5H), 3.37 (2H, d. J=8.4 Hz), 5.6 (2H, d. J=8.8 Hz), 5.4 (1H, d. J=1.16 Hz), J=4.4 Hz). (s, 2H), 4.25 (s, 2H), 4.11 (s, 5H), 3.70 (2H, d. J=8.4 Hz), 7.20 (2H, d. J=8.4 Hz), 7.40 (1H, J=1.6 Hz), J=4.4 Hz).	6	8.26 (2H, d, <i>J</i> =8.0 Hz), 8.23 (2H, d, <i>J</i> =8.0 Hz), 7.92 (1H, s), 7.55 (2H, d, <i>J</i> =8.0 Hz), 7.47 (2H, d, <i>J</i> = 8.4 Hz), 4.71 (s, 2H), 4.54 (s, 2H), 4.17 (s, 5H), 3.84 (3H, s).			
 8 8.35 (2H, d. J=8.0 Hz), 8.26 (2H, d. J=8.0 Hz), 7.96 (1H, s), 7.91 (2H, d. J=8.4 Hz), 7.53 (2H, d. J=8.4 Hz), 4.74 (s. 2H), 4.44 (s. 4.19 (s. 19), 9.51 (s. 19), 9.52 (2H, d. J=8.4 Hz), 8.23 (2H, d. J=8.4 Hz), 7.95 (1H, s), 7.73 (2H, d. J=8.0 Hz), 7.55 (2H, d. J=8.4 Hz), 4.66 (s. 2H), 4.45 (s. 4.15 (s. 5H), 8.21 (2H, d. J=8.4 Hz), 8.17 (2H, d. J=8.0 Hz), 7.93 (1H, s), 7.52 (2H, d. J=8.0 Hz), 7.28 (2H, d. J=8.4 Hz), 4.66 (s. 2H), 4.09 (s. 5H). 10a 8.21 (2H, d. J=8.4 Hz), 8.17 (2H, d. J=8.0 Hz), 7.95 (1H, s), 7.94 (2H, m), 7.49-7.57 (3H, m), 7.34 (1H, d. J=8.4 Hz), 4.76 (s. 2H), 4.46 (s. 2H), 4.09 (s. 5H). 11 7.42 (2H, d. J=8.4 Hz), 7.21 (7.36 (5H, m), 7.07 (2H, d. J=8.4 Hz), 5.51 (Hz), d. J=4.4 Hz), 4.76 (s. 2H), 4.43 (s. 2H), 4.12 (s. 2H), 4.12 (s. 5H), 3.87 (1H, d. J=18.0 Hz), 7.07 (2H, d. J=8.4 Hz), 7.27 (2H, d. J=8.4 Hz), 7.23 (1H, d. J=18.0 Hz), J=10 (Hz), J=14 Hz), 3.06 (1H, d. J=18.0 Hz), 5.52 (1H, d. J=1.1 Hz), J=4.4 Hz), (s. 2H), 4.11 (s. 5H), 3.87 (1H, d. J=18.0 Hz), 7.02 (2H, d. J=8.4 Hz), 6.03 (2H, d. J=8.1 Hz), 5.52 (1H, d. J=1.1 Hz), J=4.4 Hz), (s. 2H), 4.12 (s. 2H), 4.13 (s. 5H), 3.72 (SH), 4.77 (02 (H, d. J=8.4 Hz), 6.03 (2H, d. J=8.0 Hz), 5.52 (1H, d. J=1.1 Hz), J=4.4 Hz), (s. 2H), 4.13 (s. 5H), 3.79 (1H, d. J=1.8 Hz), (s. 2H), 4.12 (s. 2H), 4.13 (s. 5H), 3.79 (1H, d. J=1.8 Hz), (s. 2H), 4.13 (s. 5H), 3.79 (1H, d. J=1.8 Hz), (s. 2H), 4.13 (s. 5H), 3.79 (1H, d. J=1.8 Hz), (s. 2H), 4.13 (s. 3H), 3.79 (1H, d. J=1.8 Hz), (s. 2H), 4.13 (s. 3H), 3.79 (1H, d. J=1.8 Hz), 1.20 (1H, J=1.6 Hz), J=4.4 Hz), 1.40 (Hz), J=4.4 Hz), 1.41 (s. 2H), 3.79 (1H, d. J=1.8 Hz), 1.20 (1H, d. J=1.8 Hz), 1.20 (1H, d. J=1.6 Hz), J=4.4 Hz), 1.6 (2H, J=4.4 Hz), 1.20 (2H, J=4.4 Hz), 1.20 (2H, J=4.4 Hz), 1.20 (2H	7	8.18 (2H, d, <i>J</i> =8.4 Hz), 8.11 (2H, d, <i>J</i> =8.4 Hz), 7.91 (1H, s), 7.57 (2H, d, <i>J</i> =8.4 Hz), 7.00 (2H, d, <i>J</i> =8.4 Hz), 4.69 (s, 2H), 4.48 (s, 2H), 4.14 (s, 5H).			
 9 8.28 (2H. d. <i>J</i>=8.4 Hz), 8.23 (2H. d. <i>J</i>=8.4 Hz), 7.95 (1H. s), 7.73 (2H. d. <i>J</i>=8.0 Hz), 7.55 (2H. d. <i>J</i>=8.4 Hz), 4.69 (s. 2H), 4.45 (s. 4.15 (s. 5H). 108 8.21 (2H. d. <i>J</i>=8.4 Hz), 8.17 (2H. d. <i>J</i>=8.0 Hz), 7.93 (1H, s), 7.52 (2H, d. <i>J</i>=8.0 Hz), 7.28 (2H, d. <i>J</i>=8.4 Hz), 4.67 (s. 2H), 4.48 (s. 4.11 (s. 5H). 106 8.02 (1H. s), 8.19 (2H. d. <i>J</i>=8.0 Hz), 7.75 H2 (2H, m), 7.49-7.57 (3H, m), 7.34 (1H, <i>J</i>=8.4 Hz), 4.76 (s. 2H), 4.46 (s. 2H), 4.09 (s. 5H). 107 42 (2H, d. <i>J</i>=8.4 Hz), 7.21 (7.35 (5H, m), 7.07 2H (2H, m), 7.49-7.57 (3H, m), 7.34 (1H, <i>J</i>, <i>J</i>=8.4 Hz), 4.78 (s. 2H), 4.46 (s. 2H), 4.09 (s. 5H). 117 7.42 (2H, d. <i>J</i>=8.4 Hz), 7.21 (7.36 (5H, m), 7.07 (2H, <i>d</i>, <i>J</i>=8.4 Hz), 5.51 (1H, dd, <i>J</i>=11.6 Hz, <i>J</i>=4.4 Hz), (s. 2H), 4.12 (s. 2H), 4.12 (s. 5H), 3.87 (1H, dd, <i>J</i>=18.0 Hz), 7.05 (1H, <i>d</i>, <i>J</i>=8.4 Hz), 6.30 (1H, dd, <i>J</i>=18.0 Hz), 5.52 (1H, dd, <i>J</i>=11.6 Hz), 5.40 (1H), (s. 2H), 4.21 (s. 2H), 4.18 (s. 5H), 3.70 (2H, <i>d</i>, <i>J</i>=8.0 Hz), 6.81 (2H, <i>d</i>, <i>J</i>=8.8 Hz), 5.53 (1H, dd, <i>J</i>=11.2 Hz), 2.40 (Hz), (s. 2H), 4.21 (s. 2H), 4.18 (s. 5H), 3.70 (1H, dd, <i>J</i>=18.0 Hz), <i>J</i>=1.1 (Hz), 5.30 (1H, dd, <i>J</i>=11.6 Hz), <i>J</i>=4.0 (Hz), (s. 2H), 4.21 (s. 2H), 4.18 (s. 5H), 3.70 (1H, dd, <i>J</i>=18.0 Hz), <i>J</i>=4.1 (Hz), 5.40 (1H, dd, <i>J</i>=11.6 Hz), <i>J</i>=4.0 (Hz), (s. 2H), 4.21 (s. 2H), 4.18 (s. 5H), 3.70 (1H, dd, <i>J</i>=18.0 Hz), <i>J</i>=4.0 (Hz), 5.40 (1H, dd, <i>J</i>=11.6 Hz), 5.51 (1H, dd, <i>J</i>=	8	8.35 (2H, d, <i>J</i> =8.0 Hz), 8.26 (2H, d, <i>J</i> =8.0 Hz), 7.96 (1H, s), 7.91 (2H, d, <i>J</i> =8.4 Hz), 7.53 (2H, d, <i>J</i> =8.4 Hz), 4.74 (s, 2H), 4.41 (s, 2H), 4.19 (s, 5H).			
 8.21 (2H, d., <i>J</i>=8.4 Hz), 8.17 (2H, d., <i>J</i>=8.0 Hz), 7.93 (1H, s), 7.52 (2H, d., <i>J</i>=8.0 Hz), 7.28 (2H, d., <i>J</i>=8.4 Hz), 4.67 (s, 2H), 4.48 (s, 4.11 (s, 5H)). 8.02 (1H, s), 8.19 (2H, d., <i>J</i>=8.0 Hz), 7.95 (1H, s), 7.84 (1H, d., <i>J</i>=8.4 Hz), 7.51 7.59 (4H, m), 4.74 (s, 2H), 4.46 (s, 2H), 4.09 (s, 5H). 8.23 (2H, d., <i>J</i>=8.4 Hz), 7.91 (1H, s), 7.79 · 7.84 (2H, m), 7.49 - 7.57 (3H, m), 7.34 (1H, <i>J</i>, <i>J</i>=7.6 Hz), 4.78 (s, 2H), 4.43 (s, 2H), 4.12 (s, 5H). 7.42 (2H, d., <i>J</i>=8.0 Hz), 7.19 (2H, d., <i>J</i>=8.1 Hz), 5.57 (1H, dd., <i>J</i>=1.6 Hz, <i>J</i>=4.4 Hz). 7.47 (2H, d., <i>J</i>=8.0 Hz), 7.26 (2H, <i>J</i>, <i>J</i>=6.0 Hz), <i>J</i>=01 (2H, d., <i>J</i>=8.4 Hz), 5.57 (1H, dd., <i>J</i>=1.6 Hz, <i>J</i>=4.4 Hz). (s, 2H), 4.21 (s, 5H), 3.87 (1H, dd., <i>J</i>=1.6 Hz), <i>J</i>=0 (1H, dJ., <i>J</i>=1.8 Hz), 5.64 (1H, dJ., <i>J</i>=1.6 Hz), <i>J</i>=4.4 Hz). (s, 2H), 4.21 (s, 5H), 3.82 (1H, dJ., <i>J</i>=1.0 Hz), 7.05 (2H, d., <i>J</i>=8.0 Hz), 6.81 (2H, d., <i>J</i>=8.0 Hz), 5.45 (1H, dJ., <i>J</i>=1.0 Hz), <i>J</i>=4.4 Hz). (s, 2H), 4.21 (s, 5H), 3.79 (s, 3H), 3.77 (1H, dJ., <i>J</i>=1.6 Hz), <i>J</i>=0 (1H, dJ., <i>J</i>=1.6 Hz), <i>J</i>=4.4 Hz). (s, 2H), 4.21 (s, 3H), 3.79 (1H, dJ., <i>J</i>=1.0 Hz), 7.02 (2H, d., <i>J</i>=8.4 Hz), 5.30 (1H, dJ., <i>J</i>=1.6 Hz), <i>J</i>=4.4 Hz). (s, 2H), 4.23 (s, 2H), 4.18 (s, 5H), 3.79 (1H, dJ., <i>J</i>=1.0 Hz), <i>J</i>=1.2 Hz), 3.06 (1H, dJ., <i>J</i>=1.6 Hz), <i>J</i>=4.4 Hz). (s, 2H), 4.23 (s, 2H), 4.16 (s, 5H), 3.79 (1H, dJ., <i>J</i>=1.6 Hz), <i>J</i>=2.4 Hz), 5.21 (H, dJ., <i>J</i>=1.6 Hz). (s, 2H), 4.28 (s, 2H), 4.16 (s, 5H), 3.79 (1H, dJ., <i>J</i>=1.7 Hz), 3.22 (1H, dJ., <i>J</i>=1.7 Hz), <i>J</i>=4.4 Hz), (s, 2H), 4.28 (s, 2H), 4.16 (s, 5H), 3.79 (1H, dJ., <i>J</i>=1.7 Hz), 3.22 (1H, dJ., <i>J</i>=1.6 Hz), <i>J</i>=4.4 Hz). (s, 2H), 4.28 (s, 2H), 4.16 (s, 5H), 3.79 (1H, dJ., <i>J</i>=1.2 Hz), 3.22 (1H, dJ., <i>J</i>=1.6 Hz), <i>J</i>=4.4 Hz), (s, 2H), 4.28 (s, 2H), 4.16 (s, 5H), 3.79 (1H, dJ., <i>J</i>=1.7 Hz), 3.22 (1H, dJ., <i>J</i>=1.6 Hz), <i>J</i>=4.0 Hz), (s, 2H), 4.28 (s, 2H), 4.16 (s, 2H), 4.28 (Hz), 7.66 (Hz), 7.68 (2H, dJ., <i>Hz</i>), 7.73 (2H, dJ., <i>Hz</i>), 5.73 (2H,	9	8.28 (2H, d, <i>J</i> =8.4 Hz), 8.23 (2H, d, <i>J</i> =8.4 Hz), 7.95 (1H, s), 7.73 (2H, d, <i>J</i> =8.0 Hz), 7.55 (2H, d, <i>J</i> =8.4 Hz), 4.69 (s, 2H), 4.45 (s, 2H), 4.15 (s, 5H).			
10b 8.02 (1H, s), 8.19 (2H, d, J=8.0 Hz), 7.95 (1H, s), 7.84 (1H, d, J=8.4 Hz), 7.51-7.59 (4H, m), 7.44 (s, 2H), 4.46 (s, 2H), 4.49 (s, 5H), 10c 10c 8.23 (2H, d, J=8.4 Hz), 7.91 (1H, s), 7.79-7.84 (2H, m), 7.34 (1H, t), Z=8.1 Hz), 2.74 (s) (s, 2H), 4.43 (s, 2H), 4.12 (s, 1H), (s, 2H), 4.17 (s, 5H), 3.87 (1H, dd, J=116 Hz), 7.01 (2H, d, J=8.4 Hz), 5.57 (1H, dd, J=116 Hz), J=4.0 Hz), 4.59 (s, 1H), 4.52 (s, 1H), (s, 2H), 4.17 (s, 5H), 3.87 (1H, dd, J=116 Hz), 7.01 (2H, d, J=8.4 Hz), 5.84 (2H, d, J=8.0 Hz), J=2.4 (1H, dJ, J=11.6 Hz), J=4.4 Hz), (s, 2H), 4.25 (s, 2H), 4.11 (s, 5H), 3.87 (1H, dd, J=116 Hz), 7.00 (2H, d, J=8.4 Hz), 5.84 (2H, d, J=8.0 Hz), J=2.4 (1H, dJ, J=11.6 Hz), J=3.05 (1H, dJ, J=11.6 Hz), J=4.0 Hz), (s, 2H), 4.21 (s, 2H), 4.21 (s, 2H), 4.21 (s, 2H), 3.79 (1H, dJ, J=11.6 Hz), J=3.07 (1H, dJ, J=11.6 Hz), J=3.05 (1H, dJ, J=11.6 Hz), J=4.8 Hz), (s, 2H), 4.21 (s, 2H), 4.13 (s, 5H), 3.79 (1H, dJ, J=11.8 Hz), J=3.07 (1H, dJ, J=11.6 Hz), J=4.4 Hz), (s, 2H), 4.21 (s, 2H), 4.13 (s, 5H), 3.79 (1H, dJ, J=11.8 Hz), J=3.07 (1H, dJ, J=11.6 Hz), J=4.4 Hz), (s, 2H), 4.21 (s, 2H), 4.10 (s), 5H), 3.79 (1H, dJ, J=11.8 Hz), J=3.07 (1H, dJ, J=11.6 Hz), J=4.4 Hz), (s, 2H), 4.23 (s, 2H), 4.10 (s), 5H), 3.79 (1H, dJ, J=11.8 Hz), J=3.07 (1H, dJ, J=11.6 Hz), J=4.4 Hz), (s, 2H), 4.21 (s, 2H), 4.10 (s), 5H), 3.79 (1H, dJ, J=11.8 Hz), J=3.02 (1H, dJ, J=16 Hz), J=4.4 Hz), (s, 2H), 4.23 (s, 2H), 4.10 (s), 5H), 3.79 (1H, dJ, J=11.8 Hz), 7.29 (2H, J, J=8.4 Hz), 5.51 (1H, dJ, J=11.6 Hz), J=4.4 Hz), (s, 2H), 4.24 (s, 2H), 4.10 (s), 5H), 3.79 (1H, dJ, J=11.2 Hz), 3.21 (1H, dJ, J=16 Hz), J=4.4 Hz), (s, 2H), 4.24 (s, 2H), 4.10 (s), 5H), 3.79 (1H, dJ, J=11.2 Hz), 3.21 (1H, dJ, J=16 Hz), J=4.4 Hz), (s, 2H), 4.14 (s, 2H), 4.10 (s), 2H), 4.14 (s), 2H), 4.10 (s), 2H), 4.14 (s), 2H), 4.14 (s), 2H), 4.44 (s),	10a	8.21 (2H, d, <i>J</i> =8.4 Hz), 8.17 (2H, d, <i>J</i> =8.0 Hz), 7.93 (1H, s), 7.52 (2H, d, <i>J</i> =8.0 Hz), 7.28 (2H, d, <i>J</i> =8.4 Hz), 4.67 (s, 2H), 4.48 (s, 2H), 4.11 (s, 5H).			
 10e 8:23 (2H, d, =8 4 Hz), 7.91 (HL, s), 7.79-7.84 (2H, m), 7.49-7.57 (3H, m), 7.34 (1H, t, <i>j</i>=8.0 Hz), 4.78(s, 2H), 4.43 (s, 2H), 4.12 (s, 2H) 11 7.42 (2H, d, <i>j</i>=8.4 Hz), 7.21-7.36 (3H, m), 7.07 (2H, d, <i>j</i>=8.4 Hz), 5.57 (1H, dd, <i>j</i>=11.6 Hz, <i>j</i>=4.0 Hz), 4.59 (s, 1H), 4.52 (s, 1H), (s, 2H), 4.17 (s, 5H), 3.87 (HL, dd, <i>j</i>, <i>j</i>=1.6 Hz), 3.09 (HL, dd, <i>j</i>=1.8 0 Hz, <i>j</i>=4.4 Hz). 12 7.47 (2H, d, <i>j</i>=8.0 Hz), 7.26 (2H, d, <i>j</i>=8.0 Hz), 7.01 (2H, d, <i>j</i>=8.4 Hz), 6.84 (2H, d, <i>j</i>=8.4 Hz), 5.52 (1H, dd, <i>j</i>=1.16 Hz, <i>j</i>=4.4 Hz), (s, 2H), 4.25 (s, 2H), 4.11 (s, 5H), 3.82 (HL, dd, <i>j</i>=1.8 0 Hz), <i>j</i>=6.1 (2H, d) <i>j</i>=8.0 Hz), 6.84 (2H, d, <i>j</i>=8.4 Hz), 5.53 (1H, dd, <i>j</i>=1.16 Hz, <i>j</i>=4.4 Hz), (s, 2H), 4.25 (s, 2H), 4.11 (s, 5H), 3.82 (HL, dd, <i>j</i>=1.8 (Hz), 7.05 (2H, d, <i>j</i>=8.4 Hz), 5.54 (1H, dd, <i>j</i>=1.16 Hz, <i>j</i>=4.4 Hz), (s, 2H), 4.25 (s, 2H), 4.13 (s, 5H), 3.79 (c, HL), 3.77 (1H, dd, <i>j</i>=1.8 Hz), 6.93 (2H, d, <i>j</i>=8.4 Hz), 5.49 (1H, dd, <i>j</i>=1.16 Hz, <i>j</i>=4.4 Hz), (s, 2H), 4.25 (s, 2H), 4.13 (s, 5H), 3.70 (1H, dd, <i>j</i>=1.8 0 Hz), 7.12 (2H, d, <i>j</i>=8.4 Hz), 6.93 (2H, d, <i>j</i>=8.4 Hz), 5.40 (1H, dd, <i>j</i>=1.16 Hz, <i>j</i>=4.4 Hz), (s, 2H), 4.23 (s, 2H), 4.10 (s, 5H), 3.18 (1H, dd, <i>j</i>=1.8 (Hz), 7.29 (2H, d, <i>j</i>=8.4 Hz), 5.30 (1H, dd, <i>j</i>=1.16 Hz, <i>j</i>=4.4 Hz), (s, 2H), 4.23 (s, 2H), 4.10 (s, 5H), 3.18 (1H, dd, <i>j</i>=1.2 Hz), 3.20 (1H, dd, <i>j</i>=1.8 Hz), 7.30 (2H, d, <i>j</i>=8.4 Hz), 5.40 (1H, dd, <i>j</i>=1.16 Hz, <i>j</i>=4.4 Hz), (s, 2H), 4.23 (s, 2H), 4.10 (s, 5H), 3.18 (1H, dd, <i>j</i>=1.2 Hz), 3.22 (1H, dd, <i>j</i>=1.6 Hz), <i>j</i>=4.4 Hz), (s, 2H), 4.24 (s, 2H), 4.16 (s, 5H), 3.79 (1H, dd, <i>j</i>=1.76 Hz), <i>j</i>=1.21 Hz), 3.20 (1H, dd, <i>j</i>=1.6 Hz), <i>j</i>=4.4 Hz), (s, 2H), 4.24 (s, 2H), 4.16 (s, 5H), 3.79 (1H, dd, <i>j</i>=1.76 Hz), <i>j</i>=1.0 Hz), 3.55 (1H, dd, <i>j</i>=1.16 Hz), <i>j</i>=4.4 Hz), (s, 2H), 4.21 (s, 2H), 4.16 (s, 5H), 3.72 (1H, dd, <i>j</i>=1.76 Hz), <i>j</i>=70 (2H, d, <i>j</i>=8.4 Hz), 5.55 (1H, dd, <i>j</i>=1.16 Hz), <i>j</i>=4.4 Hz), (s, 2H), 4.21 (s, 2H), 4.16 (s, 5H), 3.79 (1H, dd, <i>j</i>=1.76 Hz), 7.70 (2H, d, <i>j</i>=8.4 Hz), 5.55 (1H, dd, <i>j</i>=1.12 Hz), 3.21 (1H,	10b	8 02 (1H s) 8 19 (2H d J=8 0 Hz) 7 95 (1H s) 7 84 (1H d J=8 4 Hz) 7 51-7 59 (4H m) 4 74 (e 2H) 4 46 (e 2H) 4 00 (e 5H)			
 T. 42 (2H, d. <i>j</i> = 8, 4H.2), 721-736 (5H, m), 707 (2H, d. <i>j</i> = 8, 4H.2), 557 (1H, dd. <i>j</i> = 16 Hz, <i>j</i> = 4, Hz), 552 (1H, dd. <i>j</i> = 18, Hz, <i>j</i> = 52 (1H, dz), 459 (5, 1H), 4.52 (5, 1H), (5, 2H), 417 (5, 5H), 387 (1H, dd. <i>j</i> = 18, 0Hz), 726 (2H, d. <i>j</i> = 8, 0Hz), 726 (2H, d. <i>j</i> = 8, 1Hz), 535 (2H, d. <i>j</i> = 8, 4Hz), 535 (1H, dd. <i>j</i> = 18, 0Hz, <i>j</i> = 23 (2H, d. <i>j</i> = 8, 4Hz), 535 (1H, dd. <i>j</i> = 18, 0Hz), 728 (2H, d. <i>j</i> = 8, 4Hz), 736 (2H, d. <i>j</i> = 8, 0Hz), 701 (2H, d. <i>j</i> = 8, 0Hz), 681 (2H, d. <i>j</i> = 8, 4Hz), 545 (1H, dd. <i>j</i> = 11, 6Hz, <i>j</i> = 4, 4Hz), (5, 2H), 421 (5, 2H), 418 (5, 5H), 379 (1H, dd. <i>j</i> = 18, 0Hz), 730 (2H, d. <i>j</i> = 8, 0Hz), 681 (2H, d. <i>j</i> = 8, Hz), 545 (1H, dd. <i>j</i> = 11, 6Hz, <i>j</i> = 4, 0Hz), (5, 2H), 412 (5, 2H), 413 (5, 5H), 3.79 (1H, dd. <i>j</i> = 18, 0Hz), 547 (1H, dd. <i>j</i> = 16, 0Hz), 549 (1H, dd. <i>j</i> = 16, 0Hz), (5, 2H), 425 (5, 2H), 413 (5, 5H), 3.79 (1H, dd. <i>j</i> = 18, 0Hz), 742 (2H, <i>j</i> = 8, 4Hz), 545 (1H, dd. <i>j</i> = 11, 6Hz, <i>j</i> = 4, 8Hz), (5, 2H), 433 (5, 2H), 410 (5, 5H), 3.79 (1H, dd. <i>j</i> = 18, 0Hz), 739 (2H, <i>d</i> = 8, 4Hz), 540 (1H, dd. <i>j</i> = 11, 6Hz, <i>j</i> = 4, 0Hz), (5, 2H), 433 (5, 2H), 410 (5, 5H), 3.79 (1H, dd. <i>j</i> = 12, 4Hz), 729 (2H, <i>d</i> = 8, 4Hz), 551 (1H, dd. <i>j</i> = 11, 6Hz, <i>j</i> = 4, 4Hz), (5, 2H), 428 (5, 2H), 410 (5, 5H), 3.79 (1H, dd. <i>j</i> = 12, Hz), 322 (1H, dd. <i>j</i> = 18, 0Hz), 739 (2H, <i>d</i> = 8, 4Hz), 551 (1H, dd. <i>j</i> = 11, 6Hz, <i>j</i> = 4, 8Hz), (5, 2H), 421 (5, 2H), 419 (5, 5H), 3.79 (1H, dd. <i>j</i> = 17, 2Hz), <i>j</i> = 16, 4Hz), 551 (1H, dd. <i>j</i> = 11, 6Hz, <i>j</i> = 4, 4Hz), (5, 2H), 421 (5, 2H), 419 (5, 5H), 3.79 (1H, dd. <i>j</i> = 10, Hz), 730 (2H, <i>d</i> = 8, 0Hz), 730 (2H, <i>d</i> = 8, 4Hz), 710 (2H, <i>d</i> = 8, 4Hz), 551 (1H, dd. <i>j</i> = 11, 6Hz, <i>j</i> = 4, 8Hz), (5H), 412 (5H), 419 (5H), 3.79 (1H, dd. <i>j</i> = 10, 2Hz), 321 (1H, dd. <i>j</i> = 17, 6Hz), <i>j</i> = 4, 4Hz), (5H), 412 (5H), 419 (5H), 3.79 (1H, dd. <i>j</i> = 10, 2Hz), 321 (1H, dd. <i>j</i> = 17, 6Hz), 42 (4Hz), 46 (4Hz), 46 (4Hz), 46 (4Hz), 41, 41, 41, 41, 41, 41, 41, 41, 41, 41	10c	8 23 (2H, d. <i>J</i> =8 4 Hz) 7 91 (1H, s) 7 79-7 84 (2H, m) 7 49-7 57 (3H, m) 7 34 (1H, t. <i>J</i> =8 0 Hz) 4 78 (s. 2H) 4 43 (s. 2H) 4 12 (s. 5H)			
	11	7 42 (2H d <i>L</i> =8 4 Hz) 7 21-7 36 (5H m) 7 07 (2H d <i>L</i> =8 4 Hz) 5 57 (1H dd <i>L</i> =11 6 Hz <i>L</i> =4 0 Hz) 4 59 (s 1H) 4 52 (s 1H) 4 33			
 7.47 (2H, d. J=8.0 Hz), 7.26 (2H, d. J=8.0 Hz), 7.01 (2H, d. J=8.4 Hz), 5.84 (2H, d. J=8.4 Hz), 5.52 (H, d. J,=1.6 Hz, J=4.4 Hz), (s. 2H), 4.21 (s. 5H), 3.82 (H, d. J=8.0 Hz), J=8.1 (2H, d. J=8.0 Hz), 5.83 ((JH, d. J,=1.8 Hz), 5.43 ((JH, d. J,=1.6 Hz), J=4.0 Hz), (s. 2H), 4.21 (s. 2H), 4.18 (s. 5H), 3.79 ((S, 3H), 3.77 (H, d. J,=8.4 Hz), 7.05 (H, d. J,=8.4 Hz), 5.30 ((JH, d. J,=1.6 Hz), J=4.0 Hz), (s. 2H), 4.25 (s. 2H), 4.13 (s. 5H), 3.79 ((JH, d. J,=8.4 Hz), 7.20 (2H, d. J=8.4 Hz), 7.30 (2H, d. J=8.4 Hz), 5.30 ((H, d. J,=1.6 Hz), J=4.4 Hz), (s. 2H), 4.25 (s. 2H), 4.13 (s. 5H), 3.79 ((H, d. J,=1.8, J,z,J=1.1 Hz), 3.30 ((H, d. J,=1.6 Hz), J=4.4 Hz), (s. 2H), 4.33 (s. 2H), 4.10 (s. 5H), 3.18 (H, d. J=8.4 Hz), 7.30 (2H, d. J=8.4 Hz), 5.30 ((H, d. J,=1.6 Hz), J=4.4 Hz), (s. 2H), 4.23 (s. 2H), 4.10 (s. 5H), 3.79 ((H, d. J,=4.4 Hz), 7.39 (2H, d. J=8.4 Hz), 5.51 ((H, d. J,=1.6 Hz), J=4.4 Hz), (s. 2H), 4.21 (s. 2H), 4.10 (s. 5H), 3.70 ((H, d. J=1.72 Hz), J=1.12 Hz), 3.22 (H, d. J=8.4 Hz), 5.57 ((H, d. J,=1.6 Hz), J=4.4 Hz), (s. 2H), 4.21 (s. 2H), 4.10 (s. 5H), 3.72 ((H, d. J=1.72 Hz), J=1.12 Hz), 3.22 (H, d. J=8.4 Hz), 5.57 ((H, d. J,=1.6 Hz), J=4.8 Hz), (s. 2H), 4.21 (s. 2H), 4.19 (s. 5H), 3.72 ((H, d. J=1.16 Hz), J=1.6 Hz), J=3.55 (1H, d. J,=1.6 Hz), J=4.4 Hz), (s. 2H), 4.21 (s. 2H), 4.19 (s. 5H), 3.72 ((H, d. J,=1.72 Hz), J=1.6 Hz), 5.55 ((H, d. J,=1.16 Hz), J=4.4 Hz), (s. 2H), 4.21 (s. 2H), 4.19 (s. 5H), 3.72 ((H, d. J,=1.72 Hz), J=1.16 Hz), J=3.55 ((H, d. J,=1.16 Hz), J=4.4 Hz), (s. 2H), 4.21 (s. 2H), 4.19 (s. 5H), 3.72 ((H, d. J,=1.76 Hz), 5.55 (1H, d. J,=1.16 Hz), J=4.4 Hz), (s. 2H), 4.2 (s. 2H), 4.16 (s. 5H)), 7.70 ((H, d. J,=1.72 Hz), J=4.8 Hz), (s. 2H), 4.24 (s. 2H), 4.16 (s. 2H), 4.28 (s. 2H), 4.21 (s. 2H), 4.25 (s. 2H), 4.76 (s. 2H), J=1.6 Hz), 7.62 (H, d. J=1.6 Hz), 7.63 (H, d. J=		$(s, 2H), 4.17 (s, 5H), 3.87 (1H, dd, J_1=18.0 Hz, J_2=11.6 Hz), 3.09 (1H, dd, J_1=18.0 Hz, J_2=4.4 Hz).$			
 7.43 (2H, d., <i>F</i>.80 Hz), 7.28 (2H, d., <i>F</i>.84 Hz), 7.05 (2H, d., <i>F</i>.80 Hz), 6.81 (2H, d., <i>F</i>.8 Hz), 5.45 (1H, dd., <i>J</i>, <i>i</i>=11.2 Hz, <i>J</i>, <i>s</i>=40 Hz), (s, 2H), 4.21 (s, 2H), 4.18 (s, 5H), 3.79 (s, 3H), 3.77 (1H, dd, <i>J</i>, <i>i</i>=18.0 Hz, <i>J</i>, <i>s</i>=10.6 Hz), 5.49 (1H, dd, <i>J</i>, <i>i</i>=11.6 Hz, <i>J</i>, <i>z</i>=4.4 Hz), (s, 2H), 4.25 (s, 2H), 4.13 (s, 5H), 3.79 (1H, dd, <i>J</i>, <i>i</i>=18.0 Hz), 7.29 (2H, d., <i>F</i>.8 Hz), 7.30 (2H, d., <i>J</i>=8.4 Hz), 7.30 (2H, d., <i>J</i>=8.4 Hz), 5.49 (1H, dd, <i>J</i>, <i>i</i>=11.6 Hz, <i>J</i>, <i>z</i>=4.4 Hz), (s, 2H), 4.33 (s, 2H), 4.10 (s, 5H), 3.19 (1H, dd, <i>J</i>, <i>i</i>=18.0 Hz), 7.29 (2H, d., <i>F</i>.8 Hz), 5.40 (1H, dd, <i>J</i>, <i>i</i>=11.6 Hz, <i>J</i>, <i>z</i>=4.4 Hz), (s, 2H), 4.33 (s, 2H), 4.10 (s, 5H), 3.18 (1H, dd, <i>J</i>, <i>i</i>=18.4 Hz), 5.20 (1H, dd, <i>J</i>, <i>i</i>=11.6 Hz), <i>J</i>, <i>z</i>=4.4 Hz), (s, 2H), 4.33 (s, 2H), 4.10 (s, 5H), 3.79 (1H, dd, <i>J</i>, <i>i</i>=17.2 Hz, <i>J</i>, <i>z</i>=11.2 Hz), 3.22 (1H, dd, <i>J</i>, <i>i</i>=11.6 Hz), <i>J</i>, <i>z</i>=4.4 Hz), (s, 2H), 4.28 (s, 2H), 4.16 (s, 5H), 3.79 (1H, dd, <i>J</i>, <i>i</i>=17.2 Hz, <i>J</i>, <i>z</i>=11.2 Hz), 3.22 (1H, dd, <i>J</i>, <i>i</i>=11.6 Hz), <i>J</i>, <i>z</i>=4.4 Hz), (s, 2H), 4.28 (s, 2H), 4.16 (s, 5H), 3.79 (1H, dd, <i>J</i>, <i>i</i>=17.6 Hz, <i>J</i>, <i>z</i>=4.1 Hz), 5.55 (1H, dd, <i>J</i>, <i>i</i>=11.6 Hz, <i>J</i>, <i>z</i>=4.8 Hz), (s, 2H), 4.21 (s, 2H), 4.79 (s, 5H), 3.79 (1H, dd, <i>J</i>, <i>i</i>=17.6 Hz, <i>J</i>, <i>z</i>=4.4 Hz), 5.55 (1H, dd, <i>J</i>, <i>i</i>=11.6 Hz), <i>J</i>, <i>z</i>=4.4 Hz), (s, 2H), 4.28 (s, 2H), 4.16 (s, 5H), 3.79 (1H, dd, <i>J</i>, <i>i</i>=17.6 Hz, <i>J</i>, <i>z</i>=4.4 Hz), 5.55 (1H, dd, <i>J</i>, <i>i</i>=11.6 Hz), <i>J</i>, <i>z</i>=4.4 Hz), (s, 2H), 4.2 (s, 5H), 3.79 (1H, dd, <i>J</i>, <i>i</i>=17.6 Hz, <i>J</i>, <i>z</i>=4.4 Hz), 5.55 (1H, dd, <i>J</i>, <i>i</i>=11.6 Hz), <i>J</i>, <i>z</i>=4.4 Hz), (s, 2H), 4.16 (s, 5H), 3.79 (1H, dd, <i>J</i>, <i>i</i>=17.6 Hz), <i>z</i>, <i>z</i>=4.4 Hz), 7.42 (2H, <i>d</i>, <i>J</i>=8.0 Hz), 7.73 (2H, <i>d</i>, <i>J</i>=8.4 Hz), 7.02 (2H, <i>d</i>, <i>J</i>=8.4 Hz), 7.68 (1H, dd, <i>J</i>, <i>i</i>=11.6 Hz), <i>J</i>, <i>z</i>=4.4 Hz). 7.42 (2H, <i>d</i>, <i>J</i>=8.0 Hz), 7.73 (2H, <i>d</i>, <i>J</i>=8.4 Hz), 7.16 (Hz, <i>J</i>=11.2 Hz), 3.21 (1H, dd, <i>J</i>, <i>i</i>=11.6 Hz), <i>J</i>, <i>z</i>=4.4 Hz). 7.45 (2H, <i>d</i>, <i>J</i>=8.0 Hz), 7.33 (2H, <i>d</i>, <i>J</i>=8.4 Hz), 7.10 (Hz, <i>d</i>, <i>J</i>=8.4 Hz)	12	7.47 (2H, d, <i>J</i> =8.0 Hz), 7.26 (2H, d, <i>J</i> =8.0 Hz), 7.01 (2H, d, <i>J</i> =8.4 Hz), 6.84 (2H, d, <i>J</i> =8.4 Hz), 5.52 (1H, dd, <i>J</i> ₁ =11.6 Hz, <i>J</i> ₂ =4.4 Hz), 4.65 (s, 2H), 4.25 (s, 2H), 4.11 (s, 5H), 3.82 (1H, dd, <i>J</i> ₁ =18.0 Hz, <i>J</i> ₂ =11.2 Hz), 3.06 (1H, dd, <i>J</i> ₁ =18.0 Hz, <i>J</i> ₂ =4.8 Hz), 2.33 (s, 3H).			
 7.41 (2H, d, J=8.4 Hz), 7.24 (2H, d, J=8.0 Hz), 7.02 (2H, d, J=8.4 Hz), 6.93 (2H, d, J=8.0 Hz), 5.49 (1H, dd, J₁=11.6 Hz, J₂=4.8 Hz), (s, 2H), 4.25 (s, 2H), 4.13 (s, 5H), 3.79 (1H, dd, J₁=18 0 Hz, J₂=11.2 Hz), 3.07 (1H, dd, J_1=18.0 Hz, J₂=4.4 Hz). 7.68 (2H, d, J=8.0 Hz), 7.46 (2H, d, J=8.0 Hz), 7.35 (2H, d, J=8.4 Hz), 3.82 (1H, dd, J_1=17.6 Hz, J₂=14.0 Hz), (s, 2H), 4.33 (s, 2H), 4.10 (s, 5H), 3.18 (1H, dd, J_1=18.4 Hz, J₂=4.4 Hz), 3.82 (1H, dd, J_1=17.6 Hz, J₂=11.6 Hz). 7.82 (2H, d, J=8.0 Hz), 7.49 (2H, d, J=8.0 Hz), 7.25 (2H, d, J=8.0 Hz), 7.39 (2H, d, J=8.4 Hz), 5.51 (1H, dd, J₁=11.6 Hz, J₂=4.4 Hz), (s, 2H), 4.28 (s, 2H), 4.16 (s, 5H), 3.79 (1H, dd, J=12.1 Hz), 3.22 (1H, dd, J_1=17.6 Hz, J₂=4.8 Hz), (s, 2H), 4.21 (s, 2H), 4.16 (s, 5H), 3.79 (1H, dd, J=8.0 Hz), 7.02 (2H, d, J=8.4 Hz), 5.57 (1H, dd, J₁=11.6 Hz, J₂=4.8 Hz), (s, 2H), 4.21 (s, 2H), 4.19 (s, 5H), 3.72 (1H, dd, J=17.6 Hz, J₂=11.6 Hz), 3.19 (1H, dd, J_1=17.6 Hz, J_2=4.8 Hz). 7.42 (2H, d, J=8.0 Hz), 7.277.35 (3H, m), 7.13 (1H, d, J=8.1 Hz), 7.02-6.94 (2H), 5.55 (1H, dd, J=11.6 Hz, J₂=4.0 Hz), 4.67 (s, 4.19 (s, 2H), 4.17 (s, 5H), 3.79 (1H, dd, J_1=17.6 Hz, J_2=11.6 Hz), 5.11 (Hd, J_1=17.2 Hz, J_2=4.4 Hz). 7.45 (2H, d, J=8.0 Hz), 7.33 (2H, d, J=8.4 Hz), 7.10 (2H, d, J=17.6 Hz, J=11.6 Hz, J_2=4.4 Hz). 7.56 (2H, d, J=8.0 Hz), 7.33 (2H, d, J=8.4 Hz), 7.11 (2H, d, J=17.6 Hz, J=11.6 Hz), 5.21 (H, dd, J=17.2 Hz, J_2=4.4 Hz). 7.56 (2H, d, J=8.0 Hz), 7.39 (2H, d, J=8.4 Hz), 7.11 (2H, d, J=17.6 Hz, J=11.2 Hz), 3.21 (1H, dd, J=17.2 Hz, J_2=4.4 Hz). 7.56 (2H, d, J=8.4 Hz), 7.39 (2H, d, J=8.4 Hz), 7.11 (2H, d, J=8.4 Hz), 7.68 (1H, d, J=15.6 Hz), 7.62 (2H, t, J=8.0 Hz), 7.42 (2H, t, J=8.0 Hz), 4.24 (s, 2H), 4.25	13	7.43 (2H, d, <i>J</i> =8.0 Hz), 7.28 (2H, d, <i>J</i> =8.4 Hz), 7.05 (2H, d, <i>J</i> =8.0 Hz), 6.81 (2H, d, <i>J</i> =8.8 Hz), 5.45 (1H, dd, <i>J</i> ₁ =11.2 Hz, <i>J</i> ₂ =4.0 Hz), 4.67 (s, 2H), 4.21 (s, 2H), 4.18 (s, 5H), 3.79 (s, 3H), 3.77 (1H, dd, <i>J</i> ₁ =18.0 Hz, <i>J</i> ₂ =11.6 Hz), 3.05 (1H, dd, <i>J</i> ₁ =17.6 Hz, <i>J</i> ₂ =4.0 Hz).			
 7.68 (2H, d. J=8.0 Hz), 7.46 (2H, d. J=8.0 Hz), 7.35 (2H, d. J=8.4 Hz), 7.29 (2H, d. J=8.4 Hz), 5.40 (1H, dd. J₁=11.6 Hz, J₂=4.0 Hz), (s. 2H), 4.33 (s. 2H), 4.10 (s. 5H), 3.18 (1H, dd. J₁=18.4 Hz, J₂=4.4 Hz), 3.82 (1H, dd. J₁=17.6 Hz, J₂=11.6 Hz). 7.82 (2H, d. J=8.0 Hz), 7.49 (2H, d. J=8.0 Hz), 7.25 (2H, d. J=8.0 Hz), 7.39 (2H, d. J=8.4 Hz), 5.51 (1H, dd. J₁=11.6 Hz, J₂=4.4 Hz), (s. 2H), 4.21 (s. (SH), 3.17 (1H, dd. J₁=17.2 Hz, J₂=11.2 Hz), 3.22 (1H, dd. J₁=18.0 Hz, J₂=4.4 Hz), (s. 2H), 4.21 (s. (SH), 3.72 (1H, dd. J₁=17.6 Hz, J₂=11.6 Hz), 3.19 (1H, dd. J₁=17.6 Hz, J₂=4.8 Hz), (s. 2H), 4.21 (s. 2H), 4.19 (s. 5H), 3.72 (1H, dd. J₁=17.6 Hz, J₂=11.6 Hz), 3.19 (1H, dd. J₁=17.6 Hz, J₂=4.0 Hz), 4.67 (s. 4.19 (s. 2H), 4.21 (s. 2H), 4.19 (s. 5H), 3.72 (1H, dd. J₁=17.6 Hz, J₂=11.6 Hz), 3.19 (1H, dd. J₁=17.6 Hz, J₂=4.0 Hz), 4.67 (s. 4.19 (s. 2H), 4.17 (s. 5H), 3.79 (1H, dd. J₁=17.6 Hz, J₂=11.2 Hz), 3.21 (1H, dd. J₁=11.6 Hz, J₂=4.0 Hz), 4.67 (s. 4.19 (s. 2H), 4.61 (s. 2H), 4.22 (s. 2H), 4.16 (s. 5H), 3.79 (1H, dd. J₁=17.6 Hz, J₂=11.2 Hz), 3.21 (1H, dd. J₁=17.2 Hz, J₂=4.4 Hz). 7.56 (2H, d. J=8.0 Hz), 7.33 (2H, d. J=8.4 Hz), 7.167 (2H), J_17.6 Hz), 5.75 (1H, dd. J₁=17.2 Hz, J₂=4.4 Hz). 7.56 (2H, d. J=8.0 Hz), 7.39 (2H, d. J=8.4 Hz), 7.11 (2H, d. J=8.4 Hz), 6.87 (2H, d. J=8.0 Hz), 6.81 (1H, s), 4.63 (s. 2H), 4.24 (s. 4.4 Hz), 4.44 (s. 5H). 7.56 (2H, d. J=8.0 Hz), 7.39 (2H, d. J=8.0 Hz), 4.67 (s. 2H), 4.21 (s. 5H), 4.15 (s. 2H). 9.42 (1H, s), 8.17 (2H, d. J=8.0 Hz), 7.87 (1H, d. J=15.6 Hz), 7.70 (2H, d. J=8.4 Hz), 7.68 (1H, d. J=15.6 Hz), 7.62 (2H, t. J=8.4 Hz), 7.62 (2H, t. J=8.0 Hz), 4.24 (s. 6H), 7.39 (2H, d. J=8.0 Hz), 7.44 (1H, t. J=5.6 Hz), 7.48 (1H, d. J=15.6 Hz), 7.43 (2H, d. J=8.0 Hz), 7.42 (2H, d. J=8.0 Hz), 7.43 (2H, d. J=8.0 Hz), 7.43 (2H, d. J=8.0 Hz), 7.43 (2H, d. J=8.0 Hz), 7.45 (2H, d. J=8.0 Hz)	14	7.41 (2H, d, <i>J</i> =8.4 Hz), 7.24 (2H, d, <i>J</i> =8.0 Hz), 7.02 (2H, d, <i>J</i> =8.4 Hz), 6.93 (2H, d, <i>J</i> =8.0 Hz), 5.49 (1H, dd, <i>J</i> ₁ =11.6 Hz, <i>J</i> ₂ =4.8 Hz), 4.58 (s, 2H), 4.25 (s, 2H), 4.13 (s, 5H), 3.79 (1H, dd, <i>J</i> ₁ =18.0 Hz, <i>J</i> ₂ =11.2 Hz), 3.07 (1H, dd, <i>J</i> ₁ =18.0 Hz, <i>J</i> ₂ =4.4 Hz).			
 7.82 (2H, d, <i>J</i>=8.0 Hz), 7.49 (2H, d, <i>J</i>=8.0 Hz), 7.25 (2H, d, <i>J</i>=8.0 Hz), 7.39 (2H, d, <i>J</i>=8.4 Hz), 5.51 (1H, dd, <i>J</i>₁=11.6 Hz, <i>J</i>₂=4.4 Hz), (5, 2H), 4.28 (5, 2H), 4.16 (5, 5H), 3.79 (1H, dd, <i>J</i>₁=17.2 Hz, <i>J</i>₂=11.2 Hz), 3.22 (1H, dd, <i>J</i>₁=18.0 Hz), <i>S</i>=4 0 Hz). 7.44 (2H, d, <i>J</i>=8.4 Hz), 7.27 (2H, d, <i>J</i>=8.4 Hz), 7.16 (2H, d, <i>J</i>=8.0 Hz), 6.72 (2H, d, <i>J</i>=8.4 Hz), 5.57 (1H, dd, <i>J</i>₁=11.6 Hz, <i>J</i>₂=4.8 Hz), (5, 2H), 4.21 (5, 2H), 4.19 (5, 5H), 3.72 (1H, dd, <i>J</i>₁=17.6 Hz, <i>J</i>₂=11.6 Hz), 7.026 694 (2H, s), 5.55 (1H, dd, <i>J</i>₁=11.6 Hz, <i>J</i>₂=4.0 Hz), 4.67 (s, 4.19 (s, 2H), 4.17 (s, 5H), 3.79 (1H, dd, <i>J</i>₁=17.6 Hz, <i>J</i>₂=11.2 Hz), 3.21 (1H, dd, <i>J</i>, -17.2 Hz, <i>J</i>₂=4.4 Hz). 7.45 (2H, d, <i>J</i>=8.0 Hz), 7.33 (2H, d, <i>J</i>=8.4 Hz), 7.16 -7.22 (2H, m), 6.96 (1H, t, <i>J</i>=7.6 Hz), 6.78-6.84 (1H, m), 5.55 (1H, dd, <i>J</i>, -11.6 Hz), <i>J</i>=4.0 Hz), 4.61 (s, 2H), 4.22 (s, 2H), 4.16 (s, 5H), 3.79 (1H, dd, <i>J</i>=17.6 Hz, <i>J</i>₂=11.2 Hz), 3.21 (1H, dd, <i>J</i>, -17.2 Hz, <i>J</i>₂=4.4 Hz). 7.56 (2H, d, <i>J</i>=8.0 Hz), 7.39 (2H, d, <i>J</i>=8.4 Hz), 7.11 (2H, d, <i>J</i>=8.4 Hz), 6.87 (2H, d, <i>J</i>=8.0 Hz), 6.81 (1H, s), 4.63 (s, 2H), 4.24 (s, 41.4 (s, 5H). 7.56 (2H, d, <i>J</i>=8.0 Hz), 7.39 (2H, d, <i>J</i>=8.4 Hz), 7.11 (2H, d, <i>J</i>=8.4 Hz), 7.68 (1H, d, <i>J</i>=15.6 Hz), 7.62 (2H, t, <i>J</i>=8.0 Hz), 7.43 (2H, d, <i>J</i>=8.0 Hz), 7.87 (1H, d, <i>J</i>=15.6 Hz), 7.70 (2H, d, <i>J</i>=8.4 Hz), 7.68 (1H, d, <i>J</i>=15.6 Hz), 7.62 (2H, t, <i>J</i>=8.0 T.39 (2H, d, <i>J</i>=8.0 Hz), 7.44 (1H), t, <i>J</i>=15.6 Hz), 7.65 (1H, d, <i>J</i>=15.6 Hz), 7.42 (2H, d, <i>J</i>=8.0 Hz), 7.42 (2H, d, <i>J</i>=8.0 Hz), 7.84 (1H, d, <i>J</i>=15.2 Hz), 7.68 (1H, d, <i>J</i>=15.6 Hz), 7.42 (2H, d, <i>J</i>=8.0 T.39 (2H, d, <i>J</i>=8.0 Hz), 7.42 (2H, d, <i>J</i>=8.4 Hz), 7.45 (2H, d, <i>J</i>=8.4 Hz), 7.65 (1H, d, <i>J</i>=15.6 Hz), 7.46 (2H, d, <i>J</i>=8.4 Hz), 7.65 (1H, d, <i>J</i>=15.6 Hz), 7.45 (2H, d, <i>J</i>=8.4 H	15	7.68 (2H, d, <i>J</i> =8.0 Hz), 7.46 (2H, d, <i>J</i> =8.0 Hz), 7.35 (2H, d, <i>J</i> =8.4 Hz), 7.29 (2H, d, <i>J</i> =8.4 Hz), 5.40 (1H, dd, <i>J</i> ₁ =11.6 Hz, <i>J</i> ₂ =4.0 Hz), 4.51 (s, 2H), 4.33 (s, 2H), 4.10 (s, 5H), 3.18 (1H, dd, <i>J</i> ₁ =18.4 Hz, <i>J</i> ₂ =4.4 Hz), 3.82 (1H, dd, <i>J</i> ₁ =17.6 Hz, <i>J</i> ₂ =11.6 Hz).			
 17a 7.44 (2H, d. <i>J</i>=8.4 Hz), 7.27 (2H, d. <i>J</i>=8.4 Hz), 7.16 (2H, d. <i>J</i>=8.0 Hz), 6.72 (2H, d. <i>J</i>=8.4 Hz), 5.57 (1H, dd. <i>J</i>₁=11.6 Hz, <i>J</i>₂=4.8 Hz), (s, 2H), 4.21 (s, 2H), 4.19 (s, 5H), 3.72 (1H, dd. <i>J</i>₁=17.6 Hz, <i>J</i>₂=11.6 Hz), 3.19 (1H, dd. <i>J</i>₁=17.6 Hz, <i>J</i>₂=4.8 Hz). 17b 7.42 (2H, d. <i>J</i>=8.0 Hz), 7.27-7.35 (3H, m), 7.13 (1H, d. <i>J</i>=8.4 Hz), 7.02-694 (2H, s), 5.55 (1H, dd. <i>J</i>₁=11.6 Hz, <i>J</i>₂=4.0 Hz), 4.67 (s, 4.19 (s, 2H), 4.17 (s, 5H), 3.79 (1H, dd. <i>J</i>₁=17.6 Hz, <i>J</i>₂=11.2 Hz), 3.21 (1H, dd. <i>J</i>₁=17.6 Hz, <i>J</i>₂=4.4 Hz). 17c 7.45 (2H, d, <i>J</i>=8.0 Hz), 7.33 (2H, d, <i>J</i>=8.4 Hz), 7.16-7.22 (2H, m), 6.96 (1H, <i>J</i>₁=7.6 Hz), 6.78-6.84 (1H, m), 5.55 (1H, dd. <i>J</i>₁=11.6 Hz), <i>J</i>₂=4.0 Hz), 4.61 (s, 2H), 4.22 (s, 2H), 4.16 (s, 5H), 3.79 (1H, dd. <i>J</i>_1=17.6 Hz, <i>J</i>₂=11.2 Hz), 3.21 (1H, dd. <i>J</i>₁=17.2 Hz, <i>J</i>₂=4.4 Hz). 18 7.56 (2H, d, <i>J</i>=8.4 Hz), 7.39 (2H, d, <i>J</i>=8.4 Hz), 7.11 (2H, d, <i>J</i>=8.4 Hz), 6.87 (2H, d, <i>J</i>=8.0 Hz), 6.81 (1H, s), 4.63 (s, 2H), 4.24 (s, 4.14 (s, 5H). 21 9.42 (1H, s), 8.17 (2H, d, <i>J</i>=8.0 Hz), 7.87 (1H, d, <i>J</i>=15.6 Hz), 7.70 (2H, d, <i>J</i>=8.4 Hz), 7.68 (1H, d, <i>J</i>=15.6 Hz), 7.62 (2H, t, <i>J</i>=8.0 Hz), 7.41 (1H, t, <i>J</i>=8.0 Hz), 7.45 (1H, d, <i>J</i>=15.6 Hz), 7.52 (2H, d, <i>J</i>=8.4 Hz), 7.45 (2H, d, <i>J</i>=8.0 Hz), 7.45 (2H, d, <i>J</i>=8.0 Hz), 7.45 (2H, d, <i>J</i>=8.0 Hz), 7.42 (2H, d, <i>J</i>=8.4 Hz), 7.45 (2H, d, <i>J</i>=8.4 Hz), 7.87 (1H, d, <i>J</i>=15.6 Hz), 7.65 (1H, d, <i>J</i>=15.6 Hz), 7.52 (2H, d, <i>J</i>=8.4 Hz), 7.45 (2H, d, <i>J</i>=8.0 Hz), 7.42 (2H, d, <i>J</i>=8.4 Hz), 7.45 (2H, d, <i>J</i>=8.4 Hz), 7.45	16	7.82 (2H, d, <i>J</i> =8.0 Hz), 7.49 (2H, d, <i>J</i> =8.0 Hz), 7.25 (2H, d, <i>J</i> =8.0 Hz), 7.39 (2H, d, <i>J</i> =8.4 Hz), 5.51 (1H, dd, <i>J</i> ₁ =11.6 Hz, <i>J</i> ₂ =4.4 Hz), 4.57 (s, 2H), 4.28 (s, 2H), 4.16 (s, 5H), 3.79 (1H, dd, <i>J</i> ₁ =17.2 Hz, <i>J</i> ₂ =11.2 Hz), 3.22 (1H, dd, <i>J</i> ₁ =18.0 Hz, <i>J</i> ₂ =4.0 Hz).			
 17b 7.42 (2H, d, J=8.0 Hz), 7.27-7.35 (3H, m), 7.13 (1H, d, J=8.4 Hz), 7.02-6.94 (2H, s), 5.55 (1H, dd, J₁=11.6 Hz, J₂=4.0 Hz), 4.67 (s, 4.19 (s, 2H), 4.17 (s, 5H), 3.79 (1H, dd, J₁=17.6 Hz, J₂=11.2 Hz), 3.21 (1H, dd, J₁=17.2 Hz, J₂=4.4 Hz). 17c 7.45 (2H, d, J=8.0 Hz), 7.33 (2H, d, J=8.4 Hz), 7.16-7.22 (2H, m), 6.96 (1H, t, J=7.6 Hz), 6.78-6.84 (1H, m), 5.55 (1H, dd, J₁=11.6 J₂=4.0 Hz), 4.61 (s, 2H), 4.22 (s, 2H), 4.16 (s, 5H), 3.79 (1H, dd, J₁=17.6 Hz, J₂=11.2 Hz), 3.21 (1H, dd, J₁=17.2 Hz, J₂=4.4 Hz). 18 7.56 (2H, d, J=8.4 Hz), 7.39 (2H, d, J=8.4 Hz), 7.11 (2H, d, J=8.4 Hz), 6.87 (2H, d, J=8.0 Hz), 6.81 (1H, s), 4.63 (s, 2H), 4.24 (s, 4I, 4 (s, 5H). 29 42 (1H, s), 8.17 (2H, d, J=8.0 Hz), 7.87 (1H, d, J=15.6 Hz), 7.70 (2H, d, J=8.4 Hz), 7.68 (1H, d, J=15.6 Hz), 7.62 (2H, t, J=8.0 T.33 (2H, d, J=8.4 Hz), 7.41 (1H, t, J=8.0 Hz), 4.67 (s, 2H), 4.21 (s, 5H), 4.15 (s, 2H). 23 9.41 (1H, s), 8.14 (2H, d, J=8.0 Hz), 7.87 (1H, d, J=15.6 Hz), 7.70 (2H, d, J=8.4 Hz), 7.52 (2H, d, J=8.4 Hz), 7.45 (2H, d, J=8.0 T.39 (2H, d, J=8.4 Hz), 4.64 (s, 2H), 4.24 (s, 5H), 4.13 (s, 2H), 2.43 (s, 3H). 24 9.40 (1H, s), 8.16 (2H, d, J=8.4 Hz), 7.87 (1H, d, J=15.6 Hz), 7.65 (1H, d, J=15.6 Hz), 7.48 (2H, d, J=8.0 Hz), 7.42 (2H, d, J=8.4 T.26 (2H, d, J=8.0 Hz), 4.70 (s, 2H), 4.22 (s, 5H), 4.11 (s, 2H), 3.83 (s, 3H). 24 9.40 (1H, s), 8.16 (2H, d, J=8.0 Hz), 7.87 (1H, d, J=15.6 Hz), 7.67 (1H, d, J=15.6 Hz), 7.43 (2H, d, J=8.4 T.26 (2H, d, J=8.0 Hz), 7.42 (2H, d, J=8.4 T.26 (2H, d, J=8.0 Hz), 7.43 (2H, d, J=8.0 Hz), 7.43 (2H, d, J=8.0 Hz), 7.83 (1H, d, J=15.2 Hz), 7.67 (1H, d, J=15.6 Hz), 7.45 (2H, d, J=8.0 Hz), 7.43 (2H, d, J=8.4 Hz), 4.67 (s, 2H), 4.26 (s, 5H), 4.11 (s, 2H). 25 9.42 (1H, s), 8.11 (2H, d, J=8.0 Hz), 7.83 (1H, d, J=15.6 Hz), 7.67 (1H, d, J=15.6 Hz), 7.64 (2H, d, J=8.4 T.26 (2H, d, J=8.4 Hz), 4.67 (s, 2H), 4.26 (s, 5H), 4.12 (s, 2H). 26 9.41 (1H, s), 8.18 (2H, d, J=8.4 Hz), 8.01 (2H, d, J=8.0 Hz), 7.86 (1H, d, J=15.6 Hz),	17a	7.44 (2H, d, <i>J</i> =8.4 Hz), 7.27 (2H, d, <i>J</i> =8.4 Hz), 7.16 (2H, d, <i>J</i> =8.0 Hz), 6.72 (2H, d, <i>J</i> =8.4 Hz), 5.57 (1H, dd, <i>J</i> ₁ =11.6 Hz, <i>J</i> ₂ =4.8 Hz), 4.65 (s, 2H), 4.21 (s, 2H), 4.19 (s, 5H), 3.72 (1H, dd, <i>J</i> ₁ =17.6 Hz, <i>J</i> ₂ =11.6 Hz), 3.19 (1H, dd, <i>J</i> ₁ =17.6 Hz, <i>J</i> ₂ =4.8 Hz).			
 7c 7.45 (2H, d, J=8.0 Hz), 7.33 (2H, d, J=8.4 Hz), 7.16-7.22 (2H, m), 6.96 (1H, t, J=7.6 Hz), 6.78-6.84 (1H, m), 5.55 (1H, dd, J₁=11.6 J₂=4.0 Hz), 4.61 (s, 2H), 4.22 (s, 2H), 4.16 (s, 5H), 3.79 (1H, dd, J₁=17.6 Hz, J₂=11.2 Hz), 3.21 (1H, dd, J₁=17.2 Hz, J₂=4.4 Hz). 7.56 (2H, d, J=8.4 Hz), 7.39 (2H, d, J=8.4 Hz), 7.11 (2H, d, J=8.4 Hz), 6.87 (2H, d, J=8.0 Hz), 6.81 (1H, s), 4.63 (s, 2H), 4.24 (s, 4.14 (s, 5H). 9.42 (1H, s), 8.17 (2H, d, J=8.0 Hz), 7.87 (1H, d, J=15.6 Hz), 7.70 (2H, d, J=8.4 Hz), 7.68 (1H, d, J=15.6 Hz), 7.62 (2H, t, J=8.0 T.43 (2H, d, J=8.4 Hz), 7.41 (1H, t, J=8.0 Hz), 4.67 (s, 2H), 4.21 (s, 5H), 4.15 (s, 2H). 9.41 (1H, s), 8.14 (2H, d, J=8.0 Hz), 7.87 (1H, d, J=15.2 Hz), 7.68 (1H, d, J=15.6 Hz), 7.52 (2H, d, J=8.4 Hz), 7.45 (2H, d, J=8.0 T.39 (2H, d, J=8.4 Hz), 7.44 (1H, s), 4.24 (s, 5H), 4.13 (s, 2H), 2.43 (s, 3H). 9.40 (1H, s), 8.16 (2H, d, J=8.4 Hz), 7.87 (1H, d, J=15.6 Hz), 7.65 (1H, d, J=15.6 Hz), 7.48 (2H, d, J=8.0 Hz), 7.42 (2H, d, J=8.4 T.26 (2H, d, J=8.0 Hz), 7.42 (2H, d, J=8.4 T.26 (2H, d, J=8.0 Hz), 4.22 (s, 5H), 4.11 (s, 2H), 3.83 (s, 3H). 9.42 (1H, s), 8.17 (2H, d, J=8.0 Hz), 7.85 (1H, d, J=15.2 Hz), 7.67 (1H, d, J=15.6 Hz), 7.45 (2H, d, J=8.0 Hz), 7.43 (2H, d, J=8.4 T.26 (2H, d, J=8.0 Hz), 4.67 (s, 2H), 4.26 (s, 5H), 4.11 (s, 2H). 9.42 (1H, s), 8.13 (2H, d, J=8.0 Hz), 7.85 (1H, d, J=15.2 Hz), 7.87 (1H, d, J=15.6 Hz), 7.67 (1H, d, J=15.6 Hz), 7.64 (2H, d, J=8.0 T.47 (2H, d, J=8	17b	7.42 (2H, d, <i>J</i> =8.0 Hz), 7.27-7.35 (3H, m), 7.13 (1H, d, <i>J</i> =8.4 Hz), 7.02-6.94 (2H, s), 5.55 (1H, dd, <i>J</i> ₁ =11.6 Hz, <i>J</i> ₂ =4.0 Hz), 4.67 (s, 2H), 4.19 (s, 2H), 4.17 (s, 5H), 3.79 (1H, dd, <i>J</i> ₁ =17.6 Hz, <i>J</i> ₂ =11.2 Hz), 3.21 (1H, dd, <i>J</i> ₁ =17.2 Hz, <i>J</i> ₂ =4.4 Hz).			
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 9.42 (1H, s), 8.17 (2H, d, J=8.0 Hz), 7.87 (1H, d, J=15.6 Hz), 7.70 (2H, d, J=8.4 Hz), 7.68 (1H, d, J=15.6 Hz), 7.62 (2H, t, J=8.0 7.43 (2H, d, J=8.4 Hz), 7.41 (1H, t, J=8.0 Hz), 4.67 (s, 2H), 4.21 (s, 5H), 4.15 (s, 2H). 9.41 (1H, s), 8.14 (2H, d, J=8.0 Hz), 7.84 (1H, d, J=15.2 Hz), 7.68 (1H, d, J=15.6 Hz), 7.52 (2H, d, J=8.4 Hz), 7.45 (2H, d, J=8.0 7.39 (2H, d, J=8.4 Hz), 4.64 (s, 2H), 4.24 (s, 5H), 4.13 (s, 2H), 2.43 (s, 3H). 9.40 (1H, s), 8.16 (2H, d, J=8.4 Hz), 7.87 (1H, d, J=15.6 Hz), 7.65 (1H, d, J=15.6 Hz), 7.48 (2H, d, J=8.0 Hz), 7.42 (2H, d, J=8.4 7.26 (2H, d, J=8.0 Hz), 4.72 (s, 2H), 4.22 (s, 5H), 4.11 (s, 2H), 3.83 (s, 3H). 9.42 (1H, s), 8.17 (2H, d, J=8.0 Hz), 7.85 (1H, d, J=15.2 Hz), 7.67 (1H, d, J=15.6 Hz), 7.45 (2H, d, J=8.0 Hz), 7.43 (2H, d, J=8.4 7.31 (2H, d, J=8.4 Hz), 4.67 (s, 2H), 4.26 (s, 5H), 4.14 (s, 2H). 9.41 (1H, s), 8.13 (2H, d, J=8.0 Hz), 8.03 (2H, d, J=8.0 Hz), 7.87 (1H, d, J=15.6 Hz), 7.62 (1H, d, J=15.6 Hz), 7.64 (2H, d, J=8.0 7.44 (2H, d, J=8.4 Hz), 4.61 (s, 2H), 4.19 (s, 5H), 4.12 (s, 2H). 9.43 (1H, s), 8.18 (2H, d, J=8.4 Hz), 8.01 (2H, d, J=8.4 Hz), 7.86 (1H, d, J=15.6 Hz), 7.62 (1H, d, J=15.2 Hz), 7.58 (2H, d, J=8.0 7.43 (2H, d, J=8.4 Hz), 4.62 (s, 2H), 4.24 (s, 5H), 4.15 (s, 2H). 9.45 (1H, s), 8.14 (2H, d, J=8.8 Hz), 7.93 (2H, d, J=8.0 Hz), 7.88 (1H, d, J=15.2 Hz), 7.70 (2H, d, J=8.4 Hz), 7.65 (1H, d, J=15.6 Hz), 7.44 (2H, d, J=8.0 Hz), 4.65 (s, 2H), 4.21 (s, 5H). 9.41 (1H, s), 8.16 (2H, d, J=8.4 Hz), 7.87 (1H, d, J=15.6 Hz), 7.70 (2H, d, J=8.4 Hz), 7.65 (1H, d, J=15.6 Hz), 7.44 (2H, d, J=8.0 Hz), 7.23 (1H, d, J=15.6 Hz), 7.70 (2H, d, J=8.0 Hz), 7.64 (1H, d, J=15.6 Hz), (2H, d, J=8.0 Hz), 7.23 (1H, d, J=15.6 Hz), 7.71~77.6 (2H, m), 7.68 (1H, d, J=8.0 Hz), 7.64 (1H, d, J=15.6 Hz), (2H, d, J=8.0 Hz), 7.23 (1H, s), 4.62 (s, 2H), 4.26 (s, 5H), 4.15 (s, 2H). 9.44 (1H, s), 8.19 (2H, d, J=8.4 Hz), 7.87 (1H, d, J=15.6 Hz), 7.71~77.6 (2H, m), 7.68 (1H, d, J=8.0 Hz), 7.64 (1H, d, J=15.6 Hz), (2H, d, J=8.0 H	18	7.56 (2H, d, J=8.4 Hz), 7.39 (2H, d, J=8.4 Hz), 7.11 (2H, d, J=8.4 Hz), 6.87 (2H, d, J=8.0 Hz), 6.81 (1H, s), 4.63 (s, 2H), 4.24 (s, 2H), 4.14 (s, 5H).			
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 9.42 (1H, s), 8.17 (2H, d, J=8.0 Hz), 7.85 (1H, d, J=15.2 Hz), 7.67 (1H, d, J=15.6 Hz), 7.45 (2H, d, J=8.0 Hz), 7.43 (2H, d, J=8.4 7.31 (2H, d, J=8.4 Hz), 4.67 (s, 2H), 4.26 (s, 5H), 4.14 (s, 2H). 9.41 (1H, s), 8.13 (2H, d, J=8.0 Hz), 8.03 (2H, d, J=8.0 Hz), 7.87 (1H, d, J=15.6 Hz), 7.67 (1H, d, J=15.6 Hz), 7.64 (2H, d, J=8.0 7.44 (2H, d, J=8.4 Hz), 4.61 (s, 2H), 4.19 (s, 5H), 4.12 (s, 2H). 9.43 (1H, s), 8.18 (2H, d, J=8.4 Hz), 8.01 (2H, d, J=8.4 Hz), 7.86 (1H, d, J=15.6 Hz), 7.62 (1H, d, J=15.2 Hz), 7.58 (2H, d, J=8.0 7.43 (2H, d, J=8.4 Hz), 4.62 (s, 2H), 4.24 (s, 5H), 4.15 (s, 2H). 9.45 (1H, s), 8.14 (2H, d, J=8.8 Hz), 7.93 (2H, d, J=8.0 Hz), 7.88 (1H, d, J=15.2 Hz), 7.70 (2H, d, J=8.4 Hz), 7.65 (1H, d, J=15.6 7.44 (2H, d, J=8.0 Hz), 4.65 (s, 2H), 4.21 (s, 5H), 4.16 (s, 2H). 9.41 (1H, s), 8.16 (2H, d, J=8.4 Hz), 7.87 (1H, d, J=15.6 Hz), 7.71~7.76 (2H, m), 7.68 (1H, d, J=8.0 Hz), 7.64 (1H, d, J=15.6 Hz), (2H, d, J=8.0 Hz), 7.23 (1H, s), 4.62 (s, 2H), 4.26 (s, 5H), 4.15 (s, 2H). 9.44 (1H, s), 8.19 (2H, d, J=8.0 Hz), 7.94 (1H, t, J=8.0 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.88 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.88 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.73 (1H, d, J=8.0 Hz), 7.66 (1H, d, J=15.6 Hz), 7.73 (1H, d, J=8.0 Hz), 7.66 (1H, d, J=15.6 Hz), 7.88 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.88 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=15.6 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.73 (1H, d, J=8.0 Hz), 7.66 (1H, d, J=15.6 Hz), 7.88 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.88 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.88 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.88 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.88 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.88 (1H, d, J=15.2 Hz),	24	9.40 (1H, s), 8.16 (2H, d, <i>J</i> =8.4 Hz), 7.87 (1H, d, <i>J</i> =15.6 Hz), 7.65 (1H, d, <i>J</i> =15.6 Hz), 7.48 (2H, d, <i>J</i> =8.0 Hz), 7.42 (2H, d, <i>J</i> =8.4 Hz), 7.26 (2H, d, <i>J</i> =8.0 Hz), 4.72 (s, 2H), 4.22 (s, 5H), 4.11 (s, 2H), 3.83 (s, 3H).			
 9.41 (1H, s), 8.13 (2H, d, J=8.0 Hz), 8.03 (2H, d, J=8.0 Hz), 7.87 (1H, d, J=15.6 Hz), 7.67 (1H, d, J=15.6 Hz), 7.64 (2H, d, J=8.0 7.44 (2H, d, J=8.4 Hz), 4.61 (s, 2H), 4.19 (s, 5H), 4.12 (s, 2H). 9.43 (1H, s), 8.18 (2H, d, J=8.4 Hz), 8.01 (2H, d, J=8.4 Hz), 7.86 (1H, d, J=15.6 Hz), 7.62 (1H, d, J=15.2 Hz), 7.58 (2H, d, J=8.0 7.43 (2H, d, J=8.4 Hz), 4.62 (s, 2H), 4.24 (s, 5H), 4.15 (s, 2H). 9.45 (1H, s), 8.14 (2H, d, J=8.8 Hz), 7.93 (2H, d, J=8.0 Hz), 7.88 (1H, d, J=15.2 Hz), 7.70 (2H, d, J=8.4 Hz), 7.65 (1H, d, J=15.6 7.44 (2H, d, J=8.0 Hz), 4.65 (s, 2H), 4.21 (s, 5H), 4.16 (s, 2H). 9.41 (1H, s), 8.16 (2H, d, J=8.4 Hz), 7.87 (1H, d, J=15.6 Hz), 7.71~7.76 (2H, m), 7.68 (1H, d, J=8.0 Hz), 7.64 (1H, d, J=15.6 Hz), (2H, d, J=8.0 Hz), 7.23 (1H, s), 4.62 (s, 2H), 4.26 (s, 5H), 4.15 (s, 2H). 9.44 (1H, s), 8.19 (2H, d, J=8.0 Hz), 7.94 (1H, t, J=8.0 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.80 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.80 (1H, d, J=15.2 Hz), 7.80 (1	25	9.42 (1H, s), 8.17 (2H, d, <i>J</i> =8.0 Hz), 7.85 (1H, d, <i>J</i> =15.2 Hz), 7.67 (1H, d, <i>J</i> =15.6 Hz), 7.45 (2H, d, <i>J</i> =8.0 Hz), 7.43 (2H, d, <i>J</i> =8.4 Hz), 7.31 (2H, d, <i>J</i> =8.4 Hz), 4.67 (s, 2H), 4.26 (s, 5H), 4.14 (s, 2H).			
 27 9.43 (1H, s), 8.18 (2H, d, J=8.4 Hz), 8.01 (2H, d, J=8.4 Hz), 7.86 (1H, d, J=15.6 Hz), 7.62 (1H, d, J=15.2 Hz), 7.58 (2H, d, J=8.0 7.43 (2H, d, J=8.4 Hz), 4.62 (s, 2H), 4.24 (s, 5H), 4.15 (s, 2H). 28a 9.45 (1H, s), 8.14 (2H, d, J=8.8 Hz), 7.93 (2H, d, J=8.0 Hz), 7.88 (1H, d, J=15.2 Hz), 7.70 (2H, d, J=8.4 Hz), 7.65 (1H, d, J=15.6 7.44 (2H, d, J=8.0 Hz), 4.65 (s, 2H), 4.21 (s, 5H), 4.16 (s, 2H). 28b 9.41 (1H, s), 8.16 (2H, d, J=8.4 Hz), 7.87 (1H, d, J=15.6 Hz), 7.71~7.76 (2H, m), 7.68 (1H, d, J=8.0 Hz), 7.64 (1H, d, J=15.6 Hz), (2H, d, J=8.0 Hz), 7.23 (1H, s), 4.62 (s, 2H), 4.26 (s, 5H), 4.15 (s, 2H). 28c 9.44 (1H, s), 8.19 (2H, d, J=8.0 Hz), 7.94 (1H, t, J=8.0 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.80 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.80 (1H, d, J=15.6 Hz)	26	9.41 (1H, s), 8.13 (2H, d, <i>J</i> =8.0 Hz), 8.03 (2H, d, <i>J</i> =8.0 Hz), 7.87 (1H, d, <i>J</i> =15.6 Hz), 7.67 (1H, d, <i>J</i> =15.6 Hz), 7.64 (2H, d, <i>J</i> =8.0 Hz), 7.44 (2H, d, <i>J</i> =8.4 Hz), 4.61 (s, 2H), 4.19 (s, 5H), 4.12 (s, 2H).			
 28a 9.45 (1H, s), 8.14 (2H, d, J=8.8 Hz), 7.93 (2H, d, J=8.0 Hz), 7.88 (1H, d, J=15.2 Hz), 7.70 (2H, d, J=8.4 Hz), 7.65 (1H, d, J=15.6 7.44 (2H, d, J=8.0 Hz), 4.65 (s, 2H), 4.21 (s, 5H), 4.16 (s, 2H). 28b 9.41 (1H, s), 8.16 (2H, d, J=8.4 Hz), 7.87 (1H, d, J=15.6 Hz), 7.71~7.76 (2H, m), 7.68 (1H, d, J=8.0 Hz), 7.64 (1H, d, J=15.6 Hz), (2H, d, J=8.0 Hz), 7.23 (1H, s), 4.62 (s, 2H), 4.26 (s, 5H), 4.15 (s, 2H). 28c 9.44 (1H, s), 8.19 (2H, d, J=8.0 Hz), 7.94 (1H, t, J=8.0 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=15.6 Hz), 7.86 (1H	27	9.43 (1H, s), 8.18 (2H, d, <i>J</i> =8.4 Hz), 8.01 (2H, d, <i>J</i> =8.4 Hz), 7.86 (1H, d, <i>J</i> =15.6 Hz), 7.62 (1H, d, <i>J</i> =15.2 Hz), 7.58 (2H, d, <i>J</i> =8.0 Hz), 7.43 (2H, d, <i>J</i> =8.4 Hz), 4.62 (s, 2H), 4.24 (s, 5H), 4.15 (s, 2H).			
 28b 9.41 (1H, s), 8.16 (2H, d, J=8.4 Hz), 7.87 (1H, d, J=15.6 Hz), 7.71~7.76 (2H, m), 7.68 (1H, d, J=8.0 Hz), 7.64 (1H, d, J=15.6 Hz), (2H, d, J=8.0 Hz), 7.23 (1H, s), 4.62 (s, 2H), 4.26 (s, 5H), 4.15 (s, 2H). 28c 9.44 (1H, s), 8.19 (2H, d, J=8.0 Hz), 7.94 (1H, t, J=8.0 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=15.2 Hz), 7.86 (1H, d, J=15.6 Hz), 7.86 (1H, d, J=1	28a	9.45 (1H, s), 8.14 (2H, d, <i>J</i> =8.8 Hz), 7.93 (2H, d, <i>J</i> =8.0 Hz), 7.88 (1H, d, <i>J</i> =15.2 Hz), 7.70 (2H, d, <i>J</i> =8.4 Hz), 7.65 (1H, d, <i>J</i> =15.6 Hz), 7.44 (2H, d, <i>J</i> =8.0 Hz), 4.65 (s, 2H), 4.21 (s, 5H), 4.16 (s, 2H).			
28c 9.44 (1H, s), 8.19 (2H, d, J=8.0 Hz), 7.94 (1H, t, J=8.0 Hz), 7.86 (1H, d, J=15.2 Hz), 7.73 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=15.6 Hz), 7.86	28b	9.41 (1H, s), 8.16 (2H, d, <i>J</i> =8.4 Hz), 7.87 (1H, d, <i>J</i> =15.6 Hz), 7.71~7.76 (2H, m), 7.68 (1H, d, <i>J</i> =8.0 Hz), 7.64 (1H, d, <i>J</i> =15.6 Hz), 7.48 (2H, d, <i>J</i> =8.0 Hz), 7.23 (1H, s), 4.62 (s, 2H), 4.26 (s, 5H), 4.15 (s, 2H).			
7.60-7.64 (1H, m), 7.52 (2H, d, <i>J</i> =8.4 Hz), 7.41 (1H, t, <i>J</i> =8.4 Hz), 4.65 (s, 2H), 4.24 (s, 5H), 4.17 (s, 2H).	28c	9.44 (1H, s), 8.19 (2H, d, <i>J</i> =8.0 Hz), 7.94 (1H, t, <i>J</i> =8.0 Hz), 7.86 (1H, d, <i>J</i> =15.2 Hz), 7.73 (1H, d, <i>J</i> =8.4 Hz), 7.66 (1H, d, <i>J</i> =15.6 Hz), 7.60-7.64 (1H, m), 7.52 (2H, d, <i>J</i> =8.4 Hz), 7.41 (1H, t, <i>J</i> =8.4 Hz), 4.65 (s, 2H), 4.24 (s, 5H), 4.17 (s, 2H).			

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(*n*=3)

图 4 二茂铁类化合物 4~10 的合成过程

Fig. 4 Synthetic route of ferrocenyl compounds 4–10

3.2 结构表征

所合成的二茂铁类化合物均经¹H-NMR 和 MS 分析确证。在化合物 4~10 的核磁共振氢谱中, 在 7.9 ppm 附近出现一个单峰归属于嘧啶环上氢 的特征信号; 在化合物 11~18 氢谱中, 其二氢吡 唑环上的三个烷基氢信号分别在 5.5, 3.8 和 3.0 ppm 附近出现,而用 DDQ 将二氢吡唑环氧化 成吡唑环后,3个烷基氢信号消失,并在6.8 ppm 附近出现一个芳香质子的信号,归属于吡唑环上 的氢质子信号; 在化合物 22~38 氢谱中, 出现一 对反式双键的信号(J>15.0 Hz),归属于化合物中 α,β-不饱和酮的双键质子特征信号。通过 MS 分析 发现化合物测得的分子量与理论值一致,这说明 所合成的化合物是目标产物。

3.3 生物活性

选取 MCF-7、MDA-MB-231 这 2 种人乳腺癌 细胞株和正常乳腺上皮细胞 MCF-10A 为测试细胞 株,以他莫昔芬为阳性对照药,采用 CCK8 试剂 盒测试合成的二茂铁衍生物抗乳腺癌活性。取对 数生长期的 MCF-7 或 MDA-MB-231 细胞悬浮于 含 10%胎牛血清的无酚红 DMEM 培养基中, 铺至 96 孔细胞培养板中。待细胞完全贴壁后,弃去原 培养液,加入待测查耳酮,其浓度梯度为1×10-9, 5×10^{-8} , 1×10^{-8} , 5×10^{-7} , 1×10^{-7} , 5×10^{-6} , 1×10^{-6} , 5×10^{-5} , 1×10^{-5} , $1 \times 10^{-4} \text{ mol} \cdot \text{L}^{-1}$. 物处理培养3d后,每孔加入5 µL CCK8,置于 37 ℃、5% CO2培养箱中继续孵育 4 h。使用酶标 仪在 490 nm 波长测定每孔的吸光度(OD)值,分析 实验结果,并计算出 IC50,结果见表 3。同时,为 了考察目标化合物的毒性,测试了目标化合物对 正常乳腺上皮细胞 MCF-10A 的抑制作用,并计算 出这些化合物的治疗指数(in vitro therapeutic index, IVTI)。化合物的 IVTI 值越高, 安全性越 大^[12],结果见表3。

化合		$IC_{50}/\mu mol \cdot L^{-1}$				
物	MCF-7	MDA-MB-231	MCF-10A	IC ₅₀ (MCF-10A)]		
3	25.5±1.83	10.7±1.41	>100	>9.3		
4	19.7±2.17	9.4±1.25	>100	>10.6		
5	15.9±1.44	7.5±0.96	94.8±8.27	12.6		
6	17.4±1.59	10.3±1.07	>100	>9.7		
7	18.2±2.07	7.1±0.69	>100	>14.0		
8	15.1±1.74	5.3±0.53	>100	>18.8		
9	16.8±1.86	5.9±0.64	>100	>16.9		
10a	14.6±1.55	3.8±0.36	>100	>26.3		
10b	15.2±1.43	4.4±0.58	>100	>22.7		
10c	14.9±1.68	5.2±0.74	>100	>19.2		
11	17.2±1.76	6.7±1.25	>100	>14.9		
12	13.8±1.52	5.6±0.96	>100	>17.8		
13	12.9±0.97	8.4±0.92	>100	>11.9		
14	16.5±2.14	7.0±0.85	>100	>14.0		
15	15.1±1.82	4.6±0.39	>100	>21.7		
16	13.3±1.66	4.2±0.58	96.7±9.62	23.0		
17a	10.4±1.54	3.1±0.27	>100	>32.2		
17b	12.8±1.39	3.5±0.55	>100	>28.5		
17c	11.7±1.75	4.7±0.61	>100	>21.2		
18	14.1±1.59	3.3±0.74	>100	>30.3		
22	13.5±0.82	5.4±0.29	>100	>18.5		
23	16.1±2.17	3.3±0.45	>100	>30.3		
24	10.9±0.96	6.9±0.78	>100	>14.4		
25	12.4±1.53	5.6±0.52	>100	>17.8		
26	9.7±1.18	3.1±0.54	>100	>32.2		
27	10.3±1.25	2.7±0.33	>100	>37.0		
28a	7.2±0.86	1.6±0.23	>100	>62.5		
28b	9.5±0.71	1.9±0.19	>100	>52.6		
28c	7.8±0.83	2.2±0.17	>100	>45.4		
他莫	19.3±1.35	16.5±1.43	13.7±1.17	0.8		

表3 目标化合物 4~18, 22~28 对 2 种乳腺癌和 MCF-10A

Tab. 3 Antiproliferative activities of target compounds

4-18, 22-28 on two breast cancer and MCF-10A cell lines

细胞株的增殖抑制活性(n=3)

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3.4 构效关系研究

从上述活性结果可以发现:①目标二茂铁衍 生物对荷尔蒙依赖型乳腺癌 MCF-7 细胞和 TNBCMDA-MB-231 细胞均有较强抑制活性,并显 著强于先导化合物 3。同时,这些二茂铁衍生物对 MDA-MB-231 细胞展现出了更强的选择性和抑制 活性, 其抑制 MDA-MB-231 的活性(IC50< 11 μ mol·L⁻¹)均显著地强于阳性药物他莫昔芬 (IC₅₀=16.5 µmol·L⁻¹); ②芳环(Ar)上的取代基对活 性影响较大,总的来说,芳环含有吸电子基取代 的化合物抗肿瘤活性强于相应的给电子基化合 物, 尤其是 4-F 取代的化合物 28a [IC50=(1.6± 0.23)µmol·L⁻¹]对 MDA-MB-231 展现出了最强的抑 制活性,甚至是阳性药物他莫昔芬的10倍,而进 一步将化合物 28a 芳环上的 F 从对位转移到间位 [化合物 28b, IC₅₀=(1.9±0.19)µmol·L⁻¹]或邻位[化 合物 28c, IC₅₀=(2.2±0.17)µmol·L⁻¹]均降低了抗癌 活性,这些结果说明芳环上的对取代能够提高抗 肿瘤活性。事实上,在嘧啶类化合物和二氢吡咯 类化合物中,也有着同样的规律,即 4-F 取代化合 物的抗肿瘤活性强于其相应的间位和邻位取代衍 生物;③除了取代基外,化合物中的杂环对抗肿 瘤活性也有较大的影响,其中咪唑杂环类化合物 抗肿瘤活性强于相应的二氢吡咯、吡咯和嘧啶杂 环化合物;④所合成的二茂铁衍生物对正常的乳 腺上皮细胞没有毒性并有较高的治疗指数 (IVTI>9), 而他莫昔芬[IC₅₀=(13.7±1.17)µmol·L⁻¹] 却展现出了较强的细胞毒性,其 IVTI 值仅为 0.8。

4 结论

本实验以前期获得的二茂铁查耳酮为先导化 合物,对其进行结构修饰,合成了一系列具有不 同杂环的二茂铁衍生物,这些目标化合物抗乳腺 癌活性均强于其先导化合物,并对 TNBCMBA-MD-231 细胞展现出了较强的选择性和抑制活性, 其中化合物 28a 对 MBA-MD-231 展现出了最强的 活性,分别是先导化合物和他莫昔芬的 6 和 10 倍; 此外,这些二茂铁衍生物对正常的乳腺上皮细胞 MCF-10A 没有毒性。这些结果说明,对查耳酮的 α,β-不饱和酮进行修饰能够提高其抗肿瘤活性,这 为今后发展新型、高效、低毒的抗 TNBC 药物提 供了新的思路。

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