甲氧基（MeO-）在上市药物中的关键作用解析

甲氧基普遍存在于天然产物中，因此也存在于许多天然产物衍生药物中。最近， Debora Chiodi 的综述整理了含甲氧基的药物，从甲氧基的角度介绍了 230 多种含甲氧基的小分子药物以及几种含氟甲氧基的药物。并按疾病领域进行了分类，旨在探讨甲氧基在药物分子和各类药物中的作用。

亮点

- 有 230 多种含甲氧基的小分子药物。
- 通过 SAR 和 X 射线结构阐明了甲氧基的作用。
- 讨论了其优点（如结合力）和缺点（如新陈代谢）。
- O 和 CH3 的结合产生了独特的亲水和亲油效应。
- 比较并讨论含有氟甲氧基的药物。

背景介绍

结构-活性关系（SAR）是指化学结构与生物活性之间的关系，是药物化学研究的核心。药物化学家花费大量时间优化化学结构，最大限度提高靶向活性（从而实现药物疗效的目标），并最大限度降低非靶向活性（从而实现药物安全性的目标）。这种结构的迭代修改应在考虑到结构-性质关系的前提下谨慎进行，以保持药物的类药物特性。在经典的 "Lipinski Rule of 5"以及最新的类药物空间分析中，通常会考虑分子量上限，以提高开发出口服生物药的概率。

甲氧基经常出现在天然药物中和已批准的药物中，为了提高化合物的生物活性和特性，最好用小取代基取代氢原子，以尽量减少分子量的增加。在各种 "小取代基 "中，氟（F），氯（Cl），甲基（CH3）和腈（CN）已被确定为已批准药物和药物化学设计中的关键分子。在介绍单个药物之前，先对甲氧基的一般分子特性和相互作用进行了广泛讨论。

甲氧基对配体-蛋白质结合、构象和代谢的一般影响

甲氧基团（OCH3）由氧原子和甲基组成，具有亲水和疏水的双重特性。氧原子能作为氢键受体，并通过其电子效应影响分子性质，而甲基则提供疏水性保护。甲氧基团的极性特点和其与分子其他部分的空间构象相互作用，可以影响分子的物理化学特性和与目标蛋白的相互作用。这些相互作用包括氢键形成能力、分子构象变化以及偶极-偶极相互作用，对配体与蛋白结合的亲和力和选择性有重要影响。

- 在优化氢键相互作用时，药物化学家通常会尝试匹配氢键供体（HBD）和 HBA 的强度，以便优化配体与蛋白之间的相互作用能量（图 1A）。
- 为了使平衡倾向于蛋白-配体结合状态，应将强蛋白 HBD 与强配体 HBA 配对，或将弱蛋白 HBD 与弱配体 HBA 配对。
- 蛋白质中最强的 HBD 类型（通常能形成盐桥）由带正电的氨基酸残基提供，如精氨酸（Arg）、赖氨酸（Lys）和质子化的组氨酸（protonated His）（图 1B）。
- 酪氨酸（Tyr）、谷氨酰胺（Gln）和天冬酰胺（Asn）被归类为“强”HBD，而色氨酸（Trp）、丝氨酸（Ser）、苏氨酸（Thr）、未质子化的 His 和主链酰胺 NH 被认为是“中性”HBD，半胱氨酸（Cys）被视为“弱”HBD。
- 对于配体而言，最强的 HBA 类型是在生理 pH 下呈现完整负电荷的，如羧酸根阴离子（图 1C）。

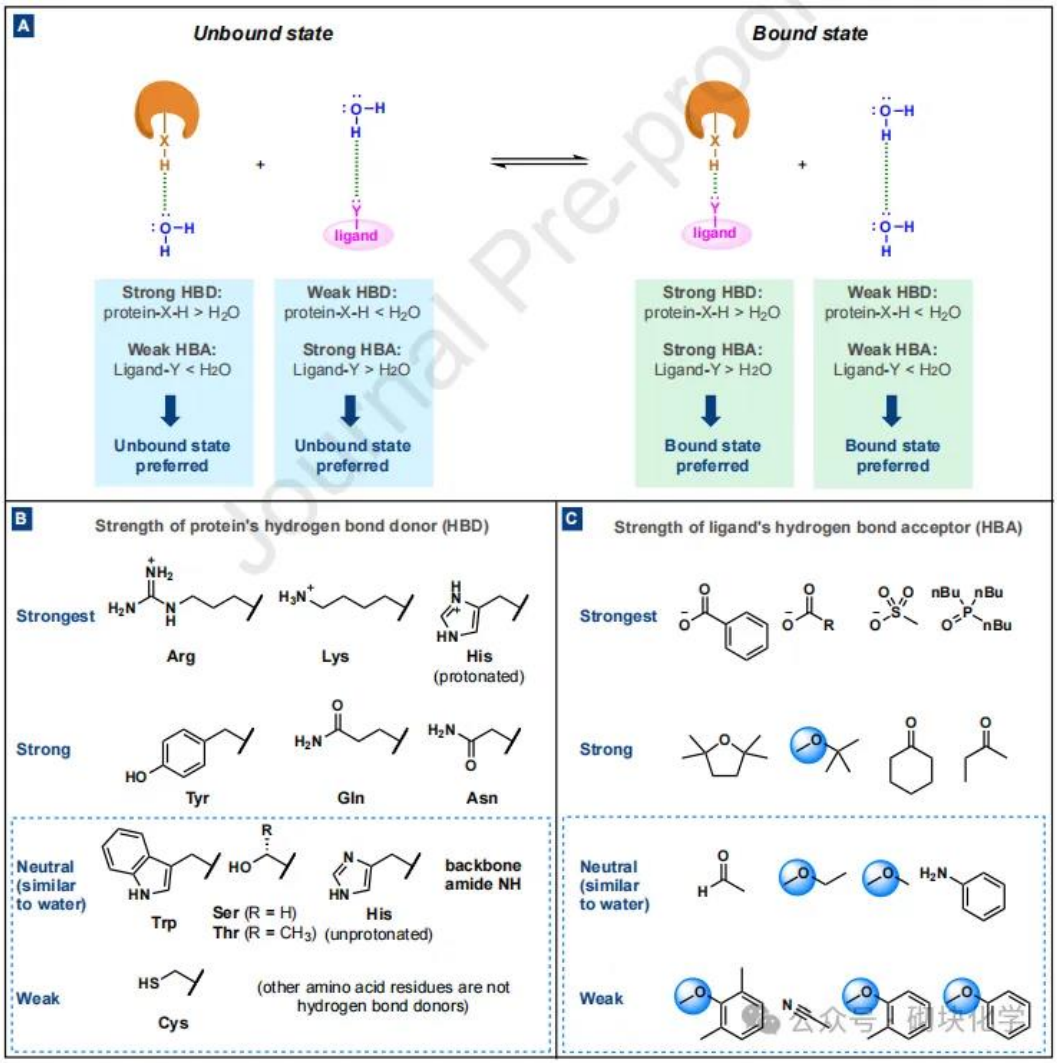


图 1. A) 根据蛋白质的 HBD 和配体的 HBA 的强度，描述未结合和结合的蛋白质-配体状态的平衡。B) 氨基酸残基中 HBD 与 H2O 的 HBD 能力的比较。C) 与 H2O 的 HBA 能力校准后的某些功能基团的 HBA 强度比较

甲氧基（OCH3）氧原子通过部分静电相互作用与轻微正电性的结构基团相互作用。

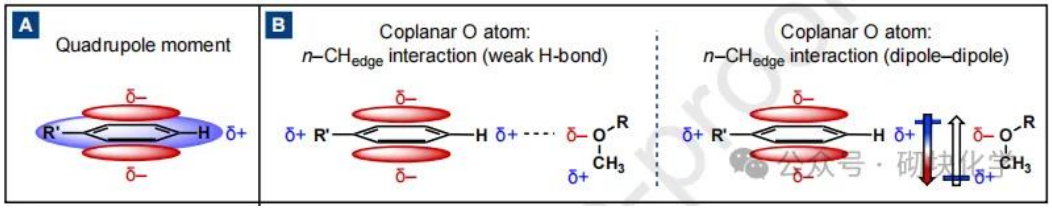


图 3. A) 与苯环电子流有关的四极矩。B) 苯环上 OCH3 的孤对电子和略带电阳性的 H 原子之间的 n-CHedge 相互作用可能具有弱 H 键或偶极-偶极 特性

- 含甲氧基化合物的构象影响分子与目标蛋白质的相互作用，特别是对于（杂）芳香族甲氧化合物，芳基-O-CH3 键的构象会因（杂）芳香环上的取代基数量而变化（图 6）。
- 在甲苯醚类化合物中，尤其是未取代的甲苯醚（A），最稳定的构象是共面形式，其中氧原子和 CH3 都与苯环在同一平面上，相比正交构象，其稳定性为 2.9 kcal/mol（12.1 kJ/mol）。
- 这种形式在热力学上更受青睐，因为甲氧基的氧原子的一个孤对电子与苯环的 π 体系共轭，这种立体电子效应克服了与烯丙基 1,3-应变相关的立体阻碍。

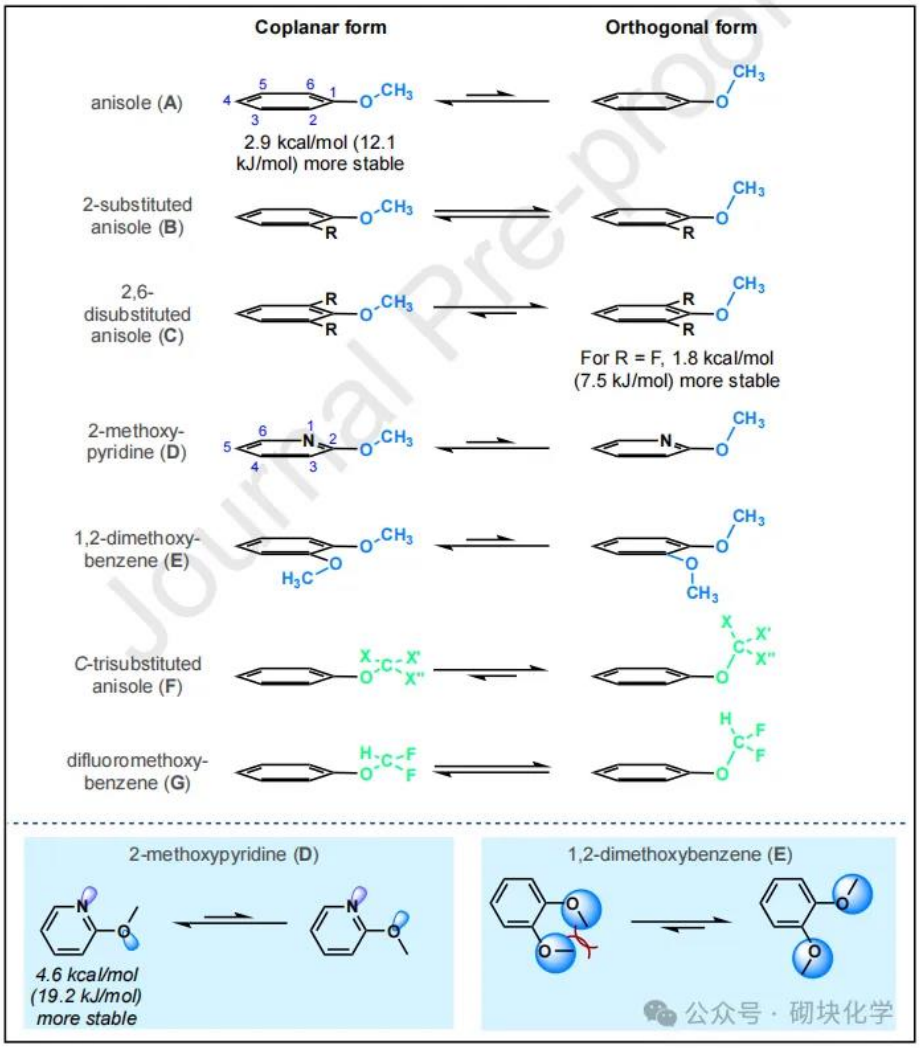


图 6. 苯甲醚构象的共面形式与正交形式。

在 2-甲氧基吡啶中，OCH3 采用一种平面地形，其中 CH3 指向吡啶 N 原子的方向，这是由于最小化环杂原子和甲氧基 O 原子上的孤对电子之间的排斥相互作用。其他的甲氧基杂环化合物也采用这种平面排列，既最小化了电子对的排斥，也对齐了偶极矩。在晶体结构中，两个 OCH3 基团通常是与苯环共面的，CH3 基团相互远离以避免立体冲突。

- 图 7 展示了 OCH3 与非芳香 π 系统（例如，蛋白质主链的酰胺基团）之间的一般相互作用。这些效应可以归因于偶极-偶极相互作用，并可以分为两类：反平行偶极排列和平行偶极排列。
- 酰胺基团的偶极矢量在 N 原子处是电正性的，在 O 原子处是电负性的，而气相中甲苯醚的偶极矢量被确定为几乎与 O-CH3 键平行（图 7A）。
- 这些矢量可以通过采用反平行偶极-偶极相互作用来能量最小化，其中相对的矢量是“侧对侧”的（图 7B），
- 或采用平行但错开的偶极-偶极相互作用，其中矢量位置足够错开以采取“头对尾”的方式（图 7C）。

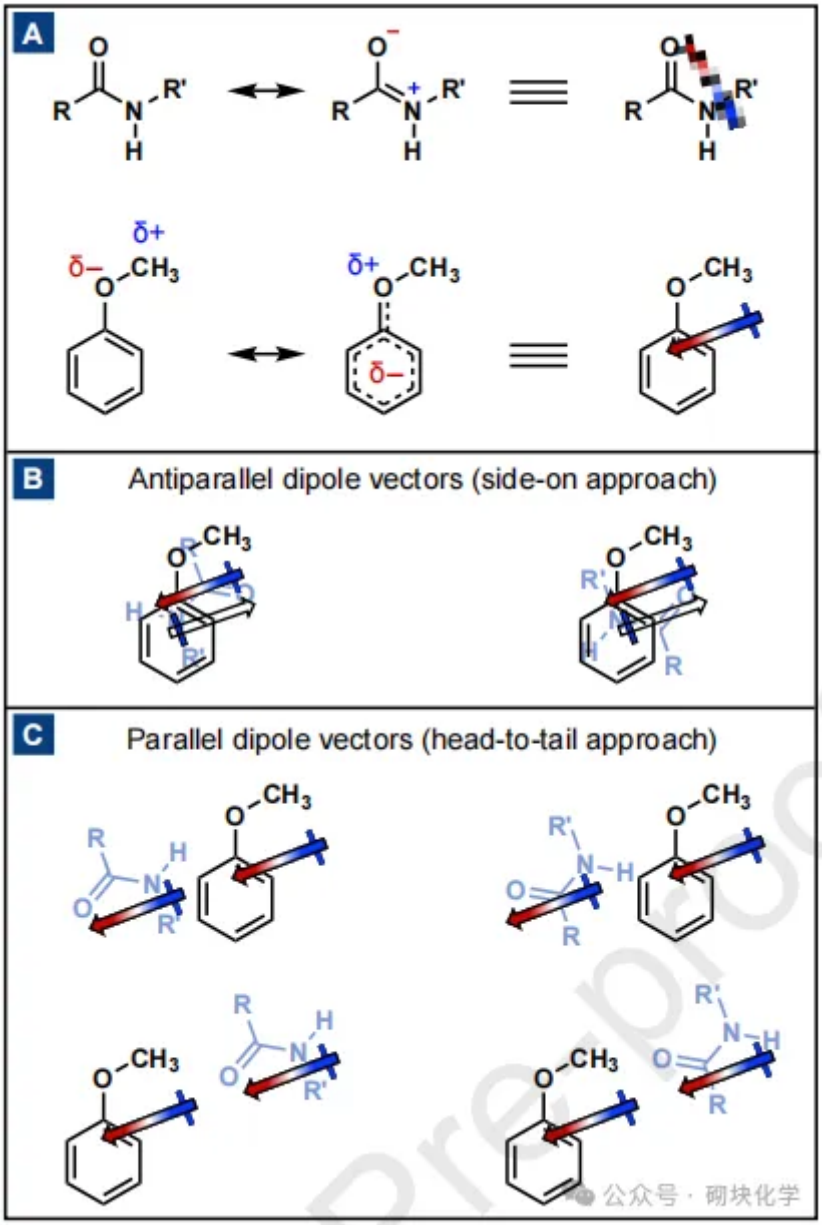


图 7. A) 羧酰胺和苯甲醚的偶极矢量。B) 偶极矢量的反平行排列作为 "侧向 "方法。C) 偶极子矢量的平行位移排列 作为 "头对尾 "方法

- 甲氧基在不同的杂环化合物中表现出不同的代谢趋势。例如，与苯甲醚（anisoles）相比，甲氧基与电子丰富的杂环（如吡啶）的结合会更容易遭受O-脱甲基化代谢,而与电子贫乏的杂环(如吡啶)结合的甲氧基代谢速率较慢。
- 甲氧基药物的代谢途径，包括O-脱甲基化（O-demethylation）和随后的葡萄糖醛酸化（glucuronidation）等第二阶段代谢过程。
- 通过改变分子结构来调节甲氧基药物的代谢稳定性。例如，通过引入氟原子或脱氧基团来减少O-脱甲基化的趋势，从而提高药物的代谢稳定性。
- 图 8C 和 8D 展示了甲氧基在不同生物异构体中的代谢情况，强调了电子效应对代谢速率的影响。

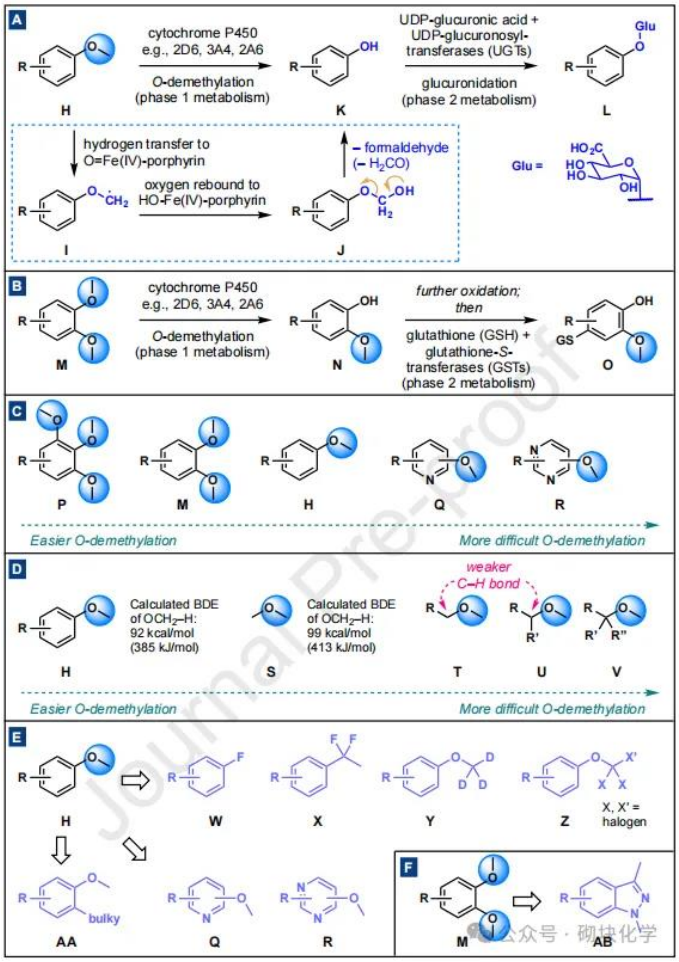
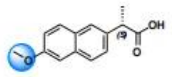
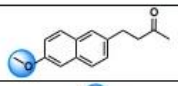
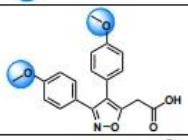
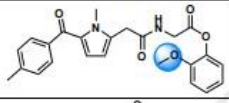
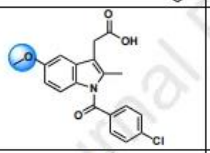
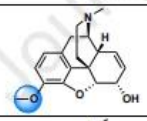
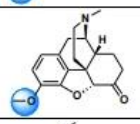
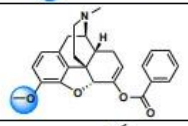
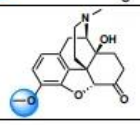


图 8. A) 含甲氧基化合物代谢清除的一般路径 （以苯甲醚 H 为例）。B) 二甲基邻苯二酚 M 的代谢途径。C) 从富电子到贫电子甲氧基（杂）烯的甲基化的难易程度。D) 从苯甲醚 H 到脂肪族甲氧基化合物（甲基醚）S-V 的 O-去甲基化的难易程度。E) 不容易发生 O-甲基化反应的苯甲醚 H 的异构体。

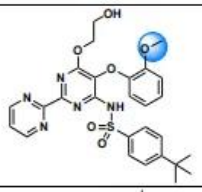
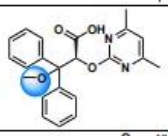
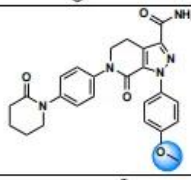
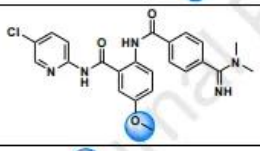
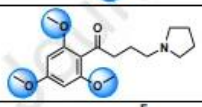
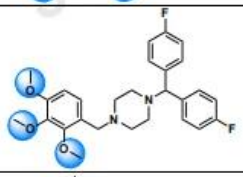
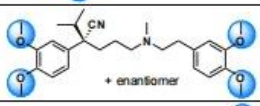
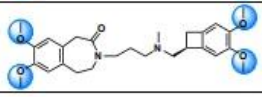
含甲氧基/含甲醚的小分子已批准药物清单

较高的烷氧基同系物，如乙氧基、异丙氧基和苄氧基（最后保留了一小部分用于含氟甲氧基药物）。下面汇总含甲氧基（或含甲醚）的小分子已批准药物清单。这些表格按化学结构、药物通用名、用途/治疗、作用机制（MOA）、PDB X 射线共晶体结构以及甲氧基的作用编排。

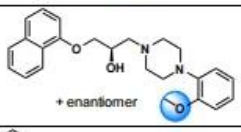
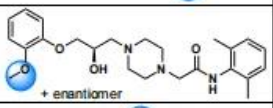
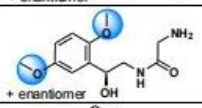
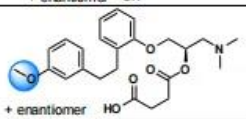
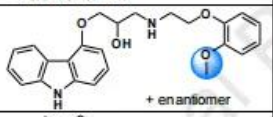
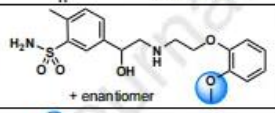
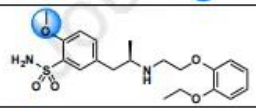
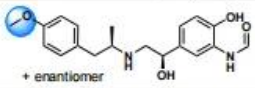
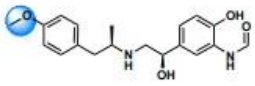
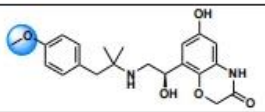
1 针对中枢神经系统（CNS）的含甲氧基药物。

No.	Drug name	Structure	Use/treatment	MOA	PDB	Role of methoxy
1	naproxen		CNS, NSAID, inflammation, pain	Nonselective COX-1 / COX-2 inhibitor	3NT1	vdW, co-planar n–CH_{edge} interactions, CH···π interactions, antiparallel dipole–dipole interactions
2	nabumetone		CNS, NSAID, inflammation, pain	Prodrug of 6-methoxy-2-naphthylaceti c acid	*See naproxen (1)*	*See naproxen (1)*
3	mofezolac		CNS, NSAID, inflammation, pain	Selective COX-1 inhibitor	5WBE	vdW, CH···O H-bonding
4	amtolmetin guacil		CNS, NSAID, inflammation, pain, arthritis	Nonselective COX-1 / COX-2 inhibitor, prodrug of tolmetin	N/A	Slows ester hydrolysis by acting as an EDG
5	indo-methacin (WHO Essential Medicine)		CNS, NSAID, inflammation, pain	Nonselective COX-1 / COX-2 inhibitor	4COX	vdW, CH···O H-bonding, co-planar n–CH_{edge} interactions
6	codeine (WHO Essential Medicine)		CNS, pain, cough (caution: severe addiction)	μ-opioid receptor agonist	*see 8EF6 for morphine*	Prodrug of morphine
7	hydrocodone		CNS, pain, cough (caution: severe addiction)	μ-opioid receptor agonist	N/A	Prodrug of hydromorphone
8	benzhydro-codone		CNS, pain, cough (caution: severe addiction)	μ-opioid receptor agonist	N/A	Prodrug of hydromorphone
9	oxycodone (WHO Essential Medicine)		CNS, pain, cough (caution: severe addiction)	μ-opioid receptor agonist	N/A	Prodrug of oxymorphone

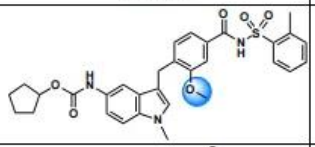
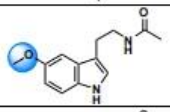
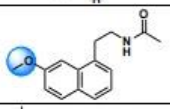
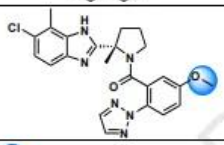
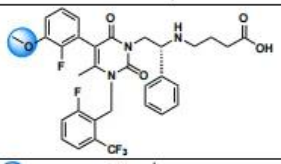
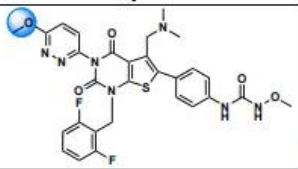
2 针对心血管系统的含甲氧基药物

No.	Drug name	Structure	Use/treatment	MOA	PDB	Role of methoxy
44	bosentan		Cardiovascular, pulmonary arterial hypertension (PAH)	Endothelin ET-A and ET-B receptor antagonist	5XPR	H-bonding, vdW
45	ambrisentan		Cardiovascular, pulmonary arterial hypertension (PAH)	Endothelin ET-A receptor antagonist	N/A	N/A
46	apixaban		Cardiovascular, anticoagulant to prevent stroke in people with nonvalvular atrial fibrillation	Factor Xa antagonist	2P16	vdW, antiparallel dipole–dipole interactions
47	betrixaban		Cardiovascular, anticoagulant	Factor Xa antagonist	N/A	Potency improve-ment and hERG reduction
48	cinepazide		Cardiovascular, acute ischemic stroke	Calcium channel blocker (undefined type)	N/A	N/A
49	lomerizine		Cardiovascular, CNS, migraines	Calcium channel antagonist (L-type and T-type)	N/A	N/A
50	verapamil (WHO Essential Medicine)		Cardiovascular, hypertension, angina, and supraventricular tachycardia	Calcium channel antagonist (L-type)	5KMH (bromo analog), 6JPA (rabbit)	vdW
51	ivabradine		Cardiovascular, heart-related chest pain and heart failure	Pacemaker current inhibitor	N/A	N/A

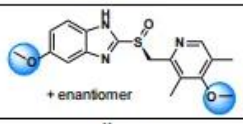
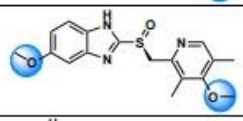
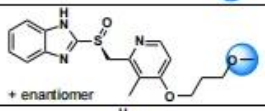
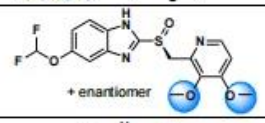
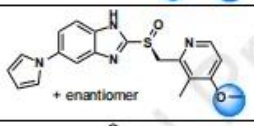
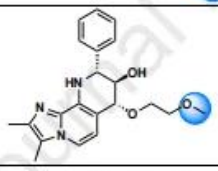
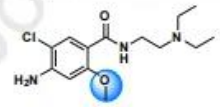
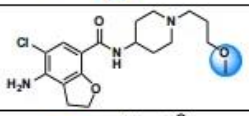
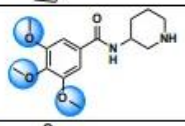
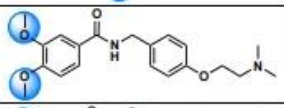
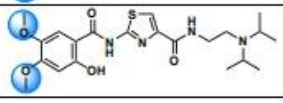
3 针对心血管、肺和泌尿系统的含甲氧基药物

No.	Drug name	Structure	Use/treatment	MOA	PDB	Role of methoxy
71	naftopidil		Urinary, benign prostatic hypertrophy	α_1-Adrenoceptor antagonist	N/A	N/A
72	ranolazine		Cardiovascular, angina; heart-related chest pain	Late sodium current inhibitor	8F6P (rat)	Intramolecular CH···O H-bonding to fix the conformation
73	midodrine		Cardiovascular, vasopressor / *hypotension*, dysautonomia	α_1-Adrenoceptor agonist, prodrug	N/A	N/A
74	sarpogrelate		Cardiovascular, blocks serotonin-induced platelet aggregation	Antagonist at the 5-HT_{2A} and 5-HT_{2B} receptors, prodrug	N/A	N/A
75	carvedilol (WHO Essential Medicine)		Cardiovascular, hypertension, congestive heart failure	Non-selective antagonist of α_1, β_1, and β_2 adrenoceptor	4AMJ (turkey)	vdW, H-bonding to stabilized water, CH···O H-bonding
76	amosulalol		Cardiovascular, hypertension	α_1/β_1 Adrenoceptor dual antagonist	*See carve-dilol (75)*	*See carvedilol (75)*
77	tamsulosin		Urinary, benign prostatic hyperplasia	α_{1a}/β_{1a} Adrenoceptor dual antagonist	N/A	N/A
78	formoterol		Respiratory, asthma, chronic obstructive pulmonary disease	Long-acting β_2 adrenoreceptor agonist	6IBL (turkey)	vdW
79	arformoterol		Respiratory, broncho-constriction, chronic obstructive pulmonary disease	Long-acting β_2 adrenoreceptor agonist	*See formo-terol (78)*	*See formoterol (78)*
80	olodaterol		Respiratory, broncho-constriction, obstructive pulmonary disease	Ultra-long-acting β_2 adreno-receptor agonist	N/A	Increases selectivity for β_2 vs β_1 adreno-receptor

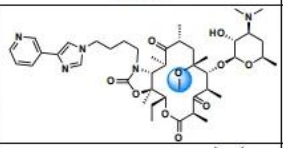
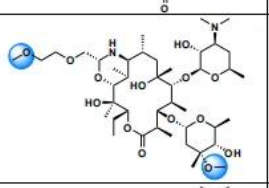
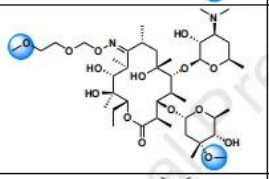
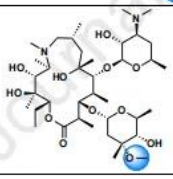
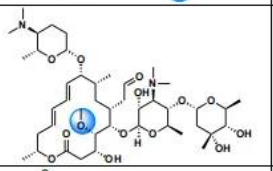
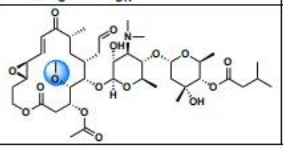
4 针对内分泌系统的含甲氧基的药物

No.	Drug name	Structure	Use/treatment	MOA	PDB	Role of methoxy
81	zafirlukast		Endocrine, respiratory, asthma	Leukotriene C_4 / D_4 / E_4 antagonist	6RZ5	vdW
82	melatonin		Endocrine, sleep disorder, circadian rhythm	MT_1 / MT_2 agonist	*See 7VGY (iodo-melatonin)*	vdW
83	agomelatine		Endocrine, sleep disorder, major depressive disorder	MT_1 / MT_2 agonist and 5-HT_{2c} antagonist	6ME5	H-bonding, vdW, parallel CH–π interactions
84	darido-rexant		Endocrine, insomnia	OX_1 / OX_2 antagonist	6TP3	vdW, π–π stacking, CH···O H-bonding
85	carbetocin (WHO Essential Medicine)		Uterotonic drug used for postpartum bleeding	Peripheral oxytocin receptor agonist	N/A	Mimics the hydroxy group in oxytocin (replaces the tyrosine OH group)
86	elagolix		Endocrine (hormonal) therapy, endometriosis-associated pain	GnRH antagonist	N/A	N/A
87	relugolix		Endocrine (hormonal) therapy, uterine fibroids, endometriosis-associated pain, and prostate cancer	GnRH antagonist	N/A	Improvement in antagonistic activity especially in the presence of serum

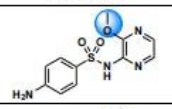
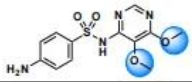
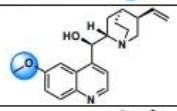
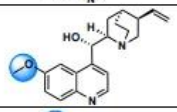
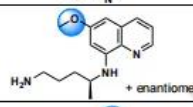
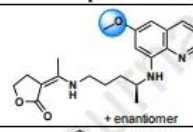
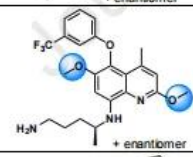
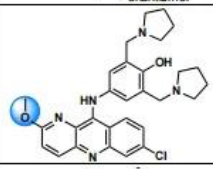
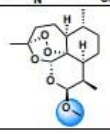
5 针对胃肠道系统的含甲氧基的药物

No.	Drug name	Structure	Use/treatment	MOA	PDB	Role of methoxy
97	omeprazole (WHO Essential Medicine)		Gastrointestinal, gastroesophageal reflux disease (GERD), peptic ulcer disease	Proton pump inhibitor (H^+ K^+ ATPase inhibitor)	N/A	EDG on pyridine to start reaction cascade
98	esomeprazole		Gastrointestinal, gastroesophageal reflux disease (GERD), peptic ulcer disease	Proton pump inhibitor (H^+ K^+ ATPase inhibitor)	N/A	EDG on pyridine to start reaction cascade
99	rabeprazole		Gastrointestinal, gastroesophageal reflux disease (GERD), peptic ulcer disease	Proton pump inhibitor (H^+ K^+ ATPase inhibitor)	N/A	Capping group for alkoxy linker
100	pantoprazole		Gastrointestinal, gastroesophageal reflux disease (GERD), peptic ulcer disease	Proton pump inhibitor (H^+ K^+ ATPase inhibitor)	N/A	EDG on pyridine to start reaction cascade
101	ilaprazole		Gastrointestinal, gastroesophageal reflux disease (GERD), peptic ulcer disease	Proton pump inhibitor (H^+ K^+ ATPase inhibitor)	N/A	EDG on pyridine to start reaction cascade
102	soraprazan		Gastrointestinal, gastroesophageal reflux disease (GERD)	Proton pump inhibitor (H^+ K^+ ATPase inhibitor)	7W49	vdW
103	metoclopramide (WHO essential medicine)		Gastrointestinal, gastroesophageal reflux disease, nausea	dopamine D_2 and 5-HT_3 antagonist, 5-HT_4 agonist	N/A	N/A
104	prucalopride		Gastrointestinal, treats chronic constipation	5-HT_4 receptor agonist	N/A	N/A
105	troxipide		Gastrointestinal, GERD, gastric cytoprotective agent	N/A	N/A	N/A
106	itopride		Gastrointestinal, dyspepsia	AChE inhibitor, dopamine D_2 receptor antagonist	N/A	N/A
107	acotiamide		Gastrointestinal, dyspepsia	AChE inhibitor, M_1 and M_2 antagonist	N/A	N/A

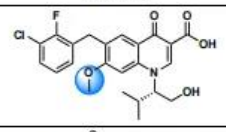
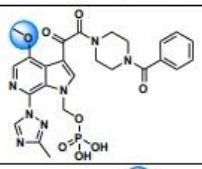
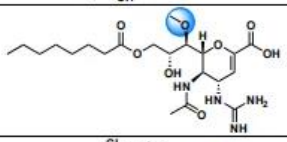
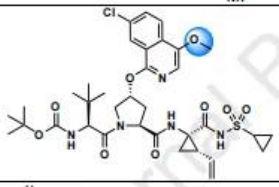
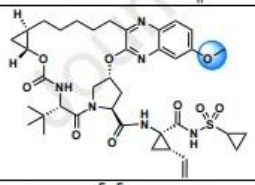
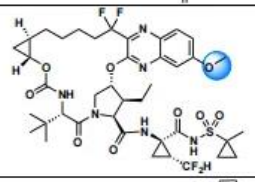
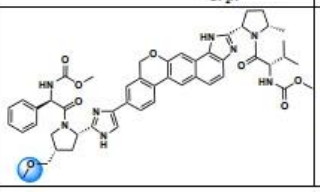
6 含甲氧基的抗菌药

No.	Drug name	Structure	Use/treatment	MOA	PDB	Role of methoxy
124	telithromycin		Bacterial infections, community acquired pneumonia	Prodrug of an erythro-mycin derivative	1YIJ	vdW, intra-molecular H-bonding, removes the acid lability of erythro-mycin (hemiketal formation)
125	dirithromycin		Bacterial infections	Prodrug of an erythro-mycin derivative	6OF1, 6XZA, 6XZB, 6XZ7	vdW, intra-molecular H-bonding, improves permeability
126	roxithro-mycin		Bacterial infections, treats respiratory tract, urinary and soft tissue infections	Prodrug of an erythro-mycin derivative	1JZZ	vdW, intra-molecular H-bonding, improves permeability
127	azithromycin (WHO essential medicine)		Bacterial infections, middle ear infections, strep throat, pneumonia, traveler's diarrhea	An aza-homolog version of erythro-mycin (**121**)	1YHQ, 1M1K	vdW, intra-molecular H-bonding
128	spiramycin		Bacterial infections	Binds to the bacterial ribosomal subunit, inhibiting protein synthesis	1KD1	vdW
129	carbomycin		Bacterial infections	Binds to the bacterial ribosomal subunit, inhibiting protein synthesis	1K8A	vdW

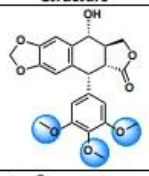
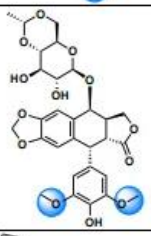
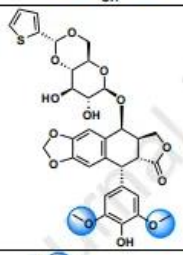
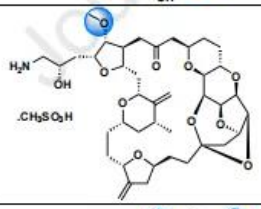
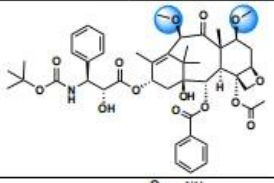
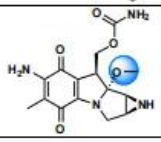
7 含甲氧基的抗菌药和抗疟药

No.	Drug name	Structure	Use/ treatment	MOA	PDB	Role of methoxy
143	sulfalene		Infection, antibiotic, urinary tract infections, malaria (as a combination drug)	DHPS inhibitor, interfering with bacterial DNA synthesis	N/A	Likely modulates the sulfonamide pK_a
144	sulfadoxine (WHO Essential Medicine)		Infection, antibiotic, malaria (as a combination drug with pyrimethamine)	DHPS inhibitor, interfering with bacterial DNA synthesis	N/A	Likely modulates the sulfonamide pK_a
145	quinine (WHO Essential Medicine)		Malaria	Increasing digestive vacuole pH, binds to purine nucleoside phosphorylase	5ZNC	vdW, likely modulates the quinoline pK_a
146	quinidine		Cardiac, heart rhythm disturbances	Modulates Na_v 1.5	6LQA	vdW
147	primaquine (WHO Essential Medicine)		Malaria, *Pneumocystis* pneumonia	Possibly generates toxic oxygen species	4FGJ	π–π stacking
148	bulaquine		Malaria, *Pneumocystis* pneumonia	Prodrug of primaquine (**147**)	N/A	N/A
149	tafenoquine		Malaria, recurring malaria, *Plasmodium vivax*	N/A	N/A	N/A
150	pyronaridine		Malaria, *Plasmodium falciparum*	N/A	N/A	N/A
151	artemether (WHO Essential Medicine, Nobel Prize in Medicine 2015)		Malaria, *Plasmodium falciparum*	Prodrug of dihydro-artemisinin	N/A	Methyl ketal prodrug that protects the hemiketal

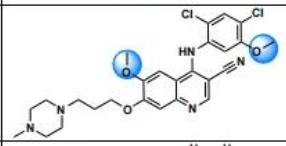
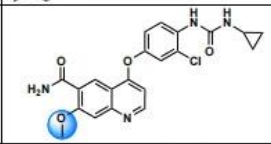
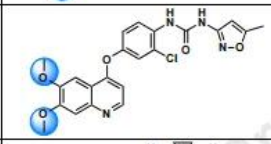
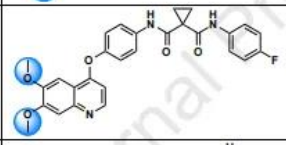
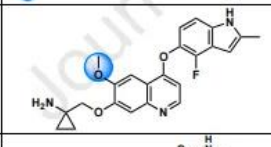
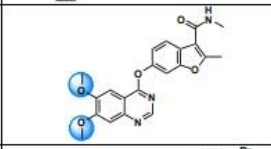
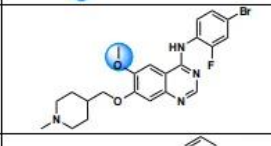
8 含甲氧基的抗病毒药物

No.	Drug name	Structure	Use/treatment	MOA	PDB	Role of methoxy
152	elvitegravir		Viral infection, HIV	Integrase inhibitor	3L2W	π–π stacking, enhances quinolone carbonyl electron density
153	fostemsavir		Viral infection, HIV	HIV entry inhibitor, a prodrug of temsavir	5U7O	Potency enhancement, vdW, electron-electron repulsion leading to orthogonal conformation
154	laninamivir octanoate		Viral infection, treatment/prophylaxis of influenza virus A/B	Neuraminidase inhibitor	4HZW	vdW
155	asunaprevir		Viral infection, hepatitis C	Hepatitis C virus NS3 protease inhibitor	4NWL	vdW, CH···O H-bonding
156	grazoprevir		Viral infection, hepatitis C	Hepatitis C virus NS3/4A protease inhibitor	3SUD (WT), 3SUE (R155K), 3SUF (D168A), 3SUG (A156T), 6C2M (Y56H)	vdW, H-bonding in some mutated variants
157	voxilaprevir		Viral infection, hepatitis C	Hepatitis C virus NS3/4A protease inhibitor	6NZT	vdW
158	velpatasvir		Viral infections, hepatitis C	Hepatitis C virus NS5A phosphoprotein inhibitor	N/A	Significantly improves oral bioavailabilty

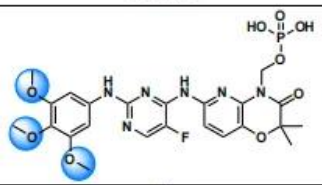
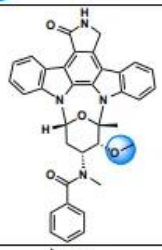
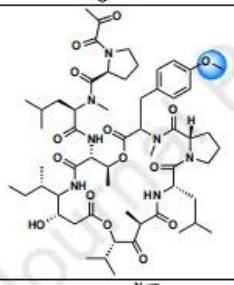
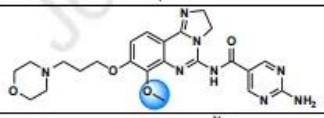
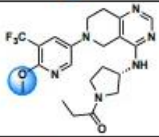
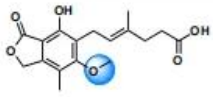
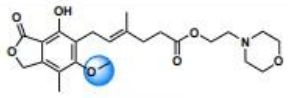
9 源自天然产品的含甲氧基抗感染和抗癌药物

No.	Drug name	Structure	Use/treatment	MOA	PDB	Role of methoxy
166	podophyllo-toxin (WHO Essential Medicine)		Infection, topical cream that is used to treat genital warts and molluscum contagiosum	Inhibits tubulin polymeri-zation and DNA topoiso-merase II	1SA1	vdW, CH···O H-bonding
167	etoposide (WHO Essential Medicine)		Cancer, non-small cell lung cancer, ovarian cancer, lymphoma	DNA topoiso-merase II inhibitor	3QX3, 5GWK	vdW, H-bonding
168	teniposide		Cancer, acute lymphocytic leukemia	DNA topoiso-merase II inhibitor	*See etopo side (167)*	*See etoposide (167)*
169	eribulin mesylate		Cancer, breast cancer, liposarcoma	Inhibits tubulin polymeri-zation, leading to cell cycle arrest	5JH7	vdW
170	cabazitaxel		Cancer, metastatic castration-resistant prostate cancer	Promotes microtubule stabilization, leading to cell cycle arrest	N/A	The OH groups are a P-gp recognition unit, but the methyl caps allow the evasion of the paclitaxel resistance mechanism of some cancer cells
171	mitomycin C		Cancer, breast cancer, resected gastric cancer	Intercalates into DNA and covalently binds to DNA to inhibit DNA synthesis	199D (solu-tion struct ure)	The methyl on the hydroxy unit confers chemical stability against epimerization; methoxy is a leaving group

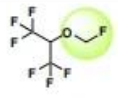
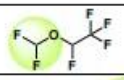
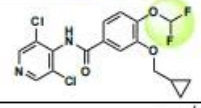
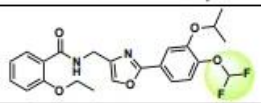
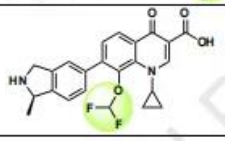
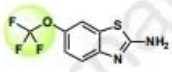
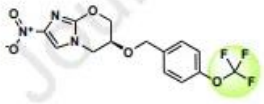
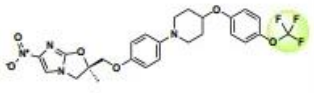
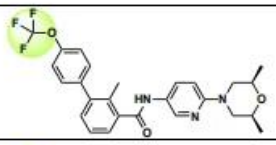
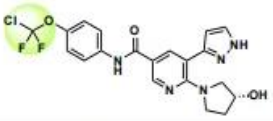
10 含甲氧基的激酶靶向抗癌药物

No.	Drug name	Structure	Use/ treatment	MOA	PDB	Role of methoxy
185	bosutinib		Cancer, leukemia	Inhibitor of non-receptor tyrosine kinases BCR-ABL1 and SRC	3UE4, 4MXO	vdW, CH···O H-bonding
186	lenvatinib		Cancer, thyroid cancer	Inhibitor of receptor tyrosine kinases VEGFRs, FGFRs, RET, KIT, and PDGFR-α	3WZD, 5ZV2	vdW
187	tivozanib		Cancer, renal cell carcinoma (RCC)	Inhibitor of receptor tyrosine kinases VEGFRs, KIT, and PDGFR	4ASE	vdW
188	cabozantinib		Cancer, thyroid cancer, hepatocellular cancer, and renal cell carcinoma (RCC)	Inhibitor of receptor tyrosine kinases MET, AXL, VEGFR2, FLT-3, RET, and KIT	N/A	N/A
189	anlotinib		Cancer, non-small-cell lung cancer	Inhibitor of receptor tyrosine kinases VEGFR, FGFR, PDGFR, and KIT	N/A	N/A
190	fruquintinib		Cancer, colorectal cancer	Inhibitor of receptor tyrosine kinases VEGFR	N/A	N/A
191	vandetanib		Cancer, thyroid cancer	Inhibitor of receptor tyrosine kinases VEGFR and EGFR	N/A	N/A
192	erlotinib (WHO Essential Medicine)		Cancer, non-small cell lung cancer (NSCLC) and pancreatic cancer	Inhibitor of receptor tyrosine kinases EGFR	1M17, 4HJO	vdW

11 含甲氧基的抗癌药和免疫抑制剂

No.	Drug name	Structure	Use/treatment	MOA	PDB	Role of methoxy
208	fostamatinib		Immunology, rheumatoid arthritis, immune thrombo-cytopenia	Inhibitor of non-receptor tyrosine kinase SYK	N/A	N/A
209	midostaurin		Cancer, acute myeloid leukemia, advanced/aggressive systemic mastocytosis	Inhibitor of receptor tyrosine kinases PKC, FLT3, KIT, PDGF, and VEGF	N/A	N/A
210	plitidepsin		Cancer, multiple myeloma	Inhibitor of receptor tyrosine kinases VEGF, and modulator of elongation factor 1 alpha 2 modulator	N/A	N/A
211	copanlisib		Cancer, lymphoma follicular lymphoma	Inhibitor of phospho-inositide 3-kinase (PI3K)	5G2N	vdW
212	leniolisib		Autoimmune diseases, activated PI3K delta syndrome (APDS)	Inhibitor of phospho-inositide 3-kinase (PI3K)	5O83	vdW
213	myco-phenolic acid		Immuno-suppressant to prevent rejection following organ transplantation	Inhibitor of inosine monophos-phate dehydro-genase	1JR1	vdW, H-bonding, EDG to carbonyl
214	myco-phenolate mofetil		Immuno-suppressant for autoimmune conditions (Crohn's disease and lupus)	Prodrug of mycophenolic acid (213)	*See myco-phenolic acid (213)*	*See myco-phenolic acid (213)*

12 所有疾病类型中的含氟甲氧基药物

No.	Drug name	Structure	Use/treatment	MOA	PDB	Role of fluoro-methoxy
236	sevoflurane		CNS, anesthesia	Reduces systemic vascular resistance, lowers blood pressure	N/A	Helps reduce volatility
237	desflurane		CNS, anesthesia	Reduces gap junctional con-ductance	N/A	Helps reduce volatility
238	roflumilast		Inflammatory, respiratory, COPD	Inhibitor of phospho-diesterase 4 (PDE4)	1XMU, 1XOQ, 3G4L	H-bonding, vdW, CH···O H-bonding
239	difamilast		Inflammatory, dermatologic, atopic dermatitis	Inhibitor of phospho-diesterase 4 (PDE4)	N/A	N/A
240	garenoxacin		Bacterial infections, Gram-positive and Gram-negative bacterial infections	DNA gyrase inhibitor, topo-isomerase IV inhibitor	*See moxi-floxacin (116)*	*See moxi-floxacin (116)*
241	riluzole		CNS, amyotrophic lateral sclerosis (ALS)	Might be inhibiting the release of glutamic acid from cultured neurons	7WDB, 7BNJ, 5V02	H-bonding (from fluorine atom), vdW
242	pretomanid		Bacterial infections, multi-drug-resistant tuberculosis	Inhibits bacterial cell wall synthesis by blocking ketomycolic acid production	N/A	N/A
243	delamanid		Bacterial infections, multi-drug-resistant tuberculosis	Inhibits bacterial cell wall synthesis by blocking ketomycolic acid production	N/A	N/A
242	sonidegib		Cancer, basal cell carcinoma	Inhibitor of the hedgehog signaling pathway	N/A	N/A
243	Asciminib		Cancer, Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML)	Allosteric protein kinase inhibitor, BCR-ABL1 inhibitor	5MO4	Halogen bonding (from Cl), vdW
100	pantoprazole	*See gastrointestinal section*	Gastrointestinal			