Indoles in Drug Discovery

Key Points

- Serve as a hydrogen bond donor to the target protein
- Offer π–π stacking or cation–π stacking with the target protein
- Majority of marketed indole - containing drugs as kinase inhibitors

Overview

The key interactions that the indole nucleus in a drug include NH serving as a hydrogen bond donor and π–π stacking or cation–π stacking with the target protein. The indole motif is a privileged fragment in drug discovery, boasting more than 17 marketed indole-containing drugs, with the majority of them as kinase inhibitors. In particular, amino- and diamino-indole fragments are especially prevalent.

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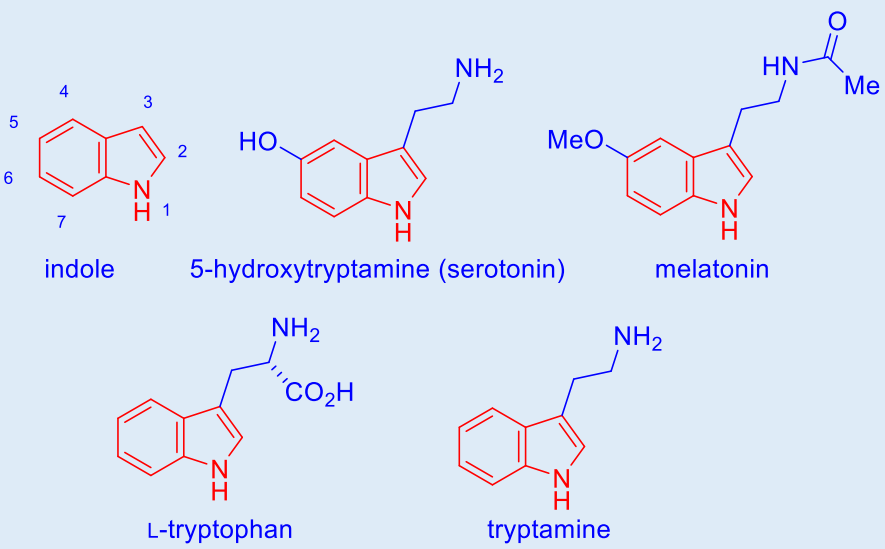
The most prominent feature of the molecule indole is its NH group. Since the lone pair of electrons on the nitrogen atom take part in maintaining indole's aromaticity, the NH is acidic (pK_a ~ 17) and often serves as a hydrogen bond donor to the target protein. In terms of ligand–protein interactions, the indole fragment of a drug may offer π–π stacking or cation–π stacking with the target protein.

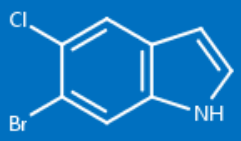
Indole embodies a myriad of natural products and pharmaceutical agents. In the human body, endogenous serotonin, 5-hydroxytryptamine (5-HT), is a monoamine neurotransmitter primarily found in the gastrointestinal tract (GIT) and central nervous system (CNS). It modulates vasoconstriction and many brain activities by binding to the serotonin receptors 5HT1–7. Another indole-containing endogenous ligand, melatonin, regulates circadian rhythms, most noticeably, sleep. In addition, indole-containing tryptamine is closely related to melatonin and the amino acid tryptophan.



Indole-containing Drugs

In addition to the hundreds of well-known indole plant alkaloids (e.g., yohimbine, reserpine, strychnine, ellipticine, lysergic acid, physostigmine, etc.), the indole ring is present in dozens of the FDA-approved drugs. The central importance of indole derivatives such as serotonin and tryptophan in living organisms has inspired medicinal chemists to design and synthesize thousands of indole-containing pharmaceuticals.

PharmaBlock Products



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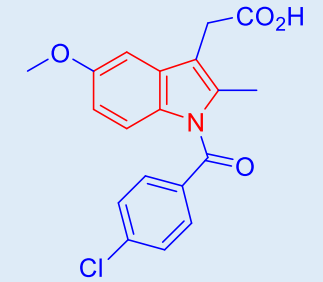
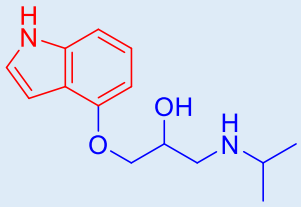
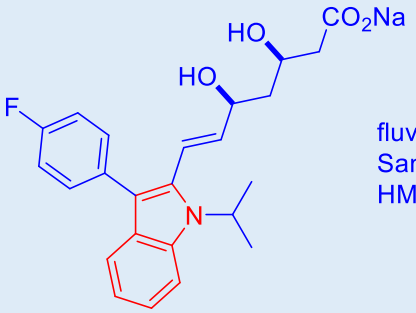
One of the early drugs containing an indole ring is Merck′s indomethacin (Indocin, **1**), a nonsteroidal anti-inflammatory drug (NSAID). Another early indole-containing drug was Sandoz′s nonselective β-blocker pindolol (Visken, **2**). Among over 20 β-blockers on the market, "me-too" drug pindolol (**2**) has the same pharmacophore as rest of them but its indole moiety provided Sandoz with novel intellectual properties (IP). Also by Sandoz, fluvastatin sodium (Lescol, **3**) is an HMG-CoA reductase inhibitor (a statin) for lowering cholesterol.



indomethacin (Indocin, **1**)
Merck, 1964
NSAID



pindolol (Visken, **2**)
Sandoz, 1977
non-selective β-blocker



fluvastatin (Lescol, **3**)
Sandoz, 1984
HMG-CoA reductase inhibitor

A class of indole-containing "triptans" are serotonin receptors 5-HT_{1B} and 5-HT_{1D} dual agonists used to treat migraines. The prototype was Glaxo′s sumatriptan (Imitrex, **4**). Following sumatriptan (**4**)′s clinical and commercial success, three "me-too" indole-containing triptan anti-migraine drugs were put on the market. They are naratriptan (Amerge, **5**), zolmitriptan (Zomig, **6**), and rizatriptan (Maxalt, **7**).

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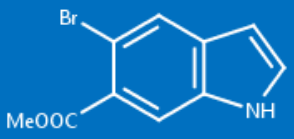

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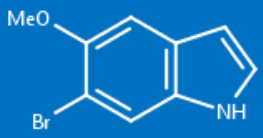

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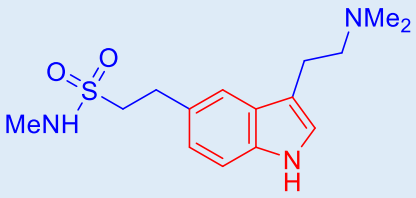
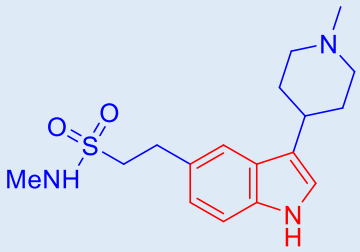
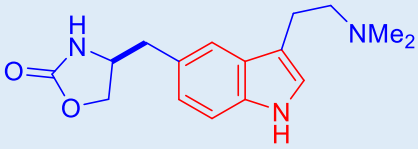


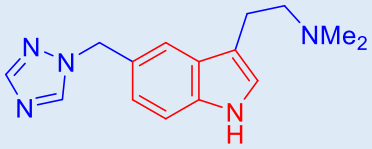
sumatriptan (Imitrex, **4**)
Glaxo, 1991
$5HT_{1D}$ and $5HT_{1B}$ agonist



naratriptan (Naramig, **5**)
GSK, 1997
$5HT_{1D}$ and $5HT_{1B}$ agonist



zolmitriptan (Zomig, **6**)
AstraZeneca, 1997
$5HT_{1D}$ and $5HT_{1B}$ agonist



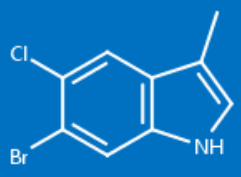
rizatriptan (Maxalt, **7**)
Merck, 1998
$5HT_{1D}$ and $5HT_{1B}$ agonist

Furthermore, Pfizer's zafirlukast (Accolate, **8**) is indicated for the treatment of mild-to-moderate asthma and chronic obstructive pulmonary disease (COPD). It is a selective and competitive antagonist of cysteinyl leukotriene-receptors (LTC_4, LTD_4, and LTE_4, LTRA). Meanwhile, Pfizer's delavirdine (Rescriptor, **9**) is a non-nucleotide reverse transcriptase inhibitor (NNRTI) for the treatment of HIV-positive patients.

Antiemetics ramosetron (Nasea, **10**) and dolasetron (Anzemet, **11**) are potent and highly selective 5-HT_3 receptor antagonists for the treatment of chemotherapy-induced nausea and vomiting.

Indole-containing vilazodone (Viibryd, **12**) bears some structural resemblance to antipsychotic drug ziprasidone (Geodon, a D_2 receptor antagonist). But in reality, it is a selective serotonin reuptake inhibitor (SSRI) and a $5TH_{1A}$ agonist in terms of its mechanism of action (MOA). On the other hand, Novartis' panobinostat (Farydak, **13**) is a histone deacetylase (HDAC) inhibitor. While its hydroxamic acid motif is the pharmacophore/warhead bound to the catalytic zinc of HDAC, its indole fragment largely serves as a space-filler.

PharmaBlock Products



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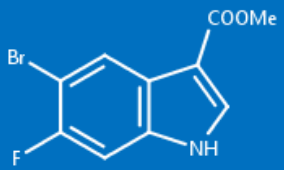

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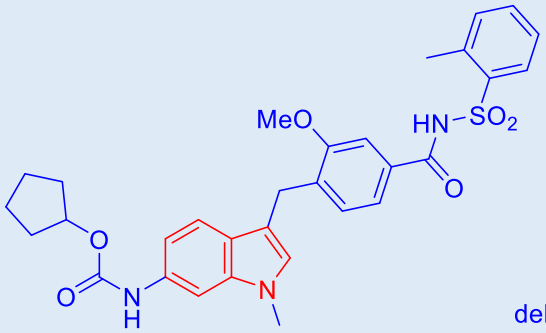
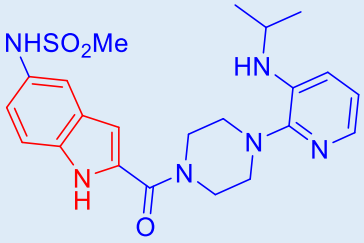
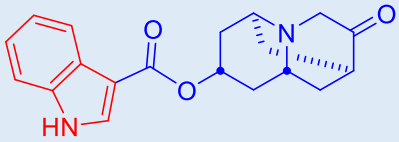


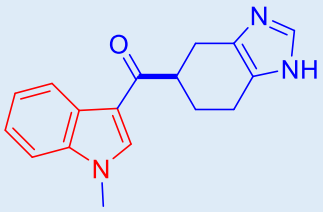
zafirlukast (Accolate, **8**)
Pfizer, 1997
LTRA



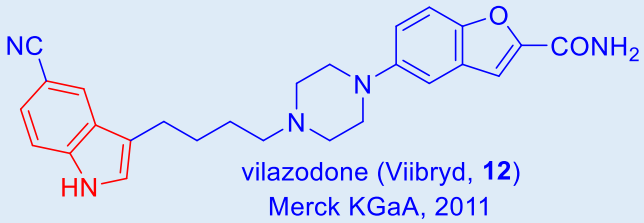
delavirdine (Rescriptor, **9**)
Pfizer, 1997
NNRTI



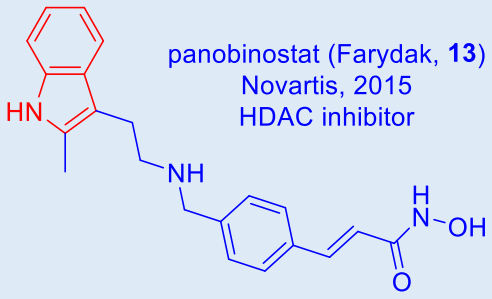
dolasetron (Anzemet, **10**)
Pfizer, 2002
5-HT_3 antagonist



ramosetron (Irribow, **11**)
Astellas, 2008
5-HT_3 antagonist



vilazodone (Viibryd, **12**)
Merck KGaA, 2011
SSRI and $5TH_{1A}$ agonist



panobinostat (Farydak, **13**)
Novartis, 2015
HDAC inhibitor

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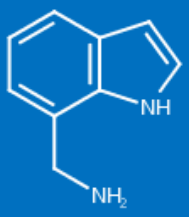

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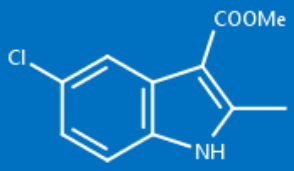

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Epidermal growth factor receptor (EGFR) inhibitors are among the earliest kinase inhibitors on the market. But resistance invariably developed and covalent inhibitors have been invented to combat the L858R and, more significantly, T790M mutations. AstraZeneca′s third generation EGFR inhibitor osimertinib (Tagrisso, **14**) is a covalent inhibitor expressly designed to overcome the T790M mutation by taking advantage of Cys-797 at EGFR′s active site. It has been shown to have the efficacy and safety to treat patients with T790M-positive EGFR-TKI resistant non-small cell lung cancer (NSCLC). In addition, Clovis′ selective poly (ADP-ribosyl) polymerase-1 (PARP-1) inhibitor rucaparib (Rubraca, **15**) contains a unique tricyclic indole core structure.

Vertex has made great strides in the field of cystic fibrosis (CF) medicines. Its tezacaftor (**16**, Symdeko when combined with ivacaftor) helps move the cystic fibrosis transmembrane conductance regulator (CFTR) protein to the correct position on the cell surface and is designed to treat people with the F508del mutation. Finally, the latest approval of an indole-containing drug by the FDA is BMS′ beclabuvir (Ximency, **17**), a hepatitis C virus non-structural protein 5B (HCV NS5B, a RNA-dependent RNA polymerase, RdRp) inhibitor for the treatment of HCV infection. It has an interesting octacyclic indole core structure.

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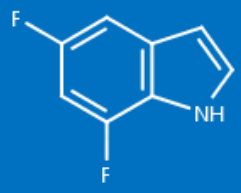

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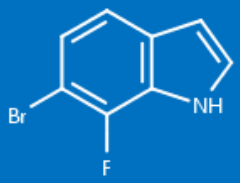

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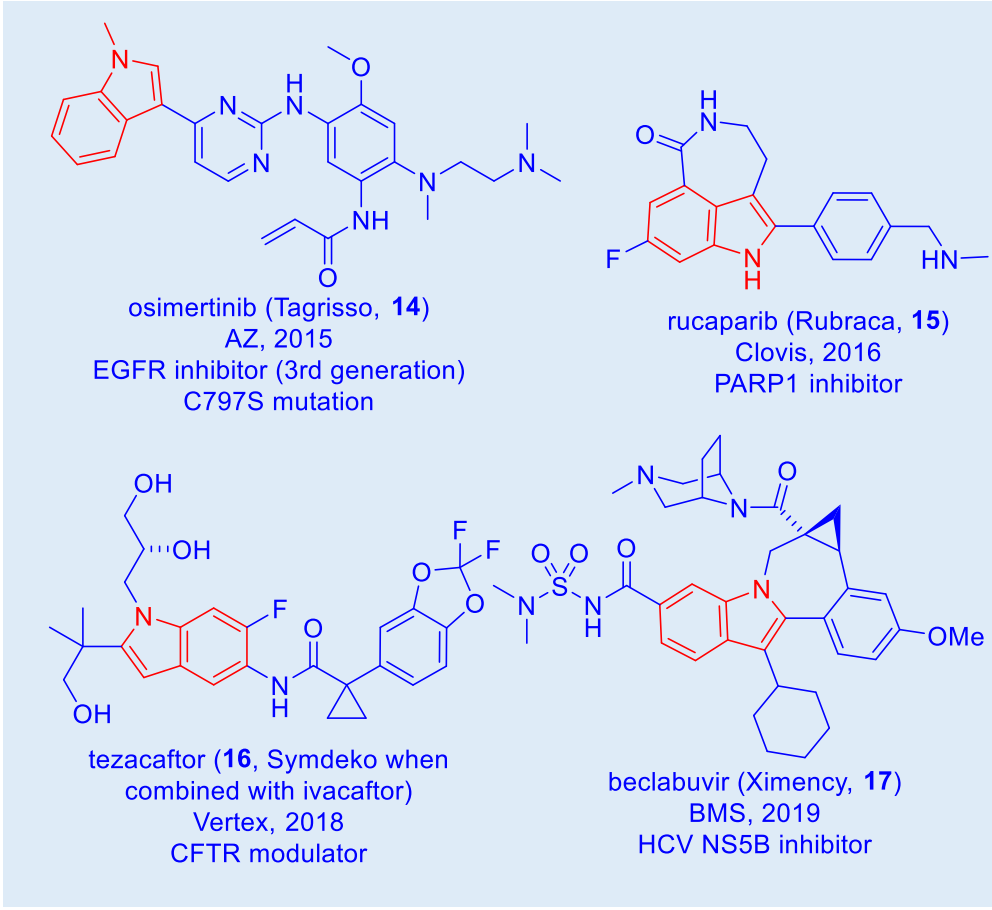

Indoles in Drug Discovery

Indole derivatives are ubiquitous in drug discovery. Rather than covering them exhaustively, only several representative bioisostere examples and potential safety liabilities of drugs containing 3-methylindole moiety are reviewed here for brevity.

1. Representative Bioisosteres

The NH group on indole often functions as a hydrogen bond donor with the drug target protein. Absence of the NH group often weakens the binding affinity exponentially. For instance, indole gloxylylamine **18** is a partial agonist of the benzodiazepine receptor with a reasonably good binding affinity (K_i = 85 nM). Isosteric replacement of the indole nucleus with benzothiophene led to compound **19**, which saw a 40-fold decrease of binding affinity toward the benzodiazepine receptor (K_i = 3.37 μM).[1]

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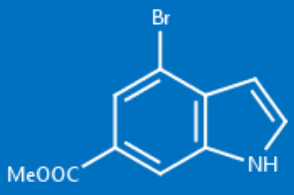

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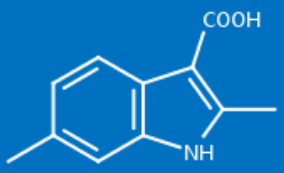

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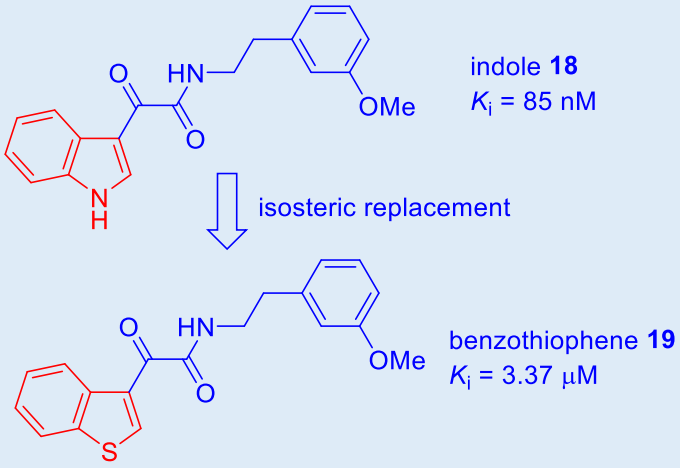
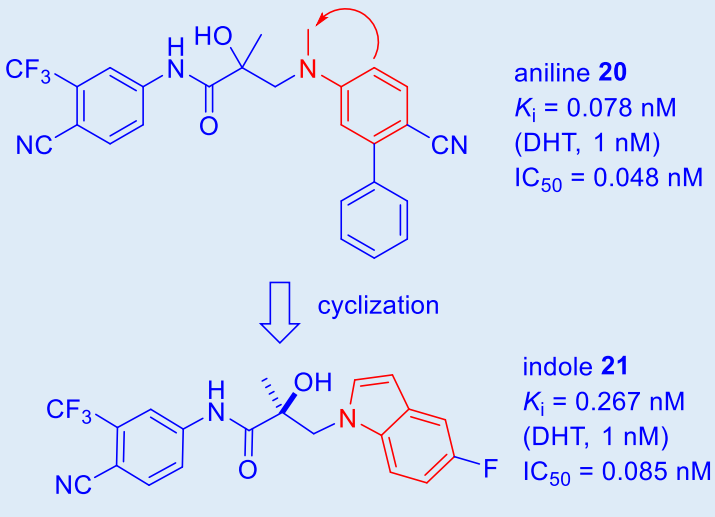


The perils of anilines have been well known as they are frequently oxidized by CYP450 *in vivo* to the corresponding iminoquinones as reactive metabolites. In contrast, the corresponding indole analogs are more benign.

Tertiary aniline **20** is a selective androgen receptor degrader (SARD) but suffered from poor metabolic stability thus lacking *in vivo* activity when administered orally. Fusion of the tertiary aniline of **20** into the B-ring led to a series of indole derivatives, as represented by **21**, that retained both the AR inhibition and SARD activities with very high potency but also with improved ligand efficiency and *in vitro* stability. Interestingly, even though the enantiomer of indole **21** had a very low binding affinity for AR (K_i >10 μM), it demonstrated comparably high SARD activities, possibly because it works as a proteolysis-targeting chimera (PROTAC).[2]



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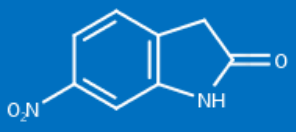

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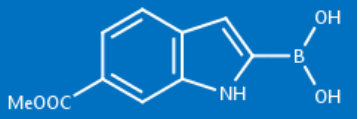
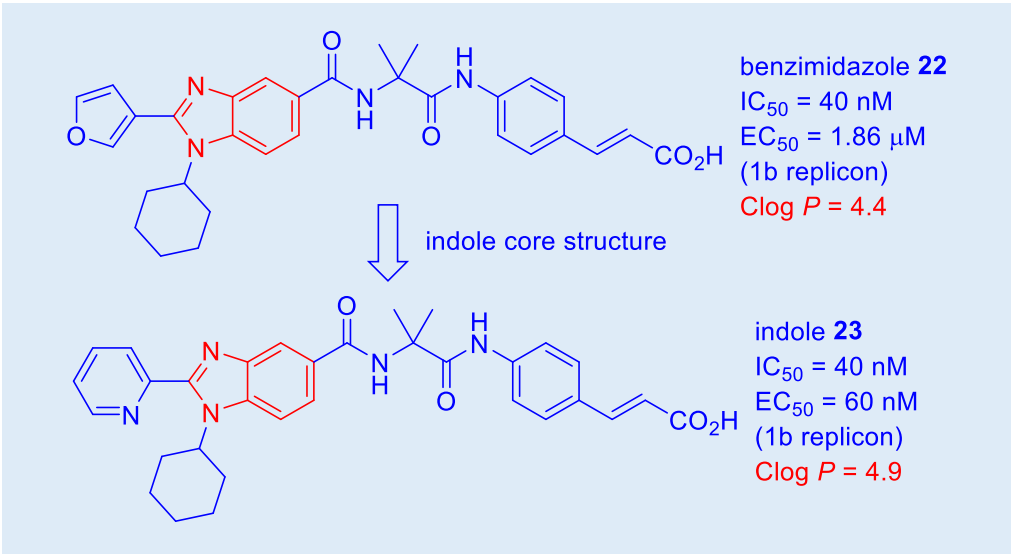


PBEB10593

Inhibition of HCV NS5B has been proven to be a fruitful MOA for treating HCV infection. Validation came when the FDA approved Gilead/PharmaTech's sofosbuvir (Sovaldi) in 2013. It quickly became a blockbuster drug and has contributed to the process of curing HCV.

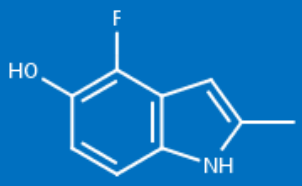
Benzimidazole-5-carboxamide **22** is a potent *allosteric* HCV NS5B inhibitor, binding to the polymerase's thumb pocket 1 finger loop. Although it has high intrinsic potency against polymerase (IC_{50} = 40 nM), its cell-based sub-genomic 1b replicon activity is low (EC_{50} = 1.86 μM). Replacement of the benzimidazole core of **22** (Clog *P* = 4.4) with more lipophilic indole-5-carboxamide analogs led to a series of inhibitors with up to 30-fold improvements in cell-based sub-genomic GT1b replicon assay. Optimization of C-2 substitution on the indole core led to the identification of analogs such as indole-5-carboxamide **23** (Clog *P* = 4.9) with EC_{50} of 60 nM (GT1b replicon). Furthermore, they showed improved pharmacokinetic properties as well.[3]



2.Possible Liabilities of Drugs Containing 3-Methylindole

The indole-ring system exists in a plethora of endogenous amino acids, neurotransmitters, and drugs. The metabolic 2,3-oxidation of the indole ring by CYP450 takes place from time to time (by indole oxygenase, IDO), but its correlation to *in vivo* toxicity is not often observed.

PharmaBlock Products



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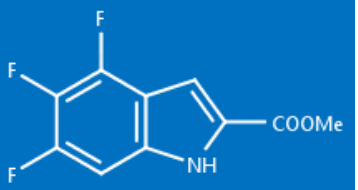
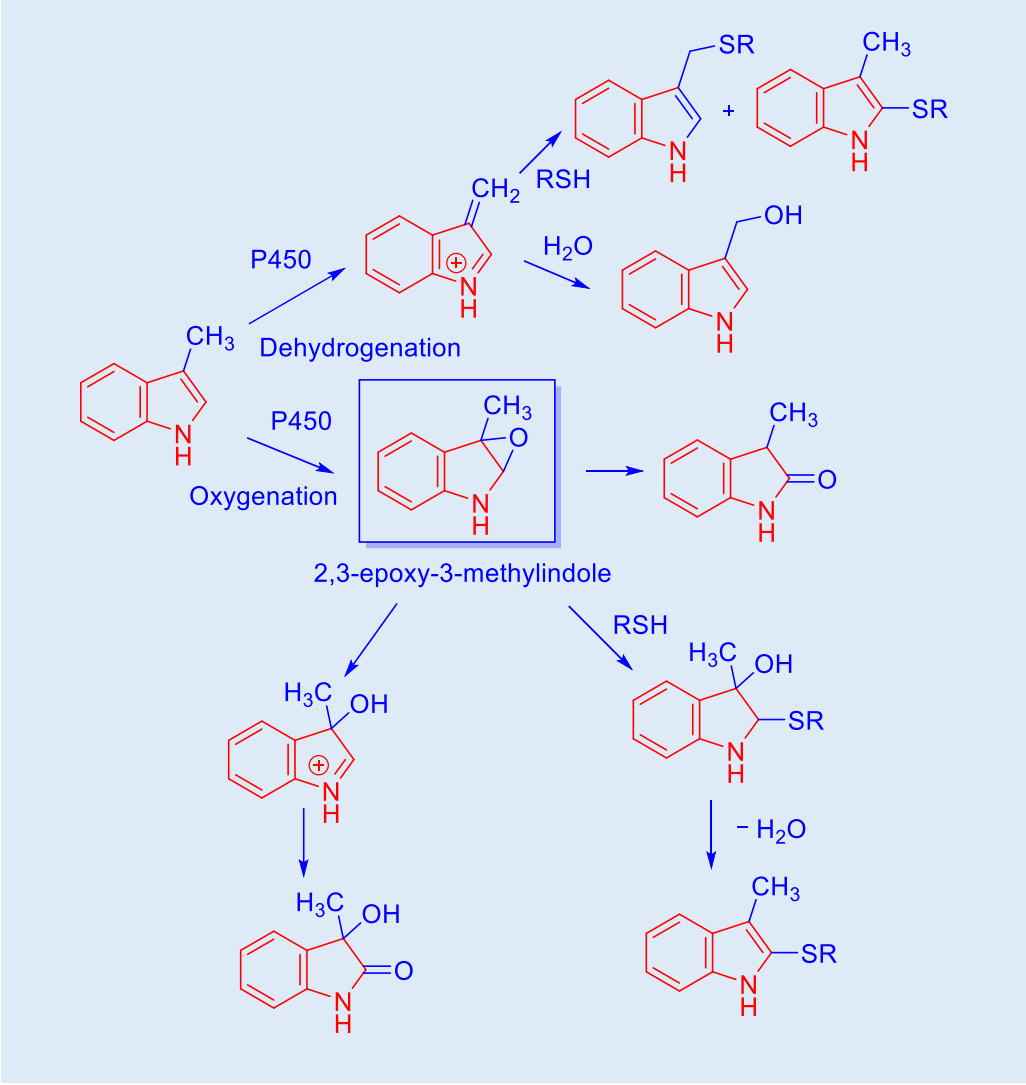


PBU2065

3-Methylindole, unfortunately, has been associated with higher risk of adverse outcomes, namely, pneumotoxin in animals. Evidence was found to support the formation of 2,3-epoxy-3-methylindoline by IDO as a reactive intermediate of the pneumotoxin 3-methylindole.[4] 3-Methylindole has been shown to form adducts with glutathione (GSH), proteins, and DNA using *in vitro* preparations.[5]

The CYP450-mediated bioactivation of 3-methylindole may be summarized here: Oxidation of the 3-methyl group occurs either directly via deoxygenation or via epoxidation of the 2,3-double bond leading to 2,3-epoxy-3-methylindole, the reactive intermediate that can be trapped by endogenous nucleophiles, such as GSH. The presence of a leaving group on the C3-methyl increases the likelihood of formation of electrophilic reactive intermediates.



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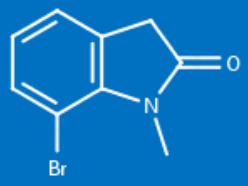

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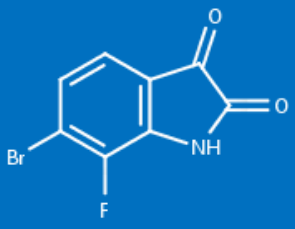
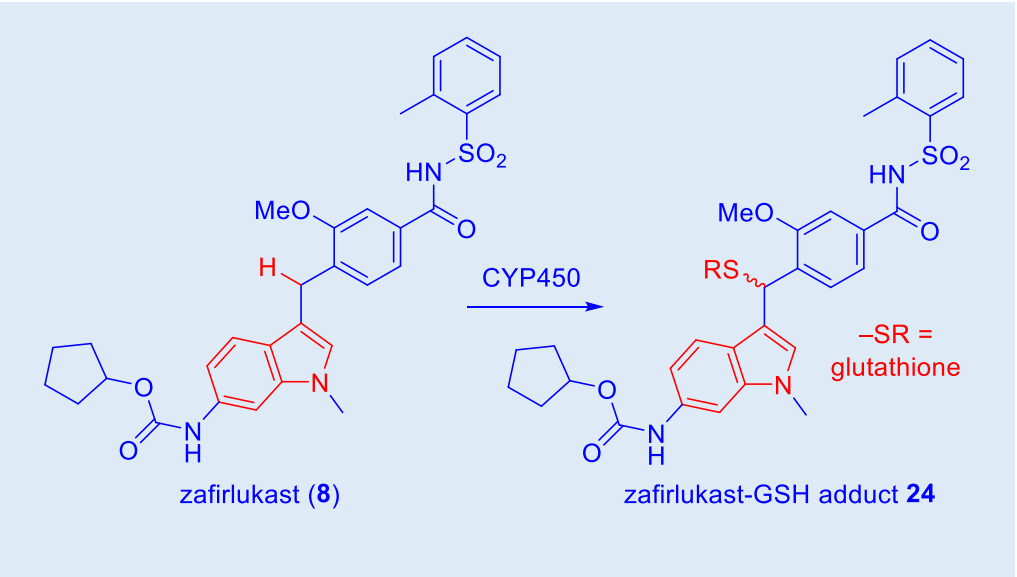


PBZX1432

Zafirlukast (**8**) has been associated with occasional idiosyncratic hepatotoxicity. Structurally, zafirlukast (**8**) is similar to 3-methylindole because it contains an *N*-methylindole moiety that has a 3-alkyl substituent on the indole ring. The results presented here describe the metabolic activation of zafirlukast (**8**) via a similar mechanism to that described for 3-methylindole. NADP(H)-dependent biotransformation of zafirlukast (**8**) by hepatic microsomes from rats and humans afforded a reactive metabolite, which was detected as its GSH adduct **24**.[6] The formation of this reactive metabolite in human liver microsomes (HLM) was shown to be exclusively catalyzed by CYP3A enzymes. Evidence for *in vivo* metabolic activation of zafirlukast (**8**) was obtained when the same GSH adduct **24** was detected in bile of rats given an *i.v.* or oral dose of the drug.

The observation of *in vitro* metabolic activation of the 3-benzylindole moiety in zafirlukast (**8**) to give the glutathione adduct **24** is an indication that the 3-methyl-indole activation pathway applies to other activated 3-alkyl indoles as well.[7]



Synthesis of Some Indole-containing Drugs

AstraZeneca's synthesis of osimertinib (**16**) commenced with condensation of 2,4-dichloro-pyrimidine (**25**) with N-methylindole to assemble adduct **26** with the help of $FeCl_3$. Further S_NAr coupling of **26** with aniline **27** in the presence of TsOH afforded 2-phenylamino-3-indolylpyrimidine **28**, which was converted to the desired osimertinib (**16**) in three additional steps.[8]

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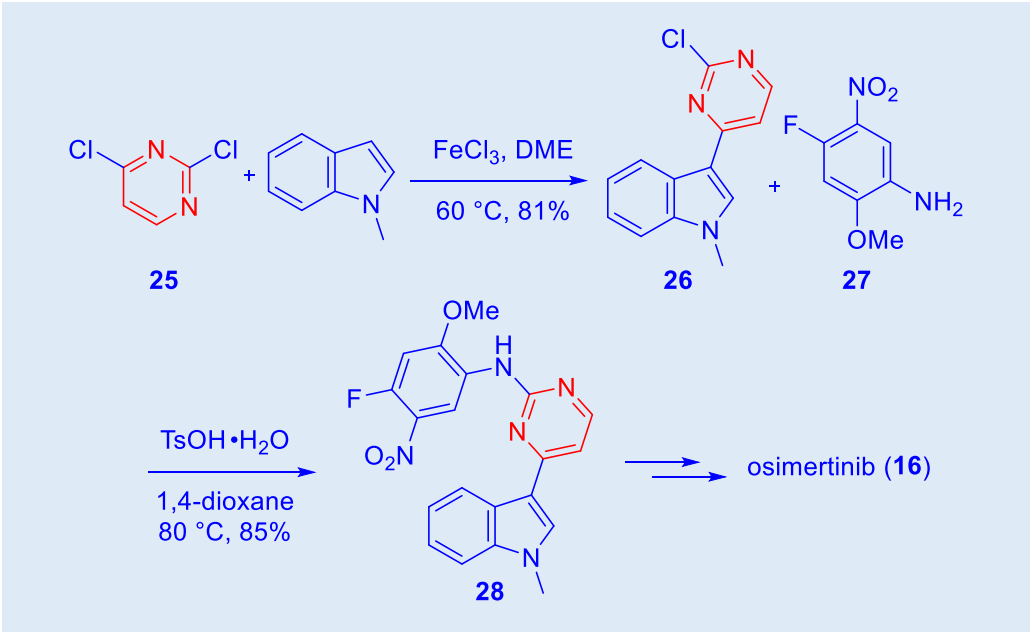
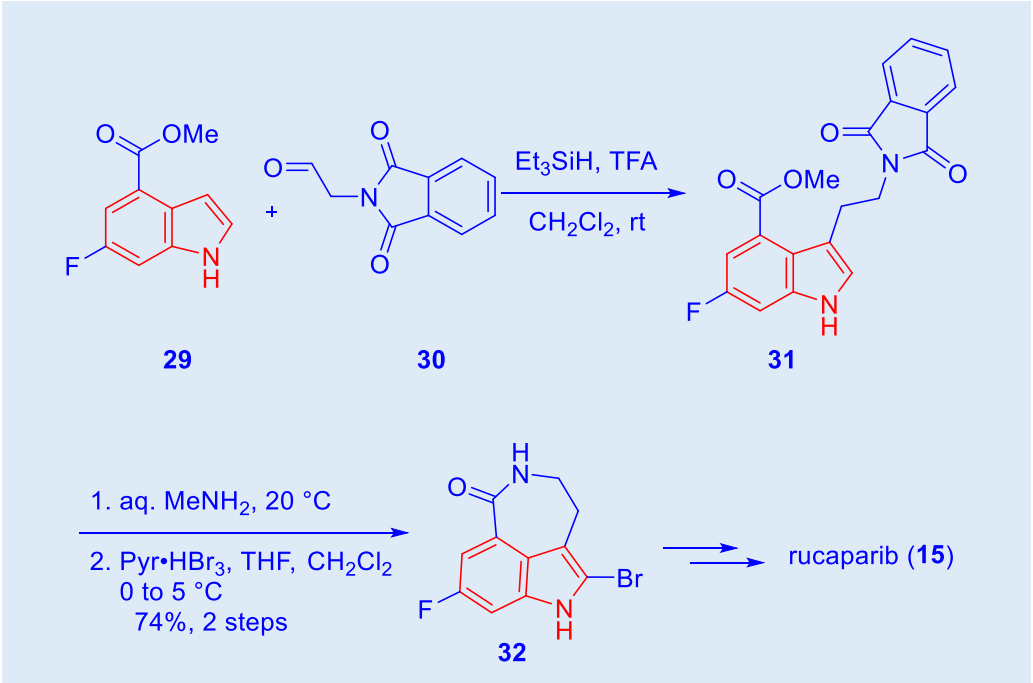


Clovis′ synthesis of rucaparib (**15**) involved a reductive condensation of methyl 6-fluoro-1*H*-indole-4-carboxylate (**29**) and freshly released aldehyde **30** (to avoid polymerization) with the aid of triethylsilane and TFA to assemble tryptamine **31**. Exposure of phthalimide **31** to aqueous methylamine released the primary amine, which underwent a simultaneous intramolecular cyclization to produce the intermediate lactam, which was smoothly brominated at the C-2 position of the indole to afford bromide **32** in 74% yield for two steps. Subsequently, a Suzuki coupling between indolyl-2-bromide **32** and the requisite arylboronic acid was followed by reductive amination with another molecule of methylamine to deliver rucaparib (**15**) in good yields.[9]



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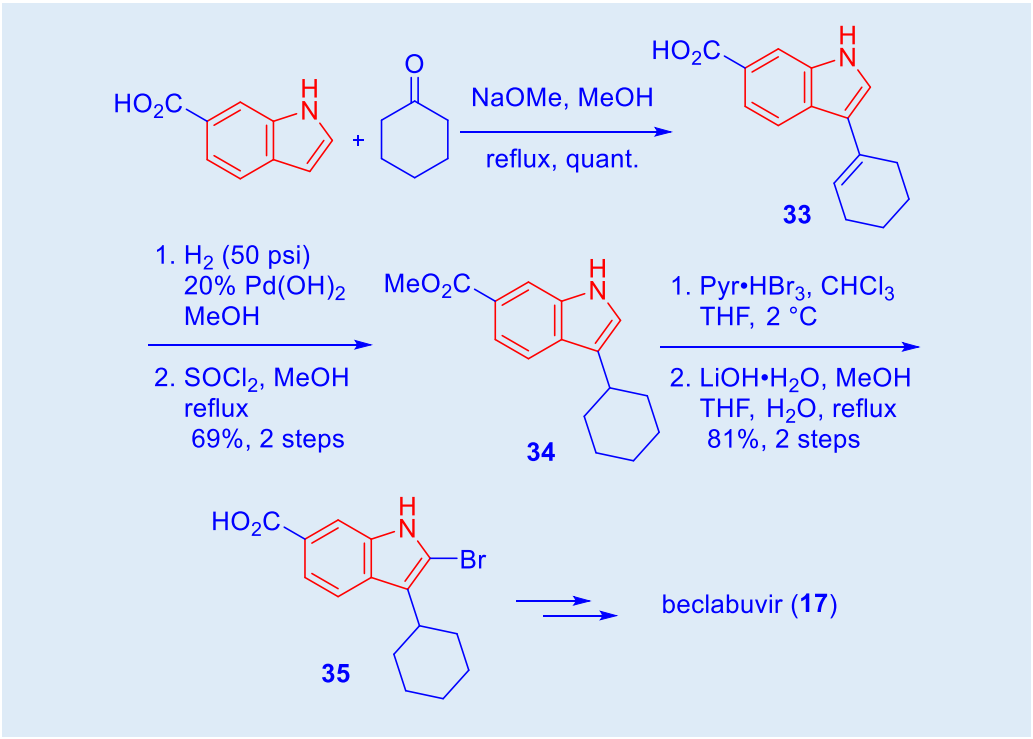
BMS's preparation of their HCV NS5B inhibitor beclabuvir (**17**) began with condensation of 1*H*-indole-6-carboxylic acid with cyclohexanone to prepare indolyl cyclohexene **33** in quantitative yield. Palladium-catalyzed hydrogenation of **33** was followed by esterification to afford indole **34**. Again, bromination was accomplished with pyridine•HBr_3 complex to provide indolyl-2-bromide **35**. Eventually, the octacyclic indole was assembled after seven additional steps to deliver beclabuvir (**17**).[10]



In summary, the key interactions that the indole nucleus in a drug include NH serving as a hydrogen bond donor and π–π stacking or cation–π stacking with the target protein. The indole motif is a privileged fragment in drug discovery, boasting more than 17 marketed indole-containing drugs, with the majority of them as kinase inhibitors. In particular, amino- and diamino-indole fragments are especially prevalent.

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