Synthetic strategies, SAR studies, and computer modeling of indole 2 and 3-carboxamides as the strong enzyme inhibitors: a review

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Abstract
Indole derivatives have been the focus of many researchers in the study of pharmaceutical compounds for many years. Researchers have investigated the effect of carboxamide moiety at positions 2 and 3, giving unique inhibitory properties to these compounds. The presence of carboxamide moiety in indole derivatives causes hydrogen bonds with a variety of enzymes and proteins, which in many cases, inhibits their activity. In this review, synthetic strategies of indole 2 and 3-carboxamide derivatives, the type, and mode of interaction of these derivatives against HLG, HIV-1, renin enzyme, and structure–activity studies of these compounds were investigated. It is hoped that indole scaffolds will be tested in the future for maximum activity in pharmacological compounds.
Keywords  Indole · Carboxamide moiety · Inhibitory activity · HLGP · HIV-1 · Renin

Abbreviations
ASSP  Active-site spatial partitioning  
BOP   (Benzotriazol-1-yl)oxytris(dimethylamino) phosphonium hexafluorophosphate  
CDI   Carbonyldiimidazole  
DMF   N,N-dimethylformamide  
DMAP  4-Dimethylanlimopyridine  
DIPEA N,N-diisopropylethylamine  
EDCI  1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide  
EFV   Efavirenz  
EtOH  Ethanol  
HBTU  3-[Bis(dimethylamino)methyl]imethyl]-3H-benzotriazol-1-oxide hexafluorophosphate  
HCTU  O-(1H-6-chlorobenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate  
HLGP  Human liver glycogen phosphorylase  
HOBt  Hydroxybenzotriazole  
HoAt  1-Hydroxy-7-azabenzotriazole  
INI   Integrase inhibitors  
KOH   Potassium hydroxide  
NMM   N-methylmorpholine  
NNRTIs Non-nucleoside reverse transcriptase inhibitors  
NRTIs Nucleoside reverse transcriptase inhibitors  
NVP   Nevirapine  
PBMC  Peripheral blood mononuclear cells  
PI    Protease inhibitors  
RT    Reverse transcription  
THF   Tetrahydrofuran  
TBTU  O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate  
WSC.HCl N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride
Introduction

The indole compound is classified in the family of heterocyclic organic compounds. The indole skeleton has a benzene ring fused to a pyrrole ring. From a chemical point of view, the nitrogen lone electron pair participates in the aromatic ring, and nitrogen does not have alkaline properties [1]. The numbering order of the indole molecule is presented in Fig. 1.

Medicinal chemistry, the study of heterocyclic compounds, especially indoles, is essential [2]. The presence of the indole scaffold in the amino acid tryptophan, neurotransmitter serotonin, and plant-based alkaloids has caused many medicinal properties. The chemistry and therapeutic study of heterocyclic compounds have been considered a powerful approach to treat a wide range of diseases [3]. In recent years, researchers have done many studies on the synthesis and biological evaluation of indole derivatives due to their biological properties and their potential to be the target [4, 5].

According to Fig. 1, the indole molecule has seven positions to accommodate different substitutions. Thus, the new derivatives of the indole can be synthesized according to these seven positions. Studies have shown that sites 1, 2, and 3 are of particular importance and are known as reactive sites for indole derivatives. The presence of the carboxamide moiety at positions 2 and 3 has led to the activity of these compounds tend to inhibit various enzymes and proteins. Many studies have been done in this regard, and various properties such as anticancer [6], antimalarial [7], anti-inflammatory [8], anti-diabetic [9–11], antimicrobial [12], antitubercular [13], antibacterial [14] and cytotoxic [7] have been reported, for indole derivatives.

Based on our experiences on synthesis of various heterocycle compounds, such as: quinoxalines [15], epoxides [16], urazoles [17, 18], pyrazolone [19], benzoxazine [20] and especially the synthesis of 3H-indoles [21], in this paper, we wish to present a comprehensive review about the synthesis, structure–activity relationship studies and computer modeling of indole 2 and 3-carboxamides as potent inhibitors of various enzymes.

Fig. 1 Numbering order of the indole molecule

Synthetic strategies of indole 2 and 3-carboxamides

The synthesis of indole derivatives has long been of interest to researchers in medicinal chemistry and organic chemistry. The methods for synthesizing the derivatives of the indole are very diverse. The main focus of this review is on the methods for synthesizing derivatives of indole 2 and 3 carboxamide and does not refer to the synthesis of indole itself. According to Fig. 2, the generalization of synthetic methods for derivatives of indole 2 and 3 carboxamide has been shown.

Regarding the derivatives of indole 2-carboxamide, references are made to methods related to the years 2003–2016. To convert the derivatives of indole to indole 2-carboxamide, several reactants are used. However, in most cases, indole 2-carboxylic acid is used as a primer compound.

In 2003, Silvestri et al. synthesized indole 2-carboxamide derivatives, given the presence of arylsulfonyl and arylthio groups in the final products. They used arylsulfonyl chlorides, arylthiodisulfides, and indoles or ethyl indole-2-carboxylate to synthesize starting compounds. They used KOH, EtOH, and THF to synthesize carboxylic acid derivatives (route a). The critical step in the synthesis of indole 2-carboxamide derivatives is the transformation of carboxylic acid to amide derivative. In the route a, CDI and ammonia or hydrazine hydrate were used to obtain indole 2-carboxamide. CDI is commonly used to convert amines to amides, carbamates and urea. Of course, the route a is very straightforward and useful, and many researchers have used CDI in the synthesis of indole 2-carboxamides [22].

Interestingly, the reaction of route b uses the ester derivative as the main intermediate. Trimethylsilyl diazomethane is used as a CH₂ source to convert indole 2-carboxylic acid to indole 2-carboxylate. In the next step, ammonium hydroxide or hydrazine hydrate is used for the synthesis of indole 2-carboxamide. CDI is commonly used to convert amines to amides, carbamates and urea. Of course, the route a is very straightforward and useful, and many researchers have used CDI in the synthesis of indole 2-carboxamides [22].

In 2006, Ragno et al. provided suitable methods for the synthesis of indolyl aryl sulfonyl 2-carboxamide derivatives. They used oxazolidinone derivatives as amine agents, EDCI, DMF, and THF solvent for the conversion of indole 2-carboxylic acid to indole 2-carboxamide. EDCI is typically used to activate the carboxyl group and to connect
it to amines for conversion to amides. In route d, DMAP plays a nucleophilic catalytic role. They also used BOP to synthesize their derivatives and gained high yields [24].

In Innovative Research, Onda et al. synthesized new compounds with the title of N-bicyclo-5-chloro-1H-indole-2-carboxamide derivatives according to the route e. In their synthetic method, WSC.HCl is the same as EDCI used as hydrochloric salt. HOBt is used for the synthesis of peptides and the conversion of carboxylic acid to the amide. Their goal was to synthesize optically active derivative concerning the indole 2-carboxamide scaffold [25, 26].

In 2012, Sindac et al. used ethyl isonipecotate as an amine reagent to synthesize indole 2-carboxamide derivatives. In route f, the synthesis steps are such that first, the ester derivative is converted to carboxylic acid and then to the carboxamide derivative. DIPEA in the reaction of route f does not have a nucleophilic role and only participates in the reaction as the base [27].

According to the pharmaceutical studies, Shonberg et al. proposed route g for the synthesis of indole 2-carboxamide derivatives. Their main goal was to connect a drug fragment to indole 2-carboxamide. They made several synthetic steps to synthesize this drug fragment. They used HCTU as the ammonium coupling agent. HCTU is a derivative of the HBTU compound. Of course, considering that HCTU has a chlorine atom at position 6, it improves reaction rate, and coupling reactions make fast and accessible [28].

In 2016, Sweidan et al. provided a simple and common method to synthesize the new indole 2-carboxamide derivatives. According to route h, from the reaction of indole 2-carboxylic acid with excess thionyl chloride in dry chloroform, is obtained indole-2-acyl chloride. In the next step, the reaction of acid chloride derivative with aminoacetophenone/benzophenone in the presence of pyridine and triethylamine produced the final products [29].

Liu et al. used TBTU to activate the carboxyl group and convert it into amide to synthesize the derivatives of indole 2-carboxamide (route i). TBTU was used as a catalytic amount. This compound is used as a coupling agent in the synthesis of peptides [30].

The synthesis of indole 3-carboxamide derivatives is very similar to the synthesis of indole 2-carboxamide derivatives. Further, the synthesis of indole 3-carboxamide from 2001 to 2017 is presented.

In 2001, Duflos et al. proposed route j for the synthesis of indole 3-carboxamide derivatives. In this method, phosphoric anhydride, acyloxypyridinium salt, imidazolide, isourea ester, and acyloxyphosphonium salt were used as carboxylic acid activators. These compounds increase the conversion rate of carboxylic acid to carboxamide [31].

In a relatively different route, Scheiper et al. used route k for the synthesis of indole 3-carboxamides. In route k, NaClO2 salt and NaH2PO4 buffer cause the oxidation of the carbaldehyde derivative to the carboxylic acid derivative. Thus, during the synthesis steps, the intermediate carbaldehyde is produced as the main intermediate. In the next step, N-Boc-piperazine is used as an amine source. In route k, the mentioned reagents act as previous reactions, and the NMM is used as a catalytic base. HoAt is used in biological reactions as a peptide coupler [32].
In 2014, Boldron et al., using previous methods and relatively simple reagents (route l), succeeded in synthesizing \(N\)-[6-(4-butanoyl-5-methyl-1H-pyrazol-1-yl)pyridazin-3-yl]-5-chloro-1-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-1H-indole-3-carboxamide (SAR216471) derivative as P2Y12 antagonist [33].

Nemoto et al. used \(\text{Me}_2\text{AlCl}\) to perform various types of synthetic reactions such as carbamoylation of indoles (route m). An interesting point in their proposed method was the use of isocyanate derivatives in the synthesis of indole carboxamides. They synthesized indole 3-carboxamide derivatives directly from indole, isocyanate, and \(\text{Me}_2\text{AlCl}\). The highest yields of their reactions were obtained in a mixture of \(\text{CH}_2\text{ClCH}_2\text{Cl-Hexane}\) as solvents [34].

In 2017, Shi et al. synthesized the indole 3-carboxamide derivatives, including amantadine ring, using oxalyl chloride, DMF, and \(\text{Et}_3\text{N}\) as the base (route n). They used (COCl)\(_2\) as a source of chloride to convert carboxylic acid derivatives to chloride acid derivatives. Eventually, the chloride acid derivatives convert to carboxamide derivatives with a high yield [35].

### The activity of indole 2 and 3-carboxamides

Extensive research over many years by researchers has shown that indole compounds exhibit numerous biological activities. As the subject of this review is the study of the indole 2 and 3 carboxamide derivatives and these compounds in particular, have inhibitory activity against HLGP, HIV-1, and renin, the structure-activity studies of these compounds are discussed below.

#### HLGP Inhibitors

Human liver glycogen phosphorylase is classified as the phosphorylase enzyme. In general, phosphorylase enzymes are a group of enzymes that add the phosphate function to a receptor. Glycogen phosphorylase is the crucial enzyme in glycogen decomposition that causes the breakdown of this molecule by adding phosphate groups and generates glucose 1-phosphate. According to the crystallographic studies, glycogen phosphorylase molecule is a homodimeric enzyme and it has four ligand-binding sites: an allosteric site, a catalytic site, a caffeine-binding site, and a dimer interface site [36–38]. The level of phosphorylase activity is directly related to blood glucose control, so the study of the inhibitory activity of this enzyme plays an essential role in reducing the harmful effects of diabetes [39–41]. Therefore, it is vital to discover and investigate the drugs that control the activity of HLGP (Fig. 3).

Researchers have studied indole 2-carboxamide derivatives for many years as suitable candidates for the inhibition of the HLGP enzyme. It is essential to understand the mechanism of interaction of HLGP and indole derivatives for the design of compounds that have the role of enzyme inhibitor. According to studies conducted in 1986 [42] and 1989 [43], it is possible to allosterically regulate the HLGP conformation by the binding of small molecule effectors and by phosphorylation of Ser14. In 2000, Rath et al. [44] studied the mechanism of interaction of the indole 2-carboxamide derivatives with HLGP, given the extensive research done in previous years [45, 46] on the design, synthesis, and crystallographic calculation of indole-2-carboxamide derivatives. Eventually, they introduced a new allosteric site for binding of indole-2-carboxamide derivatives and HLGP that would serve as the basis for the design of new inhibitors. According to their crystallographic results, the presence of carboxamide and chloroindole moiety has a direct effect on the inhibition of HLGP activity. So, they introduced molecules 2–4 as candidates. Due to the molecules 2–4, four ligand binding sites of HLGP, and experimental studies (Table 1), molecule 2 was identified as the most active compound. The results of the complexation of molecule 2 with HLGP are shown in Fig. 4. According to Fig. 4, molecule 2 spans the two types of inhibitor sites (NH carboxamide and Cl), thereby increasing the inhibitory activity of this compound. By synthesizing compound 2 and examining its inhibitory activity, IC\(_{50}\) of 6 nM was reported to be decreased compared to the previous samples (Table 1).

In 2004, Liu et al. developed new models derived from molecular docking and 3D-QSAR calculations to investigate the interaction of indole 2-carboxamide derivatives

![Fig. 3 Structure of molecule 2, (\*) inhibitor sites](image)

| Compound | Structure | IC\(_{50}\) (nM) |
|----------|-----------|---------------|
| 2        | Molecule 2 | 6             |
| 3        | Molecule 2 | 45            |
| 4        | Molecule 2 | 12,500        |

![Table 1 Structures and IC\(_{50}\) for HLGPa inhibition](table)
with HLGP [47]. Their binding models showed important aspects of the inhibitor’s conformation, subsite interaction, and hydrogen bonding. They used the results of the study by Hoover et al. [45] and incorporated compound 5 as the basis for docking and 3D-QSAR calculations. According to their experimental results (Table 2), compound 6 was identified as the most active compound and entered into molecular docking and 3D-QSAR calculations. According to Table 2 and the data obtained by Liu et al., there is a significant relationship between the binding free energies (ΔG) and the inhibitory activities (IC50) of the derivatives studied. In other words, the more favorable the interaction energy of the indole 2-carboxamide derivatives with HLGP, the inhibitory potency increases. By comparing the IC50 values of derivatives 5–14, it is found that the role of the X, R substitutions, and the chiral centers in the activity of these compounds are crucial. In Fig. 5, graphical results of the interaction of compound 6 and HLGP are shown. According to the results of docking calculations, the presences of indole ring and carboxamide moiety have a decisive role in the inhibitory activity of these compounds. The carboxamide moiety is very flexible and has both hydrophobic and polar properties. There are three hydrogen bonds between the indole derivatives and HLGP. According to Fig. 5, the first hydrogen bond is related to the interaction of indole nitrogen with the backbone carbonyl of Glu190. The second hydrogen bond is the result of the interaction of the carboxamide nitrogen with the backbone carbonyl of Thr380, and the third hydrogen bond is the interaction of the carbonyl in R moiety and the nitrogen atom of the Lys191 side chain. In 3D-QSAR calculations, they used COMFA and COMSIA methods that had similar results and confirmed the results of molecular docking calculations.

According to the research conducted up to 2008, the presence of carboxamide moiety in the indole derivatives is essential for their inhibitory activity against HLGP. In 2008, Onda et al. devoted their research to adding different groups to the carboxamide moiety [26]. They put compound 15 as the basis for the design of new molecules, according to a study by Martin et al. in 1998 [46]. Their main purpose was to replace the phenylalanine group of compound 15 with substituents having the hydroxy group. Accordingly, they synthesized indole 2-carboxamide derivatives and examined their inhibitory activity against HLGP (synthesized according to the route e). The results of their study in Table 3 show that the presence

![Fig. 4](image)

The interaction of the HLGP with the molecule 2 through the new allosteric binding sites [44]

| Compound | X   | R             | IC50 (nM) | ΔG (kcal/mol) |
|----------|-----|---------------|-----------|---------------|
| 5        | Cl  | CHOCONMe2     | 110 ± 2   | −11.98        |
| 6        | Cl  | CONMe2        | 82 ± 10   | −12.72        |
| 7        | Br  | CHOCONMe2     | 97 ± 11   | −12.32        |
| 8        | Cl  | CONHMe        | 110 ± 10  | −11.70        |
| 9        | Br  | CONMe2        | 110 ± 8   | −11.82        |
| 10       | Cl  | CHOCONMe2     | 8700 ± 1700 | −9.43       |
| 11       | Cl  | CHOCH2OH      | 6800 ± 1700 | −9.76       |
| 12       | OMe | CONMe2        | 4700 ± 300 | −9.90        |
| 13       | Cl  | COOH          | 1700 ± 490 | −11.01        |
| 14       | Cl  | CONHMe        | 220 ± 32  | −11.12        |
of hydroxy group(s) and their appropriate position, a fluoro group, and nitrogen atom in the aromatic ring increases the inhibitory activity of the compounds studied. It can be concluded that steric hindrance is more important than electronic character in determining the inhibitory activity of indole 2-carboxamide compounds. According to their studies and the evaluation of Table 3, compound 19 was identified as the most active derivative, so was examined for inhibition of glucagon-induced glucose output in cultured primary hepatocytes and for oral hypoglycemic activity in diabetic db/db mice. Their results showed that compound 19 inhibited glucose output dose-dependently with a \( IC_{50} = 0.62 \) \( \mu \)M. Interestingly, with the administration of 50 mg/kg dose of compound 19, the blood glucose level significantly decreased at 2 h postdose. The calculations of the binding interaction of compound 16 with HLGP are shown in Fig. 7. According to Fig. 7, in addition to the amide moiety interaction with the backbone of Thr380, two hydroxyl groups have direct electrostatic interactions with the imidazole ring of His57 and the backbone of Tyr185. This is important the presence of the carboxamide group in two respects: 1) the interaction of the carboxamide group with the backbone of Thr380, 2) the polar groups attach to it, and the interaction of these groups with His57 and Tyr185 (Fig. 6).

Onda et al. continued their research to design and synthesize \( N \)-bicyclo-5-chloro-1H-indole-2-carboxamide derivatives as HLGP inhibitors (synthesized according to the route e) [25]. Their strategy was to create fused rings to benzene carboxamide. During the biological evaluation, they found that the presence of large rings, such as 7-membered rings, caused steric hindrance, which interfered with the interaction of His57 with hydroxy groups and decreased inhibitory activity. It should be noted that adding methyl and hydroxy groups to the fused ring reduces the activity of these compounds, which can be attributed to the steric hindrance and intramolecular hydrogen bonding. The presence of fluorine atoms in the fused ring strengthens the inhibitory activity of the indole derivatives. According to Fig. 7, the steric hindrance around the central benzene ring is low and small substitutions such as fluorine can be added to the benzene ring [26]. According to their biological evaluation, compound 21 was identified as the most potent inhibitor with \( IC_{50} = 0.02 \) \( \mu \)M (Table 4). Considering \( IC_{50} = 0.02 \) \( \mu \)M for compound 21, further research in diabetic model mice has revealed some interesting points about this compound. Compound 21 showed an inhibition glycogenolysis value equal to 0.69 \( \mu \)M. The important thing about this compound is that the dose used to reduce plasma glucose level at 2 h postdose is 10 mg/kg. In summary, the data obtained is not sufficient to nominate a drug for more advanced research and requires more complete data. Therefore, they measured other properties of compound 21, such as pharmacokinetic profile, oral bioavailability, plasma half-life which were acceptable in male SD rats. The question that arises is why does the R-enantiomer have higher inhibitory activity than the S-enantiomer? To answer this question, they performed docking calculations using compound 21 (R-isomer) and HLGP. According to Fig. 9, the cause of the high activity

### Table 3 SAR of \( N \)-aryl and \( N \)-heteroaryl-5-chloroindolecarboxamides

| Compound | \( X \) | \( Y \) | Position | \( R \) | \( IC_{50} \) (\( \mu \)M) |
|----------|--------|--------|----------|------|------------------|
| 15       | –      | –      | –        | –    | 0.92             |
| 16       | CH     | CH     | –        | –    | 0.90             |
| 17       | CH     | CH     | 2        | F    | 0.42             |
| 18       | CH     | CH     | 3        | F    | 0.34             |
| 19       | N      | CH     | –        | –    | 0.25             |
| 20       | N      | N      | –        | –    | 0.44             |

Fig. 5 The interacting mode of compound 6 with HLGP [47]

Fig. 6 Structure of compound 15 (synthesized according to the route e)
of compound 21 is due to the lipophilic interactions of aliphatic fluorine atoms and the hydrophobic residues, such as Phe53, Pro188, and Gly186. The difference in the inhibitory activity of R and S enantiomers, according to Onda et al., is related to the inappropriate interaction of fluorine at position 1 and the methylene group at position 8. But the important thing about reducing inhibitory activity is associated with the inappropriate interaction of aliphatic fluorine groups and hydrophobic residues of HLGP. The fluorine and hydroxy groups in S-isomer have steric hindrance and thus do not interact with Phe53, Pro188, and Gly186 (Fig. 8).

**HIV-1 entry inhibitors**

In controlling the inhibition of the HIV-1 virus, it is important to pay attention to reverse transcription (RT), protease, integrase enzyme, and viral entry/fusion. RT is a key step in the life cycle of retroviruses that is responsible for the
synthesis of double-stranded (ds) DNA from a viral single-stranded (ss) RNA genome. Therefore, drugs designed to inhibit HIV-1 virus are divided into several categories: nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PI), and integrase inhibitors (INI) [48]. The main purpose of the design of HIV-1 inhibitors is to suppress the replication of HIV-1 in the long-term therapy and to maintain the function of the immune function [49]. Given that delavirdine [50] with indole 2-carboxamide skeletal is used to treat HIV-1, other indole 2-carboxamide derivatives have the potential to inhibit HIV-1 virus activity. It should be noted that many researchers have used nevirapine and efavirenz as the control to compare with indole 2-carboxamide derivatives (HIV-1 inhibition). In the following, the mechanism of action of indole 2-carboxamide derivatives and their structure–activity relationships are discussed.

In 1993, Williams et al. conducted extensive research into compound 22. Their study showed that this compound is one of the most potent and selective NNRTIs inhibitors of the HIV-1 reverse transcriptase [51]. Of course, the main problem of compound 22 is its low solubility in water. In 2003, Silvestri et al., according to the previous research [51], designed and synthesized novel indolyl aryl sulfones and tested them against HIV-1 in acutely infected MT-4 cells [22]. The purpose of their study was to investigate the structural changes in the compounds studied. They used the strategy of replacing the carboxamide side chain and examined its shift from position 2 to position 3. The results of their study showed that shifting the carboxamide moiety from 2 to 3 positions or switching it to 2-carboxy hydrazide reduced activity. Finally, the results of their research clearly showed that the anti-HIV-1 activity of the investigated compounds was dependent on the presence of benzene sulfonyl and carboxamide moiety. As a general result, sulfone derivatives have lower cytotoxicity and higher activity potential than sulfur derivatives. They found that the best results were obtained when 3-benzene sulfonyl indoles contained 2-carboxamide moiety. The ester and hydrazide residues were less active, and carboxylic acid inactivated. Given the results of their cell-based assays and the lack of inhibition of the rRT carrying the K103 mutation, it can be

**Table 5** Cytotoxicity and antiviral activities of indole 2-carboxamide derivatives

| Compound | CC_{50} (µM) | WT-IIIB EC_{50} |
|----------|-------------|-----------------|
| 22       | 45          | 0.001           |
| 23       | 4           | 0.003           |
| NVP      | >100        | 0.4             |
| EFV      | 35          | 0.004           |

*Compound concentration (µM) required to achieve 50% protection of infected MT-4 cells from WTIIIB-HIV-1-induced cytopathicity (MTT method) [23]
said that the compounds studied target the HIV-1 reverse transcriptase (Fig. 10).

Silvestri et al. in their subsequent studies used interesting strategies for the structural changes of compound 22 to test new sulfonyl indole carboxamide derivatives activity for cytotoxicity and against HIV-1 WT [23]. Methyl groups were added to the benzenesulfonyl moiety of compound 22 and one to three glycaminide/alaninamide units to its carboxamide function. Nevirapine and efavirenz were considered as reference compounds. The results of Table 5 show that the addition of 2 methyl groups and D.l-alanine unit to molecule 22 reduces its cytotoxicity (molecule 23). Compared to control drugs, molecules 22 and 23 have higher activity and less cytotoxicity. The results of their study show that the addition of methyl groups at positions 3 and 5 (phenyl ring) is most effective. The D.l-alanine unit establishes strong interactions with the target by increasing the number of hydrogen bonds (Fig. 11).

In 2005, Ragno et al. studied the binding mode and binding site of indolyl aryl sulfones using docking and 3D-QSAR calculations. In their study, they used compound 22 as the reference compound in the interaction with 14 RTs [52]. They used the structural data of 14 RTs (pdb codes: 1DTQ, 1DTT, 1EET, 1FK9, 1HNI, 1HNV, 1JLQ, 1RT1, 1RT3, 1RT4, 1RT5, 1RT7, 1VRT, and 1VRU) to explore the binding mode of the compound 22. These codes represent different non-nucleoside binding sites related to reverse transcriptase. In docking calculations, in all cases, the docked conformations were in agreement with each other, the graphical result of which is shown in Fig. 12. The interesting point about the carboxamide function in position 2 of the indole ring is that the amide carboxyl group is in some instances with indole NH in cis-state and some cases in the trans-state. So they used 3D-QSAR calculations to design new molecules that would have the proper hydrogen interactions at the carboxamide position. They used the data of Silvestri et al. [22] in their calculations. According to the calculations, 2-hydroxyethylaminocarbonyl and 2-hydroxyethylhydrazinocarbonyl substitutions were attached to carboxamide. The selected derivatives were synthesized, and their activity against WT HIV-1 and mutant strains evaluated (Table 6). According to Table 6, molecules 22, 24, and 25 have relatively good activity against WTIIIB compared to NVP and EFV. The important point about double mutant K103N-Y181C is that molecule 25 has higher activity than molecules 22 and 24. In general, the number of factors must be considered to nominate a molecule as a drug (Fig. 13).

In the years 2011 and 2012, Regina et al. [53, 54] came up with new ideas for the design of indolyl aryl sulfones. Their main purpose was to bind cycloalkylaminolo, aryl, or heteroaryl nucleus through methylene, ethylene, or ethoxy groups to the 2-carboxamide moiety and to investigate their activity against WT HIV-1 replication and HIV-1 clades in PBMC cells (Table 7). The results of their study showed that compounds 26–29 had relatively good activity against WTIIIB compared to NVP and EFV. The important point about double mutant K103N-Y101C is that molecule 25 has higher activity than molecules 22 and 24. In general, the number of factors must be considered to nominate a molecule as a drug (Fig. 13).
sodium concentration activates the renin system. This pathway is first activated by the aspartyl protease enzyme, which eventually produces angiotensin I by hydrolysis of the angiotensinogen protein [55, 56]. Since renin is the rate-limiting enzyme in this pathway, and since angiotensin has been recognized as the sole agent, a very effective anti-hypertensive have high inhibitory activity in primary T-lymphocyte cells. Molecular docking calculations of the synthesized compounds showed that the hydrogen bonding between the nitrogen atom in the carboxamide chain and Glu138:B of NNBS-HIV-1-WT RT plays a key role in controlling the activity of these compounds. Considering the structure of compounds 26–29, it can be said that the presence of 5 and 6-membered rings without steric hindrance enhances the activity of these compounds. The presence of a nitrogen atom in these rings that cause hydrogen bonding is one reason for the increased activity of these compounds. For further studies on compounds 26–29, parameters such as cytotoxicity, selectivity index, and relative factor were measured that were acceptable (Fig. 14).

### Renin Inhibitors

Renin or angiotensinogenase system is known as the blood pressure regulator as well as its electrolytes. Lowering blood pressure, reducing circulatory volume, or lowering plasma enzyme in this pathway, and since angiotensin has been recognized as the sole agent, a very effective anti-hypertensive
strategy is to prevent angiotensin I production through renin inhibition [57]. If the renin-angiotensin system is abnormally activated, blood pressure will rise too. Based on decades of efforts to discover renin inhibitors, several research groups have reported different renin inhibitors [58]. Renin inhibitors are one of the main ways to lower blood pressure, treat heart failure and have adverse effects on diabetes. Indole 3-carboxamide derivatives are very useful in inhibiting renin enzyme activity, which will be discussed further.

From 2010 to 2011, Scheiper et al. conducted extensive research on the discovery and optimization of new and non-chiral indole-3-carboxamide compounds as scaffolds for renin inhibition [32]. They reported the results of their study as an optimal compound, and in the next study used the reported compound as the basis of molecular design. Using high-throughput screening, they selected compound 30 as the base compound for future research. Due to the structure of compound 30, the other two derivatives were synthesized and evaluated. The crystallographic results of compounds 31 and 32 are shown in Fig. 15.

In fact, with the blocking of NH-carboxamide, the interactions of carbonyl-carboxamide and NH- piperazine become essential. According to Fig. 15, NH- piperazine with residues Asp32 and Asp215 appeared to form ionic hydrogen bonding interactions. Another interaction is related to the hydrogen-bonding between carboxamide oxygen and Thr77-OγH. Due to the structural properties of compounds 31 and 32, other indole 3-carboxamide derivatives were synthesized, and their inhibitory activity was investigated. Finally, compound 33 was selected as the most optimal compound in interaction with the renin enzyme (Table 8). Compound 33, with the 5-hydroxy group, establishes a favorable interaction with the imidazole ring of His287 (Fig. 16). According to the results of the crystallographic studies, the presence of polar moiety in the indole core has a positive effect on the inhibition activity of the renin enzyme. Therefore, in their next study, they used azaindole as the base compound. Nitrogen atoms were positioned at the positions of 4, 6, or 5, 7 indole molecules. According to the results of their study, the activity of azaindole and indole compounds against the renin enzyme is similar. They used their candidate compounds in further study to measure factors such as Caco-2 permeability, physicochemical data, and IC50 values in human or mouse plasma. The results of their studies showed that some azaindole derivatives have the potential of intestinal absorption. Therefore, the results of their study can serve as the basis for the initiation of advanced research [59, 60].

In 2012, Jing et al. used the ASSP method to quantitatively characterizing the nonbonding interaction profile between renin and indole 3-carboxamide derivatives [61].
In this method, the space containing the entire active site of renin is divided into thousands of small areas, and then the nonbonding potentials between renin and indoles are calculated. The advantage of the ASSP method is the use of graphical diagrams that illustrate the interactions. Their calculations were performed using the data of the paper by Scheiper et al. [32]. According to the results of their calculations, the interaction of indole 3-carboxamide derivatives with renin enzyme is primarily electrostatic, secondly hydrophobic, and thirdly steric (Fig. 17). The presence of polar and charged groups in the interaction with the renin enzyme causes hydrogen bond and salt-bridge networks. The presence of aromatic and aliphatic rings causes steric and hydrophobic interactions that are weaker than electrostatic interactions. According to their calculations, compound 33 had the highest activity against renin (Fig. 17). The activity of compound 33 depends on the presence of NH in the piperazine ring, C=O/-OH groups, F, and CH₃ groups, which enhance the electrostatic force and thus increase its activity. Removal of any of the above-mentioned groups results in a decrease in the activity of this compound. These results confirm the research of Scheiper et al.

However, many computational and theoretical studies have been conducted by researchers to study and design indole 3-carboxamide derivatives, the results of which confirm previous studies [62, 63]. In recent years, indole derivatives are shown to be active against many enzymes

| No | Code       | Structure          | Inhibitory activity against | Refs. |
|----|------------|--------------------|-----------------------------|-------|
| 2  | CP-526,423 | ![Structure](image1) | HLGP [44]                   |       |
| 3  | CP-403,700 | ![Structure](image2) | HLGP [44]                   |       |
| 4  | CP-305,494 | ![Structure](image3) | HLGP [44]                   |       |
| 15 | CP-320626  | ![Structure](image4) | HLGP [26]                   |       |
| 22 | L-737,126  | ![Structure](image5) | HIV-1 [22]                  |       |
| 34 | Patent number: WO2009014217 | ![Structure](image6) | Renin [56]                  |       |
and proteins, indicating that these compounds are still in research [64–67].

Conclusion

Indole derivatives play essential roles in pharmaceutical studies. By reviewing the synthetic methods, it was found that BOP, EDCI, HOBr, and TBTU activate the carbonyl group and convert the indole carboxylic acid to indole carboxamide. The studies have shown that indole 2-carboxamide derivatives have inhibitory activity against HLGP and HIV-1, and indole 3-carboxamide derivatives have inhibitory activity against renin. Considering the studies of investigating the inhibitory activity of indole derivatives, the presence of carboxamide moiety at positions 2 and 3 is significant from two aspects. 1) NH and CO-carboxamide form hydrogen bonds with enzymes or proteins. 2) Polar groups can bond to the carboxamide moiety and form new hydrogen bonds with enzymes or proteins. In fact, strengthening the electrostatic forces increases the inhibitory activity of indole 2 and 3-carboxamide derivatives. Research on indole compounds is not limited to academic articles and studies. Many of these derivatives are in the final stages of approval and entry into the pharmaceutical industry. Table 9 shows the indole 2 and 3-carboxamide derivatives, which are in the late stage of discovery. The result of years of research by scientists has shown that these compounds have the potential to inhibit the activity of various enzymes such as HLGP, HIV-1, and renin. Research on indole compounds is expected to continue and more drugs from these derivatives will reach final approval.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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