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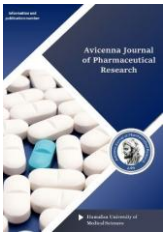

Research Article

Synthesis and Molecular Modeling of New Indole-3-(CO)-benzothiazolamide Derivatives as Renin Inhibitors

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Abstract

Novel indole-3-(CO)-benzothiazolamide derivatives (2a–e) were synthesized by reacting 3-indoleglyoxylyl chloride with various 1-aminobenzothiazole derivatives. The structures of all synthesized compounds were confirmed using IR spectroscopy, ^{1}H-NMR, ^{13}C-NMR, and mass spectrometry. Molecular docking studies were performed to evaluate their binding affinity and interactions within the renin active site using the crystal structure of renin (PDB: 3OOT). Molecular docking studies revealed that the indole-3-(CO)-benzothiazolamide derivatives bind effectively to key residues, particularly Asp32 and Thr77, with the nitro-substituted compound 2e showing the highest binding affinity (ΔG binding = –8.20 kcal mol^{-1}). Ligand efficiency analysis indicated that the unsubstituted analog 2a is the most efficient lead. These findings suggest that these new indole-3-(CO)-benzothiazolamides as a promising scaffold for the development of new non-chiral renin inhibitors.

Keywords: blood pressure, Indole-3-(CO)-benzothiazolamide, Indole-3-carboxamides, Molecular docking, Renin inhibitors

Introduction

The renin-angiotensin system (RAS) is widely recognized as a major hormonal axis that regulates blood pressure and fluid–electrolyte balance. Its activation is triggered by various physiological cues, including reduced arterial pressure, diminished circulating blood volume, or decreased plasma sodium levels. These stimuli promote the secretion of renin, an aspartyl protease enzyme. Upon release, renin acts on its sole known substrate, angiotensinogenm cleaving it to generate angiotensin I [1, 2]. Because renin mediates the rate-limiting step in this enzymatic pathway, along with the uniqueness of angiotensinogen as its only recognized substrate, makes inhibition of this step a potential approach to lowering blood pressure. In addition, appropriate pharmacological intervention in the RAS is likely to yield maximal protective outcomes for critical organs, particularly cardiac and renal tissues [3]. The search for renin-inhibiting agents has attracted significant interest over the last several decades, culminating in the introduction of aliskiren as one of the few clinically approved drugs in this class now available on the market [4].

Indole-3-carboxamides represent an attractive class of molecular scaffolds with potential renin-inhibitory activity, as the indole core provides a

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suitable aromatic and hydrophobic surface for occupying the nonpolar regions of the enzyme's binding site, while the carboxamide group can act as both a hydrogen bond donor and acceptor, stabilizing the ligand orientation within the active site. Moreover, the independent modifiability of the indole ring, the indole nitrogen, and the amide moiety renders this framework highly amenable to systematic structure–activity relationship (SAR) studies and for the simultaneous fine-tuning of potency, selectivity, and physicochemical properties [5-7]. In studies conducted by Scheiper and colleagues, non-chiral indole-3-carboxamide-based compounds were designed and synthesized. Several of these derivatives exhibited potent renin inhibition with IC_{50} values in the nanomolar range (Figure 1) [8-10]. SAR investigations within this series revealed that the nature and position of substituents on the indole core, as well as modifications to the amide portion, play a decisive role in filling hydrophobic pockets, establishing polar contacts, and enhancing inhibitory potency [10].

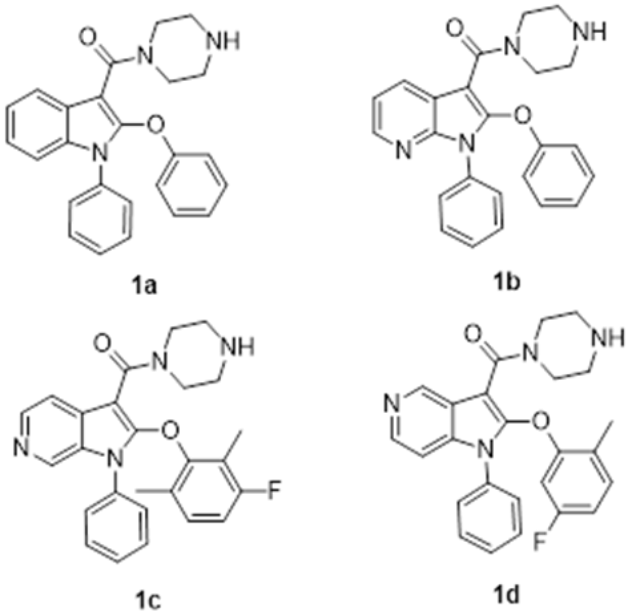

Figure 1. Some of the synthesized derivatives of indole-3-carboxamide as renin inhibitors reported in the Scheiper researches

This study describes the preparation and SAR evaluation of a new series of indole-3-carboxamides functionalized with a 2-aminobenzothiazole group (designated as indole-3-(CO)-benzothiazolamides, **2**), as potential non-chiral renin inhibitors (Figure 2). To gain insight into the essential pharmacophore and the nature of interactions within the renin binding pocket, molecular docking experiments were undertaken.

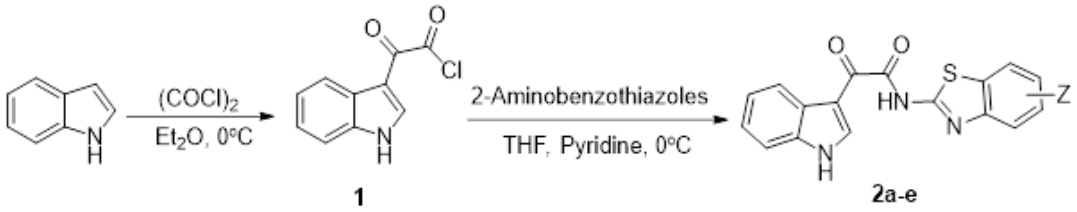

Figure 2. Synthesis of Indole-3-(CO)-benzothiazolamides

Experimental

General

All reagents and solvents were sourced from Sigma-Aldrich, Merck, and Fluka. The synthesized products were characterized using complementary spectroscopic methods, namely IR, ^{1}H-NMR, and mass spectrometry. FT-IR spectra were acquired using a Bruker Plus apparatus with KBr pellets over the range of 400–4000 cm^{-1}. ^{1}H-NMR spectra were recorded on a Bruker Avance-500 spectrometer, and

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chemical shifts are reported in ppm relative to tetramethylsilane as the internal reference. Mass spectra were obtained on an Agilent Technologies 5975C instrument.

Melting points were determined on a Stuart SMP3 apparatus and are uncorrected. Reaction progress was monitored by thin-layer chromatography on silica gel GF254 plates, using ethyl acetate/n-hexane mixtures as the developing solvent.

Preparation of 3-Indoleglyoxylyl chloride (1)

To a solution of indole (1.17 g, 10 mmol) in dry diethyl ether (25 mL) at 0°C, oxalyl chloride (1 mL,11.5 mmol) was added dropwise over 30 min. The reaction mixture was stirred at 0°C for 3 h and then allowed to warm to room temperature for 1 hour. The resulting yellow solid was collected by filtration, washed with cold diethyl ether and dried under vacuum. The yellow solid (3-indoleglyoxylyl chloride, 1) was used without further purification.

General procedure for the preparation of Indole-3-(CO)-benzothiazolamides (2a-e)

A mixture of 3-indoleglyoxylyl chloride (1) (1.0 mmol) and aminobenzothiazole (1.0 mmol) was placed in a round-bottom flask containing THF (10 mL), to which three drops of pyridine were subsequently added. The flask was immersed in an ice bath, and the resulting mixture was stirred for 2 h. Reaction progress was monitored by TLC using a solvent system of n-hexane/ethyl acetate (4:1, v/v). Upon completion, the reaction mixture was filtered, and the collected precipitate was washed with petroleum ether (2 × 5 mL). The crude products were then purified by recrystallization from hot ethyl acetate.

Physical and spectral data for the products:

N-(benzo*[d]*thiazol-2-yl)-2-(1H-indol-3-yl)-2-oxoacetamide (2a)

Dark red solid; Dec. 250-253 °C

IR (KBr): υ 3374, 3282, 1681, 1630, 1524 cm^{-1}.

MS m/z (%): 321 (23.5), 177 (92.1), 144 (100), 89 (55.2).

^{1}H-NMR (500 MHz, DMSO-*d6*): δppm 12.89 (s, 1H), 12.47 (s, 1H), 8.68-8.69 (d, 1H), 8.25 (s, 1H), 8.05-8.07 (d, 1H), 7.82-7.84 (d, 1H), 7.30-7.59 (m, 4H). ^{13}C-NMR (125 MHz, DMSO-*d6*): δppm 180, 180.23, 163.94, 157.77, 149.01, 139.31, 137.12, 132.31, 126.85, 126.34, 124.54, 124.36, 123.45, 122.38, 121.74, 121.44, 113.32, 112.41.

N-(5-ethoxybenzo*[d]*thiazol-2-yl)-2-(1H-indol-3-yl)-2-oxoacetamide (2b)

Dark red solid; Dec. 251-252 °C

IR (KBr): υ 3379, 3279, 1679, 1608, 1635, 1434 cm^{-1}.

MS m/z (%): 365 (11), 221 (81), 144 (58), 89 (100).

^{1}H-NMR (500 MHz, DMSO-*d6*): δppm 12.71 (br s, 1H), 12.50 (s, 1H), 8.68-8.69 (d, 1H), 8.25-8.26 (t, 1H), 7.57-7.71 (s, 3H), 7.04-7.06 (m, 3H), 4.04-4.10 (q, 2H, *J=0.02 Hz*), 1.33-1.36 (t, 3H, *J=0.02 Hz*). ^{13}C-NMR (125 MHz, DMSO-*d6*): δppm 180.24, 163.57, 156.20, 155.54, 143.09, 139.24, 137.10, 133.70, 127.45, 126.37, 124.33, 123.42, 122.06, 116.10, 113.31, 112.43, 105.77, 64.25, 15.17.

2-(1H-indol-3-yl)-*N*-(5-methylbenzo*[d]*thiazol-2-yl)-2-oxoacetamide (2c)

Dark red solid; Dec. 267-269 °C

IR (KBr): υ 3426, 3322, 1698, 1627, 1533, 1431 cm^{-1}.

MS m/z (%): 335 (4.7), 191 (67.6), 144 (100), 116 (60.6), 89 (54.1).

^{1}H-NMR (500 MHz, DMSO-*d6*): δppm 12.79 (br s, 1H), 12.47 (s, 1H), 8.67 (s, 1H), 8.25 (s, 1H), 7.84 (s, 1H), 7.70 (s, 1H), 7.56 (s, 1H), 7.30 (s, 3H), 2.46 (s, 3H). ^{13}C-NMR (125 MHz, DMSO-*d6*): δppm 180.29, 163.82, 156.83, 147.04, 139.27, 138.49, 137.11, 134.08, 132.46, 128.21, 126.34, 124.34, 123.43, 121.74, 121.61, 113.31, 112.41, 21.52.

N-(5-fluorobenzo*[d]*thiazol-2-yl)-2-(1H-indol-3-yl)-2-oxoacetamide (2d)

Dark red solid; Dec. 310 °C

IR (KBr): υ 3377, 3293, 1681, 1608, 1531, 1435 cm^{-1}.

MS m/z (%): 339 (25.3), 195 (100), 144 (98), 116 (52), 89 (41.8).

^{1}H-NMR (500 MHz, DMSO-*d6*): δppm 12.93 (s, 1H), 12.48 (s, 1H), 8.70 (s, 1H), 8.26 (s, 1H), 7.97 (s, 1H), 7.82 (s, 1H), 7.30 (m, 3H). ^{13}C-NMR (125 MHz, DMSO-*d6*): δppm 180.03, 163.89, 160.59, 158.20, 145.81, 139.33, 137.12, 133.65, 126.36, 124.35, 123.44, 122.65, 121.76, 114.88, 113.31, 112.42, 108.89.

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2-(1H-indol-3-yl)-*N*-(5-nitrobenzo*[d]*thiazol-2-yl)-2-oxoacetamide (2e)

Dark red solid; Dec. 310 ºC

IR (KBr): υ 3351, 3173, 1634, 1608, 1519, 1336 cm^{-1}.

MS m/z (%): 366 (1.18), 195 (96.1), 165 (60.58), 144 (100), 89 (27.6).

^{1}H-NMR (500 MHz, DMSO-*d6*): δppm 12.51 (s, 1H), 12.33 (s, 1H), 9.1 (s, 1H), 8.7 (s, 1H), 8.1 (m, 3H), 7.44 (m, 3H). ^{13}C-NMR (125 MHz, DMSO-*d6*): δppm 181.30, 164.40, 159.03, 153.82, 143.79, 141.17, 139.46, 138.50, 133.06, 132.05, 126.30, 123.52, 122.36, 121.74, 119.70, 117.33, 112.80.

Docking

Receptor preparation

The X-ray crystallographic structure of renin was obtained from the RCSB PDB (http://www.rcsb.org/). The holo-structure of renin in complex with indole-based inhibitor was selected to consider the induced-fit effect (PDB code: 3OOT resolution: 2.55 Å, R-Value Free: 0.220, R-Value Work: 0.182). The cognate ligand and water molecules were removed from the original crystallographic structure.

Ligand preparation

The studied ligands were a series of indole-3-(CO)-benzothiazolamide derivatives (Table 1). The 3D structures of the ligands were optimized using density functional theory (BP86/def2-TZVP) in combination with D3BJ empirical dispersion correction. All calculations were performed using the ORCA quantum chemistry package [11].

Binding mode prediction

All docking studies were performed using the AutoDock 4.2 suite of programs [12]. The binding site was defined by centering a grid box (60×60×60 points) on the cognate ligand in the renin crystallographic structure. In all computations, a standard protocol of 200 independent genetic algorithm runs, initial population size of 150 chromosomes, a maximum of 5,000,000 evaluations and a maximum of 27,000 generations was applied. Conformations differing by less than 2 Å in RMSD were clustered together. The binding free energy was calculated using the default empirical free-energy force field implemented in AutoDock 4.2.

Results and Discussion

Chemistry

3-Indoleglyoxylyl chloride [1] was prepared by reacting indole with oxalyl chloride [13]. Subsequent reaction of compound 1 with different 2-aminobenzothiazole derivatives afforded the final products, whose structures are presented in Table 1.

Table 1. Indole-3-(CO)-benzothiazolamide derivatives

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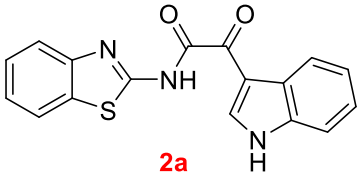
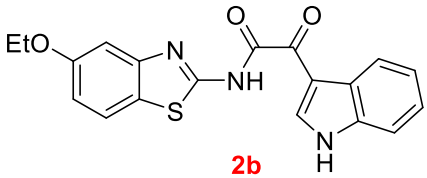
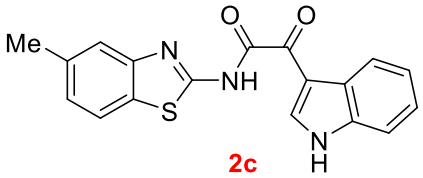
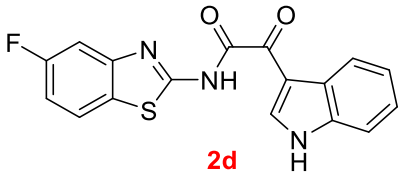
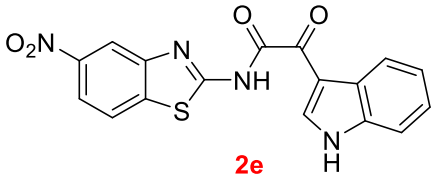
1	 2a
2	 2b
3	 2c
4	 2d
5	 2e

Examination of the product spectra revealed the same patterns. In the IR spectrum, a peak at 3374-3426 cm^{-1} is assigned to NH stretching vibrations of indole [14] and a peak appeared at 3279 cm^{-1} is related to the NH of amide [14]. A total of two peaks at 1681 and 1630 cm^{-1} indicate two carbonyl groups. In the mass spectra of the products, the molecular ion peak $[M]^{+}$ is observed, and the other peaks display the fragmentation pattern. These patterns supported the proposed structure. In the ^{1}H-NMR

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spectra, two peaks at δ = 12.89 and 12.49 ppm are assigned to the NH groups of indole and amide respectively [14]. Signals appearing at 7-9 ppm correspond to aromatic protons. For compounds 2b and 2c containing aliphatic protons, the corresponding aliphatic proton signals were clearly observed. In the ^{13}C-NMR spectra, the expected carbon signals were observed.

Molecular modeling

In the present study, molecular docking was employed to investigate the potential binding of the designed ligands to renin as a putative molecular target; however, experimental validation through further biological assays is required to confirm the proposed interactions and inhibitory activity. The docking protocol was validated by redocking the cocrystallized ligand (pdb code: 3OOT) into the active site of renin. The validity of the docking method was assessed based on its ability to reproduce the crystallographic binding pose. The difference between the pose predicted by AutoDock4 and the crystallographic pose was evaluated using the root-mean-square deviation (RMSD) of the ligand atoms. According to the obtained results, the RMSD between the predicted pose and the reference structure was 0.38 Å.

The best predicted docking conformation for the indole-3-(CO)-benzothiazolamide derivatives was assessed based on two criteria: the free energy of binding and the key contact interactions with residues associated with renin activity (Table 2 and Figure 3).

Table 2. Calculated free energy of binding, electrostatic, vdW and H-bond, ligand efficiency and clog P of indole-3-(CO)-benzothiazolamide derivatives

Compound	$\Delta G_{binding}$ (kcal mol^{-1})	Electr. (kcal mol^{-1})	vdW, H-bond (kcalmol^{-1})	LE	clog P
2a	-7.88	-0.14	-8.63	0.36	3.5
2b	-7.92	-0.16	-9.26	0.32	4.4
2c	-7.97	-0.15	-8.71	0.35	4.0
2d	-7.73	-0.17	-8.45	0.35	3.7
2e	-8.20	-0.27	-9.12	0.33	3.4

The indole-3-(CO)-benzothiazolamide derivatives, shown in Table 1, share a common framework in which the C5 position of the benzothiazole ring is substituted with CH_3, CH_3CH_2O, F and NO_2 functionalities.

According to the docking results (Table 2), the order of affinity to renin was 2e > 2c > 2b > 2a > 2d. Although the differences in binding free energy among the synthesized indole-3-(CO)-benzothiazolamide derivatives were small, compound 2e showed the highest affinity for the renin active site ($\Delta G_{binding}$: -8.20 kcal mol^{-1}). The contribution of vdW and H-bond interactions of compound 21 (-9.12 kcal mol^{-1}) in free energy of binding was greater than that of the electrostatic interactions. This trend was observed in other cases as well (Table 2). The highest van der Waals and hydrogen-bonding interaction energy was observed in compound 2b. It seems that the ethoxy group participates more efficiently than other groups at the C5 position of benzothiazole ring. However, compound 2b had the highest number of rotatable bonds in synthesized library. In this case, entropy loss in the binding process (torsional free energy) was calculated to be 1.49 kcal Mol^{-1}.

Considering the effects of C5 substitution on binding energy the ligand efficiency (LE) we calculated as $LE = \frac{\Delta G_{binding}}{N}$ that N was the number of ligand atoms excluding hydrogen atoms. LE reflects the contribution of each heavy atom of the ligand in the binding energy. Interestingly, the highest LE was observed in compound 2a, which bears no substitution at C5 position of benzothiazole ring. Therefore, from a lead-development perspective, the priority of substitution was H > CH_3 > F > NO_2 > CH_3CH_2O.

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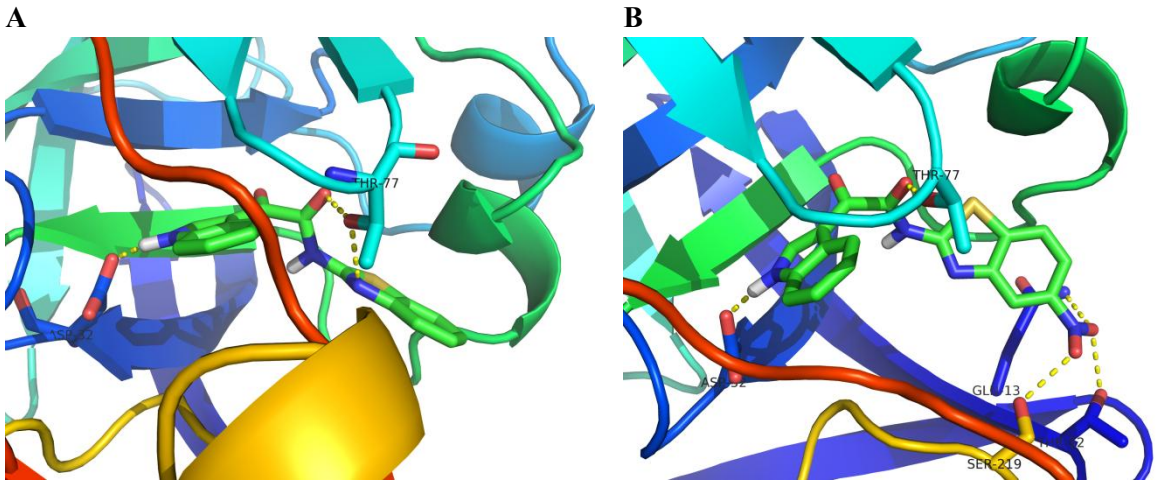

Figure 3. Orientation of compounds 2a (A) and 2e (B) in the active site of renin. Residues involving H-bond (yellow dash) represent by stick.

The key interactions were identified based on the redocking of the crystallographic ligand into its experimentally determined binding site. The resulting docking pose and interaction pattern were used as the reference for interpreting the binding mode of the newly reported compounds. The predicted binding pose of indole-3-(CO)-benzothiazolamide derivatives in the active site of renin showed similar binding patterns. Renin is an aspartyl protease and residues Asp32 and Asp215 play critical role in peptidase activity of the enzyme. Figure 3 shows the interaction of compounds 2a and 2e with the active site of renin. The indole ring in all derivatives formed hydrogen bond with key residue Asp32. Another key residue Asp215 interacted with phenyl ring of indole moiety through van der Waals interaction. Thr77 in the ceiling of the active site formed two hydrogen bonds with amide carbonyl moiety and nitrogen atom of benzothiazole ring in ligands 2a, 2c and 2d. Compounds 2e formed one hydrogen bond with Thr77 whereas compound 2b formed none. Extended interactions were observed in the case of ligands 2b and 2e. The oxygen atom of the ethoxy group in compounds 2b formed one hydrogen bond with amide moiety of Gln13. The nitro group in compounds 2e participated in hydrogen-bonding interactions with Thr12, Gln13 and Ser219 (Figure 3).

Conclusion

In summary, this study synthesized and characterized a new series of indole-3-(CO)-benzothiazolamide derivatives in two steps. It is then employed a docking approach to evaluate the potential of these derivatives as renin inhibitors. The docking results revealed that these compounds bind effectively to key renin residues, particularly Asp32 and Thr77. Among these compounds, the nitro derivative 2e showed the best binding affinity, while the unsubstituted analog 2a exhibited the highest ligand efficiency. The results suggest that the indole-3-(CO)-benzothiazolamide scaffold is a promising template for the development of new non-chiral renin inhibitors. Further structural optimization and biological testing are recommended to advance this class toward therapeutic applications.

Acknowledgments

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Competing Interests

The authors declare no competing interests.

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