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Research Article

SYNTHESIS, CHARACTERIZATION, INHIBITION OF RENIN AND ANTI MICROBIAL ACTIVITY OF SOME 3-PHENYL INDOLE DERIVATIVES

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ABSTRACT

The aim of present study was to develop renin inhibitor as anti-hypertensive drug. Selective inhibition of the renin has gained attraction as an interesting approach to control hypertension and associated cardiovascular risk factors given its unique position in the renin–angiotensin system. Using a combination of high-throughput screening, parallel synthesis, X-ray crystallography and structure-based design, we identified and optimized a novel series of potent and 3 substituted phenyl -2 (hydrazinocarbonyl)-1H indole 5 sulfonamide with remarkable potency for renin. A series of 3-phenyl Indole derivatives have been synthesized by the interaction of ethyl 5-(amino sulfonyl)-3substituted phenyl-1H-indole2 carboxylates with hydrazine hydrate and ethanol. The newly synthesized compounds were tested for antibacterial and anti-fungal activity also.

Keywords: Synthesis, Anti-hypertensive, Antibacterial activity, Anti-inflammatory activity, Indole, 3-phenyl Indole derivatives.

INTRODUCTION

The history of medicine is related to antiquity and to the very creator of this universe. In order to gain immortality to creator (BRAHAMA) gave the science of ayurveda (ayu mean life) which was propagated through his descendents mainly Daksa Prajapati. The modern drug development is now being done on a more rational basis. In this regard more and more information is being obtained in cell biochemistry and cell biology at the molecular level. The rational approach envisages a physiological basis of disease. Over the past decade advances in biotechnology have ushered in a new approach to drug discovery termed "structure based drug design" [1].

The approach to the practice of medicinal chemistry has developed from an empirical one involving organic synthesis of new compounds based on largely on modification of structure of known activity by a more logical approach. Medicinal chemistry is chemistry based discipline involving aspect of biological, medical and Pharma discovery, design, identification and preparation of biological active compound. The main objective of medicinal chemistry is the design and the production of compound that can be used as medicine for prevention, treatment, and cure of human and animal disease [2,3].

Hypertension is one of the major risk factors for cardiovascular diseases, which are the leading cause of mortality in the Western world. Lowering blood-pressure can considerably reduce the risk of myocardial infarction, stroke, heart failure and end-stage kidney disease. However, despite available therapies, approximately 70% of patients with hypertension do not reach their target blood pressure levels. Some of them yet do not respond fully to a combination of treatments. Consequently, opportunities remain for designing and developing well-tolerated effective medicines to control hypertension and associated cardiovascular diseases [4,5].

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The renin–angiotensin system (RAS) is well-established as an endocrine system involved in regulation of blood pressure and fluid electrolytes. Activation of the RAS is initiated by several signals including lowering of blood pressure, decrease in circulating volume or decrease in plasma-sodium concentration. These signals stimulate the release of the aspartyl protease renin, which cleaves angiotensinogen to produce angiotensin I. Since renin forms the rate-limiting step in this cascade and angiotensinogen is its only known substrate, inhibition of this step would be a very effective antihypertensive strategy [6,7].

Any appropriate medication affecting the RAS might also result in optimal end-organ protection, in particular for heart and kidney as shown in animal models. This might also be accompanied by a diminished potential for cough side effects, affecting 5–35% of patients treated with ACE inhibitors. Accordingly, substantial efforts were reported over the last decades to discover renin inhibitors for clinical use, for example, those structures shown in and to overcome issues like low oral bioavailability. Aliskiren (SPP100), an orally active renin inhibitor with four chiral centers is currently the only compound, which has reached the market. Consequently, several research groups have reported novel renin inhibitors on diverse scaffolds with different renin active-site binding topologies [8].

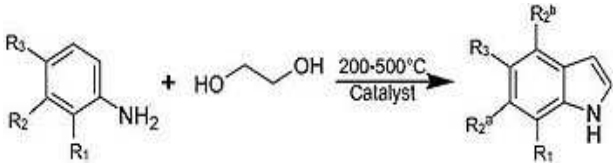
Indole is an aromatic heterocyclic organic compound. It has a bicyclic structure, consisting of a six-membered benzene ring fused to a five-membered nitrogen-containing pyrrole ring. Indole is a popular component of fragrances and the precursor to many pharmaceuticals. Compounds that contain an indole ring are called indoles. Notably, the indolic amino acid tryptophan is the precursor of the neurotransmitter serotonin. Indole is a solid at room temperature. Indole can be produced by bacteria as a degradation product of the amino acid tryptophan. It occurs naturally in human feces and has an intense fecal odor. At very low concentrations, however, it has a flowery smell, and is a constituent of many flower scents (such as orange blossoms) and perfumes. It also occurs in coal tar [9].

Indole undergoes electrophilic substitution, mainly at position 3. we report here the synthesis and inhibitory properties against all the series of 2-(hydrazinocarbonyl)-3-substituted-phenyl-1H-indole-5- substitutedphenyl) propionates, by literature procedures. Diazotization of sulfanilamide 4 led to the diazonium salt which has been coupled with the key intermediates 3 allowing the preparation of the hydrazones, which were cyclized in the presence of concentrated acid (HCl) to the indoles. The last step consisted in conversion of the ester moieties of 7 to the corresponding hydrazides by treatment with hydrazine hydrate at reflux, leading thus to the desired series of compounds [10].

Synthesis of indole

Indole is a major constituent of coal-tar, and the 220-260 °C distillation fractions is the main industrial source of the material. Indole and its derivatives can also be synthesized by a variety of methods. The main industrial routes start from aniline.

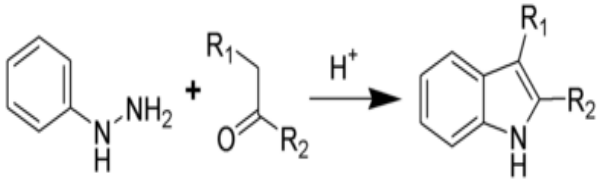
Illustrative of such large-scale syntheses, indole (and substituted derivatives) forms via vapor-phase reaction of aniline with ethylene glycol in the presence of catalysts:



Reactions are generally conducted between 200 and 500 °C. Yields can be as high as 60%. Other precursors to indole include formyltoluidine, 2-ethylaniline, and 2-(2-nitrophenyl) ethanol, all of which undergo cyclizations. Many other methods have been developed that are applicable.

The Leimgruber-Batcho indole synthesis is an efficient method of synthesizing indole and substituted indoles. Originally disclosed in a patent in 1976, this method is high-yielding and can generate substituted indoles. This method is especially popular in the pharmaceutical industry, where many pharmaceutical drugs are made up of specifically substituted indoles.

Fischer indole synthesis



One-pot microwave-assisted synthesis of indole from phenyl hydrazine and pyruvic acid.

One of the oldest and most reliable methods for synthesizing substituted indoles is the Fischer indole synthesis developed in 1883 by Emil Fischer. Although the synthesis of indole itself is problematic using the Fischer indole synthesis, it is often used to generate indoles substituted in the 2- and/or 3-positions. Indole can still be synthesized however using the Fischer indole synthesis by reacting phenyl hydrazine with pyruvic acid followed by decarboxylation of the formed indole-2-carboxylic acid. This has also been accomplished in a one-pot synthesis using microwave irradiation.

Renin-angiotensin system

Renin activates the renin-angiotensin system by cleaving angiotensinogen, produced by the liver, to yield angiotensin I, which is further converted into angiotensin II by ACE, the angiotensin-converting enzyme primarily within the capillaries of the lungs. Angiotensin II then constricts blood vessels, increases the secretion of ADH and aldosterone, and stimulates the hypothalamus to activate the thirst reflex, each leading to an increase in blood pressure. Renin is secreted from juxtaglomerular cells (of the afferent arterioles), which are activated via signaling (the release of prostaglandins) from the macula densa, which respond to the rate of fluid flow through the distal tubule, by decreases in renal perfusion pressure (through stretch receptors in the vascular wall), and by nervous stimulation, mainly through beta-1 receptor activation. A drop in the rate of flow past the macula densa implies a drop in renal filtration pressure. Renin's primary function is therefore to eventually cause an increase in blood pressure, leading to restoration of perfusion pressure in the kidneys.

RESULTS AND DISCUSSION

Chemistry

Sulfonamide I was previously reported by Salman's group, being easily prepared from sulfanilamide as starting material. Diazotization of sulfanilamide followed by condensation of the diazonium salt with ethyl 2-benzylacetoacetate led to an intermediate which was cyclized in acidic medium with formation of the ethyl ester derivative of L, which was then converted to the lead compound by treatment with hydrazine. We used a similar approach for the preparation of the series of congeners of L bearing different moieties in position 4 of the indole ring (Scheme). Condensation of ring-substituted benzyl bromides with ethyl acetoacetate gave the key intermediates, ethyl 2-acetyl-3-(substitutedphenyl) propionates (1a), by literature procedures. Diazotization of sulfanilamide led to the diazonium salt which has been coupled with the key intermediates (1a) allowing the preparation of the hydrazones (2a), which were cyclized in the presence of concentrated acid (HCl) to the indoles (3a). The last step consisted in conversion of the ester moieties of (3a) to the corresponding hydrazides by treatment with hydrazine hydrate at reflux, leading thus to the desired series of compounds (Spa-h). We have chosen the various substituents of the 3-phenyl group of indoles ar 4^{th} position (Spa-h) by considering both the limited available space within the hydrophobic pocket of the enzyme active site, as discussed above, as well as general medicinal chemistry considerations, for example, moieties that may increase lipo-or hydro solubility of the new compounds, and eventually also interacting in a positive manner with amino acid residues present in the active site region where this moiety of the inhibitors. Thus, we have incorporated 4-substituted phenyl groups possessing methyl-, halogeno- and methoxy- functionalities ensued by the presence of the additional functionality in the 3-phenyl ring may lead to diverse interactions of compounds 8 with amino acid residues within the various isoforms active sites cavity. The main interest in this class of compounds is that of detecting derivatives with a more isoform-selective profile as compared to the clinically used sulfonamides.

MATERIALS AND METHODS

All starting materials were from different manufactured company like (sd.fine chemicals, Merck, Lobachem etc.) And all the materials used without further purification all reactions were monitored by thin- layer-chromatography using TLC sheet coated with silica gel GF254 spots were visualized with UV light.

Experimental protocols

Chemistry

Buffers and chemicals were from sd.fine chemicals, Merck, Lobachem of highest purity available, and were used without further purification. All the synthesized 3 phenyl indole derivatives produced and purified in laboratory as described earlier. Melting points are recorded in open capillary one ended tubes and are uncorrected. The IR spectra (KBr) were recorded on a SHIMADZU FTIR-8300, spectrophotometer. The 1H-NMR spectra were recorded on a Bruker Advance-400 MHz spectrometer.

Ethyl 2-acetyl-3-(substitutedphenyl) propionate (1 a)

An ethanolic solution of sodium ethoxide was prepared by theaddition of sodium (1 g, 44 mmol) to dry ethanol (40 mL). Ethyl acetoacetate (20.8 g, 160.0 mmol) was added to the reaction mixture, and the solution was stirred for 10 min. at room temperature. Substituted benzyl bromide (10 g, 40 mmol) was added, and the reaction mixture was heated under reflux for 15 h. The mixture was concentrated under reduced pressure and the residue was taken up in ether (200 mL). The ether solution was washed with water (100 mL) and was dried. The residue after removal of solvent under reduced pressure was purified by fractional distillation.

2-Substitutedbenzyl-2-[N-(4-sulfonamidophenyl) hydrazono] ethanoates (2 a)

To a solution of 0.01 mol sulfanilamide in 8 ml of 37% HCl, 10 ml of 7% NaNO2 aqueous solution was added dropwise at 0 _C. This solution, containing diazonium salt, was poured into an ice-cold mixture of 4.6 g (a little excess of 0.02 mol) ethyl 2-substitutedbenzylacetoacetate, 20 ml

of EtOH, 40 ml of H2O and 5.4 g of KOH. The mixture was kept cold overnight. The hydrazone produced as an oil was separated, dissolved in Et2O, washed with H2O and dried over anhydrous Na2SO4. Et2 O was distilled; the oily residue was treated with 10 ml of 37% HCl and set aside for 5 h at room temperature. The resulting solid substance was recrystallized from EtOH.

Ethyl 5-(aminosulfonyl)-3-substitutedphenyl-1H-indole-2-carboxylates (3 a)

A mixture of 0.02 mol ethyl 2-substitutedbenzyl-2-[N-(4-sulfonamidophenyl) hydrazono] ethanoate (2a) and about 20 ml of 37% HCl was heated on a water bath for 4 h, cooled and poured into 200 ml of H2O, the crude product was filtered, washed with H2O, and recrystallized from EtOH.

2-(Hydrazinocarbonyl)-3-substitutedphenyl-1H-indole-5-sulfonamides (Sp a-h)

Ethyl 5-(aminosulfonyl)-3-substitutedphenyl-1H-indole-2-carboxylate Spa (0.01 mol, 6.9 g) was dissolved in 40 ml of EtOH, 8ml of H2NNH2.H2O was added and refluxed for 6 h, cooled andkept cold overnight. The resulting crystals were filtered off, washed with Et2O and recrystallized from EtOH/DMF.

2-(Hydrazinocarbonyl)-3-phenyl-1H-indole-5-sulfonamide sulfonamide

Yield 70%; mp 273–5_C; IR(KBr) (t, cm_1),1640 (CO) ; 1H NMR (DMSO-d6, 500 MHz) d (ppm): 4.50 (2H, s,NHNH2), 7.13 (2H, s, SO2NH2), 7.48 (2H, d, J = 8.79 Hz, Ar-H),7.53 (2H, d, J = 8.30 Hz, Ar-H), 7.58 (1H, d, J = 8.30 Hz, indole C7–H), 7.68 (1H, dd, J = 8.78,1.46 Hz, indole C6–H), 8.01 (1H, d,J = 0.98 Hz, indole C4–H), 9.14 (1H, s, CONH), 12.15 (1H, br s, indole NH).

3-(4-Chlorophenyl)-2-(hydrazinocarbonyl)-1H-indole-5-sulfonamide

Yield 70%; mp 273–5_C; IR(KBr) (t, cm_1),1640 (CO) ,712 (C-Cl); 1H NMR (DMSO-d6, 500 MHz) d (ppm): 4.50 (2H, s,NHNH2), 7.13 (2H, s, SO2NH2), 7.48 (2H, d, J = 8.79 Hz, Ar-H),7.53 (2H, d, J = 8.30 Hz, Ar-H), 7.58 (1H, d, J = 8.30 Hz, indole C7–H), 7.68 (1H, dd, J = 8.78,1.46 Hz, indole C6–H), 8.01 (1H, d,J = 0.98 Hz, indole C4–H), 9.14 (1H, s, CONH), 12.15 (1H, br s, indole NH).

3-(4-Hydroxyphenyl)-2-(hydrazinocarbonyl)-1H-indole-5-sulfonamide

Yield 70%; mp 273–5_C; IR(KBr) (t, cm_1),1640 (CO) ,1536 (C-OH); 1H NMR (DMSO-d6, 500 MHz) d (ppm): 4.50 (2H, s,NHNH2), 7.13 (2H, s, SO2NH2), 7.48 (2H, d, J = 8.79 Hz, Ar-H),7.53 (2H, d, J = 8.30 Hz, Ar-H), 7.58 (1H, d, J = 8.30 Hz, indole C7–H), 7.68 (1H, dd, J = 8.78,1.46 Hz, indole C6–H), 8.01 (1H, d,J = 0.98 Hz, indole C4–H), 9.14 (1H, s, CONH), 12.15 (1H, br s, indole NH).

3-(4-Nitrophenyl)-2-(hydrazinocarbonyl)-1H-indole- 5-sulfonamide

Yield 70%; mp 273–5_C; IR(KBr) (t, cm_1),1640 (CO) ,1342 (C-NO_2); 1H NMR (DMSO-d6, 500 MHz) d (ppm): 4.50 (2H, s,NHNH2), 7.13 (2H, s, SO2NH2), 7.48 (2H, d, J = 8.79 Hz, Ar-H),7.53 (2H, d, J = 8.30 Hz, Ar-H), 7.58 (1H, d, J = 8.30 Hz, indole C7–H), 7.68 (1H, dd, J = 8.78,1.46 Hz, indole C6–H), 8.01 (1H, d,J = 0.98 Hz, indole C4–H), 9.14 (1H, s, CONH), 12.15 (1H, br s, indole NH).

3-(4-Aminophenyl)-2-(hydrazinocarbonyl)-1H-indole- 5-sulfonamide

Yield 70%; mp 273–5_C; IR(KBr) (t, cm_1),1640 (CO) ,1572 (C-NH_2); 1H NMR (DMSO-d6, 500 MHz) d (ppm): 4.50 (2H, s,NHNH2), 7.13 (2H, s, SO2NH2), 7.48 (2H, d, J = 8.79 Hz, Ar-H),7.53 (2H, d, J = 8.30 Hz, Ar-H), 7.58 (1H, d, J = 8.30 Hz, indole C7–H), 7.68 (1H, dd, J = 8.78,1.46 Hz, indole C6–H), 8.01 (1H, d,J = 0.98 Hz, indole C4–H), 9.14 (1H, s, CONH), 12.15 (1H, br s, indole NH).

3-(4-bromophenyl)-2-(hydrazinocarbonyl)-1H-indole- 5-sulfonamide

Yield 70%; mp 273–5_C; IR(KBr) (t, cm_1),1640 (CO) ,581 (C-Br); 1H NMR (DMSO-d6, 500 MHz) d (ppm): 4.50 (2H, s,NHNH2), 7.13 (2H, s, SO2NH2), 7.48 (2H, d, J = 8.79 Hz, Ar-H),7.53 (2H, d, J = 8.30 Hz, Ar-H), 7.58 (1H, d, J = 8.30 Hz, indole C7–H), 7.68 (1H, dd, J = 8.78,1.46 Hz, indole C6–H), 8.01 (1H, d,J = 0.98 Hz, indole C4–H), 9.14 (1H, s, CONH), 12.15 (1H, br s, indole NH).

3-(4-Methylphenyl)-2-(hydrazinocarbonyl)-1H-indole-5-sulfonamide

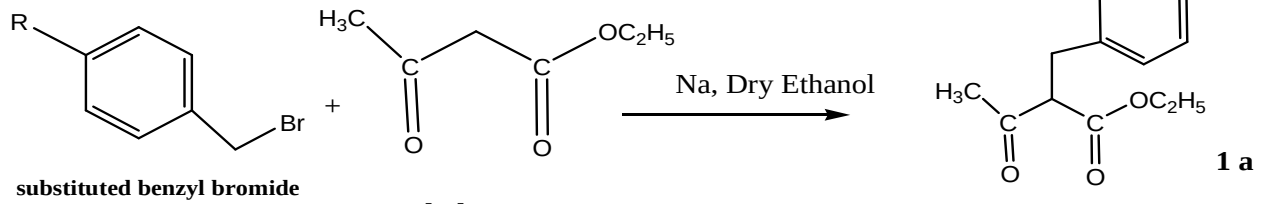
Yield 70%; mp 273–5_C; IR(KBr) (t, cm_1),1640 (CO) ,3072 (C-CH_3); 1H NMR (DMSO-d6, 500 MHz) d (ppm): 4.50 (2H, s,NHNH2), 7.13 (2H, s, SO2NH2), 7.48 (2H, d, J = 8.79 Hz, Ar-H),7.53 (2H, d, J = 8.30 Hz, Ar-H), 7.58 (1H, d, J = 8.30 Hz, indole C7–H), 7.68 (1H, dd, J = 8.78,1.46 Hz, indole C6–H), 8.01 (1H, d,J = 0.98 Hz, indole C4–H), 9.14 (1H, s, CONH), 12.15 (1H, br s, indole NH).

3-(4-Flurophenyl)-2-(hydrazinocarbonyl)-1H-indole- 5-sulfonamide

Yield 70%; mp 273–5_C; IR(KBr) (t, cm_1),1640 (CO) ,1218 (C-F); 1H NMR (DMSO-d6, 500 MHz) d (ppm): 4.50 (2H, s,NHNH2), 7.13 (2H, s, SO2NH2), 7.48 (2H, d, J = 8.79 Hz, Ar-H),7.53 (2H, d, J = 8.30 Hz, Ar-H), 7.58 (1H, d, J = 8.30 Hz, indole C7–H), 7.68 (1H, dd, J = 8.78,1.46 Hz, indole C6–H), 8.01 (1H, d,J = 0.98 Hz, indole C4–H), 9.14 (1H, s, CONH), 12.15 (1H, br s, indole NH).

Scheme

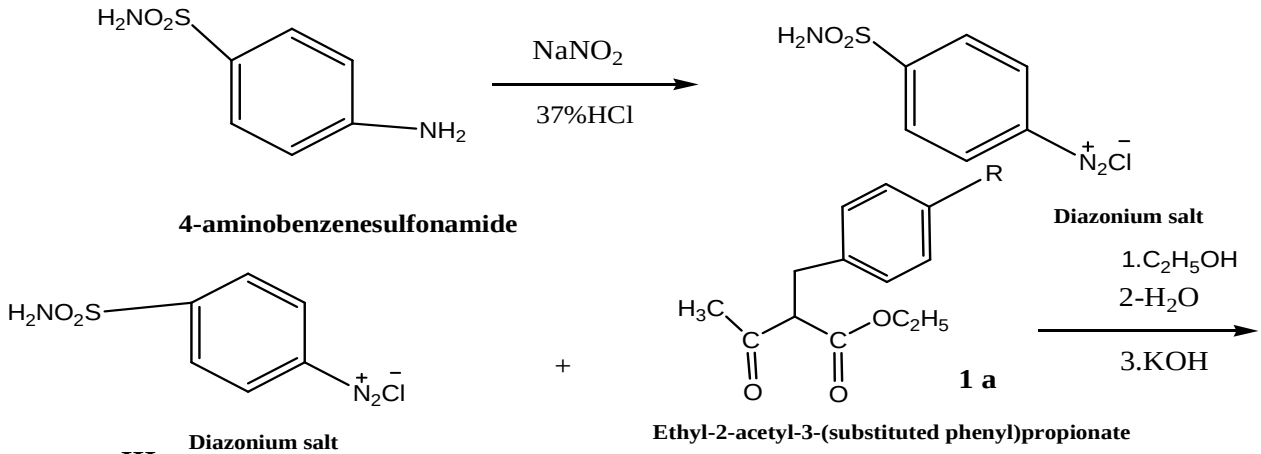
step I



substituted benzyl bromide **Ethyl acetoacetate** **1 a**

Ethyl-2-acetyl-3-(substituted phenyl)propionate

step II

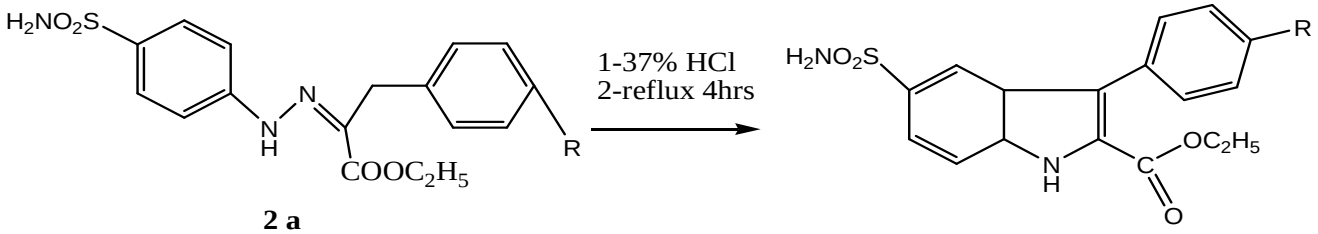


4-aminobenzenesulfonamide **Diazonium salt**

Diazonium salt **1 a**

Ethyl-2-acetyl-3-(substituted phenyl)propionate

step III



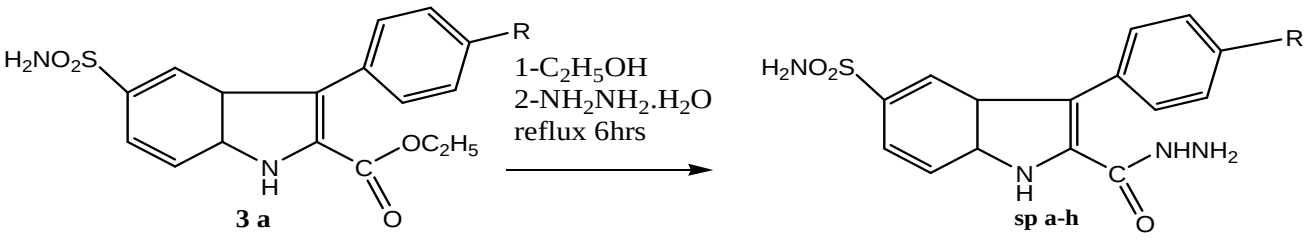
2 a

2-substituted benzyl-2-[N-(4-sulfonamido phenyl) hydrazone]ethanoate

3 a

Ethyl5-(amino sulfonyl)-3substituted phenyl-1H-indole2-corboxylate

step IV



3 a **sp a-h**

Ethyl5-(amino sulfonyl)-3substituted phenyl-1H-indole2-corboxylate

2-(hydrazino corbonyl)-3-substituted phenyl-1H-indole 5-sulfonamides

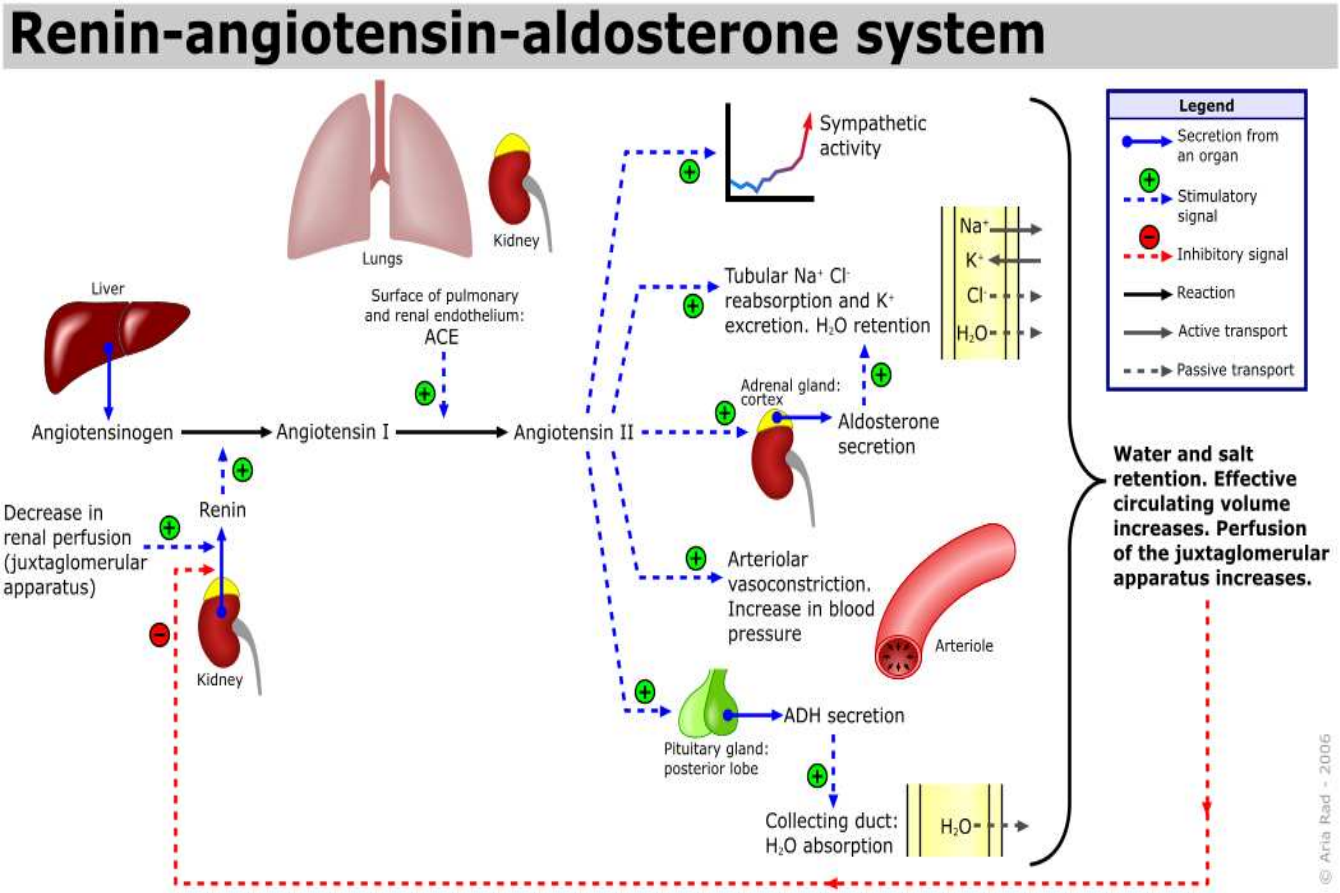


Table 1. Physico chemical properties of different 3-phenyl indole derivatives

S.No	Compound	R	Mol.Formula	M.Wt	Yield (%)	M.P	Rf value
1	Sp a	-H	$C_{15}H_{14}SO_3N_4$	330	65.8%	207^0C-209^0 C	0.721
2	Sp b	-Cl	$C_{15}H_{13}SO_3N_4Cl$	365	55.2%	209^0C-210^0C	0.734
3	Sp c	-OH	$C_{15}H_{14}SO_4N_4$	346	69.5%	211^0C-213^0C	0.754
4	Sp d	$-NO_2$	$C_{15}H_{13}SO_5N_5$	375	68.3%	206^0C-208^0C	0.643
5	Sp e	$-NH_2$	$C_{15}H_{15}SO_3N_5$	345	59.9%	217^0C-218^0C	0.654
6	Sp f	-Br	$C_{15}H_{13}SO_3N_4Br$	409	58.1%	210^0C-212^0C	0.739
7	Sp g	$-CH_3$	$C_{16}H_{16}SO_3N_4$	344	59.0%	205^0C-206^0C	0.689
8	Sp h	-F	$C_{15}H_{13}SO_3N_4F$	348	60.7%	204^0C-206^0C	0.651

Renin inhibitor activity as compared to aliskiren

Table 2. IC_{50} value of different derivatives of 3-phenyl indole.

Compounds	IC_{50} Value
Sp a	86
Sp b	$5.4x10^2$
Sp c	50
Sp d	45
Sp e	63
Sp f	$2.2x10^2$
Sp g	$1.6x10^2$
Sp h	1.5

Table 3. Biological activities of the compound SPa-SPh (500 µg/ml)

Compounds	R	Zone of inhibition (mm)				
		Antimicrobial activity (500 µg/ml)			Anti fungal activity(500 µg/ml)	
		S.aureus	B.subtilis	E.coli	C.albicans	A.niger
Spa	Cl	25	23	24	15	NS
Spb	H	23	25	20	21	NS
Spc	OH	34	22	25	21	25
Spd	NO2	27	20	22	15	NS
Spe	NH2	29	26	20	22	NS
Spf	Br	35	23	22	20	29
Spg	CH3	12	20	26	23	NS
Sph	F	20	22	24	28	26

CONCLUSION

In conclusion, we have synthesized some 3 phenyl indole derivatives (Sp a-h) and evaluated these compounds for their inhibition of renin activities. Most of them demonstrated a broad spectrum of Anti microbial activities. The simple 3 phenyl indole derivatives Sp b, Sp f and Sp g were concluded as most potent derivatives in all the cases.

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