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Synthesis and Evaluation of Substituted 1, 2, 4 Triazolinone Derivatives as Novel Angiotensin Ii Receptor Antagonists as Antihypertensive Agents

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Abstract: A set of substituted 1, 2, 4 triazolinone derivatives have been synthesized as novel angiotensin II (Ang II) receptor antagonists as antihypertensive agents. Systematic variation of the substituents at the ortho position of N- aryl triazolinones resulted in six novel compounds. The compounds have been evaluated in vivo antihypertensive activity via acute renal hypertension model. Amongst the six compounds synthesized two compounds were found to possess promising antihypertensive activity. Compounds TZN1 and TZN4 emerged as maximally active compounds comparable to Losartan and Telmisartan which are a prototype for this class of drugs. A receptor binding model is also proposed on the basis on the basis of structure–activity relationship in this study.

Key words: Antihypertensive agents · Angiotensin II receptor antagonists · Substituted triazolinones · Synthesis

INTRODUCTION

Hypertension is a major risk factor for cerebro-cardiovascular diseases, the renin-angiotensin-system (RAS) plays a pivotal role in many cardiovascular and renal diseases [1]. Angiotensin II is one of the most powerful endogenous vasoconstrictors produced by limited and very specific proteolysis of its precursor protein, angiotensin I in RAS. The action of Ang II is mediated through selective membrane bound Angiotensin II receptors Type 1 (AT_1) and Type 2 (AT_2). These receptors have been identified and belong to the G- protein coupled receptor super family (GPCRs). The AT_1 receptor exists in the blood vessels, liver, kidneys, adrenal cortex and heart and cardiovascular effects of AT II are mainly mediated by AT_1 receptor [2-4]. In the last decades several selective antagonists have been designed developed and are used to treat both hypertension and damage associated with the diseases such as arthrosclerosis and diabetes [5-15]. Meanwhile other compounds structurally related to losartan have been synthesized [16-26].

RESULT AND DISCUSSION

Chemistry: The compounds as depicted in Table 1 are synthesized via Scheme1, 2 [26] as shown in Figure 1 and 2. Alkylation of the Intermediate II by biphenyl carboxylate methyl ester followed by ester cleavage yielded the final carboxylic acid compounds. All the final compounds obtained were purified by recrystallisation and column chromatography and purity of the compounds was ascertained by thin layer chromatography [27-28]. Physico chemical characterization characterizations of the com pounds was done and structure of the compounds was established through FTIR, 1H NMR and MASS spectral data analyses.

The infrared data obtained for substituted triazolonones exhibit an identical trend of stretching frequency modes. The =C-H stretch in aromatic compounds was observed in the range of 3100-3000 cm^{-1} for all the synthesized compounds. In aromatic compounds the (-N-O-) stretching variations for nitro groups occurs at 1550 -1435 cm^{-1} (asymmetric) and

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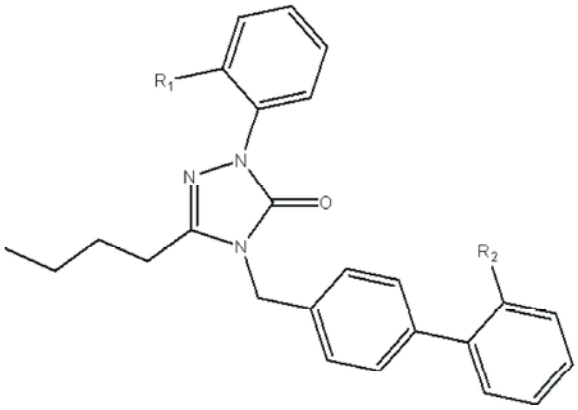
Table 1: Structure of compounds as N Aryl substituted triazolinones



S. No.	Compound Name	R_1	R_2
1.	TZN1	2-NO_2	-COOH
2.	TZN2	2,6-Cl	-COOH
3.	TZN3	2-OCH_3	-COOH
4.	TZN4	2-CF_3	-COOH
5.	TZN5	2-F	-COOH
6.	TZN6	2-NH_2	-COOH

Table 2: Physicochemical data of compounds

					Analysis %				
Comp. code	R^1	Molecular formula	M. P. (°C)	Yield (%)	C	H	N	O	X
TZN1	2-NO_2	$C_{26}H_{24}N_4O_5$	99-101	71	66.05	5.08	11.81	16.90	-
TZN2	2,6-Cl	$C_{26}H_{23}Cl_2N_3O_3$	114-115	80	62.90	4.65	8.44	9.65	14.25
TZN3	2-OCH_3	$C_{27}H_{27}N_3O_4$	105-107	45	70.85	5.93	9.15	13.98	-
TZN4	2-CF_3	$C_{27}H_{24}F_3N_3O_3$	83-85	50	65.43	4.85	8.46	9.66	11.48
TZN5	2-F	$C_{26}H_{24}FN_3O_3$	88-90	50	70.08	5.46	9.42	10.75	4.25
TZN6	2-NH_2	$C_{26}H_{26}N_4O_3$	Oily	33	70.55	5.90	12.64	10.83	-

Scheme 1:

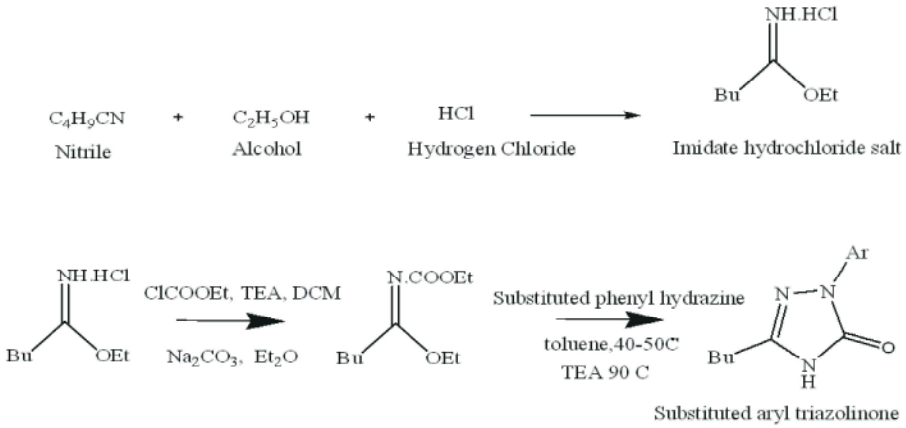


Fig. 1: Complete scheme of synthesis of substituted triazolinone

1360-1290 cm^{-1} (symmetric), the bands of 1550-1435 cm^{-1} being stronger of the two. Peaks in the region 1600-1500 cm^{-1} can be assigned to C=N, C=C in case of case of heteroaromatics. The bands 2850-2869 cm^{-1} indicate the presence of methylene group in the compounds. The aryl rings in all the compounds shows multiple peaks in the range of 7.12 to 8.19 ä due to various aromatic hydrogens surrounded by different environment

Scheme 2:

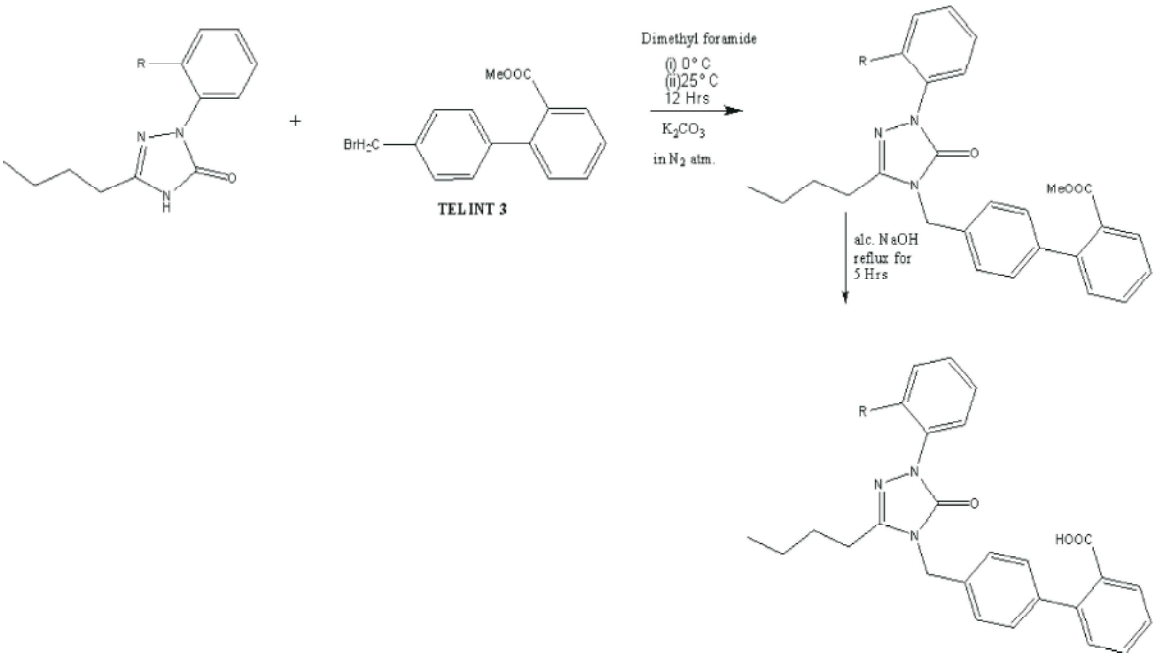


Fig. 2: Complete scheme of alkylation of substituted triazolinones

Table 3: Spectral data of compounds

Comp. code	R1	1H NMR (DMSO-d6) (d, ppm)	MS (M^+)	FTIR (KBr/cm^{-1}) observed
TZN1	2-NO_2	11.0 (s, 1H, COOH), 7.12-8.17 (m, 12H, Ar-H), 4.42 (s, 2H, CH2), 1.30 (m, 6H, CH2), 0.96 (t, 3H, CH3)	M+1	3031 (C–H Ar), 2920 (C–H aliphatic), 2840 (C–H aliphatic), 1623 (C=N), 1604-1569&1455–1438 (C=C Ar.), 1122 (C–N) 1510 (N=O sym), 1378 (N=O asy)
TZN2	2,6-Cl	11.0 (s, 1H, COOH), 7.12-8.19 (m, 11H, Ar-H), 4.42 (s, 2H, CH2), 1.33 (m, 6H, CH2), 0.96 (t, 3H, CH3)	M+2	3014 (C–H Ar), 2988, (C–H aliphatic), 2808 (C–H aliphatic), 1628 (C=N), 1609–1565, 1452–1396 (C=C Ar.), 1123 (C– N) 753 (C-Cl str)
TZN3	2-OCH_3	11.0 (s, 1H, COOH), 7.12-8.19 (m, 12H, Ar-H), 4.42 (s, 2H, CH2),1.3 (m, 6H, CH2), 0.96 (t, 3H, CH3), 3.73 (t, 3H, CH3)	M+1	3022 (C–H Ar), 2975, 2949 (C–H aliphatic), 2843 (C–H aliphatic), 1638 (C=N), 1611–1561 &1477–1431 (C=C Ar.), 1133 (C– N)
TZN4	2-CF_3	11.0 (s,1H,COOH), 7.12-8.19 (m, 12H, Ar-H), 4.42(s, 2H, CH2),1.3 (m, 6H, CH2), 0.96 (t, 3H, CH3)	M+1	3015 (C–H Ar), 2986, 2934 (C–H aliphatic), 2808 (C–H aliphatic), 1627 (C=N), 1599–1565&1458–1396 (C=C Ar.), 1123 (C– N), 740 (C-F str)
TZN5	2-F	11.0 (s,1H, COOH), 7.12-8.19 (m, 12H, Ar-H), 4.42(s, 2H, CH2),1.3 (m, 6H, CH2), 0.96 (t, 3H, CH3)	M+1	3025 (C–H Ar), 2924 (C–H aliphatic), 2843 (C–H aliphatic), 1621 (C=N), 1605–1565 &1478–1438 (C=C Ar.), 1113 (C– N), 740 (C-F str)
TZN6	2-NH_2	11.00 (s,1H,COOH), 7.12-8.19 (m, 12H, Ar-H), 4.42 (s, 2H, CH2), 1.30 (m, 6H, CH2), 0.96 (t, 3H, CH3), 4.00 (d, 2H)	M+1	3436, 3398, 3320 (NH_2), 3025 (C–H Ar) 2924 (C–H aliphatic), 2843 (C–H aliphatic), 1621 (C=N), 1605–1565 &1478–1438 (C=C Ar.), 1113 (C– N)

in different compounds. A singlet peak at 4.42 δ around can be attributed to the presence of -CH_2- methylene spacer linkage protons.

Pharmacological Evaluation (*In vivo* Activity): The antihypertensive effect of all compounds differs in maximum fall in Mean Arterial Blood Pressure (MABP)

Table 4: Antihypertensive activity of standard and compounds

S.No.	Sample No.	Mean Arterial Blood Pressure (mm-Hg)
1.	Control	134 mm Hg
2.	Losartan	92
3.	Telmisartan	89
4.	TZN1	95
5.	TZN2	97
6.	TZN3	97
7.	TZN4	91
8.	TZN5	98
9.	TZN6	117

Data are expressed in Mean±SEM,

Statistical anlalysis: Oneway ANOVA Followed By Dunnet test

*Significant, **Very Significant, *** Highly Significant

produced from initial value. The mentioned Table 4 shows the fall in BP. Both the standard drugs showed a prominent fall in MABP. The fall in blood pressure produced by losartan was from 134 mmHg to 92 mm Hg i. e. 42 mm Hg. Telmisartan has shown a maximum fall in BP to 90 mm Hg i. e. 45 mm Hg. Amongst all the compounds these compounds, maximum fall was seen for Compound TNZ4 and TNZ1 to a value of 91 AND 95 mm Hg i.e. 43 mm Hg from initial value which is comparable to that of telmisartan and greater than that of losartan. The compounds TNZ2, TNZ3, TNZ5 and TNZ6 have shown a reduction in MABP. So these compounds can be regarded as comparable to losartan in their antihypertensive action in terms of minimum blood pressure values achieved. Compound TNZ6 has shown least antihypertensive activity amongst the all synthesized compounds although they possess antihypertensive effect to some extent. Maximum lowering of BP is seen with compound TNZ4 which shown a fall of BP about 43 mm Hg. and this effect is greater than that to Losartan (42 mm Hg) and comparable to those of telmisartan (45 mm Hg) [29-31]. Data was expressed as mean and standard error of the mean of three experiments. All experimental data was statistically compared as repeated measures using one way ANOVA followed by Dunnet test (Prism Graph pad Trial Version-5). $P<0.05$ in two tailed tests was considered significant.

Experimental

Chemistry

Synthesis of Intermediate I (Scheme I), [Carbethoxyvalerimidate]: Into a cooled mixture of anhydrous acetonitrile (135 g), absolute ethyl alcohol (200 cc.) and absolute ether (120 cc.), there was introduced a slight molecular excess of hydrogen chloride. This mixture, after standing in the icebox overnight, solidified into a hard cake of white, shining plates of Ethyl valerimidate hydrochloride. Ethyl valerimidate hydrochloride (76.7 mmol) was dissolved in K_2CO_3 (aqueous, 33% w/w) and extracted with 3 X 40 mL of ether. The combined ether layers were dried over Na_2SO_4, filtered and concentrated in vacuo to give ethyl valerimidate (72%) free base as clear oil which was used directly in the ensuing reaction. A solution of ethyl valerimidate (50.3 mmol) free base, prepared above, in 90 mL of dry CH_2Cl_2 was treated with triethylamine (55.3 mmol). The resulting solution was stirred at -10 degree C in an ice-salt bath as a solution of ethyl chloroformate (50.3 mmol) in 10 ml of CH_2Cl_2 was added dropwise over 25 min. Upon completion of addition, the cooling bath was removed and the mixture was stirred at room temperature for 2 h. After evaporation of the solvent in vacuo, the residue was taken up in hexane and filtered to remove triethylamine hydrochloride. Concentration of the filtrate yielded (65%) of the desired product Ethyl N-Carbethoxyvalerimidate as a yellow oil, suitable for use in the next step without further purification.

Synthesis of Intermediate II (Scheme I) [5-n-Butyl-2-(2-susbtituted phenyl)-2, 4-dihydro-3H- 1, 2, 4-triazoline-3-one]: To a solution of substituted phenylhydrazine (2.0 mmol, generated from the hydrochloride by partitioning between ether and 1 N Na_2CO_3) in 6 mL of toluene was added Ethyl N-Carbethoxyvalerimidate (2.2 mmol) and the mixture was heated at 45-50 degree C for 1.5 h. Subsequently, (2.2 mmol) of triethylamine was added and the reaction mixture was stirred at 90 degree C overnight. The solution was cooled to room temperature and concentrated in vacuo.

Synthesis of Final Compounds [Biphenyl Acid Derivatives]: All the reactions procedures for the synthesis of Intermediates in Figure 2 were performed in inert atmosphere under nitrogen and with anhydrous solvents.

General Procedure for Alkylation with the Alkyl Bromide Possessing Protected Carboxylic Acid Moiety: Potassium carbonate (60 mmol) was added portion-wise to a solution of Intermediate I (30 mmol) in anhydrous dimethyl formamide (10 ml) under nitrogen atmosphere. The desired alkyl bromide (TELINT3, 45mmol) was then added to the reaction mixture, which was allowed to stir for 10-15 h at room temperature under nitrogen. Water (80 ml) was added and the resulting suspension was extracted with ethyl acetate. The combined organic

extracts were washed with water and passed through dried magnesium sulphate and the solution was concentrated. The resulting precipitate was collected by filtration, washed with diethyl ether and further purified by column chromatography (0.6-1.0% methanol in dichloromethane).

General Procedure for Hydrolysis of Carboxy Methyl Group to Acidic Group: A solution of Intermediate IIB (0.30 g, 0.73 mmol) in 16 ml of ethanol and 8 ml of 10% aqueous sodium hydroxide was refluxed for 5 h. After cooling, the reaction mixture was filtered and the solvent was removed under vacuum. The residue was dissolved in water and the solution was acidified to pH 3.5 with hydrochloric acid. The precipitated solid was recovered by filtration and recrystallized from aqueous ethanol to furnish the product.

Physicochemical Characterization: Thin layer chromatography was performed on E Merck, TLC SILCA GEL 60 F_{254}, 0. 2 mm thickness on precoated aluminum sheet. Solvent systems at different concentration dichloromethane methanol was used to ascertain the progress, completion of reaction and purity of the synthesized compounds. UV lamp was used for detection. Iodine vapors were used in some cases as detecting agent. Melting points were determined by open capillary method melting point apparatus and were uncorrected. Infrared spectra were taken on FT-IR spectrophotometer Shimadzu DZU 8400S at School of Pharmacy, Devi Ahilya Vishwavidyalaya, Indore. The elemental analysis (C, H, N, O, S) was done on Carlo Erba 1108 elemental analyser at Sophisticated Analytical Instrumental Facility, Central Drug Research Institute Lucknow. Mass spectra were obtained as Dart-MS (Direct Analysis in Real Time) by a JEOL-AccuTOFJMS-T100LC Mass spectrophotometer at Sophisticated Analytical Instrumental Facility, Central Drug Research Institute, Lucknow. ^{1}H NMR spectra were obtained on a Bruker advance 400 and 300 MHz NMR spectrometer at Sophisticated Analytical Instrumental Facility, Central Drug Research Institute, Lucknow.

Pharmacological Evaluation (*In vivo* Evaluation)

Renovascular Hypertension Model: Biological evaluation of a anti-hypertensive agent involves measurement of its effect on arterial blood pressure by renonvascular hypertension model. The compounds were tested for the presence of different functional group's substitution and their effect on the antihypertensive activity. Male albino wistar rats weighing 125-180g were provided by the Institutional Animal House of B.R. Nahata College of Pharmacy, Mandsaur. The acute renal hypertension blood pressure measurement model (Hauser *et al*., 2005, Gilani *et al*., 2005, Vogel *et al*., 1996) was used for evaluation.

Experimental Design: A Mercury manometer, Physiograph (Student physiographic, 3 Channel, Biodevice by Incolab, Ambala), Blood pressure transducer, Strain gage coupler. The Solutions/Chemicals required for experimental studies are Sodium chloride 0.9%, Heparin 1000 I.U. /ml Solution, Adrenalin -10 µg/100ml, Noradrenalin -10 µg/100ml, Acetylcholine -10 µg/100ml, Losartan - 5 mg/kg body weight, Telmisartan - 5 mg/kg body weight, Anesthetic agent: ketamine. HCl + xylazine. The physiograph and transducer was calibrated with the help of mercury manometer. Level of mercury in left arm of manometer was adjusted to 90-100 mm of Hg (normal blood pressure), this was done in step of 10 mm at a time and the physiograph so obtained was used as a calibration graph for further calculation. One arm of transducer syringe containing 1000 I.U. heparin solution was attached in order to prevent coagulation of blood. Male albino rats weighing about 125-180 gm were taken for the study. The animal was anesthetized by intraperitonial injection of mixture of ketamine hydrochloride and xylazine. After induction of anesthesia, left renal artery was blocked by use of artery clamp for 45 minutes. Clamping of the left renal artery was done to raise the systolic pressure. The trachea was cannulated to provide artificial respiration to animals during surgery. The jugular vein was cannulated and 0.5 ml dose of normal saline was given to animal via jugular vein, all the standard and test compounds were given to animal by this route. The carotid artery was cannulated and attached with pressure transducer. This pressure transducer was previously calibrated with the help of mercury manometer and a calibration pressure curve was obtained. After attaching the carotid cannula the renal artery clamp was removed, this caused a sharp increase in the blood pressure due to activation of renin angiotensin system and rise in the plasma renin level. Standard solution of losartan at a dose of 5 mg/kg body weight were administrated via jugular vein and after giving drug dose wait till blood pressure was not reached up to base line level. Standard solution of telmisartan at a dose of 5 mg/kg body weight were administrated via jugular vein and after giving drug dose wait till blood pressure was not reached up to base line level. Take responses of test compounds same as standard. The standard and test

compounds were administered one by one in juggler vein and they showed their response i.e. decrease in blood pressure on physiograph obtained. Change in blood produced by the six synthesized compounds was compared against that losartan and telmisartan and three responses of each sample for obtaining mean blood pressure were taken as shown in Table 4. Data was expressed as mean and standard error of the mean of three experiments. Data were statistically compared as repeated measures using one way ANOVA followed by Dunnet test (Prism Graph pad Trial Version-5). $P<0.05$ in two tailed tests was considered significant.

CONCLUSION

The compounds were subjected to biological screening for *in-vivo* antihypertensive activity. Two compounds TNZ4 and TNZ1 seems promising as new angiotensin II receptor antagonist as antihypertensive agents. Compounds TNZ4 was most active and compounds TNZ2, TNZ3, TNZ5 have also shown promising activity. Further, radio ligand binding studies and in vivo studies to determine ED_{50} and LD_{50} of these compounds can add up in designing of potential drug candidates as antihypertensive agents. The significance of such work lies in the possibility that the new compounds might be more efficacious agents against hypertension with a thorough investigation regarding the structure activity relationship, toxicity and in their biological effects, is required which could be helpful in designing novel compounds with promising antihypertensive activity.

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