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Synthesis and Evaluation of Chalcone Analogues Based Pyrimidines as Angiotensin Converting Enzyme Inhibitors

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Abstract: Hypertension is a widespread and frequently progressive ailment that imparts a foremost threat for cardiovascular and renal disorders. Mammoth efforts are needed for the synthesis of innovative antihypertensive agents to combat this lethal disease. Chalcones have shown antihypertensive activity through inhibition of Angiotensin Converting Enzyme (ACE). Hence, a series of chalcone analogues is synthesized and used as precursor for the synthesis of novel series of pyrimidines. Precursor chalcones were prepared by reacting aldehydes and ketones in presence of sodium hydroxide followed by synthesis of corresponding pyrimidines by reaction with urea in presence of potassium hydroxide. Both groups were then evaluated for their effects on ACE. The results depicted that pyrimidines were more active than chalcones with methoxy (C5 and P5) substitution showing best results to inhibit ACE. Given that chalcone analogues and pyrimidines show a potential as the angiotensin converting enzyme inhibitors.

Key words: ACE inhibitors, chalcones, hypertension, pyrimidines, renin-angiotensin system

INTRODUCTION

Hypertension is a widespread and frequently progressive ailment that imparts a foremost threat for cardiovascular and renal disorders (Chalmers, 1999, Odama and Bakris, 2000). Latest survey uncovered that the universal lumber of hypertension is an imperative and escalating public health problem worldwide and the degree of understanding, cure and management of hypertension differs by far amongst various countries. The adults affected by hypertension were 972 million all over the world in 2000 and were estimated to approach 1.56 billion by 2025 (Kearney *et al*., 2005). Physiopathologically, hypertension involves differences in at least one of hemodynamic variables (cardiac output, arterial rigidity, or peripheral resistance) that establish the assessable blood pressure. Each variable is a possible remedial aim and most probably, the alterations in these variables also add to the diversity in the pharmacologic retort of hypertensive patients. As a result, advanced treatment plans should not only concentrate on blood pressure cutback but also in normalizing vascular constitution and function. It is understood that the Renin–Angiotensin System (RAS) has a pivotal role in cardiovascular structure, water-electrolyte equilibrium and cell functions. Over-activation of this system has been the main cause of hypertensive crisis. Angiotensin Converting Enzyme (ACE) has important physiological roles in normalizing blood pressure because it is the foremost regulatory site of RAS (Bonesi *et al*., 2010). Biochemically, ACE transforms angiotensin-I, an inactive decapeptide to angiotensin-II, an octapeptide that is a potent vasoconstrictor (Ondetti and Cushman, 1982). Bradykinin, a vasodilator, is also inactivated by ACE (Ondetti and Cushman, 1982). These familiar biochemical pathways have led to the creation of ACE inhibitors such as captopril, lisinopril, enalapril and fosinopril in the treatment of hypertension (Atkinson *et al*., 1980; Brown and Vaughan, 1998). On the contrary, some of these ACE inhibitors are vulnerable to proteolysis, resulting in side effects (Sharif *et al*., 1994). Still there is a requirement for the synthesis of innovative antihypertensive agents.

In spite of a variety of biological properties, only a handful of previous reports highlighted the potential of chalcones, in lowering blood pressure via inhibition of ACE (Kang *et al*., 2003). Chalcones are the predecessors for the synthesis of flavonoids and isoflavonoids (Avila *et al*., 2008) which are the ingredients of everyday diet. Chalcones consist of a three carbon α, β-unsaturated carbonyl system. These are obtained by the condensation of aromatic aldehydes with acetophenones in attendance of alkali (Nowakowska, 2007). Chalcones undertake a variety of chemical reactions including the synthesis of

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pyrimidine, isoxazoles and miscellany of heterocyclic compounds as Pyrazolines. Chalcones play go-between role in synthesizing a number of therapeutic compounds. Remarkable therapeutic efficacy has been revealed by chalcones in the management of numerous diseases. Chalcone based derivatives have been brought to attention due to their fairly uncomplicated structures and assorted pharmacological activities. Mentionable activities of these compounds comprise anti- inflammatory (Yang *et al*., 2007; Lee *et al*., 2006; Nowakowska, 2007; Rajendra Prasad *et al*., 2009) antifungal (Siddiqui *et al*., 2012), antibacterial antimalarial (Valla *et al*., 2006; Dominguez *et al*., 2001, 2005; Motta *et al*., 2006; Liu *et al*., 2001) antitumor (Seo *et al*., 2010). Antimicrobial (Tomar *et al*., 2007; Nowakowska *et al*., 2008), antiviral (Trivedi *et al*., 2007), antituberculosis (Lin *et al*., 2002), antioxidant (Gacche *et al*., 2008) , antimitotic (Sylvie *et al*., 1998), antileishmanial (Boeck *et al*., 2006), antiplatelet (Zhao *et al*., 2005), anticancer (Won *et al*., 2005) and antihypertensive activities (Bonesi *et al*., 2010). Based on these facts, the synthesis of chalcones and chalcone based functionalized derivatives such as pyrimidine is a primary objective of this study.

MATERIALS AND METHODS

Chemicals, instrumentation and chromatographic conditions: Chemicals were acquired from E. Merck (Germany) and S. D. Fine Chemicals (India). Open tube capillary method was employed to determine melting points. By using thin layer chromatography (TLC) plates (silica gel G), the purity of the compounds was admonished in the solvent systems toluene-ethyl formate-formic acid (5:4:1) and benzene–methanol (8:2). The spots were made visible by iodine fumes or by UV glow. Perkin-Elmer 1720 FT-IR spectrometer was used to obtain the IR spectra (KBr pellets). Bruker AC 300 MHZ spectrometer was used to record the 1H NMR spectra by TMS as the inner standard in DMSO-d6/ CDCl3. Whereas, Bruker AC 200, DPX 300 and ARX 500 measured the 13C NMR (75 and 125 MHZ) spectra, at 25 °C, in CDCl3. Lastly, Carlo Erba 1108 analyzer was the device employed for the elemental analyses of the recently synthesized compounds.

Synthesisof3-(4'-aryl)-1-[(4)-carboxyphenylazomethyl]-2-propene-1-one (C1-C7): A solution of sodium hydroxide in oxygen-free distilled water was added to a mixture of ethyl 2-(4-carboxyphenylazo) acetoacetate (0.01 mol) and an aldehyde (0.01 mol) in oxygen-free ethanol, with steady stirring of the flask. For the next 24 h, the reaction mixture was stirred on a magnetic stirrer and poured on to trodden ice. The separated solid mass was filtered, rinsed with water and crystallized from ethanol to yield the required product (C1-C7) as yellow crystals (Fig. 1).

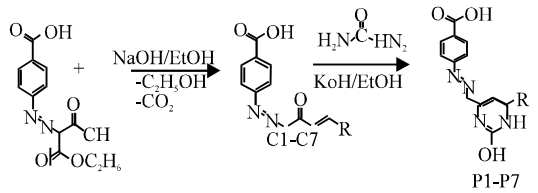

Fig. 1: Synthesis of chalcone analogues and related pyrimidines

Synthesis of 6-(4'-aryl)-4[(4)-carboxyphenylazomethyl]-2-hydroxyl-1,6 dihydropyrimidine (P1-P7): A mixture of 0.01mol urea, 1 g KOH and 0.01 mol of the required chalcone (C1-C7) in 20 mL ethanol was heated in a reflux condenser for 6 hours, cooled and poured onto trodden ice. So, the harvested solid product was filtered and recrystalized from ethanol (Fig. 1).

ACE inhibition assay: ACE inhibition assay was performed as described by Bonesi *et al.* (2010). Dansyl-L-glutamine, dansylglycine and Angiotensin I Converting Enzyme preparation from rabbit lung (EC 3.4.15.1) were acquired from Sigma-Aldrich. To obtain the final concentration ranging from 50 to 200 μg mL^{-1}, each compound was dissolved in HEPES assay buffer. For 5 min, ACE solution (25 μL) was pre-incubated with a test or control solution (25 μL) at 37°C. The enzymatic reaction was initiated by adding a combined solution (25 μL) of dansyltriglycine (7.86 mM) and dansyl-L-glutamine (0.353 mM) for an incubation time selected by plotting a calibration curve. To cease the reaction, a solution of 0.1N Na2EDTA (50 μL) was added to the mixture. HPLC reversed phase quantified the dansylglycine at 250 nm. HPLC Perkin Elmer (Series 410 LC) pump and Injector (20 μL) loop were used. For detection UV/VIS LC290 spectrophotometer was used while mobile phase was NaH2PO4 buffer (pH 7)/ acetonitrile (88:12) with flow rate 2 mL min^{-1} and run time adjusted to 30 min. From 0.2 to 25 μg mL^{-1}, linear calibration curve for dansylglycine was plotted. The concentration of dansylglycine in the test reaction was lesser than in control reaction and was articulated as percentage inhibition and calculated from the equation:

$$\text{Inhibition}\% = \frac{100 - T}{C} \times 100$$

where, T is test reaction and C is control reaction. Captopril was used as a reference ACE inhibitor.

Statistical analysis: Analysis of all the data was done by using Statistical Package for Social Sciences (SPSS) version 15.0. Every sample was measured in triplicate and the data represented as Mean±Standard Deviation (SD). The IC_{50} values were calculated by using GraphPad Prism 5 software. The values were attained from at least three determinations. Analysis of Variance (ANOVA) technique was used to analyse the data for multiple comparisons. $p<0.05$ was considered to be statistically significant.

RESULTS AND DISCUSSION

Synthesis of precursor chalcones and pyrimidines: The synthesis of chalcone and pyrimidine derivatives was performed following the steps shown in Fig. 1. In the initial step, chalcones (C1-C7) were synthesized by condensing 2-(4-carboxyphenylazo) acetoacetate 23 1 with appropriate aromatic aldehydes in dilute ethanolic sodium hydroxide solution at room temperature. The compounds (P1-P7) were synthesized by reacting the appropriate chalcone with urea and potassium hydroxide in ethanol. The purity of the compounds was determined by TLC and elemental analysis. Spectral data (IR, 1H-NMR,13C NMR and Mass) of all the newly synthesized compounds were in full agreement with the proposed structures.

3-(4'-Hydroxyphenyl)-1-[(4)-carboxyphenylazomethyl]-2-propene-1-one (C3): Yield 74%, mp. 170-172°C, IR (KBr): 1484 (N=N), 1686 (C=O), 1703 (C=O of acid), 3039 (CH), 3356 (OH); 1H–NMR (DMSO-d6): d 3.10 (s, 2H, CH2), 5.10 (s, 1H, Ar-OH), 6.44 (d, 1H, Hα), 6.93 (d, H, Hβ), 7.08–7.54 (m, 8H, aromatic), 11.03 (s, 1H, OH); 13C NMR (CDCl3): δ 58.3, 116.2, 122.9, 126.6, 127.5, 128.1, 131.1, 143.4, 156.7, 157.9, 170.3, 198.1. Mass (m/z): 310. Anal. (%) for C17H14N2O4, Calcd. C, 65.80; H, 4.55; N, 9.03; O, 20.62; Found: C, 65.67; H, 4.41; N, 8.92; O, 20.52.

3-(4'-Methoxyphenyl)-1-[(4)-carboxyphenylazomethyl]-2-propene-1-one (C5): Yield 70%, mp. 203-205°C, IR (KBr): 1159 (C-O-C), 1488 (N=N), 1682 (C=O), 1707 (C=O of acid), 3039 (CH); 1H NMR (DMSO-d6): d 3.10 (s, 2H, CH2), 3.73 (s, 1H, OCH3), 6.37 (d, 1H, Hα), 6.89 (d, 1H, Hβ), 6.92–8.10 (m, 8H, aromatic), 11.13 (s, 1H, OH) 13C NMR (CDCl3): δ 55.5, 58.4, 114.8, 122.9, 126.8, 127.4, 127.6, 127.8, 131.1, 143.1, 156.8, 160.3, 169.8, 197.2. Mass (m/z): 324. Anal. (%) for C18H16N2O4, Calcd. C, 66.66; H, 4.97; N, 8.64; O, 19.73; Found: C, 66.55; H, 4.86; N, 8.52; O, 19.61.

6-(2'-Hydroxyphenyl)-4[(4)-carboxyphenylazomethyl]-2-hydroxyl 1,6dihydropyrimidine (P2): Yield 70%, mp. 212-214°C, IR (KBr): 1568 (C = C ring skeleton Ar moiety), 1411 (C = Cring skeleton pyrimidine moiety), 1483 (N = N), 1688 (C=O of acid), 3210 (N-H), 3409 (OH); 1H NMR (DMSO-d6): δ 2.49 (2H, s, CH2), 4.47 (d, 1H, NH-CH), 4.88 (s, 1H, CH), 5.29 (s, 1H, NH), 5.89 (d, 1H, CH), 6.64-7.90 (m, 8H, Ar-H), 11.90 (s, 1H, OH), 12.39 (s, 1H, OHacid); 13C NMR (CDCl3): δ 37.2, 62.6, 115.9, 117.9, 121.6, 12.7, 123, 127.9, 128.3, 128.9, 131.3, 139.9, 154,7, 156.6, 163.9, 171.1. Mass (m/z): 352. Anal. (%) for C18H16N4O4, Calcd. C C, 61.36; H, 4.58; N, 15.90; O, 18.16; Found: C, 61.36; H, 4.58; N, 15.90; O, 18.16.

6-(4'-Hydroxyphenyl)-4[(4)-carboxyphenylazomethyl]-2-hydroxyl-1,6-dihydropyrimidine (P3): Yield 72%, mp. 249-251°C, IR (KBr): 1556 (C=C ring skeleton Ar. moiety), 1418 (C=C ring skeleton pyrimidine moiety), 1479 (N=N), 1692 (C=O of acid), 3210 (N-H), 3412 (OH); 1H NMR (DMSO-d6): δ 2.47 (s, 2H, CH2), 4.46 (d, 1H, NH-CH), 4.86 (s, 1H, OH), 5.24 (s, 1H, NH), 5.90 (d, 1H, CH), 6.60-7.96 (m, 8H, Ar-H), 11.88 (s, 1H, OH), 12.29 (s, 1H, OHacid); 13C NMR (CDCl3): δ 47.2, 62.6, 112.9, 114.1, 117.9, 120.1, 123.1, 127.8, 130.9, 131.1, 139.6, 144.9, 156.4, 163.7, 170.2. Mass (m/z): 352. Anal. (%) for C18H16N4O4, Calcd. C, 61.36; H, 4.58; N, 15.90; O, 18.16; Found: C, 61.36; H, 4.58; N, 15.90; O, 18.16.

6-(4'-Methoxyphenyl)-4[(4)-carboxyphenylazomethyl]-2-hydroxyl-1,6-dihydropyrimidine(P5): Yield 73%, mp. 219-221°C, IR (KBr): 1560 (C=C ring skeleton Ar. moiety), 1411 (C=C ring skeleton pyrimidine moiety), 1487 (N = N), 1693 (C=O of acid), 3210 (N-H), 3400 (OH); 1H NMR (DMSO-d6): δ 2.34 (s, 2H, CH2), 3.72 (s, 1H, OCH3), 4.46 (d, 1H, NH-CH), 4.85 (s, 1H, OH), 5.19 (s, 1H, NH), 5.92 (d, 1H, CH), 6.42-8.06 (m, 8H, Ar-H), 12.32 (s, 1H, OH); 13CNMR (CDCl3): δ 46.9, 56.4, 62.3, 114.9, 117.9, 122.8, 127.6, 128.7, 131.4, 136.3, 140.3, 156.4, 159.2, 163.9, 169.8. Mass (m/z): 366. Anal. (%) for C19H18N4O4, Calcd. C, 62.29; H, 4.95; N, 15.29; O, 17.47; Found: C, 62.29; H, 4.95; N, 15.29; O, 17.47.

ACE inhibitory assay: The effect of novel chalcone derivatives and chalcone based pyrimidines on ACE was investigated by ACE inhibitory assay (Table 1). ACE was inhibited by all the compounds. Amid chalcone assortment, compound C5 exhibited the maximum effect with IC_{50} value 0.256 mM. From pyrimidines compound P5 displayed lowest IC_{50} value of 0.201 mM.

It is worth mentioning that pyrimidines showed better inhibition profiles as compared to chalcones, with substitution patterns similar to chalcones (Kang *et al*., 2003). In this newly synthesized series of chalcones and pyrimidines, one ring on one side of the chemical

Table 1: ACE inhibitory activity of synthesized compounds is shown along with standard deviation; captopril was used as positive control (IC_{50} 21.3 μM)

Compound	R	Molecular Formula	IC_{50} mM±SD
C1	Phenyl	$C_{17}H_{14}N_2O_3$	0.932±0.001
C2	2-Hydroxyphenyl	$C_{17}H_{14}N_2O_4$	0.543±0.009
C3	4- Hydroxyphenyl	$C_{17}H_{14}N_2O_4$	0.410±0.003
C4	2-Nitrophenyl	$C_{17}H_{13}N_3O_5$	0.521±0.008
C5	4-Methoxyphenyl	$C_{18}H_{16}N_2O_4$	0.256±0.001
C6	3- Nitrophenyl	$C_{17}H_{13}N_3O_5$	0.447±0.004
C7	2-Chlorophenyl	$C_{17}H_{13}N_2O_3Cl$	0.512±0.005
P1	Phenyl	$C_{18}H_{16}N_4O_3$	0.856±0.007
P2	2-Hydroxyphenyl	$C_{18}H_{16}N_4O_4$	0.511±0.001
P3	4- Hydroxyphenyl	$C_{18}H_{16}N_4O_4$	0.312±0.003
P4	2-Nitrophenyl	$C_{18}H_{15}N_5O_5$	0.455±0.008
P5	4-Methoxyphenyl	$C_{19}H_{18}N_4O_4$	0.201±0.005
P6	3- Nitrophenyl	$C_{18}H_{15}N_5O_5$	0.432±0.001
P7	2-Chlorophenyl	$C_{18}H_{15}N_4O_3Cl$	0.563±0.002

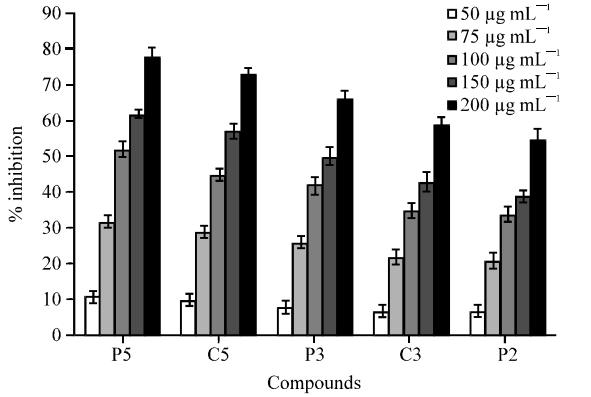

Fig. 2: Effects of most active chalcones and pyrimidines on Angiotensin converting enzyme. The graph shows % inhibition of ACE to various concentrations of compounds

structure is identical for all the compounds. Whereas, on the other side of compounds, substitution is different for each compound represented by "R". In Table 1, the type of R for each compound is mentioned. As far as structure activity relationship is concerned, both series of chalcones and pyrimidines showed marked difference in inhibiting ACE. The results obtained indicated that the pyrimidines are more active than their parent chalcones. However, in terms of substitutions and positions, the substituent compounds exhibited similar results as of parent compounds. The best inhibitor of ACE, either from chalcone analogues series (C5) or from pyrimidine series (P5) had structural similarity with each other, i.e, methoxy group at position 5 of the phenyl ring. Ideal inhibitory activity can be achieved by methoxylation at position 5 as also referred by the previous studies. The Compounds having hydroxylation at position 4 of phenyl ring exhibit better inhibitory activity contrasting to those having hydroxyl group at position 2, given that, compound C3 is more active than C2 with IC_{50} 0.410 and 0.543 mM, respectively. Likewise, in case of pyrimidines, P3 is more active than P2. Substitution of chlorine and nitro groups on the phenyl ring also enhanced the inhibition of ACE, but it is of less importance as compared to hydroxylation and Methoxylation. Each compound from both series was tested for its inhibitory effect on ACE at different concentrations ranging from 50 to 200 μg mL^{-1}. As represented in Fig. 2, both chalcones and pyrimidines show a dose dependent inhibition of ACE with derivative pyrimidines showing better inhibition compared to parent chalcones. Finally, it can be concluded that chalcones and pyrimidines having methoxylation and hydroxylation exhibited maximum percentage inhibition as represented in the Fig. 2.

CONCLUSION

The use of ACE inhibitors results in many side effects like dry cough, skin annoyance, angioedema and sometimes less bioavailability due to multiple dosing (Gomez *et al*., 1985). Consequently, the curiosity in ACE inhibitors research has amplified in recent years. A range of chalcones and pyrimidines was synthesized and tested for their potential ACE inhibitory activity. Some of these compounds can be selected for further in vitro and in vivo investigations because of their good results in this study.

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