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Potent ACE inhibitors from 5-hydroxy indanone derivatives

Hanmanth Reddy Vulupala [a], Yasodakrishna Sajja [a], Pankaj K. Bagul [b,c], Raviteja Bandla [a], Lingaiah Nagarapu [a,*], Sanjay K. Benerjee [b,c]

[a] Organic Chemistry Division II (CPC), CSIR-Indian Institute of Chemical Technology, Tarnaka, Hyderabad 500007, India, IICT/Pubs./2018/073
[b] Centre for Chemical Biology, CSIR-Indian Institute of Chemical Technology, Tarnaka, Hyderabad 500007, India
[c] Drug Discovery Research Center, Translational Health Science and Technology Institute, Faridabad 121001, India

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ABSTRACT

A novel triazole derivatives(±)-2-(hydroxymethyl)-7,8-dihydro-1*H*-indeno[5,4-b]furan-6(2H)-one (**12a–j**) were designed and synthesized by the reaction between racemic azide and terminal acetylenes under click chemistry reaction conditions followed by biological evaluation as angiotensin converting enzyme (ACE) inhibitors. β-Amino alcohol derivatives of 1-indanone (**15a–l**) were synthesized from 5-hydroxy indanone, it was reacted with epichlorohydrin and followed by oxirane ring opening with various piperazine derivatives. Among the newly synthesized compounds **12b** (IC_{50}: 1.388024 μM), **12g** (IC_{50}: 1.220696 μM), **12j** (IC_{50}: 1.312428 μM) and **15k** (IC_{50}: 1.349671 μM) and **15l** (IC_{50}: 1.330764 μM) emerged as most active non-carboxylic acid ACE inhibitors with minimal toxicity comparable to clinical drug Lisinopril.

Hypertension which causes heart failure is very common now a day, it has no symptoms, but sometimes hypertension causes symptoms such as headache, shortness of breath, dizziness, and chest pain, palpitations of the heart and nose bleeds. Hypertension is more common in men than women and in people over the age of 65 than in younger persons. Studies also reveal that angiotensin converting enzyme (ACE) inhibitors [1] are very useful in the treatment of hypertension and congestive heart failures, as ACE can inactivate the hypertensive nonapeptide bradykinin. In fact, some 30% of hypertensive patients are unable to reach their blood pressure goals. ACE inhibitors have achieved widespread usage in the treatment of cardiovascular and renal disease; ACE inhibitors decrease systemic vascular resistance without increasing heart rate and promote natriuresis. Anti-hypertensive drugs is most effective at lowering systolic blood pressure (SBP) in elderly patients with previously untreated hypertension and the percentage of patients controlled with single or sequential monotherapy [2].

1-Indanone and its analogues are useful intermediates for the synthesis of compounds some of which have applications as pharmaceuticals, especially as analgesic and antihypertensive as well as tobacco flavoring agents. Indanones are commonly used as starting agent for the synthesis of ninhydrin which is used determination of fingerprints. Substituted-2,3-dihydrobenzofurans are an important class of biologically active oxygen containing heterocyclic compounds. Natural products possessing the dihydrobenzofuran moiety exhibit a broad range of biological and pharmacological activities [3]. The indeno [5,4-*b*] furan structure is a part of the internal backbone of various important Melatonin MT1/MT2 receptors in the suprachiasmatic nucleus (SCN) for the treatment of circadian rhythm sleep disorders [4]. The invention of relates to certain indenofurans having diuretic-saluretic and antihypertensive pharmacological activity.

β-Amino alcohol moiety is ubiquitous in nature, the subfamily of β-amino cycloalkonols can be found in many natural products and synthetic bioactive molecules, such as the anti-arrhythmic vernakalantor, the inhibitors of HIV (Indinavir) and spleen tyrosine kinase (SYK) [5]. An important β-amino alcohol is propranolol, one of the first non-selective β-blockers developed, finding wide spread use in the treatment of hypertension (Fig. 1). (1,2,3)-Triazole moieties are attractive connecting units because they are stable to metabolic degradation and capable of hydrogen bonding, which can be favorable in the binding of bio-molecular targets and can improve the solubility [6]. These moiety does not occur in nature, although the synthetic molecules that contain (1,2,3)-triazole units show diverse biological activities [7].

In continuation of our research programme [8–14] to obtain novel bioactive molecules, we synthesized hitherto unreported triazole derivatives of 2-(hydroxymethyl)-7,8-dihydro-1*H*-indeno

* Corresponding author.
E-mail address: nagarapu@iict.res.in (L. Nagarapu).

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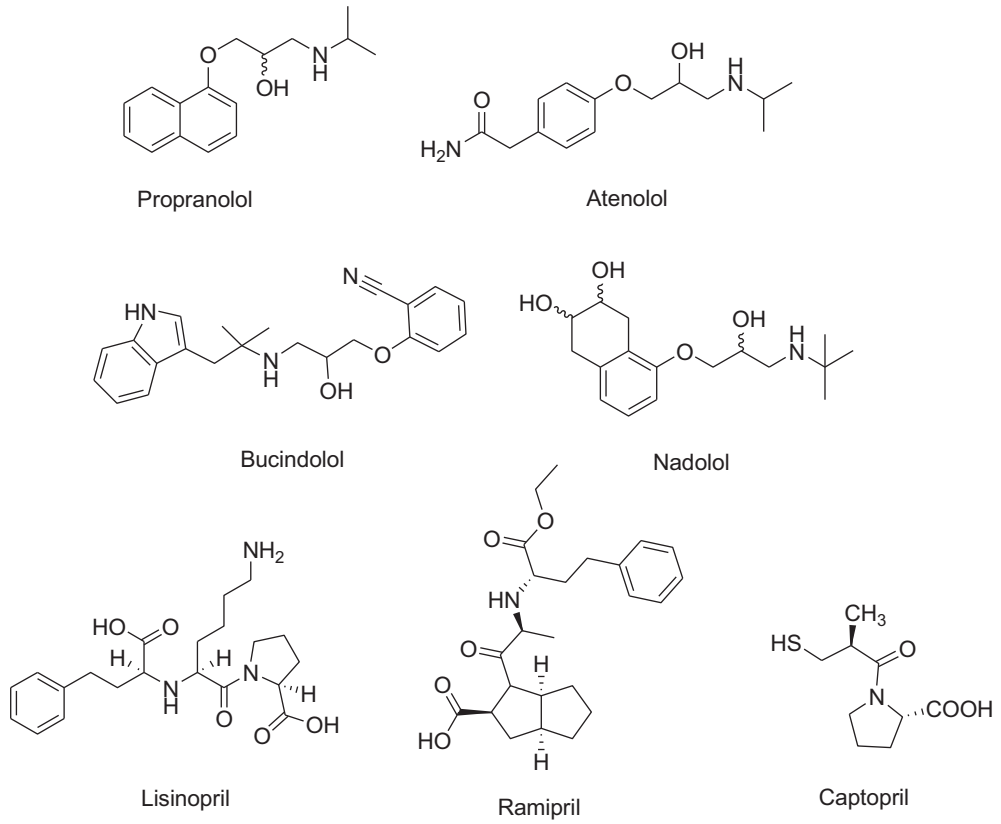

Fig. 1. Representative ACE inhibitor drugs.

[5,4-*b*]furan-6(2*H*)-one (**12a–j**). The key intermediate 2-(hydroxymethyl)-7,8-dihydro-1*H*-indeno[5,4-*b*]furan-6(2*H*)-one (**9**) (Scheme 1) [15] was reacted with Ts-Cl to form its corresponding tosyl derivative, subsequently reacted with sodium azide in DMF at 80 °C for 12 h to afford the 2-(azidomethyl)-7,8-dihydro-1*H*-indeno[5,4-*b*]furan-6(2*H*)-one (**10**). Formation of **10** was confirmed from absorption at 2091 Cm^{-1} in IR spectrum for the azido function. Next, we synthesized novel 2-((1*H*-1,2,3-triazol-1-yl)methyl)-7,8-dihydro-1*H*-indeno[5,4-*b*]furan-6(2*H*)-one derivatives (**12a–j**) *via* click chemistry reaction condition. Thus, 1,3-dipolar cycloaddition reaction of 2-(azidomethyl)-7,8-dihydro-1*H*-indeno [5,4-*b*]furan-6(2*H*)-one (**10**) and various terminal acetylene derivatives (**11a–j**), in the presence of catalytic amount of sodium ascorbate and copper sulfate at room temperature, afforded the corresponding 2-((1*H*-1,2,3-triazol-1-yl)methyl)-7,8-dihydro-1*H*-indeno[5,4-*b*]furan-6(2*H*)-one derivatives (**12a–j**) (Scheme 2) in high yields (85–95%).

The structures of these compounds were confirmed from their spectral and micro analytical data. Based on $[M^{+}+H]$ 402 its molecular formula of **12b** was established as $C_{25}H_{28}O_2N_3$. The IR spectrum of **12b** showed absorption due to C=O stretching at 1735 Cm^{-1} & furan ring containing oxygen, stretching at 1045 Cm^{-1} indicating ether linkage and triazole ring double bond absorption at 1607 Cm^{-1}. The ^1H NMR spectrum of **12b** exhibited signals arising due to typical tertiary carbon proton, multiplet at δ 5.48–5.38 integrating for one proton, triazole containing double bond proton appeared as singlet at δ 8.15. The spectrum also revealed the presence of two dd at δ 4.84 and δ 4.74 (for 2H) due to furan and triazole bridged CH_2 protons.

We synthesized novel 5-Hydroxy-2,3-dihydro-1*H*-inden-1-one *β*-amino alcohol derivatives (**15a–l**) from 5-hydroxy indanone (**6**). Compound **6** was reacted with (±)-epichlorohydrin **13** under potassium carbonate at 55 °C for 5 h, to achieve the 5-(oxiran-2-ylmethoxy)-2,3-dihydro-1*H*-inden-1-one (**14**) in 78% yield. The oxirane of **14** was opened with various substituted piperazines at reflux temperature for 20 h to give 5-Hydroxy-2,3-dihydro-1*H*-inden-1-one *β*-amino alcohol derivatives (**15a–l**) in excellent yields (Scheme 3).

The structures of these compounds were confirmed from their spectral and micro analytical data. Based on $[M + H]^{+}$ 367, molecular formula of **15a** was established as $C_{22}H_{27}O_3N_2$. The IR spectrum of **15a** showed absorption due to C=O stretching at 1700 Cm^{-1} & OH stretching at 3188 Cm^{-1} indicating that compound contains one carbonyl group, a free hydroxyl group and ether stretching at 1089 Cm^{-1}. Therefore the product was inferred to contain a indanone containing amino alcohol in final structure. ^1H NMR spectrum (300 MHz) of **15a** recorded in $CDCl_3$ exhibited signals arising due to typical secondary alcohol attached CH. The spectrum contained multiplet at *δ* 4.22–4.13 integrating for one proton, CH_2 present in between CH and oxygen shows doublet at *δ*4.09 for 2H, CH_2 present in between CH and nitrogen shows doublet at *δ*3.09 for 2H.

Effects of the compounds on the viability of enzyme (ACE) inhibition:

Angiotensin converting enzyme (ACE) inhibition of new triazole derivatives **(12a–j)** and *β*-amino alcohols **(15a–l)** were examined in vitro using recently developed high-throughput colorimetric screening method [16,17]. Most of these anti-hypertensive peptides have been characterized by the rabbit lung ACE inhibitor assay, based on the hydrolysis of the synthetic peptide hippuryl-histidyl-leucine (HHL). Angiotensin converting enzyme (ACE) hydrolyses HHL to hippuric acid (HA) and histidyl-leucine (HL). HA released is directly proportional to the ACE activity. In this screening method, the released hippuric acid from the substrate hippuryl-histidyl-leucine (HHL) was transformed into yellow color by mixing with pyridine and benzene sulfonyl chloride. The resulted yellow color was determined colorimetrically at