Bioorganic & Medicinal Chemistry 19 (2011) 4772–4781

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Synthesis and evaluation of novel 2-butyl-4-chloro-1-methylimidazole embedded chalcones and pyrazoles as angiotensin converting enzyme (ACE) inhibitors

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ARTICLE INFO

Article history:
Received 14 May 2011
Revised 27 June 2011
Accepted 28 June 2011
Available online 2 July 2011

Keywords:
Angiotensin converting enzyme
Inhibitors
Imidazole
Chalcones
Pyrazoles

ABSTRACT

A series of novel 2-butyl-4-chloro-1-methylimidazole embedded aryl and heteroaryl derived chalcones and pyrazoles were synthesized and evaluated for their angiotensin converting enzyme (ACE) inhibitory activity. The condensation of 2-butyl-4-chloro-1-methylimidazole-5-carboxaldehyde with various aryl and heteroaryl methyl ketones in the presence of 10% aqueous NaOH in methanol proceeded efficiently to give the respective chalcones in very good yields. Further, the reaction of chalcones with hydrazine hydrate in acetic acid gave substituted pyrazole analogues. Screening all 36 new compounds using ACE inhibition assay, resulted chalcones with better ACE inhibitory activity compared to the respective pyrazole analogues. Among the chalcones **4a–r**, three compounds, (*E*)-3-(2-butyl-4-chloro-1-methyl-1*H*-imidazol-5-yl)-1-(5-chlorothiophen-2-yl)prop-2-enone **4i**, (*E*)-3-(2-butyl-4-chloro-1-methyl-1*H*-imidazol-5-yl)-1-(1*H*-pyrrol-2-yl)prop-2-enone **4l**, (*E*)-3-(2-butyl-4-chloro-1-methyl-1*H*-imidazol-5-yl)-1-(dibenzo[b,d] thiophen-2-yl)prop-2-enone **4q** were resulted as most active ACE inhibitors with IC_{50} of 3.60 μM, 2.24 μM, and 2.68 μM, respectively.

1. Introduction

Research in the field of hypertension has gained worldwide importance because of its high frequency and concomitant risks associated with cardiovascular diseases.[1] It has been identified as leading risk factor for mortality and is ranked third as a cause of disability-adjusted life-years.[2] From a patho-physiological view point, hypertension involves changes in at least one of the hemodynamic variables (cardiac output, arterial stiffness or peripheral resistance) that determine measurable blood pressure.[3] Therefore each of these variables is a potential target for modulation. It is recognized that angiotensin converting enzyme (ACE) plays an important role as a regulatory site in the Renin-Angiotensin system (RAS)[4] that control excessive activation and then hypertension. Several ACE inhibitors such as Captopril, Enalapril, and Lisinopril are in clinical use for treatment of hypertension.[5] All these drugs also produce side effects[5,6] (like dry cough, hyperkalemia, rashes, loss of taste, first dose hypotension and acute renal failure), thus justifying the search for newer analogues of ACE inhibitors for safe use. In vitro screening of compounds from ethanobotanical sources have identified Butein, a natural α,β-unsaturated ketone, as one of the safe, potent ACE inhibitory compound isolated from the stems of *Rhus verniciflua*.[7a] The unique pharmacophoric structural feature of this compound is chalcone architecture.[7b] Later studies[8] on the evaluation of various aromatic chalcones also revealed potent ACE inhibitory activity. We therefore envisaged that, linking the unsaturated enone (chalcone) with various heterocyclic units could generate potential candidates for screening ACE inhibitory activity.[9] The choice of heterocyclic units is arised from clinically used drug molecules as potent RAS effectors. Among the several RAS components, Angiotensin II plays critical integral role in the pathophysiology of hypertension.[10] The drugs such as Losartan, Eprosartan, etc. developed as Angiotensin II antagonists, are clinically used in conjunction with ACE inhibitors for treating hypertension and then cardiovascular diseases.[11] In an effort to design new heterocyclic library with drug like properties, the 2-butyl imidazole unit[10] of Losartan or Eprosartan and chalcone architecture of natural Butein were embedded in one molecular frame (Fig. 1) to evaluate their potency as ACE inhibitors.[12] The choice of five member nitrogen containing substituted imidazole unit is also due to their similarity with proline unit present in Lisinopril Captopril, etc. With this design strategy, we herein describe an efficient synthesis and evaluation of ACE inhibitory activity of novel 2-butyl-4-chloro-1-methyl imidazole derived chalcones **4a–r** and pyrazoles **6a–r**. Screening all the 36 new compounds using

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doi:10.1016/j.bmc.2011.06.085

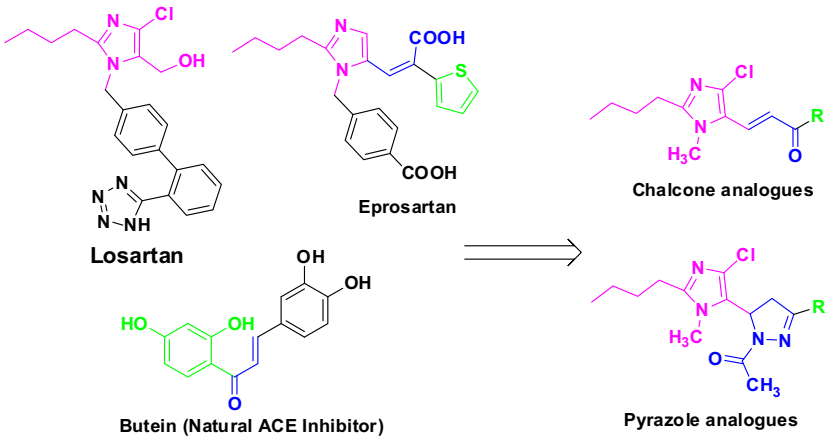


Figure 1. Design strategy for the development of new ACE inhibitors.

colorimetric ACE inhibition assay resulted three compounds, (*E*)-3-(2-butyl-4-chloro-1-methyl-1*H*-imidazol-5-yl)-1-(5-chlorothiophen-2-yl) prop-2-enone **4i**, (*E*)-3-(2-butyl-4-chloro-1-methyl-1*H*-imidazol-5-yl)-1-(1*H*-pyrrol-2-yl)prop-2-enone **4l**, (*E*)-3-(2-butyl-4-chloro-1-methyl-1*H*-imidazol-5-yl)-1-(dibenzo[b,d]thiophen-2-yl)prop-2-enone **4q** as most active ACE inhibitors.

2. Results and discussion

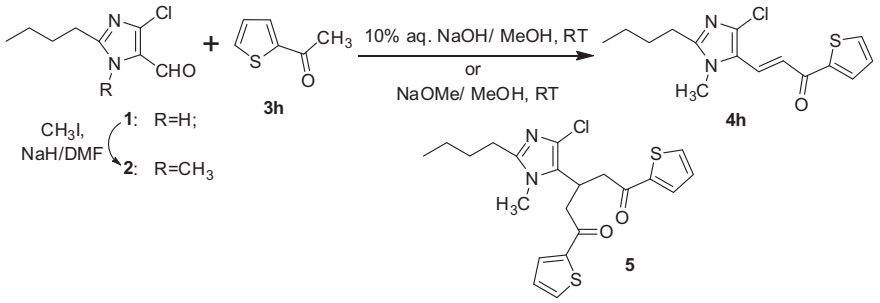
2.1. Synthesis

2-Butyl-4-chloroimidazole-5-carboxaldehyde **1** is a key intermediate in the preparation of an Angiotensin II antagonist, Losartan. It was prepared from valeronitrile by following the procedure developed in our laboratory.[14] *N*-Methylation of **1** using CH_3I, NaH in DMF gave methyl derivative **2** in very good yield. The compound **2** was characterized by NMR and mass spectral analysis. With requisite imidazole derivative **2** in hand, initially, the base catalyzed Claisen–Schmidt condensation[15] with 2-acetyl thiophene **3h** was investigated (Scheme 1). After series of experiments, the reaction was found to be most efficient when equivalent amounts of imidazole **2** and 2-acetyl thiophene **3h** were reacted in the presence of 10% aqueous sodium hydroxide in methanol to give chalcone **4h** in very good yield (83%). Comparable yield (81%) of the product **4h** was also observed in methanol solvent in the presence of equivmolar amount of sodium methoxide. But, under these conditions, formation of compound **5** (8%) was also observed when **2** was treated with 2-acetylthiophene **3h** (1.1 equiv) and sodium methoxide (1.1 equiv). Such formation of **5** could be due to Michel addition of the excess amount of **3h** on conjugated enone **4h**. In case of 10% aqueous NaOH under similar reaction conditions, the formation compound **5** is not observed even when excess of 2-acetylthiophene **3h** (1.5 equiv) was used. Having succeeded with the reaction, various aryl or heteroaryl methyl ketones **3a–r** (Fig. 2) were reacted with imidazole **2** in the presence of 10% aqueous NaOH in methanol for 3.0–5.0 h at room temperature (Scheme 2). All the reactions were preceded efficiently and gave the desired chalcones **4a–r** in excellent yields (73–88%). The products **4a–r** was fully characterized by ^{1}H and ^{13}C NMR, IR and mass (ESI and HR-MS) spectra data. The single crystal X-ray diffraction studies of **4j** unambiguously confirmed the structure (Fig. 3).

Further to obtain compounds containing pharmacophoric pyrazole unit, the chalcones **4a–r** was subjected to the condensation reaction with hydrazine hydrate. After series of experiments, the reaction of chalcones **4a–r** with hydrazine hydrate is successful in acetic acid at reflux temperature for 3.0–5.0 h (Scheme 3). All the products **6a–r** obtained in excellent yields (85–95%) were fully characterized by ^{1}H and ^{13}C NMR, IR and mass (ESI and HR-MS) spectra data. The NMR, IR and mass spectral analysis of pyrazoles derivatives revealed that the acetic acid is also participated in the condensation process and yielded pyrazoles **6a–r** as *N*-acyl derivatives. This observation is consistent with the recent literature on the synthesis of pyrazoles in acetic acid. The single crystal X-ray diffraction studies of **6i** unambiguously confirmed the structure as well as the position of *N*-acyl group on pyrazole ring system (Fig. 4).

2.2. Pharmacology

The in vitro angiotensin converting enzyme (ACE) inhibitory activity of new compounds **4a–r** and **6a–r** were measured using recent colorimetric high-throughput screening method developed by Jimsheena and Gowda.[16] Most of the antihypertensive peptides have been characterized by the rabbit lung ACE inhibitor



Scheme 1. Synthesis of 2-butyl-4-chloro-1-methylimidazole derived chalcone **4h** and its analogue **5**.

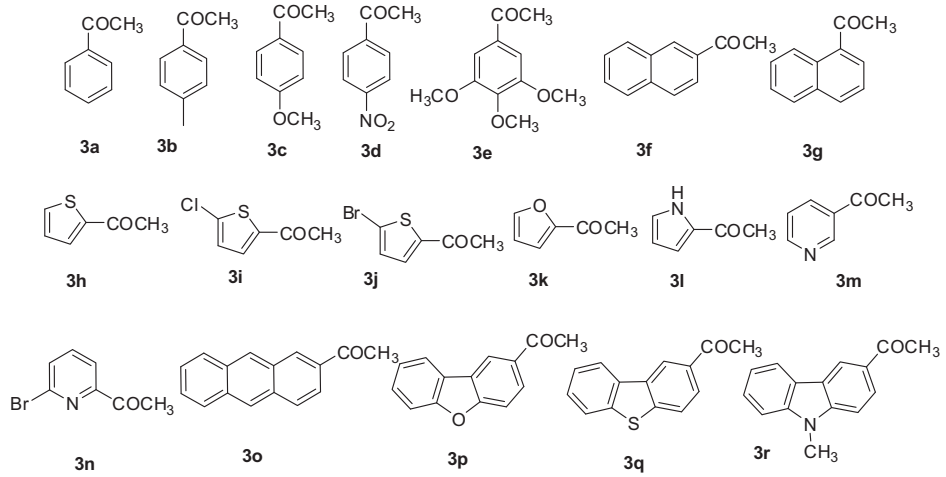
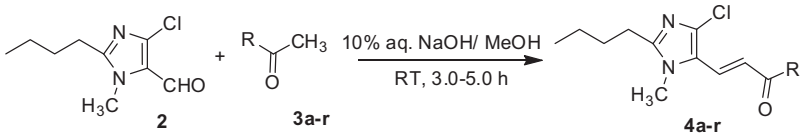


Figure 2. Aryl and heteroaryl methyl ketones used in this study.



Scheme 2. Synthesis of 2-butyl-4-chloro-1-methylimidazole derived chalcones **4a–r**.

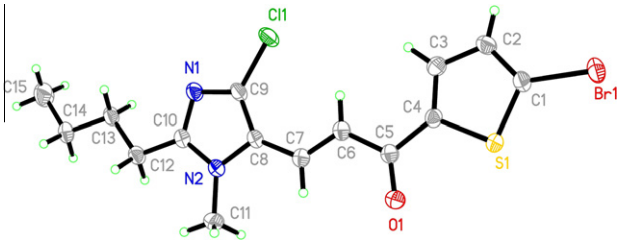
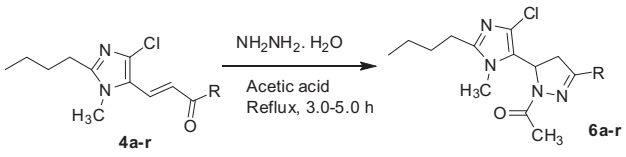


Figure 3. ORTEP representation of compound **4j** with thermal displacement ellipsoids drawn at the 30% probability.



Scheme 3. Synthesis of 2-butyl-4-chloro-1-methylimidazole derived pyrazoles **6a–r**.

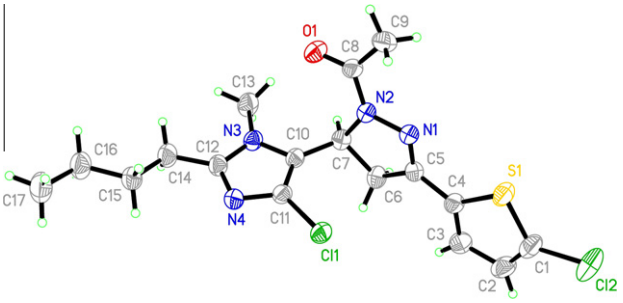


Figure 4. ORTEP representation of compound **6i** with thermal displacement ellipsoids drawn at the 30% probability.

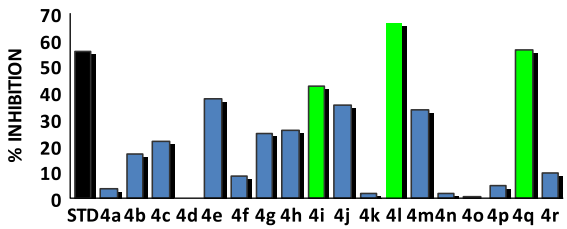


Figure 5. ACE inhibitory activity of chalcones **4a–r** (3.0 μM in DMSO). STD: Lisinopril (3.0 μM in DMSO).

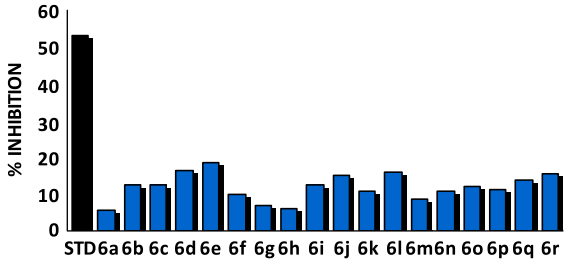


Figure 6. ACE inhibitory activity of Pyrazoles **6a–r** (3.0 μM in DMSO). STD: Lisinopril (3.0 μM in DMSO).

assay, based on the hydrolysis of the synthetic peptide hippuryl-histidyl-leucine (HHL). HHL is hydrolyzed by ACE to hippuric acid (HA) and histidyl-leucine (HL). The extent HA released is directly proportional to the ACE activity. In this screening method, the released hippuric acid from the substrate hippurryl-histyl-leucine (HHL) was transformed in to a rapid ACE assay by mixing with pyridine and benzene sulfonyl chloride. The resulting yellow color with λ_{max} at 410 nm is directly proportional to the released hippuric acid and then ACE activity. All the new compounds **4a–r** and **6a–r** tested in the desired concentrations did not show any significant absorbance at 410 nm under control conditions. Being

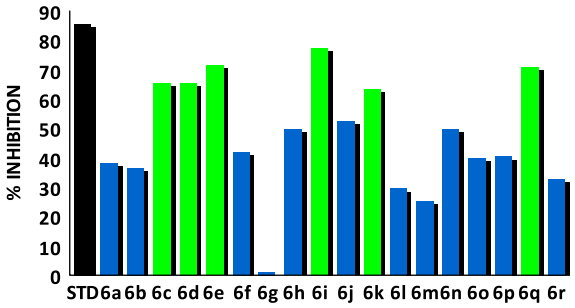


Figure 7. ACE inhibitory activity of pyrazoles **6a–r** (3.0 mM in DMSO). STD: Lisinopril (3.0 mM in DMSO).

Table 1
ACE inhibitory activity (IC_{50}) of chalcones **4i**, **4l** and **4q** and pyrazoles **6c–e**, **6i**, **6k** and **6q**

S. No.	Chalcone	IC_{50}[a] (μM)	S. No.	Pyrazole	IC_{50}[a] (mM)
1	**4i**	3.60	10	**6c**	2.33
2	**4l**	2.24	11	**6d**	2.22
3	**4q**	2.68	12	**6e**	2.12
4	Butein **7**	730.0[7a,8]	13	**6i**	1.80
5	Apigenin **8**	280.0[13b,8]	14	**6k**	2.35
6	Luteolin **9**	290.0[13b,8]	15	**6q**	2.01
7	**10**	200.0[13b,8]	16	**13**	0.213[8]
8	**11**	219.0[8]			
9	**12**	260.0[13b,8]			

[a] Values are means of three experiments, standard deviation ± 0.0003.

simple, sensitive and rapid nature, the colorimetric method is used for evaluating ACE inhibitory activity of new analogues **4a–r** and **6a–r**. Lisinopril, a known ACE inhibitor drug has been used as standard for comparison with the inhibitory activity of synthesized new analogues.

The evaluation results of all 36 new compounds for ACE inhibitory activity are presented in Figures 5–7. The experiments carried out for test compounds at 3.0 μM concentration reveal that chalcones **4a–r** possess 3–5 times better ACE inhibition compared to the respective pyrazole analogues **6a–r** (Figs. 5 and 6**).** Among the imidazole derived chalcone analogues **4a–r**, the heterocyclic derivatives such as **4i, 4l** and **4q** posses better ACE inhibitory activity compared with the substituted aryl analogues **4a–g** and **4o**. In aryl substituted chalcone analogues **4a–4g**, the trimethoxy derivative **4e** is most ACE inhibition and chalcone **4d** has least ACE inhibitory activity. Relating to the standard drug Lisinopril, two chalcone analogues **4l** and **4q** are more potent with 66% and 56% ACE inhibition, respectively (Fig. 5). Three compounds **4i**, **4l** and **4q** with greater than 40% inhibition at 3.0 μM are evaluated for IC_{50} and dose–response study (Table 1 and Fig. 9). Further to see the effective inhibitory concentration for pyrazoles **6a–r**, the experiments were performed at increased concentrations. At 3.0 mM, almost all the pyrazole derivatives except **6g** inhibited ACE activity (Fig. 7). Out of these pyrazole analogues, six compounds **6c–e**, **6i**, **6k** and **6q** with greater 60% inhibition were evaluated for IC_{50} and incremental dose–response study (Table 1). The inhibitory concentration at 50% (IC_{50}) ACE activity for tested compounds was calculated from dose–response curves obtained by plotting the percentage inhibition verses the concentration (see Supplementary data), are summarized in Table 1. The synthetic chalcone analogues **4i**, **4l** and **4q** are excellent inhibitors with IC_{50} of 3.60, 2.24, and 2.68 μM, respectively. On the other hand pyrazole analogues **6c–e**, **6i**, **6k** and **6q** exhibited IC_{50} from 1.80 to 2.35 mM. It is clear from the data that chalcone analogues **4i**, **4l** and **4q** possesses nearly 100-folds greater ACE inhibition compared to the previously described natural ACE inhibitors, Butein **7**,[7a,8] Apigenin **8**,[13b,8] Luteolin **9**,[13b,8] Quercetin glucuronide **10**,[13b,8] kaempferol-3-*O*-β-galactopyranoside **12**[13b,8] (Fig. 8) and a known synthetic analogue **11**.[8] In contrast, the investigated pyrazole derivatives **6c–e**, **6i**, **6k** and **6q** are 10-folds less ACE inhibitory activity than a literature described synthetic analogue **13**.[8]

Angiotensin converting enzyme (ACE) is zinc containing peptidyl dipeptide hydrolase.[17] The active site of ACE is known to consist of three parts: a carboxylate binding functionality such as guanidinium group of Arginine, a pocket that accommodates a hydrophobic side chain and Zinc ion. It is evident from the literatures[7a,8,13] that, in natural chalcone (for e.g., Butein **7**) or flavanioids (for e.g., Apigenin **8**, Luteolin **9**) zinc ion coordinates to carbonyl of the penultimate peptide bond of the substrate, where

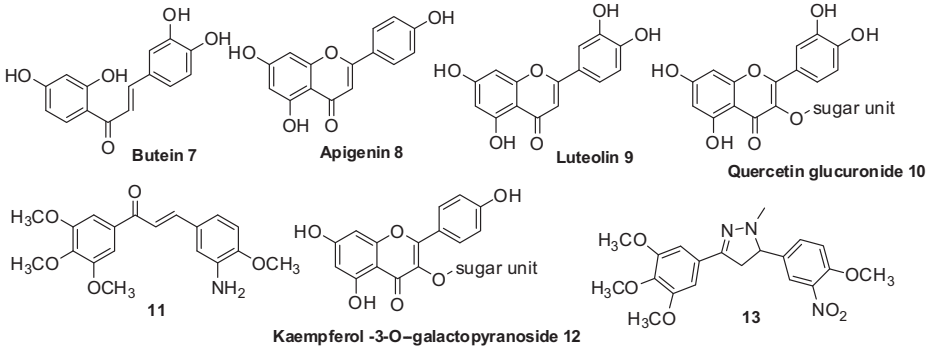


Figure 8. Examples of natural and synthetic ACE inhibitors with chalcone and pyrazole unit.

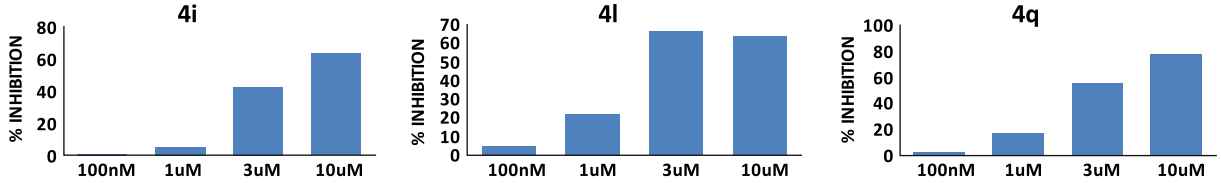


Figure 9. Concentration dependent inhibition of ACE by the most active chalcones **4i**, **4l** and **4q**.

by the carbonyl group becomes polarized and is subjected to nucleophilic attack. Such chelated complex of zinc ion in the pocket of ACE inhibits the activity. Since the synthesized new chalcones also possesses structural similarity with natural Butein **7**, it also predicted to show ACE inhibition by forming Zn-chelated complex. The increased ACE inhibition for 2-butyl-4-chloro-1-methyl imidazole embedded chalcones **4i**, **4l** and **4q** may be due to the increased strength of chelated complexes with zinc ions by heterocyclic moieties within the active site of enzyme, thus inactivating the ACE activity to the greater extent. The results obtained here will be explored further study the binding nature and to generate lead molecules for drug discovery.

3. Conclusion

In conclusion, we have described an efficient synthesis and evaluation of ACE inhibitory activity of novel 2-butyl-4-chloro-1-methylimidazole derived chalcones and pyrazoles. The chalcones **4a–r** was prepared in excellent yields through Claisen–Schmidt condensation of 2-butyl-4-chloro-1-methyl imidazole-5-carboxaldehyde **2** with aryl/heteroaryl methyl ketones **3a–r** in the presence of 10% aqueous NaOH in methanol. These chalcones **4a–r** were further derivatized with hydrazine hydrate in acetic acid to give pyrazole analogues **6a–r**. All the products and their structural characterization was carried out using NMR, IR and mass spectral data and single crystal X-ray structural analysis. Screening all the new compounds using colorimetric ACE inhibition assay resulted chalcones as more potent ACE inhibitors than the respective pyrazole analogues by thousand folds. Among the series of chalcones **4a–r**, three compounds, (*E*)-3-(2-butyl-4-chloro-1-methyl-1*H*-imidazol-5-yl)-1-(5-chlorothio- phen-2-yl)prop-2-enone **4i**, (*E*)-3-(2-butyl-4-chloro-1-methyl-1*H*-imidazol-5-yl)-1-(1*H*-pyrrol-2-yl)pro p -2-enone **4l**, (*E*)-3-(2-butyl-4-chloro-1-methyl-1*H*-imidazol-5-yl)-1-(dibenzo[b,d]thiophen-2-yl)prop-2-enone **4q** were resulted as most active ACE inhibitors with IC_{50} of 3.60 μM, 2.24 μM, and 2.68 μM, respectively. Compared with ACE inhibitory activity (IC_{50}) of various chalcones and flavanioids of synthetic and natural origin, imidazole derived chalcones **4i**, **4l** and **4q** are ~100-fold more active. The results reveal that binding of heteroaryl chalcones at ACE binding pocket is more pronounced through zinc ion chelation than the chalcones of natural origin. The information generated here could be of use to generate lead molecules for drug discovery.

4. Experimental section

Melting points were measured with a Fischer–Johns melting point apparatus and are uncorrected. IR spectra were recorded as neat liquids or KBr pellets and absorptions are reported in cm^{-1}. NMR spectra were recorded on 300 (Bruker) and 500 MHz (Varian) spectrometers in appropriate solvents using TMS as internal standard or the solvent signals as secondary standards and the chemical shifts are shown in δ scales. Coupling constants *J* are expressed in Hertz. ^{13}C NMR spectra were recorded on 75 and 125 MHz spectrometers. High-resolution mass spectra were obtained by using ESI-QTOF mass spectrometry. Reagents and all solvents were analytically pure and were used without further purification. All the experiments were monitored by analytical thin layer chromatography (TLC) performed on silica gel GF254 pre-coated plates. After elution, plate was visualized under UV illumination at 254 nm for UV active materials. Further visualization was achieved by staining with PMA and charring on a hot plate. Silica gel finer than 200 mesh was used for column chromatography. Appropriate names for all the new compounds were given with the help of ChemBioOffice 2010.

4.1. 2-Butyl-4-chloro-1-methyl-1*H*-imidazole-5-carbaldehyde 2

2-Butyl-4-chloro-1*H*-imidazole-5-carbaldehyde **1** (5.0 g, 26.7 mmol) in DMF (25 mL), NaH (1.28 g, 53.46 mmol) was added at 0 °C. After 30 min, CH_3I (4.71 g, 32.07 mmol) was added and stirred for 4 h at rt. The reaction mixture was quenched with methanol (3 mL), DMF was evaporated under vacuum, and ice cold H_2O/EtOAc 1:1 (30 mL) was added. The ethyl acetate layer was washed with water (25 mL) and brine (25 mL), dried over anhydrous sodium sulphate and evaporated under vacuum. Purification over silica gel flash column chromatography gave 2-butyl-4-chloro-1-methyl-1*H*-imidazole-5-carbaldehyde **2** (4.79 g, 89.6%) as pale yellow syrup. ^1H NMR (300 MHz, $CDCl_3$) δ 9.72 (s, 1H), 3.85 (s, 3H), 2.65 (t, *J* = 7.5 Hz, 2H), 1.68–1.78 (m, 2H) 1.36–1.46 (m, 2H), 0.97 (t, *J* = 7.5 Hz, 3H). IR (neat) 2958, 2866, 1668, 1511, 1471, 1367, 1280, 866, 706 cm^{-1} MS (ESI) *m*/*z* 201 $[M+H]^+$.

4.2. General procedure

4.2.1. Synthesis of (*E*)-3-(2-butyl-4-chloro-1-methyl-1*H*-imidazol-5-yl)-1-(thiophen-2-yl)prop-2-enone 4h

To a solution of acetyl thiophene (0.2 g, 1.5 mmol) in MeOH (2 mL) was added 10% aqueous NaOH (1.0 mL) at 0 °C with stirring. After 0.5 h, the solution of 2-butyl-4-chloro-1-methyl-1*H*-imidazole-5-carbaldehyde (0.3 g, 1.5 mmol) in MeOH was added. After completion (3.5 h, monitored by TLC), reaction mixture was extracted with ethyl acetate (15 mL), washed with water, (2 × 10 mL), brine solution (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography (hexane–ethyl acetate; 8:2) of the crude residue gave (*E*)-3-(2-butyl-4-chloro-1-methyl-1*H*-imidazol-5-yl)-1-(thio phen-2-yl)prop-2-enone as yellow solid (0.39 g, 83%).

4.2.2. (*E*)-3-(2-Butyl-4-chloro-1-methyl-1*H*-imidazol-5-yl)-1-phenylprop-2-enone 4a

Yield: 78%; mp 60 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, *J* = 6.7 Hz, 2H), 7.80 (d, *J* = 15.8 Hz, 1H), 7.60 (d, *J* = 15.8 Hz, 1H), 7.39–7.55 (m, 3H), 3.64 (s, 3H), 2.67 (t, *J* = 7.5 Hz, 2H), 1.67–1.77 (m, 2H), 1.36–1.42 (m, 2H), 0.97 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.8, 150.1, 138.2, 133.1, 132.7, 128.6, 128.4, 128.0, 127.4, 123.2, 119.5, 30.8, 29.6, 27.0, 22.4, 13.8. IR (KBr); 2956, 2866, 1658, 1591, 1456, 1365, 1270, 1215, 1177, 1017, 974, 779, 705, 642 cm^{-1}. MS (ESI) *m*/*z* 303 $[M+H]^+$; HR-MS (ESI) calcd for $C_{17}H_{20}N_2OCl$ $[M+H]^+$: 303.1264. Found: 303.1272.

4.2.3. (*E*)-3-(2-Butyl-4-chloro-1-methyl-1*H*-imidazol-5-yl)-1-*p*-tolylprop-2-enone 4b

Yield: 75%; mp 96 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.3 Hz, 2H), 7.80 (d, *J* = 15.4 Hz, 1H), 7.58 (d, *J* = 15.4 Hz, 1H), 7.26 (d, *J* = 7.9 Hz, 2H), 3.64 (s, 3H), 2.66 (t, *J* = 7.5 Hz, 2H), 2.43 (s, 3H), 1.67–1.77 (m, 2H), 1.36–1.48 (m, 2H), 0.97 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.6, 150.0, 143.3, 135.5, 132.1, 129.2, 128.4, 127.1, 123.1, 119.6, 30.8, 29.5, 26.9, 22.4, 21.6, 13.7. IR (KBr) 2925, 2857, 1657, 1592, 1458, 1408, 1262, 1180, 1031, 980, 821, 733, 586 cm^{-1}. MS (ESI) *m*/*z* 317 $[M+H]^+$; HR-MS (ESI) calcd for $C_{18}H_{22}N$ OCl $[M+H]^+$: 317.1420. Found: 317.1423.

4.2.4. (*E*)-3-(2-Butyl-4-chloro-1-methyl-1*H*-imidazol-5-yl)-1-(4-methoxyphenyl)prop-2-enone 4c

Yield: 73%; mp 102 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.4 Hz, 2H), 7.80 (d, *J* = 15.4 Hz, 1H), 7.57 (d, *J* = 15.4 Hz, 1H), 6.94 (d, *J* = 8.6 Hz, 2H), 3.88 (s, 3H), 3.64 (s, 3H), 2.66 (t, *J* = 7.5 Hz, 2H), 1.66–1.77 (m, 2H), 1.38–1.44 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.3, 163.3, 149.8, 131.9, 131.0, 130.6, 126.7, 123.2, 119.7, 113.8, 55.2, 30.8, 29.7,

27.0, 22.4, 13.8. IR (KBr) 2924, 2854, 1654, 1578, 1456, 1372, 1255, 1170, 1106, 1018, 828, 736 cm^{-1}. MS (ESI) *m/z* 333 $[M+H]^+$; HR-MS (ESI) calcd for $C_{18}H_{22}N_2O_2Cl$ $[M+H]^+$: 333.1369. Found: 333.1382.

4.2.5. (*E*)-3-(2-Butyl-4-chloro-1-methyl-1*H*-imidazol-5-yl)-1-(4-nitrophenyl)prop-2-enone 4d

Yield: 85%; mp 134 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.35 (d, J = 8.3 Hz, 2H), 8.14 (d, J = 8.3 Hz, 2H), 7.77 (d, J = 15.1 Hz, 1H), 7.65 (d, J = 15.1 Hz, 1H), 3.67 (s, 3H), 2.70 (t, J = 7.5 Hz, 2H), 1.67–1.79 (m, 2H), 1.37–1.47 (m, 2H), 0.97 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.5, 151.1, 142.9, 129.2, 129.1, 123.9, 123.1, 118.2, 30.9, 29.7, 29.6, 27.1, 13.8. IR (KBr) 2954, 2862, 1654, 1580, 1518, 1460, 1340, 1269, 1212, 1029, 965, 842, 760, 708 cm^{-1}. MS (ESI) *m/z* 348 $[M+H]^+$; HR-MS (ESI) calcd for $C_{17}H_{19}N_3ClO_3Cl$ $[M+H]^+$: 348.1127. Found: 348.1133.

4.2.6. (*E*)-3-(2-Butyl-4-chloro-1-methyl-1*H*-imidazol-5-yl)-1-(3,4,5-trimethoxyphenyl)prop-2-enone 4e

Yield: 77%; mp110 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, J = 15.4 Hz, 1H), 7.55 (d, J = 15.4 Hz, 1H), 7.23 (s, 2H), 3.94 (s, 6H), 3.87 (s, 3H), 3.65 (s, 3H), 2.67 (t, J = 7.5 Hz, 2H), 1.67–1.78 (m, 2H), 1.37–1.46 (m, 2H), 0.97 (t, J = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.5, 153.1, 149.8, 142.6, 133.2, 132.0, 127.0, 123.1, 119.5, 105.9, 60.6, 56.0, 30.7, 29.5, 26.9, 22.4, 13.8. IR (KBr) 2935, 1652, 1575, 1457, 1410, 1333, 1260, 1124, 999, 829, 710 cm^{-1}. MS (ESI) *m/z* 393 $[M+H]^+$; HR-MS (ESI) calcd for $C_{20}H_{26}N_2ClO_4$ $[M+H]^+$: 393.1581. Found: 393.1582.

4.2.7. (*E*)-3-(2-Butyl-4-chloro-1-methyl-1*H*-imidazol-5-yl)-1-(naphthalen-2-yl)prop-2-enone 4f

Yield: 84%; mp106 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.39 (d, J = 8.6 Hz, 1H), 8.02 (d, J = 8.6 Hz, 1H), 7.75–7.93 (m, 4H), 7.45–7.56 (m, 3H), 3.50 (s, 3H), 2.55 (t, J = 6.9 Hz, 2H), 1.60–170 (m, 2H), 1.33–1.43 (m, 2H), 0.93 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.0, 150.2, 135.5, 132.6, 129.8, 129.6, 128.5, 128.3, 127.7, 127.4, 126.6, 124.3, 123.6, 123.2, 119.7, 30.9, 29.7, 27.0, 22.4, 13.8. IR (KBr) 2958, 2853, 1657, 1564, 1436, 1360, 1276, 1176, 1048, 975, 807, 723 cm^{-1}. MS (ESI) *m/z* 353 $[M+H]^+$; HR-MS (ESI) calcd for $C_{21}H_{22}N_2ClO$ $[M+H]^+$: 353.1420. Found: 353.1428.

4.2.8. (*E*)-3-(2-Butyl-4-chloro-1-methyl-1*H*-imidazol-5-yl)-1-(naphthalen-1-yl)prop-2-enone 4g

Yield: 82%; mp 68 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.45 (d, J = 8.3 Hz, 1H), 7.96 (d, J = 8.3 Hz,1H), 7.81–7.87 (m, 2H), 7.49–7.58 (m, 5H), 3.63 (s, 3H), 2.67 (t, J = 7.5 Hz, 2H), 1.67–1.77 (m, 2H), 1.36–1.48 (m, 2H), 0.97 (t, J = 7.3 Hz 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 193.9, 150.7, 137.1, 133.8, 131.9, 130.4, 128.4, 128.0, 127.4, 127.3, 126.4, 125.7, 124.5, 123.9, 122.9, 31.1, 29.5, 27.0, 22.3, 13.7. IR (KBr) 2957, 2865, 1657, 1584, 1461, 1272, 1100, 969, 804, 779, 725 cm^{-1}. MS (ESI) *m/z* 353 $[M+H]^+$; HR-MS (ESI) calcd for $C_{21}H_{22}N_2ClO$ $[M+H]^+$: 353.1420. Found: 353.1410.

4.2.9. (*E*)-3-(2-Butyl-4-chloro-1-methyl-1*H*-imidazol-5-yl)-1-(thiophen-2-yl)prop-2-enone 4h

Yield: 83%; mp 99 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, J = 3.7 Hz, 1H), 7.63–7.70 (m, 2H), 7.57 (d, J = 15.1 Hz, 1H), 7.15 (t, J = 3.7 Hz, 1H), 3.65 (s, 3H), 2.67 (t, J = 7.5 Hz, 2H), 1.68–1.78 (m, 2H), 1.36–1.46 (m, 2H), 0.97 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.5, 150.2, 145.7, 133.6, 131.5, 128.1, 126.7, 122.9, 119.6, 30.8, 29.5, 27.0, 22.4, 13.8. IR (KBr) 2929, 2865, 1643, 1586, 1411, 1262, 1225, 1063, 967, 840, 727 cm^{-1}. MS (ESI) *m/z* 309 $[M+H]^+$.

4.2.10. (*E*)-3-(2-Butyl-4-chloro-1-methyl-1*H*-imidazol-5-yl)-1-(5-chlorothiophen-2-yl)prop-2-enone 4i

Yield: 80%; mp 96 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.55–7.59 (m, 3H), 6.98 (dd, J = 2.0 Hz, J = 2.0 Hz, 1H), 3.64 (s, 3H), 2.67 (t, J = 7.7 Hz, 2H), 1.67–1.77 (m, 2H), 1.36–1.46 (m, 2H), 0.97 (t, J = 7.1 Hz, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.4, 150.4, 132.8, 130.8, 127.6, 127.1, 122.9, 118.3, 30.9, 29.6, 27.1, 22.5, 13.9. IR (KBr) 2925, 2855, 1646, 1597, 1459, 1418, 1273, 1218, 1016, 966, 801, 724 cm^{-1}. MS (ESI) *m/z* 343 $[M+H]^+$.

4.2.11. (*E*)-1-(5-Bromothiophen-2-yl)-3-(2-butyl-4-chloro-1-methyl-1*H*-imidazol-5-yl)prop-2-enone 4j

Yield: 88%; mp 118 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.52–7.55 (m, 3H), 7.12 (d, J = 3.9 Hz, 1H), 3.63 (s, 3H), 2.67 (t, J = 7.5 Hz, 2H), 1.67–1.77 (m, 2H), 1.37–1.46 (m, 2H), 0.97 (t, J = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.2, 150.5, 147.2, 132.8, 131.4, 127.2, 122.9, 122.7, 118.5, 30.9, 29.6, 27.1, 22.5, 13.8. IR (KBr) 2954, 1635, 1580, 1457, 1408, 1270, 1216, 1069, 989, 959, 805, 725, 618 cm^{-1}. MS (ESI) *m/z* 387 $[M+H]^+$; HR-MS (ESI) calcd for $C_{15}H_{17}N_2OSBr$ Cl $[M+H]^+$: 386.9933. Found: 386.9919.

4.2.12. (*E*)-3-(2-Butyl-4-chloro-1-methyl-1*H*-imidazol-5-yl)-1-(furan-2-yl)prop-2-enone 4k

Yield: 86%; mp 125 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.62 (m, 3H), 7.26 (d, J = 3.0 Hz, 1H), 6.57 (d, J = 2.2 Hz, 1H) 3.66 (s, 3H), 2.68 (t, J = 7.5 Hz, 2H), 1.67–1.77 (m, 2H), 1.36–1.48 (m, 2H), 0.97 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.8, 153.8, 150.3, 146.3, 132.8, 126.7, 123.1, 119.1, 117.2112.5, 31.0, 29.6, 27.0, 22.4, 13.8. IR (KBr) 2950, 2863, 1653, 1560, 1461, 1263, 1041, 967, 769, 726 cm^{-1}. MS (ESI) *m/z* 293 $[M+H]^+$; HR-MS (ESI) calcd for $C_{15}H_{18}N_2O_2$ Cl $[M+H]^+$: 293.1056. Found: 293.1066.

4.2.13. (*E*)-3-(2-Butyl-4-chloro-1-methyl-1*H*-imidazol-5-yl)-1-(1*H*-pyrrol-2-yl)prop-2-enone 4l

Yield: 82%; mp 136 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 10.08 (br s, 1H), 7.56 (s, 2H), 7.05 (d, J = 16.7 Hz, 2H), 6.26–6.31 (m, 1H), 3.64 (s, 3H), 2.67 (t, J = 7.5 Hz, 2H), 1.67–1.77 (m, 2H), 1.35–1.48 (m, 2H), 0.96 (t, J = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.4149.7, 133.3, 122.0, 125.2, 123.2, 120.6, 116.4, 111.1, 30.9, 29.7, 27.1, 22.5, 13.9. IR (KBr) 2924, 2861, 1613, 1455, 1274, 1214, 964, 735 cm^{-1}. MS (ESI) *m/z* 292 $[M+H]^+$; HR-MS (ESI) calcd for $C_{15}H_{19}N_3OCl$ $[M+H]^+$: 292.1216. Found: 292.1221.

4.2.14. (*E*)-3-(2-Butyl-4-chloro-1-methyl-1*H*-imidazol-5-yl)-1-(pyridin-3-yl)prop-2-enone 4m

Yield: 74%; mp 98 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 9.21 (s, 1H), 8.78 (s, 1H), 8.27 (d, J = 7.5 Hz, 1H), 7.75 (d, J = 15.8 Hz 1H), 7.65 (d, J = 15.8 Hz, 1H), 7.45 (dd, J = 4.5 Hz, J = 3.0 Hz, 1H), 3.67 (s, 3H), 2.69 (t, J = 6.7 Hz, 2H), 1.67–1.78 (m, 2H), 1.36–1.49 (m, 2H), 0.97 (t, J = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.6, 152.9, 150.8, 149.5, 135.6, 133.3, 128.4, 123.5, 122.9, 118.2, 30.6, 29.5, 27.0, 22.3, 13.7. IR (KBr) 2925, 1638, 1580, 1401, 1256, 1105, 1047, 967, 731 cm^{-1}. MS (ESI) *m/z* 304 $[M+H]^+$; HR-MS (ESI) calcd for $C_{16}H_{19}N_3ClO$ $[M+H]^+$: 304.1216. Found: 304.1219.

4.2.15. (*E*)-1-(6-Bromopyridin-2-yl)-3-(2-butyl-4-chloro-1-methyl-1*H*-imidazol-5-yl)prop-2-enone 4n

Yield: 77%; mp 120 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.20 (d, J = 16.2 Hz, 1H), 8.02 (d, J = 7.3 Hz, 1H), 7.69–7.75 (m, 2H), 7.64 (d, J = 6.7 Hz, 1H), 3.73 (s, 3H), 2.69 (t, J = 7.5 Hz, 2H), 1.68–1.78 (m, 2H), 1.36–1.49 (m, 2H), 0.97 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.9, 154.9, 150.9, 141.3, 139.0, 134.7, 131.2, 128.4, 123.6, 121.5, 117.6, 31.5, 29.6, 27.0, 22.4, 13.8. IR (KBr) 2925, 2856, 1656, 1584, 1456, 1427, 1256, 1148, 1031, 974, 810,

783, 701, 609 cm^{-1}. MS (ESI) *m/z* 382 $[M+H]^+$; HR-MS (ESI) calcd for $C_{16}H_{18}N_3OClBr$ $[M+H]^+$: 382.0321. Found: 382.0341.

4.2.16. (*E*)-1-(Anthracen-2-yl)-3-(2-butyl-4-chloro-1-methyl-1*H*-imidazol-5-yl)prop-2-enone 4o

Yield: 80%; mp 138 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.60 (s, 1H), 8.41 (s, 1H), 7.97–8.08 (m, 5H), 7.67 (d, *J* = 15.8 Hz, 1H), 7.46–7.54 (m, 2H), 3.68 (s, 3H), 2.69 (t, *J* = 7.5 Hz, 2H), 1.67–1.80 (m, 2H), 1.37–1.51 (m, 2H), 0.98 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.6, 150.1, 134.8, 133.1, 132.5, 132.0, 131.1, 130.3, 129.5, 129.1, 128.8, 128.4, 128.1, 127.1, 126.5, 126.1, 125.8, 123.2, 119.4 30.8, 29.5, 26.9, 22.4, 13.8. IR (KBr) 2924, 2853, 1657, 1586, 1460, 1265, 1175, 1096, 877, 735 cm^{-1}. MS (EI) *m/z* 367 [M−Cl].

4.2.17. (*E*)-3-(2-Butyl-4-chloro-1-methyl-1*H*-imidazol-5-yl)-1-(dibenzo[b,d]furan-2-yl)prop-2-enone 4p

Yield: 84%; mp 122 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.62 (s, 1H), 8.17 (t, *J* = 6.7 Hz, 1H), 8.03 (d, *J* = 8.3 Hz, 1H), 7.95 (d, *J* = 15.1 Hz,1H), 7.56–7.68 (m, 3H), 7.47 (t, *J* = 6.7 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 1H), 3.67 (s, 3H), 2.68 (t, *J* = 7.5 Hz, 2H), 1.69–1.79 (m, 2H), 1.37–1.49 (m, 2H), 0.98 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.3, 158.9, 156.9, 150.2, 133.4, 128.0, 127.9, 127.4, 123.3, 121.7, 121.0, 119.7, 111.9, 30.9, 29.6, 27.1, 22.5, 13.8. IR (KBr) 2951, 1655, 1597, 1267, 1194, 1016, 812, 748 cm^{-1}. MS (EI) *m/z* 357 [M−Cl].

4.2.18. (*E*)-3-(2-Butyl-4-chloro-1-methyl-1*H*-imidazol-5-yl)-1-(dibenzo[b,d]thiophen-2-yl)prop-2-enone 4q

Yield: 87%; mp 120 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.24 (t, *J* = 3.9 Hz, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 7.90–7.96 (m, 2H), 7.83 (t, *J* = 5.8 Hz, 1H), 7.65 (d, *J* = 15.4 Hz, 1H), 7.46–7.49 (m, 2H), 3.65 (s, 3H), 2.67 (t, *J* = 7.5 Hz, 2H), 1.68–1.78 (m, 2H), 1.39–1.49 (m, 2H), 0.97 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.1, 150.0, 144.4, 139.7, 135.3, 134.7, 127.4, 127.3, 126.4, 124.9, 122.9, 122.7, 122.0, 121.9, 119.6, 30.9, 29.6, 27.1, 22.5, 13.9. IR (KBr) 2928, 2859, 1655, 1594, 1458, 1416, 1265, 1191, 1072, 966, 824, 731, 616 cm^{-1}. MS (ESI) *m/z* 409 $[M+H]^+$; HR-MS (ESI) calcd for $C_{23}H_{22}N_2OSCl$ $[M+H]^+$: 409.1141. Found: 409.1127.

4.2.19. (*E*)-3-(2-Butyl-4-chloro-1-methyl-1*H*-imidazol-5-yl)-1-(9-methyl-9*H*-carbazol-3-yl)prop-2-enone 4r

Yield: 81%; mp 163 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.82 (d, *J* = 1.5 Hz, 1H), 8.17–8.24 (m, 2H), 8.05 (d, *J* = 15.8 Hz, 1H), 7.70 (d, *J* = 15.8 Hz, 1H), 7.50–7.55 (m, 1H), 7.40–7.46 (m, 2H), 7.29–7.34 (m, 1H), 3.90 (s, 3H), 3.67 (s, 3H), 2.71 (t, *J* = 7.5 Hz, 2H), 1.69–1.80 (m, 2H), 1.37–1.51 (m, 2H), 0.97 (t, *J* = 6.7 Hz, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.9, 150.0, 143.7, 129.5, 126.7, 126.6, 126.2, 123.0, 122.2, 121.8, 120.6, 120.5, 120.1, 119.9, 30.9, 29.6, 29.3, 27.0, 22.4, 13.7. IR (KBr) 2931, 2863, 1624, 1543, 1463, 1245, 1189, 1016, 735, 607 cm^{-1}. MS (ESI) *m/z* 406 $[M+H]^+$: HR-MS (ESI) calcd for $C_{24}H_{25}N_3OCl$ $[M+H]^+$: 406.1686. Found: 406.1668.

4.2.20. 3-(2-Butyl-4-chloro-1-methyl-1*H*-imidazol-5-yl)-1,5-di(thiophen-2-yl)pentane-1,5-dione 5

Yield 8%: syrup, ^1H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, *J* = 3.5 Hz, 2H), 7.59 (d, *J* = 4.9 Hz, 2H), 7.08 (t, *J* = 3.9 Hz, 2H), 4.00–4.10 (m, 1H), 3.80 (dd, *J* = 6.7 Hz, *J* = 10.0 Hz, 2H), 3.69 (s, 3H), 3.14 (dd, *J* = 4.7 Hz, *J* = 12.0 Hz, 2H), 2.53 (t, *J* = 7.7 Hz, 2H), 1.53–1.63 (m, 2H), 1.23–1.32 (m, 2H), 0.90 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 191, 146.3, 143.7, 134.0, 132.2, 128.2, 126.4, 124.9, 42.0, 30.7, 29.6, 26.9, 26.1, 22.3, 13.7. IR (neat) 3095, 2925, 2856, 1660, 1413, 1359, 1266, 855, 725 cm^{-1}. MS (ESI) *m/z* 435 $[M+H]^+$.

4.3. General procedure

4.3.1. Synthesis of (*E*)-3-(2-butyl-4-chloro-1-methyl-1*H*-imidazol-5-yl)-1-(thiophen-2-yl)prop-2-enone 6h

To a solution of chalcone **4h** (0.5 g, 1.62 mmol) in acetic acid (15 ml) was added drop wise hydrazine hydrate (0.4 ml, 8.12 mmol) and heated at 120 °C for 3.0 h. After completion (TLC) the reaction mixture was poured in ice water, extracted with ethyl acetate (3 × 10 ml), dried over sodium sulfate and evaporated under reduced pressure. The crude residue was chromatographed over silica gel column to give product **6h** as a crystalline solid.

4.3.2. 1-(5-(2-Butyl-4-chloro-1-methyl-1*H*-imidazol-5-yl)-3-phenyl-4,5-dihydro-1*H*-pyrazolyl)ethanone 6a

Yield: 86%; mp 102 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.13 (t, *J* = 3.7 Hz, 2H), 7.35–7.40 (m, 3H), 5.40 (dd, *J* = 5.2 Hz, *J* = 6.7 Hz, 1H), 3.66 (s, 3H), 3.41–3.62 (m, 2H), 2.59 (t, *J* = 6.7 Hz, 2H), 2.32 (s, 3H), 1.62–1.72 (m, 2H), 1.33–1.43 (m, 2H), 0.94 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 153.2, 146.3, 130.9, 130.0, 128.4, 126.3, 125.2, 124.5, 49.6, 38.5, 30.5, 29.4, 26.6, 22.2, 21.4, 13.6. IR (KBr); 2925, 2862, 1657, 1590, 1416, 1357, 1326, 1252, 1138, 1029, 948, 854, 762, 690 cm^{-1}. MS (ESI) *m/z* 359 $[M+H]^+$; HR-MS (ESI) calcd for $C_{19}H_{24}N_4OCl$ $[M+H]^+$: 359.1638. Found: 359.1649.

4.3.3. 1-(5-(2-Butyl-4-chloro-1-methyl-1*H*-imidazol-5-yl)-3-*p*-tolyl-4,5-dihydro-1*H*-pyrazolyl)ethanone 6b

Yield: 89%; mp 116 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.3 Hz, 2H), 7.20 (d, *J* = 7.9 Hz, 2H), 5.38 (dd, *J* = 5.8 Hz, *J* = 6.6 Hz, 1H), 3.69 (s, 3H), 3.59 (dd, *J* = 12.4 Hz, *J* = 5.0 Hz,1H), 3.46 (dd, *J* = 6.0 Hz, *J* = 11.5 Hz, 1H), 2.60 (t, *J* = 6.6 Hz, 2H), 2.40 (s, 3H), 2.32 (s, 3H), 1.64–1.74 (m, 2H), 1.36–1.46 (m, 2H), 0.94 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 153.7, 146.7, 140.6, 129.4, 128.3, 126.5, 125.4, 49.7, 38.8, 30.8, 29.6, 26.9, 22.4, 21.7, 21.5, 13.8. IR (KBr) 2925, 2855, 1660, 1436, 1323, 1250, 1140, 1033, 858, 819, 754, 619 cm^{-1}. MS (ESI) *m/z* 373 $[M+H]^+$; HR-MS (ESI) calcd for $C_{20}H_{26}N_4OCl$ $[M+H]^+$: 373.1795. Found: 373.1799.

4.3.4. 1-(5-(2-Butyl-4-chloro-1-methyl-1*H*-imidazol-5-yl)-3-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazolyl)ethanone 6c

Yield: 92%; mp 140 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.3 Hz, 2H), 6.89 (d, *J* = 9.0 Hz, 2H), 5.38 (dd, *J* = 6.0 Hz, *J* = 6.7 Hz, 1H), 3.84 (s, 3H), 3.70 (s, 3H), 3.58 (dd, *J* = 12.8 Hz, *J* = 4.5 Hz, 1H), 3.45 (dd, *J* = 6.0 Hz, *J* = 11.3 Hz, 1H), 2.60 (t, *J* = 6.7 Hz, 2H), 2.32 (s, 3H), 1.64–1.74 (m, 2H),1.36–1.46 (m, 2H), 0.95 (t, *J* = 7.5 Hz, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 161.3, 153.4, 146.7, 128.1, 124.8, 123.7, 114.2, 55.3, 49.7, 38.9, 30.8, 29.7, 26.9, 22.5, 21.7, 13.9. IR (KBr) 2924, 2852, 1664, 1607, 1460, 1405, 1326, 1258, 1173, 1024, 831, 755, 616, 544 cm^{-1}. MS (ESI) *m/z* 389 $[M+H]^+$; HR-MS (ESI) calcd for $C_{20}H_{26}N_4O_2Cl$ $[M+H]^+$: 389.1744. Found: 389.1761.

4.3.5. 1-(5-(2-Butyl-4-chloro-1-methyl-1*H*-imidazol-5-yl)-3-(4-nitrophenyl)-4,5-dihydro-1*H*-pyrazolyl)ethanone 6d

Yield: 95%; mp 125 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.26 (d, *J* = 9.0 Hz, 2H), 7.89 (d, *J* = 9.0 Hz, 2H), 5.46 (dd, *J* = 6.0 Hz, *J* = 6.7 Hz, 1H) 3.71 (s, 3H), 3.48–3.67 (m, 2H), 2.62 (t, *J* = 6.7 Hz, 2H), 2.35 (s, 3H), 1.63–1.73 (m, 2H), 1.33–1.43 (m, 2H), 0.94 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 151.2, 148.5, 147.1, 137.0, 127.1, 125.6, 124.5, 124.0, 114.2, 50.3, 38.4, 30.8, 29.6, 26.8, 22.4, 21.6, 13.8. IR (KBr) 2924, 2853, 1670, 1575, 1518, 1441, 1402, 1344, 1320, 1249, 1140, 848, 751, 690 cm^{-1}. MS (ESI) *m/z* 404 $[M+H]^+$; HR-MS (ESI) calcd for $C_{19}H_{23}N_5O_3Cl$ $[M+H]^+$: 404.1489. Found: 404.1494.

4.3.6. 1-(5-(2-Butyl-4-chloro-1-methyl-1*H*-imidazol-5-yl)-3-(3,4,5-trimethoxyphenyl)-4,5-dihydro-1*H*-pyrazolyl)ethanone 6e

Yield: 94%;mp 120 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.91 (s, 2H), 5.41 (dd, J = 6.0 Hz, J = 6.7 Hz,1H), 3.89 (s, 6H), 3.86 (s, 3H), 3.35–3.68 (m, 5H), 2.61 (t, J = 6.7 Hz, 2H), 2.33 (s, 3H), 1.62–1.72 (m, 2H), 1.35–1.45 (m, 2H), 0.94 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 153.2, 146.4, 140.2, 126.2, 125.0, 124.6, 103.8, 60.4, 55.9, 49.7, 38.7, 30.5, 29.5, 26.5, 22.2, 21.4, 17.5, 13.7. IR (KBr) 2933, 2871, 1657, 1572, 1463, 1415, 1364, 1248, 1209, 1127, 1000, 851, 765 cm^{-1}. MS (ESI) *m/z* 449 $[M+H]^+$; HR-MS (ESI) calcd for $C_{22}H_{30}N_4O_4Cl$ $[M+H]^+$: 449.1955. Found: 449.1970.

4.3.7. 1-(5-(2-Butyl-4-chloro-1-methyl-1*H*-imidazol-5-yl)-3-(naphthalen-2-yl)-4,5-dihydro-1*H*-pyrazolyl)ethanone 6f

Yield: 91%; mp142 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, J = 8.3 Hz, 1H), 7.89 (s, 1H), 7.81 (d, J = 6.0 Hz, 3H), 7.48 (t, J = 4.5 Hz, 2H), 5.38 (dd, J = 6.0 Hz, J = 6.0 Hz, 1H), 3.51–3.67 (m, 5H), 2.59 (t, J = 8.3 Hz, 2H), 2.36 (s, 3H), 1.62–172 (m, 2H), 1.34–1.44 (m, 2H), 0.93 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 153.5, 146.7, 134.1, 132.9, 128.6, 128.4, 127.8, 127.1, 126.8, 126.6, 125.4, 124.7, 123.2, 49.9, 38.6, 30.7, 29.6, 26.7, 22.4, 21.6, 13.8. IR (KBr); 2926, 2853, 1652, 1466, 1392, 1306, 1251, 1120, 981, 945, 808, 781 cm^{-1}. MS (ESI) *m/z* 409 $[M+H]^+$; HR-MS (ESI) calcd for $C_{23}H_{26}N_4OCl$ $[M+H]^+$: 409.1795. Found: 409.1806.

4.3.8. 1-(5-(2-Butyl-4-chloro-1-methyl-1*H*-imidazol-5-yl)-3-(naphthalen-1-yl)-4,5-dihydro-1*H*-pyrazolyl)ethanone 6g

Yield: 93%; mp 148 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.16 (d, J = 8.4 Hz, 1H), 7.87 (t, J = 7.3 Hz, 2H), 7.40–7.60 (m, 4H), 5.39 (dd, J = 5.6 Hz, J = 6.9 Hz, 1H), 3.63–3.89 (m, 5H), 2.61 (t, J = 6.7 Hz, 2H), 2.42 (s, 3H), 1.65–1.75 (m, 2H), 1.33–1.44 (m, 2H), 0.95 (t, J = 7.3 Hz, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 153.7, 146.6, 134.2, 131.5, 130.8, 128.7, 127.7, 127.6, 126.8, 126.3, 125.5, 124.9, 124.7, 123.4, 48.8, 41.4, 30.8, 29.7, 26.9, 22.5, 21.9, 14.0. IR (KBr):2924, 2857, 16521461, 1420, 1387, 1304, 1249, 1140, 1028, 952, 807, 779. MS (ESI) *m/z:* 409 $[M+H]^+$; HR-MS (ESI) calcd for $C_{23}H_{26}N_4OCl$ $[M+H]^+$: 409.1795. Found: 409.1805.

4.3.9. 1-(5-(2-Butyl-4-chloro-1-methyl-1*H*-imidazol-5-yl)-3-(thiophen-2-yl)-4,5-dihydro-1*H*-pyrazolyl)ethanone 6h

Yield: 94%; mp 90 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (dd, J = 1.1 Hz, J = 3.9 Hz, 1H), 7.24 (dd, J = 1.1 Hz, J = 2.6 Hz, 1H), 7.07 (dd, J = 3.7 Hz, J = 1.3 Hz, 1H), 5.43 (dd, J = 5.8 Hz J = 11.7 Hz, 1H), 3.60–3.70 (m, 4H), 3.47 (dd, J = 5.8 Hz, J = 11.7 Hz, 1H), 2.61 (t, J = 7.7 Hz, 2H), 2.32 (s, 3H), 1.63–1.73 (m, 2H), 1.35–1.45 (m, 2H), 0.93 (t, J = 7.3 Hz, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 149.3, 146.9, 134.4, 128.6, 128.4, 127.5, 125.4, 124.5, 49.9, 39.4, 30.7, 29.6, 26.8, 22.4, 21.6, 13.7. IR (KBr) 2923, 2855, 1653, 1456, 1409, 1317, 1252, 1138, 1024, 948, 836, 720, 619, 580 cm^{-1}. MS (ESI) *m/z* 365 $[M+H]^+$: HR-MS (ESI) calcd for $C_{17}H_{22}N_4OSCl$ $[M+H]^+$: 365.1202. Found: 365.1200.

4.3.10. 1-(5-(2-Butyl-4-chloro-1-methyl-1*H*-imidazol-5-yl)-3-(5-chlorothiophen-2-yl)-4,5-dihydro-1*H*-pyrazolyl)ethanone 6i

Yield: 92%; mp 150 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.98 (s, 1H), 6.87 (s, 1H), 5.38 (dd, J = 4.8 Hz, J = 7.6 Hz, 1H), 3.68 (s, 3H), 3.55 (t, J = 12.5 Hz, 1H), 3.43 (dd, J = 4.8 Hz, J = 12.5 Hz, 1H), 2.60 (t, J = 7.6 Hz, 2H), 2.27 (s, 3H), 1.63–1.72 (m, 2H), 1.32–1.42 (m, 2H), 0.95 (t, J = 6.7 Hz, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 148.5, 147.0, 133.6, 133.1, 127.7, 126.7, 125.5, 124.4, 50.1, 38.8, 30.8, 29.6, 26.8, 22.4, 21.6, 13.7. IR (KBr) 2938, 2871, 1660, 1593, 1551, 1455, 1409, 1319, 1255, 1132, 1011, 953, 845, 820, 747 cm^{-1}. MS (ESI) *m/z* 399 $[M+H]^+$; HR-MS (ESI) calcd for $C_{17}H_{21}N_4OSCl_2$ $[M+H]^+$: 399.0813. Found: 399.0814.

4.3.11. 1-(3-(5-Bromothiophen-2-yl)-5-(2-butyl-4-chloro-1-methyl-1*H*-imidazol-5-yl)-4,5-dihydro-1*H*-pyrazolyl)ethanone 6j

Yield: 85%; mp 142 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.00 (d, J = 3.6 Hz, 1H), 6.95 (d, J = 3.9 Hz, 1H), 5.38 (dd, J = 5.6 Hz, J = 7.1 Hz, 1H), 3.67 (s, 3H), 3.56 (dd, J = 12.7 Hz, J = 4.6 Hz, 1H), 3.42 (dd, J = 5.6 Hz, J = 11.7 Hz, 1H), 2.59 (td, J = 2.6 Hz, J = 4.9 Hz, 2H), 2.27 (s, 3H), 1.65–1.71 (m, 2H), 1.36–1.43 (m, 2H), 0.94 (t, J = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6148.1, 146.7, 136.2, 130.3, 128.3, 125.7, 124.3, 116.4, 50.6, 38.8, 30.7, 29.6, 26.9, 22.5, 21.6, 13.3. IR (KBr) 2927, 2858, 1658, 1549, 1453, 1408, 1318, 1249, 1128, 1022, 949, 843, 792, 744 cm^{-1}. MS (ESI) *m/z* 443 $[M+H]^+$; HR-MS (ESI) calcd for $C_{17}H_{21}N_4OSClBr$ $[M+H]^+$: 443.0307. Found: 443.0325.

4.3.12. 1-(5-(2-Butyl-4-chloro-1-methyl-1*H*-imidazol-5-yl)-3-(furan-2-yl)-4,5-dihydro-1*H*-pyrazolyl)ethanone 6k

Yield: 88%; mp 138 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, J = 1.5 Hz, 1H), 6.78 (d, J = 3.3 Hz, 1H), 6.51 (dd, J = 1.7 Hz, J = 1.7 Hz, 1H), 5.36 (dd, J = 6.0 Hz, J = 6.4 Hz, 1H), 3.40–3.69 (m, 5H), 2.60 (t, J = 6.7 Hz, 2H), 2.31 (s, 3H), 1.64–1.74 (m, 2H), 1.34–1.46 (m, 2H), 0.95 (t, J = 7.3 Hz, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 146.9, 146.5, 145.0, 144.3, 125.6, 124.5, 111.9, 111.6, 49.4, 38.5, 30.7, 29.7, 26.9, 22.5, 21.7, 13.9. IR (KBr) 2927, 2853, 1660, 1550, 1434, 1383, 1319, 1253, 1165, 1131, 1006, 947, 852, 763, 588 cm^{-1}. MS (ESI) *m/z* 349 $[M+H]^+$; HR-MS (ESI) calcd for $C_{17}H_{22}N_4O_2Cl$ $[M+H]^+$: 349.1431. Found: 349.1439.

4.3.13. 1-(5-(2-Butyl-4-chloro-1-methyl-1*H*-imidazol-5-yl)-3-(1*H*-pyrrol-2-yl)-4,5-dihydro-1*H*-pyrazolyl)ethanone 6l

Yield: 94%; mp 157 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.06 (s, 1H), 6.91 (s, 1H), 6.41 (s, 1H), 6.22 (s,1H), 5.35 (dd, J = 6.0 Hz, J = 6.6 Hz,1H), 3.38–3.68 (m, 5H), 2.60 (t, J = 6.9 Hz, 2H), 2.26 (s, 3H), 1.63–1.73 (m, 2H), 1.33–1.43 (m, 2H), 0.94 (t, J = 7.1 Hz, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 150.7, 147.1, 133.1, 129.0, 125.3, 21.6, 112.5, 110.3, 49.4, 38.6, 30.8, 29.8, 26.9, 22.5, 21.7, 13.9. IR (KBr) 2925, 2856, 1641, 1464, 1406, 1255, 1115, 1028, 959, 737, 607 cm^{-1}. MS (ESI) *m/z* 348 $[M+H]^+$; HR-MS (ESI) calcd for $C_{17}H_{23}N_5OCl$ $[M+H]^+$: 348.1591. Found: 348.1574.

4.3.14. 1-(5-(2-Butyl-4-chloro-1-methyl-1*H*-imidazol-5-yl)-3-(pyridin-3-yl)-4,5-dihydro-1*H*-pyrazolyl)ethanone 6m

Yield: 92%; mp 46 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.88 (s, 1H), 8.66 (d, J = 5.2 Hz, 1H), 8.14 (d, J = 8.3 Hz, 1H), 7.39 (dd, J = 5. 8 Hz, J = 3.0 Hz, 1H), 5.45 (dd, J = 6.0 Hz, J = 6.7 Hz, 1H), 3.71 (s, 3H), 3.47–3.67 (m, 2H), 2.63 (t, J = 6.7 Hz, 2H), 2.34 (s, 3H), 1.63–1.73 (m, 2H), 1.33–1.43 (m, 2H), 0.94 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 150.6, 147.4, 133.8, 127.4, 125.5, 124.6, 123.7, 122.3, 49.9, 38.3, 30.8, 29.7, 26.8, 22.4, 21.6, 13.9. IR (KBr) 2958, 2928, 1661, 1595, 1460, 1410, 1262, 1178, 1047, 966, 811, 720, 684 cm^{-1}. MS (ESI) *m/z* 360 $[M+H]^+$; HR-MS (ESI) calcd for $C_{18}H_{23}N_5OCl$ $[M+H]^+$: 360.1591. Found: 360.1587.

4.3.15. 1-(3-(6-Bromopyridin-2-yl)-5-(2-butyl-4-chloro-1-methyl-1*H*-imidazol-5-yl)-4,5-dihydro-1*H*-pyrazolyl)ethanone 6n

Yield: 91%; mp 120 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, J = 7.5 Hz, 1H), 7.53 (t, J = 7.5 Hz, 1H), 7.42 (d, J = 7.5 Hz, 1H) 5.35 (dd, J = 6.0 Hz, J = 6.7 Hz, 1H), 3.62–3.74 (m, 4H), 3.52 (dd, J = 6.0 Hz, J = 12.8 Hz, 1H), 2.56 (t, J = 7.5 Hz, 2H), 2.26 (s, 3H), 1.57–1.67 (m, 2H), 1.29–1.39 (m, 2H), 0.88 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 153.9, 151.4, 146.8, 141.6, 138.4, 128.6, 125.2, 124.6, 119.7, 50.2, 38.5, 30.7, 29.5, 26.7, 22.3, 21.5, 13.7. IR (KBr) 2924, 2855, 1666, 1549, 1465, 1402, 1325, 1255, 1157, 1129, 1037, 950, 858, 798, 752 cm^{-1}. MS (ESI) *m/z* 438 $[M+H]^+$; HR-MS (ESI) calcd for $C_{18}H_{22}N_5OClBr$ $[M+H]^+$: 438.0696. Found: 438.0695.

4.3.16. 1-(3-(Anthracen-2-yl)-5-(2-butyl-4-chloro-1-methyl-1*H*-imidazol-5-yl)-4,5-dihydro-1*H*-pyrazolyl)ethanone 6o

Yield: 87%; mp 184 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (d, J = 5.0 Hz, 2H), 7.95–8.05 (m, 5H), 7.43–7.52 (m, 2H), 5.39–5.45 (m, 1H), 3.71 (s, 3H), 3.64–3.69 (m, 2H), 2.63 (t, J = 7.7 Hz, 2H), 2.39 (s, 3H), 1.65–1.76 (m, 2H), 1.37–1.47 (m, 2H), 0.95 (t, J = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 153.7, 146.9, 132.5, 132.1, 131.7, 130.9, 128.8, 128.2, 128.1, 127.9, 127.4, 126.4, 126.1, 125.9, 122.6, 50.8, 38.9, 30.1, 29.7, 26.9, 22.5, 21.7, 13.8. IR (KBr): 2922, 2853, 1665, 1412, 1325, 1254, 1135, 895, 855, 744 cm^{-1}. MS (ESI) *m/z:* 459 $[M+H]^+$; HR-MS (ESI) calcd for $C_{27}H_{28}N_4OCl$ $[M+H]^+$: 459.1951. Found: 459.1952.

4.3.17. 1-(5-(2-Butyl-4-chloro-1-methyl-1*H*-imidazol-5-yl)-3-(dibenzo[b,d]furan-2-yl)-4,5-dihydro-1*H*-pyrazolyl)ethanone 6p

Yield: 93%; mp 145 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.96 (d, J = 7.7 Hz, 1H), 7.86 (d, J = 8.4 Hz,1H), 7.57 (d, J = 9.2 Hz, 2H), 7.46 (t, J = 7.3 Hz, 1H), 7.34 (t, J = 7.3 Hz, 1H), 5.43 (dd, J = 5.0 Hz, J = 6.6 Hz, 1H), 3.52–3.69 (m, 5H), 2.61 (t, J = 7.5 Hz, 2H), 2.38 (s, 3H), 1.63–1.73 (m, 2H), 1.33–1.43 (m, 2H), 0.94 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 157.1, 156.5, 153.4, 146.6, 127.6, 126.0, 125.6, 124.6, 123.5, 123.0, 120.7, 118.9, 111.9, 111.7, 109.6, 49.8, 38.9, 30.6, 29.5, 26.7, 22.3, 21.6, 13.7. IR (KBr) 2957, 2927, 2856, 1659, 1436, 1414, 1363, 1324, 1255, 1197, 1125, 1021, 842, 752, 622 cm^{-1}. MS (ESI) *m/z* 449 $[M+H]^+$; HR-MS (ESI) calcd for $C_{25}H_{26}N_4O_2Cl$ $[M+H]^+$: 449.1744. Found: 449.1733.

4.3.18. 1-(5-(2-Butyl-4-chloro-1-methyl-1*H*-imidazol-5-yl)-3-(dibenzo[b,d]thiophen-2-yl)-4,5-dihydro-1*H*-pyrazolyl)ethanone 6q

Yield: 87%; mp 130 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (s, 1H), 8.14–8.19 (m, 1H), 7.82–7.89 (m, 3H), 7.44–7.47 (m, 2H), 5.43 (dd, J = 5.4 Hz, J = 6.0 Hz, 1H), 3.60–3.17 (m, 5H), 2.62 (t, J = 7.7 Hz, 2H), 2.39 (s, 3H), 1.64–1.74 (m, 2H), 1.36–1.46 (m, 2H), 0.95 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 153.4, 146.6, 141.6, 139.8, 135.9, 135.1, 127.6, 127.2, 124.7, 124.6, 122.9, 121.8, 119.6, 49.9, 38.9, 30.9, 29.7, 26.8, 22.5, 21.7, 13.9. IR (KBr) 2957, 2866, 1658, 1593, 1415, 1313, 1255, 1136, 1025, 858, 760, 618 cm^{-1}. MS (ESI) *m/z* 465 $[M+H]^+$; HR-MS (ESI) calcd for $C_{25}H_{26}N_4OSCl$ $[M+H]^+$: 465.1515. Found: 465.1494.

4.3.19. 1-(5-(2-Butyl-4-chloro-1-methyl-1*H*-imidazol-5-yl)-3-(9-methyl-9*H*-carbazol-3-yl)-4,5-dihydro-1*H*-pyrazolyl)ethanone 6r

Yield: 85%; mp 194 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (s,1H), 8.04 (d, J = 7.5 Hz, 1H), 7.82 (d, J = 8.3 Hz, 1H), 7.44 (t, J = 7.5 Hz, 1H), 7.31 (t, J = 8.3 Hz, 2H), 7.22 (t, J = 7.5 Hz,1H), 5.23 (dd, J = 6.0 Hz, J = 5.2 Hz, 1H), 3.79 (s, 3H), 3.59 (s, 3H), 3.30–3.55 (m, 2H), 2.58 (t, J = 7.5 Hz, 2H), 2.36 (s, 3H), 1.60–1.70 (m, 2H), 1.31–1.43 (m, 2H), 0.92 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 154.4, 146.5, 141.8, 141.3, 126.6, 124.9, 124.2, 122.7, 122.5, 121.9, 120.3, 119.5, 118.9, 108.6, 108.5, 49.6, 39.0, 30.6, 29.6, 29.0, 26.7, 22.4, 21.6, 13.8. IR (KBr); 2926, 2861, 1652, 1443, 1412, 1323, 1250, 1125, 950, 853, 747, 621 cm^{-1}. MS (ESI) *m/z* 462 $[M+H]^+$; HR-MS (ESI) calcd for $C_{26}H_{29}N_5OCl$ $[M+H]^+$: 462.2060. Found: 462.2060.

4.4. ACE inhibition assay

ACE inhibition assay was performed using the method described by Jimsheena and Gowda. Rabbit lung tissue was used as a source of ACE enzyme. 1 g of rabbit lung was homogenized with 10 mL of 0.05 M sodium borate buffer pH 8.2 containing 0.3 M NaCl and 0.5% Triton X-100 at 4 °C followed by centrifugation at 15,000 rpm for 60 min at 4 °C. Supernatant was used as a source of ACE enzyme for this assay. ACE activity was assayed by monitoring the release of Hippuric acid (HA) from the hydrolysis of hippuryl-histidyl-leucine (HHL) (Sigma–Aldrich, USA). 15 μl of ACE solution was preincubated with test and standard drug solution (75 μl each) for 10 min at 37 °C. The enzyme reaction was started by adding 125 μl of 0.05 M sodium borate buffer (pH 8.2) containing 0.3 M NaCl and 50 μl of 5 mM substrate (HHL) followed by incubation at 37 °C for 30 min. The reaction was arrested by the addition of 0.2 mL of 1 M HCl. After stopping the reaction, 0.4 mL of pyridine (SD Fine chemical, India) was added followed by 0.2 mL of BSC (SD Fine chemical, India). The solution was mixed by inversion for 1 min and cooled on ice. The yellow color developed was measured at 410 nm. The decreased concentration of HA in the test reaction compared with the control reaction was expressed as percentage inhibition and calculated from the equation: Inhibition% = $100 - [T/C] \times 100$, where T = absorbance of test reaction and C = absorbance of control reaction. The therapeutic drug Lisinopril was used as reference ACE inhibitor. The inhibitory concentration 50% (IC_{50}) was calculated by nonlinear regression. The dose–response curve was obtained by plotting the percentage inhibition versus the concentrations.

Acknowledgments

Authors are thankful to Dr. J.S. Yadav, Director, Heads of Organic Chemistry Division-II and Chemical Biology, IICT, Hyderabad for encouragement and support. Financial assistance from MLP projects (S.K.), DBT Project (BT/HRD/35/02/09/2008 to SKB) is also duly acknowledged. D.A. (SRF) is thankful to CSIR for fellowship.

Supplementary data

Copies of ^{1}H, ^{13}C NMR and mass spectra of all the new compounds **4a**–**r**, **5**, **6a**–**r**; CCDC 823201 (for **4j**) and CCDC 823202 (for **6i**) contain the crystallographic data and can be obtained free of charge from the Cambridge Crystallographic Data centre via http://www.ccdc.cam.ac.uk/data_request/cif.

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2011.06.085.

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