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Substituted imidazole derivatives as novel cardiovascular agents

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ABSTRACT

A series of novel substituted imidazole derivatives were synthesized and have been screened *in vivo* for their hypotensive and acute toxicity activities. Out of seventeen compounds eight compounds **(2b, 2c, 3b, 3c, 3f, 4a, 4b and 4c)** have shown good hypotensive & bradycardiac responses. Compounds **3b, 3c, 3f & 4c** have shown better activity than reference drug clonidine. All the compounds have shown ALD50>1000mg/kg with maximum in **2e & 4c** (>1200mg/kg).

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For a long time adrenoceptors ($\alpha_1\alpha_2$ &β)[1] have been attractive therapeutical target because they serve a large variety of physiological action & functional processes namely cardiovascular regulation. Alpha blockers are vasodilators (drugs that relax blood vessels) and do not affect cardiac output. One of the major advantage of alpha blockers is that they lower cholesterol especially LDL, triglycerides and raises HDL. Studies have documented that abnormal enlargement of left heart ventricle improves with use of alpha blocker.[2] These drugs may also help to control diabetes and relieve the symptoms of benign prostate hypertrophy (enlarged prostate).[3] Imidazole nucleus exhibits broad spectrum cardiovascular[4–6] activities. There are indeed a large number of compounds (Fig. 1) able to interact with α_2- adrenoceptors having heterocyclic nucleus like imidazole and oxazole e.g. medetomidene **[I]**, idazoxan **[II]**, moxonidine **[III]**, clonidine **[V]** & rilmenidine **[IV].**[7] It has been demonstrated that clonidine is α_2 adrenoceptor agonist. Clonidine and these agents stimulate α_2 /imidazoline receptors present in medulla oblongata of CNS.[8–10] Subsequently it has been elucidated that the central neurochemical modulation of baroreceptor reflex occurs at the level of various medullary nuclei of GRN which is rich in α - adrenoceptors and clonidine like drugs have been shown to interact with α_2 receptors present at these site.[11] These α_2 receptors present in central and peripheral nerve endings reduce the nor-epinephrine release. They decrease blood pressure (BP) by reducing cardiac output, relaxation of capacitance vessels with reduction in peripheral vascular resistance.[12]

The compounds having imidazole nucleus have shown to interact with α_2- adrenoceptors[13,14] & lower systemic blood pressure. Hence substituted aryl imidazoles have been extensively utilized for the synthesis of compounds having cardiovascular activity.[15] Earlier reports have elucidated that incorporation of various pharmacophore at position-1 of heterocyclic compounds viz. imidazole[16] and pyrazolines[17] markedly modulate hypotensive activity. Therefore it was thought worthwhile to synthesize some new

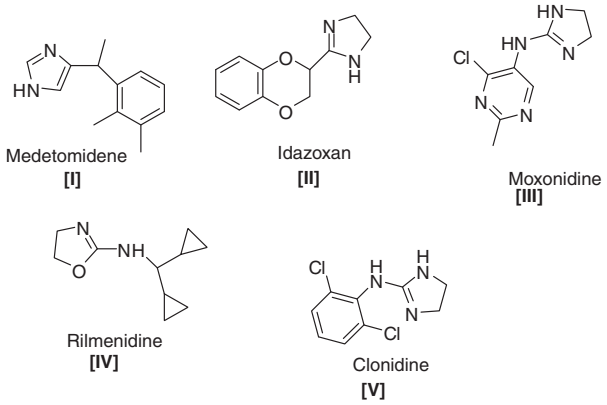

Figure 1.

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substituted imidazole derivatives by incorporating hydrazides,[18] arylidine hydrazide & oxadiazole moieties[19] at 1-position of imidazole with a hope to get better novel antihypertensive agent.

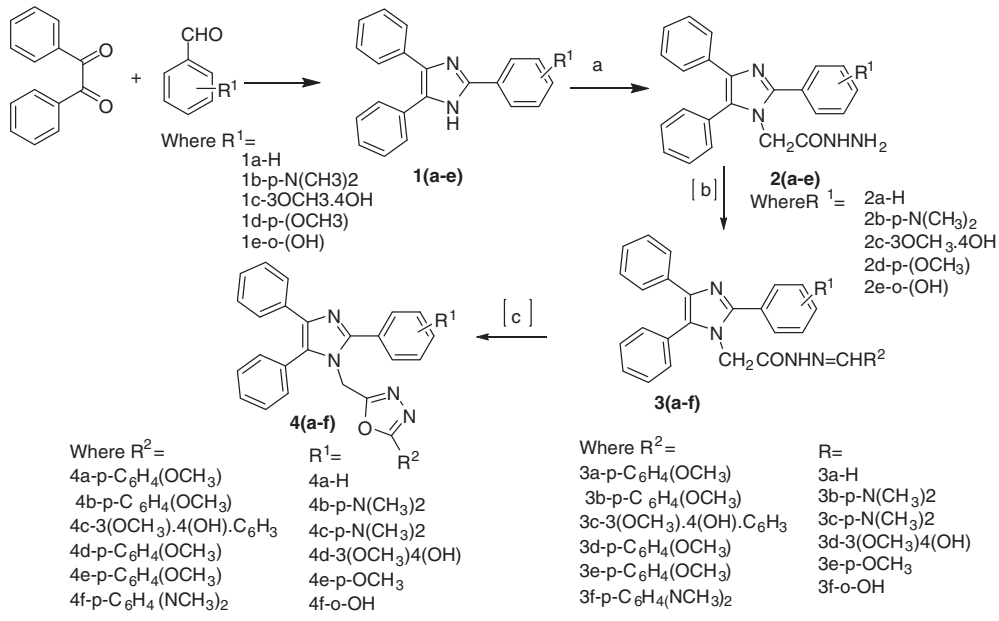
The substituted imidazoles **1(a-e)** were synthesized by treating benzyl group with substituted aryl aldehydes and ammonium acetate as ammonia source, in the presence of catalytic amount of $NiCl_2{\cdot}6H_2O$ supported onto acidic alumina.[20] Michael condensation of **1(a-e)** with ethylchloroacetate in the presence of dry K_2CO_3 and subsequent treatment of reaction mixture with hydrazine hydrate in the presence of DMF afforded compounds **2(a-e)** which were further reacted with different aromatic aldehydes to undergo mannich reaction furnishing substituted benzylidene-1H-imidazole-(1-yl) acetohydrazide **3(a-f)**. These compounds were further reacted (Scheme 1) with PTSA/$ZnCl_2$[#] in the presence of DMF or with warm glacial acetic acid & ferric chloride to afford final compounds **4 (a-f)**. All the synthesized compounds were well characterized by spectroscopic data like IR, mass, NMR and elemental analysis.[21] These compounds were tested for their hypotensive activities Table-1 & ALD50 activities.

All these new compounds **2(a-e)**, **3(a-f)**, **4(a-f)** were tested *in vivo* in order to evaluate their hypotensive activity according to following standard method discussed below.

The study was carried in cats of either sex, the weight of cats were between the ranges of 2.5 to 4 kg, anaesthetized with alpha –chloralose (80 mg /kg, i.v.) and maintained on artificial respiration. The femoral vein and artery of one side were cannulated with polyethylene tubing. The venous catheter was used for the stathum P 23 db pressure transducer for recording the blood pressure on one channel of polygraph (polyrite, India). Heart rate was calculated either from the pressure pulse recording or from the electrocardiogram (ECG lead II) recorded on another channel of the polygraph. The effect of the synthesized compounds & reference drug clonidine were studied on the blood pressure & heart rate and on the pressure response evoked either by carotid occlusion (CO) for 10 sec or by i.v. injection of nor epinephrine (1-2 μg). Changes observed in blood pressure were classified as immediate and delayed. Any changes which occurred from the control level within 5 minutes were taken as immediate and changes after a period of 5 minutes were taken as delayed following the administration of test compounds.

The active compounds were investigated for approximate lethal dose (ALD50). Mice (either sex) weighing 20-25 grams were used for this study. They have been fasted overnight (about 18 hr), were given water adlibitum & maintained at the temperature of 24 ±2 °C. In this acute toxicity test, performed for determination of LD 50 value (the dose which will kill 50%of the animals) single dose of compounds were used in each animal on one occasion only. Values were determined by obscuring mortality within 25 hours after oral drug administration with the help of feeding cannula according to the methods observed by Smith.[22] In the present study all the active compounds have shown ALD50>1000mg/kg with maximum in **2e & 4c** (>1200mg/kg).

Screening of all seventeen compounds, in dose of 2.5 mg/kg & reference drug clonidine in dose of 10 mg/kg respectively was performed (Table 1). First series of compounds **2 (a-e)** have shown hypotension and bradycardia in immediate and delayed phases except compounds **2c** and **2e** both of which exhibited tachycardia in delayed phase. Maximum effect was shown by compound **2b** which produced immediate & delayed hypotension each -30 & change in heart rate -18 in immediate & -27 delayed phase. In second series of compounds **3(a-f),** compound **3b, 3c**, **3f** have shown good hypotensive response and bradycardia except **3d & 3e** which exhibited slight hypotension in immediate & delayed phases and have shown no change in heart rate. In last series of compounds **4(a-f)** again all the compounds except **4d & 4e** produced hypotension & bradycardia. Maximum cardiovascular activity was exhibited by **4c**. Most of the compounds have shown decrease in carotid occlusion response (↓ which shows that they have central action as well. The reference drug clonidine has produced hypotension & bradycardia (in 10 mg/kg dose) of similar range. Compounds **2b, 2c, 3b, 3c, 3f, 4a, 4c** have shown even better hypotensive response than reference drug in efficacy. It was observed that compound **2b** having R^1 as N $(CH_3)_2$ showed maximum immediate & delayed fall in blood pressure -30 each. It is clear that conversion of these compounds to substituted arylidine acetohydrazides **3(a-f)** enhanced the activity. Compound **3b** having R^1 as N-$(CH_3)_2$ and R^2 as p- OCH_3 (C_6H_4) and **3c** having R^1 as N $(CH_3)_2$ and R^2as 3-(OCH_3)4-OH(C_6H_3) have shown immediate and delayed responses -45, -50 and -80 & -55 respectively. It is clear from the



Scheme 1. Reagents and conditions: (a) $ClCH_2COOEt$/dry K_2CO_3, $NH_2NH_2.H_2O$/DMF reflux 6 hr; (b) R′CHO, few drops of glacial acetic acid, MeOH reflux, 3 h; (c) PTSA/$ZnCl_2$, DMF or warm glacial acetic acid & ferric chloride refluxed 3 hr.

Table 1
Cardiovascular effects for compounds **2**(**a**–**e**), **3**(**a**–**f**), **4**(**a**–**f**)

Comp	Resting BP (mmHg)	Change in blood pressure (mmHg)		Change in heart rate (bpm)		Co* response	NE** response
		Immediate	Delayed	Immediate	Delayed		
2a	120	−25	−15	−6	−6	–	–
2b	110	−30	−30	−18	−27	↓	–
2c	122	−30	−20	–	↑	↓	↑
2d	134	−20	−5	−16	−21	–	–
2e	140	−22	−17	−21	↑	–	–
3a	128	−15	–	−8	−11	–	–
3b	132	−45	−50	−12	−14	↓	–
3c	116	−80	−55	−14	−20	↓	–
3d	126	−10	–	–	–	↓	↑
3e	136	−5	−5	–	–	↓	–
3f	130	−60	−35	−8	−11	↓	–
4a	112	−50	−10	–	–	↓	–
4b	110	−15	−10	−6	−10	↓	↓
4c	130	−50	−20	−6	−14	↓	–
4d	134	−10	−10	–	–	–	–
4e	128	−10	+10	–	–	↓	↓
4f	132	−15	+5	−5	−5	–	–
Clonidine	126	−15	−26	−8	−15	↓	↓

+ indicates rise in and − indicates fall in blood pressure and heart rate, respectively, ↑ indicates potentiation and ↓ indicates inhibition of pressor response, –indicates no effect on CO &NE response. Decrease/increase in responses—we have taken more than 20–25 mm Hg of decrease or 10 mm Hg of increase as decrease or increase in BP and 6–12 beats per minute of decrease or increase was taken as decrease/increase in heart rate (HR)

* Note: Carotid Occlusion (CO) response—when we occluded both the carotid arteries for 10 s there was a rise in BP. Hypotensive drugs which act centrally to block or reduce this CO response.

** Nor-epinephrine response; Nor-epinephrine (NE) response—showed the peripheral action of NE on BP. Peripheral acting antihypertensive agents decrease this response.

results obtained that cyclization of substituted arylidine acetohydrazides **3(a-f)** into their corresponding oxadiazole derivatives in general reduced the hypotensive activity of compounds **4(a-f)**, however compounds **4a & 4c** showed maximum hypotensive activity within this series of compounds. Compound **3c** i.e. 2-(5-(4-dimethylamino) phenyl)-2, 4-Diphenyl -1H–imidazole-1yl) N′-(4- hydroxyl-3-methoxy-benzylidene) - acetohydrazide was found to be most active compound of this series.

In conclusion, seventeen compounds **2(a-e), 3(a-f), 4(a-f)** were synthesized as a novel series of substituted imidazole analogues. These compounds are showing promising anti-hypertensive activity in cat models weighing 2.5-4 kg and having ALD50 dose > 1000 mg/kg in mice (either sex) weighing 20-25 grams which is safe. Out of the seventeen synthesized compounds eight compounds have shown good hypotensive activity. Compounds **2b, 2c**, **3b, 3c 3f, 4a & 4c** have shown better efficacy than reference drug clonidine. Compound **3c** was found to be most active compound of this series. All the active compounds have shown ALD50>1000mg/kg with maximum in **2e & 4c** (>1200mg/kg). The present study suggested that the newly synthesized imidazole derivatives are new lead for blood pressure lowering. These molecules can be very useful for further optimization work in anti-hypertensive activity.

#end note- PTSA/$ZnCl_2$ gave better yield than glacial acetic acid & ferric chloride.

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References

1. Hieble, J. P.; Bondinell, W. E.; Ruffolo, R. R. *J.Med. Chem.* **1995**, *38*, 3415.
2. Toja, Hong. I.; Kaplan, Norman M. *JAMA* **1990**, *264*(8), 1015.
3. Khoury, A. F.; Kalpana, Norman M. *The JAMA* **1991**, *266*(3), 394.
4. Stephen, A.Munk; Dales, A.; Harcourt, Premilla N.Arasasingham, James, A. Bruke; *J. Med. Chem.* **1997**,40,18.
5. Mealy, N.; Castaner, J. *Drug of Future* **1996**, *21*(2), 139.
6. Robinson, K. A.; Robinson, C. P.; Castaner, J. *Drugs of Future* **1996**, *21*(11), 1129.
7. Eglen, R. M.; Hudson, A. L.; Kendall, D. A.; Nutt, D. J.; Morgan, N. G.; Wilson, V. G.; Dillon, M. P. *TIPS* **1998**, *19*, 381.
8. Schmidt, H. *Eur.J.of Pharmacol* **1969**, *6*, 8.
9. Schmidt, H. *Actual Pharmacol* **1971**, *24*, 93.
10. Sinha, J. N.; Tangri, K. K.; Bhargava, K. P.; Schmitt, H. *Recent advances in hypertension* **1975**, *1*, 97.
11. Nath, R.; Mukherjee, D.; Khattri, S.; Pant, K. K.; Saxena, A. K.; Mishra, N.; Shina, J. N. *Asia pacific Journal of Pharmacology* **2001**, *15*, 1.
12. 12. B.G. Katzung, Basic & Clinical Pharmacology, nineth ed., Mc Graw-Hill,New York, 2004 (Chapter 11), pp. 160-183.
13. Pigini, M.; Quaglia, W.; Gentili, F.; Marucci, G.; Cantalamessa, F.; Frranchini, S.; Sorbi, C.; Brasili, L. *Bioorg. Med. Chem.* **2000**(8), 883.
14. Francesco, G.; Francesco, G.; Mario, G.; Alessandro, P., et al *J.Med. Chem.* **2004**(47), 6160.
15. Matier, W. L.; Owens, D. A.; Comer, W. T.; Deitchman, D.; Ferguson, H. C.; Seidehamel, R. J.; Young, J. R. *J. Med. Chem.* **1973**, *16*(8), 901.
16. Francesco, G.; Pascal, B.; Livio, B.; Mariangela, C.; Antonio, C., et al *J.Med. Chem.* **2002**, *45*, 32.
17. Malhotra, V.; Pathak, S. R.; Nath, R.; Mukherjee, D.; Shanker, K. *Indian journal of Chemistry* **2002**, *41B*, 1310.
18. Sanchez-Salvatoria, M. D. L. A.; Rieos, C.; Vidrio, H. *Cardiovascular Research* **1998**, *37*(3), 748.
19. Deshmukh, A. A.; Sattur, P. B.; Sheth, U. K. *Indian Journal of Exp.Biol* **1976**, *4*, 166.
20. Heravi, Majid M.; Bakhtiari, Khadijeh; Oskooie, Hossein A.; Taheri, Shima *Journal of Molecular Catalysis A: Chemical* **2007**, *263*(1-2), 279.
21. Compound **1a**. Yield 72%; mp 182 °C;MS (FAB) (M+1): 296; IR (KBr) υ in cm^{-1}: 3421 (–NH, imidazole ring), 1596 (C=N cyclic 1460, 1490 (C=C stretching), 2781 (C–H stretching);^1H NMR ($CDCl_3$) δ in ppm: 7.22–7.48 (m, 15H, ArH), 10.4 (1H, NH exchangeable); Anal. Calcd for $C_{12}H_{16}N_2$: C, 85.13; H, 5.4; N, 9.45. Found: C, 85.10; H, 5.3; N, 9.40. Compound **1b**.Yield, 80%; mp 210 °C; MS (FAB) (M+1): 338, IR(KBr) υ in cm^{-1}: 3421 (NH imidazole ring), 1596 (C=N cyclic),1460, 1490 (C=C str), 2781 (C–H str); ^1H NMR ($CDCl_3$) δ in ppm: 6.65–7.48 (m,14H, ArH),10.4 (1H, NH exchangeable), 2.8 (s, 6H, $N(CH_3)_2$); Anal. Calcd for $C_{23}H_{20}N_3$: C, 81.65; H, 5.91; N, 12.42. Found; C, 81.63; H, 5.90; N, 12.40. Compound **1c**: Yield, 56%; mp 156 °C; MS (FAB) (M+1): 342, IR(KBr) υ in cm^{-1}: 3421 (NH imidazole ring),1596 (C=N cyclic),1460, 1490 (C=C str), 2781 (C–H str); ^1H NMR ($CDCl_3$) δ in ppm: 6.65–7.48 (m, 13H, ArH), 10.4 (1H, NH exchangeable with D_2O), 3.73 (s, 3H, NCH_3), 5.0 (1H, OH); Anal. Calcd for $C_{22}H_{18}N_2O_2$: C, 80.98; H, 5.52; N, 8.58. Found: C, 80.80; H, 5.42; N, 8.52. Compound **1d**: Yield, 80%; mp 210 °C; MS (FAB) (M+1): 326; IR (KBr) υ in cm^{-1}: 3421 (NH imidazole ring),1596 (C=N cyclic),1460, 1490 (C=C str), 2781 (C–H str); ^1H NMR ($CDCl_3$) δ in ppm: 6–7.8 (m, 14H, ArH), 12.5 (br s, 1H, –NH), 3.8 (s, 3H, OCH_3; Anal. Calcd for $C_{22}H_{18}N_2O$: C, 80.98; H, 5.52; N, 8.58. Found: C, 80.92; H, 5.56; N, 8.50. Compound **1e**. Yield, 67%, mp 180 °C; MS (FAB) (M +1): 312, IR (KBr) υ in cm^{-1}: 3421 (NH imidazole ring), 1596 (C=N cyclic), 1460, 1490 (C=C str), 2781 (C–H str), ^1H NMR ($CDCl_3$) δ in ppm:6.83–7.48 (m, 14H, ArH), 10.4 (^1H, NH exchangeable with D_2O), 5.0 (1H, OH); Anal. Calcd for $C_{21}H_{16}N_2O$: C, 80.76; H, 5.12; N, 8.97. Found: C, 80.71; H, 5.10; N, 8.95.

Compound **2a**. Yield, 70%; mp 210 °C; MS (FAB) (M+1): 368; IR(KBr) υ in cm^{-1}: 3421 (NH imidazole ring), 1596 (C=N cyclic), 1460, 1490 (C=C str), 2781 (C–H str); ^1H NMR ($CDCl_3$) δ in ppm: 7.2–7.4 (m,15H, ArH), 4.6 (s, 2H, N–CH_2CO), 8.0 (br s, 1H, NH), 2.0 (br s, 2H, NH_2); Anal. Calcd for $C_{23}H_{20}N_4O$: C, 75.00; H, 5.43; N, 15.21. Found: C, 74.80; H, 5.40; N, 15.18. Compound **2b**.Yield, 72%; mp 198 °C; MS (FAB) (M+1): 411; IR (KBr) υ in cm^{-1}: 3421 (NH imidazole ring), 1596 (C=N cyclic), 1460, 1490 (C=C str), 2781 (C–H str); ^1H NMR ($CDCl_3$) δ in ppm: 6.6–7.4 (m, 14H, ArH), 2.8 (s, 6H, N–CH_3), 4.6 (s, 2H, N–CH_2–CO), 8.0 (br s ^1H, NH), 2.0 (br s, 2H, NH_2); Anal. Calcd for $C_{25}H_{25}N_5O$: C, 72.99; H, 6.08; N, 17.03. Found: C, 72.94; H, 6.02; N, 17.00. Compound **2c**. Yield: 52%; mp 170 °C; MS (FAB) (M+1): 414; IR (KBr) υ in cm^{-1}: 3421 (NH imidazole ring), 1596 (C=N cyclic), 1460, 1490 (C=C str), 2781 (C–H str); ^1H NMR ($CDCl_3$) δ in ppm: 6.6–7.4 (m, 13H, ArH), 3.7 (s, 3H, OCH_3), 5.0 (br, 1H, OH), 4.6 (s, 2H, NCH_2CO), 8.0 (br s ^1H, NH), 2.0 (br s, 2H, NH_2); Anal. Calcd for $C_{24}H_{22}N_4O_3$: C, 69.56; H, 5.31; N, 13.5. Found: C, 69.51; H, 5.28; N, 13.0. Compound **2d**. Yield: 69%; mp 184 °C; MS (FAB) (M+1): 398; IR(KBr) υ in cm^{-1}: 3421 (NH imidazole ring), 1596 (C=N cyclic), 1460, 1490 (C=C str), 2781 (C–H str); ^1H NMR ($CDCl_3$) δ in ppm: 6.8–7.4 (m, 14H, ArH), 3.7 (s, 3H, OCH_3), 4.6 (s, 2H, N–CH_2–CO), 8.0 (br s, 1H, NH), 2.0 (br s, 2H, NH_2); Anal. Calcd for $C_{24}H_{22}N_4O_2$: C, 72.36; H, 5.52; N, 14.07. Found: C, 72.30, H, 5.50; N, 14.00. Compound **2e**. Yield: 64%; mp 153 °C; MS (FAB) (M+1): 384; IR (KBr) υ in cm^{-1}: 3421 (NH imidazole ring), 1596 (C=N cyclic), 1460, 1490 (C=C str), 2781 (C–H str), ^1H NMR ($CDCl_3$) δ in ppm: 6.7–7.4 (m, 14H, ArH), 5.0 (br s, 1H, OH), 4.6 (s, 2H, N–CH_2–CO), 8.0 (br s 1H, NH), 2.0 (br s, 2H, NH_2); Anal. Calcd for $C_{23}H_{20}N_4O_2$: C, 71.87; H, 5.20; N, 14.50. Found: C, 71.30; H, 5.19; N, 14.00. Compound **3a**. Yield, 57%; mp 243 °C; MS (FAB) (M+1): 486, IR (KBr) υ in cm^{-1}: 3421 (NH imidazole ring), 1596 (C=N cyclic), 1460, 1490 (C=C str), 2781 (C–H str); ^1H NMR ($CDCl_3$) δ (ppm): 6.8–7.4 (m, 19H, ArH), 4.6 (s, 2H, N–CH_2–CO), 8.1 (s, 1H, CH=N), 3.73 (s, 3H, CH_3); Anal. Calcd for $C_{31}H_{26}N_4O_2$: C, 71.87; H, 5.20; N, 14.50. Found: C, 71.30; H, 5.19; N, 14.00. Compound **3b**. Yield, 65%; mp 210 °C; MS (FAB) (M +1): 529; IR (KBr) υ (cm^{-1}): 3421 (NH imidazole ring), 1596 (C=N cyclic), 1460, 1490 (C=C str), 2781 (C–H str), ^1H NMR ($CDCl_3$) δ (ppm): 6.8–7.5 (m, 18H, ArH), 2.8 (s, 6H, NCH_3), 3.7 (s, 3H, OCH_3), 4.6 (s, 2H, NCH_2CO), 8.0 (br s, 1H, NH), 8.1 (s, 1H, N=CHAr); Anal. Calcd for $C_{33}H_{31}N_5O_2$: C, 74.86; H, 5.86; N, 13.23. Found: C, 74.80, H, 5.82; N, 13.20. Compound **3c**.Yield 70%; mp 117 °C; MS (FAB) (M+1): 545; IR (KBr) υ (cm^{-1}): 3421 (NH imidazole ring), 1596 (C=N cyclic), 1460, 1490 (C=C str), 2781 (C–H str), ^1H NMR ($CDCl_3$) δ in ppm 6.6–7.4 (m, 17H, ArH), 2.8 (s, 6H, NCH_3), 4.6 (s, 2H, NCH_2CO), 8.1 (s, 1H, N=CHAr), 3.1 (s, 3H, OCH_3), 5.0 (s, 1H, OH); Anal. Calcd for $C_{33}H_{31}N_5O_3$: [Calcd, C, 74.85; H, 5.68; N, 12.84. Found: C, 74.80; H, 5.65; N, 12.80. Compound **3d**. Yield, 68%; mp 156 °C; MS (FAB) (M+1): 532; IR (KBr) υ in cm^{-1}: 3421 (NH imidazole ring), 1596 (C=N cyclic), 1460, 1490 (C=C str), 2781 (C–H str); ^1H NMR ($CDCl_3$) δ in ppm: 6.8–7.5 (m, 17H, ArH), 3.7 (s, 6H, OCH_3), 5.0 (s, 1H, OH), 4.6 (s, 2H, N–CH_2–CO), 8.1 (s, 1H, N=CHAr); Anal. Calcd for $C_{32}H_{28}N_4O_4$: C, 72.18; H, 5.26; N, 10.52. Found: C, 72.14; H, 5.21; N, 10.50. Compound **3e**. Yield, 63%; mp 205 °C; MS (FAB) (M+1): 516; IR (KBr) υ(cm^{-1}): 3421 (NH imidazole ring), 1596 (C=N cyclic), 1460, 1490 (C=C str), 2781 (C–H str); ^1H NMR ($CDCl_3$) δ (ppm): 6.8–7.5 (m, 18H, ArH), 3.7 (s, 6H, OCH_3), 4.6 (s, 2H, NCH_2CO), 8.1 (s, 1H, N=CHAr); Anal. Calcd for $C_{32}H_{28}N_4O_3$: C, 74.41; H, 5.42; N, 10.85. Found: C, 74.38; H, 5.38; N, 10.80. Compound **3f**. Yield, 58%; mp 140 °C; MS (FAB) (M+1): 384; IR (KBr) υ (cm^{-1}): 3421 (NH imidazole ring), 1596 (C=N cyclic), 1460, 1490 (C=C str), 2781 (C–H str), ^1H NMR ($CDCl_3$) δ (ppm): 6.5–7.4 (m, 18H, ArH), 5.0 (br s, 1H, OH) 4.6 (s, 2H, NCH_2CO), 8.0 (br s, 1H, NH), 2.0 (br s, 2H, NH_2), 2.85 (s, 6H, $N(CH_3)_2$); Anal. Calcd for $C_{32}H_{29}N_5O_2$: C, 74.56; H, 5.63; N, 13.59. Found: C, 74.51; H, 5.58; N, 13.51. Compound **4a**. Yield, 52%; mp 175 °C; MS (FAB) (M+1): 484, ^1H NMR ($CDCl_3$) δ in ppm: 6.8–7.4 (m, 19H, ArH), 4.9 (s, 2H, NCH_2CO), 3.7 (s, 3H, CH_3); Anal. Calcd for $C_{31}H_{26}N_4O_2$: C, 76.85; H, 4.95; N, 11.57. Found: C, 76.81; H, 4.91; N, 11.50. Compound **4b**.Yield, 58%; mp 180 °C; MS (FAB) (M+1): 527, ^1H NMR ($CDCl_3$) δ in ppm: 6.4–7.4 (m, 18H, ArH), 2.8 (s, 6H, NCH_3), 3.7 (s, 3H, OCH_3), 4.9 (s, 2H, NCH_2CO); Anal. Calcd for $C_{33}H_{29}N_5O_2$: C, 75.14; H, 5.50; N, 13.2. Found: C, 75.10; H, 5.43; N, 13.0. Compound **4c**.Yield, 61%; mp 140 °C; MS (FAB) (M+1): 543; ^1H NMR ($CDCl_3$) δ in ppm: 6.6–7.4 (m, 17H, ArH), 2.8 (s, 6H, NCH_3), 4.9 (s, 2H, NCH_2CO), 3.7 (s, 3H, OCH_3), 5.0 (s, 1H, OH); Anal. Calcd for $C_{33}H_{29}N_5O_3$: C, 72.9; H, 5.34; N, 8.83. Found: C, 72.4; H, 5.30; N, 8.74. Compound **4d**. Yield 53%; mp 179 °C, MS (FAB) (M+1): 530; ^1H NMR ($CDCl_3$) δ in ppm: 6.8–7.5 (m, 17H, ArH), 3.7 (s, 6H, OCH_3), 5.0 (s, 1H, OH), 4.9 (s, 2H, NCH_2CO); Anal. Calcd for $C_{32}H_{26}N_4O_4$: C, 72.45; H, 4.90; N, 10.56. Found: C, 72.40; H, 4.83; N, 10.50. Compound **4e**. Yield, 57%; mp 152 °C; MS (FAB) (M+1): 514; ^1H NMR ($CDCl_3$) δ in ppm: 6.8–7.5 (m, 18H, ArH), 3.7 (s, 6H, OCH_3), 4.9 (s, 2H, NCH_2CO); Anal. Calcd for $C_{32}H_{26}N_4O_3$: C, 74.70; H, 5.05; N, 10.89. Found: C, 74.67; H, 5.00; N, 10.80. Compound **4f**. 2-(1((5-(4-Dimethyl amino)phenyl)-1,3,4-oxadiazole-2-yl)methyl)-2,4-diphenyl-1*H*-imidazole-5-yl)phenol: Yield, 46%; mp 160 °C; MS (FAB) (M+1): 499; ^1H NMR (CDCl3) δ in ppm: 6.7–7.4 (m, 18H, ArH), 5.0 (br s, 1H, OH), 4.9 (s, 2H, NCH_2CO), 2.8 (s, 6H, $N(CH_3)_2$); Anal. Calcd for $C_{32}H_{27}N_5O_2$: C, 76.95; H, 5.41; N, 11.22. Found: C, 76.90; H, 5.32; N, 11.18.

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