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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and pharmacological evaluation of novel 1-(piperidin-4-yl)-1*H*-benzo[*d*]imidazol-2(3*H*)-one derivatives as potential antimicrobial agents

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Abstract Novel compounds of biological interest were synthesized by in situ reduction of Schiff's base of 5,6-dimethoxy indanone and 1-(piperidin-4-yl)-1*H*-benzo[*d*]imidazol-2(3*H*)-one in the presence of $Ti(OiPr)_4$ and $NaBH_3CN$. Further alkylation using different alkyl/aryl halides in the presence of NaH in DMF gave a series of novel compounds. A formation of newly synthesized compounds was confirmed on the basis of their spectral and elemental analysis. Further these compounds were screened for their antimicrobial activity and found to have promising antibacterial and antifungal activity.

Keywords 1-(Piperidin-4-yl)-1*H*-benzo[*d*]imidazol-2(3*H*)-one · 5,6-Dimethoxy indanone · In situ reduction of Schiff's base · Antimicrobial agents

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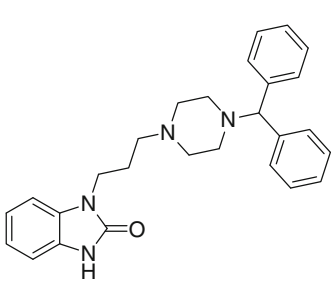
Introduction

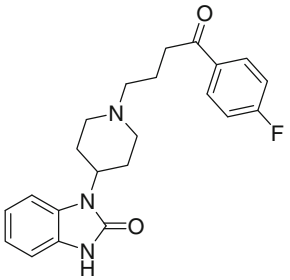
Benzimidazoles are extremely prevalent in pharmaceuticals (Kleemann *et al*., 1999). Two of the top 25 selling drugs, esomeprazole and lansoprazole, contain the benzimidazole core structure. Benzimidazolone derivatives have been found to exhibit anti-HIV (Barreca *et al*., 2007), antitrichinellosis (Mavrova *et al*., 2005), antinociceptive (Nacak *et al*., 1999), antitumor activities (Khodarahmi *et al*., 2005), and other pharmacological activities. For instance, it has been reported in recent literature that benzimidazolone bearing a sugar or piperidine residue on the aromatic nitrogen effectively inhibits the growth of bacteria (Vora *et al*., 2010 and Messaoudi *et al*., 2004).

Benzimidazolone containing Piperidine nucleus is a constituent of many bioactive heterocyclic compounds that are of wide interest because of their diverse biological and clinical applications (Kleemann *et al*., 1999). They exhibit a wide variety of interesting biochemical and pharmacological properties including CNS-inhibitors and anti-inflammatory agents (Yoshinao *et al*., 1978), for inhibiting emesis or mental disorders (Raymond *et al*., 1996), ORL1-receptor agonists, antimuscarinic agents (Ito *et al*., 2000), treatment of glaucoma (Wayne *et al*., 1998), selective NOP antagonist (Kawamoto *et al*., 1999), treatment of obesity (Lynch *et al*., 2005), and treatment of type 2 diabetes (Liang *et al*., 2006). In hope to synthesize novel potential antimicrobial derivatives using backbone of Domperidone which itself is an active API (anti-emetic drug), 1-(piperidin-4-yl)-1*H*-benzo[*d*]imidazol-2(3*H*)-one, a series of 5-chloro-3-(1-(5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-yl)piperidin-4-yl)-1-alkyl-1*H*-benzo[*d*]imidazol-2(3*H*)-ones are prepared.

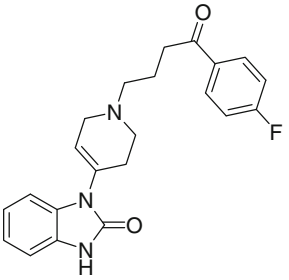
Benzimidazolone containing piperidine-based drug



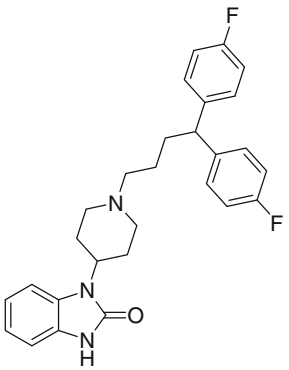
Oxatomide
(antiallergic)



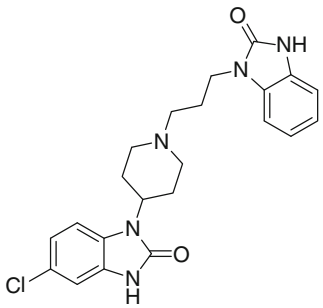
Benperidol
(neuroleptic)



Droperidol
(neuroleptanesthesia)



Pimozide
(neuroleptic)



Domperidone
(anti-emetic)

Experimental

Reagents, instrumentation and measurements

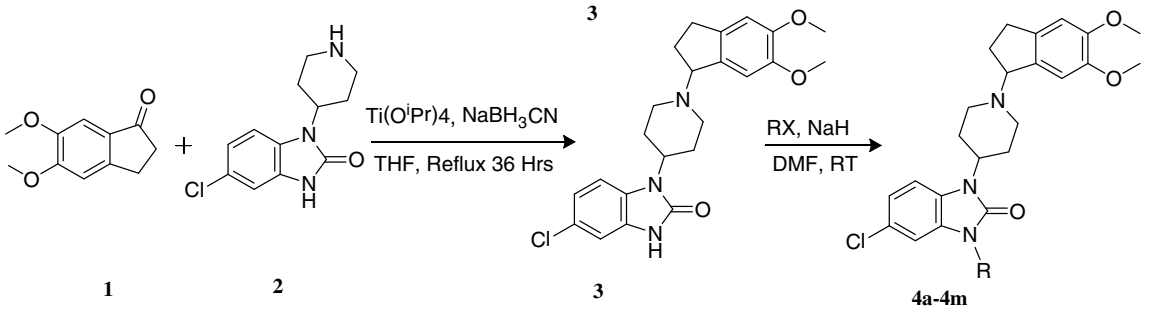
Melting points were determined in open capillary tubes and are uncorrected. NMR was recorded either in $CDCl_3$ or DMSO-d^6 on a Bruker Avance 400 MHz and signal is given in ppm (δ) relative to TMS. Elementary analyses were taken on Euro EA 3000 elementary analysis instrument. LCMS were measured on Agilent 1100 Series MS spectrometer. MS were measured on a Waters ZQ 2000 spectrometer. All the solvent and materials are reagent grades and purified before use. Log *P* were calculated by Chembiodraw. Purity of all reagents and products were checked by TLC (hexane: ethylacetate; 70:30).

5,6-Dimethoxy-1-indanone**1** was prepared according to the literature procedure (Haadsma-Svensson *et al*., 2001) in 60.0 % overall yield based on 3,4-dimethoxybenzaldehyde purity was confirmed by TLC and mp. 5-Chloro-1-(piperidin-4-yl)-1*H*-benzo[*d*]imidazol-2(3*H*)-one**2** was obtained from Galaxy PharmaChem (Vadodara,Gujarat,India). Its purity was confirmed by TLC and mp.

Antimicrobial study

The in vitro antimicrobial activity of the compounds **4a**–**4m** were studied by disk agar diffusion technique at a different concentration 50 mg/mL using Dimethylformamide as solvent. The specific bacterial culture was spread uniformly over nutrient agar in Petri plates. Then the test solution, standard, and control of known similar concentrations were spotted in sample wells at specific distance. The zones of inhibition were measured after 24 h. The in vitro antibacterial activity was performed against Gram-positive bacteria including *Staphylococcus aureus* (MTCC 96), *Streptococcus pyogenes* (MTCC 442) and Gram negative bacteria including *Escherichia coli* (MTCC 443) and *Pseudomonas aeruginosa* (MTCC 424). Yeast including *Candida albicans* (MTCC 227) and fungi *Aspergillus clavatus* (MTCC 1323) were used to test antifungal activity. Known antibiotics like Ampicillin and Chloramphenicol (the reference antibacterial drugs) and Fluconazole (the reference antifungal drug) were used for comparison. The antimicrobial activities are summarized in Table 1.

Reaction scheme



*Synthesis of 5-chloro-1-(1-(5,6-dimethoxy-2,3-dihydro-1H-inden-1-yl)piperidin-4-yl)-1H-benzo[d]imidazol-2(3H)-one (**3**)*

A solution of 10.0 g (0.052 mol) 5,6-dimethoxy-1-indanone, 13.1 g (0.052 mol) 5-chloro-1-(piperidin-4-yl)-1*H*-benzo[*d*]imidazol-2(3*H*)-one, and 26.0 g (0.067 mol) titanium(IV) isopropoxide in 400 mL THF was stirred for 18 h at reflux temperature. Sodium cyanoborohydride 3.27 g (0.052 mol) was added at room temperature with stirring, again reflux was continued for 20 h. Water (200 mL) was added, and the mixture was filtered through Celite. The filter cake was washed thoroughly with ethanol, the filtrate was evaporated, and the residue was purified by chromatography on silica gel (hexane/ethyl-acetate 3–8 %) to yield a beige solid; (10.7 g, 48 %): mp 229–231 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 10.1$ (s, 1 H, NH), 7.34 (s, 1 H, ArH), 7.2 (d, 1 H, ArH), 7.15–6.9 (d, 1 H, ArH), 6.7 (dd 1 H, ArH), 4.4 (m, 1 H, CH), 4.25 (t, 1 H, indane CH), 3.85 (s, 6 H, $2OCH_3$),2.9–2.85 (t, 2 H, indane CH_2), 2.6–2.5 (t, 2 H, CH_2), 2.4 (m, 2 H, indane CH_2), 2.3 (m, 2 H, CH_2), 2.1–2.0 (m, 2 H, indane CH_2), 1.9–1.8 (m, 2 H, CH_2) ppm;ESI MS: *m/z* 427.8 (M+); Anal. Calcd. for $C_{23}H_{26}ClN_3O_3$: C, 64.55; H,6.12; Cl,8.28; N,9.82; O,11.22; Found: C, 64.86; H, 6.78; N, 9.35.

Table 1 Antibacterial and antifungal activity of novel compounds at concentration 50 mg/mL in DMF (**4a–m**)

Compound no.	Zone diameter of growth inhibition in mm					
	Antibacterial activity				Antifungal activity	
	Gram +ve		Gram −ve		*C. albicans*	*A clavatus*
	S. aureus	*S. pyrogenes*	*E. coli*	*P. aeruginosa*		
4a	19	16	13	10	19	18
4b	13	11	19	09	18	25
4c	15	14	11	11	19	24
4d	12	12	13	12	17	14
4e	10	13	14	15	24	15
4f	11	10	11	13	25	17
4g	17	09	19	09	16	19
4h	13	11	17	10	17	22
4i	14	16	12	11	15	14
4j	11	14	15	13	07	21
4k	20	11	13	08	10	11
4l	18	16	10	11	17	13
4m	13	18	14	16	18	10
Ampicillin	18	19	20	20	–	–
Chloramphenicol	21	20	23	21	–	–
Fluconazole	–	–	–	–	24	24

*General procedure for 5-chloro-1-(1-(5,6-dimethoxy-2,3-dihydro-1H-inden-1-yl)piperidin-4-yl)-3-alkyl-1H-benzo[d]imidazol-2(3H)-one (**4a–4m**)*

To the suspension of 1000 mg (2.34 mol) of 5-chloro-1-(1-(5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-yl)piperidin-4-yl)-1*H*-benzo[*d*]imidazol-2(3*H*)-one **3,** 1.2 equivalent (2.34 mol) of the corresponding alkyl halide and 5.0 mL DMF, 125 mg (2.57 mol) NaH (50 % suspension in mineral oil) was charged at room temperature, reaction was stirred at room temperature for 15 h, and the mixture was cooled to 10 °C. The mixture was quenched with 10 mL water and extracted with 15 mL ethylacetate. Organic phases were pooled, and dried with $MgSO_4$, and the solvents were removed in vacuo. The residue was purified by chromatography on silica gel (ethyl acetate/hexane, 2–8 %) to yield **4a**–**4m**.

Analytical data

*5-Chloro-1-(1-(5,6-dimethoxy-2,3-dihydro-1H-inden-1-yl)piperidin-4-yl)-3-ethyl-1H-benzo[d]imidazol-2(3H)-one (**4a**)* Off-white powder; yield: 200 mg (18.77 %); mp 149–151 °C; 1H NMR (CDCl3, 400 MHz): $\delta = 7.63$ (s, $J = 2.1$ Hz, 1 H, ArH), 7.60–7.58 (d, 1 H, ArH), 6.95–6.93 (d, $J = 2.0$, 8.3 Hz, 1 H, ArH), 6.67–6.65 (d, 1 H, ArH), 4.20–4.14 (m, 1 H, CH), 4.03–3.97 (t, 1 H, indane CH), 3.84 (s, 6 H, 2OCH3), 3.75 (m, 2 H, CH2), 2.92 (t, 2 H, CH2), 2.83–2.70 (m, 3 H, indane CH2), 2.61–2.54 (m, 2 H, CH2), 2.35–2.25 (m, 1 H, CH), 2.19–2.13 (m, 2 H, CH2), 2.00 (ddd, $J = 3.5$, 7.1, 8.0 Hz, 1 H, CH), 1.90–1.81 (m, 2 H, CH2), 1.20 (t, $J = 6.9$ Hz, 3 H, CH3) ppm; 13C NMR (CDCl3, 40 MHz): $\delta = 154.3$ (C-17), 148.0 (C-13,14), 137.4 (C-10), 136.6 (C-11), 131.4 (C-19), 129.3 (C-20), 128.0 (C-23), 122.3 (C-22), 111.2 (C-21), 109.0 (C-12), 108.1 (C-24), 108.0 (C-15), 68.9 (C-7), 56.2 (C-28), 56.0 (C-26), 53.8 (C-4), 49.8 (C-2,6), 38.0 (C-30), 32.1 (C-8), 31.6 (C-9), 29.7 (C-3,5), 13.5 (C-31) ppm; TOF MS: *m/z* 456.97 (M+); Anal. Calcd. for $C_{25}H_{30}ClN_3O_3$: C,65.85; H,6.63; Cl,7.78; N,9.22; O,10.53; Found: C, 65.86; H, 6.78; N, 9.25.

*5-Chloro-1-(1-(5,6-dimethoxy-2,3-dihydro-1H-inden-1-yl)piperidin-4-yl)-3-propyl-1H-benzo[d]imidazol-2(3H)-one (**4b**)* White Powder; yield: 240 mg (24.13 %); mp 108–110 °C; 1H NMR (400 MHz, CDCl3):$\delta = 7.35$ (s, 1 H, ArH), 7.34–7.29 (d, 1 H, ArH), 7.07 (d, 1 H, ArH), 6.85– 6.82 (dd, 1 H, ArH), 4.3–4.27 (m, 1 H, CH), 4.13 (t, 1 H, indane CH), 3.76–3.72 (s, 6 H, 2-OCH3), 3.71 (t, 2 H, CH2), 2.96–2.8 (t, 2 H, indane CH2), 2.78–2.56 (t, 4 H, 2CH2), 2.40–2.22 (m, 2H, indane CH2), 2.05 (m, 4 H, CH2), 2.00 (ddd, 2 H, indane CH2), 1.69–1.66 (m, 2 H, CH2), 0.86–0.82 (t, 3 H, CH3) ppm; 13C NMR (CDCl3, 40 MHz): 152.9 (C-17), 148.7 (C-13), 147.8 (C-14), 135.2 (C-10,11), 130.3 (C-19), 126.9 (C-23), 125.0 (C-20), 120.2 (C-22), 109.8 (C-21), 108.2 (C-12), 108.0 (C-15), 107.9 (C-24), 69.2 (C-7), 55.7(C-28), 55.4 (C-26), 51.3 (C-4), 45.2 (C-2,6), 41.8 (C-30), 30.4 (C-8), 29.1 (C-3,5), 21.0 (C-31), 10.9 (C-32) ppm; TOF MS: *m/z* 470.003(M+); Anal. Calcd. For $C_{26}H_{32}ClN_3O_3$: C,66.44;H,6.86;Cl,7.54;N,8.94;O,10.21; Found: 66.50;H,6.90;N,8.90.

*3-Butyl-5-chloro-1-(1-(5,6-dimethoxy-2,3-dihydro-1H-inden-1-yl)piperidin-4-yl)-1H-benzo[d]imidazol-2(3H)-one (**4c**)* White powder, yield: 430 mg (38.02 %); mp 139–140 °C; 1H NMR (400 MHz, CDCl3):$\delta = 7.32$ (s, 1 H, ArH), 7.30–7.28 (d, 1 H, ArH), 7.06–7.04 (d, 1 H, ArH), 6.85–6.81 (dd, 1 H, ArH), 4.30–4.27 (m, 1 H, CH), 4.12 (t, 1 H, indane CH), 3.81–3.72 (s, 6 H, 2OCH3), 3.58–3.54 (t, 2 H, CH2), 2.95–2.84 (t, 2 H, indane CH2), 2.79–2.56 (t, 2 H, CH2), 2.40–2.22 (m, 2 H, indane CH2), 2.04–2.02 (m, 2 H, CH2), 2.01–1.99 (m, 2 H, CH2), 1.68–1.66 (m, 2 H, CH2), 0.89–0.85 (t, 3 H, CH3) ppm; 13C NMR (CDCl3, 40 MHz):152.8 (C-17), 148.7 (C-13), 147.8 (C-14), 135.1 (C-10), 134.1 (C-11), 130.2 (C-19), 126.9 (C-23), 125.0 (C-20), 120.2 (C-22), 109.8 (C-21), 108.2 (C-12), 108.0 (C-15), 107.9 (C-24), 69.2 (C-7), 55.7 (C-28), 55.4 (C-26), 51.3 (C-4), 50.1 (C-2,6), 45.2 (C-30), 40.1 (C-8), 39.8 (C-9), 30.4 (C-3,5), 29.7 (C-31), 19.3 (C-32), 13.5 (C-33) ppm;TOF MS: *m/z* 484.030(M+); Anal. Calcd. For $C_{27}H_{34}ClN_3O_3$: C,67.00;H,7.08;Cl,7.32;N,8.68;O,9.92; Found: C,67.03;H,7.09;N,7.70.

*5-Chloro-1-(1-(5,6-dimethoxy-2,3-dihydro-1H-inden-1-yl)piperidin-4-yl)-3-isobutyl-1H-benzo[d]imidazol-2(3H)-one (**4d**)* Off-white powder, yield: 290 mg (25.59 %); mp 137–139 °C, 1H NMR (400 MHz CDCl3):$\delta = 7.67$ (s, 1 H, ArH), 7.60–7.58 (d, 1 H, ArH), 6.91–6.90 (d, 1 H, ArH), 6.67–6.66 (dd, 1 H, ArH), 4.19–4.13 (m, 1 H, CH), 4.03–3.98 (t, 1 H, indane CH), 3.84–3.78 (s, 6 H, 2OCH3), 3.57–3.58 (d, 2 H, CH2), 2.96–2.88 (t, 2 H, indane CH2),2.76–2.55 (t, 2 H, CH2), 2.36 – 2.25 (m, 2 H, indane CH2), 2.20–2.14 (m, 2 H, CH2), 2.10–2.03 (m, 1 H, CH), 2.0–1.93 (m, 2 H, CH2), 1.88–1.80 (m, 2 H, CH2), 0.94–0 0.92 (d, 3 H, 2CH3) ppm; 13C NMR (CDCl3, 40 MHz): 152.8 (C-17), 148.7 (C-13), 147.8 (C-14), 135.1 (C-10), 134.1 (C-11), 130.2 (C-19), 126.9 (C-23), 125.0 (C-20), 120.2 (C-22), 109.8 (C-21), 108.2 (C-12), 108.0 (C-15), 107.9 (C-24), 69.2 (C-7), 55.7 (C-28), 53.8 (C-4), 49.8(C-2,6),32.0 (C-8), 31.6 (C-9), 29.7 (C-3,5), 27.5 (C-31), 20.10 (C-32,34) ppm; TOF MS: *m/z* 484.11(M+); Anal. Calcd. For $C_{27}H_{34}ClN_3O_3$: C,67.00;H,7.08;Cl,7.32;N,8.68;O,9.92; Found: C,67.03;H,7.09;N,8.70.

*5-Chloro-1-(1-(5,6-dimethoxy-2,3-dihydro-1H-inden-1-yl) piperidin-4-yl)-3-(methoxymethyl)-1H-benzo[d]imidazol-2(3H)-one (**4e**)* Cream powder, yield: 240 mg (22.64 %); mp 125–126 °C, 1H NMR (400 MHz, CDCl3):δ = 7.85 (s, 1 H, ArH), 7.79–7.77 (d, 1 H, ArH), 6.93–6.90 (d, 1 H, ArH), 6.67–6.66 (dd, 1H, ArH), 5.07 (s, 2 H, CH2), 4.17–4. 13 (m, 1 H, indane CH), 4.03–3.97 (t, 1 H, indane CH), 3. 84–3.78 (s, 6 H, 2OCH3), 3.52 (s, 3 H, CH3), 2.94–2.77 (t, 2 H, indane CH2), 2.76–2.55 (t, 2 H, CH2), 2.36–2.25 (m, 2 H, indane CH2), 2.19–2.13(m,2H,CH2), 2.02–1.93 (m,2H,indane CH2), 1.89–1.81 (m, 2 H, CH2) ppm; 13C NMR (CDCl3, 40 MHz):152.9 (C-17), 148.7 (C-13), 147.8 (C-14), 135.7 (C-10), 135.2 (C-11), 134.1 (C-19), 132.1 (C-23), 129.8 (C-20), 129.2, 128.6, 127.0, 125.1(C-22), 120.7(C-21), 110.1 (C-12), 108.2 (C-24), 107.9 (C-15), 69. 2 (C-7), 55.7 (C-32), 55.4 (C-26), 51.5 (C-4), 50.1 (2,6), 38.8 (C-8), 30.4 (C-9), 29.1 (C-3,5) ppm, TOF MS: *m/z* 472.2(M+); Anal. Calcd. For $C_{25}H_{30}ClN_3O_4$: C,63. 62;H,6.41;Cl,7.51;N,8.90;O, 13.56; Found: C,6368;H,6. 52;N,8.88.

*3-Benzyl-5-chloro-1-(1-(5,6-dimethoxy-2,3-dihydro-1H-inden-1-yl)piperidin-4-yl)-1H-benzo[d]imidazol-2(3H)-one (**4f**)* Off white, yield: 300 mg (24.78 %); mp 172–174 °C, 1H NMR (400 MHz,CDCl3):δ = 7.34 (s, 1 H, ArH), 7.31–7.30 (d, 1 H, ArH), 7.28 (d, 1 H, ArH), 7.27(d, 1 H, ArH), 7.25 (t, 1 H, ArH), 7.22(t, 1 H, ArH), 7.07–7.05 (d, 1 H, ArH), 6. 86–6.82 (dd, 1 H, ArH), 5.03 (s, 2 H, CH2), 4.31–4.28 (m, 1 H, CH), 4.17 (t, 1 H, indane CH), 3.75–3.72 (s, 6 H, 2OCH3), 2.94–2.88 (t, 2 H, CH2), 2.75–2.58(t, 2 H, CH2), 2.43–2.27 (m, 2 H, indane CH2), 2.25–2.05 (m, 2 H, CH2), 2.03–2.00 (m, 2 H, indane CH2), 1.98–1.73 (m, 2 H, CH2), 1.64 (m, 2 H, CH2) ppm; 13C NMR (CDCl3, 40 MHz): 153.0 (C-17), 148.7 (C-13), 147.8 (C-14), 136.6 (C-10), 135.2 (C-11), 134.1 (C-31), 129.9 (C-19), 128.6 (C-23), 127.4 (C-20), 127.2 (C-33,35), 127.0 (C-34), 125.0 (C-22), 120.5 (C-21), 110.0 (C-12), 108.2 (C-24), 107.9 (C-15), 69. 2 (C-7), 55.7 (C-28), 55.4 (C-26), 51.5 (C-4), 50.1 (C-2,6), 45.2 (C-30), 30.4 (C-8), 29.1 (C-9), 29.0 (C-3,5) ppm, TOF MS: *m/z* 518.10(M+); Anal. Calcd. For $C_{30}H_{32}ClN_3O_3$: C, 69.55; H, 6.23; Cl, 6.84; N, 8.11; O, 9.27; Found: C, 69.45; H, 6.14; N, 8.23.

*5-Chloro-3-(4-chlorobenzyl)-1-(1-(5,6-dimethoxy-2,3-dihydro-1H-inden-1-yl)piperidin-4-yl)-1H-benzo[d]imidazol-2(3H)-one (**4g**)* Off-white powder, yield: 610 mg (47.27 %); mp 176–176.5 °C, 1H NMR (400 MHz,CDCl3):δ = 7.40 (s, 1 H, ArH), 7.38–7.32 (d, 1 H, ArH), 7.08 (d, 1 H, ArH), 6. 98–6.85 (dd, 1 H, ArH), 6.82 (s, 1 H, ArH), 5.03 (s, 2 H, CH2), 4.31–4.27 (m, 1 H, CH), 4.16 (t, 1 H, indane CH), 3. 75–3.72 (s, 6 H, 2OCH3), 2.94–2.80 (t, 3 H, indane CH2), 2.78–2.74 (t, 2 H, CH2), 2.72–2.57 (t, 2 H, CH2), 2.42–2. 37 (m, 2 H, indane CH2), 2.26–2.21 (m, 2H, CH2), 2.06–2. 00 (m, 2 H, indane CH2), 1.98–1.65 (m, 2 H, CH2) ppm; 13C NMR (CDCl3, 40 MHz):152.9 (C-17), 148.7 (C-13), 147.8 (C-14), 135.7 (C-10), 135.2 (C-11), 134.1 (C-31), 132.1 (C-34), 129.8 (C-19), 129.2 (C-32,36), 128.6 (C-23), 127.0 (C-20), 125.1 (C-33,35), 120.7 (C-22), 110.1 (C-21), 108.2 (C-12), 107.9 (C-24,15), 69.2 (C-7), 55.7 (C-28), 55. 4 (C-26), 51.5 (C-4), 50.1 (C-2,6), 45.2 (C-30), 30.4 (C-8,9), 29.1 (C-3,5) ppm; TOF MS: *m/z* 552.16(M+); Anal. Calcd. For $C_{30}H_{31}Cl_2N_3O_3$: C, 65.22; H, 5.66; Cl, 12.83; N, 7.61; O, 8.69; Found: C, 65.15; H, 5.82; N, 7.5.

*5-Chloro-1-(1-(5,6-dimethoxy-2,3-dihydro-1H-inden-1-yl) piperidin-4-yl)-3-(4-nitrobenzyl)-1H-benzo[d]imidazol-2(3H)-one (**4h**)* Cream powder, yield: 220 mg (16.72 %); mp 106–108 °C, 1H NMR (CDCl3, 400 MHz):δ = 8.28–8.26 (d, 1 H, ArH), 7.61 (s, 1 H, ArH), 7.44–7.42 (d, 1 H, ArH), 7.38 (d, 1 H, ArH), 7.17–7.15 (d, 1 H, ArH), 6.93–6.89 (dd, 1H, ArH), 5.27 (s, 2 H, CH2), 4.38–4.35 (m, 1 H, CH), 4.25 (t, 1 H, indane CH), 3.82–3.79 (s, 6H, 2OCH3), 2.91–2.87 (t, 2 H, indane CH2), 2.85–2.79 (t, 2 H, indane CH), 2. 77–2.65 (t, 2 H, CH2), 2.50–2.48 (m, 2 H, indane CH2), 2. 34–2.15 (m, 2 H, CH2), 2.12–2.09 (m, 2 H, indane CH2), 2. 06–1.74 (m, 2 H, CH2) ppm; 13C NMR (CDCl3, 40 MHz): 152.9 (C-17), 148.7 (C-13), 147.8 (C-14), 146.9 (C-34), 144.4 (C-31), 135.2 (C-10), 129.8 (C-11), 128.3 (C-19), 127.1 (C-23), 125.2 (C-20), 123.8 (C-32,36), 120.8 (C-33,35), 110.2 (C-22),111.01 (C-21), 108.2 (C-12),108.8 (C-24), 107.9 (C-15), 69.2 (C-7), 55.7 (C-28), 55.4 (C-26), 51. 6 (C-4), 50.1 (C-2,6), 43.1 (C-30), 30.6 (C-8), 30.4 (C-9), 29.0 (C-3,5) ppm; TOF MS: *m/z* 563.0(M+); Anal. Calcd. For $C_{30}H_{31}ClN_4O_5$:C, 64.00; H, 5.55; Cl, 6.30; N, 9.95; O, 14.21; Found: C, 64.80; H, 5.68; N, 9.96.

*Ethyl 2-(6-chloro-3-(1-(5,6-dimethoxy-2,3-dihydro-1H-inden-1-yl)piperidin-4-yl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)acetate (**4i**)* Off white, yield: 220 mg (18.32 %); mp 208–210 °C, 1H NMR (400 MHz CDCl3):δ = 7.38 (d, 1 H, ArH), 7.35–7.33 (s, 1 H, ArH), 7.11–7.09 (d, 1 H, ArH), 6.87–6.83 (dd, 1 H, ArH), 4.70 (s, 2 H, CH2), 4.20–4.60 (m, 1 H, CH), 4.12–4.06 (m, 2 H, CH2), 4.02–3.98 (t, 1 H, indane CH), 3.84 (s, 6H, 2OCH3), 2.94–2.88 (t, 2 H, indane CH2), 2.82–2.77 (t, 2 H, CH2), 2.76–2.71 (t, 2 H, CH2), 2.33–2.26 (m, 2 H, indane CH2), 2.22–2.14 (m, 2 H, CH2), 2.02–1.92 (m, 2 H, CH2), 1.9–1.82 (m, 2 H, CH2), 1.32–1.28 (t, 3 H, CH3) ppm; 13C NMR (CDCl3, 40 MHz):167.9 (C-31), 152.8 (C-17), 147.8 (C-13,14), 137.3 (C-10,11) 131.54 (C-19),131.06 (C-23),130.2 (C-20), 122.2 (C-22), 111.7 (C-21), 110.0 (C-12), 108.6 (C-15), 107.9 (C-24), 69.3 (C-7), 61.1 (C-33), 55.6 (C-28), 55.5 (C-26), 53.7 (C-4), 49.75 (C-2,6),47.1 (C-30), 32.2 (C-8,9), 30.4 (C-3,5), 13.9 (C-34) ppm; TOF MS: *m/z* 514.22(M+); Anal. Calcd. For $C_{27}H_{32}ClN_3O_5$:C,63.09;H,6.27;Cl,6. 90;N,8.17;O, 15.56; Found: C,63.18;H,6.36;N,8.25.

*Ethyl 6-chloro-3-(1-(5,6-dimethoxy-2,3-dihydro-1H-inden-1-yl)piperidin-4-yl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-1-carboxylate (**4j**)* Cream powder, yield: 300 mg (25.68 %); mp 185–190 °C, 1H NMR (400 MHz CDCl3):$\delta = 7.38$ (d, 1 H, ArH), 7.35–7.33 (s, 1 H, ArH), 7.11–7.09 (d, 1 H, ArH), 6.87–6.83 (dd, 1 H, ArH), 4.20–4.60 (m, 1 H, CH), 4.12–4.06 (m, 2 H, CH2), 4.02–3.98 (t, 1 H, indane CH), 3.84 (s, 6H, 2OCH3), 2.94–2.88 (t, 2 H, indane CH2), 2.82–2.77 (t, 2 H, CH2), 2.76–2.71 (t, 2 H, CH2), 2.33–2.26 (m, 2 H, indane CH2), 2.22–2.14 (m, 2 H, CH2), 2.02–1.92 (m, 2 H, CH2), 1.9–1.82 (m, 2 H, CH2), 1.32–1.28 (t, 3 H, CH3) ppm; 13C NMR (CDCl3, 40 MHz): 167.8 (C-30), 152.8 (C-17), 147.75 (C-13,14), 137.3 (C-10,11) 131.46 (C-19),131.01 (C-23),130.2 (C-20), 122.2 (C-22), 111.7 (C-21), 110.06 (C-12), 108.61 (C-15), 107.89 (C-24), 69.29 (C-7), 61.1 (C-32), 55.6 (C-28), 55.5 (C-26), 53.7 (C-4), 49.75 (C-2,6), 32.2 (C-8,9), 30.4 (C-3,5), 13.96 (C-33) ppm;TOF MS: *m/z* 499.98(M+); Anal. Calcd. For $C_{26}H_{30}ClN_3O_5$: C,62.46;H,6.05;Cl,7.09;N,8.40;O, 16.00; found: C,62.55;H,6.15;N,8.45.

*6-Chloro-3-(1-(5,6-dimethoxy-2,3-dihydro-1H-inden-1-yl) piperidin-4-yl)-N,N-diethyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-1-carboxamide (**4k**)* Off-white powder, yield: 300 mg (26.12 %); mp 195–198 °C, 1H NMR (400 MHz CDCl3):$\delta = 7.35$ (s, 1 H, ArH), 7.34–7.29 (d, 1 H, ArH), 7.07 (d, 1 H, ArH), 6.85–6.82 (dd, 1 H, ArH), 4.3–4.27 (m, 1 H, CH), 4.13 (t, 1 H, indane CH), 3.76–3.72 (s, 6 H, 2OCH3), 3.71 (t, 2 H, CH2), 2.96–2.8 (t, 2 H, indane CH2), 2.78–2.56 (t, 4 H, 2CH2), 2.40–2.22 (m, 2H, indane CH2), 2.05 (d, 2 H, CH2), 2.00 (ddd, 2 H, indane CH2), 1.69-1.66 (m, 2 H, CH2), 0.86–0.82 (t,3 H, CH3) ppm;13C NMR (CDCl3, 40 MHz): 168.01 (C-30),152.9 (C-17), 148.7 (C-13), 147.8 (C-14), 135.2 (C-10,11), 130.3 (C-19), 126.9 (C-23),125.0 (C-20), 120.2 (C-22), 109.8 (C-21), 108.2 (C-12), 108.0 (C-15), 107.9 (C-24), 69.2 (C-7), 55.7 (C-28), 55.4 (C-26), 53.01 (C-4),51.3 (C-2,6), 35.5 (C-8,9), 30.4 (C-3,5), 20.0 (C-34,36), 15.9 (C-35,37) ppm; TOF MS: *m/z* 527.2(M+); Anal. Calcd. For $C_{28}H_{35}ClN_4O_4$: C,63.81;H,6.69;Cl,6.73;N,10.63;O,12.14; Found: C,63.85;H,6.72;N,10.55.

*5-Chloro-3-(2-chloroethyl)-1-(1-(5,6-dimethoxy-2,3-dihydro-1H-inden-1-yl)piperidin-4-yl)-1H-benzo[d]imidazol-2(3H)-one (**4l**)* Cream powder, yield: 340 mg (29.56 %); mp 179–182 °C, 1H NMR (400 MHz CDCl3):$\delta = 7.33$ (s, 1 H, ArH), 7.34–7.30(d, 1 H, ArH), 7.06 (d, 1 H, ArH), 6.87–6.8 (dd, 1 H, ArH), 4.35–4.3 (m, 1 H, CH), 4.2 (t, 1 H, indane CH), 3.78–3.75 (s, 6 H, 2OCH3), 3.71 (t, 2 H, CH2), 2.96–2.8(t, 2 H, indane CH2), 2.78–2.56 (t, 4 H, 2CH2), 2.40–2.22 (m, 2 H, indane CH2), 2.05 (m, 4 H, CH2), 2.00 (ddd, 2 H, indane CH2), 1.69–1.66 (t, 2 H, CH2), 0.86–0.82 (t, 2 H, CH2) ppm; 13C NMR (CDCl3, 40 MHz): 152.9 (C-17), 148.7 (C-13), 147.8 (C-14), 135.2 (C-10,11), 131.36 (C-19),130.3 (C-20),126.9 (C-23), 125.0 (C-22), 109.8 (C-21), 108.2 (C-12), 108.0 (C-24), 107.9 (C-15), 69.2 (C-7), 55.7 (C-28), 55.4 (C-26), 51.3 (C-4), 49.2 (C-2,6), 39.0 (C-31), 38.8 (C-30), 32.3 (C-8), 31.4 (C-9), 29.1 (C-3,5) ppm; TOF MS: *m/z* 490.78 (M+); Anal. Calcd. For $C_{25}H_{29}Cl_2N_3O_3$:C,61.23;H,5.96;Cl,14.46;N,8.57;O, 9.79; Found: C,61.50;H,5.72;N,8.67.

*5-Chloro-1-(1-(5,6-dimethoxy-2,3-dihydro-1H-inden-1-yl) piperidin-4-yl)-3-(3-(dimethylamino)propyl)-1H-benzo[d]imidazol-2(3H)-one (**4m**)* Off-white powder, yield: 300 mg (25.5 %); mp 185–190 °C, 1H NMR (400 MHz CDCl3):$\delta = 7.7$ (s, 1 H, ArH), 7.61–7.57 (d, 1 H, ArH), 6.93–6.91 (d, 1 H, ArH), 6.69–6.65 (dd, 1 H, ArH), 4.30–4.23 (m, 1 H, CH), 4.1–4.03 (t, 1 H, indane CH), 3.88–3.84 (s, 6 H, 2OCH3), 3.60–3.59 (d, 2 H, CH2), 3.55–3.53 (s, 1 H, 2NCH3), 3.00–2.96 (t, 2 H, indane CH2), 2.85–2.80 (t, 2 H, CH2), 2.36–2.25 (m, 2 H, indane CH2), 2.11–2.00 (m, 2 H, CH2), 1.96–1.93 (m, 2 H, CH2), 1.88–1.80 (m, 2 H, CH2) ppm; 13C NMR (CDCl3, 40 MHz): 152.8 (C-17), 148.7 (C-13), 147.8 (C-14), 135.1 (C-10), 134.1 (C-11), 130.2 (C-19), 126.9 (C-23), 125.0 (C-20), 120.2 (C-22), 109.8 (C-21), 108.2 (C-12), 108.0 (C-15), 107.9 (C-24), 69.2 (C-7), 55.7 (C-28), 55.4 (C-26), 51.3 (C-4), 49.8 (C-2,6), 49.4 (C-30), 32.0 (C-8), 31.6 (C-3,5), 29.7 (C-31), 27.5 (C-32), 20.10 (C-34,36) ppm; TOF MS: *m/z* 513.80 (M+); Anal. Calcd. For$C_{28}H_{37}ClN_4O_3$:C,65.55;H,7.27;Cl,6.91;N,10.92;O, 9.36; Found:C,65.67;H,7.10;N,10.95.

Result and discussion

A series of different alkyl/ary substituents on 5-chloro-1-(1-(5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-yl)piperidin-4-yl)-1*H*-benzo[*d*]imidazol-2(3*H*)-one was synthesized in order to get novel bioactive compounds. The purity of compounds was analyzed by TLC. The structures of all compounds were confirmed by ^{1}H –NMR,^{13}C-NMR, Mass analysis, and Elemental analyses. The supporting informations can be seen from the spectral data.

From the result of antifungal data shows that compounds **4e, 4f** were active against *C. albicans*. While compounds **4b, 4c, 4h, 4j** were active against *A. clavatus*. Further Antibacterial study shows that compounds **4a, 4k, 4l, 4g** were active against *Staphylococcus aureus*. In case of *E. coli* compounds **4b, 4g, 4h** show good activity.

Conclusion

In conclusion, the synthesized compounds **4a**–**m** have remarkable antifungal and antibacterial activity. The activity of compounds with different alkyl/aryl substituents indicates the importance of functional groups in enhancing

the antimicrobial activity of a compound. This class of compounds has already proved the efficacy of compounds and has a bright prospect for the discovery of many new drugs used in the treatment of fungal and bacterial infections. Finally, it can be concluded that this class of compounds certainly holds great promise toward the pursuit to discover novel classes of antimicrobial agents.

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