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European Journal of Medicinal Chemistry 41 (2006) 599–604
EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY
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Original article

Synthesis and anti-bacterial activity of some novel 2-(6-fluorochroman-2-yl)-1-alkyl/acyl/aroyl-1*H*-benzimidazoles

Bobba Venkata Siva Kumar [a,b], Sanjay Dashrath Vaidya [a], Ramanatham Vinod Kumar [a], Shekar Bhaskar Bhirud [a], Ramchandra Bhimrao Mane [b,*]

[a] *Glenmark Research Center, Plot No. A-607, T.T.C. Industrial Area, M.I.D.C. Mahape Navi Mumbai 400 709, India*
[b] *Department of Chemistry, Shivaji University, Kolhapur, Maharashtra 416 004, India*

Received in revised form 25 December 2005; accepted 2 January 2006
Available online 09 March 2006

Abstract

Synthesis of some novel 2-(6-fluorochroman-2-yl)-1-alkyl/acyl/aroyl-1*H*-benzimidazoles by the condensation of *o*-phenylenediamine with 6-fluoro-3,4-dihydro-2*H*-chroman-2-carboxylic acid, and subsequent reactions with different types of electrophiles, have been reported. Some compounds exhibited promising anti-bacterial activity against *Salmonella typhimurium*; however, they showed poor activity against *S. aureus*. The biological activity against PDE IV for potential anti-asthamatic effect, and against DP–IV and PTP 1B for potential anti-diabetic effects was disappointing.

Keywords: Antibacterial activity; Benzimidazole; Alkylation; acylation

1. Introduction

Benzimidazole nucleus is a constituent of many of the bioactive heterocyclic compounds that exhibit a range of biological activities. Specifically, this nucleus is a constituent of Vitamin-B12 [1]. The biological activities of the compounds containing this basic moiety have been well documented [2]. Some of them like albendazole, mebendazole and thiabendazole are widely used as antihelmintic drugs [3] as well (Fig. 1). Similarly, 2-substituted benzimidazoles and their derivatives have been found to be potent biologically active compounds [4]. Owing to the immense importance and varied bioactivities exhibited by benzimidazoles, efforts have been made from time to time to generate libraries of these compounds and screen them for potential biological activities [5]. Further, 6-fluoro-3,4-dihydro-2*H*-chroman-2-carboxlic acid [6] is an integral part of 1-adrenoceptor antagonist known as nebivolol [7] which exhibits activities ranging from antianginal and antiischaemic and vasodilator, anti-diabetic; anti-microbial, cardiovascular, tranquilizer and virucidal. Further, its also an integral part of hydantoin based drugs such as fidarestat [8], an aldose reductase inhibitor used for the treatment of a psychiatric disease, bipolar disorder, major depression, schizoaffective disorder, schizophrenia, dementia of elderly, affective psychoses, episodic axis II psychotic conditions, multiple sclerosis, amyotrophic lateral sclerosis and Alzheimer's disease. Fidarestat which is commercially known as muscimol, prevents the accumulation of sorbitol in the brain and central nervous system (Fig. 2).

Looking at the importance of benzimidazoles and 6-fluoro-3,4-dihydro-2*H*-chroman-2-carboxlic acid in biological systems, it was thought that it would be worthwhile to design and synthesize compounds containing both benzimidazole and the latter acid to generate a series of new benzimidazole derivatives and screen them for potential biological activities. We have previously reported the synthesis of some novel and biologically active benzimidazoles and analogs in connection with our on-going project on bioactive benzimidazoles and analogs [9,10]. In continuation of our work on bioactive benzimidazoles, we now wish to report our results towards the synthesis of some novel 2-(6-fluorochroman-2-yl)-1-alkyl/acyl/aroyl-1*H*-benzimidazoles.

* Corresponding author. Fax: +91 22 2778 0376.
E-mail address: manerb_chem.@yahoo.com (R.B. Mane).

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doi:10.1016/j.ejmech.2006.01.006

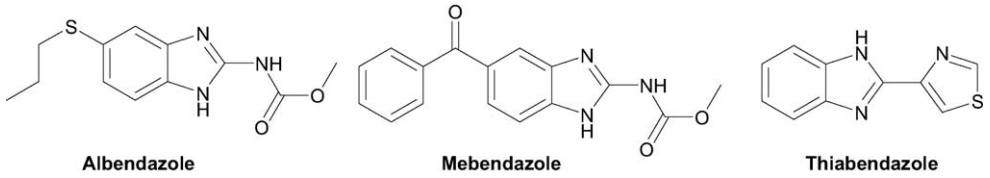


Fig. 1.

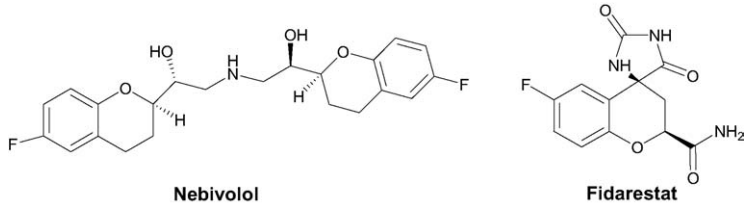


Fig. 2.

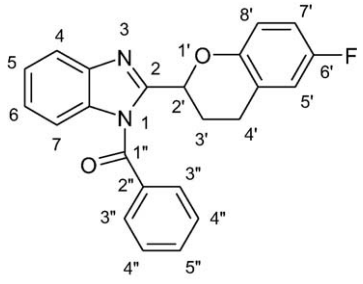
2. Results and discussion

Condensation of *o*-phenylenediamine (OPDA) (**1**) with 6-fluoro-3,4-dihydro-2*H*-chroman-2-carboxlic acid [6] (**2**) in refluxing 4 N HCl [11] (Phillips' conditions) for 4 h (Scheme 1), followed by simple work-up yielded a colorless compound having m.p. 232–235 °C and in 85% yield. Based on the observed spectral and analytical data the compound was assigned the structure as 2-(6-fluorochroman-2-yl)-1*H*-benzimidazole (**3**).

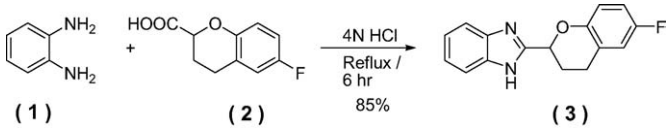
The compound **3** was also synthesized by the condensation of **1** with **2** in the presence of *Eaton's reagent* [12] (1:10 mixture of phosphorous pentoxide/methanesulfonic acid, an efficient and convenient alternative to polyphosphoric acid (PPA) [13] for cyclodehydration reactions). In order to reduce the reaction time the condensation of **1** and **2** was carried out in PPA under microwave irradiation [14] for 3 min which also yielded the compound **3** in comparable and sometimes in higher yields than the conventional methods. The alkylation and acylation of **3** with various electrophilic reagents yielded the *N*-alkylated/acylated derivatives (Scheme 2). The physical and spectral data of the compounds **4a–4o** is presented in Table 1.

In an alternate route compound **4a** has also been synthesized by direct condensation of *N*-methyl-OPDA dihydrochloride [15] (**5**) with **2** in refluxing 4 N HCl as in case of preparation of compound **3** described above (Scheme 3).

Following numbering has been followed for NMR assignment.



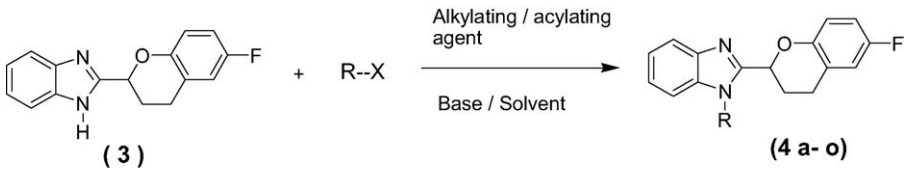
(4g)



Scheme 1.

3. Biological activity

All the compounds prepared herein were screened for their potential biological activities such as, antibacterial activity against *Staphylococcus aureus* (Gram positive) and *Salmonella*



(4a, R = Methyl), (4b, R = Ethyl), (4c, R = Propyl),(4d, R = *n*-Butyl)
(4e, R = -CO-O-Ethyl),(4f, R = -CO-O-*tert* Butyl)
(4g, R = -CO-Phenyl), (4h, R = $-SO_2-CF_3$), (4i, R = $-SO_2$-Phenyl), (4j, R = $-SO_2-C_6H_4$-Me-*p*)
(4k ,R = -Benzyl), (4l, R = *p*-Fluorobenzyl), (4m, R = *p*-Bromobenzyl), (4n, R = *p*-Methylbenzyl)
(4o, R = *p*-*tert*-Butylbenzyl)

Scheme 2.

Table 1
Physical and spectral characterization data for the new compounds prepared[a]

Compound	Yield %	m.p. °C	^{1}H-NMR[b] (δ ppm)	^{13}C-NMR (δ ppm)	EI-MS ($M^+ + 1$)
3 $C_{16}H_{13}FN_2O$ 2-(6-fluorochroman-2-yl)-1*H*-benzimidazole	85	232–233	2.23–2.41 (m, 2H, 3′–CH_2), 2.80–3.04 (m, 2H, 4′–CH2), 5.42 (dd, J = 8.7 and 8.7 Hz, 1H, 2′–H), 6.87–7.01 (m, 3H, 5′, 7′ and 8′ Ar–H), 7.16–7.22 (m, 2H, 4 and 5–Ar–H), 7.55 (s, 2H, 4 and 7–Ar–H), 12.6 (bs, 1H, NH).	23.20 (–CH_2), 25.36 (CH_2), 70.11 (CH), 114.16, 114.45, 115.50, 115.80, 117.95, 118.06, 123.32, 123.42, 125.58, 131.94, 148.85, 148.87, 151.83, 154.98, 158.11 (aromatic carbons).	269
4a $C_{17}H_{15}FN_2O$ 2-(6-fluorochroman-2-yl)-1-methyl-1*H*-benzimidazole	84	130–132	δ 2.52–2.67 (m, 2H, 3′–CH_2), 3.0–3.06 (m, 2H, 4′–CH_2), 3.92 (s, 3H, CH_3), 5.37 (dd, J = 9.60 and 9.90 Hz, 1H, 2′–CH), 6.78–6.81 (m, 3H, 5′, 7′ and 8′ Ar–H), 7.25–7.38 (m, 3H, 4, 5 and 6 Ar–H), 7.75–7.78 (m, 1H, 7–Ar–H,).	δ 24.54 (–CH_2), 24.90 (–CH_2), 30.61 (–NCH_3),71.31,(–OCH), 109.25, 114.022 (d, $^2J_{C–F}$ = 23.32 Hz), 115.49 (d, $^2J_{C–F}$ = 22.57 Hz), 117.523 (d, $^3J_{C–F}$ 8.25 Hz), 119.98, 122.98 (d, $^3J_{C–F}$ = 5.4 Hz), 136.11, 141.80, 149.60, 149.62, 151.36, 156.97 (d, $^1J_{C–F}$ = 237 Hz) (aromatic carbons).	283
4b $C_{18}H_{17}FN_2O$ 2-(6-fluorochroman-2-yl)-1-Ethyl 1*H*-benzimidazole	86	126–127	1.53(t, J = 6.9 Hz, 1′–CH_3), 2.54–2.69 (m, 2H, 3′–CH_2), 3.01–3.07 (m, 2H, 4′-CH_2), 4.39 (q, J = 6.9 Hz, 2H, 2″–CH_2), 5.34 (dd, J = 9.60 and 9.90 Hz, 1H), 6.76–6.83 (m, 3H, 5′, 7′ and 8′ Ar–H), 7.25–7.32 (m, 2H, 5, 6–Ar–H), 7.38–7.40 (m, 1H, 4–Ar–H), 7.76–7.79 (m, 1H, 7–Ar–H).	14.85(CH_3),24.17(–CH_2), 24.58(–CH_2), 38.80 (N–CH_2), 70.72 (–OCH), 109.045, 113.515 (d, $^2J_{C–F}$ = 23 Hz), 115.00, (d, $^2J_{C–F}$ = 22.57 Hz), 117.028 (d, $^3J_{C–F}$ = 8 Hz), 119.62, 121.61, 122.523 (d, $^3J_{C–F}$ = 6.9 Hz), 134.52, 141.56, 149.17, 149.19, 150.39, 156.461 (d, $^1J_{C–F}$ = 237.22 Hz) (aromatic carbons).	297
4c $C_{19}H_{19}FN_2O$ 2-(6-fluorochroman-2-yl)-1-propyl-1*H*-benzimidazole	85	115–116	1.04 (t, J = 7.6 Hz, 3H, 1″–CH_3), 1.93–2.01 (m, 2H, 2″–CH_2), 2.52–2.71 (m, 2H, 3′–CH_2), 3.02–3.07 (m, 2H, 4′-CH_2), 4.22–4.35 (m, 2H, 1″–CH_2), 5.35 (dd, J = 9.60 and 9.90 Hz, 1H, 2′–CH), 6.77–6.85 (m, 3H, 5′, 7′ and 8′–Ar–H), 7.27–7.31 (m, 2H, 5 and 6–Ar–H), 7.39–7.42 (m, 1H, 4–Ar–H), 7.78–7.81 (m, 1H, 7–Ar–H).	11.49 (CH_3), 23.34 (CH_2), 24.57 (CH_2), 25.04 (CH_2), 45.97 (NCH_2), 71.05 (OCH), 109.86, 114.092 (d, $^2J_{C–F}$ = 23.17 Hz), 115.567 (d, $^2J_{C–F}$ = 22.27 Hz), 117.567 (d, $^3J_{C–F}$ = 7.95 Hz), 120.16, 122.15, 123.01, 135.50, 142.10, 149.87, 149.87, 151.25, 157.50 (d, $^1J_{C–F}$ = 237.52 Hz) (aromatic carbons).	311
4d $C_{20}H_{21}FN_2O$ 2-(6-fluorochroman-2-yl)-1-butyl-1*H*-benzimidazole	89	116–117	0.99 (t, J = 7.6 Hz, 3H, 4″–CH_3), 1.42–1.49 (m, 2H, 3″–CH_2), 1.86–1.94 (m, 2H, 2″-CH_2), 2.54–2.71 (m, 2H, 3′–CH_2), 3.01–3.07 (m, 2H, 4′–CH_2), 4.26–4.36 (m, 2H, 1″–CH_2), 5.34 (dd, J = 9.9 and 10.2 Hz, 1H, 2′–CH), 6.76–6.85 (m, 3H, 5′, 7′ and 8′–Ar–H), 7.25–7.33 (m, 2H, 5 and 6–Ar–H,), 7.38–7.41 (m, 1H, 4–Ar–H), 7.78–7.81 (m, 1H, 7–Ar–H).	13.84 (CH_3), 20.35 (CH_2), 24.59(CH_2), 25.05 (CH_2), 32.12 (CH_2), 44.28 (NCH_2), 71.08 (OCH), 109.82, 114.104 (d, $^2J_{C–F}$ = 23 Hz), 115.588 (d, $^2J_{C–F}$ = 22.57 Hz), 117.559 (d, $^3J_{C–F}$ = 8 Hz) 120.19, 122.15, 123.088 (d, $^3J_{C–F}$ = 11.45 Hz), 135.49, 142.13, 149.85, 151.21, 157.115 (d, $^1J_{C–F}$ = 237.52 Hz) (aromatic carbons).	325
4e $C_{19}H_{17}FN_2O_3$ Ethyl 2-(6-fluorochroman-2-yl)-1*H*-benzimidazole-1-carboxylate	89	150–151	1.51 (t, J = 7.2 Hz, 3H, CH_3), 2.39–2.55 (m, 2H, 3′–CH_2), 2.90–3.05 (m, 2H, 4′–CH_2), 4.58 (q, J = 7.2 Hz, 2H, O–CH_2), 5.86 (dd, J = 9.0 and 9.6 Hz, 1H, 2′–CH), 6.79–6.90 (m, 3H, 5′, 7′ and 8′–Ar–H), 7.36–7.42 (m, 2H, 5 and 6–Ar–H), 7.80–7.83 (m, 1H, 4–Ar–H), 7.96–7.99 (m, 1H, 7–Ar–H).	14.16 (CH_3), 24.70 (CH_2), 26.14 (CH_2), 64.43 (OCH_2), 71.97 (OCH), 113.964 (d, $^2J_{C–F}$ = 22.87 Hz), 114.96, 115.241 (d, $^2J_{C–F}$ = 22.65 Hz), 117.931 (d, $^3J_{C–F}$ = 8.3.2 Hz), 120.64, 122.947 (d, $^3J_{C–F}$ = 7.425 Hz), 124.60, 125.35, 132.785, 141.95, 150.07, 150.46, 153.387, 156.981 (d, $^1J_{C–F}$ = 236.92 Hz) (aromatic carbons).	341
4f $C_{21}H_{21}FN_2O_3$ *tert*-butyl 2-(6-fluorochroman-2-yl)-1*H*-benzimidazole-1-carboxylate	88	113–115	1.69 (s, 9H, *tert* butyl), 2.42–2.52 (m, 2H, 3′–CH_2), 2.95–3.04 (m, 2H, 4′–CH_2), 5.83 (dd, J = 9.0 and 9.3 Hz, 2′–CH), 6.78–6.89 (m, 3H, 5′, 7′ and 8′–Ar–H), 7.33–7.40 (m, 2H, 5 and 6–Ar–H), 7.79–7.82 (m, 1H, 4–Ar–H), 7.95–7.98 (m, 1H, 7–Ar–H).	24.67(CH_3), 25.97 (CH_2), 27.95(CH_2), 71.90 (OCH), 85.94 (O–C *tert* butyl), 113.93 (d, $^2J_{C–F}$ = 23.17 Hz), 114.09, 114.87, 115.260, 117.860 (d, $^2J_{C–F}$ = 22.57 Hz), 120.51, 122.939 (d, $^3J_{C–F}$ = 7.4 Hz), 124.31, 125.14, 133.04, 141.84, 148.45, 150.41, 153.26, 156.928 (d, $^1J_{C–F}$ = 237 Hz) (aromatic carbons).	369
4g $C_{23}H_{17}FN_2O_2$ [2-(6-fluorochroman-2-yl)-1*H*-benzimidazol-1-yl] phenyl methanone	90	188–190	2.57–2.63 (m, 2H, 3′–CH_2), 2.94–3.06 (m, 2H, 4′–CH_2), 5.60 (dd, J = 9.3 and 9.3 Hz, 1H, 2′–CH), 6.50–6.54 (m, 1H, 5′–Ar–H), 6.65–6.77 (m, 2H, 7′ and 8–Ar–H), 6.83 (d, J = 7.8 Hz, 1H, Ar–H), 7.13–7.19 (m, 1H, Ar–H), 7.26–7.33 (m, 1H, Ar–H), 7.51–7.56 (m, 2H, Ar–H), 7.69–7.75 (m, 1H, 4–Ar–H), 7.80–7.83 (m, 3H, 7, 3″–Ar–H).	23.85 (CH_2), 24.93 (CH_2), 70.88 (OCH), 112.81,113.84 (d, $^2J_{C–F}$ = 22.87 Hz), 115.327 (d, $^2J_{C–F}$ = 22.35 Hz), 117.687 (d, $^3J_{C–F}$ = 8.32 Hz), 120.49, 123.016 (d, $^3J_{C–F}$ = 7.4 Hz) 123.89, 124.46, 129.04, 130.29, 132.78,134.07,134.46,141.91,149.56,153.78,157.0565 (d, $^1J_{C–F}$ = 237.3 Hz) (aromatic carbons), 168.66 (carbonyl carbon).	373
4h	90	118–120	2.48–2.65 (m, 2H, 3′–CH_2), 2.99–3.04 (m, 2H, 4′–CH_2), 5.60 (dd, J = 9.0 and 9.3 Hz, 1H, 2′–CH), 6.80–6.82 (m, 3H, 5′, 7′ and 8′–Ar–H), 7.47–7.50 (m, 2H, 5 and 6–Ar–H), 7.83–7.90 (m, 2H, 4 and 7–Ar-H).	24.32 (CH_2), 25.88 (CH_2), 70.28 (OCH), 113.87, 114.203 (d, $^2J_{C–F}$ = 23.17 Hz), 115.33 (d, $^2J_{C–F}$ = 22.65 Hz), 117.32, 117.82 (d, $^3J_{C–F}$ = 8 Hz), 121.54, 122.703 (d, $^3J_{C–F}$ = 7.4 Hz), 126.378, 126.97, 132.78, 141.279, 149.857, 152.067, 157.220 (d, $^1J_{C–F}$ = 237.82 Hz) (aromatic carbons).	399

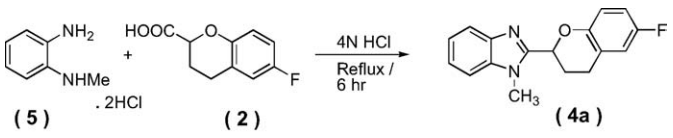
(continued)

Table 1 *(continued)*

Compound	Yield %	m.p. °C	^{1}H-NMR[b] (δ ppm)	^{13}C-NMR (δ ppm)	EI-MS ($M^+ + 1$)
$C_{17}H_{12}F_4N_2O_3S$ 2-(6-fluorochroman-2-yl)-1-trifluoromethane-sulfonyl-1*H*-benzimidazole					
4i $C_{22}H_{17}FN_2O_3S$ 2-(6-fluorochroman-2-yl)-1-benzenesulfonyl-1*H*-benzimidazole	88	150–150	2.47–2.67 (m, 2H, 3′–CH_2), 2.95–3.08 (m, 2H, 4′–CH_2), 5.94 (dd, J = 9.3 and 9.6 Hz, 1H, 2′–CH), 6.52–6.57 (m, 1H, 5′–Ar–H), 6.76–6.85 (m, 2H, 7′ and 8′–Ar–H), 7.36–7.46 (m, 2H, Ar–H), 7.52–7.57 (m, 2H, Ar–H), 7.64–7.69 (m, 1H, Ar–H), 7.76–7.79 (m, 1H, Ar–H), 8.05–8.08 (m, 3H, 7 and 3″–Ar–H).	24.68 (CH_2), 26.04 (CH_2), 70.64 (OCH), 113.938 (d, $^2J_{C–F}$ = 24 Hz), 115.478 (d, $^2J_{C–F}$ = 22.65 Hz), 117.410 (d, $^3J_{C–F}$ = 8 Hz), 120.99, 123.064 (d, $^3J_{C–F}$ = 7.2 Hz), 125.00, 125.90, 127.18, 129.43,133.03,134.64,138.37,141.46,150.00,151.82, 157.038 (d, $^1J_{C–F}$ = 237.5 Hz) (aromatic carbons).	409
4j $C_{23}H_{19}FN_2O_3S$ 2-(6-fluorochroman-2-yl)-1-tosyl-1*H*-benzimidazole	90	145–146	2.42 (s, 3H, –CH_3), 2.46–2.66 (m, 2H, 3′–CH_2), 2.93–3.12 (m, 2H, 4′–CH_2), 5.94 (dd, J = 9.9 and 9.9 Hz, 1H, 2′–CH), 6.61–6.66 (m, 1H, 5′–Ar–H), 6.77–6.86 (m, 2H, 7′ and 8′–Ar–H), 7.26–7.44 (m, 4H, Ar–H), 7.75–7.78 (m, 1H, Ar–H), 7.96 (d, J = 8.4 Hz, 2H, 3″–Ar–H), 8.03–8.06 (m, 1H, 7–Ar–H).	21.68 (CH_3), 24.76 (CH_2), 26.26 (CH_2), 70.71 (OCH), 113.959 (d, $^2J_{C–F}$ = 23.17 Hz), 115.379 (d, $^2J_{C–F}$ = 22.65 Hz), 117.471 (d, $^3J_{C–F}$ = 8 Hz), 120.95, 123.096 (d, $^3J_{C–F}$ = 7.4 Hz), 124.91,125.78,127.32,130.03, 132.94,135.29,141.54,146.07,150.15,151.88, 157.062 (d, $^1J_{C–F}$ = 237.6 Hz) (aromatic carbons).	423
4k $C_{23}H_{19}FN_2O$ 2-(6-fluorochroman-2-yl)-1-benzyl-1*H*-benzimidazole	84	156–158	2.47–2.67 (m, 2H, 3′–CH_2), 2.88–3.05 (m, 2H, 4′–CH_2), 5.30 (dd, J = 9.6 and 9.6 Hz, 1H, 2′–CH), 5.58 (s, 2H, 1″–CH_2), 6.50–6.54 (m, 1H, 5′–Ar–H), 6.69–6.79 (m, 2H, 7′ and 8′–Ar–H), 7.07–7.10 (m, 2H, Ar–H), 7.22–7.29 (m, 6H, Ar–H), 7.79–7.83 (m, 1H, Ar–H).	24.83 (CH_2), 25.31 (CH_2), 48.05 (NCH_2), 71.57 (OCH), 110.38, 114.273 (d, $^2J_{C–F}$ = 22.65 Hz), 115.724 (d, $^2J_{C–F}$ = 22.65 Hz), 117.86 (d, $^3J_{C–F}$ = 8 Hz), 120.44, 122.70, 123.482 (d, $^3J_{C–F}$ = 7.5 Hz), 126.59, 127.98, 129.04, 136.05, 136.45, 142.26, 149.78, 149.81, 151.87, 157.273 (d, $^1J_{C–F}$ = 236.92 Hz) (aromatic carbons).	359
4l $C_{23}H_{18}F_2N_2O$ 2-(6-fluorochroman-2-yl)-1-(4-fluorobenzyl)-1*H*-benzimidazole	86	155–156	2.55–2.68 (m, 2H, 3′–CH_2), 2.91–3.08 (m, 2H, 4′–CH_2), 5.31 (dd, J = 9.0 and 9.6 Hz, 1H, 2′–CH), 5.56 (s, 2H, 1″–CH_2), 6.51–6.55 (m, 1H, 5′–Ar–H), 6.73–6.81 (m, 2H, 7′ and 8′–Ar–H), 6.96–7.12 (m, 3H, Ar–H), 7.24–7.31 (m, 4H, Ar–H), 7.82 (d, J = 6.9 Hz, 1H, Ar–H).	23.87 (CH_2), 24.57 (CH_2), 46.29 (NCH_2), 69.85 (OCH), 111.10, 114.497 (d, $^2J_{C–F}$ = 23.17 Hz), 115.608 (two doublets, $^2J_{C–F}$ = 22.57 Hz), 117.538 (d, $^3J_{C–F}$ = 8.32 Hz), 119.83, 122.30, 123.26, 123.918 (d, $^3J_{C–F}$ = 7.72 Hz), 129.102 (d, $^3J_{C–F}$ = 8.02 Hz), 133.47, 135.49, 141.96, 149.99, 151.94, 156.512 (d, $^1J_{C–F}$ = 234.07 Hz), 161.665 (d, $^1J_{C–F}$ = 241.875 Hz) (aromatic carbons).	377
4m $C_{23}H_{18}BrFN_2O$ 2-(6-fluorochroman-2-yl)-1-(4-bromobenzyl)-1*H*-benzimidazole	88	156–157	2.53–2.64 (m, 2H, 3′–CH_2), 2.91–3.09 (m, 2H, 4′–CH_2), 5.32 (dd, J = 9.0 and 9.3 Hz, 1H, 2′–CH), 5.54 (s, 2H, 1″–CH_2), 6.48–6.53 (m, 1H, 5′–Ar–H), 6.72–6.81 (m, 2H, 7′ and 8′–Ar–H), 6.99 (d, J = 8.4 Hz, 2H, Ar–H), 7.19–7.32 (m, 3H, Ar–H), 7.43 (d, J = 8.4 Hz, 2H, Ar–H), 7.83 (d, J = 7.2 Hz, 1H, Ar–H)	24.31 (CH_2), 24.84 (CH_2), 47.19 (NCH_2), 71.27 (OCH), 109.95, 114.077 (d, $^2J_{C–F}$ = 23.17 Hz), 115.541 (d, $^2J_{C–F}$ = 22.35 Hz), 117.553 (d, $^3J_{C–F}$ = 8 Hz), 120.30, 121.64, 122.619, 122.997 (d, $^3J_{C–F}$ = 7.5 Hz) 123.55 128.103, 131.926, 135.273, 135.605, 142.065, 149.434, 151.559, 156.624 (d, $^1J_{C–F}$ = 237.82 Hz) (aromatic carbons).	438
4n $C_{24}H_{21}FN_2O$ 2-(6-fluorochroman-2-yl)-1-(4-methylbenzyl)-1*H*-benzimidazole	85	197–198	2.31 (s, 3H, 5″–Ar–CH_3), 2.52–2.62 (m, 2H, 3′–CH_2) 2.95–3.00 (m, 2H, 4′–CH_2), 5.30 (d, J = 9.3 and 9.3 Hz, 1H, 2′–CH), 5.55 (s, 2H, 1″–CH_2), 6.58–6.62 (m, 1H, 5′–Ar–H), 6.73–6.80 (m, 2H, 7′ and 8′–Ar–H), 6.99–7.11 (m, 4H, Ar–H), 7.25 (s, 3H, Ar–H), 7.81(d, J = 6.3 Hz, 1H, Ar–H).	21.03 (CH_3), 24.38 (CH_2), 24.88 (CH_2), 47.42 (NCH_2), 71.17 (OCH), 110.168, 113.968 (d, $^2J_{C–F}$ = 22.87 Hz), 115.443 (d, $^2J_{C–F}$ = 22.57 Hz), 117.616 (d, $^3J_{C–F}$ = 8 Hz), 120.13,122.35, 122.651 (d, $^3J_{C–F}$ = 7.42 Hz), 123.32,126.34,129.44,133.12,135.80,137.45,142.05, 149.64,151.62, 157.054 (d, $^1J_{C–F}$ = 237.525 Hz) (aromatic carbons).	373
4o $C_{27}H_{27}FN_2O$ 2-(6-fluorochroman-2-yl)-1-(4-*tert*-butylbenzyl)-1*H*-benzimidazole	89	191–192	1.28 (s, 9H, 5″–Ar–*tert* butyl), 2.48–2.66 (m, 2H, 3′–CH_2), 2.89–3.07 (m, 2H, 4′–CH_2), 5.31 (dd, J = 9.6 and 9.6 Hz, 1H, 2′–CH), 5.56 (s, 2H, 1″–CH_2), 6.52–6.56 (m, 1H, 5′–Ar–H), 6.71–6.79 (m, 2H, 7′ and 8′–Ar–H), 7.03 (d, J = 8.1 Hz, 2H, Ar–H), 7.26–7.32 (m, 5H, Ar–H), 7.82 (d, J = 5.7 Hz, 1H, Ar–H).	24.38 (CH_2), 24.86 (CH_2), 31.27 (CH_3), 34.50 (C-*tert* butyl), 47.32 (NCH_2), 71.12 (OCH), 110.18,113.964 (d, $^2J_{C–F}$ = 22.87 Hz), 115.449 (d, $^2J_{C–F}$ = 22.35 Hz), 117.65 (d, $^3J_{C–F}$ = 7.95 Hz), 120.18, 122.38, 122.73 (d, $^3J_{C–F}$ = 7.42 Hz), 123.35, 125.72, 126.09, 133.23, 135.90, 142.07, 149.64, 150.76,151.66, 157.088 (d, $^1J_{C–F}$ = 237.525 Hz) (aromatic carbons	415

[a] All the new compounds prepared gave satisfactory elemental analysis data;

[b] ^{1}H-NMR spectra for compounds **3** and **4l** were recorded in DMSO-d_6 and all other in $CDCl_3$.



Scheme 3.

typhimurium (Gram negative) bacterial strains. Cephalexin was used as a reference standard. The results of the antibacterial activity screening of the tested compound are summarized in Table 2. Most of the compounds tested were found to have good antibacterial activity against *Salmonella typhimurium*; however, they were found to have poor activity against *Staphylococcus aureus*. Also they were tested against PDE–IV for potential anti asthamatic effect, and against DP–IV and PTP1B for potential anti diabetic effects. Unfortunately, the results were disappointing.

4. Experimental section

Melting points are uncorrected and were recorded on a MRVIS Series, Lab India Instrument. TLC analysis was done using pre-coated silica gel plates and visualization was done using iodine/UV lamp. IR spectra were recorded on a Perkin-Elmer Spectrum One FT-IR spectrometer. ^{1}H- and ^{13}C-NMR spectra were recorded on a Varian Mercury Vx SWBB 300 MHz spectrometer. Elemental analysis was carried out on a Perkin-Elmer Series–II C H N S O Analyzer 2400. Microwave irradiation was done on a Bioceramic-CE2933, 28 l microwave oven. *o*-Phenylenediamine, alkylating, acylating and aroylating agents were obtained from commercial suppliers. 6-Fluoro-3,4-dihydro-2*H*-chroman-2-carboxlic acid was prepared following literature procedure [6]. All the solvents used were of commercial grade only.

Table 2
Antibacterial activity of compounds against *Salmonella typhimurium*

Compound	Concentration (μg/ml)						
	0.1	1	10	100	200	500	APP. MIC
3	++	++	+	P	–	–	200
4a	++	++	++	P	–	–	200
4b	++	++	+	P	–	–	200
4c	++	++	+	P	–	–	200
4d	++	++	++	+	P	–	500
4e	+	+	P	P	–	–	200
4f	+	+	+	P	–	–	200
4g	++	++	+	P	–	–	200
4h	++	++	P	+	P	P	> 1000
4i	++	++	++	P	–	–	200
4j	++	++	P	+	P	P	> 1000
4k	++	++	++	+	–	–	200
4l	++	++	++	+	–	–	200
4m	++	++	++	++	P	–	500
4n	++	++	P	P	–	–	200
4o	++	++	+	P	–	–	200
Cephalexin	++	++	+	P	–	–	200

Symbols: Total inhibition, no growth of organism: –; poor growth compared to controls: P; medium growth compared to controls: +; confluent growth, no inhibition: ++.

4.1. Synthesis of 2-(6-fluorochroman-2-yl)-1H-benzimidazole (3)

A mixture of *o*-phenylenediamine (OPDA) (**1**) (1.08 g, 10 mmol), 6-fluorochroman-2-carboxylic acid [6] (**2**) (2.35 g, 12 mmol) and 4 N HCl (10 ml) was refluxed in an oil bath for 6 h (as monitored by TLC). The reaction mixture was then cooled to room temperature and neutralized with aqueous sodium bicarbonate (10%) solution. The solid separated was filtered, washed with water (2 × 25 ml) and dried under vacuum to obtain the crude product which was recrystallized from hot aqueous ethanol to yield off-white crystalline compound **3**.

4.2. Synthesis of compound 3 via Eaton's reagent

A mixture of **2** (1.96 g, 10 mmol), OPDA (1.08 g, 10 mmol) and P_2O_5-MSA (15 ml) (1:10 mixture) (*Eaton's reagent*) was heated with stirring at 100 °C for 5 h. The reaction was then quenched with aqueous saturated bicarbonate solution till neutral pH and extracted with ethyl acetate (3 × 50 ml). The organic layer was washed with water (2 × 25 ml), brine (2 × 25 ml) and dried over anhydrous magnesium sulfate and distilled to get compound **3** (2.14 g, 80%), which was recrystallized from aq. ethanol to obtain the pure compound **3** (m.p. = 232–235 °C).

4.3. Synthesis of compound 3 via microwave irradiation

A mixture of **2** (1.96 g, 10 mmol) and OPDA (1.08 g, 10 mmol) in polyphosphoric acid (10 g) was stirred and irradiated in a microwave oven at 100 W for 3 min at 170 °C. The reaction mixture was then cooled to room temperature and neutralized with ice-cold concentrated potassium hydroxide solution to obtain neutral pH. The solid separated out was filtered, washed with water (3 × 50 ml) dried under vacuum (2.27 g, 85%) and the crude product was recrystallized from aq. ethanol to obtain the pure compound **3** (m.p. = 232–235 °C).

4.4. General procedure for the synthesis of compounds 4a–4d

To a solution of compound **3** (2 mmol) in acetone (50 ml) was added finely powdered anhydrous potassium carbonate (4 mmol), triethylbenzylammonium bromide (TEBAB, 0.1 mmol) followed by the addition of respective alkylating agent (3 mmol). The reaction mixture was then refluxed for 5 h in case of **4a** and 24 h in case of **4b** (TLC monitoring). Acetone from the reaction mixture was then evaporated under vacuum to get a residue. Water (50 ml) was added to the residue and extracted with ethyl acetate (2 × 75 ml). The ethyl acetate layer was washed with water (2 × 50 ml), brine (2 × 15 ml) and dried over anhydrous sodium sulfate. Distillation of the solvent yielded the corresponding alkylated products **4a–4d**. The crude compounds were recrystallized from hot aqueous ethanol to yield pure products.

4.5. Alternate synthesis of **4a**

A mixture of *N*-methy1-*o*-phenylenediamine dihydrochloride, **5** (1.95 g, 10 mmol), and compound **2** (2.62 g, 15 mmol) was taken in a solution of 4 N HCl (10 ml) and refluxed in a water bath for 6 h (TLC monitoring) The reaction mixture was then cooled to room temperature and neutralized with 10% aqueous sodium bicarbonate solution. It was then extracted with ethyl acetate and the organic extract was washed with aq. sodium bicarbonate (2 × 25 ml), water (2 × 50 ml), brine (15 ml) and dried over anhydrous sodium sulfate. Distillation of the solvent yielded the crude compound which was recrystallized from hot aq. ethanol to obtain pure product **4a** (2.2 g, 83%).

4.6. General procedure for the synthesis of compounds **4e–4j**

To a solution of compound **3** (2 mmol) in pyridine (5 ml) was added slowly respective acyl or arylsulfonyl chloride (3 mmol) at 0 °C. After the addition was complete, the temperature of the reaction mixture was allowed to slowly rise to room temperature and stirred at this temperature for 2 h (TLC monitoring). A solution of 2 N HCl was the added to the reaction mixture until neutral, when a solid separated out. The solid was filtered, washed with water (2 × 30 ml) and dried under vacuum to obtain the corresponding N-substiuted derivatives **4e–4j**, respectively. The crude compounds were recrystallized from hot aq. ethanol to obtain pure products.

4.7. General procedure for the synthesis of compounds **4k–4o**

To a solution of compound **3** (2 mmol) in acetonitrile (20 ml) was added aqueous sodium hydroxide solution (5%, 5 ml) and the mixture was stirred for 15 min. Substituted benzyl bromide (2.4 mmol) was then added slowly with stirring to the reaction mixture at 0 °C. After the addition was complete, the temperature of the reaction mixture was allowed to slowly rise to room temperature and stirred at this temperature for 24 h (TLC monitoring). After the completion of the reaction, acetonitrile from the reaction mixture was evaporated under vacuum to obtain a residue. Water was added to the residue to obtain a solid, which was then filtered, washed with excess of water (2 × 100 ml) and filtered. The crude compounds were recrystallized from hot aq. ethanol to obtain pure products and the products were dried under vacuum to obtain the corresponding N-substituted derivatives **4k–4o**, respectively.

5. Conclusion

In conclusion, we have demonstrated the synthesis of a series of novel benzimidazole derivatives by the condensation of OPDA with 6-fluoro-3,4-dihydro-2*H*-chroman-2-carboxlic acid and subsequent reactions at the benzimidazole–NH with different electrophilic reagents under different conditions. Some of the compounds were found to have good antibacterial activity against *Salmonella typhimurium*; however, they were found to have less activity against *S. aureus*. These compounds were also tested against PDE–IV for potential anti asthamatic effect, and against DP–IV and PTP1B for potential anti diabetic effects. Unfortunately, the results were disappointing.

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