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Synthesis and antimicrobial activity of some new of 2-(furan-2-yl)-1-(piperidin-4-yl)-1*H*-benzo[*d*]imidazole derivatives

Tejasvi H. Parmar,[a] Chetan B. Sangani,*[a] Nilesh D. Parmar,[b] and Pradip C. Bhalodiya[a]

[a]*Department of Chemistry, Shri M.M Patel Institute of Sciences and Research, Kadi Sarva Vishwavidyalaya, Gandhinagar - 382023, India*

[b]*Department of Chemistry, Saurashtra University, Rajkot-360 005, Gujarat, India*

Email: chetansangani1986@yahoo.com; tejashparmar@gmail.com

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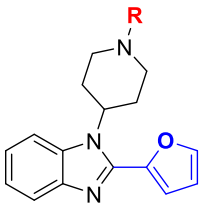
Abstract

We report a series of new heterocyclic compounds containing the imidazole scaffold were synthesized such as 2-(furan-2-yl)-1-(piperidine-4-yl)-1*H*-benzo[*d*]imidazole derivative. Due to the biological activities of imidazole as antimicrobial agents, in the present work, all the synthesized compounds were characterized by ^{1}H NMR and LC-MS analysis and some of the compounds are characterized by ^{13}C NMR. All the synthesized compounds were evaluated for their antimicrobial activity against Gram *+ve* and Gram *-ve* bacteria and different fungal species which demonstrated good to moderate antimicrobial activity, in which compounds **7b** and **7l** shows highest antimicrobial activity.



R = Different acyl chloride, acids and sulphonyl chloride derivatives

Keywords: Sodium dithionate, HATU reagent, furan-2-carbaldehyde, antimicrobial activity

Introduction

Heterocycles of benzimidazole are important substructures identified in natural products and pharmacologically active molecules.[1-5] A different derivative of imidazole act as an inhibitor of p38 MAP kinase,[6] glucagon receptors,[7] plant growth regulators,[8] therapeutic agents,[9] antibacterial,[10] and also antitumor,[11] some of the derivatives used as an ionic liquid which highly benefits to the green chemistry. The synthesis of benzimidazole derivatives plays important role in the biological activities of these compounds induced by the heterocyclic ring. Benzimidazole derivatives display a wide range of biological and pharmaceutical active such as antiulcer activity antimicrobial, antiviral, antidiabetic and anticancer activity.[12-17]

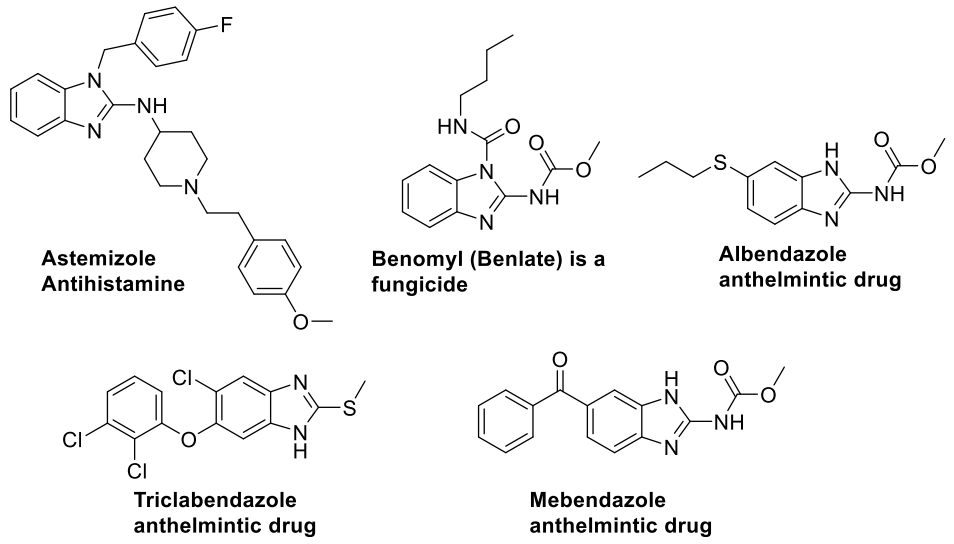


Figure 1: Representative examples of some drugs containing a benzimidazole moiety

Commonly benzimidazole synthesized by condensation with carboxylic acids or their functional derivatives and *o*-aminoanilines.[18-24] Drawbacks of these conditions are dehydrating reaction conditions, high temperature, and very strong acid catalysts.

Intramolecular cyclization of *o*-bromoaryl derivatives in the presence of copper(II)oxide nanoparticles in solvent DMSO,[25] and the intramolecular cyclocondensation of some aryl amino oximes by using of methane sulfonyl chloride and triethylamine[26] can also be used to produce benzimidazole derivatives. However, all these synthetic routes require expensive metal catalysts, toxic solvents.

Due to diverse range of biological activity and use of benzimidazole derivative in material chemistry and use as ionic solvent development of new synthetic method is an important area. We have synthesized novel benzimidazole derivatives in four steps via reductive cyclization of n-piperidine substituted nitroaniline with 2-furfuryl using sodium dithionite [27,28] and piperidine amine coupling with commercially available acid, acyl chloride, and sulphonyl chloride.

Results and Discussion

In this work we describe the synthesis of amide and sulphonamide derivative of 2-(furan-2-yl)-1-(piperidine-4-yl)-1*H*-benzo[*d*]imidazole from n-substituted benzene diamine. Spectral data and physical data of this

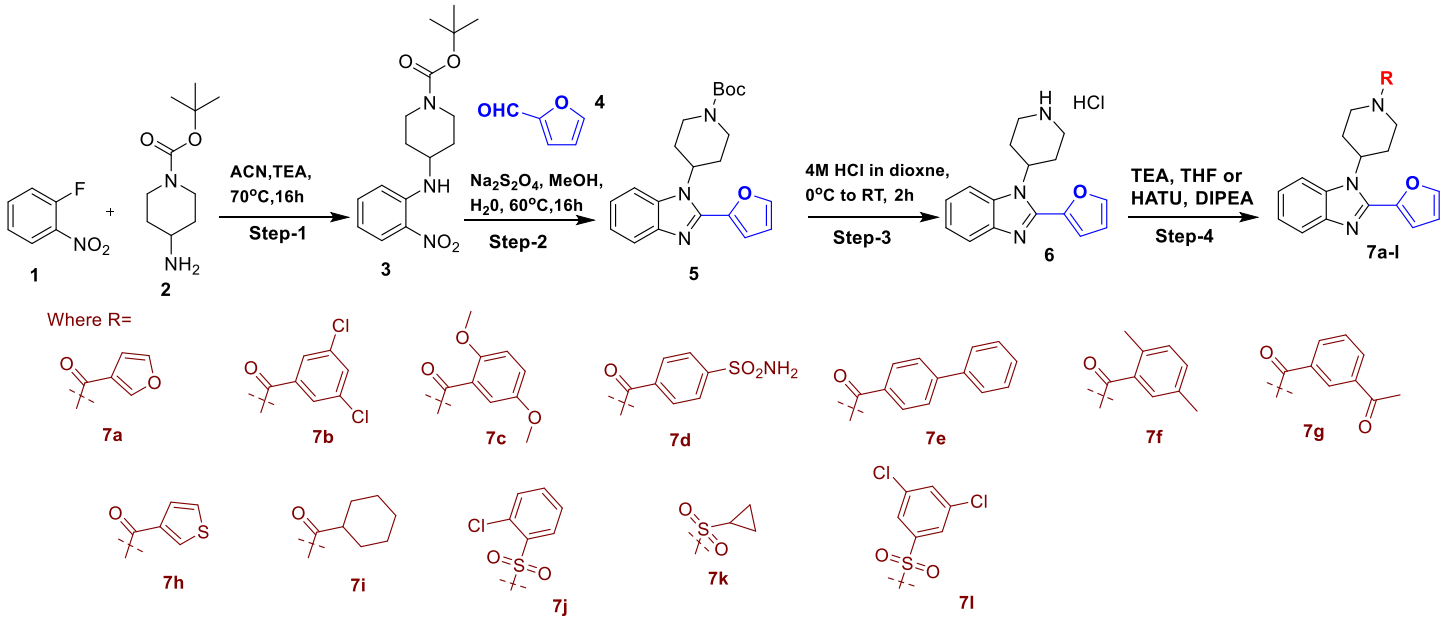
molecules are not reported in the literature. For these molecules starting material are commercially available and reaction conditions having good yield, no hazardous chemicals and less reaction time.

1-Fluoro-2-nitrobenzene and tert-butyl 4-aminopiperidine-1-carboxylate coupling reaction by using ACN, TEA (3 eq) at 70 °C for overnight with 70% yield. For this coupling reaction performed at gram scale, product **3** was isolated pure without column purification and directly used in the next step with furan-2 aldehyde (**4**) in the presence of dithionite (4 eq.), MeOH: H_2O (1:1) at 60 °C for overnight. After completion of the reductive cyclization, distilled out the MeOH and added water, product (**5**) was precipitated out and which was pure and reduced the purification. Product (**5**) was subject to 4M HCl in dioxane at 0°C to RT for 2 h and isolated 2-(furan-2-yl)-1-(piperidin-4-yl)-1*H*-benzo[*d*]imidazole HCl salt (**6**).

2-(Furan-2-yl)-1-(piperidin-4-yl)-1*H*-benzo[*d*]imidazole HCl salt was derivatised with different acid, acyl chloride and sulphonyl chloride. For the acyl chlorides and sulphonyl chloride performed the reaction with TEA in THF at 0°C to RT for 3-4 hrs.

For acid-amine coupling, the standard procedure was employed by using HATU, DIPEA, and DMF at 0°C to RT for 2-3 hr. After completion of the reaction, the reaction mixture was quenched with ice cold water and the product was precipitated in a pure state without column purification

From the results of *in vitro* antimicrobial activity data indicate that the **7c**, **7g** and **7k** exhibited potent activity against *E.coli*, *S.typhi*, *Micrococcus* and *B. megaterium* and **7a**, **7b**, **7d** and **7h** showed moderate activity while others showed no or little activity. The compound **7b** and **7l** showed highest antimicrobial activity against all the bacterial species and fungal species due to the dichloro substituent and with sulfonamide and amide bond.



Scheme 1

Antimicrobial activities. Antibacterial and antifungal activity was tested by the standard agar cup method. All the synthesized compound (**7a**-**7l**) were tested for their *in vitro* antimicrobial activity against Gram +*ve* (*Bacillus megaterium, Micrococcus spp*.), Gram -*ve* (*E.coli,, S. typi*) and fungal spps. (*Ganoderma spp., A.niger, A.flavus and Penicullium spp*.) taking streptomycin, ciprofloxacin, and nystatin as standard drugs. A suspension of 24 to 48 h grown fresh bacterial and fungal culture was prepared in N-broth and Potato Dextrose broth

respectively. All the bacterial and fungal suspensions were equally spread onto the sterile Muller Hinton and PDA respectively with the help of sterile swabs. Wells were made in the plates (1 cm) with the help of sterile cork borer. The standard antibiotics were dissolved in sterile distilled water up to 200 µg/mL of final concentration. The culture to be tested was dissolved in DMSO up to the final concentration of 1 mg/mL and 0.1 mL of it was loaded into the well. The plate was incubated at 4 °C for 20 minutes for proper diffusion of chemical and then the plates were incubated in upward position for 24 hrs at 37 °C for bacterial culture and 48 hrs at 25 °C for fungal cultures. The control activity against DMSO was also performed. After an incubation zone of inhibition was observed and measured.

Table 1. Antimicrobial activity of 2-(furan-2-yl)-1-(piperidin-4-yl)-1*H*-benzo[*d*]imidazole derivatives

Code	Antibacterial activity				Antifungal activity			
	Antibacterial activity (zone in cm), concentration: 1mg/mL				Antifungal activity (zone in cm), concentration: 1mg/mL			
	Gram +*ve* Bacteria		Gram -*ve* Bacteria					
	B. megaterium	Micrococcus spp.	S. typi.	E. coli	Penicillium spp.	Ganoderma spp.	A. Niger	A. flavus
7a	-	-	1.8	-	1.2	0.9	-	0.5
7b	2.5	3	2.1	2	2.8	3.2	3.0	3.5
7c	1.3	1.5	1.9	-	2.1	2.5	2.7	2.6
7d	2	1.8	1.6	1.1	0.8	1.0	0.5	-
7e	1.2	1	-	1.1	0.6	-	0.9	0.6
7f	0.9	1.3	1.2	1.2	-	1.1	0.8	0.9
7g	2.4	2.8	1.9	2.2	2.5	3.5	2.9	3.4
7h	1.2	1.9	1.7	-	1.5	1.9	2	1.8
7i	-	1.7	1.2	1.9	0.9	0.5	1.0	-
7j	1.5	-	1.2	1	2.1	3	2.5	2.9
7k	2.6	2.9	1.8	2	1.0	0.7	0.5	0.8
7l	1.2	-	1.7	-	2.1	2.8	3.0	2.9
Streptomycin (200 µg/mL)	3	2	2	3.2	-	-	-	-
Ciprofoxacin (200 µg/mL)	3.8	4	4	3	-	-	-	-
Nystatin 200 µg/ml	-	-	-	-	3.2	4	3.5	3.8

Conclusions

The aim of the present work was to synthesize, characterize and screen the antimicrobial activity of new 2-(furan-2-yl)-1-(piperidin-4-yl)-1*H*-benzo[*d*]imidazole derivatives. The imidazole ring was cyclized via reductive

cyclization with furfural and sodium dithionate. Compounds **7b** and **7l** show the highest antimicrobial activity against all species of bacteria and fungi.

Experimental Section

General. All purchased chemicals were used without further purification. Reactions were monitored by thin layer chromatography (TLC) on silica gel-G plates (G60 F254 (Merck)) of 0.5 mm thickness, visualizing with ultraviolet light (254 and 365 nm), or with iodine vapor or aq. KMnO4. Melting points were determined Kofler hot plate apparatus. NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer (400 MHz for ^{1}H NMR and 101 MHz for ^{13}C NMR) respectively in deuterated solvents like $CDCl_3$ (7.26) or DMSO-d_6 (2.5) and chemical shifts are referenced to the solvent residual signals with respect to tetramethylsilane; ^{1}H NMR chemical shifts are designated using the following abbreviations as well as their combinations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad signal, coupling constants in Hz. Elemental analysis was carried out on Euro EA 3000 elemental analyser and the results are in agreement with the structures assigned. LCMS spectra were recorded on a Shimadzu LCMS-9030 spectrometer. Solvents were evaporated with a Büchi rotary evaporator. Purification was performed by column chromatography using silica gel (60-120 mesh size), borosil glass column having a length about 1000 mm and pet ether: ethyl acetate as a solvent system.

Tert-butyl 4-((2-nitrophenyl)amino)piperidine-1-carboxylate (3). 1-Fluoro-2-nitrobenzene **1** (3.0 g, 21.26 mmol) and tert-butyl 4-aminopiperidine-1-carboxylate **2** (5.32 g, 26.58 mmol) was heated in the presence of TEA (9.2 mL, 63.82 mmol) in ACN (30 mL) at 70 °C for 16 h. Afterwards water (100 mL) was added and resulting mixture was extracted with ethyl acetate (3 × 50 mL). The combine organic were dried over (Na_2SO_4) and concentrated to dryness. The remaining crude mixture was chromatographed on a silica gel column using EtOAc/*n*-hexane (3:7) to give **3** as a yellow liquid (4.7 g, 70%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.08 (dd, *J* 1.2, 8.8 Hz, 1H), 7.94 (t, *J* 18.8 Hz, 1H), 7.55 (t, *J* 14.8 Hz, 1H), 7.201 (d, *J* 8.8 Hz, 1H), 3.83-3.92 (m, 3H), 2.90-2.99 (m, 4H), 1.92-1.98 (m, 2H), 1.23 (s, 9H). MS: *m/z* [M-] 321.3.

***tert*-Butyl 4-(2-(furan-2-yl)-1*H*-benzo[*d*]imidazol-1-yl)piperidine-1-carboxylate (5).** *tert*-Butyl 4-((2-nitrophenyl)amino)piperidine-1-carboxylate **3** (3.0 g, 9.33 mmol) and furan-2-carbaldehyde **4** (0.897 g, 9.33 mmol) was added to methanol (30 mL), and $Na_2S_2O_4$ (4.87 g, 27.66 mmol) with water (30 mL) and reaction was heated at 70 °C for 16 h. Concentrated the reaction mixture and added water (100 mL) solid was precipitated filter it and dry it under vacuum to give **5** (3.0 g, 87.4%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.52 (s, 9H), 1.93 (d, *J* 11.2 Hz, 2H), 2.25-2.35 (m, 2H), 2.95 (br, 2H), 4.135 (br, 2H), 4.93-4.99 (m, 1H), 6.77-6.79 (m, 1H), 7.16 (d, *J* 3.6 Hz, 1H), 7.24-7.29 (m, 2H), 7.69-7.70 (m, 2H), 7.98-7.98 (d, *J* 1.2 Hz, 1H). MS: *m/z* [M+1] 368.2.

2-(Furan-2-yl)-1-(piperidin-4-yl)-1*H*-benzo[*d*]imidazole hydrochloride (6). *tert*-Butyl 4-(2-(furan-2-yl)-1*H*-benzo[*d*]imidazol-1-yl)piperidine-1-carboxylate **5** (3.0 g, 2.61 mmol) was added in 1,4-dioxane (30 mL) cool at 0 °C was added 4M HCl in dioxane drop wise and stirred at rt for 16 h. Filtered the solid and dry it under vacuum to obtained **6** (2.3 g, 92.73%) as an off white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.22 (d, br, *J* 8.0 Hz, 2H), 2.94 (d, br, *J* 3.6 Hz, 2H), 3.21-3.30 (m, 2H), 3.48 (d, br *J* 12.0 Hz, 2H), 5.27-5.29 (m, 1H), 6.98-6.99 (m, 1H), 7.53-7.57 (m, 2H), 7.79-7.83 (m, 2H), 8.27 (s, 1H), 8.53-8.55 (m, 1H), 9.27-9.29 (m, br, 1H) HCl salt and 9.91 (s, br, 1H) HCl salt. MS: *m/z* [M+1] 268.1.

(4-(2-(Furan-2-yl)-1*H*-benzo[*d*]imidazol-1-yl)piperidin-1-yl)(furan-3-yl)methanone (7a). 2-(Furan-2-yl)-1-(piperidin-4-yl)-1*H*-benzo[*d*]imidazole hydrochloride **6** (150 mg, 0.493 mmol) was added in THF (3 mL), trimethylamine (0.21 mL, 1.48 mmol) cool to 0 °C. furan-3-carbonyl chloride (70.9 mg, 0.543 mmol) was dilute with THF (1 mL) added drop wise at 0 °C, stirred for 16 h at rt, extracted with ethyl acetate (3 × 20 mL) and dried over anhydrous Na_2SO_4 and concentrated in vacuum. The crude product was purified by column chromatography on silica gel (eluent: 0-50% *n*-Hexane/EtOAc) to afford the product **7a** as an off white solid (0.1 g, 56%); mp 183-186°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.2-2.0 (m, 2H), 2.41-2.44 (m, 2H), 3.52-3.63 (m, 2H), 4.69-4.81 (m, 2H), 5.04-5.10 (m, 1H), 6.77 (s, 1H), 6.79-6.80 (m, 1H), 7.19 (d, *J* 1.8 Hz, 1H), 7.25-7.30 (m, 2H), 7.68-7.70 (m, 1H), 7.78 (s, 1H), 7.82-7.84 (m, 2H), 8.01 (s, 1H), 8.144 (s, 1H); LC-MS, RT: 1.609 min., 100%, λmax: 308 nm; MS: *m/z* [M+1] 362.3; Anal. Calc. for $C_{21}H_{19}N_3O_3$: C, 69.79; H, 5.30; N, 11.63; Found: C, 69.72; H, 5.25; N, 11.60%.

(3,5-Dichlorophenyl)(4-(2-(furan-2-yl)-1*H*-benzo[*d*]imidazol-1-yl)piperidin-1-yl)methanone (7b). 2-(Furan-2-yl)-1-(piperidin-4-yl)-1*H*-benzo[*d*]imidazole hydrochloride **6** (150 mg, 0.493 mmol) was added in THF (3 mL), trimethylamine (0.21 mL, 1.48 mmol) cool to 0 °C. 3,5-dichlorobenzoyl chloride (113.7 mg, 0.543 mmol) was dilute with THF (1 mL) added drop wise at 0 °C, stirred for 16 h at rt. Extracted with ethyl acetate (3 × 20 mL) and dried over anhydrous Na_2SO_4 and concentrated in vacuum. The crude product was purified by column chromatography on silica gel (eluent: 0-60% *n*-Hexane/EtOAc) to afford the product (3,5-dichlorophenyl)(4-(2-(furan-2-yl)-1*H*-benzo[*d*]imidazol-1-yl)piperidin-1-yl)methanone as an off white solid (0.15 g, 69%). mp 143-146 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.99-2.03 (m, 2H), 2.41-2.44 (m, 2H), 3.52-3.63 (m,2H), 4.69-4.81 (m, 2H), 5.04-5.10 (m, 1H), 6.79-6.80 (m, 1H), 7.18 (d, *J* 3.2 Hz, 1H), 7.25-7.32 (m, 2H), 7.63 (d, *J* 2.0 Hz, 2H), 7.67-7.69 (m, 1H), 7.75 (d, *J* 2.0 Hz, 1H), 7.99-8.03 (m, 2H); LC-MS, RT: 2.012 min, 98.96%, λmax: 254 nm; MS: *m/z* [M+1] 442.2; Anal. Calc. for $C_{23}H_{19}Cl_2N_3O_2$: C, 62.74; H, 4.35; N, 9.54; Found: C, 62.70; H, 4.31; N, 9.49%.

(2,5-Dimethoxyphenyl)(4-(2-(furan-2-yl)-1*H*-benzo[*d*]imidazol-1-yl)piperidin-1-yl)methanone (7c). 2,5-dimethoxybenzoic acid (98.95 mg, 0.543 mmol) was added in DMF (3 mL) cool to 0°C, HATU (281 mg, 0.74 mmol) was added and stirred for 30 min at 0°C. 2-(furan-2-yl)-1-(piperidin-4-yl)-1*H*-benzo[*d*]imidazole hydrochloride **6** (150 mg, 0.493 mmol) was added portion wise and stirred for 30 min at 0°C. DIPEA (0.27 mL, 0.156 mmol) was added dropwise at 0 °C and stirred for 16 h. Extracted with ethyl acetate (3 × 15 mL) and dried over anhydrous Na_2SO_4 and concentrated in vacuum. The crude product was purified by column chromatography on silica gel (eluent: 0-60% *n*-Hexane/EtOAc) to afford the product (2,5-dimethoxyphenyl)(4-(2-(furan-2-yl)-1*H*-benzo[*d*]imidazol-1-yl)piperidin-1-yl)methanone as yellow solid (150 mg, 70.4%); mp 110-114 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.83-1.90 (m, 2H), 2.06-2.10 (m, 2H), 2.90-2.98 (m, 1H), 3.18-3.25 (m, 1H), 3.44-3.50 (m, 1H), 3.74-377 (m, 4H), 3.88 (s, 2H), (4-OCH_3 split in 4H and 2H), 4.73-4.76 (m, 1H), 5.10 (s, br, 1H), 6.79 (s, 1H), 6.96 (d, *J* 1.2 Hz, 1H), 6.98-7.05 (m, 1H), 7.16-7.19 (m, 1H), 7.27-7.31 (m, 1H), 7.36-7.40 (m, 1H), 7.66-7.72 (m, 1H), 7.89-7.91 (m, 1H), 8.01 (s, 1H); ^{13}C-NMR (101 MHz, DMSO-d_6): δ 166.49, 153.68, 149.45, 149.33, 145.55, 145.49, 144.80, 144.73, 144.02, 143.84, 143.60, 134.12, 133.88, 126.95, 126.90, 123.18, 122.74, 120.44, 120.06, 115.30, 115.22, 113.90, 113.80, 113.51, 113.07, 112.81, 112.54, 56.57, 56.45, 56.00, 55.00, 54.52, 46.39, 46.00, 30.58, 30.46, 30.23, 30.02; LC-MS, RT: 1.602 min, 100%, λmax: 302 nm; MS: *m/z* [M+1] 432.4; Anal. Calc. for $C_{25}H_{25}N_3O_4$: C, 69.59; H, 5.84; N, 9.74; Found: C, 69.53; H, 5.79; N, 9.69%.

4-(4-(2-(Furan-2-yl)-1*H*-benzo[*d*]imidazol-1-yl)piperidine-1-carbonyl)benzenesulfonamide (7d). 4-sulfamoylbenzoic acid (109.2 mg, 0.543 mmol) was added in DMF (3 mL) cool to 0 °C, HATU (281 mg, 0.74 mmol) was added and stirred for 30 min at 0 °C. 2-(furan-2-yl)-1-(piperidin-4-yl)-1*H*-benzo[*d*]imidazole hydrochloride **6** (150 mg, 0.493 mmol) was added portion wise and stirred for 30 min at 0 °C. DIPEA (0.27 mL, 0.156 mmol) was added dropwise at 0 °C and stirred for 16 h. Extracted with ethyl acetate (3 × 15 mL) and dried over anhydrous Na_2SO_4 and concentrated in vacuum. The crude product was purified by column

chromatography on silica gel (eluent: 0-70% *n*-Hexane/EtOAc) to afford the product 4-(4-(2-(furan-2-yl)-1*H*-benzo[*d*]imidazol-1-yl)piperidine-1-carbonyl)benzenesulfonamide as yellow solid (140 mg, 65.71%); mp 248-251 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.83-1.90 (m, 2H), 1.92-2.05 (m, 3H), 2.51 (m,1H), 2.90-3.01 (m, 2H), 3.64 (m, 1H), 4.73 (m, 1H), 5.06 (s, br, 1H), 6.79 (s, br, 1H), 7.17-7.29 (m, 3H), 7.48 (m, 2H), 7.73 (m, 2H), 7.93 (m, 4H); LC-MS, RT: 1.463 min, 100%, λmax: 254 nm; MS: *m/z* [M+1] 451.3; Anal. Calc. for $C_{23}H_{22}N_4O_4S$: C, 61.32; H, 4.92; N, 12.44; Found: C, 61.26; H, 4.85; N, 12.38%.

[1,1'-Biphenyl]-4-yl(4-(2-(furan-2-yl)-1*H*-benzo[*d*]imidazol-1-yl)piperidin-1-yl)methanone (7e). [1,1'-biphenyl]-4-carboxylicacid (107.6 mg, 0.543 mmol) was added in DMF (3 mL) cool to 0 °C, HATU (281 mg, 0.74 mmol) was added and stirred for 30 min at 0 °C. 2-(furan-2-yl)-1-(piperidin-4-yl)-1*H*-benzo[*d*]imidazole hydrochloride **6** (150 mg, 0.493 mmol) was added portion wise and stirred for 30 min at 0 °C. DIPEA (0.27 mL, 0.156 mmol) was added dropwise at 0 °C and stirred for 16 h. Extracted with ethyl acetate (3 × 15 mL) and dried over anhydrous Na_2SO_4 and concentrated in vacuum. The crude product was purified by column chromatography on silica gel (eluent: 0-50% *n*-Hexane/EtOAc) to afford the product [1,1'-biphenyl]-4-yl(4-(2-(furan-2-yl)-1*H*-benzo[*d*]imidazol-1-yl)piperidin-1-yl)methanone as yellow solid (170 mg, 79.79%); mp 128-131 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.24-1.34 (m, 3H), 1.97 (s, br, 2H), 3.01 (m, 1H), 3.85 (m, 1H), 4.74 (m, 1H), 5.08 (s, br, 1H), 6.80 (s, br, 1H), 7.18 (s, br, 1H), 7.29 (s, br, 2H), 7.41-7.50 (m, 3H), 7.64 (s, 2H), 7.72-7.77 (m, 5H),7.92 (s, 1H), 8.03 (s, 1H); ^{13}C-NMR (101 MHz, DMSO-d_6): δ 169.51, 145.52, 144.88, 144.06, 143.66, 141.69, 139.86, 135.54, 134.16, 129.53, 128.36, 128.12, 127.29, 127.19, 123.28, 122.75, 120.11, 113.94, 113.49, 112.60, 55.08, 54.05, 47.16, 41.65, 30.63, 29.89, 29.51, 18.55, 17.19; LC-MS, RT: 1.788 min, 99%, λmax: 254 nm; MS: *m/z* [M+1] 448.4; Anal. Calc. for $C_{29}H_{25}N_3O_2$: C, 77.83; H, 5.63; N, 9.39; Found: C, 77.76; H, 5.59; N, 9.33%.

(2,5-Dimethylphenyl) (4-(2-(furan-2-yl)-1*H*-benzo[*d*]imidazol-1-yl)piperidin-1-yl)methanone (7f). 2,5-dimethylbenzoic acid (82 mg, 0.543 mmol) was added in DMF (3 mL) cool to 0 °C, HATU (281 mg, 0.74 mmol) was added and stirred for 30 min at 0 °C. 2-(furan-2-yl)-1-(piperidin-4-yl)-1*H*-benzo[*d*]imidazole hydrochloride **6** (150 mg, 0.493 mmol) was added portion wise and stirred for 30 min at 0 °C. DIPEA (0.27 mL, 0.156 mmol) was added dropwise at 0 °C and stirred for 16 h. Extracted with ethyl acetate (3 × 15 mL) and dried over anhydrous Na_2SO_4 and concentrated in vacuum. The crude product was purified by column chromatography on silica gel (eluent: 0-70% *n*-Hexane/EtOAc) to afford the product (2,5-dimethylphenyl)(4-(2-(furan-2-yl)-1*H*-benzo[*d*]imidazol-1-yl)piperidin-1-yl)methanone as yellow solid (155 mg, 72.75%); mp 150-154 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.25 (m, 6H), 1.86 (s, br, 1H), 2.09 (s, br, 1H), 2.32 (m, 2H), 2.96-3.02 (m, 1H), 3.23-3.29 (m, 1H), 3.63 (s, br, 1H), 4.77 (s, br, 1H), 5.049 (s, 1H), 6.68 (d, *J* 7.2 Hz, 1H), 6.99 (s, 1H), 7.14-7.29 (m, 5H), 7.68-7.70 (m, 1H), 7.89-8.03 (m, 2H); LC-MS, RT: 1.675 min, 95.43%, λmax: 202 nm, MS: *m/z* [M+1] 400.4; Anal. Calc. for $C_{25}H_{25}N_3O_2$: C, 75.16; H, 6.31; N, 10.52; Found: C, 75.10; H, 6.25; N, 10.47%.

(4-(2-(Furan-2-yl)-1*H*-benzo[*d*]imidazol-1-yl)piperidin-1-yl)(thiophen-3-yl)methanone (7g). 3-acetylbenzoic acid (89 mg, 0.543 mmol) was added in DMF (3 mL) cool to 0 °C, HATU (281 mg, 0.74 mmol) was added and stirred for 30 min at 0 °C. 2-(furan-2-yl)-1-(piperidin-4-yl)-1*H*-benzo[*d*]imidazole hydrochloride **6** (150 mg, 0.493 mmol) was added portion wise and stirred for 30 min at 0 °C. DIPEA (0.27 mL, 0.156 mmol) was added dropwise at 0 °C and stirred for 16 h. Extracted with ethyl acetate (3 × 15 mL) and dried over anhydrous Na_2SO_4 and concentrated in vacuum. The crude product was purified by column chromatography on silica gel (eluent: 0-60% *n*-Hexane/EtoAc) to afford the product (4-(2-(furan-2-yl)-1*H*-benzo[*d*]imidazol-1-yl)piperidin-1-yl)(thiophen-3-yl)methanone as yellow solid (145 mg, 68%); mp 155-158 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.91-2.06 (m, 4H), 2.64 (s, 3H), 3.02 (m, 2H), 3.71 (m, 1H), 4.75 (m, 1H), 5.07 (S, 1H), 6.80 (S, 1H), 7.19 (d, *J* 2.8 Hz, 1H), 7.25-7.32 (m, 2H), 7.64-7.70 (m, 2H), 7.81 (d, *J* 7.2 Hz, 1H), 7.95 (d, *J* 7.2 Hz, 1H), 8.03-8.07 (m, 3H); LC-

MS, RT: 1.727 min, 90.8%, λmax: 254 nm; MS: *m/z* [M+1] 414.2; Anal. Calc. for $C_{25}H_{23}N_3O_3$: C, 72.62; H, 5.61; N, 10.16; Found: C, 72.57; H, 5.56; N, 10.10%.

(4-(2-(Furan-2-yl)-1*H*-benzo[*d*]imidazol-1-yl)piperidin-1-yl)(thiophen-3-yl)methanone (7h). Thiophene-3-carboxylic acid (69 mg, 0.543 mmol) was added in DMF (3 mL) cool to 0 °C, HATU (281 mg, 0.74 mmol) was added and stirred for 30 min at 0 °C. 2-(furan-2-yl)-1-(piperidin-4-yl)-1*H*-benzo[*d*]imidazole hydrochloride **6** (150 mg, 0.493 mmol) was added portion wise and stirred for 30 min at 0 °C. DIPEA (0.27 mL, 0.156 mmol) was added dropwise at 0 °C and stirred for 16 h. Extracted with ethyl acetate (3 × 15 mL) and dried over anhydrous Na_2SO_4 and concentrated in vacuum. The crude product was purified by column chromatography on silica gel (eluent: 0-75% *n*-Hexane/EtOAc) to afford the product (4-(2-(furan-2-yl)-1*H*-benzo[*d*]imidazol-1-yl)piperidin-1-yl)(thiophen-3-yl)methanone as yellow solid (130 mg, 69.7%); mp 172-176 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.00 (m, 2H), 2.40-2.43 (m, 2H), 3.04 (m, 2H), 4.04 (m, 1H), 4.67 (m, 1H), 5.066 (t, *J* 24.0 Hz, 1H), 6.79 (s, 1H), 7.18 (d, *J* 2.8 Hz, 1H), 7.24-7.33 (m, 3H), 7.65-7.67 (m, 2H), 7.86-7.91 (m, 2H), 8.01 (s, 1H); LC-MS, RT: 1.734 min, 100%, λmax: 254 nm, MS: *m/z* [M+1] 378.2; Anal. Calc. for $C_{21}H_{19}N_3O_2S$: C, 66.82; H, 5.07; N, 11.13; Found: C, 66.77; H, 5.01; N, 11.07%.

Cyclohexyl (4-(2-(furan-2-yl)-1*H*-benzo[*d*]imidazol-1-yl)piperidin-1-yl)methanone (7i). Cyclohexanecarboxylic acid (69 mg, 0.543mmol) was added in DMF (3mL) cool to 0 °C, HATU (281 mg, 0.74 mmol) was added and stirred for 30 min at 0 °C. 2-(furan-2-yl)-1-(piperidin-4-yl)-1*H*-benzo[*d*]imidazole hydrochloride **6** (150 mg, 0.493 mmol) was added portion wise and stirred for 30 min at 0 °C. DIPEA (0.27 mL, 0.156 mmol) was added dropwise at 0 °C and stirred for 16 h. Extracted with ethyl acetate (3 × 15 mL) and dried over anhydrous Na_2SO_4 and concentrated in vacuum. The crude product was purified by column chromatography on silica gel (eluent: 0-70% *n*-Hexane/EtOAc) to afford the product cyclohexyl(4-(2-(furan-2-yl)-1*H*-benzo[*d*]imidazol-1-yl)piperidin-1-yl)methanone as yellow solid (130 mg, 69.7%); mp 208-212 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.17-1.47 (m, 6H), 1.67-1.76 (m, 4H), 1.97-2.09 (m, 2H), 2.20-2.22 (m, 2H), 2.68 (m, br, 2H), 3.16-3.22 (m, 1H), 4.13-4.16 (m, 1H), 4.63 (d, *J* 12.0 Hz, 1H), 5.02 (t, *J* 24.0 Hz, 1H), 6.78 (t, *J* 3.2 Hz, 1H), 7.16 (d, *J* 3.2 Hz, 1H), 7.22-7.28 (m, 2H), 7.67-7.69 (m, 2H), 7.98 (s, 1H); ^{13}C-NMR (101 MHz, DMSO-d_6): δ 173.96, 145.43, 144.89, 144.03, 143.64, 134.16, 123.23, 122.70, 120.17, 113.90, 113.07, 112.56, 55.11, 44.73, 31.30, 30.40, 29.72, 26.12, 25.69; LC-MS, RT: 1.624 min, 100%, λmax: 247 nm, MS: *m/z* [M+1] 378.4; Anal. Calc. for $C_{23}H_{27}N_3O_2$: C, 73.18; H, 7.21; N, 11.13; Found: C, 73.12; H, 7.17; N, 11.08%.

1-(1-((2-Chlorophenyl)sulfonyl)piperidin-4-yl)-2-(furan-2-yl)-1*H*-benzo[*d*]imidazole (7j). 2-(Furan-2-yl)-1-(piperidin-4-yl)-1*H*-benzo[*d*]imidazole hydrochloride **6 (**150 mg, 0.493 mmol) was added in THF (3 mL), trimethylamine (0.21 mL, 1.48 mmol) cool to 0 °C. 2-chlorobenzenesulfonyl chloride (114.6 mg, 0.543 mmol) was dilute with THF (1 mL) added drop wise at 0 °C, stirred for 16 h at rt. Extracted with ethyl acetate (3 × 20 mL) and dried over anhydrous Na_2SO_4 and concentrated in vacuum. The crude product was purified by column chromatography on silica gel (eluent: 0-50% DCM/EtOAc) to afford the product 1-(1-((2-chlorophenyl)sulfonyl)piperidin-4-yl)-2-(furan-2-yl)-1H-benzo[d]imidazole as an off white solid (0.14 g, 64.1%); mp 128-132 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.98-2.05 (m, 2H), 2.34-2.40 (m, 2H), 3.11 (t, *J* 24.0 Hz, 2H), 3.97 (d, *J* 12.0 Hz, 2H), 4.95 (t, *J* 12.4 Hz, 1H), 6.75-6.76 (m, 1H), 7.15 (d, *J* 3.2 Hz, 1H), 7.24-7.27 (m, 2H), 7.40-7.42 (m, 1H), 7.62-7.69 (m, 2H), 7.75-7.83 (m, 1H), 7.96 (d, *J* 1.2 Hz, 1H), 8.10 (dd, *J* 1.6, 8.0 Hz, 1H); LC-MS, RT: 1.969 min, 98.27%, λmax: 254 nm, MS: *m/z* [M+1] 442.2; Anal. Calc. for $C_{22}H_{20}ClN_3O_3S$: C, 59.79; H, 4.56; N, 9.51; Found: C, 59.75; H, 4.50; N, 9.45%.

1-(1-(Cyclopropylsulfonyl)piperidin-4-yl)-2-(furan-2-yl)-1*H*-benzo[*d*]imidazole (7k). 2-(Furan-2-yl)-1-(piperidin-4-yl)-1*H*-benzo[*d*]imidazole hydrochloride **6** (150 mg, 0.493 mmol) was added in THF (3 mL), trimethylamine (0.21 mL, 1.48 mmol) cool to 0 °C. Cyclopropanesulfonyl chloride (76.35 mg, 0.543 mmol) was dilute with THF (1 mL) added drop wise at 0 °C, stirred for 16 h at rt. Extracted with ethyl acetate (3 × 20 mL)

and dried over anhydrous Na_2SO_4 and concentrated in vacuum. The crude product was purified by column chromatography on silica gel (eluent: 0-50% DCM/EtOAc) to afford the product 1-(1-(cyclopropylsulfonyl)piperidin-4-yl)-2-(furan-2-yl)-1*H*-benzo[*d*]imidazole as an off white solid (0.110 g, 59.97%); mp 117-120 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.98-1.00 (m, 2H), 1.04-1.08 (m, 2H), 2.04-2.06 (m, 2H), 2.34-2.40 (m,2H), 2.69-2.75 (m, 1H), 3.11 (t, *J* 23.2 Hz, 2H), 3.83 (d, *J* 12.0 Hz, 2H), 4.91-4.98 (m, 1H), 6.78-6.79 (m, 1H), 7.18 (d, *J* 3.6 Hz, 1H), 7.24-7.31 (m, 2H), 7.68 (d, *J* 2.0 Hz, 1H), 7.75-7.77 (m, 2H), 8.01 (d, *J* 1.2 Hz, 1H); ^{13}C-NMR (101 MHz, DMSO-d_6): δ 145.56, 144.78, 144.12, 143.68, 134.05, 123.33, 122.74, 120.19, 113.93, 113.20, 112.55, 54.46, 46.08, 30.15, 26.15, 4.61; LC-MS, RT: 1.793 min, 98.37%, λmax: 254 nm, MS: *m/z* [M+1] 372.2; Anal. Calc. for $C_{19}H_{21}N_3O_3S$: C, 61.44; H, 5.70; N, 11.31; Found: C, 61.40; H, 5.65; N, 11.25%.

1-(1-((3,5-Dichlorophenyl)sulfonyl)piperidin-4-yl)-2-(furan-2-yl)-1*H*-benzo[*d*]imidazole (7l). 2-(Furan-2-yl)-1-(piperidin-4-yl)-1*H*-benzo[*d*]imidazole hydrochloride **6** (150 mg, 0.493 mmol) was added in THF (3 mL), trimethylamine (0.21 mL, 1.48 mmol) cool to 0 °C. 3,5-dichlorobenzenesulfonyl chloride (133.3 mg, 0.543 mmol) was dilute with THF (1 mL) added drop wise at 0 °C, stirred for 16 h at rt. Extracted with ethyl acetate (3 × 20 mL) and dried over anhydrous Na_2SO_4 and concentrated in vacuum. The crude product was purified by column chromatography on silica gel (eluent: 0-50% DCM/EtOAc) to afford the product 1-(1-((3,5-dichlorophenyl)sulfonyl)piperidin-4-yl)-2-(furan-2-yl)-1*H*-benzo[*d*]imidazole as an off white solid (0.120 g, 51.02%); mp 189-192 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.92-2.00 (m, 2H), 2.34-2.42 (m, 2H), 2.79-2.85 (m, 2H), 3.97-4.00 (d, *J* 12.0 Hz, 2H), 4.87 (t, *J* 24.4 Hz, 1H), 6.74 (t, *J* 4.8 Hz, 1H), 7.14 (d, *J* 3.2 Hz, 1H), 7.22-7.27 (m, 2H), 7.39-7.69 (m, 1H), 7.92 (d, *J* 1.6 Hz, 2H), 7.96 (d, *J* 1.2 Hz, 1H), 8.17 (s, 1H); ^{13}C-NMR (101 MHz, DMSO-d_6): δ 145.52, 144.58, 144.10, 143.65, 140.64, 136.09, 133.96, 133.38, 126.42, 123.12, 122.72, 120.23, 113.89, 112.81, 112.47, 53.75, 45.93, 29.44; LC-MS, RT: 2.271 min, 100%, λmax: 254 nm, MS: *m/z* [M+1] 478.0; Anal. Calc. for $C_{22}H_{19}Cl_2N_3O_3S$: C, 55.47; H, 4.02; N, 8.82; Found: C, 55.42; H, 3.97; N, 8.78%.

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Supplementary Material

Copies of ^{1}H NMR, ^{13}C NMR and LC-MS spectra of synthesized compounds are available in the Supplementary Material.

References

1. Heers, J.; Backx, L. J. J.; Mostmans, J. H.; Van Cutsem, J. *J. Med. Chem.* **1979**, *22*, 1003. https://doi.org/10.1021/jm00194a023
2. Hunkeler, W.; Mohler, H.; Pieri, L.; Polc, P.; Bonetti, E. P.; Cumin, R.; Schaffner, R.; Haefely, W. *Nature* **1981**, *290*, 514. https://doi.org/10.1038/290514a0

3. Brimblecombe, R. W.; Duncan, W. A. M.; Durant, G. J.; Emmett, J. C.; Ganellin, C. R.; Parsons, M. E. *J. Int. Med. Res*. **1975**, *3*, 86. https://doi.org/10.1177/030006057500300205
4. Tanigawara, Y.; Aoyama, N.; Kita, T.; Shirakawa, K.; Komada, F.; Kasuga, M.; Okumura, K. *Clin. Pharmacol Ther.* **1999**, *66*, 528. https://doi.org/10.1016/S0009-9236(99)70017-2
5. Wauquier, A.; Van Den Broeck, W. A. E.; Verheyen, J. L.; Janssen, P. A. J. *Eur. J. Pharmacol.* **1978**, *47*, 367. https://doi.org/10.1016/0014-2999(78)90117-6
6. Lee, J. C.; Laydon, J. T.; McDonnell, P. C.; Gallagher, T. F.; Kumer, S.; Green, D.; McNulty, D.; Blumenthal, M. J.; Keys, J. R.; Vatter, S. W. L.; Strickler, J. E.; McLaughlin, M. M.; Siemens, I. R.; Fisher, S. M.; Livi, G. P.; White, J. R.; Adams, J. L.; Young, P. R. *Nature* **1994**, *372*, 739. https://doi.org/10.1038/372739a0
7. De Laszlo, S. E.; Hacker, C.; Li, B.; Kim, D.; MacCoss, M.; Mantalo, N.; Pivnichnny, J. V.; Colwell, L.; Koch, G. E.; Cascieri, M. A.; Hagmenn, W. K. *Bioorg. Med. Chem. Lett*. **1999**, *9*, 641. https://doi.org/10.1016/S0960-894X(99)00081-5
8. Beaulieu, C.; Wang, Z.; Denis, D.; Greig, G.; Lamontagne, S.; O'Neill, G.; Slipetz, D.; Wang, J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3195. https://doi.org/10.1016/j.bmcl.2004.04.005
9. Schmierer, R.; Mildenberger, H.; Buerstell, H. German Patent 1987, 361464; *Chem. Abstr*. **1988**, *108*, 37838.
10. Heeres, J.; Backx, L. J. J.; Mostmans, J. H.; Van Custem, J. *J. Med. Chem*. **1979**, *22*, 1003. https://doi.org/10.1021/jm00194a023
11. Antolini, M.; Bozzoli, A.; Ghiron, C.; Kennedy, G.; Rossi, T.; Ursini, A. *Bioorg. Med. Chem. Lett*. **1999**, *9*, 1023. https://doi.org/10.1016/S0960-894X(99)00112-2
12. Wang, L.; Woods, K. W.; Li, Q.; Barr, K. J.; McCroskey, R. W.; Hannick, S. M.; Gherke, L.; Credo, R. B.; Hui, Y. H.; Marsh, K.; Warner, R.; Lee, J. Y.; Zielinsky-Mozong, N.; Frost, D.; Rosenberg, S. H.; Sham, H. L. *J. Med. Chem.* **2002**, *45*, 1697. https://doi.org/10.1021/jm010523x
13. Grassi, A.; Ippen, J.; Bruno, M.; Thomas, G.; Bay, P. *Eur. J. Pharmacol*. **1991,** *195*, 251-259. https://doi.org/10.1016/0014-2999(91)90543-Y
14. Ozkay, Y.; Tunali, Y.; Karaca, H.; Isikdag, I. *Eur. J. Med. Chem.* **2010**, *45*, 3293-3298. https://doi.org/10.1016/j.ejmech.2010.04.012
15. The American Society of Health-System Pharmacists. Retrieved Aug 18, 2015.
16. Spasov, A. A.; Yozhitsa, I. N.; Bugaeva, L. I.; Anisimova, V. A. *Pharm. Chem. J.* **1999**, *33*, 232. https://doi.org/10.1007/BF02510042
17. Rückle, T.; Biamonte, M.; Grippi-Vallotton, T.; Arkinstall, S.; Cambet, Y.; Camps, M.; Gotteland, J. P. *J. Med. Chem*. **2004**, *47*, 6921-6934. https://doi.org/10.1021/jm031112e
18. Wagner, E. C.; Millett, W. H. *Org. Synth.* **1943**, *2*, 65.
19. Grimmet, M. R.; Katritzky, A. R.; Rees, C. W. *Comprehensive Heterocyclic Chemistry*, Pergamon Press, Oxford, **1984**, *5*, 104-105.
20. Panda, S. S.; Malik, R.; Jain, S. C. *Curr.Org. Chem*. **2012**, *16*, 1905-1919. https://doi.org/10.2174/138527212802651232

21. Cee, V. J.; Downing, N. S. *Tetrahedron Lett*. **2006**, *47*, 3747-3750. https://doi.org/10.1016/j.tetlet.2006.03.112
22. Sluiter, J.; Christoffers, J. *Synlett* **2009**, *1*, 63-66.
23. Bastug, G.; Eviolitte, C.; Markó; I. E. *Org. Lett*. **2012**, *14*, 3502-3505. https://doi.org/10.1021/ol301472a
24. Yan, Y.; Zhong, Q. F.; Zhao, N.; Liu, G. *Mol. Divers*. **2012**, *16*, 157-162. https://doi.org/10.1007/s11030-011-9343-0
25. Saha, P.; Ramana, T.; Purkait, N.; Ali, M. A.; Paul, R.; Punniyamurthy, T. *J. Org. Chem.* **2009**, *74*, 8719-8725. https://doi.org/10.1021/jo901813g
26. Wray, B. C.; Stambuli, J. P. *Org. Lett*. **2010**, *12*, 4576-4579. https://doi.org/10.1021/ol101899q
27. Oda, S; Shimizu, H.; Aoyama, Y.; Ueki, T. ; Shimizu, S.; Osato, H.; Takeuchi, Y. *Org. Process Res. Dev*. **2012**, *16*, 96-101. https://doi.org/10.1021/op200251c
28. Yang, D.; Fokas, J.; Li, J.; Yu, L.; Baldino, C. M. *Synthesis* **2005**, *1*, 47-56. https://doi.org/10.1055/s-2004-834926
29. Kojima T, Mochizuki M, Takai T, Hoashi Y, Morimoto S, Seto M, Nakamura M, Kobayashi K, Sako Y, Tanaka M, Kanzaki N, Kosugi Y, Yano T, Aso K. *Bioorg Med Chem*. **2018**, May 15;*26*(9), 2229-2250 https://doi.org/10.1016/j.bmc.2018.01.020

