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Original article

Synthesis and antimicrobial evaluation of amide derivatives of benzodifuran-2-carboxylic acid

Jigar N. Soni, Shubhangi S. Soman*

Department of Chemistry, Faculty of Science, The M.S. University of Baroda, Vadodara 390002, India

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ABSTRACT

We have synthesized various amide derivatives of benzodifuran-2-carboxylic acid from resorcinol. Reaction of 7-hydroxy-4-methylcoumarin with chloroacetone in anhydrous K_2CO_3 and dry acetone gave ether derivative of 7-hydroxy-4-methylcoumarin **3** which on reaction with N-bromosuccinimide in chloroform gave corresponding 3-bromo derivative **4**. Cyclization of bromo derivative in 10% ethanolic KOH gave benzodifuran-2-carboxylic acid **5**. This acid was converted into acid chloride using oxalyl chloride and then substituted with different amines in presence of base, triethylamine to give amide derivatives of benzodifuran-2-carboxylic acid **6**. All compounds were screened for antimicrobial activity against two Gram positive bacteria *Staphylococus aureus* and *Bacillus subtilis*, two Gram negative bacteria *E. coli* and *P. aeruginosa* and one fungus *Candida albicans*.

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1. Introduction

The incidence of bacterial and fungal infections have increased significantly in the past 25 years. The evolution of antibacterial resistance in bacterial strains against the currently available antibacterial agents is an increasing concern in recent years. For instance Gram positive bacterial pathogens such as *Staphylococus aureus* (*S. aureus*) is resistant to Methicillin, *Streptococcus pneumoniae* and *Enterococci* are resistant to Penicillin and Vancomycin respectively [1] while Gram negative bacteria are resistant to β lactams, quinolones and macrolides [2]. Since *Candida albicans* (*C. albicans*) and *Aspergillus fumigatus* (*A. fumigatus*) are the main causative fungi of the systemic mycosis, antifungal drugs for treating patients of deep mycosis should have a broad antifungal spectrum including at least these microorganisms. Currently only four classes of antifungal drugs, polyene macrolides (amphotericin B), azoles (fluconazole, miconazole, itraconazole and voriconazole) flucytosine and candins (caspofungin acetate and micafungin) are available for treatment of systemic micosis. Unfortunately none of them is ideal in terms of efficacy, antifungal spectrum or safety. Although amphotericin B is efficacious against both candidiasis and aspergillosis, it shows severe renal toxicity. The antifungal spectra of fluconazole and flucytosine are narrow (mainly against *C. albicans*) and they are prone to develop drug resistance.

In order to overcome the threat of wide spread multi drug resistance in Gram positive and Gram negative bacterial strains as well as fungi, there is ongoing demand for new antimicrobial agents.

Furan and its derivatives show wide range of activity. Benzofurans having various amide, ester, ether and thioether derivatives with varying functional groups show antifungal activity [3–6]. 3-substituted benzofuran-2-amide derivatives are reported as cysteine protease inhibitors [7] and anti proliferative agents against lung cancer cell lines [8]. Benzofuran and benzothiophene derivatives substituted with amide effectively inhibits ischemic cell death and can be useful in many other diseases [9]. Various 2-substituted amide derivatives of benzofuran are reported as potent orexin receptor antagonist [10] and anti hyperlipidemic agents [11]. Various 2-substituted benzofuran amide derivatives and 2, 3-substituted benzofuran derivatives are reported to show good antimicrobial activity [12,13]. Ethyl ester derivatives of 4-hydroxy-3-methyl-6-phenylbenzofuran-2-carboxylic acid have been reported as antitumor agents [14]. Various 2-substituted vinyl ester derivatives of benzofuran and benzodifuran have been reported as angiogenesis inhibitors [15]. Benzofuran-2-biphenyl sulfonamide derivatives are useful in treatment of osteoarthritis [16]. Substituted benzofuran-1, 3-diazepin derivatives are reported to show CNS depressant effect [17].

Literature survey reveals that various benzofuran amide derivatives show antimicrobial as well as CNS activities, while little work is reported on benzodifuran derivatives. In continuation of our work on search for antimicrobial agents [18,19] we report

* Corresponding author. Tel.: +91 265 2795552.
E-mail address: shubhangiss@rediffmail.com (S.S. Soman).

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herein synthesis and antimicrobial evaluation of series of amide derivatives of benzodifuran carboxylic acid.

2. Result and discussion

2.1. Chemistry

Pechmann reaction of resorcinol with ethyl acetoacetate in presence of sulfuric acid gave 7-hydroxy-4-methyl-coumarin [20] **2** which was condensed [21] with chloroacetone in presence of anhydrous K_2CO_3 and dry acetone gave 4-methyl-7-(2-oxopropoxy)-coumarin **3**. Bromination [22] of **3** using N-bromo-succinimide in dry chloroform gave unexpected product 3-bromo-4-methyl-7-(2-oxopropoxy)-coumarin **4**. Cyclization [21] of **4** in 10% alkaline ethanol gave 3,5-dimethylbenzo[1,2-b:5,4-b′]difuran-2-carboxylic acid **5** as major product. Acid **5** was converted into acid chloride using oxalyl chloride and DMF in dry dichloromethane which on substitution reaction with different amines in dry dichloromethane in presence of base triethylamine gave corresponding amides as shown in Scheme 1.

All the compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR, Elemental analyses and Mass spectra. IR spectrum of **3** exhibited bands at 1710 and 1736 cm^{-1} for ketone carbonyl and lactone group respectively. In ^{1}H NMR of **3** doublet at δ 2.32 and triplet at δ 2.42 for three protons each confirmed the presence of CH_3 group at C-4 and $COCH_3$ group. Singlet at δ 4.66 for two protons indicated CH_2 group and doublet at δ 6.17 for one proton at C-3 confirmed the formation of **3**. After bromination, in ^{1}H NMR of **4**, the disappearance of peak at δ 6.17 indicated the presence of Br at C-3 which was further confirmed by its mass spectrum which showed M^+ and $[M + 2]^+$ peaks at *m/z* 310 and 312 of equal intensity.

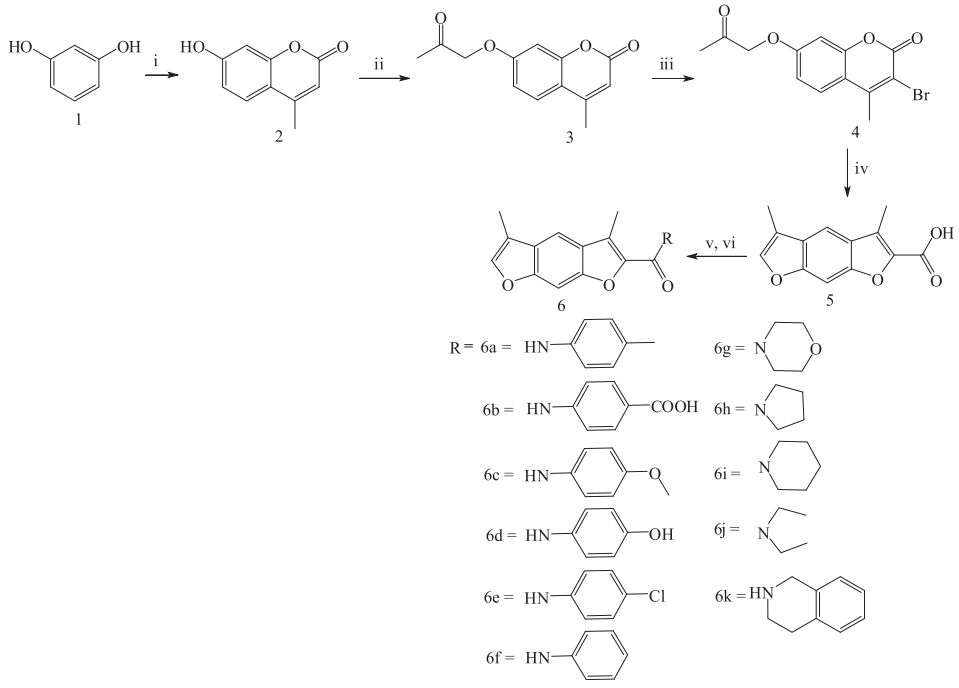
In IR spectrum of **5**, the bands at 3428 and 1680 cm^{-1} indicated presence of COOH group which was further confirmed by solubility of **5** in saturated $NaHCO_3$ solution and reprecipitation of it by HCl. In the ^{1}H NMR spectrum of **5**, the doublet at δ 2.27 (J = 1.6 Hz) and singlet at δ 2.60 for three protons each indicated presence of CH_3 group at C-5 and C-3 respectively. The doublet at δ 7.82 for one proton with J = 1.6 Hz indicated proton at C-6 and two singlets at δ 7.84 and 7.92 for one proton each confirmed the linear ring fusion. In mass spectrum of **5**, the peak at *m/z* at 231 indicated $[M + 1]^+$ peak thus confirmed the formation of **5**. Various amide derivatives of benzodifuran carboxylic acid **6** were prepared by converting acid **5** into corresponding acid chloride by using oxalyl chloride and then substituting it with various amines in presence of base like triethylamine. The amides **6** now insoluble in $NaHCO_3$ indicated the formation of **6** which was further confirmed by their IR, ^{1}H NMR, ^{13}C NMR, mass spectra and elemental analyses.

2.2. Biological evaluation

All the synthesized compounds were screened by Broth dilution method [23] for their antibacterial activity against two Gram positive bacteria *S. Aureus* and *B. Subtilis*, two Gram negative bacteria *E. coli* and *P. Aeruginosa*. They were also evaluated for their *in vitro* antifungal activity against *C. Albicans*. Concentration of compounds was ranging from 40 μg to 600 μg. The lowest concentrations of the compounds that prevented visible growth are given in Table 1. It was determined that the solvent had no antibacterial or antifungal activities against any of the test microorganisms. Ciprofloxacin and Flucanazole were used as standard drugs also tested under the similar conditions for comparison. The results are summarized in Table 1.

The minimum inhibitory concentration (MIC) of the synthesized compounds against highly inhibited organisms is reported in Table 1. Compounds **6c**, **6h** and **6j** showed moderate effects against Gram positive bacteria *S. aureus* while compound **6a**, **6b**, **6d**, **6e**, **6g** and **6k** showed moderate activity against Gram positive bacteria *B. subtilis*. Only compound **6e** showed moderate activity against Gram negative bacteria *E. coli* while all these compounds found less active against *P. aeruginosa* (MIC 600 μg/ml).

It was observed that methyl or methoxy group at p- position of amine showed moderate activity while pyrrolidine ring also showed moderate activity against Gram positive bacteria *S. aureus*,



Scheme 1. Condition: (i) ethyl acetoacetate, H_2SO_4, 12 h (ii) chloroacetone, K_2CO_3, dry acetone, 6h (iii) N-bromosuccinimide, chloroform, 6 h (iv) 10% KOH in ethanol, 3 h (v) dichloromethane, DMF, oxalyl chloride, 4 h (vi) dichloromethane, triethylamine, various amines, 12 h.

Table 1
MIC determination of antibacterial and antifungal agent (μg).

Sr. no.	MIC (μg)				
	S. aureus	*B. subtilis*	*E. coli*	*P. aeruginosa*	*C. albicans*
	(gm +ve bacteria)		(gm −ve bacteria)		(Fungi)
6a	200	200	≥600	≥600	≥600
6b	600	160	400	600	600
6c	160	400	≥600	≥600	≥600
6d	600	200	600	≥600	≥600
6e	400	200	200	≥600	≥600
6f	600	400	600	600	600
6g	400	200	600	≥600	≥600
6h	160	400	400	≥600	600
6i	400	200	600	≥600	≥600
6j	160	400	400	600	600
6k	400	160	≥600	≥600	600
Ciprofloxacin	5	2	15	7.5	–
Flucanazole	–	–	–	–	5

while all other amines except **6c**, **6f**, **6h** and **6k** when used showed moderate activity against Gram positive bacteria *B. subtilis*.

All these amide derivatives of benzodifuran carboxylic acid showed high MIC values (600 μg/ml) against Gram negative bacteria *E. coli* and *P. aeruginosa*, as well as fungus *C. albicans*.

3. Conclusion

In conclusion, eleven benzodifuran amides were synthesized and screened for their antimicrobial activity as well as their MIC against all test organisms. The presence of electron withdrawing group at para position of amine showed moderate activity against Gram positive bacteria *B. subtilis* (**6b**, **6d**, **6e** and **6g**) while presence of electron releasing group at para position of amine showed moderate activity against *S. aureus*. All the synthesized amide derivatives of benzodifuran carboxylic acid showed higher MIC values (600 μg/ml) against Gram negative bacteria *P. aeruginosa*, and fungus *C. albicans*. These compounds can also be explored for orexin receptor antagonist activity.

4. Experimental

4.1. Chemistry

Reagent grade chemicals and solvents were purchased from commercial supplier and used without purification. TLC was performed on silica gel F254 plates (Merck). Silica gel (100–200 mesh) was used for column chromatographic purification. Melting points are uncorrected and were measured in open capillary tubes, using a Rolex melting point apparatus. IR spectra were recorded as KBr pellets on Perkin Elmer RX 1 spectrometer. ^{1}H NMR and ^{13}C NMR spectral data were recorded on Advance Bruker 400 spectrometer (400 MHz) with $CDCl_3$ or DMSO-d_6 as solvent and TMS as internal standard. *J* values are in Hz. Elemental analyses were recorded on Thermosinnigan Flash 11-12 series EA. Mass spectra were determined by ESI/MS, using a Shimadzu LCMS 2020 apparatus.

4.1.1. 7-Hydroxy-4-methyl-2H-chromen-2-one ***2***

Compound **1** (10 g, 0.0908 mol) was dissolved in ethyl acetoacetate (12 ml, 0.095 mol) with constant shaking in reaction flask. Concentrated sulfuric acid (20 ml) was added in 3–4 portions and reaction mixture was kept overnight at room temperature. Reaction mass poured into crushed ice to obtain pale yellow colored solid which was filtered, dried and recrystallized using ethanol gave yellow crystalline product (11.81 g, 74%); mp: 190–193 °C (Lit. 185 °C [20]).

4.1.2. 4-Methyl-7-(2-oxopropoxy)-2H-chromen-2-one ***3***

To the solution of **2** (5 g, 0.0289 mol) in dry acetone (50 ml) and anhydrous potassium carbonate (13.98 g, 0.1011 mol), chloroacetone (2.54 ml, 0.0318 mol) was added very slowly. Reaction mixture refluxed for 6 h in water bath. Reaction mass poured into crushed ice to obtain brown solid product, which was filtered, dried and crystallized using ethanol to afford light brown solid (3.22 g, 49%); mp: 155–158 °C (Lit. 157 °C [21]); IR (KBr): 1736 (lactone), 1710 (>C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.32 (3H, d, $J = 2.4$ Hz, CH_3), 2.42 (3H, t, $J = 1.2$, 2 Hz, CH_3), 4.66 (2H, s, CH_2), 6.17 (1H, d, $J = 1.2$ Hz, ArH), 6.77 (1H, t, $J = 2.8$, 4 Hz, ArH), 6.90 (1H, dd, $J = 2.4$, 8.8 Hz, ArH), 7.54 (1H, t, $J = 3.2$, 5.6 Hz, ArH); ^{13}C NMR (400 MHz, $CDCl_3$): δ 18.7, 26.6, 72.9, 101.8, 112.3, 112.5, 114.4, 125.9, 152.4, 155.1, 160.5, 161.0, 203.7; MS *m/z* 177.0 $[M + 1-70]^+$ and 175 $[M - 1-70]^+$.

4.1.3. 3-Bromo-4-methyl-7-(2-oxopropoxy)-2H-chromen-2-one ***4***

Compound **3** (5 g, 0.0216 mol) dissolved in chloroform (50 ml) and N-bromosuccinimide (4.24 g, 0.0238 mol) added in the reaction flask. Reaction mixture refluxed for 6 h in water bath. Excess solvent distilled under reduced pressure to obtain solid which was washed with hot water thrice, filtered, dried and crystallized using glacial acetic acid to obtain pale yellow solid (4.21 g, 63%); mp: 189–193 °C; IR (KBr): 1710 (>C=O), 1681 (lactone) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.33 (3H, s, CH_3), 2.62 (3H, s, CH_3), 4.67 (2H, s, CH_2), 6.78 (1H, s, ArH), 6.94 (1H, d, $J = 8.8$ Hz, ArH), 7.61 (1H, d, $J = 8.8$ Hz, ArH); ^{13}C NMR (400 MHz, DMSO-d_6): δ 19.8, 26.6, 72.8, 101.7, 109.1, 113.5, 113.6, 127.6, 152.3, 153.4, 156.9, 161.5, 203.5; MS *m/z* 311 $[M]^+$, 312.9 $[M + 2]^+$ and 310.7 $[M - 1]^+$.

4.1.4. 3,5-Dimethylbenzo[1,2-b:5,4-b′]difuran-2-carboxylic acid ***5***

Compound **4** (5 g, 0.0161 mol) was dissolved in 50 ml 10% ethanolic potassium hydroxide solution and refluxed for 3 h in water bath. Excess ethanol distilled under reduced pressure and reaction mixture poured into crushed ice, concentrated hydrochloric acid was slowly added until pH 2. The solid obtained was filtered, dissolved in saturated solution of sodium bicarbonate, filtered and reprecipitated with concentrated HCl. Then it was filtered and dried. The crude product was purified using column chromatography by using pet. ether:ethyl acetate (7:3) as eluent gave light brown solid (1.55 g, 42%); mp: 260–264 °C; IR (KBr): 3428 (OH), 3091, 3061, 2925, 2863, 2828 (CH_3, CH), 1680 (>C=O) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.27 (3H, d, $J = 1.2$ Hz, CH_3), 2.59 (3H, s, CH_3), 7.82 (1H, d, $J = 1.6$ Hz, ArH), 7.84 (s, 1H, ArH), 7.92 (1H, s, ArH); ^{13}C NMR (400 MHz, DMSO-d_6): δ 8.1, 9.7, 94.9, 111.2, 115.6, 125.2, 125.8, 126.9, 141.8, 155.4, 161.5; MS *m/z* 231.0 $[M + 1]^+$ and 228.9 $[M - 1]^+$.

4.1.5. General procedure for ***6***

Compound **5** (0.5 g, 0.0022 mol) dissolved in dichloromethane (25 ml) and 3-4 drops of DMF slowly added in reaction flask. Oxalyl chloride (0.75 ml, 0.0088 mol) was added slowly in the reaction mixture and stirred at room temperature for 3 h. Solvent distilled under reduced pressure and dried under high vacuum to remove oxalyl chloride. Reaction mass was dissolved in dichloromethane (30 ml) and amine (1.1 eq.) along with catalytic amount of triethylamine (0.64 ml, 0.0046 mol) were added and allowed to stir at room temperature for overnight. Reaction mixture was washed with saturated sodium bicarbonate (20 ml) and then with 10% concentrated hydrochloride solution (20 ml). Solvent passed through Na_2SO_4 and removed under reduced pressure to give solid. Crude solid product was purified using column chromatography by using Pet. Ether:Ethyl acetate (9:1) as eluent.

4.1.5.1. 3,5-Dimethyl-N-(p-tolyl)benzo[1,2-b:5,4-b′]difuran-2-carboxamide ***6a***. This compound obtained as white solid (0.24 g, 35%); mp: 192–194 °C; IR (KBr): 3421 (NH), 3133, 3032, 2956, 2924 (CH_3, CH), 1670 (>C═O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.34 (3H, d, $J = 1.6$ Hz, CH_3), 2.37 (3H, s, CH_3), 2.77 (3H, s, CH_3), 7.23 (2H, d, $J = 8$ Hz, ArH), 7.48 (1H, d, $J = 1.2$ Hz, ArH), 7.58 (1H, d, $J = 0.4$ Hz, ArH), 7.63 (2H, d, $J = 8.4$ Hz, ArH), 7.68 (1H, s, ArH), 8.34 (1H, s, NH); ^{13}C NMR (400 MHz, $CDCl_3$): δ 8.0, 9.2, 20.9, 94.4, 110.0, 115.5, 119.9, 123.7, 126.4, 126.8, 129.6, 134.1, 135.0, 142.3, 142.6, 151.7, 155.4, 158.0; Ele. Ana. for $C_{20}H_{17}NO_3$ % Cal. C, 75.22; H, 5.37; N, 4.39, Found C, 75.43; H, 5.28; N, 4.27; MS *m/z* 320.0 $[M + 1]^+$.

4.1.5.2. 4-(3,5-Dimethylbenzo[1,2-b:5,4-b′]difuran-2-carboxamido) benzoic acid ***6b***. This compound obtained as yellow solid (0.08 g, 9%); mp: > 300 °C; IR (KBr): 3676 (OH), 1694 (>C═O), 1684 (>C═O) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.28 (3H, s, CH_3), 2.66 (3H, s, CH_3), 7.83 (2H, t, $J = 1.2$, 2.8 Hz, ArH), 7.92–7.99 (5H, m, ArH), 10.69 (1H, s, COOH); ^{13}C NMR (400 MHz, DMSO-d_6): δ 8.1, 9.6, 95.0, 111.1, 115.7, 120.2, 123.9, 126.1, 126.2, 127.0, 130.6, 143.0, 143.1, 143.5, 151.7, 155.2, 158.6, 167.4; Ele. Ana. for $C_{20}H_{15}NO_5$ % Cal. C, 68.76; H, 4.33; N, 4.01, Found C, 68.43; H, 4.33; N, 3.69; MS *m/z* 252.9 $[M + 1–98]^+$.

4.1.5.3. N-(4-methoxyphenyl)-3,5-dimethylbenzo[1,2-b:5,4-b′]difuran-2-carboxamide ***6c***. This compound obtained as light brown solid (0.31 g, 43%); mp: 178–180 °C; IR (KBr): 3419 (NH), 1671 (>C═O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.33 (3H, d, $J = 1.2$ Hz, CH_3), 2.76 (3H, s, CH_3), 3.84 (3H, s, $-OCH_3$), 6.95 (2H, dd, $J = 2$, 6.8 Hz ArH), 7.48 (1H, d, $J = 1.2$ Hz, ArH), 7.57 (1H, d, $J = 0.4$ Hz, ArH), 7.64 (1H, d, $J = 2.4$ Hz, ArH), 7.65 (1H, d, $J = 2$ Hz, ArH), 6.67 (1H, s, ArH), 8.30 (1H, s, NH); ^{13}C NMR (400 MHz, $CDCl_3$): δ 8.1, 9.2, 55.5, 94.4, 109.9, 114.2, 115.5, 121.7, 123.5, 126.4, 126.8, 130.6, 142.2, 142.7, 151.7, 155.4, 156.5, 158.0; Ele. Ana. for $C_{20}H_{17}NO_4$ % Cal. C, 71.63; H, 5.11; N, 4.18, Found C, 71.40; H, 5.04; N, 4.04; MS *m/z* 336.0 $[M + 1]^+$.

4.1.5.4. N-(4-hydroxyphenyl)-3,5-dimethylbenzo[1,2-b:5,4-b′]difuran-2-carboxamide ***6d***. This compound obtained as yellowish solid (0.27 g, 39%); mp: 244–246 °C; IR (KBr): 3418 (NH), 3372 (OH), 1644 (>C═O) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.28 (3H, d, $J = 1.2$ Hz, CH_3), 2.63 (3H, s, CH_3), 6.74 (2H, dd, $J = 2.4$, 6.8 Hz, ArH), 7.58 (2H, dd, $J = 2$, 6.8 Hz, ArH), 7.82 (2H, dd, $J = 0.4$, 1.6 Hz, ArH), 7.91 (1H, s, ArH), 9.38 (1H, s, NH), 10.19 (1H, s, OH); ^{13}C NMR (400 MHz, DMSO-d_6): δ 8.2, 9.5, 94.9, 110.8, 115.4, 115.7, 122.3, 122.9, 126.4, 126.8, 130.3, 143.4, 143.7, 151.6, 154.3, 155.0, 158.0; Ele. Ana. for $C_{19}H_{15}NO_4$ % Cal. C, 71.02; H, 4.71; N, 4.36, Found C, 71.19; H, 4.69; N, 4.00; MS *m/z* 322.0 $[M + 1]^+$ and 319.8 $[M-1]^+$.

4.1.5.5. N-(4-chlorophenyl)-3,5-dimethylbenzo[1,2-b:5,4-b′]difuran-2-carboxamide ***6e***. This compound obtained as yellowish solid (0.38 g, 51%); mp: 190–192 °C; IR (KBr): 3389 (NH), 1684 (>C═O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.34 (3H, d, $J = 1.2$ Hz, CH_3), 2.76 (3H, s, CH_3), 7.37 (2H, dd, $J = 2$, 6.8 Hz, ArH), 7.49 (1H, d, $J = 1.2$ Hz, ArH), 7.58 (1H, d, $J = 0.8$ Hz, ArH), 7.69–7.72 (3H, m, ArH), 8.38 (1H, s, NH); ^{13}C NMR (400 MHz, $CDCl_3$): δ 8.0, 9.3, 94.4, 110.1, 115.6, 121.1, 124.3, 126.2, 127.0, 129.1, 129.4, 136.1, 142.3, 142.4, 151.7, 155.6, 158.0; Ele. Ana. for $C_{19}H_{14}ClNO_3$ % Cal. C, 67.16; H, 4.15; N, 4.12, Found C, 66.89; H, 4.33; N, 3.98; MS *m/z* 340.0 $[M + 1]^+$ and 337.8 $[M - 2]^+$.

4.1.5.6. 3,5-Dimethyl-N-phenylbenzo[1,2-b:5,4-b′difuran-2-carboxamide ***6f***. This compound obtained as white solid (0.28 g, 42%); mp: 182–184 °C; IR (KBr): 3421 (NH), 1669 (>C═O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.34 (3H, d, $J = 1.6$ Hz, CH_3), 2.77 (3H, s, CH_3), 7.17–7.20 (1H, m, ArH), 7.41 (2H, m, ArH), 7.48 (1H, d, $J = 1.6$ Hz, ArH), 7.59 (1H, d, $J = 0.4$ Hz, ArH), 7.69 (1H, s, ArH), 7.75 (2H, dd, $J = 0.4$, 1.2 Hz, ArH), 8.39 (1H, s, NH); ^{13}C NMR (400 MHz, $CDCl_3$): δ 8.1, 9.3, 94.4, 110.0, 115.6, 119.9, 124.0, 124.5, 126.3, 126.9, 129.1, 137.5, 142.3, 142.5, 151.7, 155.5, 158.1; Ele. Ana. for $C_{19}H_{15}NO_3$ % Cal. C, 74.74; H, 4.95; N, 4.59, Found C, 74.84; H, 5.15; N, 4.65; MS *m/z* 306.0 $[M + 1]^+$.

4.1.5.7. (3,5-Dimethylbenzo[1,2-b:5,4-b′]difuran-2-yl)(morpholino) methanone ***6g***. This compound obtained as white solid (0.26 g, 40%); mp: 136–140 °C; IR (KBr): 3059, 2955, 2917, 2859 (CH_3, CH_2, CH), 1623 (>C═O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.32 (3H, d, $J = 1.2$ Hz, CH_3), 2.56 (3H, s, CH_3), 3.83 (8H, s, CH_2), 7.46 (1H, d, $J = 1.2$ Hz, ArH), 7.53 (1H, d, $J = 0.4$ Hz, ArH), 7.63 (1H, s, ArH); ^{13}C NMR (400 MHz, $CDCl_3$): δ 8.1, 9.3, 67.1, 94.4, 109.4, 115.5, 122.2, 125.6, 126.6, 142.1, 143.7, 151.9, 155.0, 161.0; Ele. Ana. for $C_{17}H_{17}NO_4$ % Cal. C, 68.21; H, 5.72; N, 4.68, Found C, 68.54; H, 5.67; N, 4.85; MS *m/z* 300.0 $[M + 1]^+$.

4.1.5.8. (3,5-Dimethylbenzo[1,2-b:5,4-b′]difuran-2-yl)(pyrrolidin-1-yl)methanone ***6h***. This compound obtained as yellowish solid (0.235 g, 38%); mp: 108–110 °C; IR (KBr): 3097, 2961, 2919, 2887 (CH_3, CH_2, CH), 1617 (>C═O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.99 (4H, s, CH_2), 2.32 (3H, d, $J = 1.2$ Hz, CH_3), 2.66 (3H, s, CH_3), 3.85 (4H, t, CH_2), 7.45 (1H, d, $J = 1.2$ Hz, ArH), 7.51 (1H, d, $J = 0.4$ Hz, ArH), 7.64 (1H, s, ArH); ^{13}C NMR (400 MHz, $CDCl_3$): δ 8.1, 9.5, 23.8, 26.6, 46.9, 48.0, 94.2, 109.4, 115.5, 122.4, 125.8, 126.4, 142.0, 151.9, 155.0; Ele. Ana. for $C_{17}H_{17}NO_3$ % Cal. C, 72.07; H, 6.05; N, 4.94, Found C, 71.89; H, 6.03; N, 5.14; MS *m/z* 284.0 $[M + 1]^+$.

4.1.5.9. (3,5-Dimethylbenzo[1,2-b:5,4-b′]difuran-2-yl)(piperidin-1-yl)methanone ***6i***. This compound obtained as yellowish solid (0.215 g, 33%); mp: 110–112 °C; IR (KBr): 3106, 2942, 2857 (CH_3, CH_2, CH), 1635 (>C═O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.71 (6H, t, CH_2), 2.32 (3H, d, $J = 1.2$ Hz, CH_3), 2.51 (3H, s, CH_3), 3.69 (4H, m, CH_2), 7.45 (1H, d, $J = 1.6$ Hz, ArH), 7.53 (1H, d, $J = 0.4$ Hz, ArH), 7.60 (1H, s, ArH); ^{13}C NMR (400 MHz, $CDCl_3$): δ 8.1, 9.1, 24.7, 94.4, 109.1, 115.4, 120.0, 125.7, 126.4, 142.0, 144.7, 152.0, 154.7, 161.0; Ele. Ana. for $C_{18}H_{19}NO_3$ % Cal. C, 72.71; H, 6.44; N, 4.71, Found C, 72.44; H, 6.29; N, 5.02; MS *m/z* 298.0 $[M + 1]^+$.

4.1.5.10. N,N-Diethyl-3,5-dimethylbenzo[1,2-b:5,4-b′]difuran-2-carboxamide ***6j***. This compound obtained as brown viscous liquid (0.318 g, 51%); IR (Neat): 3108, 3062, 2973, 2932 (CH_3, CH_2, CH), 1627 (>C═O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.30 (6H, t, $J = 7.2$ Hz, CH_3), 2.33 (3H, d, $J = 1.2$ Hz, CH_3), 2.54 (3H, s, CH_3), 3.56 (4H, q, CH_2), 7.45 (1H, d, $J = 1.2$ Hz, ArH), 7.52 (1H, d, $J = 0.4$ Hz, ArH), 7.61 (1H, d, $J = 0.8$ Hz, ArH); ^{13}C NMR (400 MHz, $CDCl_3$): δ 8.1, 9.2, 94.3, 109.1, 115.5, 120.6, 125.8, 126.4, 141.9, 145.0, 151.8, 154.8, 161.6; MS *m/z* 286.0 $[M + 1]^+$.

4.1.5.11. (3,4-Dihydroisoquinolin-2(1H)-yl)(3,5-dimethylbenzo[1,2-b:5,4-b′]difuran-2-yl)methanone ***6k***. This compound obtained as yellowish solid (0.235 g, 31%); mp: 96–98 °C; IR (KBr): 3063, 3023, 2921, 2854 (CH_3, CH_2, CH), 1628 (>C═O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.33 (3H, d, $J = 1.6$ Hz, CH_3), 2.55 (3H, d, CH_3), 3.06 (2H, S, CH_2), 3.98 (2H, d, CH_2), 4.91 (2H, d, CH_2), 7.22 (4H, d, $J = 3.6$ Hz, ArH), 7.47 (1H, d, $J = 1.6$ Hz, ArH), 7.56 (1H, s, ArH), 7.64 (1H, s, ArH); ^{13}C NMR (400 MHz, $CDCl_3$): δ 8.1, 9.3, 94.5, 109.3, 115.5, 121.7, 125.7, 126.5, 126.7, 142.1, 144.3, 152.0, 154.9; Ele. Ana. for $C_{22}H_{19}NO_3$ % Cal. C, 76.50; H, 5.54; N, 4.06, Found C, 76.37; H, 5.61; N, 4.20; MS *m/z* 346.0 $[M + 1]^+$.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2014.01.026. These data include MOL files and InChIKeys of the most important compounds described in this article.

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