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Microwave-assisted parallel synthesis of benzofuran-2-carboxamide derivatives bearing anti-inflammatory, analgesic and antipyretic agents

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ABSTRACT

A series of benzofuran-2-carboxamides of biological and medicinal significance were synthesized by a microwave-assisted one-pot parallel approach *via O*-alkylation/Knoevenagel condensation. All the compounds were characterized and assayed for their in *vivo* anti-inflammatory, analgesic and antipyretic activities. The activity data of all compounds were listed and discussed in detail, among which some derivatives exhibited potent activities of particular interest.

The amide bond exists widely in both natural and synthetic compounds. It is a core structure in pharmaceutical chemistry, being present in 25% of all synthetic drugs[1]. Partially, benzofuran-2-carboxamide derivatives are now known to possess extensive biological and medicinal activities such as anti-cancer,[2-4] anti-depression,[5,6] antimicrobial,[7] anti-hyperlipidemic,[8,9] nAChR agonist,[10,11] PtS inhibitor,[12] virus cell entry inhibitor,[13] Cathepsin K inhibitor[14] and MMP-13 inhibitor[15] activities. Even though, many synthetic approaches are reported to make these moieties, still there is a demand for new methods. Thus, the use of combinatorial approaches to the high-throughput synthesis of this drug-like scaffold would be a powerful advance in helping to speed up drug discovery.

On the other hand, microwave-assisted synthesis has become increasingly popular within the drug discovery due to their advantages of speed and convenience.[16-19] Comparing with the classic thermal transmission, microwave heating can effectively increase the rate of heating and chemical reaction. Furthermore, dedicated commercial microwave reactors have been developed for microwave-assisted parallel and combinatorial chemistry. A series of compounds can be prepared, sequentially in an automated single-mode instrument or in a parallel multimode instrument with multiple reactions.

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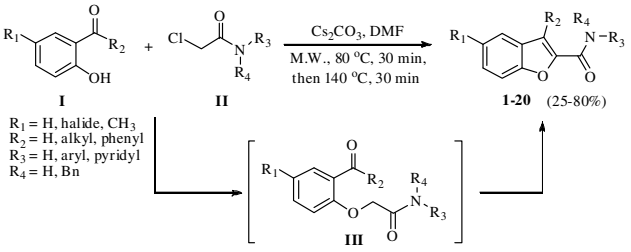
Thus, using computer managed automatic microwave technology, synthesis of compound libraries for lead compounds including their screening and optimization can be achieved within very short span of time that required by classical thermal methods. In continuation to our previous efforts towards microwave assisted transformations,[20,21] we herein present a novel one-pot parallel approach via *O*-alkylation/Knoevenagel–condensation sequence under microwave conditions to obtain the library of benzofuran-2-carboxamide derivatives and their anti-inflammatory, analgesic and antipyretic activities in detail.



Scheme 1. Microwave assisted benzofuran-2-carboxamides in one hour

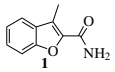
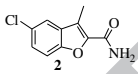
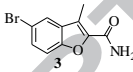
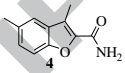
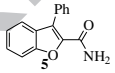
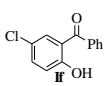
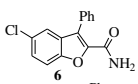
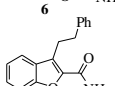
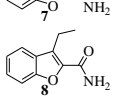
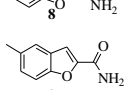
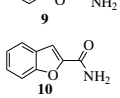
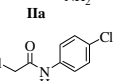
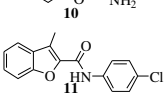
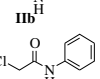
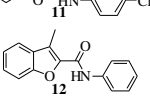
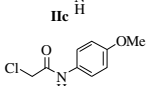
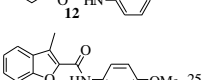
Generally, the carboxamide bond formation is typically mediated between carboxylic acid and amine by one of a myriad of coupling reagents, such as EDCI, DCC and CDI. However, the lack of diversity of commercial benzofuran-2-carboxylic acid brings a challenge to construct benzofuran-2-carboxamide library, because synthesis of these acid compounds must undergo a three-step two-pot or three-pot procedure that is time-consuming with low efficiency.[22,23] Our sequential studies on

Smiles rearrangement[24] for the synthesis of *N*-substituted anilines turned out to be a Knoevenagel condensation with 2-acylphenols within an hour. This encouraged us to avoid difficulties mentioned above and to achieve efficient synthesis of benzofuran-2-carboxamide library. Thus, we've designed a novel microwave-assisted one-pot *O*-alkyalation/Knoevenagel-condensation reaction sequence. Preliminarily, 2-chloroacetyl amides were prepared by simple acetylation of amines with 2-chloroacetyl chloride. Thereafter, the reaction between these amides and 2-acyl/formyl phenols afforded corresponding benzofuran-2-carboxamide under microwave irradiation in two-step one-pot manner involving *O*-alkylation of phenols followed by Knoevenagel type condensation as shown in Scheme 1.

As a model reaction, we first examined the reaction of 1-(5-bromo-2-hydroxyphenyl)ethanone (1 equiv.) with 2-chloroacetamide (1.2 equiv.) in DMF in the presence of different bases (2.5 equiv.). The reaction mixture was irradiated by microwave at 80 °C for 30 min followed at 145 °C for 30 min. After removing the solvent under reduced pressure, the residue was directly adsorbed on silica gel and purified by flash column chromatography (CombiFlash automatic, Teledyne, Inc.). Among all the bases used, Cs_2CO_3 (45% yield) found to be better than K_2CO_3 (35% yield) or Na_2CO_3 (30% yield). By changing the solvent from DMF to CH_3CN or addition of KI as catalyst along with all the above bases lead to drastic decrease in yields. Now, with the optimal reaction conditions in hand, the scope of microwave-assisted one-pot synthesis between 2-acyl phenols and 2-chloroacetyl amines was explored through a parallel approach and the yields of products (**1**-**20**) have been presented in Table 1.[25] The structures of all synthesized benzofuran-2-carboxamide derivatives were confirmed by NMR and HRMS analysis where the known compounds (**1, 3-5** and **8**[26a], **9**[26a,b], **6**[26c], **10**[26d,e] and **12**[26f]) are matched with the reported data. In addition, this method is faster and exploits the use of microwave over conventional heating processes which take more than 7 h for Knoevenagel condensation.[26e]

The two protons of NH_2 of *N*-unsubstituted benzofuran-2-carboxamide derivatives (**1**-**10**) showed separate signals in the ^{1}H NMR. For example, ^{1}H NMR of compound **9** showed two protons of NH_2 exhibited different peaks. Only one chemical shift for amino proton was observed in ^{1}H NMR of *N*-monosubstituted benzofuran-2-carboxamides (**11-19**). The products with low yields can be accounted by functional groups present either in amides or phenols, which affect the transformation. Even though, there is no big difference in the yields from all phenols, the ones with an electron withdrawing aryl group (**2**, **3** & **6**) or an aldehyde at acyl subunit (**9** and **10**) gave comparatively low yields. A substitution on the nitrogen of chloroacetamides also made considerable decrease in the yields to obtain adducts. Aryl amides with electron withdrawing group on aryl group (**11** and **16**) gave moderate yields. The aryl amides with electron donating group (**13**, **17**, **18** and **19**) ended up with comparatively low yields may be due to mesomeric effects, which decreases the stability of carbanion in Knoevenagel condensation. A dibenzyl substituted chloroacetamide gave the corresponding product in good yields. The advantages over other synthetic methods involve short reaction periods, parallel synthesis, and moderate to good yields. After characterization, all the benzofuran-2-carboxamide derivatives were evaluated for their anti-inflammatory, analgesic and anti-pyretic activities at 50 mg/kg p.o.

Table 1. Benzofuran-2-carboxamides from orthoacetylphenols and 2-chloroacetamides.

Entry	2-Acyl/formylphenol	Chloroacetamide	Conditions[a]	Product	Yield (%)[b]
1	 **Ia**	 **IIa**	2.5 equiv of Cs_2CO_3 in DMF	 **1**	75
2	 **Ib**	 **IIa**	2.5 equiv of Cs_2CO_3 in DMF	 **2**	49
3	 **Ic**	 **IIa**	2.5 equiv of Cs_2CO_3 in DMF	 **3**	45
4	 **Id**	 **IIa**	2.5 equiv of Cs_2CO_3 in DMF	 **4**	59
5	 **Ie**	 **IIa**	2.5 equiv of Cs_2CO_3 in DMF	 **5**	50
6	 **If**	 **IIa**	2.5 equiv of Cs_2CO_3 in DMF	 **6**	74
7	 **Ig**	 **IIa**	2.5 equiv of Cs_2CO_3 in DMF	 **7**	70
8	 **Ih**	 **IIa**	2.5 equiv of Cs_2CO_3 in DMF	 **8**	76
9	 **Ii**	 **IIa**	2.5 equiv of Cs_2CO_3 in DMF	 **9**	50
10	 **Ij**	 **IIa**	2.5 equiv of Cs_2CO_3 in DMF	 **10**	43
11	 **Ia**	 **IIb**	2.5 equiv of Cs_2CO_3 in DMF	 **11**	57
12	 **Ia**	 **IIc**	2.5 equiv of Cs_2CO_3 in DMF	 **12**	55
13	 **Ia**	 **IIc**	2.5 equiv of Cs_2CO_3 in DMF	 **13**	25
14	 **Ia**	**IId**	2.5 equiv of Cs_2CO_3 in DMF	**14**	47
15	**Ia**	**IIe**	2.5 equiv of Cs_2CO_3 in DMF	**15**	53
16	**Ig**	**IIc**	2.5 equiv of Cs_2CO_3 in DMF	**16**	43
17	**Ia**	**IIf**	2.5 equiv of Cs_2CO_3 in DMF	**17**	30
18	**Ig**	**IIf**	2.5 equiv of Cs_2CO_3 in DMF	**18**	30
19	**Ie**	**IIf**	2.5 equiv of Cs_2CO_3 in DMF	**19**	40
20	**Ia**	**IIg**	2.5 equiv of Cs_2CO_3 in DMF	**20**	65

[a]30 min (*t*) at 80 °C and further 30 min (*t*) at 145 °C. Reaction time (*t*) is the hold time after ramp time 10 min.

[b]Yields refer to isolated pure compounds after column chromatography.

Table 2. Anti-inflammatory activity of benzofuran-2-carboxamide derivatives (**1-20**) by carrageenan induced rat paw edema method in rats, analgesic activity by tail flick method and antipyretic activity by brewer's yeast induced method.

Entry	Anti-inflammatory activity Increase in paw volume ml ± SEM (% inhibition of inflammation)				Analgesic activity % Increase in reaction time	Antipyretic activity % Reduction in rectal temperature
	1h	2h	3h	4h	60 min	5 h
Control	0.34±0.002	0.74±0.002	0.91±0.002	1.03±0.002	—	—
Diclofenac	0.25±0.010	0.27±0.011	0.25±0.016	0.27±0.001 (74)	—	—
Pentazocine	—	—	—	—	217	—
Paracetamol	—	—	—	—	—	74
1	0.35±0.009	0.77±0.017	0.84±0.005	1.00±0.013 (3)	2	5
2	0.37±0.007	0.72±0.005	0.88±0.009	1.00±0.007 (3)	1	6
3	0.30±0.005**	0.47±0.003**	0.76±0.007**	0.83±0.009** (19)	172	45
4	0.36±0.005	0.73±0.008	0.85±0.007	0.96±0.011 (7)	134	46
5	0.34±0.012	0.87±0.007	0.86±0.009	1.00±0.010 (3)	136	6
6	0.29±0.005	0.44±0.012	0.77±0.005	0.82±0.013 (20)	153	46
7	0.34±0.007	0.76±0.018	0.86±0.011	0.99±0.011 (4)	135	6
8	0.30±0.004	0.46±0.007	0.77±0.005	0.83±0.012 (19)	152	45
9	0.29±0.005**	0.36±0.007**	0.37±0.005**	0.36±0.009** (64)	160	64
10	0.38±0.003	0.85±0.015	0.89±0.003	1.00±0.008 (3)	134	7
11	0.29±0.007**	0.35±0.005**	0.37±0.002**	0.37±0.002** (64)	160	46
12	0.33±0.011	0.42±0.015	0.44±0.005	0.51±0.005 (50)	161	48
13	0.33±0.009**	0.38±0.007**	0.39±0.004**	0.39±0.005** (60)	167	49
14	0.29±0.009**	0.37±0.002**	0.38±0.003**	0.35±0.003** (66)	138	68
15	0.34±0.012	0.65±0.013	0.66±0.011	0.79±0.004 (23)	153	47
16	0.33±0.009**	0.38±0.005**	0.38±0.005**	0.38±0.005** (63)	160	45
17	0.30±0.005	0.42±0.005	0.71±0.002	0.80±0.002 (22)	169	63
18	0.33±0.005**	0.39±0.007**	0.38±0.003**	0.38±0.013** (63)	160	62
19	0.32±0.013**	0.34±0.007**	0.35±0.005**	0.37±0.002** (64)	160	60
20	0.33±0.009**	0.39±0.007**	0.39±0.007**	0.38±0.009** (63)	160	46

SEM- standard error mean; n=6, *p <0.05, **p <0.01, ***p <0.001; -, not determined.

Anti-inflammatory activity was evaluated against carrageenan-induced paw edema method in Wistar rats.[27] The results are shown in Table 2. The standard drug diclofenac sodium was administered at dose of 20 mg/kg p.o. which gives 74% inhibition of inflammation at 4 h. Among the *N*-unsubstituted benzofuran-2-carboxamide derivatives, compound **9** showed good anti-inflammatory activity (65% inhibition) compared to other scaffolds. The methyl group at 5-position of benzofuran ring might be responsible for the anti-inflammatory activity.

In the *N*-substituted series, compounds **11**, **12**, **13**, **14**, **16**, **18**, **19** and **20** exhibited significant activity (50-66% inhibition) as compared to other compounds. The remaining benzofuran-2-carboxamide derivatives showed weak anti-inflammatory activity. Radiant heat tail-flick method in rats was used to screen the analgesic activity.[28] The effects of synthesized compounds and reference drug pentazocine (10 mg/kg i.p.) have been shown in Table 2 and expressed as percentage analgesia. Except compounds **1** and **2**, all the other synthesized compounds showed significant analgesia activity with 134-172% increase in reaction after 1 h treatment.

Furthermore, the antipyretic activity was evaluated against brewer's yeast induced method.[29] Paracetamol was used as standard drug at a dose of 150 mg/kg p.o. The percentage reduction in temperature after 5 h are summarized in Table 2, indicates that the compounds **9**, **14**, **17** and **18** exhibit potent antipyretic activity causing more than 58% reduction in rectal temperature. The compounds **3**, **4**, **6**, **8**, **11**, **12**, **13**, **15**, **16**, **19** and **20** showed moderate activity (45-49%) as compared with other tested series.

In conclusion, a new series of benzofuran-2-carboxamide derivatives has been prepared by one pot microwave-assisted parallel synthesis that involves an *O*-alkylation followed by Knoevenagel condensation reaction sequence. All the compounds were fully characterized by spectral data. Most of the twenty synthesized compounds exhibited significant activities, among which, compound **9**, **11, 14, 18** and **19** showed best anti-inflammatory, analgesic and anti-pyretic activities. This indicates that benzofuran-2-carboxamide derivatives can be considered as potential anti-inflammatory, analgesic and anti-pyretic agents. Further studies in relation to cytotoxicity and ADME are also warranted for the better understanding.

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Supplementary data

Detailed analytical data for all compounds and their biological activities have been provided in the supporting information.

References and notes

1. Ghose, A. K.; Viswanadhan, V. N.; Wendoloski, J. J. *J. Comb. Chem.* **1998**, *1*, 55–68.
2. Choi, M.-J.; Jung, K. H.; Kim, D.; Lee, H.; Zheng, H.-M.; Park, B. H.; Hong, S.-W.; Kim, M.-H.; Hong, S.; Hong, S.-S. *Cancer Lett.* **2011**, *306*, 190–195.
3. Parekh, S.; Bhavsar, D.; Savant, M.; Thakrar, S.; Bavishi, A.; Parmar, M.; Vala, H.; Radadiya, A.; Pandya, N.; Serly, J.; Molnár, J.; Shah, A. *Eur. J. Med. Chem.* **2011**, *46*, 1942–1948.
4. Hranjec, M.; Sović, I.; Ratkaj, I.; Pavlović, G.; Ilić, N.; Valjalo, L.; Pavelić, K.; Kraljević Pavelić, S.; Karminski-Zamola, G. *Eur. J. Med. Chem.* **2013**, *59*, 111–119.
5. Heinrich, T.; Böttcher, H.; Gericke, R.; Bartoszyk, G. D.; Anzali, S.; Seyfried, C. A.; Greiner H. E.; van Amsterdam, C. *J. Med. Chem.* **2004**, *47*, 4684–4692.
6. Dawson, L. A.; Watson, J. M. CNS Neurosci. Ther. 2009, 15, 107.
7. Alper-Hayta, S.; Arisoy, M.; Temiz-Arpaci, Ö.; Yildiz, I.; Aki, E.; Özkan, S.; Kaynak, F. *Eur. J. Med. Chem.* **2008**, *43*, 2568–2578.
8. Shattat, G.; Al-Qirim, T.; Sweidan, K.; Shahwan, M.; El-Huneidi, W.; Al-Hiari, Y. *J. Enzyme Inhib. Med. Chem.* **2010**, *25*, 751–755.
9. Al-Qirim, T.; Shattat, G.; Sweidan, K.; El-Huneidi, W.; Sheikha, G. A.; Khalaf, S. Hikmat, R. A. *Arch. Pharm. Chem. Life Sci.* **2012**, *345*, 401–406.
10. Boess, F. G.; De Vry, J.; Erb, C.; Flessner, T.; Hendrix, M.; Luithle, J.; Methfessel, C.; Riedl, B.; Schnizler, K.; van der Staay, F.-J.; van Kampen, M.; Wiese, W. B.; Koenig, G. *J. Pharmacol. Exp. Ther.* **2007**, *321*, 716–725.
11. Mazurov, A. A.; Kombo, D. C.; Hauser, T. A.; Miao, L.; Dull, G.; Genus, J. F.; Fedorov, N. B.; Benson, L.; Sidach, S.; Xiao, Y.; Hammond, P. S.; James, J. W.; Miller, C. H.; Yohannes, D. *J. Med. Chem.* **2012**, *55*, 9793–9809.
12. Sledz, P.; Silvestre; H. L.; Hung, A.W.; Ciulli, A.; Blundell, T. L.; Abell, C. *J. Am. Chem. Soc.* **2010**, *132*, 4544–4545.
13. Whitby, L. R.; Lee, A. M.; Kunz, S.; Oldstone, M. B. A.; Boger, D. L. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3771–3774.
14. Yamashita, D. S.; Marquis, R. W.; Xie, R.; Nidamarthy, S. D.; Oh, H. J.; Jeong, J. U. ; Erhard, K. F.; Ward, K.W.; Roethke, T. J.; Smith, B. R.; Cheng, H.Y.; Geng, X.; Lin, F.; Offen, P. H.; Wang, B.; Nevins, N. ; Head, M. S.; Haltiwanger, R.. C.; Sarjeant, A. A. N.; Sands, L. M. L.; Zhao, B.; Smith, W. W.; Janson, C. A.; Gao, E.; Tomaszek, T.; McQueney, M .; James, I. E.; Gress, C. J.; Zembryki, D. L. ; Lark, M. W.; Veber, D. F. *J. Med. Chem.* **2006**, *49*, 1597–1612.
15. Chen, J. M.; Nelson, F. C.; Levin, J. I.; Mobilio, D.; Moy, F. J.; Nilakantan, R.; Zask, A.; Powers, R. *J. Am. Chem. Soc.* **2000**, *122*, 9648–9654.
16. Shipe, W. D.; Wolkenberg, S. E.; Lindsley, C. W. *Drug Discov. Today: Technol.* **2005**, *2*, 155–161.
17. Mavandadi, F.; Pilotti, Å. *Drug Discov. Today* **2006**, *11*, 165–174.
18. Alcázar, J.; Oehlrich, D. *Future Med. Chem.* **2010**, *2*, 169–176.
19. Kappe, C. O.; Stadler, A.; Dallinger, D. *Microwaves in Organic and Medicinal Chemistry*, 2nd ed., Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany **2012**.
20. Meng, L.-J.; Vijaykumar, B. V. D.; Zuo, H.; Li, Z.-B.; Gautam, D.; Jang, K.; Shin, D.-S. *Tetrahedron: Asymmetry* **2012**, *23,* 1029–1037.
21. Meng, L.-J.; Zuo, H.; Vijaykumar, B. V. D.; Gautam, D.; Choi, K.-M.; Jang, K.; Yoon, Y.-J.; Shin, D.-S. *Bull. Korean Chem. Soc.* **2013**, *34*, 585–589.
22. Kennis, L. E. J.; Bischoff, F. P.; Mertens, C. J., Love, C. J.; Van den Keybus, F. A. F.; Pieters, S.; Braeken, M., Megens, A. A. H. P.; Leysen, J. E. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 71–74.
23. Aboraia, A. S.; Yee, S. W.; Gomaa, M. S.; Shah, N.; Robotham, A. C.; Makowski, B.; Prosser, D.; Brancale, A.; Jones, G.; Simons, C. *Bioorg. Med. Chem.* **2010**, *18*, 4939–4946.
24. (a) Xie, Y.-S.; Vijaykumar, B. V. D.; Jang, K.; Shin, H.-H.; Zuo, H.; Shin, D.-S. *Tetrahedron Lett.* **2013**, *54*, 5151–5154. (b) Xie, Y.-S.; Vijaykumar, B. V. D.; Jang, K.; Choi, K.-M.; Zuo, H.; Yoon, Y.-J.; Shin, D.-S. *Bull. Korean Chem. Soc.* **2013**, *34*, 3881–3884.
25. See supporting information for complete data.
26. (a) Rene, L.; Royer. R. *Bull. Soc. Chim. Fr.* **1971**, 4329. (b) Lee, J.; Khanapure, S. P.; Kim, H.-O.; Rajur, R.; Li, B.; Williams, J. D.; Pai, R.; Peet, N. P. *Synth. Commun.* **2010**, *40*, 3390–3396. (c) Walker, G. N.; Smith, R. T. *J. Org. Chem.* **1971**, *36*, 305–308. (d) Bundesmann, M. W.; Coffey, S. B.; Wright, S. W. *Tetrahedron Lett.* **2010**, *51*, 3879–3882. (e) Bathe, A. US20100036139(A1), Feb. 11, 2010. (f) Marriott, K.-S. C.; Morrison, A. Z.; Moore, M.; Olubajo, O.; Stewart, L. E. *Bioorg. Med. Chem. Lett.* **2012**, *20*, 6856–6861.
27. Winter, C. A.; Risely, E. A.; Nuss, G. W. *Proc. Soc. Exp. Biol. Med.* **1962**, *111*, 544–547.
28. D'Armour, F. E.; Smith, D. L. *J. Pharmacol. Exp. Ther.* **1941**, *72*, 74–79.
29. Loux, J. J.; DePalma, P. D.; Yankell, S. L. *Toxicol. Appl. Pharmcol.* **1972**, *22*, 672–675.

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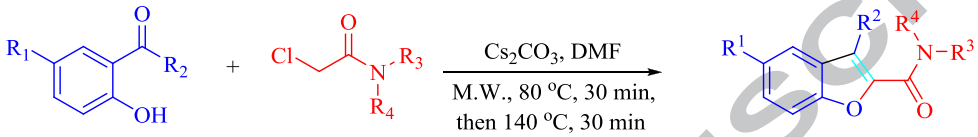

I
R_1 = H, halide, CH_3
R_2 = H, alkyl, phenyl

II
R_3 = H, aryl, pyridyl
R_4 = H, Bn

1-20 (25-80%)
anti-inflammatory, analgesic and antipyretic