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Microwave-assisted synthesis of carboxanilides as non steroidal anti-inflammatory agents

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ABSTRACT

A series of 3-hydroxybenzofuran-2-carboxanilides were prepared by microwave irradiation and conventional heating method. Microwave irradiation method gives better yield as that of conventional heating with a shorter reaction time. Compounds were characterized by physical data, elemental analysis and spectral data. All the new compounds were screened for anti-inflammatory activity by carrageenan induced rat paw edema method by using diclofenac sodium as a standard. Compounds **2c**, **2e** and **2f** showed very good anti-inflammatory activity.

Keywords: benzofuran, microwave irradiation, anti-inflammatory activity, carboxanilide.

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INTRODUCTION

Use of microwave technology in organic and inorganic reaction is reported in a number of publications [1-3]. The combination of solvent free condition and microwave irradiation leads to large reduction in reaction time, enhancement in conversion, easier work up and sometimes in selectivity with several advantages of an ecofriendly approach. Further, its unique capabilities allow its applications in transformations which are difficult or impossible to carry out by means of conventional method [4].

Although microwave reactions were begun in domestic microwave ovens, they are conducted in more sophisticated chemical microwave ovens now-a-days [5]. The existence of 'hot spots', inhomogeneity of the microwave field in the region to be heated the handicap in measuring the temperature of reaction, possibility of explosion, are some of the main defects of microwave oven reactions [6]. However, rotating the reaction platform that averages the field can decrease the inhomogeneity of the field. The temperature can be measured by taking out the sample at interval as required [7].

Acute and chronic inflammation and different types of arthritis are the inflammatory disorders, which are a big blow to humanity and continual search for newer non steroidal anti-inflammatory agents is the only way to fortify against this awaful threat.

The benzofuran derivatives constitute highly valuable heterocyclic moieties found in the structure of many natural and synthetic products [8, 9]. Derivatives of these compounds are known to possess important pharmaceutical [10], antifungal [11], antitumor [12] and other bioorganic properties [13]. Further as a class, salicylanilides have been reported with a wide variety of interesting biological properties [14]. Salicylanilides inhibits the interleukin-12p40 production[15] which mediates the inflammation in normal immune defence as well as inflammatory diseases such as rheumatoid arthritis, asthma, psoriasis and Crohn's disease [16, 17].

This stimulated our interest in the synthesis of benzofuran analogs of salicylanilides in which the benzene moiety of salicylanilide is replaced by benzofuran moiety. Ethyl 3-hydroxybenzofuran-2-carboxylate was prepared by single pot synthesis [18] from methyl salicylate and diethylbromomalonate. The reaction of this with various aromatic amines in presence of catalytic amount of hydrochloric acid under conventional heating and microwave irradiation method gives 3-hydroxybenzofuran-2-carboxanilides.

MATERIALS AND METHODS

Experimental

Melting points were determined in open capillary tubes and are uncorrected. The FT-IR spectra were recorded in KBr on SHIMADZU FTIR-8400S spectrophotometer. ^{1}H NMR spectra

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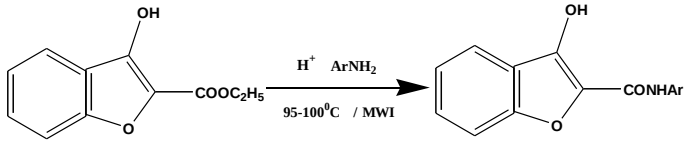
were recorded in $CDCl_3$ on a Varian Mercury YH-300, using TMS as an internal standard. Microwave irradiations were carried out in a LG intellocook MS-1921HE with RF output of 700W.

General procedures

Typical procedure for the synthesis of 3-hydroxybenzofuran-2-carboxanilides by conventional heating method.

An intimate mixture of **1** (0.01 mol), aromatic amine (0.011 mol) and 3-4 drops of concentrated hydrochloric acid was left overnight at room temperature and then heated to 95^0-100^0C for 9 hrs. The product obtained was washed with diethyl ether (2x25ml) to remove unreacted starting materials. The ether insoluble crystals of 3-hydroxybenzofuran-2-carboxanilides were collected and recrystallised from aqueous ethanol.



1 **2a-h**

Ar= **a** C_6H_5 **d** $C_6H_4CH_3$(o) **g** $C_{10}H_7$

b $C_6H_4CH_3$(p) **e** C_6H_4ClF(m, p) **h** $C_6H_4OCH_3$(p)

c C_6H_4Cl(p) **f** C_6H_4Cl(o)

Typical procedure for the synthesis of 3-hydroxybenzofuran-2-carboxanilides by microwave irradiation method.

Table No- 1. Physical data of the compounds (2a-h)

Sr. No	Compound	MP °C	Yield (%) Heating	Yield (%) MWI	Power W	Time Heating Min	Time MWI Min
01	2a	84	45	70	500	540	2
02	2b	128	40	65	500	540	2
03	2c	125	14	61	500	540	2
04	2d	98	10	68	500	540	4
05	2e	103	15	30	500	540	4
06	2f	111	60	70	500	540	5
07	2g	98	34	69	500	540	5
08	2h	102	28	63	500	540	4

*** All the compounds were crystallised from aqueous ethanol.**

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An intimate mixture of **1** (0.01 mol), aromatic amine (0.011 mol) and 3-4 drops of concentrated hydrochloric acid was subjected to Microwave irradiation for different time period as mentioned in table No-1 under 500W. The product obtained was washed with diethyl ether (2x25ml) to remove unreacted starting materials. The ether insoluble crystals of 3-hydroxybenzofuran-2-carboxanilides were collected and recrystallised from aqueous ethanol.

Spectral data for 3-Hydroxybenzofuran-2-carboxanilide (2a): IR (KBr, cm^{-1}): 1692 (C=O), 3377 (NH). ^1H NMR ($CDCl_3$): δ 7-7.8 m (9H, ArH), δ 7.91 s (1H, OH), δ 9.42 bs (NH). Anal. Calcd for $C_{15}H_{11}NO_3$: C, 71.14; H, 4.34; N, 5.53. Found: C, 70.10; H, 4.45; N, 5.60.

Spectral data for 3-Hydroxybenzofuran-2 N-(4-methylphenyl) carboxamide (2b): IR (KBr, cm^{-1}): 1685 (C=O), 3370 (NH). ^1H NMR ($CDCl_3$): δ 2.40 s (3H, $ArCH_3$), δ 7.1-7.9 m (8H, ArH), δ 8.15 s (1H, OH), δ 9.40 bs (NH). Anal. Calcd for $C_{16}H_{13}NO_3$: C, 71.91; H, 4.86; N, 5.24. Found: C, 71.90; H, 4.90; N, 5.30.

Spectral data for 3-Hydroxybenzofuran-2 N-(4-chlorophenyl) carboxamide (2c): IR (KBr, cm^{-1}): 1680 (C=O), 3300 (NH). ^1H NMR ($CDCl_3$): δ 7.1-7.8 m (8H, ArH), δ 8.10 s (1H, OH), δ 9.40 bs (NH). Anal. Calcd for $C_{15}H_{10}NO_3Cl$: C, 62.60; H, 3.47; N, 4.86. Found: C, 62.58; H, 3.44; N, 4.80.

Spectral data for 3-Hydroxybenzofuran-2 N-(2-methylphenyl) carboxamide (2d): IR (KBr, cm^{-1}): 1680 (C=O), 3270 (NH). ^1H NMR ($CDCl_3$): δ 2.45 s (3H, $ArCH_3$), δ 7-7.9 m (8H, ArH), δ 8.10 s (1H, OH), δ 9.42 bs (NH). Anal. Calcd for $C_{16}H_{13}NO_3$: C, 71.91; H, 4.86; N, 5.24. Found: C, 72.00; H, 4.90; N, 5.22.

Spectral data for 3-Hydroxybenzofuran-2 N-(3-chloro-4-fluorophenyl) carboxamide (2e): IR (KBr, cm^{-1}):1670 (C=O), 3380 (NH). ^1H NMR ($CDCl_3$): δ 7-7.8 m (7H, ArH), δ 8.15 s (1H, OH), δ 9.40 bs (NH). Anal. Calcd for $C_{15}H_9NO_3ClF$: C, 58.91; H, 2.94; N, 4.58. Found: C, 58.90; H, 2.90; N, 4.60.

Spectral data for 3-Hydroxybenzofuran-2 N-(2-chlorophenyl) carboxamide (2f): IR (KBr, cm^{-1}):1640 (C=O), 3320 (NH). ^1H NMR ($CDCl_3$): δ 7-7.9 m (8H, ArH), δ 8.10 s (1H, OH), δ 9.40 bs (NH). Anal. Calcd for $C_{15}H_{10}NO_3Cl$: C, 62.60; H, 3.47; N, 4.86. Found: C, 62.58; H, 3.44; N, 4.80.

Spectral data for 3-Hydroxybenzofuran-2 N-(naphthyl-1yl) carboxamide (2g): IR (KBr, cm^{-1}):1670 (C=O), 3290 (NH). ^1H NMR ($CDCl_3$): δ 7-7.8 m (11H, ArH), δ 7.90 s (1H, OH), δ 9.40 bs (NH). Anal. Calcd for $C_{19}H_{13}NO_3$: C, 75.24; H, 4.29; N, 4.62. Found: C, 75.29; H,4.26 ; N, 4.60.

Spectral data for 3-Hydroxybenzofuran-2 N-(4-methoxyphenyl) carboxamide (2h): IR (KBr, cm^{-1}): 1680 (C=O), 3300 (NH). ^1H NMR ($CDCl_3$): δ 3.9 s (3H, $ArOCH_3$), δ 7.1-7.8 m (8H, ArH), δ 8.10 s (1H, OH), δ 9.42 bs (NH). Anal. Calcd for $C_{16}H_{13}NO_4$: C, 67.84; H, 4.59; N, 4.94. Found: C, 67.85; H, 4.55; N, 4.90.

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Biological activity

Table No- 2. Biological activity data of the compounds (2a-h)

Sr.No	Compound	Dose mg/kg	Mean difference in paw volume+ S.E after 3 hrs(ml)	Percentage of inhibition
01	Control	-	0.90±0.03	-
02	Diclofenac	100	0.14±0.01*	84
03	2a	100	0.37±0.02*	58
04	2b	100	0.41±0.02*	54
05	2c	100	0.34±0.01*	62
06	2d	100	0.57±0.05*	36
07	2e	100	0.31±0.02*	65
08	2f	100	0.36±0.01*	60
09	2g	100	0.44±0.05*	51
10	2h	100	0.39±0.02*	56

Values are expressed as mean ± SEM (n=5)

* $P < 0.001$ when compared to control group

All the compounds were screened for anti-inflammatory activity[19-21] by Carrageenan induced rat paw edema method. Diclofenac sodium was used as standard. Rats were divided into control, standard and different test groups comprising of six animals in each group. They were fasted overnight with free access to water before experiment. In all groups acute inflammation was induced by subplantar injection of 0.1 ml of freshly prepared 1% suspension of Carrageenan in the right hind paw of the rats and paw volume was measured Plethysmometrically at 0 hour and 3 hr after carrageenan injection. Rats of test groups were administered orally with test compounds 100 mg/kg and the standard group with diclofenac 100 mg/kg orally in 2% aqueous acacia one hr before injection of carrageenan. Control group received only vehicle. Mean difference in paw volume was measured and percentage of inhibition of edema was calculated and given in table No-2

RESULT AND DISCUSSION

All the compounds were synthesized by both conventional heating and microwave irradiation method. The conventional heating method is time consuming while microwave irradiation method gives better yield with shorter reaction time. The further increase in irradiation time does not increase the yield. Anilides of substituted aromatic amines gives lesser reaction yields as compared to aniline. The para substituted aromatic amine gives the lowest yield compared to ortho and bisubstituted aromatic amine. The compounds have been characterized by comparing their melting points and mixed melting points. All the compounds were characterized for IR and ^{1}H NMR spectral analysis along with elemental analysis. IR spectra of the compounds **2a-h** exhibited an absorption band in the region of 3300 cm^{-1} due to NH and strong band in the region of 1680 cm^{-1} due to carbonyl of anilide. The ^{1}H NMR spectral data for all compounds revealed a broad singlet at δ 9.40 due to NH proton, singlet at δ 8.10 due to OH and multiplates at δ 7.0-7.9 due to aromatic protons.

All the new compounds have been screened for anti-inflammatory activity. Some of the compounds showed considerable anti-inflammatory activity compared to diclofenac sodium. The compounds **2c**, **2e** and **2f** showed good anti-inflammatory activity that is prepared from substituted anilines. In the present protocol, we observed better yields in a shorter period compared to the reaction carried out by conventional heating method.

CONCLUSION

In conclusion, we have described a highly efficient microwave-induced procedure for the preparation of carboxanilides that occurs remarkably fast, under mild conditions, using inexpensive reagents and a household microwave oven as the irradiation source. The advantage of this environmentally benign and safe protocol include a simple reaction set-up, application of commonly available reagents and catalysts, high product yield, short reaction time as well as the elimination of solvents.

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