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Aqua mediated facile synthesis of 2-(5/7-fluorinated-2-oxoindolin-3-ylidene)-N- (4-substituted phenyl) hydrazine carbothioamides

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ABSTRACT

A simple, clean, environmentally benign route to the synthesis of biologically important fluorinated hydrazine carbothioamides is achieved under microwave irradiation in aqueous medium by the reaction of fluorinated indole–2,3-diones and 4-chloro/bromo/methyl phenyl thiosemicarbazides.

Keywords: Aqueous media, Microwave irradiation, Fluorinated indole-2, 3-dione, substituted thiosemicarbazides.

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INTRODUCTION

The development of efficient and mild methods for heterocyclic compound synthesis represents a broad area of organic chemistry [1], [2]. In recent years, microwave-assisted reactions are well established and have gained popularity [3]. The beneficial effects of microwave irradiation are finding an increased role in multiple kilogram scale in fine chemicals and drugs [4], especially in cases when usual methods require forcing conditions or prolonged reaction times. Green chemistry is helpful to chemists in research, development and production for development of more eco-friendly and efficient products, which may also have significant financial benefits [5]. It is now going to become an essential tool in the field of synthetic chemistry. The development of Green Chemistry redefines the role of a solvent: "An ideal solvent facilitates the mass transfer but does not dissolve". In addition, a desirable green solvent should be natural, nontoxic, cheap and readily available with additional benefits of aiding the reaction, separation or catalyst recycling. Water is ideally suited for this purpose owing to its non-toxic character. Its enormous abundance on this planet makes water a readily accessible alternative. There are also advantages from an economic point of view [6]. Under microwave irradiation; water is rapidly heated to high temperatures, enabling it to act as a less polar pseudo-organic solvent. Moreover, precise control of the reaction temperature is easily achieved because of the very high heat capacity of water.

The indole nucleus is one of the most ubiquitous scaffolds found in natural products, pharmaceuticals, functional materials, and agrochemicals [7], [8], [9]. Several indole derivatives that occur in nature possess pharmacological activity. These include the hapalindole alkaloids, which exhibit significant antibacterial and antimycotic activity. Other indole alkaloids are uleine, aspidospermidine, the ibophyllidine alkaloids, brevicolline and numerous tryptamine derivatives, which exhibit important biological activities [10], [11], [12]. Thiosemicarbazide derivatives are also associated with important biological activities [13].

Introducing fluorine into a molecule can lead to unexpected effects [14]. The high electronegativity of fluorine modulates the reactivity pattern of the host molecule [15]. A recent review [16] has highlighted pesticides containing the CF_3O group and its authors have argued that a CF_3O substituent can advantageously replace a fluorine atom in most molecules with the benefit of increased lipid solubility. Many drugs with enhanced effectiveness and selectivity contain the CF_3O moiety. Aromatic ring bearing the CF_3O group parallel the alkoxy group with respect to electron withdrawal, whilst also serving to deactivate the aromatic ring system thereby imparting superior stability to drugs containing such substituent.

Despite of few reports on the reaction of fluorinated 1H indole-2, 3-dione with thiosemicarbazide by conventional thermal heating [17], utility of microwaves in such reactions has received only limited study. Further, reaction of fluorinated 1H-indole-2, 3-dione with thiosemicarbazide in aqueous media under microwave irradiation has not been studied so far. In view of the above, it was thought worthwhile to explore the use of microwave for the synthesis of some potent bioactive indole derivatives.

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Hence, In continuation to our general interest on the economic and environmentally benign synthesis of biodynamic heterocycles[18] and particular interest on use of aqueous medium [19] for heterocyclic synthesis, we report herein for the first time the microwave promoted, economic, ecofriendly, and facile synthesis of 2-(5/7-fluorinated -2-oxoindolin-3-ylidene)-N-(4-substitutedphenyl)hydrazine carbothioamides **3** (Scheme-1). Compound **3** is synthesized by the reaction of 5/7- fluorinated 1H-indole-2, 3-diones **1** and 4-substituted (Cl/Br/CH_3) phenyl thiosemicarbazide **2** in aqueous medium containing catalytic amount of montmorillonite K10 clay under microwave irradiation. This reaction proceeds in 3-6 minutes at 200watts power under microwave irradiation in comparison to conventional syntheses, which occurs in 6-7 hours requiring excessive use of solvent and extra labor for separation and purification of compounds. Substituted thiosemicarbazides **2** are also prepared in the laboratory by the literature method [20]. The products are characterized on the basis of IR, ^{1}HNMR and Mass spectroscopic data.

MATERIALS AND METHODS

All chemicals were obtained Sigma Aldrich, Jaipur. All chemicals and solvents used were of analytical grade.

Experimental

Melting points were determined on a Toshniwal apparatus. The elemental and spectral analyses of synthesized compounds have been carried out at SAIF Punjab University, Chandigarh. The purity of compounds was checked on thin layers of silica gel in various non-aqueous solvent systems, e.g. benzene: ethylacetate (9:1), benzene: Petroleum ether (8:2), benzene: dichloromethane (8:2). IR spectra were recorded in KBr on a Perkin Elmer Infrared RXI FTIR spectrophotometer and ^{1}H NMR spectra were recorded on Bruker Avance II 400 NMR Spectrometer using DMSO-d_6 and $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal reference standard. Mass spectrum of representative compound was recorded on Micromass Q –T mass spectrometer of Micro. The microwave-assisted reactions were carried out in a commercial multimode MW oven equipped with inverter technology and also attached with a magnetic stirrer and reflux condenser, operating at 1000W generating 2450 MHz frequency.

Synthesis of 4-substituted phenylthiosemicarbazide (2): It was prepared by the literature method [20] with slight modification.

Compounds 3a-h was synthesized by two different methods.

Conventional method [21]**:** An equimolar mixture of fluorinated indole-2, 3-dione **1** (.01mol) and substituted thiosemicarbazide **2** (.01mol) in ethanol was refluxed for 7 h. The completion of the reaction was checked by TLC. The excess of ethanol was distilled off and the cooled, refluxed residual was poured into ice-cold water. The solid thus obtained was filtered, washed with water, dried and crystallized from ethanol.

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Microwave irradiation Method:

General procedure for the Synthesis of 2-(5-trifluoromethoxy-2-oxoindolin-3-ylidene)-hydrazine carbothioamides 3a: An equimolar (0.01mol) mixture of **1a** and **2a** in water containing catalytic amount of clay taken in 250ml conical flask was irradiated inside microwave oven for 4-6 minutes at 200watts. After the completion of the reaction (as monitored by TLC), product formed was filtered and recrystallized from ethanol. m.p. 249-252 °C Yield 86% IR (KBr, cm^{-1}): 3430(N-H stretching of indole), 3238(N-H stretching of hydrazine carbothioamide), 1699(C=O str), 1155 (C=S str), ^{1}HNMR (DMSO-d_6): δ 7.47(d,1H,C_4H proton), 7.88(d, 1H C_6H proton),8.02 (d, 1H C_7H of indole),8.20 (s,2H, NH_2 of hydrazine carbothioamide moiety),10.90 (s,1H, NH of indole),12.43 (s,1H,NH of hydrazine carbothioamide) ppm. Anal. Calcd for $C_{10}H_7N_4O_2SF_3$: C, 39.47; H, 2.30; N, 18.42%. Found: C, 38.40; H, 2.27; N, 18.38 MS: $[M]^+$at m/z 304.

Antibacterial activity

Materials and Methods: Synthesized compounds were screened for their antibacterial activity against Gram-positive bacteria Bacillus *cereus* (MTCC 0430) and Gram-negative bacteria *Enterobacter aerogenes* (MTCC 2824) by the Agar Well Diffusion method [22]. 5 ml aliquot of nutrient broth was inoculated with the test organism and incubated at 37 ^{0}C for 24 hours. Sterile nutrient agar plates were also prepared and holes of 5 mm diameter were cut using a sterile cork borer ensuring proper distribution. The test organisms after 24 hours of incubation were spread onto separate agar plates. The chemical compounds were dissolved in DMSO at a particular concentration and poured into appropriately labelled holes using a pipette in aseptic conditions. A hole containing DMSO served as a control. The plates were left at room temperature for two hours to allow the diffusion of the sample followed by incubation at 37 ^{0}C for 24 hours in inverted position. The antimicrobial activity was determined by measuring the diameter of the zone (mm) showing complete inhibition with respect to control (DMSO) (Table 2).

Table: 2 Antibacterial screening results of compounds 3a-h

S.No	Diameter of Zone (mm) of Inhibition against *Bacillus cerus* (MTCC 0430)	Diameter of Zone (mm) of Inhibition against *Enterobacter aerogenes*. (MTCC 2824)
DMSO	20	20
3a	12	02
3b	17	05
3c	09	03
3d	03	04
3e	07	06
3f	09	08
3g	06	05
3h	08	04

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Among all the compounds tested, none of the compound was found active against gram positive and gram-negative bacteria.

RESULTS AND DISCUSSION

In view of the medicinal importance of the products and considering the limitations of the conventional heating method (50-57% yield; Time: 6-7hrs), we have studied the reaction of 1H-indole-2, 3-dione derivatives **1** with 4-substituted phenyl thiosemicarbazide **2** in water containing catalytic amount of clay under microwave irradiation.

For the synthesis of hydrazine carbothioamides **3**, we initially attempted the dry reaction of **1** with **2** on montmorillonite K10 clay under microwave irradiation but yield obtained was very low (40-50%). Further, we explored the reaction in water without using any catalyst; the target compound obtained in poor yield and required longer reaction time under microwaves. To maximize the yield and shorten the reaction time and utilizing the fact that "montmorillonite has emerged as an environmentally benign solid catalyst", we attempted the reaction in aqueous medium containing catalytic amount of montmorillonite K10 clay and achieved success as target compounds **3a-h** obtained in 80-95% yields. The reaction of **1** with **2** was also carried out conventionally in ethanol containing few drops of acetic acid. A comparative study of the reaction time and yields of the products under microwave irradiation and conventional heating (Table-1) showed that the use of microwave irradiation substantially reduced the reaction times from hours scale to minutes scale and appreciably increased the yields. The present method indicates operational simplicity, shorter reaction time, and higher yields, which can prove this procedure as a useful alternative for the synthesis of biodynamic heterocycles.

Scheme-1

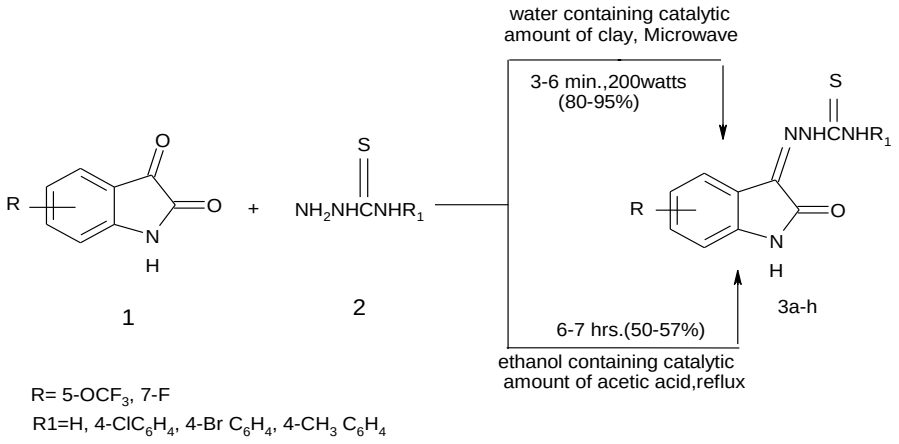

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Table 1: Physical data of the compounds 3a-h

S.No.	R	R_1	Molecular Formula*	Microwave Irradiation Method A		Conventional Heating Method B		M.pt. (°C)
				Time (min.)	Yield (%)	Time (h)	Yield (%)	
3a	5-OCF_3	H	$C_{10}H_7N_4O_2SF_3$	3	86	7	50	249
3b	7-F	H	$C_9H_7N_4OSF$	6	80	7	50	263
3c	5-OCF_3	4-Cl C_6H_4	$C_{16}H_{10}N_4O_2SClF_3$	4	86	7	52	251
3d	7-F	4-Cl C_6H_4	$C_{15}H_{10}N_4OSClF$	6	84	7	52	243
3e	5-OCF_3	4-Br C_6H_4	$C_{16}H_{10}N_4O2SBrF_3$	4	86	7	57	216
3f	7-F	4-Br C_6H_4	$C_{15}H_{10}N_4OSBrF$	6	88	7	55	241
3g	5-OCF_3	4-$CH_3C_6H_4$	$C_{17}H_{13}N_4O_2SF_3$	4	90	7	53	237
3h	7-F	4-$CH_3C_6H_4$	$C_{16}H_{13}N_4OSF$	4	95	7	52	255

CONCLUSION

We have developed a simple, economic and eco-friendly highly efficient synthetic strategy for exclusive synthesis of biologically important new 2-(5/7-fluorinated-2-oxoindolin-3-ylidene)-N- (4-Cl/ Br/CH_3- phenyl) hydrazine carbothioamides **3a-h** in water with greater yields than the previously reported conventional methods.

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