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Solvent free synthesis, crystal studies, docking studies and antibacterial properties of some novel fluorinated pyridazinone derivatives

H.B.V. Sowmya [a], T.H. Suresha Kumara [a,c,*], G. Nagendrappa [a], Jerry P. Jasinski [b], Sean P. Millikan [b], Gilish Jose [a], Dileep R [c], P.S. Sujan Ganapathy [a]

[a] PG Department of Chemistry, Jain University, Bull Temple Road, Chamarajpet, Bangalore 560026, India
[b] Department of Chemistry, Keene State College, Keene, NH 03435-2001, USA
[c] Department of Chemistry, GITAM University, Bengaluru Campus, Doddaballapur, Bangalore North, Karnataka 561203, India

HIGHLIGHTS

- Novel fluorinated pyridazinone derivatives were synthesized.
- X-ray crystallographic study of 3a and 3f were carried out.
- *In vitro* antibacterial screening was carried out.
- Docking studies was carried out.

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ABSTRACT

The solvent free synthesis of six 6-(3,5-difluorophenyl)-4,5-dihydropyridazin-3(2*H*)-one derivatives was carried out by microwave irradiation of a pulverized mixture of 4-(3,5-difluorophenyl)-4-oxobutanoic acid and substituted hydrazine hydrochloride in presence of catalytic amount of acetic acid at 150 °C/75 W for 5 min. Single crystals of two derivatives, $C_{16}H_{12}N_2OF_2$ [**3a**] and $C_{16}H_{11}N_2OF_3$ [**3f**] were formed allowing for structural analysis. [$C_{16}H_{12}N_2OF_2$]: orthorhombic, Pbcn; a = 17.1583(5) Å, b = 11.3751(3) Å, c = 13.7704(4) Å, V = 2687.67(13) Å^3, Z = 8, 173(2) K, μ(Cu Kα) = 0.920 mm^{-1}, D_{calc} = 1.415 g/mm^3, 16553 reflections, 2651 unique (R_{int} = 0.0298); R_1 = 0.0394 ($I > 2\sigma(I)$) and wR_2 = 0.1118 (all data). [$C_{16}H_{11}N_2OF_3$]: triclinic, P-1, a = 7.4837(4) Å, b = 13.3707(10) Å, c = 13.7194(9) Å, α = 76.622(6)°, β = 88.771(5)°, γ = 81.453(5)°, V = 1320.60(16) Å^3, Z = 4, 173(2) K, μ(Cu Kα) = 1.087 mm^{-1}, D_{calc} = 1.530 g/mm3, 8522 reflections, 5092 unique (R_{int} = 0.0277); R_1 = 0.0441 ($I > 2\sigma(I)$) and wR_2 = 0.1289 (all data). Preliminary antibacterial properties and docking studies are described for all the six derivatives.

1. Introduction

Synthesis of new organofluorine compounds has effected numerous applications in agrochemistry and pharmaceutical chemistry [1,2]. The compounds of pyridazinone have possessed potential antibacterial, antifungal and antiviral properties, including anti-HIV activities [1–4]. Various 3-(2*H*)-pyridazinone derivatives have shown anticancer [4], analgesic and anti-inflammatory [4–6], anticonvulsant [7], cardiotonic and hypotensive [8,9] and antiulcer activities [10]. In view of such a wide range of applications of pyridazinones [1–10], their biological activities and related properties have been extensively studied. The synthetic procedures for these compounds have usually involved an excess of solvents, expensive acid or base catalysts and long reaction times [11a–e]. In order to minimize the undesirable environmental consequences caused by using such procedures [12], chemists have been paying much attention to avoid the use of solvents, costly catalysts and chemicals that do not become part of the products.

We report here the synthesis of a series of fluorinated pyridazinone derivatives (**3a–f**) through Microwave assisted organic synthesis (MAOS). MAOS has shown broad applications as a very efficient way to accelerate the course of many organic reactions, producing high yields and higher selectivity, lower quantities of side products and, consequently, easier work-up and purification of the products. MAOS is considered as a "green" technology, principally since many organic reactions can be carried out in solvent-free conditions [13,14].

As a part of studying their biological occupation, we have carried out docking studies, antibacterial activity and report here the result of solvent free synthesis, docking studies, and antibacterial activity of six new 3-(2*H*)-pyridazinone derivatives.

* Corresponding author at: Department of Chemistry, GITAM University, Bengaluru Campus, Doddaballapur, Bangalore North, Karnataka 561203, India. Tel.: +91 9916588466; fax: +91 80 28098002.
E-mail address: suresha.kumara@gmail.com (T.H. Suresha Kumara).

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2. Experimental

General: Melting points were recorded in an open capillary and uncorrected. Chemicals were obtained from SD-fine, Sigma–Aldrich companies and were used without further purification. The microwave reactions were carried out in Biotage initiator at 150 °C and 75 W. The CHN analysis was recorded in Elementar vario MICRO cube. ESI-MS spectra were measured by using 5 mM ammonium acetate:acetonitrile (95:5 mixture) and 5 mM acetonitrile:ammonium acetate (5:95 mixture) as mobile phases A and B, respectively, by using an OpenLynx ESI-LC/MS spectrometer. IR spectra were recorded as KBr pellets on a Jasco FTIR 460 plus spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using Bruker AV-400 spectrometers with TMS as an internal reference. The purity of the synthesized compounds was demonstrated by TLC and further purification was made by the recrystallization process. Single crystals were obtained by slow the evaporation technique.

*2.1. Microwave assisted solid phase synthesis of 6-(3,5-difluorophenyl)-2-phenyl-4,5-dihydropyridazin-3(2H)-one (**3a**)*

A mixture of 4-(3,5-difluorophenyl)butanoic acid (100.00 mg, 0.46 mmol) and phenylhydrazine hydrochloride (67.60 mg, 0.46 mmol) was ground up in the presence of a catalytic amount of acetic acid for about 10 min. It was quantitatively transferred to an 8 mL vial which was subsequentially capped. The capped vial was placed into the Biotage microwave initiator and focused to microwave irradiation with a power of 75 W at 150 °C for about 1 min. An additional four such microwave irradiation trials were carried out, i.e., for total period of 5 min. After completion of the reaction mixture, monitored by TLC, it was transferred quantitatively to 50 mL of ice cold water present in a 100 mL baker with stirring. The resulting solid obtained was collected by filtration, washed with dilute $NaHCO_3$ and then with water, dried and purified by recrystallization from ethyl acetate in the presence of a catalytic amount of activated animal charcoal. The yield of the product **3a** obtained was 89% (120 mg, 0.42 mmol). The other products (**3b–f**) were similarly synthesized by using corresponding microwave irradiation time Table 3. The analytical data of the products **3a–f** is depicted below.

*2.2. 6-(3,5-Difluorophenyl)-2-phenyl-4,5-dihydropyridazin-3(2H)-one (**3a**)*

White crystal; IR (cm^{-1}, KBr): 2950 (CH), 1719 (CO); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.78–2.82 (m, 2H), 3.03–3.07 (m, 2H), 6.83–6.88 (m, 1H), 7.27–7.55 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.7, 27.8, 30.92, 105.1, 105.4, 105.6, 109.0, 109.1, 109.2, 109.3, 111.9, 112.1, 113.4, 120.1, 129.5, 129.6, 138.5, 138.6, 142.2, 142.3, 149.3, 149.3, 149.4, 161.3, 161.9, 161.9, 162.0, 163.7, 164.4, 164.5, 164.9; Positive LC-ESI-MS, *m*/*z*: 305.1 $[M+H]^{+1}$,306.6 $[M+H]^{+2}$; Anal. Calcd. for $C_{16}H_{12}F_2N_2O$: C, 67.14; H, 4.22, N, 9.28; Found: C, 66.90, H, 2.11, N, 8.99.

*2.3. 6-(3,5-Difluorophenyl)-2-(4-methoxyphenyl)-4,5-dihydropyridazin-3(2H)-one (**3b**)*

Off white powder; IR (cm^{-1}, KBr): 2900 (CH), 1699 (CO); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.77–2.81 (m, 2H), 3.02–3.06 (m, 2H), 3.83 (s, 3H), 6.82–6.87 (m, 1H), 6.93–6.97 (m, 2H), 7.27–7.44 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.8, 27.6, 29.7, 30.65, 55.5, 55.9, 104.8, 105.1, 105.3, 108.9, 109.0, 109.1, 109.2, 113.6, 113.8, 113.9, 114.1, 114.3, 126.4, 126.6, 126.7, 131.5, 134.1, 138.7, 138.8, 138.9, 148.4, 148.4, 148.5, 158.4, 161.9, 162.0, 164.3, 164.4, 165.0; Positive LC-ESI-MS, *m*/*z*: 318.2 $[M]^{+2}$, 317.1 $[M]^{+1}$; Anal. Calcd. for $C_{17}H_{14}F_2N_2O_2$: C, 64.54, H, 4.47, N, 8.88; Found: C, 64.52, H, 4.30, N, 8.99.

*2.4. 6-(3,5-Difluorophenyl)-2-p-tolyl-4,5-dihydropyridazin-3(2H)-one (**3c**)*

White crystal; IR (cm^{-1}, KBr): 2911 (CH), 1700 (CO); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.43 (s, 3H), 2.77–2.81 (m, 2H), 3.02–3.06 (m, 2H), 6.82–6.87 (m, 1H), 7.22–7.42 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.1, 22.8, 27.7, 30.9, 104.8, 105.1, 105.3, 108.9, 108.9, 109.1, 109.1, 124.9, 129.3, 136.9, 138.5, 138.8, 138.9, 139.0, 148.4, 148.5, 161.9, 162.0, 164.3, 164.5, 164.9.0; Positive LC-ESI-MS, *m*/*z*: 302.1 $[M]^{+2}$, 301.2 $[M]^{+1}$; Anal. Calcd. for $C_{17}H_{14}F_2N_2O$: C, 67.97, H, 4.71, N, 9.34; Found: C, 67.86, H, 4.66, N, 9.04.

*2.5. 4-(3-(3,5-Difluorophenyl)-6-oxo-5,6-dihydropyridazin-1(4H)-yl)benzonitrile (**3d**)*

White powder; IR (cm^{-1}, KBr): 2920 (CH), 1703 (CO); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.81–2.85 (m, 2H), 3.06–3.10 (m, 2H), 6.87–6.93 (m, 1H), 7.30–7.36 (m, 2H), 7.68–7.82 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.8, 27.9, 105.4, 105.7, 105.9, 109.1, 109.1, 109.2, 109.3, 109.3, 109.6, 118.6, 124.2, 124.3, 127.8, 132.5, 138.2, 138.3, 138.4, 144.4, 150.2, 161.9, 162.1, 164.4, 164.5, 165.1; Positive LC-ESI-MS, *m*/*z*: 313.1 $[M]^{+2}$, 312.2 $[M]^{+1}$; Anal. Calcd. for $C_{17}H_{11}F_2N_3O$: C, 65.59, H, 3.56, N, 13.51; Found: C, 65.53, H, 3.51, N, 13.19.

*2.6. 6-(3,5-Difluorophenyl)-4,5-dihydropyridazin-3(2H)-one (**3e**)*

White crystal; IR (cm^{-1}, KBr): 3188 (NH), 2941 (CH), 1689 (CO); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.61–2.65 (m, 2H), 2.92–2.97 (m, 2H), 6.82–6.87 (m, 1H), 7.20–7.28 (m, 2H), 8.69 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.4, 26.1, 30.9, 104.8, 105.0, 105.3, 108.7, 108.8, 108.9, 109.0, 138.7, 138.8, 138.9, 147.9, 161.9, 162.0, 164.3, 164.4, 164.9; Positive LC-ESI-MS, *m*/*z*: 212.1 $[M]^{+2}$, 211.1 $[M]^{+1}$; Anal. Calcd. for $C_{10}H_8F_2N_2O$: C, 57.15, H, 3.88, N, 13.31; Found: C, 57.00, H, 3.65, N, 13.10.

*2.7. 6-(3,5-Difluorophenyl)-2-(3-fluorophenyl)-4,5-dihydropyridazin-3(2H)-one (**3f**)*

White crystal; IR (cm^{-1}, KBr): 2901 (CH), 1721 (CO); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.79–2.83 (m, 2H), 3.03–3.07 (m, 2H), 6.84–7.43 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.8, 27.7, 30.9, 104.9, 105.4, 108.9, 109.0, 109.1, 109.2, 124.5, 124.9, 125.1, 125.3, 126.9, 127.1, 128.4, 128.6, 128.9, 138.7, 138.9, 141.0, 148.7, 148.7, 148.8, 161.1, 162.0, 164.3, 164.5, 164.9; Positive LC-ESI-MS, *m*/*z*: 306.2 $[M]^{+2}$, 305.1 $[M]^{+1}$; Anal. Calcd. for $C_{16}H_{11}F_3N_2O$: C, 63.15, H, 3.64, N, 9.20; Found: C, 63.11, H, 3.55, N, 9.00.

*2.8. Anti bacterial activity of the compounds **3a–f***

The bacterial pathogenic clinical isolates were maintained in Genohelix Biobabs, A Division of CASB, Jain University, Bangalore, and were used as a source for anti-bacterial activity studies. The test bacterial pathogens included *Staphylococcus aureus, Bacillus cereus* and *Escherichia coli.*

Antibacterial activities of the compounds (**3a–f**) were studied by the agar-well diffusion method [15]. Test cultures of the bacterial pathogens were prepared by transferring a loop full of bacteria from nutrient agar slants into Mueller Hinton broth and incubated at 37 ± 1 °C for 2 h. Lawn cultures of the test pathogens were prepared by swabbing sterile Mueller Hinton agar plates with 2 h old