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Short communication

# Synthesis and evaluation of the biological activities of some 3-{[5-(6-methyl-4-aryl-2-oxo-1,2,3,4-tetrahydropyrimidin-5-yl)--1,3,4-oxadiazol-2-yl]-imino}-1,3-dihydro-2*H*-indol-2-one derivatives

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Reaction of ethyl-6-methyl–2-oxo-4-aryl-1,2,3,4-tetrahydropyrimidin-5-carboxylates (**1a-i**) with hydrazine hydrate yielded 6-methyl-2-oxo-4-aryl-1,2,3,4-tetrahydropyrimidin-5-carbohydrazides (**2a-i**). These products, on reaction with cyanogen bromide, gave 5-(5-amino-1,3,4--oxadiazol-2-yl)-6-methyl-4-aryl-3,4-dihydropyrimidin-2(1*H*)-ones (**3a-i**). The resultant aminooxadiazolylpyrimidinones were condensed with isatin to obtain various 3-{[5-(6-methyl-4-aryl-2-oxo-1,2,3,4-tetrahydropyrimidin--5-yl)-1,3,4-oxadiazol-2-yl]-imino}-1,3-dihydro-2*H*-indol--2-ones (**4a-i**). These products were characterized by IR, $^1$H NMR, mass spectra and elemental analysis. Products (**4a-i**) revealed promising antibacterial, antifungal and antioxidant activity.

*Keywords:* pyrimidinyl oxadiazole amines, pyrimidinone oxadiazolyl indolinones, antibacterial, antifungal, antioxidant

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Pyrimidines are well known for their anticancer, antimicrobial, antioxidant and antiviral activities (1–5). Oxadiazoles are well known for their antifungal, antibacterial, anticancer and anticonvulsant activity (6–10). Indoles are also well known compounds for their antimicrobial, anticancer**,** antioxidant and antiviral activity (11–15). In the present investigation nine pyrimidinone-oxadiazolyl indolinones were prepared. The synthesized indole derivatives of oxadiazolyl-pyrimidinones were tested for their antimicrobial and antioxidant activities.

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## EXPERIMENTAL

Melting points were determined using MP-DS, TID 2000 apparatus Veego Instruments Corporation (India) and were uncorrected. IR spectra were recorded using KBr on a JASCO FT/IR-410 spectrophotometer (Japan). $^1$H NMR spectra were recorded in $CDCl_3$ on FT-NMR Brucker (Germany) using tetramethyl silane as internal standard. Mass spectra were recorded on a SHIMADZU QP 5000 mass spectrometer (70 eV) (Japan). Microanalysis was done on a Perkin Elmer model 240 CHN analyzer (USA). Purity of the products was tested by using TLC glass plates coated with silica gel G and ethanol/chloroform/pyridine/hexane (1:1:4:2) as the developing solvent.

Synthetic pathway is depicted in Scheme 1 and physico-chemical data are given in Tables I and II.

*Table I. Analytical data for compounds **3a-i** and **4a-i***

| Compd. No | Yield (%) | M.p. (°C) | Molecular formula | Elemental analysis (%) calcd./found | | |
|---|---|---|---|---|---|---|
| | | | | C | H | N |
| **3a** | 62 | 342–344 | $C_{13}H_{13}N_5O_2$ | 57.56/57.28 | 4.79/4.9 | 25.83/25.71 |
| **3b** | 68 | 301–303 | $C_{13}H_{12}ClN_5O_2$ | 51.14/51.32 | 3.93/3.79 | 22.95/22.76 |
| **3c** | 56 | 298–300 | $C_{13}H_{11}ClN_5O_2$ | 46.01/45.86 | 3.24/3.41 | 20.65/20.81 |
| **3d** | 67 | 230–232 | $C_{16}H_{19}N_5O_5$ | 53.18/53.29 | 5.26/5.40 | 19.39/19.27 |
| **3e** | 68 | 217–219 | $C_{16}H_{19}N_5O_2$ | 61.34/61.16 | 6.07/6.23 | 22.36/22.47 |
| **3f** | 70 | 298–299 | $C_{13}H_{12}N_6O_4$ | 49.37/49.51 | 3.79/3.92 | 26.58/26.62 |
| **3g** | 71 | 290–292 | $C_{13}H_{12}FN_5O_2$ | 54.17/54.29 | 4.17/4.27 | 24.30/24.41 |
| **3h** | 69 | 308–310 | $C_{15}H_{18}N_6O_2$ | 57.32/57.23 | 5.73/5.49 | 26.75/26.89 |
| **3i** | 70 | 302–304 | $C_{14}H_{15}N_5O_4$ | 52.99/52.79 | 4.73/4.61 | 22.08/22.21 |
| **4a** | 60 | 184–186 | $C_{21}H_{16}N_6O_3$ | 63.00/63.15 | 4.00/4.12 | 21.00/21.12 |
| **4b** | 70 | 240–242 | $C_{21}H_{15}ClN_6O_3$ | 58.06/58.21 | 3.46/3.35 | 19.35/19.42 |
| **4c** | 58 | 200–202 | $C_{21}H_{14}ClN_6O_3$ | 53.73/53.51 | 2.98/3.11 | 17.91/18.02 |
| **4d** | 67 | 196–198 | $C_{24}H_{22}N_6O_6$ | 58.77/58.60 | 4.49/4.63 | 17.14/17.26 |
| **4e** | 68 | 248–250 | $C_{24}H_{22}N_6O_3$ | 65.16/65.27 | 4.97/5.10 | 19.00/19.18 |
| **4f** | 70 | 222–224 | $C_{21}H_{15}N_7O_5$ | 56.63/56.72 | 3.37/3.47 | 22.02/22.20 |
| **4g** | 62 | 208–210 | $C_{21}H_{15}FN_6O_3$ | 60.29/60.37 | 3.59/3.75 | 20.09/20.17 |
| **4h** | 65 | 297–299 | $C_{23}H_{21}N_7O_3$ | 62.30/62.07 | 4.74/4.49 | 22.12/22.01 |
| **4i** | 72 | 198–200 | $C_{22}H_{18}N_6O_5$ | 59.19/59.29 | 4.03/4.19 | 18.83/18.72 |

*Synthesis of ethyl 6-methyl-2-oxo-4-aryl-1,2,3,4-tetrahydro pyrimidin-5-carboxylates (**1a-i**) (16)*

Urea (0.5 mol), ethylacetoacetate (0.75 mol) and aromatic aldehyde (0.75 mol) were mixed in ethanol (25 mL). A catalytic amount of conc. HCl was added to the mixture, which was then refluxed for three hours. The contents were kept in refrigerator overnight. The solid separated out was filtered off. The filtrate was further refluxed on a water bath for 1.5 hour. A solid separated out on cooling was filtered and recrystallized from ethanol [m.p. 210–212 °C; m.p. lit. 210 °C (16)].

*Synthesis of 6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidin-5-carbohydrazides (**2a-i**) (16)*

To 0.1 mol of **1a** in ethanol (20 mL), hydrazine hydrate (0.1 mol) was added, followed by a catalytic amount of conc. $H_2SO_4$ (3 drops). The mixture was refluxed for two hours. Excess solvent was removed and, on cooling, a solid was formed. The solid was crystallized from ethanol [m.p. 196–198 °C; lit. 197 °C (16)].

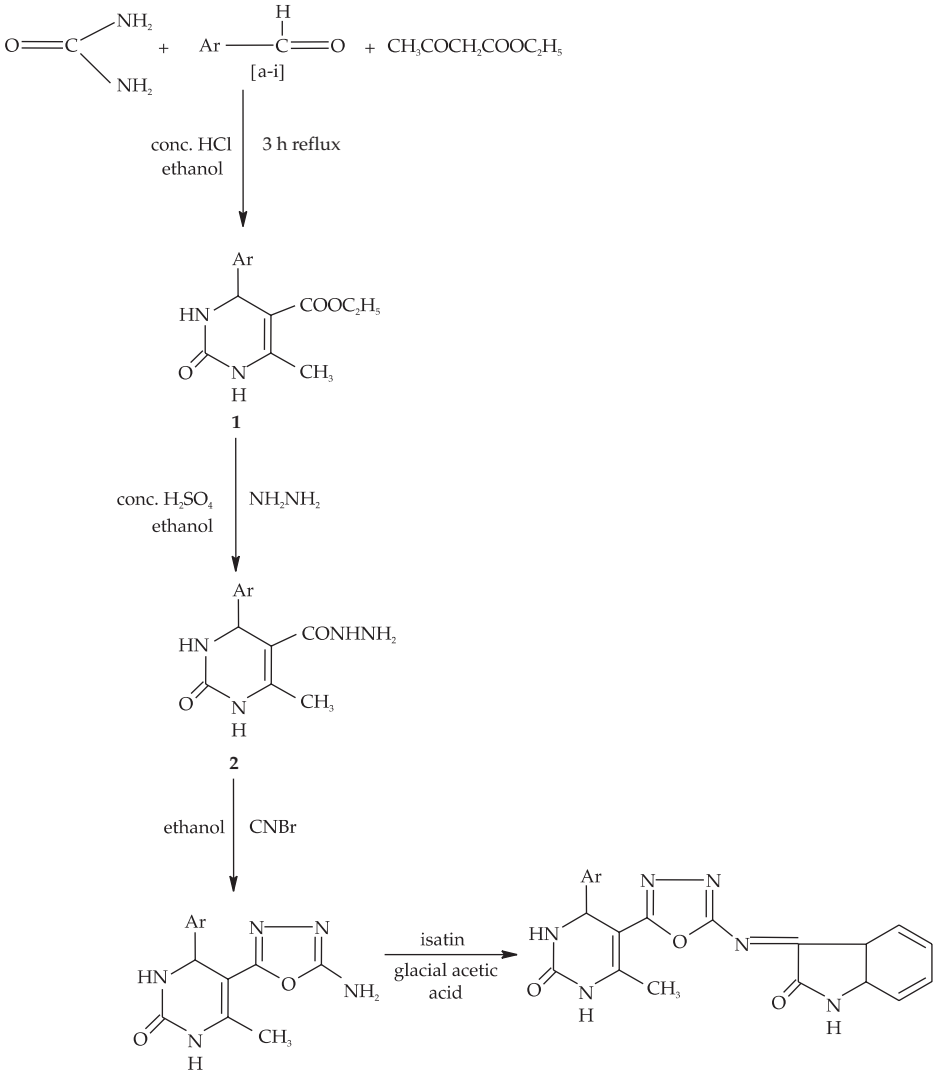
*Synthesis of 5-(5-amino-1,3,4-oxadiazol-2-yl)-6-methyl-4-aryl-2-oxo-1,2,3,4-tetrahydropyrimidin-2-(1H)-ones (**3a-i**)*

To 0.01 mol of **2a** in absolute ethanol (25 mL), an aqueous solution of sodium bicarbonate (2 g in 5 mL water) was added and stirred for a few minutes at room temperature. Cyanogen bromide (0.01 mol, 1.05 g) was then added and stirring was continued for 36 h. Concentration of the reaction mixture to ¼ of its volume left a residue, which was poured over crushed ice (10). The solid separated was filtered, dried and crystallized from ethanol when product **3a** was obtained. The procedure was repeated for other compounds of the series. The analytical data are given in Table I.

*Table II. IR, $^1$H NMR and mass spectral data for compounds **3a-i** and **4a-i***

| Compd. No. | Mass (*m*/z) | IR ($\nu$, cm$^{-1}$) | $^1$H NMR ($\delta$, ppm) |
|---|---|---|---|
| **3a** | 269 | 3480, 2927, 1734, 1608, 1571, 1247 | 7.48–7.62 (m, 5H, Ar-H), 6.85–6.93 (d, 1H, $C_4$-H), 5.1 (s, 1H, $N_1$-H), 5.31–5.34 (d, 1H, $N_3$-H), 5.42 (s, 2H, $NH_2$), 1.26 (s, 3H, $C_6$-$CH_3$) |
| **3b** | 303 | 3475, 2922, 1732, 1615, 1574, 1340 | 7.58–7.86 (m, 4H, Ar-H), 6.86–6.94 (d, 1H, $C_4$-H), 5.3 (s, 1H, $N_1$-H), 5.35–5.44 (d, 1H, $N_3$-H), 5.60 (s, 2H, $NH_2$), 1.28 (s, 3H, $C_6$-$CH_3$) |
| **3c** | 338 | 3479, 2925, 1725, 1611, 1576, 1349 | 7.52–8.34 (m, 3H, Ar-H), 6.88–7 (d, 1H, $C_4$-H), 5.37–5.48 (d, 1H, $N_3$-H), 5.5 (s, 1H, $N_1$-H), 5.62 (s, 2H, $NH_2$) 1.3 (s, 3H, $C_6$-$CH_3$) |
| **3d** | 359 | 3470, 2921, 1727, 1615, 1579, 1342 | 7.35–7.76 (m, 2H, Ar-H), 6.84–6.91 (d, 1H, $C_4$-H), 5.0 (s, 1H, $N_1$-H), 5.32–5.4 (d, 1H, $N_3$-H), 5.64 (s, 2H, $NH_2$), 1.24 (s, 3H, $C_6$-$CH_3$), 3.8 (s, 6H, C'$_3$-$OCH_3$, C'$_5$-$OCH_3$), 3.7 (s, 3H, $C_4$-$OCH_3$) |

| | | | |
|---|---|---|---|
| **3e** | 311 | 3472, 2930, 1739, 1620, 1574, 1345 | 7.3–7.75 (m, 4H, Ar-H), 6.85–6.94 (d, 1H, $C_4$-H), 5.12 (s, 1H, $N_1$-H), 5.33–5.41 (d, 1H, $N_3$-H), 5.58 (s, 2H, $NH_2$), 2.89–3.00 (m, 1H, $C'_4$-CH), 1.2–1.4 (d, 6H, $C'_4$-$CH(CH_3)_2$), 1.24 (s, 3H, $C_6$-$CH_3$) |
| **3f** | 314 | 3480, 2926, 1736, 1617, 1577, 1347 | 7.62–8.32 (m, 4H, Ar-H), 6.98–7.1 (d, 1H, $C_4$-H), 5.32 (s, 1H, $N_1$-H), 5.48–5.59 (d, 1H, $N_3$-H), 5.6 (s, 2H, $NH_2$), 1.4 (s, 3H, $C_6$-$CH_3$) |
| **3g** | 287 | 3482, 2923, 1737, 1609, 1572, 1340 | 7.4–7.73 (m, 4H, Ar-H), 6.87–6.95 (d, 1H, $C_4$-H), 5.2 (s, 1H, $N_1$-H), 5.36–5.38 (d, 1H, $N_3$-H), 5.44 (s, 2H, $NH_2$), 1.29 (s, 3H, $C_6$-$CH_3$) |
| **3h** | 312 | 3486, 2929, 1731, 1617, 1578, 1350 | 7.29–7.82 (m, 4H, Ar-H), 6.83–6.92 (d, 1H, $C_4$-H), 4.8 (s, 1H, $N_1$-H), 5.28–5.32 (d, 1H, $N_3$-H), 5.4 (s, 2H, $NH_2$), 1.57 (s, 6H, $C'_4$-$N(CH_3)_2$), 1.24 (s, 3H, $C_6$-$CH_3$) |
| **3i** | 315 | 3478, 2924, 1728, 1619, 1580, 1346 | 7.7 (s, 1H, OH), 7.25–7.75 (m, 3H, Ar-H), 6.83–6.90 (d, 1H, $C_4$-H), 4.87 (s, 1H, $N_1$-H), 5.30–5.32 (d, 1H, $N_3$-H), 5.41 (s, 2H, $NH_2$), 3.8 (s, 3H, $OCH_3$), 1.22 (s, 3H, $C_6$-$CH_3$) |
| **4a** | 400 | 3478, 2927, 1734, 1608, 1571, 1247, 1222 | 9.3 (s, 1H, $N_1'$-H), 7.3–7.9 (m, 9H, Ar-H), 6.85–6.93 (d, 1H, $C_4$-H), 5.34–5.42 (d, 1H, $N_3$-H), 5.1 (s, 1H, $N_1$-H), 1.26 (s, 3H, $C_6$-$CH_3$) |
| **4b** | 434 | 3475, 2922, 1732, 1615, 1574, 1340, 1215 | 9.4 (s, 1H, $N_1'$-H), 7.4–8.0 (m, 8H, Ar-H), 6.86–6.94 (d, 1H, $C_4$-H), 5.35–5.44 (d, 1H, $N_3$-H), 5.3 (s, 1H, $N_1$-H), 1.28 (s, 3H, $C_6$-$CH_3$) |
| **4c** | 469 | 3479, 2925, 1725, 1611, 1576, 1349, 1225 | 9.6 (s, 1H, $N_1'$-H), 7.46–8.24 (m, 7H, Ar-H), 6.88–7 (d, 1H, $C_4$-H), 5.37–5.48 (d, 1H, $N_3$-H), 5.5 (s, 1H, $N_1$-H), 1.3 (s, 3H, $C_6$-$CH_3$) |
| **4d** | 490 | 1471, 2921, 1727, 1615, 1579, 1342, 1217 | 9.1 (s, 1H, $N_1'$-H), 7.2–7.8 (m, 6H, Ar-H), 6.84–6.91 (d, 1H, $C_4$-H), 5.32–5.4 (d, 1H, $N_3$-H), 5.0 (s, 1H, $N_1$-H), 1.24 (s, 3H, $C_6$-$CH_3$), 3.8 (s, 6H, $C'_3$-$OCH_3$, $C'_5$-$OCH_3$), 3.7 (s, 3H, $C_4$-$OCH_3$) |
| **4e** | 442 | 3474, 2930, 1739, 1620, 1574, 1345, 1219 | 9.1 (s, 1H, $N_1'$-H), 7.29–7.85 (m, 8H, Ar-H), 6.85–6.94 (d, 1H, $C_4$-H), 5.33–5.41 (d, 1H, $N_3$-H), 5.12 (s, 1H, $N_1$-H), 2.89–3.00 (m, 1H, $C'_4$-CH), 1.2–1.4 (d, 6H, $C'_4$-$CH(CH_3)_2$), 1.24 (s, 3H, $C_6$-$CH_3$) |
| **4f** | 445 | 3477, 2926, 1736, 1617, 1577, 1347, 1220 | 9.7 (s, 1H, $N_1'$-H), 7.56–8.36 (m, 8H, Ar-H), 6.98–7.1 (d, 1H, $C_4$-H), 5.48–5.59 (d, 1H, $N_3$-H), 5.6 (s, 1H, $N_1$-H), 1.4 (s, 3H, $C_6$-$CH_3$) |
| **4g** | 418 | 3470, 2923, 1737, 1609, 1572, 1340, 1224 | 9.32 (s, 1H, $N_1'$-H), 7.39–7.98 (m, 8H, Ar-H), 6.87–6.95 (d, 1H, $C_4$-H), 5.36–5.44 (d, 1H, $N_3$-H), 5.2 (s, 1H, $N_1$-H), 1.29 (s, 3H, $C_6$-$CH_3$) |
| **4h** | 443 | 3476, 2929, 1731, 1617, 1578, 1350, 1216 | 9.28 (s, 1H, $N_1'$-H), 7.28–7.92 (m, 8H, Ar-H), 6.83–6.92 (d, 1H, $C_4$-H), 5.32–5.4 (d, 1H, $N_3$-H), 4.8 (s, 1H, $N_1$-H), 1.57 (s, 6H, $C'_4$-$N(CH_3)_2$), 1.24 (s, 3H, $C_6$-$CH_3$) |
| **4i** | 446 | 3469, 2924, 1728, 1619, 1580, 1346, 1219 | 9.27 (s, 1H, $N_1'$-H), 7.7 (s, 1H, OH), 7.25–7.89 (m, 7H, Ar-H), 6.83–6.90 (d, 1H, $C_4$-H), 5.31–5.41 (d, 1H, $N_3$-H), 4.87 (s, 1H, $N_1$-H), 3.8 (s, 3H, $OCH_3$), 1.22 (s, 3H, $C_6$-$CH_3$) |




Ar = a: $C_6H_5$, b: 2-Cl-$C_6H_4$, c: 2,4-$(Cl)_2$-$C_6H_3$, d: 3,4,5-$(OCH_3)_3$-$C_6H_2$,
e: 4-$CH(CH_3)_2$-$C_6H_4$, g: 4-F-$C_6H_4$, h: 3-OH-4-$OCH_3$-$C_6H_3$, i: 4-$N(CH_3)_2$-$C_6H_4$

Scheme 1

*Synthesis of 3-{[5-(6-methyl-4-aryl-2-oxo-1,2,3,4-tetrahydropyrimidin-5-yl)-1,3,4-oxadiazol-2-yl]-imino}-1,3-dihydro-*2H*-indol-2-one (**4a-i**)*

Compound **3a** (0.01 mol) and isatin (0.01 mol) were refluxed in methanol in the presence of a catalytic amount of glacial acetic acid for 30 min and cooled. The solid separated was filtered off and crystallized (17). The other derivatives were prepared in the same manner. The analytical and spectral data are given in Tables I and II.

## *Antibacterial and antifungal studies*

Antibacterial screening of the synthesized compounds **4a-i** was performed by the agar disc diffusion method (17). The organisms used were *Staphylococcus aureus* (NCIM 2079), *Bacillus subtilis* (NCIM 2063), *Escherichia coli* (NCIM 2118) and *Pseudomonas aeruginosa* (NCIM 2036). The minimum inhibitory concentration (*MIC*) was determined by the serial dilution technique using dimethyl sulphoxide (DMSO) as solvent. DMSO was used as a negative control. Ciprofloxacin was used as the standard in all antibacterial screening studies.

The antifungal screening of compounds **4a-i** was done by the agar disc diffusion method (18)**.** *Aspergillus niger* (NCIM 596) and *Candida albicans* (NCIM 3102) were used as test organisms. Dimethyl sulphoxide was used as a solvent and fluconazole was used as a standard. A control experiment with dimethyl sulphoxide alone was done for antifungal studies.

The results of antimicrobial studies are presented in Table III.

*Table III. MIC data for compounds **4a-i**[a]*

| Compd. No. | **4a** | **4b** | **4c** | **4d** | **4e** | **4f** | **4g** | **4h** | **4i** | Reference |
|---|---|---|---|---|---|---|---|---|---|---|
| *S. aureus*[c] | 25.0 | 100.0 | 50.0 | 12.5 | 200.0 | 25.0 | 50.0 | 200.0 | 50.0 | 12.5 |
| *P. aeruginosa*[c] | 25.0 | 150.0 | 100.0 | 50.0 | 200.0 | 100.0 | 100.0 | 150.0 | 25.0 | 25.0 |
| *E. coli*[c] | 12.5 | 150.0 | 50.0 | 12.5 | 100.0 | 25.0 | 100.0 | 100.0 | 12.5 | 6.0 |
| *B. subtilis*[c] | 6.0 | 100.0 | 12.5 | 6.0 | 15.0 | 25.0 | 100.0 | 100.0 | 6.0 | 6.0 |
| *A. niger*[d] | 12.5 | 100.0 | 100.0 | 12.5 | 100.0 | 25.0 | 100.0 | 150.0 | 6.0 | 12.5 |
| *C. albicans*[d] | 25.0 | 150.0 | 50.0 | 6.0 | 200.0 | 25.0 | 200.0 | 100.0 | 6.0 | 6.0 |

[a] $\mu g\ mL^{-1}$; [b] solvent DMSO; [c] reference standard ciprofloxacin; [d] reference standard fluconazole.

## *Antioxidant studies*

Free radical scavenging activity of the test compounds **4a-i** was studied by the diphenyl picryl hydrazyl (DPPH) assay method (19). Drug stock solution (1 mg $mL^{-1}$) was diluted to final concentrations of 2, 4, 6, 8 and 10 $\mu g\ mL^{-1}$ in methanol. DPPH methanol solution (1 mL, 0.3 mmol) was added to 2.5 mL of drug solutions of different concentra-

tions and allowed to react at room temperature. After 30 min the absorbance values were measured at 518 nm and converted into the percentage antioxidant activity. Methanol was used as the solvent and ascorbic acid as the standard. The trials were done in triplicate. The inhibitory concentration ($IC_{50}$) value, representing the concentration required to exhibit 50% antioxidant activity, was extrapolated from the graph plotted with percentage antioxidant activity (AA %) on the y axis and concentration on the x axis (Fig. 1). Results are presented in Table IV.

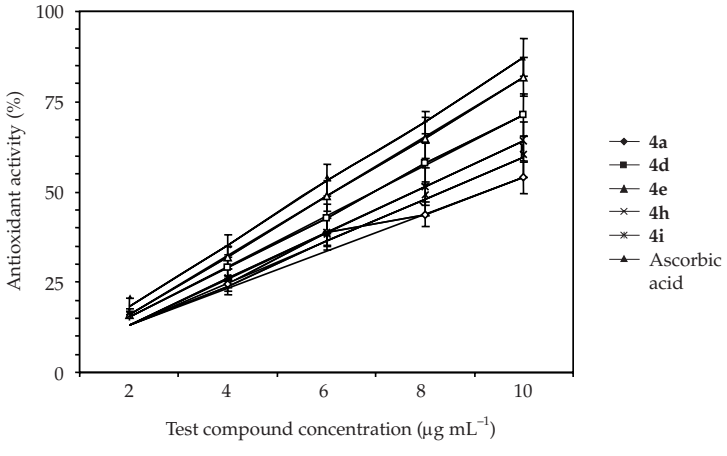



Fig. 1. Screening of antioxidant activity by the DPPH assay.

*Table IV. Antioxidant activity of compounds* ***4a-i***

| Compd. No. | $IC_{50}$[b] (μg mL$^{-1}$)[a] |
|---|---|
| **4a** | 9.21 ± 0.71 |
| **4b** | c |
| **4c** | c |
| **4d** | 7.03 ± 0.64 |
| **4e** | 6.2 ± 0.55 |
| **4f** | c |
| **4g** | c |
| **4h** | 7.21 ± 0.15 |
| **4i** | 8.42 ± 0.84 |
| Ascorbic acid[a] | 5.68 ± 0.46 |

[a] Standard substance.
[b] Mean ± SD, $n$ = 3.
[c] Low antioxidant activity ($IC_{50}$ > 10 μg mL$^{-1}$).

## RESULTS AND DISCUSSION

The reaction of 6-methyl-2-oxo-4-aryl-1,2,3,4-tetrahydropyrimidin-5-carbohydrazides (**2a-i**) with cyanogen bromide ended up in the formation of 5-(5-amino-1,3,4-oxadiazol--2-yl)-6-methyl-4-aryl-3,4-dihydropyrimidin-2(1*H*)-ones (**3a-i**). The reaction of 5-(5-amino-1,3,4-oxadiazol-2-yl)-6-methyl-4-aryl-3,4-dihydropyrimidine-2-ones (**3a-i**) with isatin gave the target compounds 3-{[5-(6-methyl-4-aryl-2-oxo-1,2,3,4-tetrahydropyrimidin-5--yl)-1,3,4-oxadiazol-2-yl]-imino}-1,3-dihydro-2*H*-indol-2-ones (**4a-i**).

In the present study, the intermediate 5-(5-amino-1,3,4-oxadiazol-2-yl)-6-methyl-4--aryl-3,4-dihydropyrimidin-2(1*H*)-ones (**3a**), formed by the reaction of 6-methyl-2-oxo-4--aryl-1,2,3,4-tetrahydropyrimidin-5-carbohydrazide (**2a**) with cyanogen bromide, showed IR bands at 3480, 2927, 1734, 1608, 1571 and 1247 $cm^{-1}$, respectively, for N-H, C-H aliphatic, C=O aromatic, C=C aromatic, C=N and C-N. The $^1H$ NMR spectra (Table II) showed multiplets between $\delta$ 7.48–7.62 ppm indicating the presence of five aromatic protons. A doublet at 5.34–5.42 ppm represents the proton attached to nitrogen at the third position of pyrimidine and that at 5.1 ppm accounted for the proton attached to nitrogen at the first position of pyrimidine. A singlet at $\delta$ 5.3 ppm accounted for the amino protons. A singlet at $\delta$ 1.26 ppm accounted for methyl proton on the pyrimidine nucleus. The mass spectrum showed the molecular ion *m/z* at 269. Product **3a** on refluxing with isatin for 30 min afforded 3-{[5-(6-methyl-4-aryl-2-oxo-1,2-tetrahydropyrimidin-5-yl)--1,3,4-oxadiazol-2-yl]-imino}-1,3-dihydro-2*H*-indol-2-ones (**4a**). IR spectra (Table II) showed bands at 3478, 2927, 1734, 1608, 1571, 1347 and 1222 $cm^{-1}$, respectively, for N-H, C-H aliphatic, C=O aromatic, C=C aromatic, C=N and C-N. $^1H$ NMR spectra (Table II) showed a singlet at $\delta$ 9.3 ppm corresponding to NH indole. Multiplets between $\delta$ 7.3–7.9 ppm showed the presence of nine aromatic protons. A doublet at $\delta$ 5.34–5.42 ppm represents the proton attached to nitrogen at the third position of pyrimidine and that at 5.1 ppm accounted for the proton attached to nitrogen at the first position of pyrimidine. A singlet at $\delta$ 1.26 ppm accounted for methyl proton on the pyrimidine nucleus. The mass spectrum showed the molecular ion *m/z* at 400. Major fragmentation peaks appeared at 147, 137, 119, 92 and 43.

Elemental analysis data together with spectral data revealed that compounds **4a-i** were successfully synthesized.

Antibacterial, antifungal and antioxidant activities of all the newly prepared compounds are shown in Tables III and IV.

The antibacterial activity of compounds **4a**, **4d** and **4i** is considerable and is equivalent to that of the reference drug ciprofloxacin. Compound **4a** with unsubstituted phenyl subtituent showed the highest degree of activity against *Pseudomonas aeruginosa* and *Bacillus subtilis*, **4d** with trimethoxy phenyl subtituent against *Staphylococcus aureus* and *Bacillus subtilis*, whereas **4i** possess *p*-amino dimethyl phenyl group showed activity against *Bacillus subtilis* and *Pseudomonas aeruginosa*.

The antifungal studies showed that **4i** possesses superior activity against *Aspergillus niger* than the other compounds and the reference drug fluconazole. Compounds **4a** and **4d** also possess comparable activity against *Aspergillus niger* when compared to the standard. Both **4d** and **4i** showed equivalent activity with reference drug against *Candida albicans*.

The above studies revealed that compounds **4a**, **4d** and **4i** showed comparable antimicrobial activity against the tested bacteria and fungi. The unsubstituted phenyl, trimethoxy phenyl and *p*-amino dimethyl phenyl derivatives of the title compound were found to be the lead antimicrobial agents.

The antioxidant studies revealed that compound **4e** with isopropyl substitution showed the best free radical scavenging activity, comporable to that of ascorbic acid, followed by **4d** and **4h** which showed comparable activity.

## CONCLUSION

Antimicrobial studies revealed that the most promising compounds are **4i** (3-{5-[6--methyl-4-(4,4-dimethylaminophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidin-5-yl]-1,2,3,4-oxadiazol-2-yl}-imino-1,3-(dihydro-2*H*-indol-2-one); **4d** (3-{5-[6-methyl-4-(3,4,5-bimethoxyphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidin-5-yl]-1,3,4-oxadiazol-2-yl}imino-1,3-dihydro-2*H*-indol-2-one); and **4a** (3-{[5-(6-methyl-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidin--5-yl)-1,3,4-oxadiazol-2-yl]-imino}-1,3-dihydro-2*H*-indol-2-one). Based on the above studies, the promising compounds can be evaluated for *in vivo* antimicrobial studies as a future perspective. Antioxidant activity of **4e** shows promise for future antimitotic screening.

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*S A Ž E T A K*

## Sinteza i biološko djelovanje derivata 3-{[5-(6-metil-4-aril-2-okso-1,2,3,4-tetrahidropirimidin-5-il)--1,3,4-oksadiazol-2-il]-imino}-1,3-dihidro-2*H*-indol-2-ona

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Derivati 6-metil-2-okso-4-aril-1,2,3,4-tetrahidropirimidin-5-karbohidrazida (**2a-i**) pripravljeni su reakcijom etil-6-metil–2-okso-4-aril-1,2,3,4-tetrahidropirimidin-5-karboksilata (**1a-i**) i hidrazin hidrata. Iz njih su sa cijanogen bromidom priređeni 5-(5-amino-1,3,4--oksadiazol-2-il)-6-metil-4-aril-3,4-dihidropirimidin-2(1*H*)-oni (**3a-i**). Kondenzacijom nastalih aminooksadiazolilpirimidinona s izatinom dobiveni su 3-{[5-(6-metil-4-aril-2-okso-

-1,2-tetrahidropirimidin-5-il)-1,3,4-oksadiazol-2-il]-imino}-1,3-dihidro-2*H*-indol-2-oni (**4a-i**). Produkti **4** karakterizirani su uobičajenim spektroskopskim metodama (IR, $^1$H NMR, spektar masa) i elementarnom analizom. Biološko vrednovanje ukazuje da spojevi **4a-i** imaju značajno antibakterijsko, antimikotsko i antioksidativno djelovanje.

*Ključne riječi:* pirimidinil oksadiazol amini, pirimidinon oksadiazolil indolinoni, antibakterijsko, antimikotsko i antioksidativno djelovanje

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