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Synthesis and antimicrobial activity of 3,4-dihydropyrimidin-2(1*H*)-one derivatives containing a hydrazone moiety

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Abstract: The title compounds were synthesized and characterized by IR, ^{1}H NMR, ^{13}C NMR and HRMS data. Their antimicrobial activities against bacterial strains *Escherichia coli* and fungal strains *Aspergillus niger* were evaluated.

Keywords: 3,4-dihydropyrimidin-2(1*H*)-ones; antimicrobial activity; hydrazone; synthesis.

Introduction

3,4-Dihydropyrimidin-2(1*H*)-ones have attracted considerable attention due their wide range of biological activities, including antitumor [1], antioxidative [2], antibacterial [3], antifungal [4], anti-inflammatory [5] and antihypertensive properties [6]. They have also been identified as calcium channel modulators [7], A_{2B} adenosine receptor antagonists [8], HIV-1 replication inhibitors [9] and human DNA ligase 1 inhibitors [10]. Hydrazones also exhibit a wide range of diverse biological activities [11–17]. In view of the biological significance of 3,4-dihydropyrimidin-2(1*H*)-ones and hydrazones, we designed and synthesized a series of novel 3,4-dihydropyrimidin-2(1*H*)-one derivatives bearing a hydrazone moiety and evaluated their antimicrobial activities against bacterial strains *Escherichia coli* and fungal strains *Aspergillus niger*.

Results and discussion

The preparation of target compounds **3a–r** is shown in Scheme 1. First, 5-methoxycarbonyl-4-[(4-methoxycarbonyl)phenyl]-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (**1a**) and its 5-ethoxycarbonyl analog **1b** were synthesized by three-component condensation reaction of ethyl acetoacetate or methyl acetoacetate, urea and 4-methoxycarbonylbenzaldehyde in ethanol in the presence of *p*-toluenesulfonic acid as catalyst. Then, products **1a** and **1b** were allowed to react with hydrazine in ethanol under reflux to afford the corresponding hydrazine derivatives **2a** and **2b**. Apparently for steric reasons, the methoxycarbonyl or ethoxycarbonyl group (COR_1) at the dihydropyrimidinone ring of **1a** and **1b** did not react with hydrazine to give the hypothetical compound **4**. In the final step, the target compounds **3a–r** were prepared by a condensation reaction of **2a** or **2b** with different aromatic aldehydes in ethanol in the presence of acetic acid. Structures of all synthetic compounds were confirmed by analysis of IR, ^{1}H NMR, ^{13}C NMR and HRMS data.

All synthesized compounds were evaluated for their antimicrobial activities against bacterial strains *E. coli* and fungal strains *A. niger*. All compounds show moderate inhibitory effect against the bacterial and fungal strains. Most of them show better inhibitory activity than the starting materials **1a** and **1b**. Compounds **3b**, **3f**, **3i**, **3j** and **3l** demonstrate good antibacterial activity which is nearly equal to that of the reference antibiotic ciprofloxacin. Compound **3a** is an excellent antifungal agent, the activity of which is comparable to that of the reference antibiotic fluconazole.

Conclusions

New 3,4-dihydropyrimidin-2(1*H*)-ones containing a hydrazone moiety were designed, synthesized and evaluated for antimicrobial activities against *E. coli* and *A. niger*. All compounds show moderate inhibitory activities against *E. coli* and *A. niger*. Compounds **3b**, **3f**, **3i**, **3j** and **3l** show good antibacterial activity and compound **3a** is an excellent antifungal agent.

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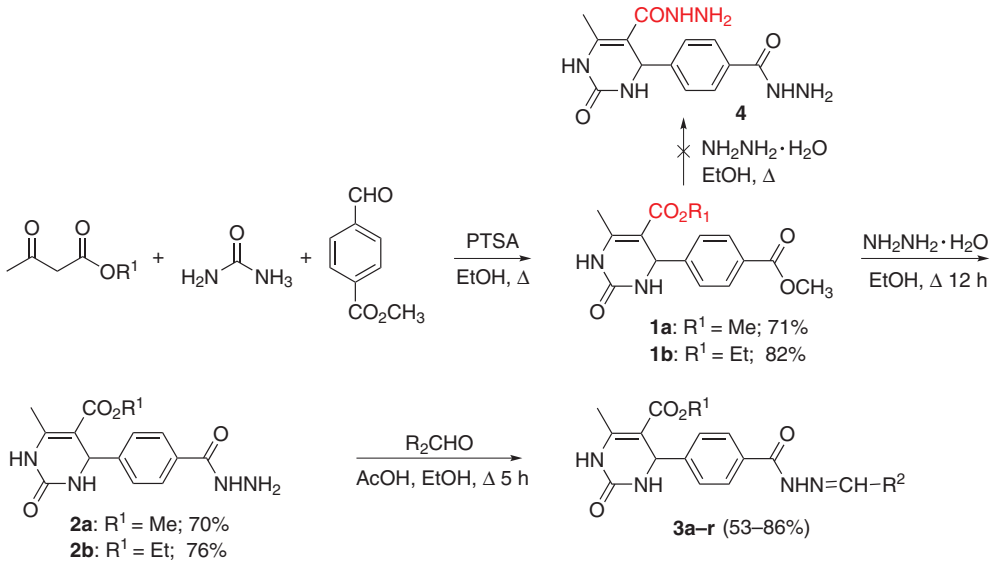

3a: R^1 = Me; R^2 = Ph
3b: R^1 = Me; R^2 = 4-methoxy-C_6H_4
3c: R^1 = Me; R^2 = 4-(N,N-dimethylamino)-C_6H_4
3d: R^1 = Me; R^2 = 2-hydroxy-C_6H_4
3e: R^1 = Me; R^2 = 4-nitro-C_6H_4
3f: R^1 = Me; R^2 = 4-chloro-C_6H_4
3g: R^1 = Me; R^2 = 4-bromo-C_6H_4
3h: R^1 = Me; R^2 = 3-nitro-C_6H_4
3i: R^1 = Me; R^2 = 2,4-dichloro-C_6H_4
3j: R^1 = Et; R^2 = Ph
3k: R^1 = Et; R^2 = 4-methoxy-C_6H_4
3l: R^1 = Et; R^2 = 4-(N,N-dimethylamino)-C_6H_4
3m: R^1 = Et; R^2 = 2-hydroxy-C_6H_4
3n: R^1 = Et; R^2 = 4-nitro-C_6H_4
3o: R^1 = Et; R^2 = 4-chloro-C_6H_4
3p: R^1 = Et; R^2 = 4-bromo-C_6H_4
3q: R^1 = Et; R^2 = 3-nitro-C_6H_4
3r: R^1 = Et; R^2 = 2,4-dichloro-C_6H_4

Scheme 1

Experimental

Reagents were purchased from commercial sources and used without further purification. Melting points were determined on a Yanaco micro melting point apparatus and are uncorrected. Infrared spectra were recorded on a Nicolet 6700 infrared spectrometer. NMR spectra were recorded at 400 MHz (^{1}H) and 100 MHz (^{13}C) on a Bruker spectrometer using TMS as an internal standard and DMSO-d_6 as solvent. High resolution mass spectra (HRMS) were obtained on a Thermo Scientific spectrometer using electrospray ionization (ESI).

General procedure for the preparation of 1a and 1b

These compounds were prepared using the following modification of a published procedure [18]. A mixture of ethyl acetoacetate or methyl acetoacetate (20 mmol), urea (20 mmol), 4-methoxycarbonylbenzaldehyde (20 mmol) and *p*-toluenesulfonic acid (10 mol%) in ethanol (100 mL) was stirred and heated under reflux. After cooling, the resulting solid product was filtered and crystallized from ethanol to afford pure compound **1a,b**.

4-[4-(Methoxycarbonyl)phenyl]-5-methoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (1a) White solid; yield 71%; mp 247–249°C; ^{1}H NMR: δ 9.28 (s, 1H, -NH), 7.92 (d, 2H, *J* = 7 Hz, Ar-H), 7.82 (s, 1H, NH), 7.37 (d, 2H, *J* = 7 Hz, Ar-H), 5.21 (s, 1H, CH), 3.84 (s, 3H, OCH_3), 3.53 (s, 3H, OCH_3), 2.25 (s, 3H, CH_3). HRMS. Calcd for $C_{15}H_{16}N_2O_5$, $[M]^+$: *m/z* 304.1054. Found: *m/z* 304.1052.

5-Ethoxycarbonyl-4-[4-(methoxycarbonyl)phenyl]-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (1b) White solid; yield 82%; mp 191–193°C; ^{1}H NMR: δ 9.27 (s, 1H, -NH), 7.93 (d, 2H, *J* = 8 Hz, Ar-H), 7.82 (s, 1H, -NH), 7.38 (d, 2H, *J* = 8 Hz, Ar-H), 5.22 (d, 1H, *J* = 3 Hz, CH), 3.99–3.96 (m, 2H, OCH_2), 3.83 (s, 3H, OCH_3), 2.26 (s, 3H, CH_3), 1.08 (t, 3H, *J* = 7 Hz, OCH_2CH_3). HRMS. Calcd for $C_{16}H_{19}N_2O_5$, $[M+H]^+$: *m/z* 319.1288. Found: *m/z* 319.1299.

General procedure for the preparation of 2a and 2b

A solution of **1a** or **1b** (10 mmol) and hydrazine hydrate (80%, 50 mmol) in absolute ethanol (20 mL) was heated under reflux for 12 h. Upon cooling, the resultant precipitate was filtered and crystallized from ethanol to give the hydrazide derivative **2a,b**.

4-[4-(Hydrazinocarbonyl)phenyl]-5-methoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (2a) White solid; yield 70%; mp 273–275°C; ^{1}H NMR: δ 9.69 (s, 1H, NH), 9.25 (s, 1H, NH), 7.78 (s, 1H, NH), 7.74 (d, 2H, *J* = 8 Hz, Ar-H), 7.27 (d, 2H, *J* = 8 Hz, Ar-H), 5.17 (d, 1H, *J* = 3.5 Hz, CH), 4.47 (s, 2H, NH_2), 3.53 (s, 3H, OCH_3), 2.25 (s, 3H, CH_3). HRMS. Calcd for $C_{14}H_{17}N_4O_4$, $[M+H]^+$: *m/z* 305.1224. Found: *m/z* 305.1235.

5-Ethoxycarbonyl-4-[4-(hydrazinocarbonyl)phenyl]-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (2b) White solid; yield 76%; mp

268–269°C; ^{1}H NMR: δ 9.71 (s, 1H, NH), 9.24 (s, 1H, NH), 7.77 (d, 3H, *J* = 8 Hz, Ar-H, NH), 7.30 (d, 2H, *J* = 8 Hz, Ar-H), 5.19 (s, 1H, CH), 4.49 (s, 1H, NH_2), 3.98 (d, 2H, *J* = 7 Hz, OCH_2), 2.26 (s, 3H, CH_3), 1.08 (t, 3H, *J* = 7 Hz, OCH_2CH_3); ^{13}C NMR: δ 166.2, 165.7, 152.5, 149.1, 148.1, 132.8, 127.6, 126.6, 99.3, 59.7, 54.2, 18.2, 14.5. HRMS. Calcd for $C_{15}H_{19}N_4O_4$, $[M+H]^+$: *m/z* 319.1401. Found: *m/z* 319.1415.

General procedure for the preparation of 3a–r

A mixture of **2a** or **2b** (2 mmol) and aromatic aldehyde (2.2 mmol) in ethanol/DMF was heated under reflux for 5 h in the presence of catalytic amount of glacial acetic acid, then cooled and poured into ice water. The resultant precipitate was filtered and crystalized from ethanol/DMF to obtain the target compound **3a–r**.

4-[4-(2-Benzylidenehydrazinocarbonyl)phenyl]-5-methoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (3a) White solid; yield 83%; mp 274–277°C; IR: *ν* 3286, 3253, 3054, 2954, 1696, 1643, 1606, 1540, 1434, 1335, 1270, 1235, 1084 cm^{-1}; ^{1}H NMR: δ 11.82 (s, 1H, CH), 9.32 (s, 1H, NH), 8.45 (s, 1H, NH), 7.87 (d, 3H, *J* = 7 Hz, Ar-H, -NH), 7.74 (d, 2H, *J* = 6 Hz, Ar-H), 7.46 (d, 3H, *J* = 6 Hz, Ar-H), 7.39 (d, 2H, *J* = 7 Hz, Ar-H), 5.24 (d, 1H, *J* = 2.8 Hz, CH), 3.56 (s, 3H, OCH_3), 2.29 (s, 3H, CH_3); ^{13}C NMR: δ 166.2, 163.5, 152.5, 149.5, 148.7, 148.2, 134.8, 133.1, 130.5, 129.3, 128.4, 127.6, 126.7, 99.0, 54.2, 51.3, 18.4. HRMS. Calcd for $C_{21}H_{21}N_4O_4$, $[M+H]^+$: *m/z* 393.1557. Found: *m/z* 393.1555.

4-[4-(2-(4-Methoxybenzylidene)hydrazinocarbonyl)phenyl]-5-methoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (3b) White solid; yield 76%; mp 258–260°C; IR: *ν* 3344, 3232, 3145, 3037, 2946, 2838, 1684, 1645, 1607, 1512, 1455, 1439, 1292, 1234, 1106 cm^{-1}; ^{1}H NMR: δ 11.67 (s, 1H, CH), 9.30 (s, 1H, NH), 8.38 (s, 1H, NH), 7.84 (d, 3H, *J* = 7 Hz, Ar-H, NH), 7.68 (d, 2H, *J* = 8 Hz, Ar-H), 7.37 (d, 2H, *J* = 8 Hz, Ar-H), 7.03 (d, 2H, *J* = 8 Hz, Ar-H), 5.23 (d, 1H, *J* = 2.4 Hz, CH), 3.82 (s, 3H, OCH_3), 3.55 (s, 3H, OCH_3), 2.28 (s, 3H, CH_3); ^{13}C NMR: δ 166.2, 163.3, 161.3, 152.5, 149.5, 148.5, 148.1, 133.3, 129.2, 128.3, 127.4, 126.7, 114.8, 99.1, 55.8, 54.2, 51.3, 18.3. HRMS. Calcd for $C_{22}H_{23}N_4O_5$, $[M+H]^+$: *m/z* 423.1663. Found: *m/z* 423.1657.

4-[4-(2-(4-*N*,*N*-Dimethylaminophenylbenzylidene)hydrazinocarbonyl)phenyl]-5-methoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (3c) Yellow solid; yield 75%; mp 188–190°C; IR: *ν* 3435, 3232, 3124, 2942, 1682, 1653, 1627, 1611, 1597, 1523, 1432, 1366, 1337, 1241, 1188, 1088 cm^{-1}; ^{1}H NMR: δ 11.51 (s, 1H, -CH), 9.31 (s, 1H, NH), 8.29 (s, 1H, NH), 7.83 (d, 3H, *J* = 8 Hz, Ar-H, -NH), 7.54 (d, 2H, *J* = 8 Hz, Ar-H), 7.36 (d, 2H, *J* = 8 Hz, Ar-H), 6.76 (d, 2H, *J* = 8 Hz, Ar-H), 5.23 (d, 1H, *J* = 2.4 Hz, CH), 3.55 (s, 3H, OCH_3), 2.98 (s, 6H, $N(CH_3)_2$), 2.28 (s, 3H, CH_3); ^{13}C NMR: δ 166.2, 163.1, 152.5, 152.0, 149.5, 149.1, 148.3, 133.5, 128.9, 128.3, 126.7, 122.1, 112.3, 99.1, 54.2, 51.3, 40.2, 18.3. HRMS. Calcd for $C_{23}H_{26}N_5O_4$, $[M+H]^+$: *m/z* 436.1979. Found: *m/z* 436.1961.

4-[4-(2-(2-Hydroxybenzylidene)hydrazinocarbonyl)phenyl]-5-methoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (3d) White solid; yield 85%; mp 292–294°C; IR: *ν* 3419, 3232, 3158, 3067, 2954, 1690, 1659, 1646, 1619, 1565, 1494, 1436, 1341, 1300, 1245, 1088 cm^{-1}; ^{1}H NMR: δ 12.07 (s, 1H, OH), 11.28 (s, 1H, CH), 9.32 (s, 1H, NH), 8.63 (s, 1H, NH), 7.89 (d, 1H, *J* = 8 Hz, Ar-H), 7.86 (s, 1H, NH),7.55 (d, 1H, *J* = 8 Hz, Ar-H), 7.39 (d, 2H, *J* = 8 Hz, Ar-H), 7.31 (t, 1H, *J* = 8 Hz, Ar-H), 6.95–6.91 (m, 2H, Ar-H), 5.23 (d, 1H, *J* = 3.2 Hz, CH), 3.55 (s, 3H, OCH_3), 2.28 (s, 3H, CH_3); ^{13}C NMR: δ 166.2, 163.2, 157.9, 152.5, 149.6, 148.9, 148.7, 132.5, 131.9, 130.0, 128.5, 126.8, 119.8, 119.1, 116.9, 99.0, 54.2, 51.3, 18.4. HRMS. Calcd for $C_{21}H_{21}N_4O_5$, $[M+H]^+$: *m/z* 409.1506. Found: *m/z* 409.1501.

5-Methoxycarbonyl-6-methyl-4-[4-(2-(4-nitrobenzylidene)hydrazinocarbonyl)phenyl]-3,4-dihydropyrimidin-2(1*H*)-one (3e) White solid; yield 86%; mp 188–190°C; IR: *ν* 3311, 3211, 3108, 3058, 2954, 2838, 1701, 1661, 1607, 1556, 1515, 1431, 1386, 1283, 1222, 1091 cm^{-1}; ^{1}H NMR: δ 12.12 (s, 1H, CH), 9.32 (s, 1H, NH), 8.54 (s, 1H, NH), 8.31 (d, 2H, *J* = 8 Hz, Ar-H), 8.00 (d, 2H, *J* = 8 Hz, Ar-H), 7.88 (d, 3H, *J* = 8 Hz, Ar-H, NH), 7.40 (d, 2H, *J* = 8 Hz, Ar-H), 5.24 (d, 1H, *J* = 3.2 Hz, CH), 3.55 (s, 3H, OCH_3), 2.28(s, 3H, CH_3); ^{13}C NMR: δ 166.2, 163.8, 152.5, 149.6, 149.0, 148.3, 145.7, 141.1, 132.8, 128.6, 128.5, 126.8, 124.5, 99.0, 54.2, 51.3, 18.3. HRMS. Calcd for $C_{21}H_{20}N_5O_6$, $[M+H]^+$: *m/z* 438.1408. Found: *m/z* 438.1412.

4-[4-(2-(4-Chlorobenzylidene)hydrazinocarbonyl)phenyl]-5-methoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (3f) White solid; yield 85%; mp 288–290°C; IR: *ν* 3365, 3253, 3112, 2975, 2822, 1718, 1693, 1654, 1638, 1613, 1539, 1431, 1283, 1231, 1088 cm^{-1}; ^{1}H NMR: δ 11.88 (s, 1H, CH), 9.31 (s, 1H, NH), 8.43 (s, 1H, NH), 7.76 (d, 3H, *J* = 6 Hz, Ar-H, NH), 7.76 (d, 2H, *J* = 8 Hz, Ar-H), 7.53 (d, 2H, *J* = 8 Hz, Ar-H), 7.38 (d, 2H, *J* = 8 Hz, Ar-H), 5.23 (d, 1H, *J* = 2.8 Hz, CH), 3.55 (s, 3H, OCH_3), 2.28 (s, 3H, CH_3); ^{13}C NMR: δ 166.2, 163.6, 152.5, 149.6, 148.7, 146.8, 135.0, 133.8, 133.0, 129.4, 129.2, 128.4, 126.8, 99.0, 54.2, 51.3, 18.3. HRMS. Calcd for $C_{21}H_{20}ClN_4O_4$, $[M+H]^+$: *m/z* 427.1168. Found: *m/z* 427.1178.

4-[4-(2-(4-Bromobenzylidene)hydrazinocarbonyl)phenyl]-5-methoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (3g) White solid; yield 83%; mp > 300°C; IR: *ν* 3365, 3249, 3116, 2971, 2813, 1718, 1693, 1656, 1639, 1606, 1536, 1432, 1285, 1231, 1092 cm^{-1}; ^{1}H NMR: δ 11.88 (s, 1H, CH), 9.31 (s, 1H, NH), 8.41 (s, 1H, NH), 7.86 (d, 3H, *J* = 7 Hz, Ar-H, NH), 7.67 (t, 4H, *J* = 8 Hz, Ar-H), 7.38 (d, 2H, *J* = 8 Hz, Ar-H), 5.23 (d, 1H, *J* = 2.8 Hz, CH), 3.55 (s, 3H, OCH_3), 2.28 (s, 3H, CH_3); ^{13}C NMR: δ 166.2, 163.6, 152.5, 149.6, 148.7, 146.9, 134.1, 133.0, 132.3, 129.4, 128.4, 126.8, 123.8, 99.0, 54.2, 51.3, 18.3. HRMS. Calcd for $C_{21}H_{20}BrN_4O_4$, $[M+H]^+$: *m/z* 471.0662. Found: *m/z* 471.0649.

5-Methoxycarbonyl-6-methyl-4-[4-(2-(3-nitrobenzylidene)hydrazinocarbonyl)phenyl]-3,4-dihydropyrimidin-2(1*H*)-one (3h) White solid; yield 79%; mp 296–298°C; IR: *ν* 3357, 3220, 3091, 2945, 1707, 1642, 1606, 1529, 1432, 1350, 1286, 1229, 1094 cm^{-1}; ^{1}H NMR: δ 12.09 (s, 1H, CH), 9.31 (s, 1H, -NH), 8.56 (s, 2H, NH, Ar-H), 8.28 (d, 1H, *J* = 7 Hz, Ar-H), 8.17 (d, 1H, *J* = 7 Hz, Ar-H), 7.87 (d, 3H, *J* = 8 Hz, NH, Ar-H), 7.78 (t, 1H, *J* = 7 Hz, Ar-H), 7.39 (d, 2H, *J* = 8 Hz, Ar-H), 5.23 (d, 1H, *J* = 2.4 Hz, CH), 3.81 (s, 3H, OCH_3), 3.55 (s, 3H, OCH_3), 2.28 (s, 3H, CH_3); ^{13}C NMR: δ 166.2, 163.7, 152.5, 149.6, 148.9, 148.7, 145.8, 136.7, 133.9, 132.8, 131.0, 128.6, 126.8, 124.7, 121.4, 99.0, 54.2, 51.3, 18.3. HRMS. Calcd for $C_{21}H_{20}N_5O_6$, $[M+H]^+$: *m/z* 438.1408. Found: *m/z* 438.1413.

4-[4-(2-(2,4-Dichlorobenzylidene)hydrazinocarbonyl)phenyl]-5-methoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (3i) White solid; yield 77%; mp 279-281°C; IR: *ν* 3353, 3216, 3104, 2942, 1700, 1652, 1611, 1559, 1436, 1294, 1226, 1100 cm^{-1}; ^{1}H NMR: δ 12.09 (s, 1H, -CH), 9.31 (s, 1H, NH), 8.80 (s, 1H, NH), 8.03 (d, 1H, *J* = 8 Hz, Ar-H), 7.88 (d, 2H, *J* = 8 Hz, Ar-H), 7.86 (s, 1H, NH), 7.73 (s, 1H, Ar-H), 7.53 (d, 1H, *J* = 8 Hz, Ar-H), 7.39 (d, 2H, *J* = 8 Hz, Ar-H), 5.23 (d, 1H, *J* = 3.2 Hz, CH), 3.55 (s, 3H, OCH_3), 2.28 (s, 3H,-CH_3); ^{13}C NMR:

δ 166.1, 163.5, 152.5, 149.6, 148.9, 143.0, 135.5, 134.3, 132.7, 131.2, 129.9, 128.5, 126.8, 99.0, 54.2, 51.3, 18.4. HRMS. Calcd for $C_{21}H_{19}Cl_2N_4O_4$, $[M+H]^+$: *m/z* 461.0778. Found: *m/z* 461.0744.

4-[4-(2-Benzylidenehydrazinocarbonyl)phenyl]-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (3j) White solid; yield 76%; mp 228–230°C; IR: *ν* 3241, 3112, 2983, 2934, 1715, 1685, 1646, 1610, 1559, 1536, 1450, 1370, 1287, 1226, 1096 cm^{-1}; ^1H NMR: δ 11.79 (s, 1H, CH), 9.26 (s, 1H, NH), 8.44 (s, 1H, NH), 7.86 (d, 2H, *J* = 8 Hz, Ar-H), 7.82 (s, 1H, NH), 7.72 (d, 2H, *J* = 7 Hz, Ar-H), 7.45~7.37 (m, 5H, Ar-H), 5.23 (d, 1H, *J* = 3.2 Hz, CH), 4.02–3.97 (m, 2H, OCH_2), 2.27 (s, 3H, CH_3), 1.11 (t, 3H, *J* = 7 Hz, OCH_2CH_3); ^{13}C NMR: δ 165.7, 163.5, 152.5, 149.3, 148.8, 148.2, 134.8, 133.0, 130.5, 129.3, 128.4, 127.5, 126.8, 99.3, 59.7, 54.3, 18.3, 14.5. HRMS. Calcd for $C_{22}H_{23}N_4O_4$, $[M+H]^+$: *m/z* 407.1714. Found: *m/z* 407.1694.

5-Ethoxycarbonyl-4-[4-(2-(4-methoxybenzylidene)hydrazinocarbonyl)phenyl]-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (3k) White solid; yield 70%; mp 173–175°C; IR: *ν* 3240, 3109, 2978, 2837, 1704, 1652, 1607, 1511, 1453, 1366, 1287, 1254, 1226, 1093 cm^{-1}; ^1H NMR: δ 11.68 (s, 1H, CH), 9.27 (s, 1H, NH), 8.38 (s, 1H, NH), 7.86 (d, 2H, *J* = 8 Hz, Ar-H), 7.83 (s, 1H, NH), 7.66 (d, 2H, *J* = 8 Hz, Ar-H), 7.38 (d, 2H, *J* = 8 Hz, Ar-H), 7.00 (d, 2H, *J* = 8 Hz, Ar-H), 5.25 (s, 1H, CH), 4.00–3.97 (m, 2H, OCH_2), 3.79 (s, 3H, OCH_3), 2.28 (s, 3H, CH_3), 1.10 (t, 3H, *J* = 7 Hz, OCH_2CH_3); ^{13}C NMR: δ 165.7, 163.3, 161.3, 152.5, 149.2, 148.7, 148.2, 133.2, 129.2, 128.3, 127.3, 126.8, 114.8, 99.3, 59.7, 55.7, 54.3, 18.2, 14.5. HRMS. Calcd. for $C_{23}H_{25}N_4O_5$, $[M+H]^+$: *m/z* 437.1819. Found: *m/z* 437.1828.

5-Ethoxycarbonyl-4-[4-(2-(4-*N*,*N*-dimethylaminophenylbenzylidene)hydrazinocarbonyl)phenyl]-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (3l) Yellow solid; yield 53%; mp 184–186°C; IR: *ν* 3238, 3116, 2979, 2801, 1705, 1680, 1652, 1607, 1523, 1364, 1286, 1225, 1092 cm^{-1}; ^1H NMR: δ 11.50 (s, 1H, CH), 9.26 (s, 1H, NH), 8.29 (s, 1H, NH), 7.83 (s, 3H, NH, Ar-H), 7.53 (d, 2H, *J* = 6 Hz, Ar-H), 7.37 (d, 2H, *J* = 6 Hz, Ar-H), 6.73 (d, 2H, *J* = 6 Hz, Ar-H), 5.24 (s, 1H, CH), 4.00-3.98 (m, 2H, OCH_2), 2.95 (s, 6H, $N(CH_3)_2$), 2.28 (s, 3H, CH_3), 1.10 (s, 3H, OCH_2CH_3); ^{13}C NMR: δ 165.7, 163.3, 152.5, 152.0, 149.2, 149.1, 148.5, 133.4, 128.9, 128.2, 126.7, 122.0, 112.2, 99.3, 59.8, 54.3, 40.1, 18.3, 14.5. HRMS. Calcd for $C_{24}H_{28}N_5O_4$, $[M+H]^+$: *m/z* 450.2136. Found: *m/z* 450.2112.

5-Ethoxycarbonyl-4-[4-(2-(2-hydroxybenzylidene)hydrazinocarbonyl)phenyl]-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (3m) White solid; yield 73%; mp 270–272°C; IR: *ν* 3356, 3219, 3107, 2971, 1716, 1689, 1654, 1641, 1614, 1531, 1490, 1456, 1278, 1228, 1087 cm^{-1}; ^1H NMR: δ 12.06 (s, 1H, OH), 11.31 (s, 1H, CH), 9.28 (s, 1H, NH), 8.63 (s, 1H, NH), 7.90 (s, 2H, Ar-H), 7.83 (s, 1H, NH), 7.52~7.29 (m, 4H, Ar-H), 6.93 (s, 2H, Ar-H), 5.25 (s, 1H, CH), 3.99 (s, 2H, OCH_2), 2.28 (s, 3H, CH_3), 1.11 (s, 3H, OCH_2CH_3); ^{13}C NMR: δ 165.7, 163.2, 158.0, 152.5, 149.3, 149.1, 148.8, 132.4, 131.8, 130.0, 128.4, 126.9, 119.8, 119.1, 116.9, 99.3, 59.8, 54.3, 18.3, 14.5. HRMS. Calcd for $C_{22}H_{23}N_4O_5$, $[M+H]^+$: *m/z* 423.1663. Found: *m/z* 423.1657.

5-Ethoxycarbonyl-6-methyl-4-[4-(2-(4-nitrobenzylidene)hydrazinocarbonyl)phenyl]-3,4-dihydropyrimidin-2(1*H*)-one (3n) White solid; yield 85%; mp 251–253°C; IR: *ν* 3246, 3116, 2979, 1726, 1698, 1646, 1606, 1520, 1457, 1343, 1286, 1225, 1096 cm^{-1}; ^1H NMR: δ 12.09 (s, 1H, CH), 9.26 (s, 1H, NH), 8.53 (s, 1H, NH), 8.29 (d, 2H, *J* = 8 Hz, Ar-H), 7.98 (d, 2H, *J* = 8 Hz, Ar-H), 7.87 (d, 2H, *J* = 8 Hz, Ar-H), 7.82 (s, 1H, NH), 7.39 (d, 2H, *J* = 8 Hz, Ar-H), 5.23 (d, 1H, *J* = 2.4 Hz, CH), 4.02-3.97 (m, 2H, OCH_2), 2.26 (s, 3H, CH_3), 1.11 (t, 3H, *J* = 7 Hz, OCH_2CH_3); ^{13}C NMR: δ 165.7, 163.7, 152.5, 149.3, 149.1, 148.3, 145.7, 141.1, 132.7, 128.4, 126.8, 124.5, 99.2, 59.7, 54.3, 18.3, 14.5. HRMS. Calcd for $C_{22}H_{22}N_5O_6$, $[M+H]^+$: *m/z* 452.1565. Found: *m/z* 452.1530.

4-[4-(2-(4-Chlorobenzylidene)hydrazinocarbonyl)phenyl]-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (3o) White solid; yield 83%; mp 279–281°C; IR: *ν* 3356, 3220, 3119, 2971, 2817, 1717, 1689, 1655, 1641, 1606, 1540, 1494, 1453, 1370, 1284, 1228, 1087 cm^{-1}; ^1H NMR: δ 11.85 (s, 1H, CH), 9.26 (s, 1H, NH), 8.43 (s, 1H, NH), 7.86 (d, 2H, *J* = 8 Hz, Ar-H), 7.82 (s, 1H, NH), 7.74 (d, 2H, *J* = 8 Hz, Ar-H), 7.50 (d, 2H, *J* = 8 Hz, Ar-H), 7.38 (d, 2H, *J* = 8 Hz, Ar-H), 5.23 (d, 1H, *J* = 3.2 Hz, CH), 4.02~3.97 (m, 2H, OCH_2), 2.27 (s, 3H, CH_3), 1.11 (t, 3H, *J* = 7 Hz, OCH_2CH_3); ^{13}C NMR: δ 165.7, 163.5, 152.5, 149.3, 148.9, 146.9, 135.0, 133.7, 132.9, 129.4, 129.1, 128.4, 126.8, 99.3, 59.7, 54.3, 18.3, 14.5. HRMS. Calcd for $C_{22}H_{22}ClN_4O_4$, $[M+H]^+$: *m/z* 441.1324. Found: *m/z* 441.1341.

4-[4-(2-(4-Bromobenzylidene)hydrazinocarbonyl)phenyl]-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (3p) White solid; yield 79%; mp 286–287°C; IR: *ν* 3240, 3104, 2978, 2929, 1702, 1664, 1646, 1610, 1532, 1486, 1460, 1370, 1286, 1222, 1092 cm^{-1}; ^1H NMR: δ 11.87 (s, 1H, CH), 9.27 (s, 1H, NH), 8.41 (s, 1H, NH), 7.87 (d, 2H, *J* = 8 Hz, Ar-H), 7.83 (s, 1H, NH), 7.67 (d, 2H, *J* = 8 Hz, Ar-H), 7.62 (d, 2H, *J* = 8 Hz, Ar-H), 7.39 (d, 2H, *J* = 8 Hz, Ar-H), 5.25 (d, 1H, *J* = 2.8 Hz, CH), 4.02–3.97 (m, 2H, OCH_2), 2.28 (s, 3H, CH_3), 1.10 (t, 3H, *J* = 7 Hz, OCH_2CH_3); ^{13}C NMR: δ 165.7, 163.6, 152.5, 149.2, 148.9, 147.0, 134.1, 132.9, 132.3, 129.4, 128.4, 126.8, 123.8, 99.3, 59.7, 54.3, 18.3, 14.5. HRMS. Calcd for $C_{22}H_{22}BrN_4O_4$, $[M+H]^+$: *m/z* 485.0819. Found: *m/z* 485.0824.

5-Ethoxycarbonyl-6-methyl-4-[4-(2-(3-nitrobenzylidene)hydrazinecarbonyl)phenyl]-3,4-dihydropyrimidin-2(1*H*)-one (3q) White solid; yield 78%; mp 271–273°C; IR: *ν* 3344, 3236, 3108, 2979, 2929, 1699, 1654, 1610, 1561, 1531, 1353, 1287, 1225, 1092 cm^{-1}; ^1H NMR: δ 12.05 (s, 1H, CH), 9.26 (s, 1H, NH), 8.54 (s, 2H, NH, Ar-H), 8.23 (d, 1H, *J* = 7 Hz, Ar-H), 8.13 (d, 1H, *J* = 7 Hz, Ar-H), 7.87 (d, 2H, *J* = 8 Hz, Ar-H), 7.82 (s, 1H, NH), 7.73 (t, 1H, *J* = 7 Hz, Ar-H), 7.39 (d, 2H, *J* = 8 Hz, Ar-H), 5.23 (d, 1H, *J* = 2.8 Hz, CH), 4.02-3.97 (m, 2H, OCH_2), 2.27 (s, 3H, CH_3), 1.11 (t, 3H, *J* = 7 Hz, OCH_2CH_3); ^{13}C NMR: δ 165.7, 163.7, 152.5, 149.2, 149.1, 145.7, 136.7, 133.8, 132.7, 130.9, 128.5, 126.8, 124.6, 121.3, 99.3, 59.7, 54.3, 18.3, 14.5. HRMS. Calcd for $C_{22}H_{22}N_5O_6$, $[M+H]^+$: *m/z* 452.1565. Found: *m/z* 452.1528.

4-[4-(2-(2,4-Dichlorobenzylidene)hydrazinocarbonyl)phenyl]-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (3r) White solid; yield 76%; mp 297–299°C; IR: *ν* 3357, 3228, 3108, 2929, 2809, 1695, 1652, 1607, 1590, 1557, 1469, 1378, 1284, 1230, 1101 cm^{-1}; ^1H NMR: δ 9.26 (s, 1H, NH), 8.78 (s, 1H, NH), 8.00 (d, 1H, *J* = 8 Hz, Ar-H), 7.88 (d, 2H, *J* = 8 Hz, Ar-H), 7.82 (s, 1H, NH), 7.63 (s, 1H, Ar-H), 7.46 (d, 1H, *J* = 8 Hz, Ar-H), 7.39 (d, 2H, *J* = 8 Hz, Ar-H), 5.24 (d, 1H, *J* = 2.8 Hz, CH), 4.01–3.95 (m, 2H, OCH_2), 2.27 (s, 3H, -CH_3), 1.09 (t, 3H, *J* = 7 Hz, OCH_2CH_3); ^{13}C NMR: δ 165.7, 163.5, 152.5, 149.3, 149.1, 143.0, 135.5, 134.3, 132.6, 131.2, 129.8, 128.4, 126.9, 99.3, 59.7, 54.4, 18.3, 14.5. HRMS. Calcd for $C_{22}H_{21}Cl_2N_4O_4$, $[M+H]^+$: *m/z* 475.0934. Found: *m/z* 475.0928.

Antimicrobial activity

The antimicrobial activities were determined against bacterial strain *E. coli* and fungal strain *A. niger* by the standardized disk

diffusion method [19] at 50 μg/mL concentration in DMSO. The antimicrobial activity was determined by measuring the diameter of inhibition zone. Ciprofloxacin and fluconazole were used as standard drugs against bacterial and fungal strains, respectively, at 50 μg/mL concentration.

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