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Original research paper

Synthesis and antimicrobial evaluation of some 6-aryl-5-cyano-2-thiouracil derivatives

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A series of 6-aryl-5-cyano-2-thiouracil derivatives (**1a-d**) was synthesized by the reaction of ethyl cyanoacetate with thiourea and aldehydes. These products were used as intermediate compounds for the synthesis of a number of thiouracil derivatives (**2a-d** to **10a-d**). All compounds were screened for antibacterial and antifungal activities. Some of the prepared compounds, 6-(4-fluorophenyl)-4--oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (**2a**), 4-oxo-2-thioxo-6-(3,4,5-trimethoxyphenyl)-1,2,3,4--tetrahydropyrimidine-5-carboxamide (**2d**), 6-(4-fluorophenyl)-4-hydrazino-2-thioxo-1,2-dihydropyrimidine-5-cabonitrile (**7a**) and 4-hydrazino-2-thioxo-6-(3,4,5-trimethoxyphenyl)-1,2-dihydropyrimidine-5-carbonitrile (**7d**) revealed promising antimicrobial activity.

Keywords: 6-aryl-5-cyano-2-thiouracil, antibacterial activity, antifungal activity

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It is well known that pyrimidine derivatives are of great biological interest, especially as antimicrobial, antiviral, anti-inflammatory and antitumor agents (1–7). Some series of pyrimido[4,5-*d*]pyrimidine-2,5-dione derivatives show antimicrobial activity against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli* and antifungal activity against *Candida albicans* and *Aspergillus niger*, as proved by Sharma *et al.* (8). Bacimethrin (5-hydroxymethyl-2-methoxy-pyrimidin-4-amine) is a pyrimidine antibiotic active against several staphylococcal infections (9). 2-Thiouracils and 6-aryl-2-thiouracils are well known for their antifungal, antibacterial, anticancer and antiviral activity (10–12). The aim of this study was to synthesize new 6-aryl-5-cyano-2-thiouracil derivatives and to investigate their antimicrobial activity.

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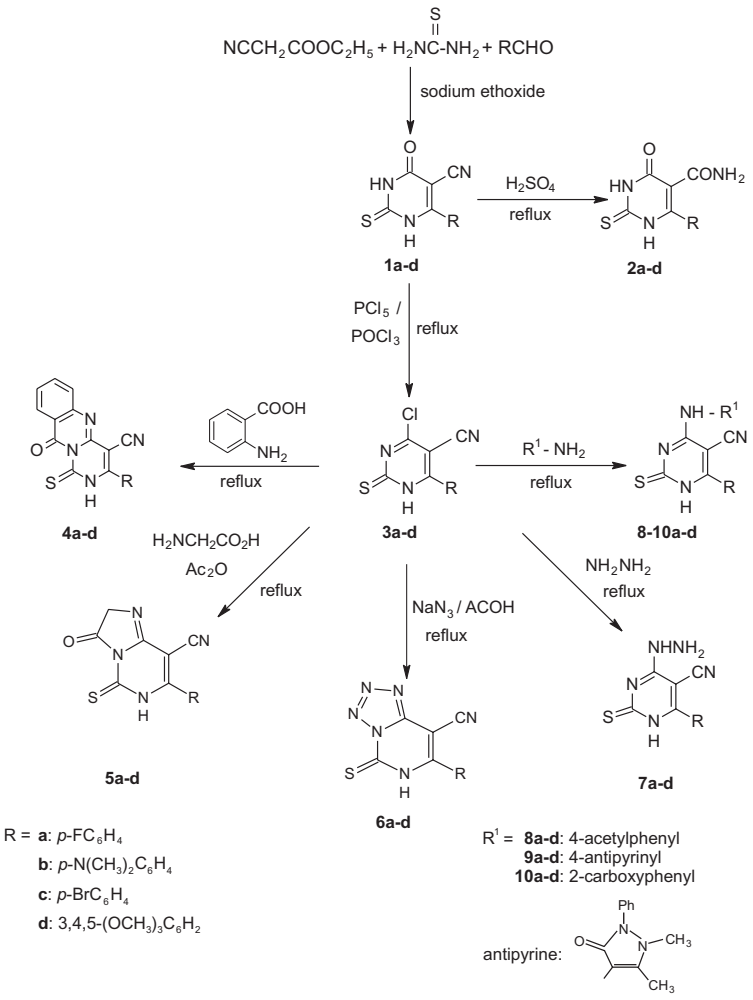
EXPERIMENTAL

All melting points were uncorrected and were measured using an Electro-thermal IA9100 apparatus (Shimadzu, Japan). Microanalytical data were performed using a Vario, Elementar apparatus (Shimadzu). The IR spectra (KBr) were recorded on a Perkin-Elmer1650 spectrophotometer (USA). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury (300 MHz) spectrometer (Varian, UK) and the chemical shifts were expressed in ppm relative to TMS as internal reference. Mass spectra were recorded on a 70 eV EI Ms-QP 1000 EX (Shimadzu).



Shema 1

Table I. Elemental analysis of the newly prepared compounds ***1-10***

Compd.	Yield (%)	M.p. (°C)	Mol. formula (M_r)	Elemental analysis calcd./found(%)		
				C	H	N
1a	80	235–236	$C_{11}H_6FN_3OS$ (247.24)	53.44 53.58	2.45 2.38	17.00 17.09
1b	74	230–232	$C_{13}H_{12}N_4OS$ (272.32)	57.34 57.29	4.44 4.30	20.57 20.46
1c	83	225–226	$C_{11}H_6BrN_3OS$ (308.12)	42.87 42.95	1.96 2.09	13.64 13.76
1d	77	245–247	$C_{14}H_{13}N_3O_4S$ (319.33)	52.66 52.72	4.10 4.19	13.16 12.95
2a	45	100–102	$C_{11}H_8FN_3O_2S$ (265.26)	49.81 49.70	3.04 2.90	15.84 15.72
2b	48	118–120	$C_{13}H_{14}N_4O_2S$ (290.34)	53.78 53.69	4.86 4.75	19.30 19.41
2c	45	158–160	$C_{11}H_8BrN_3O_2S$ (326.12)	40.51 40.66	2.47 2.56	12.88 12.73
2d	51	180–182	$C_{14}H_{15}N_3O_5S$ (337.35)	49.84 49.72	4.48 4.57	12.46 12.67
3a	92	158–160	$C_{11}H_5ClFN_3S$ (265.69)	49.73 49.60	1.90 2.12	15.82 15.70
3b	85	179–180	$C_{13}H_{11}ClN_4S$ (290.77)	53.70 53.81	3.81 3.75	19.27 19.35
3c	83	118–120	$C_{11}H_5BrClN_3S$ (326.59)	40.45 40.54	1.54 1.63	12.87 12.76
3d	93	138–140	$C_{14}H_{12}ClN_3O_3S$ (337.78)	49.78 49.85	3.58 3.64	12.44 12.52
4a	82	160–162	$C_{18}H_9FN_4OS$ (348.35)	62.06 62.18	2.60 2.72	16.08 16.17
4b	80	200–202	$C_{20}H_{15}N_5OS$ (373.43)	64.33 64.45	4.05 4.18	18.75 18.83
4c	75	116–118	$C_{18}H_9BrN_4OS$ (409.22)	52.83 52.75	2.22 2.35	13.69 13.78
4d	75	218–20	$C_{21}H_{16}N_4O_4S$ (420.44)	59.99 60.10	3.84 3.72	13.33 13.42
5a	70	190–192	$C_{13}H_7FN_4OS$ (286.28)	54.54 54.66	2.46 2.58	19.57 19.66
5b	73	195–197	$C_{15}H_{13}N_5OS$ (311.36)	57.86 57.98	4.21 4.37	22.49 22.35
5c	70	200–202	$C_{13}H_7BrN_4OS$ (347.18)	44.97 44.78	2.03 1.86	16.14 16.28
5d	72	208–210	$C_{16}H_{14}N_4O_4S$ (358.37)	53.62 53.72	3.94 4.08	15.63 15.75

Compd.	Yield (%)	M.p. (°C)	Mol. formula (M_r)	Elemental analysis calcd./found(%)		
				C	H	N
6a	72	200–202	$C_{11}H_5FN_6S$ (272.26)	48.53 48.66	1.85 1.96	30.87 30.75
6b	70	210–212	$C_{13}H_{11}N_7S$ (297.33)	52.51 52.65	3.73 3.87	32.97 33.12
6c	65	205–207	$C_{11}H_5BrN_6S$ (333.16)	39.66 39.78	1.51 1.66	25.22 25.10
6d	75	180–182	$C_{14}H_{12}N_6O_3S$ (344.34)	48.83 48.96	3.51 3.42	24.41 24.53
7a	65	212–214	$C_{11}H_8FN_5S$ (261.27)	50.57 50.42	3.09 2.90	26.80 26.93
7b	62	260–262	$C_{13}H_{14}N_6S$ (286.35)	54.53 54.70	4.93 5.15	29.35 29.24
7c	66	190–192	$C_{11}H_8BrN_5S$ (322.18)	41.01 41.18	2.50 2.64	21.74 21.62
7d	68	215–217	$C_{14}H_{15}N_5O_3S$ (333.36)	50.44 50.58	4.54 4.42	21.01 21.10
8a	60	160–162	$C_{19}H_{13}FN_4OS$ (364.39)	62.63 62.75	3.60 3.52	15.38 15.26
8b	62	188–190	$C_{21}H_{19}N_5OS$ (389.47)	64.76 64.88	4.92 5.08	17.98 18.10
8c	60	210–212	$C_{19}H_{13}BrN_4OS$ (425.30)	53.66 53.72	3.08 3.13	13.17 13.10
8d	65	200–202	$C_{22}H_{20}N_4O_4S$ (436.48)	60.54 60.64	4.62 4.78	12.84 12.72
9a	70	195–197	$C_{22}H_{17}FN_6OS$ (432.47)	61.10 61.22	3.96 4.09	19.43 19.35
9b	75	215–217	$C_{24}H_{23}N_7OS$ (457.55)	63.00 63.09	5.07 5.18	21.43 21.32
9c	71	160–162	$C_{22}H_{17}BrN_6OS$ (493.37)	53.56 53.45	3.47 3.55	17.03 16.92
9d	74	170–172	$C_{25}H_{24}N_6O_4S$ (504.56)	59.51 59.40	4.79 4.67	16.66 16.78
10a	70	180–182	$C_{18}H_{11}FN_4O_2S$ (366.36)	59.01 59.12	3.03 3.11	15.29 15.15
10b	75	165–167	$C_{20}H_{17}N_5O_2S$ (391.44)	61.37 61.48	4.38 4.46	17.89 17.78
10c	72	170–172	$C_{18}H_{11}BrN_4O_2S$ (427.27)	50.60 50.72	2.59 2.67	13.11 13.04
10d	77	160–162	$C_{21}H_{18}N_4O_5S$ (438.45)	57.53 57.44	4.14 4.09	12.78 12.84

Physicochemical and spectral data for the synthesized compounds are given in Tables I and II. Target compounds were synthesized as outlined in Scheme 1.

Table II. Spectral data of the newly prepared compounds ***1-10***

Compd.	IR (cm^{-1})	(^{1}H NMR) (ppm)	^{13}C NMR (ppm)	Mass (*m*/*z*, % abundance)
1a	3400–3000 (2NH, stretching) 2230 (CN) 1690 (C=O)	6.5–7.2 (m, 4H, Ar-H), 10, 10.7 (s, 2H, 2NH, D_2O exchangeable)	175.1 (C=S), 90.4, 161.8 (thiouracil C=C), 160 (C=O), 114.9, 125.3, 131.2, 151.9 (benzene C), 115.3 (CN)	247 [M^+] (57.59 %)
1b	3450–3050 (2NH, stretching) 2200 (CN) 1680 (C=O)	2.3, 2.5 (s, 6H, $2CH_3$), 6.5–7.2 (m, 4H, Ar-H), 10, 10.5 (s, 2H, 2NH, D_2O exchangeable)	177.2 (C=S), 86.7, 159.6 (thiouracil C=C), 158.2 (C=O), 113.8, 127.9, 130.4, 152.47 (benzene C), 40.3 ($2CH_3$),115.2 (CN)	272 [M^+] (100 %)
1c	3450–3015 (2NH, stretching) 2235 (CN) 1685 (C=O)	6.8–7.5 (m, 4H, Ar-H), 10.2, 11.1 (s, 2H, 2NH, D_2O exchangeable)	175.1 (C=S), 92.2, 160 (thiouracil C=C), 158.5 (C=O), 115, 128.8, 133.4, 150.3 (benzene C), 114.05 (CN)	307 [M+] (19.6 %), 309 [M+2] (19.8 %)
1d	3450–3110 (2NH, stretching) 2215 (CN) 1675 (C=O)	3.1–3.4 (s, 9H, OCH_3), 6.8 (s, 2H, Ar-H), 10.2, 11.1 (s, 2H, 2NH, D_2O exchangeable)	178.04 (C=S), 88.7, 159.7 (thiouracil C=C),157.9 (C=O), 114.8, 130.4, 151.7, 152 (benzene C), 55.4, 55.7 ($3CH_3$), 115.3 (CN)	319 [M^+] (57.59 %)
2a	3450–3010 (NH_2, 2NH) 1660 ($CONH_2$) 1700 (C=O)	5.1 (s, 2H, $CONH_2$ D_2O exchangeable), 7.2–8 (m, 4H, Ar-H), 10.4, 11.5 (s, 2H, 2NH, D_2O exchangeable)	80.2, 162.6 (thiouracil C=C), 160 (2C=O), 175.9 (C=S), 115.4, 127.8, 130.5, 161.3 (benzene C)	265 [M^+] (18 %)
2b	3500–3020 (NH_2, 2NH) 1660 ($CONH_2$) 1695 (C=O)	2.3, 2.5 (s, 6H, $2CH_3$), 5 (s, 2H, $CONH_2$, D_2O exchangeable), 6.5–7.2 (m, 4H, Ar-H, 10,11.5 (s, 2H, N-H, D_2O exchangeable)	82.4, 161.8 (thiouracil C=C), 160.9 (2C=O), 176.2 (C=S), 113, 124.4, 127.1, 143.7 (benzene C), 43.6 ($2CH_3$ aliphatic)	290 [M^+] (23 %)
2c	3455–3000 (NH_2, 2NH) 1664 ($CONH_2$) 1704 (C=O)	5.1 (s, 2H, $CONH_2$, D_2O exchangeable), 7.2–8 (m, 4H, Ar-H), 10.4,11.5 (s, 2H, 2NH, D_2O exchangeable)	85.1, 163 (thiouracil C=C), 160.9 (2C=O), 175.7 (C=S), 122.3, 128.4, 131.7, 133.9 (benzene C)	325 [M^+] (15.3 %), 327 [M+2] (15.1 %)
2d	3500–3100 (NH_2, 2NH) 1660 ($CONH_2$) 1710 (C=O)	3.8– 4 (s, 9H, $3OCH_3$, 5.2 (s, 2H, $CONH_2$, D_2O exchangeable), 7.3 (s, 2H, Ar-H), 11–11.6 (s, 2H, 2NH, D_2O exchangeable)	80.9, 161.8 (thiouracil C=C), 160.9 (2C=O), 176.1 (C=S), 115.1, 129.2, 132.4, 148.5 (benzene C), 56.3 ($3CH_3$ aliphatic)	337 [M^+] (17 %)

3a	3350 (NH, stretching) 2230 (CN) 1270 (C=S)	7.1–7.7 (m, 4H, Ar-H), 11.8 (s, 1H, -NH, D_2O exchangeable)	88.2, 160 (thiouracil C=C), 159.2 (C=N), 180 (C=S), 115.4, 127.8, 130.5, 161.3 (benzene C), 117.2 (CN)	265 [M^+] (100 %), 267 [M+2] (33 %)
3b	3200 (NH, stretching) 2210 (CN) 1275 (C=S)	2.8 (6H, s, $2CH_3$), 7.1–7.4 (4H, m, Ar-H), 11.2 (1H, s, NH, D_2O exchangeable)	84.3, 158 (thiouracil C=C), 157.3 (C=N), 182 (C=S), 113, 124.4, 127.1, 143.7 (benzene C), 43.6 ($2CH_3$ aliphatic),	117.2 (CN) 290 [M^+] (90 %), 292 [M+2] (32 %)
3c	3300 (NH, stretching) 2215 (CN) 1275 (C=S)	2.8 (6H, s, $2CH_3$), 7.1–7.4 (4H, m, Ar-H), 11.2 (1H, s, NH, D_2O exchangeable)	82.5, 160.9 (thiouracil C=C), 159.2 (C=N), 182 (C=S), 122.3, 128.4, 131.7, 133.9 (benzene C), 117.2 (CN)	325 [M^+] (59 %), 327 [M^{+2}] (24 %)
3d	3310 (NH, stretching) 2225 (CN) 1272 (C=S)	7.4 (S, 2H, Ar-H), 10 (s, 1H, -NH, D_2O exchangeable)	81.1,158 (thiouracil C=C), 157.9 (C=N), 182 (C=S), 115.1, 129.2, 132.4, 148.5 (benzene C), 56.3 ($3CH_3$ aliphatic), 117 (CN)	337 [M^+] (100 %), 339 [M^{+2}] (33 %)
4a	3000 (NH, stretching) 2200 (CN) 1670 (C=O)	6.7–7.6 (m, 8H, Ar-H), 11.2 (s, 1H, -NH, D_2O exchangeable)	164 (C=N), 167.7 (C=O), 75, 169 (thiouracil C=C),178 (C=S), 115.4, 122.1, 127, 127.1, 127.8, 128.6, 130.5, 133.2, 147.8, 161.3 (2 benzene C), 117 (CN)	348 [M^+] (24.4 %)
4b	3100 (NH, stretching) 2210 (CN) 1675 (C=O)	2.5, 2.8 (s, 6H, $2CH_3$), 6.6–8 (m, 8H, Ar-H), 11.2 (s, 1H, -NH, D_2O exchangeable)	163 (C=N), 165 (C=O), 77, 170 (thiouracil C=C), 178 (C=S), 113, 122.1, 124.4, 127, 127.1, 128.6, 143.7, 147.8 (2 benzene C), 43.7 ($2CH_3$ aliphatic), 117 (CN)	373 [M^+] (51.7 %)
4c	3120 (NH, stretching) 2215 (CN) 1680 (C=O)	7–7.6 (m, 8H, Ar-H), 11.2 (s, 1H, -NH, D_2O exchangeable)	163 (C=N), 168 (C=O), 75, 170 (thiouracil C=C), 177 (C=S), 122.1, 122.3, 127, 127.1, 128.4, 128.6, 131.7, 133.2, 133.9, 147.8 (2 benzene C), 117 (CN)	408 [M^+] (19.2 %), 410 [M^{+2}] (19.1 %)
4d	3100 (NH, stretching) 2225 (CN) 1677 (C=O)	3, 3.5, 3.8 (s, 9H, $3OCH_3$), 7.5–8.1 (m, 6H, Ar-H), 11.2 (s, 1H, -NH, D_2O exchangeable)	164 (C=N), 166 (C=O), 77, 169 (thiouracil C=C), 175 (C=S), 115.1, 122.1, 127, 127.1, 128.6, 129.2, 132.4, 133.2, 147.8, 148.5 (2 benzene C), 117 (CN), 56.2 ($3CH_3$, aliphatic)	420 [M^+] (70.1 %)
5a	3300 (NH, stretching) 2240 (CN) 1670 (C=O)	6.8 (s, 2H, imidazo), 7.3–8 (m, 4H, Ar-H), 10.2 (s, 1H, -NH, D_2O exchangeable)	181 (C=S), 79.5, 175.9 (C=C thiouracil), 168 (C=N), 50 (CH_2 aliphatic), 174 (C=O), 115.4, 127.8, 130.5, 161.3 (benzene C), 115.7 (CN)	286 [M^+] (33 %)

5b	3200 (NH, stretching) 2235 (CN) 1675 (C=O)	6.9 (s,2H, imidazo), 2.5 (s, 6H, 2 CH_3), 7.7–8.5 (m, 4H, Ar-H), 10 (s, 1H, -NH, D_2O exchangeable)	183 (C=S), 78.7, 178 (C=C thiouracil), 166 (C=N), 53.2 (CH_2 aliphatic), 175 (C=O), 113.8, 124.4, 127.1, 143.7 (benzene C), 43.7 ($2CH_3$ aliphatic), 117.2 (CN)	311 [M^+] (20.2 %)
5c	3145 (NH, stretching) 2228 (CN) 1668 (C=O)	6.8 (s, 2H, imidazo), 7–8 (m, 4H, Ar-H), 10.2 (s, 1H, -NH, D_2O exchangeable)	183 (C=S), 79.9, 172.4 (C=C thiouracil), 164 (C=N), 50.8 (CH_2 aliphatic), 171.3 (C=O), 122.3, 128.4, 131.7, 133.9 (benzene C), 117 (CN)	346 [M^+] (20.6 %), 348 [M+2] (20.7 %)
5d	3162 (NH, stretching) 2210 (CN) 1670 (C=O)	3.1, 3.2, 3.7 (s, 9H, 3 OCH_3), 6.8 (s, 2H, imidazo), 7.3 (s, 2H, Ar-H), 11.2 (s, 1H, -NH, D_2O exchangeable)	183 (C=S), 79.1, 174 (C=C thiouracil), 167 (C=N), 53.1 (CH_2 aliphatic), 172.7 (C=O), 115.1, 129.2, 132.4, 148.5 (benzene C), 117.4 (CN), 56.2 (3 CH_3 aliphatic)	358 [M^+] (35 %)
6a	3270 (NH, stretching) 2220 (CN) 1270 (C=S)	7.4–8.4 (m, 4H, Ar-H), 10.1 (s, 1H, -NH, D_2O exchangeable)		272 [M^+] (65.2 %)
6b	3265 (NH, stretching) 2225 (CN) 1260 (C=S)	2.5, 3.5 (s, 2H, $2CH_3$), 7.6–7.9 (m, 4H, Ar-H), 11.1 (s, 1H, -NH, D_2O exchangeable)		297 [M^+] (70 %)
6c	3250 (NH, streching) 2230 (CN) 1275 (C=S)	7–8.4 (m, 4H, Ar-H), 10.1 (s, 1H, -NH, D_2O exchangeable)		332 [M^+] (14.6 %), 334 [M+2] (15 %)
6d	3260 (NH, streching) 2215 (CN) 1265 (C=S)	3.1, 3.2, 3.7 (s, 9H, $3OCH_3$), 7, 7.3 (s, 2H, Ar-H), 11.2 (s, 1H, -NH, D_2O exchangeable)		344 [M^+] (15.5 %).
7a	3460–3200 (NH_2, 2NH) 2200 (CN) 1270 (C=S)	5.1–5.7 (s, 3H, NH, NH_2, D_2O exchangeable), 7.3–7.8 (m, 4H, Ar-H), 10.3 (s, 1H, -NH, D_2O exchangeable)	84.5, 167.1 (C=C thiouracil), 164 (C=N), 180 (C=S), 115.4, 127.8, 130.5, 161.3 (benzene C), 117 (CN),	261 [M^+] (15.4 %)
7b	3460–3200 (NH_2, 2NH) 2222 (CN) 1265 (C=S)	2.5,3 (s, 6H, $2CH_3$), 5.3–5.7 (s, 3H, NH, NH2, D_2O exchangeable), 6.5–7.5 (m, 4H, Ar-H), 10.6 (s, 1H, -NH, D_2O exchangeable)	88.2, 168.9 (C=C thiouracil), 164 (C=N), 182 (C=S), 113, 124.4, 127.1, 143.7 (benzene C), 43.5 ($2CH_3$ aliphatic), 117 (CN),	286 [M^+] (44.7 %)
7c	3490–3264 (NH_2, 2NH) 2225 (CN) 1275 (C=S)	5.2–5.7 (s, 3H, NH, NH_2, D_2O exchangeable), 7.3–7.8 (m, 4H, Ar-H), 10.5 (s, 1H, -NH, D_2O exchangeable)	87.9, 169 (C=C thiouracil), 164 (C=N), 182 (C=S), 122.3, 128.4, 131.7, 133.9 (benzene C), 117 (CN),	321 [M^+] (24.8 %), 323 [M+2] (24.7 %)

7d	3490–3300 (NH_2, 2NH) 2230 (CN) 1268 (C=S)	3.1, 3.2, 3.7 (s, 9H, $3OCH_3$), 5.1–5.7 (s, 3H, NH, NH_2, D_2O exchangeable), 6.6 (s, 2H, Ar-H), 10.2 (s, 1H, -NH, D_2O exchangeable)	85.8, 167.5 (C=C thiouracil), 163 (C=N), 183 (C=S), 115, 129.2, 132.4, 148.5 (benzene C), 117 (CN), 55.5 ($3CH_3$ aliphatic)	333 [M^+] (15.3 %)
8a	3456–3210 (2NH, stretching) 2200 (CN) 1690 (C=O)	2.4 (s, 3H, $COCH_3$), 7.8–8.2 (m, 8H, Ar-H), 10, 10.5 (s, 2H, 2NH, D_2O exchangeable)	88, 168.2 (C=C thiouracil), 164 (C=N), 180 (C=S), 115, 115.1, 115.5, 127.4, 127.8, 129.4, 130.5, 151.1, 161.3 (2 benzene C), 188 (C=O), 116.2 (CN), 22.8 (acetyl CH_3)	364 [M^+] (18 %)
8b	3450–3100 (2NH, stretching) 2225 (CN) 1680 (C=O)	2.3 (s, 3H, $COCH_3$), 2.5, 3, 3.3 (s, 6H, $2CH_3$), 7.2–8 (m, 8H, Ar-H), 10, 10.4 (s, 2H, 2NH, D_2O exchangeable)	86, 167.3 (C=C thiouracil), 164 (C=N), 180 (C=S), 113, 115, 24.4, 127.1, 127.4, 129.4, 143.7, 151.1 (2 benzene C), 43.2 ($2CH_3$ aliphatic), 190 (C=O), 116.2 (CN), 22.8 (acetyl CH_3)	389 [M^+] (25 %)
8c	3500–3200 (NH, stretching) 2030 (CN) 1690 (C=O)	2.4 (s, 3H, $COCH_3$), 7.5–8 (m, 8H, Ar-H), 10, 10.3 (s 2H, 2NH, D_2O exchangeable)	85, 166.2 (C=C thiouracil), 162 (C=N), 180 (C=S), 115, 122.3, 127.4, 128.4, 129.4, 131.7, 133.9, 151.1 (2 benzene C), 190 (C=O), 117 (CN), 22.8 (acetyl CH_3)	424 [M^+] (14.2 %), 426 [M+2] (14.3 %)
8d	3550–3300 (NH, stretching) 2230 (CN) 1690 (C=O)	3, 3.2, 3.7 (s, 9H, $3OCH_3$), 2.3 (s, 3H, $COCH_3$), 7.2–8 (m, 6H, Ar-H), 10, 10.5 (s, 2H, 2NH, D_2O exchangeable)	82, 168.5 (C=C thiouracil), 163 (C=N), 180 (C=S), 110, 115, 127.4, 129.2, 129.4, 132.4, 148.5, 151.1 (2 benzene C), 190 (C=O), 117 (CN), 22.5 (acetyl CH_3), 55.5 ($3CH_3$ aliphatic)	436 [M^+] (9.8 %)
9a	3480–3300 (2NH, stretching) 2200 (CN) 1690 (C=O)	1.9 (s, 3H, -CH_3), 2.5 (s, 3H, N-CH_3), 7–7.8 (m, 9H, Ar-H), 10, 10.5 (s, 2H, 2NH, D_2O exchangeable)	84, 166 (C=C thiouracil), 164 (C=N), 182 (C=S), 116, 133.5 (C=C antipyrene), 160 (C=O), 112, 115.4, 118.9, 127.8, 129, 130.5, 142.2, 161 (2 benzene C), 15, 35 (2 CH_3 aliphatic), 117 (CN)	432 [M^+] (12.2 %)
9b	3470–3200 (2NH, stretching) 2225 (CN) 1680 (C=O)	2.2 (s, 3H, -CH_3), 2.5 (s, 3H, N-CH_3), 3.1–3.4 (s, 6H, $2CH_3$), 7.4–7.9 (m, 9H, Ar-H), 10.2, 11 (s, 2H, 2NH, D_2O exchangeable)	85.2, 168 (C=C thiouracil), 164 (C=N), 182 (C=S), 116.2, 133.6 (C=C antipyrene), 161 (C=O), 112, 113, 118.9, 124.4, 127.1, 129, 142.2, 143.7 (2 benzene C), 14.9, 35.3, 43 (4 CH_3 aliphatic), 117.4 (CN)	457 [M^+] (14.9 %)

9c	3480–3210 (2NH, stretching) 2215 (CN) 1690 (C=O)	2 (s, 3H, -CH_3), 2.5 (s, 3H, N-CH_3), 6.8–7.8 (m, 9H, Ar-H), 10.1, 10.6 (s, 2H, 2NH, D_2O exchangeable)	85.4, 168.3 (C=C thiouracil), 164 (C=N), 184 (C=S), 116.6, 135 (C=C antipyrene) 160.7 (C=O), 112, 118.9, 122.3, 128.4, 129, 131.7, 133.9, 142.2 (2 benzene C), 14.9, 35.5 (2 CH_3 aliphatic), 117.2 (CN)	494 [M^+] (12.3 %), 492 [M+2] (12.5 %)
9d	3460–3250 (2NH, stretching) 2225 (CN) 1690 (C=O)	2.2 (s, 3H, -CH_3), 2.5 (s, 3H, N-CH_3), 3.1–3.4 (s, 9H, OCH_3), 7–.5 (m, 7H, Ar-H), 9.5, 11 (s, 2H, 2NH, D_2O exchangeable)	85.5, 167.6 (C=C thiouracil), 164 (C=N), 182 (C=S), 116.3, 133.7 (C=C antipyrene), 160.7 (C=O), 112, 115, 118.9, 129, 129.2, 132.4, 142.2, 148.5 (2 benzene C), 14.9, 35.2, 55.6 (5 CH_3 aliphatic), 117.9 (CN)	504 [M^+] (11.4 %)
10a	3495–3300 (2NH, stretching) 2200 (CN) 1700 (C=O)	7.8–8.2 (m, 8H, Ar-H), 10, 10.4 (s, 2H, 2NH, D_2O exchangeable), 12 (s, 1H, COOH, D_2O exchangable)	90, 166 (C=C thiouracil), 162 (C=N), 178 (C=S), 115, 115.4, 117.2, 118.4, 127.8, 130.5, 130.9, 134.5, 148.3, 161.3 (2 benzene C), 117.9 (CN), 170 (Carboxyl C)	366 [M^+] (62 %)
10b	3468–3100 (NH, stretching) 2225 (CN) 1710 (C=O)	2.3, 2.5 (s, 6H, 2CH_3), 7.2–8 (m, 8H, Ar-H), 10,10.4 (s, 2H, 2NH, D_2O exchangeable), 12 (s, 1H, COOH, D_2O exchangeable)	90, 167 (C=C thiouracil), 161 (C=N), 179 (C=S), 113, 115, 117, 118.4, 124.4, 127.1, 130.9, 134.5, 143.7, 148.3, (2 benzene C), 117.9 (CN), 43.2 (2CH_3 aliphatic), 171 (Carboxyl C)	391 [M^+] (58 %)
10c	3485–3200 (NH, stretching) 2250 (CN) 1730 (C=O)	7.5–8.2 (m, 8H, Ar-H), 10, 10.5 (s, 2H, 2NH, D_2O exchangeable), 12 (s, 1H, COOH, D_2O exchangeable)	88, 164 (C=C thiouracil), 162 (C=N), 179 (C=S), 115, 116, 117, 118.4, 122.3, 128.4, 131.7, 133.9, 134.5, 148.3 (2 benzene C), 117.9 (CN),170 (Carboxyl C)	426 [M^+] (55.1 %), 428 [M+2] (55.2 %)
10d	3469–3190 (NH, stretching) 2200 (CN) 1720 (C=O)	3, 3.2, 3.7 (9H, 3OCH_3), 7–8 (m, 6H, Ar-H), 10, 10.4 (s, 2H, 2NH, D_2O exchangeable), 12 (s, 1H, COOH, D_2O exchangeable)	90, 169 (C=C thiouracil), 162 (C=N), 179 (C=S), 115, 129.2, 132.4, 148 (benzene C), 117 (CN), 170.5 (Carboxyl C), 55.5 (3 CH_3 aliphatic)	438 [M^+] (60 %)

Syntheses

*6-Aryl-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitriles (**1a-d**).* – Synthesis of compounds **1a-d** was performed according to the literature (13). A mixture of ethyl cyanoacetate (11.3 mL, 0.1 mol), thiourea (7.6 g, 0.1 mol) and the appropriate aldehyde [*p*-fluorobenzaldehyde (1.24 g, 0.1 mol), *p*-dimethylamino benzaldehyde (1.49 g, 0.1 mol), *p*-bromobenzaldehyde (1.85 g, 0.1 mol) and 3,4,5-trimethoxy benzaldehyde (1.96 g, 0.1

mol)] in 50 mL sodium ethoxide (2.3 g, 0.1 mol) was stirred for 24 h at room temperature and poured onto ice-water, acidified with dil. HCl to give precipitates, which were filtered, dried and recrystallized from DMF/water to give compounds **1a-d**, respectively.

*6-Aryl-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamides (**2a-d**).* – The appropriate thiouracil derivative, **1a** (2.47 g, 0.01 mol), **1b** (2.72 g, 0.01 mol), **1c** (3.08 g, 0.01 mol) or **1d** (3.19 g, 0.01 mol) in conc. sulphuric acid (40 mL), was refluxed for 3 h, cooled, poured onto ice-water and neutralized with ammonia to give compounds **2a-d**, respectively, in the form of precipitates, which were filtered, dried and recrystallized from DMF/water.

*6-Aryl-4-chloro-2-thioxo-1,2-dihydropyrimidine-5-carbonitriles (**3a-d**).* – The appropriate thiouracil derivative, **1a** (2.47 g, 0.01 mol), **1b** (2.72 g, 0.01 mol), **1c** (3.08 g, 0.01 mol) or **1d** (3.19 g, 0.01 mol), was heated under reflux in phosphorus oxychloride (25 mL) and phosphorus pentachloride (2 g, 0.01 mol) for 8 h, cooled and poured onto ice to precipitate compounds **3a-d**, which were washed with petroleum ether, filtered off and dried under vacuum.

*3-Aryl-10-oxo-1-thioxo-2,10-dihydro-1*H*-pyrimido[6,1-*b*]quinazoline-4-carbonitriles (**4a-d**).* – A mixture of the appropriate thiouracil, **3a** (2.65 g, 0.01 mol), **3b** (2.90 g, 0.01 mol), **3c** (3.26 g, 0.01 mol) or **3d** (3.37 g, 0.01 mol), and anthranilic acid (1.37 g, 0.01 mol) was refluxed in butanol (50 mL) for 10–12 h, cooled, filtered, dried and recrystallized from DMF/water to give compounds **4a-d**, respectively.

*7-Aryl-3-oxo-5-thioxo-2,3,5,6-tetrahydroimidazo[1,2-c]pyrimidine-8-carbonitriles (**5a-d**).* – A mixture of the appropriate thiouracil, **3a** (2.65 g, 0.01 mol), **3b** (2.90 g, 0.01 mol), **3c** (3.26 g, 0.01 mol) or **3d** (3.37 g, 0.01 mol) and glycine (0.75 g, 0.01 mol), was refluxed in butanol (30 mL) for 6-9 h, cooled and the separated solid was refluxed with acetic anhydride (10 mL) for 3 h, cooled, filtered, dried and recrystallized from DMF/water to yield compounds **5a-d**, respectively.

*7-Aryl-5-thioxo-5,6-dihydrotetrazolo[1,5-c]pyrimidine-8-carbonitriles (**6a-d**).* – A mixture of the appropriate thiouracil, **3a** (2.65 g, 0.01 mol), **3b** (2.90 g, 0.01 mol), **3c** (3.26 g, 0.01 mol) or **3d** (3.37 g, 0.01 mol) and sodium azide (0.65 g, 0.01 mol), was refluxed in glacial acetic acid (30 mL) for 5–8 h, cooled and the solid was filtered, dried and recrystallized from DMF/water to give compounds **6a-d**, respectively.

*6-Aryl-4-hydrazino-2-thioxo-1,2-dihydropyrimidine-5-carbonitriles (**7a-d**).* – A mixture of the appropriate thiouracil, **3a** (2.65 g, 0.01 mol), **3b** (2.90 g, 0.01 mol), **3c** (3.26 g, 0.01 mol) or **3d** (3.37 g, 0.01 mol) and hydrazine hydrate (20 mL, 99 %), was refluxed in methanol (30 mL) for 20 min, cooled, stirred for 24 h and poured onto ice-water. The solid obtained was filtered, dried and recrystallized from DMF/water to yield compounds **7a-d**, respectively.

*4-(p-Acetyl-phenylamino)-6-aryl-2-thioxo-1,2-dihydropyrimidine-5-carbonitrile (**8a-d**).* – A mixture of the appropriate thiouracil, **3a** (1.32 g, 0.05 mol), **3b** (1.45 g, 0.05 mol), **3c** (1.36 g, 0.05 mol) or **3d** (1.68 g, 0.05 mol) and *p*-aminoacetophenone (0.67 g, 0.05 mol), was refluxed in 25 mL anhydrous pyridine for 10 h, cooled, poured onto ice-HCl, filtered, dried and recrystallized from ethyl acetate to give compounds **8a-d**, respectively.

*4-(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-ylamino)-6-aryl-2-thioxo-1,2--dihydropyrimidine-5-carbonitrile (**9a-d**) and 2-[5-cyano-6-aryl-2-thioxo-1,2-dihydropyrimidine--4-yl-amino]-benzoic acid (**10 a-d**). General procedure.* – A mixture of the appropriate thiouracil, **3a** (1.325 g, 0.05 mol), **3b** (1.45 g, 0.05 mol), **3c** (1.36 g, 0.05 mol) or **3d** (1.68 g, 0.05 mol) and 4-amino-1,5-dimethyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one (4-aminoantipyrine) (1 g, 0.05 mol) or anthranilic acid (0.68 g, 0.05 mol), was refluxed in 25 mL methanol containing 1 mL anhydrous pyridine for 12 h, cooled, poured onto ice-HCl, filtered, dried and recrystallized from DMF/water to give **9a-d** or **10a-d**, respectively.

Antimicrobial activity

All compounds were evaluated for antibacterial activity against *Bacillus subtilis* (ATCC 6051), *Staphylococcus aureus* (ATCC 12600) (Gram-positive), *Escherichia coli* (ATCC 11775) (Gram-negative) and *Candida albicans* (ATCC 26555) and *Aspergillus flavus* (ATCC--11495) (fungi) microorganisms using the disc diffusion method. Disc diffusion sensitivity test was done in the manner identical to that of Bauer *et al.* (14). All microorganisms used were obtained from the culture collection of the Department of Microbiology, Microanalytical Centre, Faculty of Science, Cairo University, Cairo, Egypt.

Media for disc sensitivity tests were nutrient agar and Müller-Hinton agar (MHA) purchased from Difco (USA). Non-sterile powder of tested compounds and penicillin and nystatin standards were dissolved in sterile DMSO to yield 2.0 μg mL^{-1} solution, and passed through a 0.2-μm membrane filter (Millipore Corp, USA). Penicillin (Bioanalyse, Turkey) and nystatin (Sigma-Aldrich, USA) were used as reference substances. Inhibition zones were measured in millimeters at the end of an incubation period of 48 h at 28 °C.

RESULTS AND DISCUSSION

Chemistry

A series of 6-aryl-5-cyano-2-thiouracils (**1a-d**) were newly synthesized in a facile manner from thiourea, ethyl cyanoacetate and different aldehydes in sodium ethoxide instead of anhydrous K_2CO_3/ethanol (14) with better yield. 6-Aryl-5-carboxamide-2-thioxo-2,3-dihydropyrrimidine-4-(1*H*)-ones (**2a-d**) were obtained by the reaction of thiouracils **1a-d** with concentrated sulphuric acid. Thiouracils **1a-d** were converted to 4-chloropyrimidines **3a-d** by refluxing with a mixture of phosphorus oxychloride/phosphorus pentachloride (15). The chloropyrimidine derivatives **3a-d** were used as the starting material for preparation of new heterocyclic compounds. Thus, **3a-d** reacted with anthranilic acid, glycine, sodium azide or hydrazine hydrate to yield 10-oxo-3-aryl-1-thioxo-2,10-dihydro-1*H*-pyrimido[6,1-*b*]quinazoline-4-carbonitriles (**4a-d**), 7-aryl-3-oxo-5-thioxo-2,3,5,6-tetrahydroimidazo[1,2-*c*] pyrimidine-8-carbonitriles (**5a-d**), 7-aryl-5-thioxo-5,6-dihydrotetrazolo[1,5-*c*]pyrimidine-8-carbonitriles (**6a-d**) and 6-aryl-4-hydrazino-2-thioxo--1,2-dihydropyrimidine-5-carbonitriles (**7a-d**), respectively. Reaction of **3a-d** with 4-aminoacetophenone in anhydrous pyridine gave (4-acetyl-phenylamino)-6-aryl-2-thioxo--1,2-dihydropyrimidine-5-carbonitriles (**8a-d**). Finally, 4-amino pyrimidines **9a-d** and **10a-d** were obtained by the reaction of **3a-d** with amines, namely, 4-amino-1,5-dimethyl-2-phe-

nyl-1,2-dihydro-3*H*-pyrazol-3-one (4-aminoantipyrine) or anthranilic acid, respectively, in absolute ethanol containing pyridine. The structures of new compounds were confirmed by MS, IR, ^{1}H NMR and ^{13}C NMR as well as elemental analysis. IR spectra of compounds **1a-d** showed CN bands at 2200–2235 cm^{-1} and a stretching NH band at 3450–3000 cm^{-1}. The ^{13}C NMR spectra displayed signals for C=O carbon and for CN carbon at position C-5 of the molecule. The rest of the spectrum was in good agreement with the structures. The recorded IR spectra of compounds **2a-d** showed the absence of CN as well as the presence of amide carbonyl at 1660 cm^{-1} and ^{1}H NMR showed a singlet signal for $CONH_2$ proton at 5.1 ppm. Moreover, the ^{13}C NMR spectrum showed the presence of two C=O signals corresponding to C=O of thiouracil and amide. Also, the structures of **3a-d** were established on the basis of IR, which showed the absence of C=O, while ^{1}H NMR spectra revealed a signal for NH proton instead of two signals like in **2a-d**. Their mass spectra gave the characteristic fragmentation pattern due to the presence of chlorine atoms in the compounds. The IR spectra of compounds **4a-d** showed the presence of C=O group (Table II). The ^{1}H and ^{13}C NMR spectra of products **4a-d** were compatible with the proposed structure. The IR spectra of compounds **5a-d** showed the presence of C=O group; their ^{13}C NMR spectrum displayed signals for C=O carbon and for CH_2 aliphatic carbon. The rest of the spectrum was in good agreement with the structures. Compounds **6a-d** and **7a-d** were confirmed by spectral data (Table II) and the mass spectrum studies of these compounds gave additional evidence for the proposed structures. ^{1}H NMR for **8a-d** showed singlet signals for $COCH_3$ and two NH, for **9a-d** signals for CH_3, N-CH_3 and two NH, for **10a-d s**ignals for two NH) and COOH. Also, MS spectra gave their molecular ion peaks (Table II). The ^{13}C NMR spectra for compounds **8-10** were compatible with the proposed structures.

Antimicrobial activity

The data presented in Table III showed that compounds **2a-d** and **7a-d** possess a pronounced antimicrobial activity against *Staphylococcus aureus*, *Bacillus subtilis* and *Escherichia coli* compared to the reference drug penicillin. As far as antifungal activity is concerned, compounds **7a-d** exhibited even stronger activity than nystatin against *Candida albicans* and compounds **2a**, **2d**, **3a**, **7a** and **7d** against *Aspergillus flavus.* Compounds **1**, **2** and **3a-d** showed moderate activity against the fungus *Candida albicans* and compounds **4a** and **6d** displayed moderate activity against the fungus *Aspergillus flavus*. Compounds **9**, **10a-d**, **1**, **3a-d**, **4c**, **5a**,**d** and **6a**,**c** were either inactive or moderately to fairly active against the tested bacteria. To sum up all tested compounds have moderate to high antibacterial activity, except compounds **9a-d** and **10a-d**, which are inactive. Compounds **2a,c** and **7a** showed the highest antibacterial activity whereas compounds **7a**,**d** exhibited good to excellent results against *Candida albicans* and *Aspergillus flavus.* The present study revealed that conversion of cyano group at 5′-position to amide (**2a-d**) caused a pronounced inhibition effect against Gram-positive (*Staphylococcus aureus*, *Bacillus subtilis*) and Gram-negative (*Escherichia coli*) bacteria. The same effects were observed after transformation of Cl group into $NHNH_2$ (**7a-d**). On the other hand, increased antibacterial activity was achieved by incorporation of chloro moiety as in 4-chloro-6-(4-fluorophenyl)-2--thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (**3a**). However, cyclization to pyrimidoquinazolines, imidazopyrimidines, tetrapyrimidines, or incorporation of 4-aminoacetophenone as in 10-oxo-1-thioxo-3-(3,4,5-trimethoxyphenyl)-2,10-dihydro-1*H*-yrimido[6,1-*b*]

Table III. Antimicrobial activity of the synthesized compounds

Compd.[a]	Inhibition zone diameter (mm)				
	S. aureus	*B. subtilis*	*E. coli*	*C. albicans*	*A. flavus*
1a	14	10	14	13	–
1b	13	9	12	12	–
1c	15	12	14	14	–
1d	13	10	13	13	–
2a	39	25	38	14	18
2b	30	23	30	13	–
2c	35	24	34	15	–
2d	30	22	30	16	22
3a	18	14	18	16	17
3b	16	12	14	14	–
3c	17	13	15	15	–
3d	15	14	14	14	–
4a	20	17	19	–	11
4b	20	16	21	–	–
4c	18	18	16	–	–
4d	22	21	23	–	–
5a	18	19	19	–	–
5b	24	15	21	–	–
5c	20	16	16	–	–
5d	16	15	25	–	–
6a	19	15	21	–	–
6b	22	16	22	–	–
6c	18	17	20	–	–
6d	25	18	22	–	14
7a	30	26	28	28	44
7b	26	28	30	23	–
7c	28	25	27	27	–
7d	27	30	33	24	29
8a	23	14	27	–	–
8b	23	12	25	–	
8c	22	13	26	–	–
8d	24	12	24	–	–
Penicillin[b]	20	14	12	–	–
Nystatin[b]	–	–	–	17	15

– No inhibition.
[a] 2.0 μg mL^{-1} in DMSO.
DMSO shows no activity.

quinazoline-4-carbonitrile (**4d**), 7-[4-(dimethylamino)phenyl]-3-oxo-5-thioxo-2,3,5,6-tetrahydroimidazo[1,2-*c*]pyrimidine-8-carbonitrile (**5b**), 7-[4-dimethylamino)phenyl]-5,6-dihydrotetrazolo[1,5-*c*]pyrimidine-8-carbonitrile (**6b**), 5-thioxo-7-(3,4,5-trimethoxyphenyl)-5,6--dihydrotetrazolo[1,5-*c*]pyrimidine-8-arbonitrile (**6d**) and 4-[(4-acetylphenyl)amino]-6-(4--fluorophenyl)-2-thioxo-1,2-dihydropyrimidine-5-carbonitrile (**8a**) increased antibacterial activity. However, incorporation of 4-amino-1,5-dimethyl-2-phenyl-1,2-dihydro-3H--pyrazol-3-one (4-aminoantipyrine) or anthranilic acid ring to the thiouracil derivatives as in **9**, **10a-d** diminished antimicrobial activity. The structure activity relationship suggested that thiouracils containing amide or hydrazine hydrate moiety showed higher antibacterial and antifungal activities than other derivatives.

CONCLUSIONS

Antimicrobial studies have revealed that the most promising compounds are 6-(4--fluorophenyl)-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (**2a**), 4-oxo-2--thioxo-6-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxamide (**2d**), 6--(4-fluorophenyl)-4-hydrazino-2-thioxo-1,2-dihydropyrimidine-5-cabonitrile (**7a**) and 4-hydrazino-2-thioxo-6-(3,4,5-trimethoxyphenyl)-1,2-dihydropyrimidine-5-carbonitrile (**7d**)**.** Based on the above studies, the promising compounds can be submitted to *in vivo* antimicrobial studies as a future perspective.

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SAŽETAK

Sinteza i antimikrobno vrednovanje nekoliko 6-aril-5-cijano-2-tiouracil derivata

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Polazeći iz etil-cijanoacetata, tiouree i odgovarajućeg aldehida sintetizirana je serija 6-aril-5-cijano-2-tiouracil derivata (**1a-d**), koji su potom upotrijebljeni za dobivanje tiouracil derivata (**2a-d** do **10a-d**). Svim spojevima ispitano je antibakterijsko i antimikotsko djelovanje. Neki od sintetiziranih spojeva, 6-(4-fluorofenil)-4-okso-2-tiokso-1,2,3,4-tetrahidropirimidin-5-karboksamid (**2a**), 4-okso-2-tiokso-6-(3,4,5-trimetoksifenil)-1,2,3,4-tetrahidropirimidin-5-karboksamid (**2d**), 6-(4-fluorofenil)-4-hidrazino-2-tiokso-1,2-dihidropirimidin-5-kabonitril (**7a**) i 4-hidrazino-2-tiokso-6-(3,4,5-trimetoksifenil)-1,2-dihidropirimidin-5-karbonitril (**7d**) imaju značajno antimikrobno djelovanje.

Ključne riječi: 6-aril-5-cijano-2-tiouracil, antibakterijsko djelovanje, antimikotsko djelovanje

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