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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF N,6-DIARYL-4-METHYL-2-OXO-1,2,3,6-TETRAHYDROPYRIMIDINE-5-CARBOXAMIDES

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N,6-Diaryl-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine-5-carboxamides were synthesized by a three-component reaction of acetoacetanilides (2,4-dimethylacetoacetanilide, *o*-acetoacetaniside, 2-chloroacetoacetanilide), aromatic aldehydes, and urea. The structures of the products were established by IR and PMR spectroscopy and mass spectrometry. The antimicrobial activity of the synthesized compounds was studied.

Keywords: synthesis, 2-oxo-1,2,3,6-tetrahydropyrimidine-5-carboxamide derivatives, antimicrobial activity

Compounds containing a pyrimidine ring in their structure are known to exhibit a broad spectrum of biological activity [1, 2]. Compounds with pronounced antimicrobial activity have been found among dihydropyrimidin-2(1*H*)-one derivatives [3, 4].

We first synthesized previously unknown *N*,6-diaryl-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine-5-carboxamid es (**I** – **XX**) in order to prepare new biologically active compounds with this type of activity.

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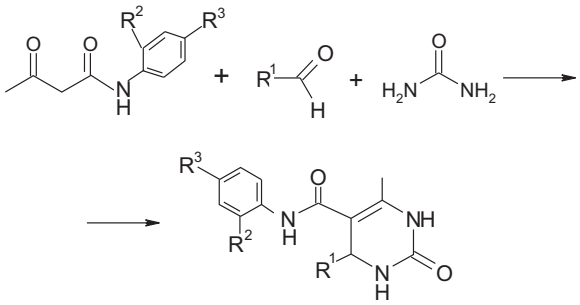
Scheme 1



I – III: R^1=3-$NO_2C_6H_4$ (I), 4-ClC_6H_4 (II), 2-FC_6H_4 (III), R^2=CH_3, R^3=H; IV – IX: R^1=C_6H_5 (IV), 4-ClC_6H_4 (V), 2-FC_6H_4 (VI), 3-FC_6H_4 (VII), 3-$NO_2C_6H_4$ (VIII), 2-ClC_6H_4 (IX), R^2=R^3=CH_3; X – XV: R^1=C_6H_5 (X), 4-ClC_6H_4 (XI), 4-HOC_6H_4 (XII), 2-$CH_3OC_6H_4$ (XIII), 2-ClC_6H_4 (XIV), 2-FC_6H_4 (XV), R^2=CH_3Î, R^3=H; XVI – XX: R^1=C_6H_5 (XVI), 2-ClC_6H_4 (XVII), 4-ClC_6H_4 (XVIII), 3-$NO_2C_6H_4$ (XIX), 4-$CH_3C_6H_4$ (XX), R^2=2-Cl, R^3=H.

The synthesis was carried out by a three-component condensation of acetoacetanilides, aromatic aldehydes, and urea taken in an equimolar ratio without solvent or catalyst at 120 – 150°C for 5 – 7 min (Scheme 1).

TABLE 1. Constants and Yields of **I** – **XX**

Compound	Yield, %	mp, °C	Empirical formula
I	64	225 – 227	$C_{19}H_{18}N_4O_4$
II	84	217 – 219	$C_{19}H_{18}ClN_3O_2$
III	72	213 – 215	$C_{19}H_{18}FN_3O_2$
IV	47	257 – 259	$C_{20}H_{21}N_3O_2$
V	84	252 – 254	$C_{20}H_{20}ClN_3O_2$
VI	89	214 – 216	$C_{20}H_{20}FN_3O_2$
VII	84	254 – 256	$C_{20}H_{20}FN_3O_2$
VIII	71	246 – 248	$C_{20}H_{20}N_4O_4$
IX	78	236 – 238	$C_{20}H_{20}ClN_3O_2$
X	74	175 – 177	$C_{19}H_{19}N_3O_3$
XI	84	213 – 215	$C_{19}H_{18}ClN_3O_3$
XII	87	242 – 244	$C_{19}H_{19}N_3O_4$
XIII	92	239 – 241	$C_{20}H_{21}N_3O_4$
XIV	70	236 – 238	$C_{19}H_{18}ClN_3O_3$
XV	78	219 – 220	$C_{19}H_{18}FN_3O_3$
XVI	69	195 – 197	$C_{18}H_{16}ClN_3O_2$
XVII	74	214 – 216	$C_{18}H_{15}Cl_2N_3O_2$
XVIII	81	185 – 187	$C_{18}H_{15}Cl_2N_3O_2$
XIX	85	219 – 221	$C_{18}H_{15}ClN_4O_4$
XX	64	223 – 225	$C_{19}H_{18}ClN_3O_2$

Compounds **I** – **XX** were colorless crystalline solids that were soluble in DMF, DMSO, and $CHCl_3$ and in HOAc and EtOH with heating and insoluble in H_2O, toluene, and benzene (Table 1).

IR spectra of **I** – **XX** showed bands due to stretching vibrations of amide (1660 – 1680 cm^{-1}), NH (3150 – 3200 cm^{-1}), and C=C (1600 – 1620 cm^{-1}).

PMR spectra of the *N*,6-diaryl-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine-5-carboxamides had characteristic resonances for aromatic protons and their substituents; a singlet for the CH_3 protons in the range 1.78 – 2.21 ppm; a doublet for the H-6 proton in the range 5.20 – 5.69 ppm with $J_{1,6}$ = 1.80 – 2.48 Hz; two resonances for the H-3 proton in the range 7.85 – 8.94 ppm, a doublet for the H-1 proton of the pyrimidine ring in the range 7.23 – 7.86 ppm with $J_{1,6}$ = 1.80 – 2.48 Hz; and a singlet for the NH proton of the side chain in the range 8.74 – 9.80 ppm (Table 2).

TABLE 2. Spectral Data for **I** – **XX**

Compound	IR spectrum, ν, cm^{-1}	PMR spectrum, δ, ppm, *J*/Hz
I		1.82 (s, 3H, 4-CH_3), 2.21 (s, 3H, C$\underline{H}_3C_6H_4$), 5.46 (d, 1H, $J_{1,6}$ = 2.4, H-6), 7.48 (m, 8H, $NO_2C_6\underline{H}_4$, $CH_3C_6\underline{H}_4$, 9.78 (s, 1H, NH), 8.97 and 8.98 (2s, 1H, NH-3 and OH-2), 7.80 (d, 1H, $J_{1,6}$ = 2.4, H-1).
II	1620 (C=C), 1660 (CON), 3200 (NH).	1.84 (s, 3H, 4-CH_3), 2.19 (s, 3H, C$\underline{H}_3C_6H_4$), 5.40 (d, 1H, $J_{1,6}$ = 2.4, H-6), 7.60 (m, 8H, $ClC_6\underline{H}_4$, $CH_3C_6\underline{H}_4$), 9.80 (s, 1H, NH), 8.93 and 8.94 (2s, 1H, NH-3 and OH-2), 7.86 (d, 1H, $J_{1,6}$ = 2.4, H-1)
III		1.86 (s, 3H, 4-CH_3), 2.07 (s, 3H, C$\underline{H}_3C_6H_4$), 5.59 (d, 1H, $J_{1,6}$ = 2.4, H-6), 6.98 – 7.31 (m, 8H, $FC_6\underline{H}_4$, $CH_3C_6\underline{H}_4$), 8.86 (s, 1H, NH), 8.56 and 8.57 (2s, 1H, NH-3 and OH-2), 7.26 (d, 1H, $J_{1,6}$ = 2.4, H-1).
IV	1620 (C=C), 1680 (CON), 3200 (NH).	1.81 (s, 3H, 4-C$\underline{H}_3$), 2.06 and 2.18 [2s, 6H, $(C\underline{H}_3)_2C_6H_3$], 5.38 (d, 1H, $J_{1,6}$ = 2.48, H-6), 7.23 [m, 8H, $(CH_3)_2C_6\underline{H}_3$, $C_6\underline{H}_5$), 8.89 (s, 1H, NH), 8.64 and 8.66 (2s, 1H, NH-3 and OH-2), 7.26 (d, 1H, $J_{1,6}$ = 2.48, H-1).
V		1.79 (s, 3H, 4-CH_3), 2.08 and 2.21 [2s, 6H, $(C\underline{H}_3)_2C_6H_3$], 5.32 (d, 1H, $J_{1,6}$ = 2.48, H-6), 7.25 [m, 7H, $(CH_3)_2C_6\underline{H}_3$, $ClC_6\underline{H}_4$], 8.74 (s, 1H, NH), 8.56 and 8.57 (2s, 1H, NH-3 and OH-2), 7.43 (d, 1H, $J_{1,6}$ = 2.48, H-1).
VI	1600 (C=C), 1670 (CON), 3160 (NH).	1.82 (s, 3H, 4-CH_3), 2.06 and 2.20 [2s, 6H, $(C\underline{H}_3)_2C_6H_3$], 5.58 (d, 1H, $J_{1,6}$ = 2.48, H-6), 7.23 [m, 7H, $(CH_3)_2C_6\underline{H}_3$, $FC_6\underline{H}_4$], 8.81 (s, 1H, NH), 8.57 and 8.59 (2s, 1H, NH-3 and OH-2), 7.31 (d, 1H, $J_{1,6}$ = 2.48, H-1).
VII	1610 (C=C), 1660 (CON), 3180 (NH).	1.86 (s, 3H, 4-CH_3), 2.09 and 2.21 [2s, 6H, $(C\underline{H}_3)_2C_6H_3$], 5.31 (d, 1H, $J_{1,6}$ = 2.48, H-6), 7.23 [m, 7H, $(CH_3)_2C_6\underline{H}_3$, $FC_6\underline{H}_4$], 8.76 (s, 1H, NH), 8.57 and 8.58 (2s, 1H, NH-3 and OH-2), 7.31 (d, 1H, $J_{1,6}$ = 2.48, H-1).
VIII	1600 (C=C), 1670 (CON), 3200 (NH).	1.82 (s, 3H, 4-CH_3), 2.02 and 2.14 [2s, 6H, $(C\underline{H}_3)_2C_6H_3$], 5.38 (d, 1H, $J_{1,6}$ = 2.48, H-6), 7.23 [m, 7H, $(CH_3)_2C_6\underline{H}_3$, $NO_2C_6\underline{H}_4$], 8.85 (s, 1H, NH), 8.33 and 8.34 (2s, 1H, NH-3 and OH-2), 7.36 (d, 1H, $J_{1,6}$ = 2.48, H-1).
IX		1.78 (s, 3H, 4-CH_3), 2.05 and 2.17 [2s, 6H, $(C\underline{H}_3)_2C_6H_3$], 5.69 (d, 1H, $J_{1,6}$ = 2.48, H-6), 6.73 – 7.36 [m, 7H, $(CH_3)_2C_6\underline{H}_3$, $ClC_6\underline{H}_4$], 8.87 (s, 1H, NH), 8.59 and 8.60 (2s, 1H, NH-3 and OH-2), 7.34 (d, 1H, $J_{1,6}$ = 2.48, H-1).
X		2.15 (s, 3H, 4-CH_3), 3.64 (s, 3H, CH_3O), 5.20 (d, 1H, $J_{1,6}$ = 2.4, H-6), 7.26 (m, 9H, $CH_3OC_6\underline{H}_4$, $C_6\underline{H}_5$), 8.74 (s, 1H, NH), 8.13 and 8.14 (2s, 1H, NH-3 and OH-2), 7.51 (d, 1H, $J_{1,6}$ = 2.4, H-1).
XI	1615 (C=C), 1678 (CON), 3160 (NH).	2.14 (s, 3H, 4-CH_3), 3.66 (s, 3H, CH_3O), 5.24 (d, 1H, $J_{1,6}$ = 2.4, H-6), 7.33 (m, 8H, $CH_3OC_6\underline{H}_4$, $ClC_6\underline{H}_4$), 8.75 (s, 1H, NH), 8.13 and 8.14 (2s, 1H, NH-3 and OH-2), 7.70 (d, 1H, $J_{1,6}$ = 2.4, H-1).
XII		2.18 (s, 3H, 4-CH_3), 3.63 (s, 3H, CH_3O), 5.34 (d, 1H, $J_{1,6}$ = 2.4, H-6), 7.33 (m, 8H, $CH_3OC_6\underline{H}_4$, $HOC_6\underline{H}_4$), 8.80 (s, 1H, NH), 8.23 and 8.24 (2s, 1H, NH-3 and OH-2), 7.70 (d, 1H, $J_{1,6}$ = 2.4, H-1).
XIII	1620 (C=C), 1680 (CON), 3150 (NH).	2.21 (s, 3H, 4-CH_3), 3.65 and 3.78 (2s, 6H, $2CH_3O$), 5.56 (d, 1H, $J_{1,6}$ = 2.4, H-6), 7.03 (m, 8H, $CH_3OC_6H_4$, $CH_3POC_6H_4$), 8.87 (s, 1H, NH), 8.04 and 8.05 (2s, 1H, NH-3 and OH-2), 7.23 (d, 1H, $J_{1,6}$ = 2.4, H-1).
XIV		2.20 (s, 3H, 4-CH_3), 3.65 (s, 3H, CH_3O), 5.60 (d, 1H, $J_{1,6}$ = 2.4, H-6), 6.62 – 7.37 (m, 8H, $CH_3OC_6\underline{H}_4$, $ClC_6\underline{H}_4$), 8.82 (s, 1H, NH), 7.85 and 7.86 (2s, 1H, NH-3 and OH-2), 7.78 (d, 1H, $J_{1,6}$ = 2.4, H-1).
XV		2.13 (s, 3H, 4-CH_3), 3.66 (s, 3H, C$\underline{H}_3OC_6H_4$), 5.50 (d, 1H, $J_{1,6}$ = 2.4, H-6), 6.68 – 7.66 (m, 8H, $FC_6\underline{H}_4$, $CH_3OC_6\underline{H}_4$), 8.75 (s, 1H, NH), 8.20 and 8.21 (2s, 1H, NH-3 and OH-2), 7.72 (d, 1H, $J_{1,6}$ = 2.4, H-1).
XVI		2.13 (s, 3H, 4-CH_3), 5.23 (d, 1H, $J_{1,6}$ = 2.48, H-6), 6.98 – 7.43 (m, 9H, $C_6\underline{H}_5$, $ClC_6\underline{H}_4$), 8.89 (s, 1H, NH), 8.68 and 8.69 (2s, 1H, NH-3 and OH-2), 7.52 (d, 1H, $J_{1,6}$ = 2.48, H-1).
XVII		2.13 (s, 3H, 4-CH_3), 5.68 (d, 1H, $J_{1,6}$ = 2.48, H-6), 6.85 – 7.27 (m, 8H, $ClC_6\underline{H}_4$, $ClC_6\underline{H}_4$), 8.96 (s, 1H, NH), 8.73 and 8.74 (2s, 1H, NH-3 and OH-2), 7.36 (d, 1H, $J_{1,6}$ = 2.48, H-1).
XVIII		2.13 (s, 3H, 4-CH_3), 5.30 (d, 1H, $J_{1,6}$ = 2.48, H-6), 7.20 – 7.41 (m, 8H, $ClC_6\underline{H}_4$, $ClC_6\underline{H}_4$), 9.86 (s, 1H, NH), 7.92 and 7.93 (2s, 1H, NH-3 and OH-2), 7.85 (d, 1H, $J_{1,6}$ = 2.48, H-1).
XIX		2.20 (s, 3H, 4-CH_3), 5.63 (d, 1H, $J_{1,6}$ = 2.48, H-6), 6.95 – 7.37 (m, 8H, $NO_2C_6\underline{H}_4$, $ClC_6\underline{H}_4$), 8.92 (s, 1H, NH), 8.94 and 8.93 (2s, 1H, NH-3 and OH-2), 7.24 (d, 1H, $J_{1,6}$ = 2.48, H-1).
XX		2.20 (s, 3H, 4-CH_3), 3.4 (s, 3H, C$\underline{H}_3C_6H_4$), 5.20 (d, 1H, $J_{1,6}$ = 2.48, H-6), 6.87 – 7.44 (m, 8H, $CH_3C_6\underline{H}_4$, $ClC_6\underline{H}_4$), 9.80 (s, 1H, NH), 8.54 and 8.55 (2s, 1H, NH-3 and OH-2), 7.23 (d, 1H, $J_{1,6}$ = 2.48, H-1).

TABLE 3. Antimicrobial Activity of **I** – **XX**

Compound	Minimum inhibiting concentration (MIC), μg/mL		Compound	Minimum inhibiting concentration (MIC), μg/mL	
	St. aureus	*E. coli*		*St. aureus*	*E. coli*
I	500	500	XII	500	1000
II	1000	1000	XIII	500	1000
III	1000	1000	XIV	1000	1000
IV	500	500	XV	500	500
V	500	1000	XVI	500	500
VI	1000	1000	XVII	500	1000
VII	1000	1000	XVIII	1000	1000
VIII	500	1000	XIX	1000	1000
IX	1000	1000	XX	n/a	500
X	500	500	Chloramine B	500	250
XI	500	500	Dioxidine	62.5 – 1000	3.9 – 62.5

The mass spectrum of **IV** showed a peak for the molecular ion with *m*/*z* 335 $[M]^+$ and peaks for fragment ions with 121 $[(CH_3)_2C_6H_3NH]^+$ and with *m*/*z* 77 for $[Ph]^+$; that of **XIII**, with *m*/*z* 352 for $[M - CH_3]^+$, 245 for $[M - CH_3OC_6H_4NH]^+$, 123 for $[CH_3OC_6H_4NH_2]^+$, and 77 for $[Ph]^+$, which confirmed the given structure.

EXPERIMENTAL CHEMICAL PART

IR spectra were recorded in mineral oil on a Specord M-80 spectrophotometer. PMR spectra were recorded in DMSO-d_6 with TMS internal standard on a Bruker 500 spectrometer (operating frequency 500.13 MHz). Mass spectra were obtained on a Finnigan MAT INCOS-50 instrument with ionization energy 70 eV.

***N*,6-Diaryl-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine-5-carboxamides (I – XX).** (General method). A mixture of acetoacetic acid *N*-arylamide (0.01 mol), aromatic aldehyde (0.01 mol), and urea (0.01 mol) was held at 120 – 150°C for 5 – 7 min until gas evolution ceased and then cooled. The precipitate was worked up with EtOH, filtered off, and recrystallized from EtOH (Table 1).

EXPERIMENTAL BIOLOGICAL PART

Antimicrobial activity was determined by successive dilutions of a solution of the tested compound in meat peptone broth (MPB). The activity was studied with respect to *S. aureus* and *E. coli*. The bacterial loading per mL of culture liquid was 250,000 microbes. Experimental results were evaluated 18 – 20 h after storing the test and control samples in a thermostat at 36 – 37°C. The presence of growth or its inhibition in the bacterial cultures because of the bacteriostatic action of the compounds was recorded. The minimum inhibiting concentration (MIC, μg/mL) that inhibited growth of the bacterial cultures was taken as the active dose.

The antimicrobial activity of the 20 compounds was studied. It was found that compounds **I** – **XX** exhibited weak antimicrobial activity (Table 3).

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