HETEROCYCLES, Vol. 78, No. 7, 2009, pp. 1787 - 1798. © The Japan Institute of Heterocyclic Chemistry
Received, 16th February, 2009, Accepted, 12th March, 2009, Published online, 13th March, 2009
DOI: 10.3987/COM-09-11682

SYNTHESIS AND ANTIMICROBIAL EVALUATION OF NEW PYRAZOLE, THIOPHENE, THIAZOLE AND 1,3,4-THIADIAZOLE DERIVATIVES INCORPORATING PYRIMIDINE RING

Ahmad M. Farag,[1]* Nabila A. Kheder,[1] and Yahia N. Mabkhot[2]

[1]Department of Chemistry, Faculty of Science, Cairo University, Giza 12613, Egypt. [2]Department of Chemistry, Faculty of Science, King Saud University, 2455, Riyadh 11751, Saudi Arabia

*Corresponding author: E-mail: afarag49@yahoo.com

Abstract – The utility of 3-oxo-*N*-(pyrimidin-2-yl)butanamide (**1**) in the synthesis of some new pyrazole, thiophene, thiazole**,** and 1,3,4-thiadiazole derivatives pendant to a pyrimidine ring is reported. Antimicrobial evaluation of some selected examples from the synthesized products was carried out and showed moderate activity.

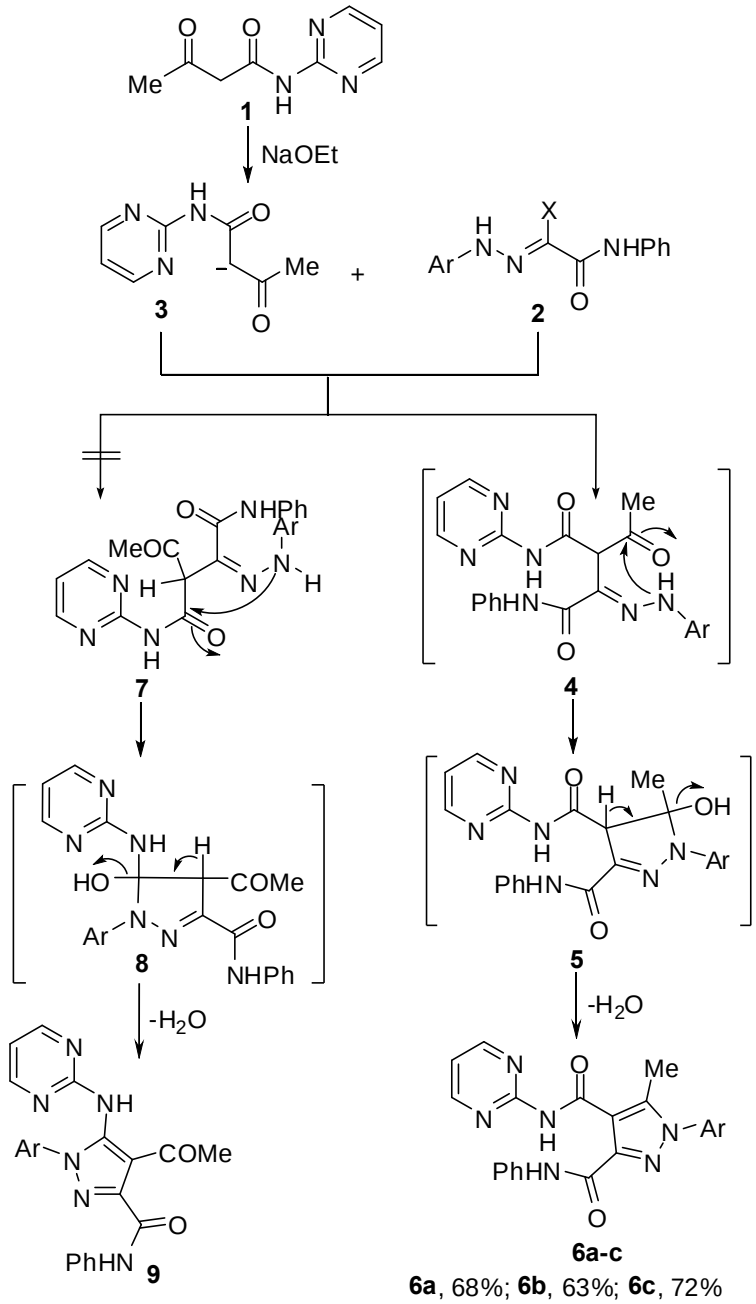
INTRODUCTION

Pyrimidines are of considerable chemical and biological importance[1,2] because of their association to the nucleic acids. In medicinal chemistry, pyrimidine derivatives have been very well known for their therapeutic applications. Compounds containing the pyrimidine ring system have been shown to possess antitumor, antibacterial, antifungal, antimalarial and anticonvulsant activities.[1–5] Some are valuable drugs for the treatment of hyperthyroidism, acute leukemia in children and adult granulocytic leukemia.[5] Furthermore, several pyrimidines are used in polymer and supramolecular chemistry.[6,7] In view of these reports and in continuation of our recent research on the synthesis of a variety heterocyclic ring systems which could be adapted for establishing small libraries,[8-25] we report here on a convenient access to new pyrazole**,** thiophene, thiazole and 1,3,4-thiadiazole derivatives incorporating a pyrimidine moiety.

RESULTS AND DISCUSSION

As a part of ongoing program aiming at the synthesis of heterocyclic ring systems containing pyrimidine moiety for biological screening,[11,12,15,23] the reaction of 3-oxo-*N*-(pyrimidin-2-yl)butanamide (**1**)[26] with the hydrazonoyl halides **2a-c**[27] was investigated as a convenient route to the target compounds. Thus, treatment of the butanamide **1** with the appropriate hydrazonoyl halides **2a-c**, in ethanolic sodium

ethoxide solution, furnished, in each case, one isolable product. The isolated products were assigned the pyrazole structures **6a-c** according to their elemental analyses and spectral data (Scheme 1). The other possible structure **9a-c** was ruled out on the basis of the IR and ^{1}H NMR spectra of the isolated products. The IR spectrum of compound **6a**, taken as a typical example of the prepared series, exhibited absorption bands at 1655, 1686, 3155 and 3292 cm^{-1} corresponding to two carbonyl and two imino functions, respectively. Its ^{1}H NMR spectrum showed signals at δ 2.49, due to CH_3 and two D_2O-exchangeable signals at δ 11.19 and 13.90 corresponding to two NH protons, in addition to an aromatic multiplet in the region δ 7.13-7.80. In addition, its mass spectrum gave molecular ion peak at *m/z* 398.

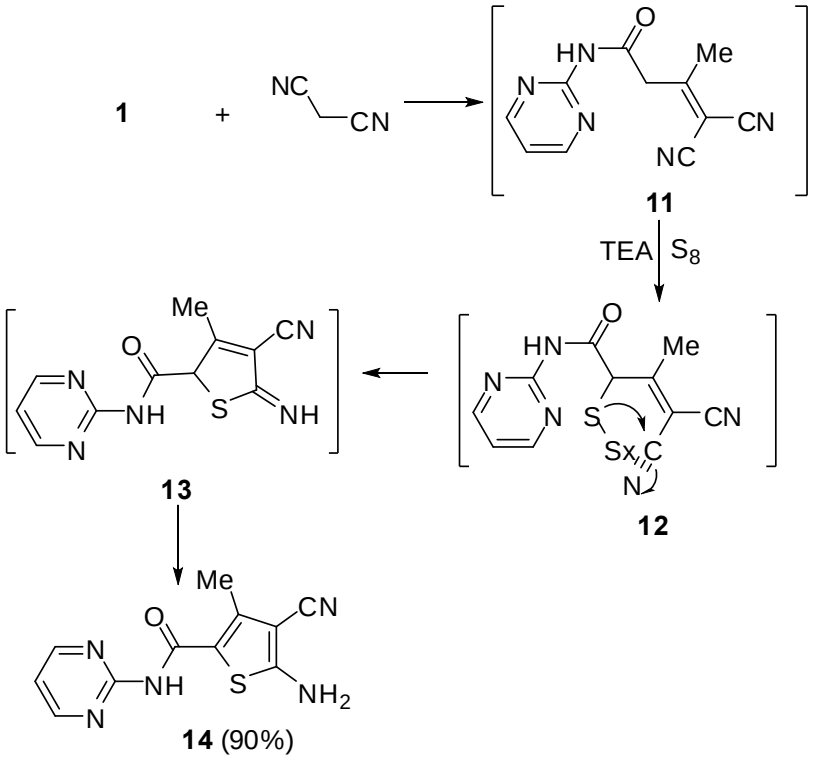


6a, 68%; **6b**, 63%; **6c**, 72%

2-9: **a**, Ar = C_6H_5; **b**, Ar = 4-MeC_6H_4; **c**, Ar = 4-ClC_6H_4

Scheme 1

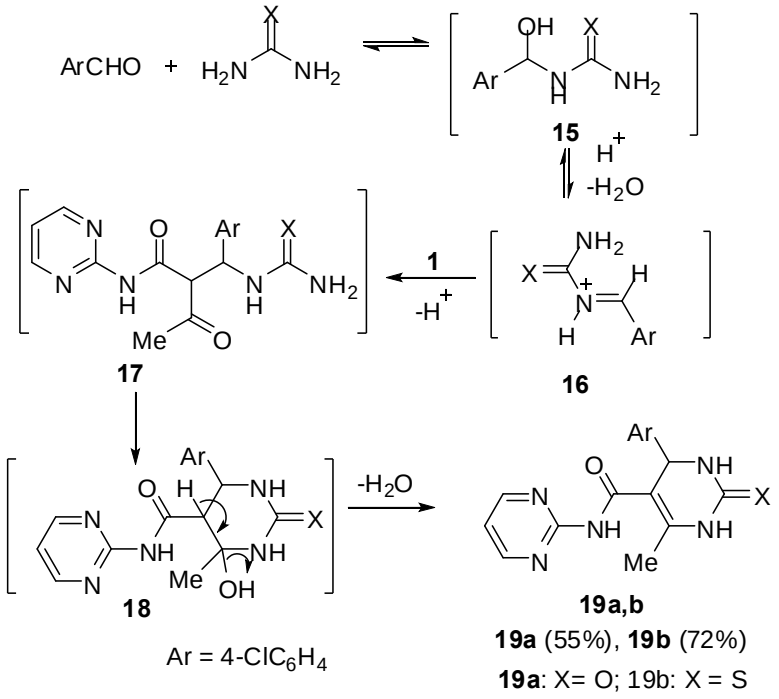
It has been reported that 2-amino-3-functionally substituted thiophene derivatives are useful precursors in azo-dye industry and are utilized as intermediates for the pharmaceutically important thieno[2,3-*d*]-pyrimidines.[28,29] Synthesis of 2-amino-3-cyanothiophenes may be readily achieved by condensation of a ketone with malononitrile and elemental sulfur.[30] Therefore, it is worthwhile to investigate the reaction of the butanamide **1** with elemental sulfur and malononitrile which led to a product identified as 5-amino-4-cyano-3-methyl-*N*-(pyrimidin-2-yl)thiophene-2-carboxamide (**14**) (Scheme 2). The IR spectrum of compound **14** exhibited absorption bands at 1638, 2206, 3206-3165 and 3420 cm^{-1} due to carbonyl, nitrile, amino and imino functions, respectively. Its ^1H NMR spectrum revealed signal at δ 2.39 due to CH_3 protons and two D_2O-exchangeable signals at δ 6.02 and 7.80 corresponding to amino and NH protons, in addition to an aromatic multiplet in the region δ 7.33-9.96.



Scheme 2

Acid catalyzed condensation reaction of a ternary mixture of the butanamide **1**, urea and 4-chlorobenzaldehyde in EtOH afforded a product identified as 4-(4-chlorophenyl)-6-methyl-2-oxo-*N*-(pyrimidin-2-yl)-1,2,3,4-tetrahydropyrimidine-5-carboxamide (**19a**) (Scheme 3). IR spectrum of compound **19a** revealed absorption bands at 1666, 1675, 3069, 3094 and 3200 cm^{-1} corresponding to two carbonyl and three imino functions, respectively. Its ^1H NMR spectrum showed signals at δ 2.10, 5.34 due to CH_3 and CH protons and three D_2O-exchangeable signals at δ 9.45, 10.07 and 10.44 corresponding to three imino functions, in addition to an aromatic multiplet in the region δ 7.13-8.62. In a similar

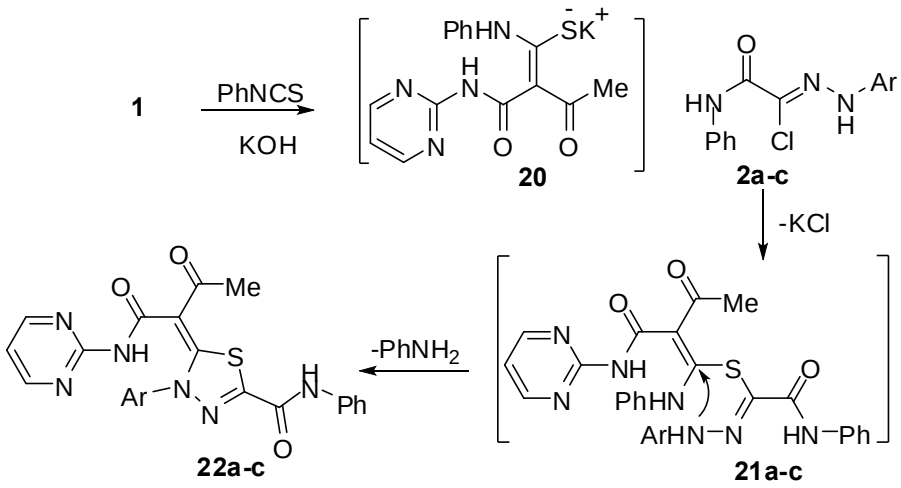
manner, 4-(4-chlorophenyl)-6-methyl-*N*-(pyrimidin-2-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (**19b**) was obtained by the acid catalyzed condensation reaction of a ternary mixture of the butanamide **1**, thiourea and 4-chlorobenzaldehyde in EtOH (Scheme 3). The ^{1}H NMR spectrum of **19b** revealed signals at δ 2.25, 5.13 due to CH_3 and CH protons and three D_2O-exchangeable signals at δ 7.73, 9.2 and 13.1 corresponding to three imino function, in addition to an aromatic multiplet in the region δ 7.23-7.93. Also, its mass spectrum revealed a molecular ion peak at *m/z* 360.



Scheme 3

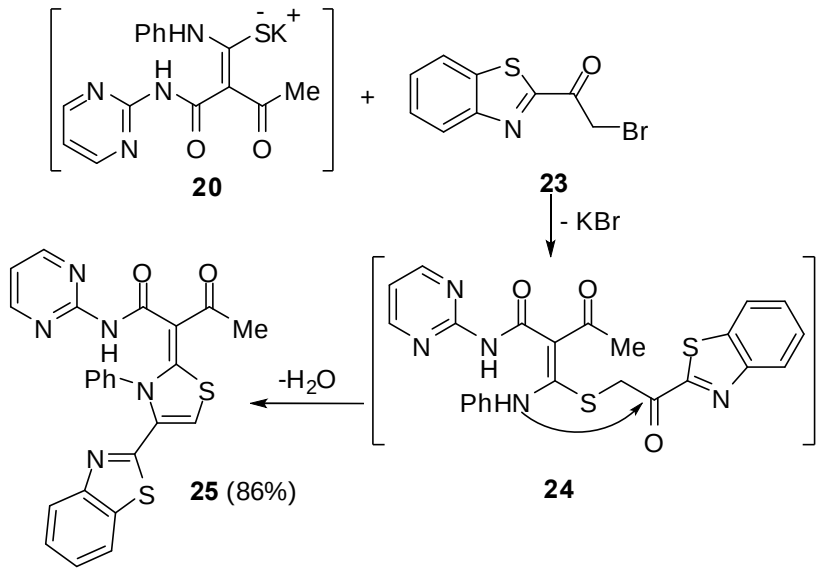
Reaction of the butanamide **1** with phenyl isothiocyanate in dimethylformamide, in the presence of potassium hydroxide, followed by addition of an equimolar amount of the appropriate hydrazonoyl chloride **2a-c**, furnished, in each case, only one isolable product (as tested by TLC analysis). The reaction products were identified as the 5-(1,3-dioxo-1-(pyrimidin-2-ylamino)butan-2-ylidene)-*N*-phenyl-4-aryl-4,5-dihydro-1,3,4-thiadiazole-2-carboxamide structure **22a-c** (Scheme 4) as confirmed by the elemental analyses, IR, ^{1}H NMR and mass spectra of the isolated products. The IR spectrum of compound **22a**, taken as a typical example, revealed absorption bands at 1638, 1647, 1667, 3283 and 3383 due to three carbonyl groups and two NH functions, respectively. The ^{1}H NMR spectrum of the same compound showed signals at δ 2.49 due to CH_3 protons, two D_2O-exchangeable signals at δ 10.17 and 11.71 due to two NH protons, in addition to an aromatic multiplet in the region δ 7.01-7.78. The aforementioned results indicate that the reaction of the potassium salt **20** with the hydrazonoyl chlorides **2a-c** proceeds, in each case, *via* loss of aniline molecule from the non-isolable intermediates **21a-c** (Scheme 4).

Similarly, the potassium salt **20** reacts with 1-(benzothiazol-2-yl)-2-bromoethanone (**23**)[31] under the same reaction conditions to afford 2-(4-(benzothiazol-2-yl)-3-phenylthiazol-2(3*H*)-ylidene)-3-oxo-*N*-(pyrimidin-2-yl)butanamide (**25**) (Scheme 5). The structure of the isolated product was inferred from its elemental analysis and spectral data. For example, its IR spectrum exhibited absorption bands at 1638, 1690 and 3217 m^{-1} due to two carbonyl groups and NH function, respectively.



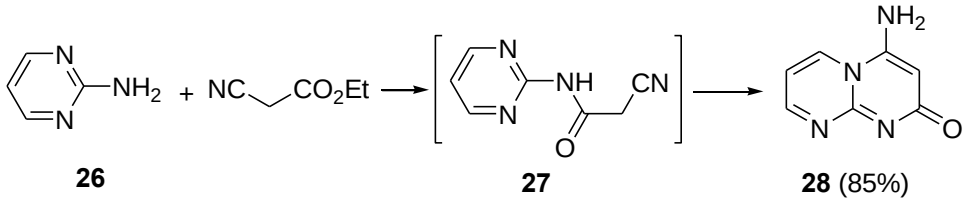
Scheme 4

Its ^{1}H NMR spectrum revealed signals at δ 2.49 due to CH_3 protons, D_2O-exchangeable signal at δ 10.87 due to NH proton, in addition to an aromatic multiplet in the region δ 7.14-9.85.



Scheme 5

Treatment of 2-aminopyrimidine (**26**) with ethyl cyanoacetate led to the formation of 4-amino-2-*H*-pyrimido[1,2-*a*]pyrimidin-2-one (**28**) *via* intramolecular cyclization of the none isolable intermediate 2-cyano-*N*-(pyrimidin-2-yl)acetamide (**27**) (Scheme 6). The IR spectrum of the pyrimidopyrimidine **28** showed absorption bands at 1651, 3200 and 3329 cm^{-1} due to carbonyl and NH_2 groups, respectively. Its ^1H NMR spectrum revealed D_2O-exchangeable signal at δ 5.23 due to NH_2 protons, in addition to pyrimidine protons at δ 5.72-6.56. Whereas, its mass spectrum gave a molecular ion peak at *m/z* 162. All attempts to isolate the intermediate 2-cyano-*N*-(pyrimidin-2-yl)acetamide (**27**) were unsuccessful.



Scheme 6

CONCLUSION

In conclusion, the reactivity of 3-oxo-*N*-(pyrimidin-2-yl)butanamide (**1**) was investigated as a versatile and readily accessible building block for the synthesis of new heterocyclic compounds incorporating a pyrimidine moiety of biological and pharmaceutical importance.

EXPERIMENTAL

All melting points were measured on a Gallenkamp melting point apparatus. The infrared spectra were recorded in potassium bromide disks on a pye Unicam SP 3300 and Shimadzu FT IR 8101 PC infrared spectrophotometers. The NMR spectra were recorded on a Varian Mercury VX-300 NMR spectrometer. ^1H spectra were run at 300 MHz in dimethyl sulphoxide (DMSO-d_6). Chemical shifts were related to that of the solvent. Mass spectra were recorded on a Shimadzu GCMS-QP 1000 EX mass spectrometer at 70 e.V Elemental analyses and the biological evaluation of the selected newly synthesized heterocyclic compounds were carried out at the Microanalytical Center of Cairo University, Giza, Egypt. 3-Oxo-*N*-(pyrimidin-2-yl)butanamid (**1**),[26] 2-oxo-2-phenylamino-*N*-arylethanehydrazonoyl chlorides **2a-c**,[27] and 2-bromo-1-(benzothiazol-2-yl)ethanone (**23**)[31] were prepared according to the reported literature procedures.

Reaction of the butanamide 1 with 2-oxo-2-phenylamino-N-arylethanehydrazonoyl chlorides (2a-c).

General procedure

Butanamid **1** (1.79 g, 10 mmol) was added to a stirred ethanolic sodium ethoxide solution [prepared from

sodium metal (0.23 g, 10 mmol) and absolute EtOH (20 mL)]. After stirring for 15 min, the appropriate hydrazonoyl halide **2a-c** (10 mmol) was added and the reaction mixture left to stir at rt for further 12 h. The solid product that formed was collected by filtration, washed with water and dried. Recrystallization from the proper solvent afforded the pyrazole derivatives **6a-c**.

5-Methyl-N^3,1-diphenyl-N^4-(pyrimidin-2-yl)-1H-pyrazole-3,4-dicarboxamide (6a). Yield (68%), mp 238-240 ^oC (DMF/EtOH); IR (KBr) ν 3292 (NH), 3155 (NH), 1686 (C=O), 1655 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.49 (s, 3H, CH_3), 7.13-7.80 (m, 13H, ArH's), 11.19 (s, br., 1H, D_2O-exchangeable, NH), 13.90 (s, br., 1H, D_2O-exchangeable, NH); MS, *m/z* (%) 400 (5.0), 399 (14.8), 398 (M^+, 15.5), 122 (21.4). Anal. Calcd for $C_{22}H_{18}N_6O_2$: C, 66.32; H, 4.55; N, 21.09. Found: C, 66.28; H, 4.49; N, 21.03%.

5-Methyl-N^3-phenyl-N^4-(pyrimidin-2-yl)-1-p-tolyl-1H-pyrazole-3,4-dicarboxamide (6b). Yield (63%), mp 250-1 ^oC (DMF/EtOH); IR (KBr) ν 3356 (NH), 3020 (NH), 1674 (C=O), 1655 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.26 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 7.15-7.56 (m, 13H, ArH's and NH), 11.05 (s, br., 1H, D_2O-exchangeable, NH). Anal. Calcd for $C_{23}H_{20}N_6O_2$: C, 66.98; H, 4.89; N, 20.38. Found: C, 66.92; H, 4.85; N, 20.40%.

1-(4-Chlorophenyl)-5-methyl-N^3-phenyl-N^4-(pyrimidin-2-yl)-1H-pyrazole-3,4-dicarboxamide (6c). Yield (72%), mp 260-1 ^oC (DMF/EtOH); IR (KBr) ν 3356 (NH), 3155 (NH), 1692 (C=O), 1674 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.49 (s, 3H, CH_3), 7.12-7.57 (m, 13H, ArH's and NH), 11.12 (s, br., 1H, D_2O-exchangeable, NH). Anal. Calcd for $C_{22}H_{17}N_6O_2Cl$: C, 61.04; H, 3.96; N, 19.41; Cl, 8.19. Found: C, 61.09; H, 3.98; N, 19.49; Cl, 8.13%.

5-Amino-4-cyano-3-methyl-N-(pyrimidin-2-yl)thiophene-2-carboxamide (14).

To a solution of butanamide **1** (3.58 g, 20 mmol) in EtOH (20 mL), elemental sulfur (0.64 g, 20 mmol), malononitrile (1.32 g, 20 mmol), and a catalytic amount of triethylamine was added. The reaction mixture was heated at 60-65 ^oC for 30 min, then allowed to cool. The precepitated solid was filtered off, washed with EtOH and recrystallized from DMF/EtOH mixture to give brown solid of the thiophene derivative **14** in 90% yield, mp 250-1 ^oC (DMF/ EtOH); IR (KBr) ν 3420 (NH), 3165 and 3206 (NH_2), 2206 (C≡N), 1638 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.39 (s, 3H, CH_3), 6.20 (s, 2H, D_2O-exchangeable, NH_2), 7.33 (m, 1H), 7.8 (s, 1H, D_2O-exchangeable, NH), 8.53 (d, 1H), 9.96 (d, 1H); MS *m/z* (%) 263 (9.5), 122 (0.8), 94 (1.6), 79 (26.8). Anal. Calcd for $C_{11}H_9N_5OS$: C, 50.95; H, 3.50; N, 27.01; S, 12.37. Found: C, 50.89; H, 3.41; N, 26.93; S, 12.36%.

Reaction of 3-oxo-N-(pyrimidin-2-yl)butanamide (1) with p-chlorobenzaldehyde and urea or thiourea.

General procedure

To a solution of the butanamide **1** (0.358 g, 2 mmol), 4-chlorobenzaldehyde (0.255 g, 2 mmol) in EtOH (20 mL), acetic acid (1 mL), urea (0.12 g, 2 mmol) or thiourea (0.152 g, 2 mmol) were added. The reaction mixture was refluxed for 4 h, then allowed to cool. The solid product so formed was filtered off,

washed with EtOH and dried. Recrystallization from EtOH afforded the corresponding tetrahydropyrimidine **19a,b**, respectively.

4-(4-Chlorophenyl)-6-methyl-2-oxo-N-(pyrimidin-2-yl)-1,2,3,4-tetrahydropyrimidine-5-carboxamide (19a). Yield (55%), mp 160-61 °C (EtOH); IR (KBr) ν 3200 (NH), 3094 (NH), 3069 (NH), 1675 (C=O), 1666 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.10 (s, 3H, CH_3), 5.34 (d, 1H, CH, J = 2.7 Hz), 7.13-8.62 (m, 7H, ArH's), 9.45 (s, br., 1H, D_2O-exchangeable, NH), 10.07 (s, br., 1H, D_2O-exchangeable, NH), 10.44 (s, br., 1H, D_2O-exchangeable, NH). Anal. Calcd for $C_{16}H_{14}N_5O_2Cl$: C, 55.90; H, 4.10; N, 20.37; Cl, 10.31. Found: C, 55.89; H, 4.15; N, 20.42; Cl, 10.28%.

4-(4-Chlorophenyl)-6-methyl-N-(pyrimidin-2-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (19b). Yield (72%), mp 165-66 °C (EtOH); IR (KBr) ν 3431 (NH), 3193 (NH), 1682 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.25 (s, 3H, CH_3), 5.13 (d, 1H, CH, J = 3.3 Hz), 7.23 (d, 1H, J = 8.4 Hz), 7.38 (d, 1H, J = 8.4 Hz), 7.55 (m, 2H), 7.93 (m, 3H), 7.73 (s, br., 1H, D_2O-exchangeable, NH), 9.2 (s, br., 1H, D_2O-exchangeable, NH), 13.1 (s, br., 1H, D_2O-exchangeable, NH); MS *m/z* 361 (1.6), 360 (M^+, 1.4), 359 (5.5), 237 (M^+-123, 57.1). Anal. Calcd. for $C_{16}H_{14}N_5OSCl$: C, 53.41; H, 3.92; N, 19.46; S, 8.91; Cl, 9.85. Found: C, 53.36; H, 3.91; N, 19.43; S, 8.88; Cl, 9.83%.

5-(1,3-Dioxo-1-(pyrimidin-2-ylamino)butan-2-ylidene)-N-phenyl-4-aryl-4,5-dihydro-1,3,4-thiadiazole-2-carboxamide 22a-c.

General Procedure

To a stirred solution of potassium hydroxide (0.11 g, 2 mmol) in DMF (20 mL) was added the butanamide **1** (0.358 g, 2 mmol). After stirring for 30 min, phenyl isothiocyanate (0.27 g, 2 mmol) was added to the resulting mixture. Stirring was continued for 6 h, and then the appropriate hydrazonoyl chloride **2** (2 mmol) was added portionwise over a period of 30 min. After the addition was complete, the reaction mixture was stirred for additional 12 h, during which the hydrazonoyl chloride went into solution and a yellowish colored product precipitated. The solid product was filtered off, washed with EtOH and dried. Recrystallization from EtOH/DMF afforded yellow crystals of the corresponding products **22a-c**.

5-(1,3-Dioxo-1-(pyrimidin-2-ylamino)butan-2-ylidene)-N,4-diphenyl-4,5-dihydro-1,3,4-thiadiazole-2-carboxamide (22a). Yield (77%), mp 215-6 °C (DMF/EtOH); IR (KBr) ν 3383 (NH), 3283 (NH), 1667 (C=O), 1647 (C=O), 1638 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.49 (s, 3H, CH_3), 7.01-7.78 (m, 13H, ArH's), 10.17 (s, br., 1H, D_2O-exchangeable, NH), 11.71 (s, br., 1H, D_2O-exchangeable, NH). Anal. Calcd for $C_{23}H_{18}N_6O_3S$: C, 60.25; H, 3.96; N, 18.33; S, 6.99. Found: C, 60.20; H, 3.92; N, 18.38; S, 7.01%.

5-(1,3-Dioxo-1-(pyrimidin-2-ylamino)butan-2-ylidene)-N-phenyl-4-p-tolyl-4,5-dihydro-1,3,4-thiadiazole-2-carboxamide (22b). Yield (71%), mp 265-266 °C (DMF/EtOH); IR (KBr) ν 3389 (NH), 3200 (NH), 1674 (C=O), 1647 (C=O), 1631 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.26 (s, 3H, CH_3), 2.29 (s, 3H,

CH_3), 7.10-7.87 (m, 12H, ArH's), 10.69 (s, 1H, D_2O-exchangeable, NH), 11.0, (s, 1H, D_2O-exchangeable, NH). Anal. Calcd for $C_{24}H_{20}N_6O_3S$: C, 61.00; H, 4.27; N, 17.79; S, 6.79. Found: C, 60.97; H, 4.30; N, 17.77; S, 6.73%.

4-(4-Chlorophenyl)-5-(1,3-dioxo-1-(pyrimidin-2-ylamino)butan-2-ylidene)-N-phenyl-4,5-dihydro-1,3,4-thiadiazole-2-carboxamide (22c). Yield (80%), mp 215-216 ^oC (DMF/EtOH); IR (KBr) ν 3395 (NH), 3165 (NH), 1663 (C=O), 1632 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.49 (s, 3H, CH_3), 7.13-7.74 (m, 12H, ArH's), 10.16 (s, br., 1H, D_2O-exchangeable, NH), 11.59 (s, br., 1H, D_2O-exchangeable, NH). Anal. Calcd for $C_{23}H_{17}N_6O_3SCl$: C, 56.04; H, 3.48; N, 17.05; S, 6.50; Cl, 7.19. Found: C, 56.09; H, 3.52; N, 17.09; S, 6.55; Cl, 7.15%.

2-(4-(Benzothiazol-2-yl)-3-phenylthiazol-2(3H)-ylidene)-3-oxo-N-(pyrimidin-2-yl)butanamide (25). To a stirred solution of potassium hydroxide (0.11 g, 2 mmol) in DMF (20 mL) was added the butanamide **1** (0.358 g, 2 mmol). After stirring for 30 min, phenyl isothiocyanate (0.27 g, 2 mmol) was added to the resulting mixture. Stirring was continued for 6 h, then 1-(benzothiazol-2-yl)-2- bromoethanone (**23**) (0.512 g, 2 mmol) was added portionwise over a period of 30 min. After the addition was complete, the reaction mixture was stirred for additional 12 h, during which the reactant dissolved and a yellowish colored product precipitated. The solid product was filtered off, washed with water and dried. Recrystallization from EtOH/DMF afforded orange crystals of **25**. Yield (68%), mp 245-246 ^oC (DMF/EtOH): IR (KBr) υ 3217 (NH), 1690 (C=O), 1638 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.49 (s, 3H, CH_3), 7.14-9.85 (m, 13H, ArH's), 10.87 (s, br., 1H, D_2O-exchangeable, NH). Anal. Calcd for $C_{24}H_{17}N_5O_2S_2$: C, 61.13; H, 3.63; N, 14.85; S, 13.60. Found: C, 61.18; H, 3.60; N, 14.89; S, 13.57%.

4-Amino-2-H-pyrimido[1,2-a]pyrimidin-2-one (28).

In a 250 mL three necked round–bottomed flask, fitted with air condenser and thermometer were placed ethyl cyanoacetate (1.13 g, 10 mmol). The flask was immersed in an oil bath heated to 100-110 ^oC then 2-aminopyrimidine (0.95 g, 10 mmol) was added portionwise over a period of 30 min. and heating was continued for an additional 15 min. The reaction flask was removed from the oil bath, then left to cool and triturated with EtOH. The solid product was filtered off washed with EtOH and dried. Recrystallization from DMF afforded the pyrimido[1,2-*a*]pyrimidin **28** in 85% yield, mp 300-1 ^oC (DMF); IR (KBr) ν 3200-3329 (NH_2), 1651 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 5.23 (s, 2H, D_2O-exchangeable NH_2), 5.72 (s, 1H, CH), 6.51-6.56 (m, 3H, ArH's); MS *m/z* (%) 165 (16.2), 163 (65.4), 162 (M^+, 100), 122 (35.3). Anal. Calcd for $C_7H_6N_4O$: C, 51.85; H, 3.73; N, 34.55. Found: C, 51.89; H, 3.65; N, 34.53%.

ANTIMICROBIAL ACTIVITY

Compounds **6a-c**, **14**, **19a** and **19b** were tested for their antimicrobial activities using two fungal species,

namely *Aspergillus fumigatus* (**AF**) and *Candida albicans* (**CA**). Also, two bacteria species namely, *Escherichia coli (***EC***) and Staphylcoccus aureus (***SA***),* were used for antimicrobial screening. The organisms were tested against the activity of solutions of concentration of 5 mg/mL of each compound using an inhibition zone diameter in cm (IZD) as criterion for the antimicrobial activity. The fungicide Amphotricine and the bactericide Tetracycline were used as references to evaluate the potency of the tested compounds under the same conditions. The results are summarized in Table 1.

IZD = 2-10 mm beyond control = + (low activity).

IZD = 11-24 mm beyond control = ++ (moderate activity).

IZD = 25-35 mm beyond control = +++ (high activity).

Table 1. Antibacterial and Antifungal Activities of Selected Examples of the Synthesized Compounds

Compound No.	**Inhibition Zone Diameter (IZD) (mm/mg Compound Tested)**			
	(EC)	**(SA)**	**(CA)**	**(AF)**
Control	0.0	0.0	0.0	0.0
6a	11 ++	11 ++	0.0	0.0
6b	0.0	0.0	0.0	0.0
6c	11 ++	11 ++	0.0	0.0
14	17 ++	16 ++	14 ++	15 ++
19a	13 ++	14 ++	0.0	0.0
19b	14 ++	15 ++	0.0	0.0
Tetracycline	32 +++	34 +++	–	–
Amphotricine	–	–	20 ++	16 ++

The test results revealed that all compounds exhibited moderate activity against two bacterial species, except compound **6b** showed no activity. All compounds exhibited almost no activity against *Aspergillus fumigatus* (**AF**), *Candida albicans* (**CA**) except compound **14** which showed moderate activity.

REFERENCES

1. K. Undheim and T. Benneche, In Comprehensive Heterocyclic Chemistry II, ed. by A. R. Katritzky, C. W. Rees, and E. V. F. Scriven, Pergamon Press, London, 1996, Vol. 6, Chapter 2, pp. 93-231.
2. D. J. Brown, R. F. Evans, and W. B. Cowden, In The Pyrimidines, ed. by E. C. Taylor and A. Weissberger, Eds., John Wiley, New York, 1994, Vol. 52.
3. M. Johar, T. Manning, D. Y. Kunimoto, and R. Kumar, *Bioorg. Med. Chem.*, 2005, **13**, 6663.
4. N. Azas, P. Rathelot, S. Djekou, F. Delmas, A. Gellis, C. Di Giorgio, P. Vanelle, and D. Timon, P. *Il Farmaco*, 2003, **58**, 1263.
5. A. Agarwal, K.Srivastava, S. K. Puri, and P. M. S. Chauhan, *Bioorg. Med. Chem.*, 2005, **13**, 4645.
6. a) R. Gompper, H. J. Mair, and K. Polborn, *Synthesis*, 1997, 696; b) T. Kanbara, T. Kushida, N. Saito, I. Kuwajima, K. Kubota, and T. Yamamoto, *Chem. Lett.*, 1992, 583.
7. a) G. S. Hanan, D. Vilkmer, U. S. Schubert, J. M. Lehn, G. Baum, and D. Fenske, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1842; b) D. M. Bassani, J. M. Lehn, G. Baum, and D. Fenske, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1845; c) A. Semenov, J. P. Spatz, M. Moller, J. M. Lehn, B. Sell, D. Schubert, C. H. Weidl, and U. S. Schubert, *Angew. Chem. Int. Ed.*, 1999, **38**, 2547.
8. M. R. Shaaban, T. S. Saleh, and A. M. Farag, *Heterocycles*, 2009, **78**, 151.
9. N. A. Kheder, E. S. Darwish, and K. M. Dawood, *Heterocycles*, 2009, **78**, 177.
10. M. R. Shaaban, T. S. Saleh, and A. M. Farag, *Heterocycles*, 2009, **78**, 699.
11. N. A. Kheder, Y. N. Mabkhot, and A. M. Farag, *Heterocycles*, 2009, **78**, 937.
12. N. A. Kheder, Y. N. Mabkhot, and A. M. Farag, *Heterocycles*, 2008, **75**, 887.
13. N. A. Kheder, Y. N. Mabkhot, and A. M. Farag, *Heterocycles*, 2008, **75**, 2937.
14. A. M. Farag, A. S. Mayhoub, S. E. Barakat, and A. H. Bayomi, *Bioorg. Med. Chem.*, 2008, **16**, 4569.
15. N. A. Kheder, Y. N. Mabkhot, and A. M. Farag, *Synth. Commun.*, 2008, **38**, 3170.
16. N. A. Kheder, Y. N. Mabkhot, and A. M. Farag, *Arkivoc*, 2008, **xvii**, 107.
17. K. M. Dawood, A. M. Farag, and N. A. Kheder, *Arkivoc* 2008, **xv**, 166.
18. M. R. Shaaban, T. S. Saleh, A. S. Mayhoub, A. Mansour, and A. M. Farag, *Bioorg. Med. Chem.*, 2008, **16**, 6344.
19. A. M. Farag, A. S. Mayhoub, S. E. Barakat, and A. H. Bayomi, *Bioorg. Med. Chem.*, 2008, **16**, 881.
20. A. S. Girgis, N. Mishriky, A. M. Farag, W. I. El-Eraky, and H. Farag, *Eur. J. Med. Chem.*, 2008, **43**, 1818.

21. A. M. Farag, Y. M. Elkholy, and K. A. Ali, *J. Heterocycl. Chem*., 2008, **45**, 279.
22. M. R. Shaaban, T. M. A. Eldebss, A. F. Darweesh, and A. M. Farag, *J. Heterocycl. Chem*., 2008, **45**, 1739.
23. M. R. Shaaban, T. S. Saleh, and A. M. Farag, *Heterocycles*, 2007, **71**, 1765.
24. A. M. Farag, K. M. Dawood, and N. A. Kheder, *J. Chem. Res*., 2007, 472.
25. K. M. Dawood, A. M. Farag, and H. A. Abdel-Aziz, *Heteroatom Chem*., 2007, **18**, 294.
26. B. P. Singh, P. K. Armakar, A. K. D. Mazumdar, and K. P. Banerjee, *J. Ind. Chem. Soc.*, 1992, **69**, 212.
27. A. S. Shawali and A. O. Abdelhamid, *Tetrahedron*, 1971, **27**, 2517.
28. T. Isobe, T. Nagao, Y. Takashi, M. Miyagaki, S. Ito, H. Azuma, and M. Ishikawa, Jpn. Kokai Tokkyo Koho. JP, 0307, 265 (1991) [*Chem. Abstr*., 1991, **114**, 228948y].
29. D. L. Temple, J. P. Yevich, R. R. Convington, C. A. Hanning, R. J. Seidehamel, H. K. Mackey, and M. J. Bartek, *J. Med. Chem.*, 1979, **22**, 505.
30. K. Gewald, E. Schinke, and H. Böttcher, *Chem. Ber.*, 1966, **99**, 94.
31. S. N. Sawhney and J. Sing, *Ind. J. Chem.*, 1970, **8**, 882.