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Synthesis and Antibacterial Evaluation of Tetrahydropyrimidine-5-carboxamide

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A series of new dihydropyrimidine-2*H*-ones/thiones were synthesized and evaluated *in vitro* for their antibacterial activity. Characterization of newly synthesized dihydropyrimidones was done by physical and spectral data. All the synthesized compounds were evaluated for their antibacterial activity. Amongst all, compounds **3e** and **4e** registered high activity against the bacterial strain when compared to standard drug.

Keywords: Dihydropyrimidones, Biginelli reactions, Grindstone technique, Antibacterial.

INTRODUCTION

Biginelli compounds or dihydropyrimidinones (DHPMs) exhibit a broad spectrum of biological activity. For example, some of these compounds are very potent calcium channel blockers and act as antihypertensive, antiviral, antitumor and anti-inflammatory agents [1-8]. Previous studies on biological activity of dihydropyridines (DHPs) have revealed that dihydropyridines having carbamoyl moieties at 3rd and 5th positions showed significant antituberculosis activity [9]. These observations have prompted us to undertake the designing of new dihydropyrimidinones derivatives against microbial resistance. The presence of several interacting functional groups in Biginelli compounds determines their great synthetic potentiality [5]. Hence, the required dihydropyrimidinones were synthesized according to the procedure described by Pathak *et al.* [10]. In addition to this, we addressed the i*n vitro* antibacterial evaluation of synthesized compounds.

EXPERIMENTAL

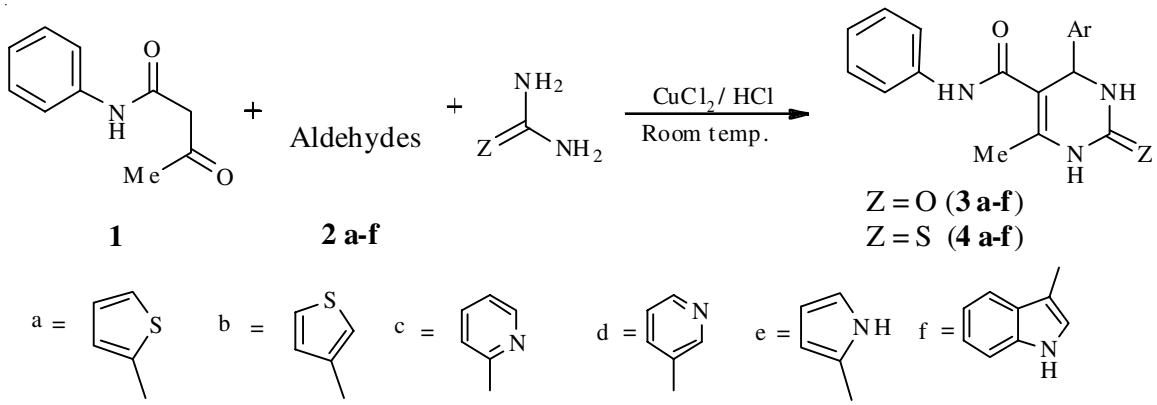
Melting points were recorded in open capillary tube and are uncorrected. IR spectra were recorded in KBr on 8400S Shimadzu FT-IR Spectrophotometer and NMR spectra were scanned on a Bruker 300 MHz Spectrometer in $CDCl_3$/DMSO-d_6 using TMS as internal standard. The chemical shifts are expressed in δ-scale. Elemental analyses were carried out on Perkin-Elmer 2400 II instrument. Purity of synthesized compounds was checked by TLC using silica gel-G and spots were detected in iodine chamber.

General procedure for the preparation of 4-(aryl)-6-methyl-2-oxo-*N*-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamides: A mixture of an heterocyclic aldehyde (0.01 mol), *N*-phenylacetoacetamide (0.01 mol), urea/thiourea (0.01 mol), cupric chloride (0.01 mol) and 2-3 drops of conc. HCl was ground together to give a syrup under solvent-free condition which was left overnight. The contents were poured into ice-cold water and the product that separated was filtered, dried and crystallized. All the compounds have been synthesized as per reported procedure [10](**Scheme-I**).

4-(Thiophen-2-yl)-6-methyl-2-oxo-*N*-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3a): Yield: 88 %, m.p.: 152 °C (aq. EtOH); IR (KBr, ν_{max}, cm^{-1}): 3378, 3270 (NH), 1676 (C=O of amide). ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 2.11 (s, 3H, 6-CH_3), 5.60 (s, 1H, H-4), 7.04-8.30 (m, 8H, Ar-H), 8.68 (s, 1H, 3-N*H*), 8.87 (s, 1H, 1-N*H*), 9.41 (s, 1H, N*H* of amide). ^{13}C NMR (75 MHz): δ 18.1, 51.8, 109.5, 120.4, 121.6, 125.6, 128.0 128.9, 133.2, 137.6, 144.2, 147.1, 148.4, 152.3, 162.8.

4-(Thiophen-3-yl)-6-methyl-2-oxo-*N*-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3b): Yield: 84 %, m.p.: 143-145 °C (aq. EtOH); IR (KBr, ν_{max}, cm^{-1}): 3379, 3272 (NH), 1678 (C=O of amide). ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 2.12 (s, 3H, 6-CH_3), 5.58 (s, 1H, H-4), 7.10-8.22 (m, 8H, Ar-H), 8.69 (s, 1H, 3-N*H*), 8.90 (s, 1H, 1-N*H*), 9.38 (s, 1H, N*H* of amide). ^{13}C NMR (75 MHz): δ 21.1, 51.4, 110.2, 121.7, 126.2, 128.4 129.1, 134.1, 138.2, 145.2, 148.1, 148.8, 153.4, 163.1.

4-(Pyridin-2-yl)-6-methyl-2-oxo-*N*-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3c): Yield: 89 %,



Scheme-I: Synthetic route for the synthesis of 3,4-dihydropyrimidines

m.p.: 178 °C (aq. EtOH); IR (KBr, ν_{max}, cm^{-1}): 3378, 3268 (NH), 1682 (C=O of amide) . ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 2.24 (s, 3H, 6-CH_3), 5.54 (s, 1H, H-4), 7.20-8.26 (m, 9H, Ar-H), 8.06 (s, 1H, 3-N*H*), 8.16 (s, 1H, 1-N*H*), 8.72 (s, 1H, N*H* of amide). ^{13}C NMR (75 MHz): δ 18.2, 51.8, 107.8, 119.8, 123.2, 126.2, 126.9, 127.4, 128.2, 128.4, 138.2, 143.1, 150.2, 163.7.

4-(Pyridin-3-yl)-6-methyl-2-oxo-*N*-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3d): Yield: 92.5 %, m.p.: 129-130 °C (aq. EtOH); IR (KBr, ν_{max}, cm^{-1}): 3380, 3278 (NH), 1677 (C=O of amide) . ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 2.22 (s, 3H, 6-CH_3), 5.55 (s, 1H, H-4), 7.14-8.20 (m, 9H, Ar-H), 8.24 (s, 1H, 3-N*H*), 8.30 (s, 1H, 1-N*H*), 9.22 (s, 1H, N*H* of amide). ^{13}C NMR (75 MHz): δ 18.6, 52.4, 108.8, 121.8, 123.1, 127.5, 128.9, 130.4, 131.8 132.4, 138.2, 143.1, 150.2, 163.7.

4-(Pyrrol-2-yl)-6-methyl-2-oxo-*N*-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3e): Yield: 83 %, m.p.: 184 °C (aq. EtOH); IR (KBr, ν_{max}, cm^{-1}): 3380, 3278 (NH), 167 (C=O of amide) . ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 2.22 (s, 3H, 6-CH_3), 5.48 (s, 1H, H-4), 6.32-7.14 (s, 3H, Ar-H), 7.56-8.19 (s, 5H, Ar-H), 8.24 (s, 1H, 3-N*H*), 8.30 (s, 1H, 1-N*H*), 9.18 (s, 1H, N*H* of amide), 10.92 (s, 1H, pyrrole-N*H*). ^{13}C NMR (75 MHz): δ 18.8, 52.6, 109.4, 111.2, 120.4, 123.1, 127.5, 128.9, 130.4, 131.5 132.3, 137.8, 142.9, 151.4, 162.8.

4-(Indol-2-yl)-6-methyl-2-oxo-*N*-phenyl-1,2,3,4-tetrahydro-pyrimidine-5-carboxamide (3f): Yield: 93 %, m.p.: 134 °C (aq. EtOH); IR (KBr, ν_{max}, cm^{-1}): 3378, 3284 (NH), 1672 (C=O of amide) . ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 2.18 (s, 3H, 6-CH_3), 5.34 (s, 1H, CH-4), 7.21-7.62 (m, 10H, Ar-H), 7.88 (s, 1H, 3-N*H*), 8.76 (s, 1H, 1-N*H*), 9.32 (s, 1H, N*H* of amide), 11.02 (s, 1H, Indole-N*H*). ^{13}C NMR (75 MHz): δ 18.5, 51.8, 108.4, 111.2, 121.6, 123.7, 126.9, 128.9, 130.4, 131.5 132.3, 137.8, 142.9, 151.4, 162.8.

4-(Thiophen-2-yl)-6-methyl-2-thioxo-*N*-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (4a): Yield: 86 %, m.p.: 132 °C (aq. EtOH); IR (KBr, ν_{max}, cm^{-1}): 3269, 3178 (NH), 1676 (C=O of amide), 1440 (C=S) . ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 2.18 (s, 3H, 6-CH_3), 5.60 (s, 1H, H-4), 7.04-8.30 (m, 8H, Ar-H), 8.72 (s, 1H, 3-N*H*), 8.96 (s, 1H, 1-N*H*), 9.48 (s, 1H, N*H* of amide). ^{13}C NMR (75 MHz): δ 19.8, 52.2, 109.5, 120.4, 121.6, 125.6, 128.0 128.9, 133.2, 137.6, 144.2, 147.1, 148.4, 152.3, 162.8.

4-(Thiophen-3-yl)-6-methyl-2-thioxo-*N*-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (4b): Yield: 85 %, m.p.: 163-165 °C (aq. EtOH); IR (KBr, ν_{max}, cm^{-1}): 3264, 3172 (NH), 1678 (C=O of amide), 1438 (C=S) . ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 2.12 (s, 3H, 6-CH_3), 5.60 (s, 1H, H-4), 7.10-8.22 (m, 8H, Ar-H), 8.72 (s, 1H, 3-N*H*), 8.98 (s, 1H, 1-N*H*), 9.44 (s, 1H, N*H* of amide). ^{13}CNMR (75 MHz, $CDCl_3$ + DMSO-d_6): δ 21.1, 51.4, 110.2, 121.7, 126.2, 128.4 129.1, 134.1, 138.2, 144.6, 146.8, 147.2, 152.6, 163.8.

4-(Pyridin-2-yl)-6-methyl-2-thioxo-*N*-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (4c): Yield: 92 %, m.p.: 186 °C (aq. EtOH); IR (KBr, ν_{max}, cm^{-1}): 3278, 3168 (NH), 1682 (C=O of amide), 1440 (C=S) . ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 2.24 (s, 3H, 6-CH_3), 5.54 (s, 1H, H-4), 7.12-8.32 (m, 9H, Ar-H), 8.24 (s, 1H, 3-N*H*), 8.42 (s, 1H, 1-N*H*), 8.78 (s, 1H, N*H* of amide). ^{13}C NMR (75 MHz): δ 18.2, 51.8, 107.8, 119.8, 123.2, 126.2, 126.9, 127.4, 128.2, 128.4, 138.2, 143.1, 150.2, 163.7.

4-(Pyridin-3-yl)-6-methyl-2-thioxo-*N*-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (4d): Yield: 90 %, m.p.: 137 °C (aq. EtOH); IR (KBr, ν_{max}, cm^{-1}): 3280, 3174 (NH), 1677 (C=O of amide), 1436 (C=S). ^{1}HNMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 2.22 (s, 3H, 6-CH_3), 5.48 (s, 1H, H-4), 7.16-8.25 (m, 9H, Ar-H), 8.32 (s, 1H, 3-N*H*), 8.42 (s, 1H, 1-N*H*), 9.26 (s, 1H, N*H* of amide). ^{13}C NMR (75 MHz): δ 18.6, 52.4, 108.8, 121.8, 123.1, 127.5, 128.9, 130.4, 131.8 132.4, 138.2, 143.1, 150.2, 163.7.

4-(Pyrrol-2-yl)-6-methyl-2-thioxo-*N*-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (**4e**): Yield: 86 %, m.p.: 177-179 °C (aq. EtOH); IR (KBr, ν_{max}, cm^{-1}): 3268, 3166 (NH), 1662 (C=O of amide), 1434 (C=S) . ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 2.22 (s, 3H, 6-CH_3), 5.48 (s, 1H, H-4), 6.32-7.14 (s, 3H, Ar-H), 7.56-8.19 (s, 5H, Ar-H), 8.24 (s, 1H, 3-N*H*), 8.30 (s, 1H, 1-N*H*), 9.24 (s, 1H, N*H* of amide), 10.96 (s, 1H, pyrrole-N*H*). ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): δ 20.8, 52.6, 109.4, 111.2, 121.4, 123.1, 127.5, 128.9, 130.4, 131.5, 132.3, 137.8, 142.9, 150.4, 161.6.

4-(Indol-2yl)-6-methyl-2-thioxo-*N*-phenyl-1,2,3,4-tetrahydro-pyrimidine-5-carboxamide (4f): Yield: 91 %; m.p.: 127 °C (aq. EtOH); IR (KBr, ν_{max}, cm^{-1}): 3270, 3184 (NH), 1672 (C=O of amide), 1440 (C=S) . ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 2.26 (s, 3H, 6-CH_3), 5.44 (s, 1H, CH-4), 7.26-7.88 (m, 10H, Ar-H), 7.96 (s, 1H, 3-N*H*), 8.67 (s, 1H, 1-N*H*),

9.43 (s, 1H, N*H* of amide), 10.98 (s, 1H, Indole-N*H*). ^{13}C NMR (75 MHz): δ 20.5, 52.0, 108.4, 111.2, 121.6, 123.7, 126.9, 128.9, 130.4, 131.5 132.3, 137.8, 142.9, 151.4, 164.8.

RESULTS AND DISCUSSION

Antibacterial activity: The antibacterial activity was assessed by the disk diffusion method [11-14]. Compounds **3a-f** and **4a-f** were evaluated for *in vitro* activity against *Staphylococcus aureus* and *Salmonella typhi* at a concentration of 10 µg/mL in meat peptone agar medium. Amikacin was used as a standard for antibacterial screening. For each biological activity test, two to three experiments were performed and the average zone of inhibition was reported in Table-1.

TABLE-1
ANTIBACTERIAL ACTIVITY OF COMPOUNDS **3a-f** AND **4a-f**

Compd. No.	Zone of inhibition (mm) at 10 µg/mL		Compd. No.	Zone of inhibition (mm) at 10 µg/mL	
	S. aureus	*S. typhi*		*S. aureus*	*S. typhi*
3a	11	12	**4a**	10	12
3b	10	11	**4b**	12	11
3c	12	10	**4c**	13	13
3d	11	13	**4d**	11	16
3e	14	18	**4e**	15	20
3f	13	14	**4f**	12	15
Amikacin (Standard)	16	22	Amikacin (Standard)	16	22

All 12 compounds **3a-f** and **4a-f** were evaluated for antibacterial activity. Compounds **3e**, **3f**, **4c** and **4e** exhibited high activity against Gram-positive bacteria, *S. aureus*; of these **4e** registered very high activity against *S. aureus.* Compounds **3e**, **3f**, **4d**, **4e** and **4f** showed high activity against Gram-negative bacteria, *S. typhi*; of these **3e** and **4e** registered very high activity against *S. typhi* and all other compounds showed moderate antibacterial activity.

Conclusion

In summary, a simple, efficient and more eco-friendly grinding technique is developed for the synthesis of 3,4-dihydropyrimidinone using heterocyclic aldehyde. Moreover, the catalyst used is easily available and inexpensive. Adopting the above technique, six dihydropyrimidine-2*H*-ones (**3a-f**) and six dihydropyrimidine-2*H*-thiones (**4a-f**) have been prepared and characterized by IR and ^{1}H NMR. Furthermore, dihydropyrimidinone derivative contains carbamoyl group in 5-position. These observations have prompted us to undertake the synthesis of new dihydropyrimidinones derived from *N*-phenylacetoacetamide as 1,3-dicarbonyl component with a great interest to evaluate them for further pharmacological studies.

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