Nisheeth C. Desai* and Malay J. Bhatt

Catalytic synthesis and antimicrobial activity of *N*-(3-chloro-2-oxo-4-phenylazetidin-1-yl)-4-(1*H*-indol-3-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamides

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Abstract: In continuation of our work towards synthesizing bio-active molecules we developed and optimized the methodology for novel *N*-(3-chloro-2-oxo-4-phenylazetidin-1-yl)-4-(1*H*-indol-3-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide analogues from readily available starting materials. We focused on the pressing demand to find eco-friendly pathways by means of catalytic optimization of the process. All synthesized compounds were screened for *in vitro* antibacterial and antifungal activities on *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Staphylococcus pyogenes*, *Candida albicans*, *Aspergillus niger*, and *Aspergillus clavatus* species.

Keywords: antimicrobial; 2-azetidinone; catalyst; indole; β-lactam; MIC; 1,2,3,4-tetrahydropyrimidine.

Introduction

Recently our group has synthesized indole derivatives as antimicrobial agents [1]. The indole system is an important structural component of many pharmaceutical agents, such as antidepressant [2], anticonvulsant [3], antifungal [4], antiviral [5] and anti-inflammatory [6] drugs. Indole alkaloids also show antibacterial activity [7]. The C-3-substituted indoles are an important core moiety for the synthesis of many biologically active inhibitors of HIV-1 [8], antioxidant [9] and cytotoxic [10] agents. Another biologically important agents are tetrahydropyrimidines. Few efficient synthetic methods for synthesis of polysubstituted tetrahydropyrimidines have been reported [11]. Pyrimidine based analogous are widely known as, anti-inflammatory agents, COX inhibitors, anticancer, antiallergic, analgesic [12, 13], antiviral and antimicrobial agents [14, 15]. The β-lactams are the third biologically important class of compounds. The β-lactam skeleton is the key structural unit responsible for the antibacterial property of the most widely employed antibacterial agents [16]. 2-Azetidinones demonstrate numerous other interesting biological properties, and they are inhibitors of cholesterol absorption [17], human cytomegalovirus (HCMV), protease [18] and thrombin [19]. Several derivatives are antihyperglycemic [20], antitumor [21], anti-HIV [22], anti-inflammatory, analgesic [23], antimalarial [24], antifungal [25] and antiproliferative agents. Several selected bioactive derivatives of the three systems mentioned above are shown in Figure 1.

The first synthesis of 1,2,3,4-tetrahydropyrimidines has been reported by Biginelli [26]. In this paper we report synthesis of tetrahydropyrimidine derivatives **4a–o** that are substituted with indole and β-lactam moieties. Only a single research paper has reported synthesis of a single member of this class of compounds [27].

Results and discussion

Chemistry

The indolylpyrimidine **1** was synthesized by one-pot three-component Biginelli reaction (Scheme 1). The preparation of **1** was optimized by using different solvents including acetonitrile, methanol, ethanol, DMF, THF, PPA and various catalysts including HCl, H_2SO_4, and a large number of inorganic salts. The best yield of **1** of 94% was obtained by reacting indole-3-carboxaldehyde (0.75 mol), ethyl acetoacetate (0.75 mol) and thiourea (0.50 mol) in ethanol in the presence of the catalyst $SnCl_2{\cdot}2H_2O$ (15 mmol).

***Corresponding author: Nisheeth C. Desai,** Department of Chemistry (DST-FIST Sponsored and UGC NON-SAP), Mahatma Gandhi Campus, Maharaja Krishnakumarsinhji Bhavnagar University, Bhavnagar 364002, India, e-mail: dnisheeth@rediffmail.com
Malay J. Bhatt: Department of Chemistry (DST-FIST Sponsored and UGC NON-SAP), Mahatma Gandhi Campus, Maharaja Krishnakumarsinhji Bhavnagar University, Bhavnagar 364002, India

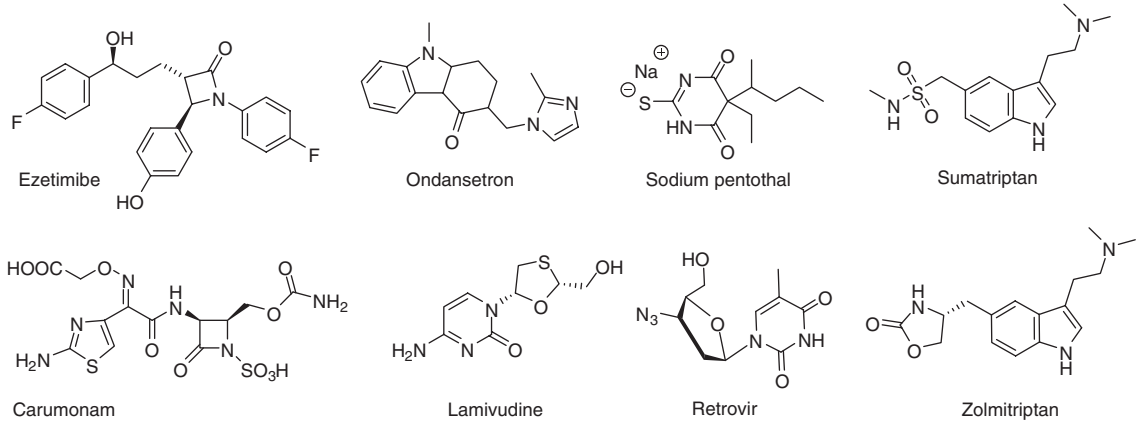
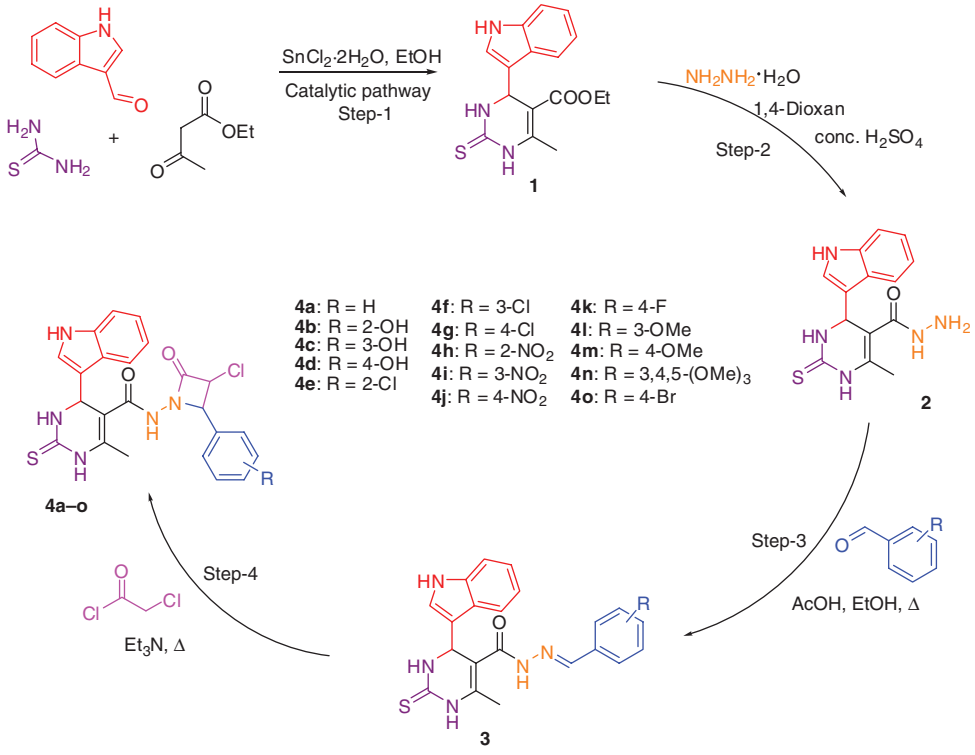


Figure 1 Marketed drugs having structural similarity with compounds **4a–o**.



Scheme 1 Synthesis route for preparation of compounds **4a–o**.

Ethanol was the standard azeotropic mixture containing 95% of EtOH. In the second step, a hydrazide **2** was prepared by treatment of compound **1** with hydrazine hydrate. Then, Schiff bases **3** were prepared by condensation of the hydrazide **2** with aromatic aldehydes. Cyclization of compounds **3** in the presence of triethylamine furnished the desired β-lactams **4a–o**. The final products were thoroughly characterized by elemental analysis and spectral methods. These compounds were screened for antimicrobial activity.

Antimicrobial activity

The activity of compounds was determined as per the National Committee for Clinical Laboratory Standards

Table 1 Biological screening results of the most active compounds.

No.	Minimum inhibitory concentration (MIC) for bacteria (μg/mL)				Minimum inhibitory concentration (MIC) for fungi (μg/mL)		
	E. coli MTCC 443	*P. aeruginosa* MTCC 1688	*S. aureus* MTCC 96	*S. pyogenes* MTCC 442	*C. albicans* MTCC 227	*A. niger* MTCC 282	*A. clavatus* MTCC 1323
4a	–	–	–	–	500	–	–
4b	–	–	–	–	500	–	–
4e	25	–	12.5	50	100	100	–
4f	–	–	–	–	500	–	–
4k	25	50		50	500	–	100
4l	–	–	–	–	100	50	–
4n	–	–	–	–	500	–	25
4o	–	–	50	–	250	–	–
Ciprofloxacin	**25**	**25**	**50**	**50**	–	–	–
Griseofulvin	–	–	–	–	**500**	**100**	**100**

Bold values indicate the standard MIC of standard drugs.

(NCCLS) protocol using Mueller–Hinton Broth (t–Diackinss on, USA) [28–33]. All compounds were evaluated against Gram-positive bacteria (*S. aureus*, *S. pyogenes*), Gram-negative bacteria (*E. coli*, *P. aeruginosa*) and fungi (*C. albicans*, *A. niger and A. clavatus*) strains. Ciprofloxacin (for bacteria) and griseofulvin (for fungi) were used as the reference antibiotics. The results for the most active compounds are given in Table 1. As can be seen, compound **4e** is the most promising antibacterial agent. Compound **4n** exhibits excellent activity against *A. clavatus* with the MIC value that is several-fold higher (12.5–25 μg/mL) than the MIC value of the reference drug griseofulvin.

Conclusion

$SnCl_2 \cdot 2H_2O$ is a highly active heterogeneous solid catalyst for the Biginelli reaction leading to the key substrate **1**. The synthesized compounds **4a–o** were screened for their *in vitro* antibacterial and antifungal activity. The new compounds **4a–o** presented here clearly differ in their antimicrobial activity depending on the type of substituent in hybrid molecules. It can be seen from the activity results that halogen derivatives are as the most potent agents against bacterial strains and fungal strains. Compounds **4e**, **4k** and **4o** exhibit outstanding antibacterial properties. Compounds **4l** and **4n** are antifungal agents.

Experimental

The progress of the reactions was monitored and purity of compounds **4a–o** were checked on TLC [aluminum plates coated with silica gel 60, F_{245} (E. Merck)] eluting with chloroform/methanol (9:1). Elemental analysis was carried out on a Perkin-Elmer 2400 CHN analyzer. IR spectra were recorded on a Perkin-Elmer FT-IR spectrophotometer in KBr pellets. ^{1}H NMR spectra (300 MHz) were recorded on a Varian Gemini 300, and ^{13}C NMR spectra (100 MHz) were recorded on a Varian Mercury-400 spectrometer in DMSO-d_6 with tetramethylsilane as the internal reference. Melting points are not corrected. Mass spectra were scanned on a Shimadzu LC-MS 2010 spectrometer.

Ethyl 4-(1*H*-indol-3-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1)

Compound **1** was synthesized according to the literature procedure [26] with the following modification. Thiourea (0.5 mol), ethyl acetoacetate (0.75 mol) and indole-3-carbaldehyde (0.75 mol) were dissolved in ethanol (95%) (35 mL). Amongst various catalysts tested for the reaction; $SnCl_2 \cdot 2H_2O$ was found to be highest yielding (96%) catalyst. The progress of reaction was monitored by TLC. After completion of reaction, the mixture was cooled and red crystals were separated. The pure product obtained as red solid was filtered and dried. It was further crystallized from methanol: yield 94%; mp 247°C; IR: 3560, 3353, 3054, 2921, 2863, 1725, 1180 cm^{-1}; ^{1}H NMR: δ 11.52 (s, 1H), 10.8 (s, 1H), 7.86 (s, 1H), 6.9–7.6 (m, 5H), 4.05 (q, J = 7 Hz, 2H), 4.26 (s, 1H), 2.32 (s, 3H), 1.20 (t, J = 7 Hz, 3H); ^{13}C NMR: δ 180.1, 168.6, 159.8, 135.6, 128.4, 122.7, 111.3, 104.6, 62.1, 57.2, 18.4, 14.6; LC-MS: *m/z* 315.10 (M^+). Anal. Calcd for $C_{16}H_{17}N_3O_2S$: C, 61.32; H, 4.82; N, 13.41. Found: C, 61.28; H, 4.89; N, 13.32.

4-(1*H*-Indol-3-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide (2)

A mixture of compound **1** (0.01 mol), hydrazine hydrate (0.01 mol) and $SnCl_2 \cdot 2H_2O$ (15 mmol) in 1,4-dioxane (20 mL) was heated under reflux for 8 h, then cooled and poured onto crushed ice. The resultant greenish precipitate was filtered, dried and crystallized from 95% ethanol: yield 80%; mp 208°C; IR: 3545, 3330, 2145, 3063, 2915, 2856, 1192 cm^{-1}; ^{1}H NMR: δ 11.52 (s, 1H), 10.8 (s, 1H), 9.42 (s, 1H), 7.86 (s, 1H), 6.9–7.6 (m, 5H), 4.55 (s, 2H), 4.18 (s, 1H), 2.3 (s, 3H); ^{13}C NMR: δ 179.5,

165.3, 159.4, 137.2, 127.6, 123, 111.4, 59.4, 19.3; LC-MS: *m/z* 301.10 (M^+). Anal. Calcd for $C_{14}H_{15}N_5OS$: C, 55.80; H, 5.02; N, 23.24. Found: C, 55.72; H, 5.11; N, 23.32.

N'-Benzylidene-4-(1*H*-indol-3-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbohydrazides 3a–o

The following procedure for **3a** is representative. Other hydrazides were obtained in a similar way. A mixture of benzaldehyde (0.01 mol), 4-(1*H*-indol-3-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide (**2**, 0.01 mol) and a catalytic amount of glacial acetic acid in ethanol (10 mL) was heated under reflux for 5–6 h. After cooling, the resulting crystals were filtered and crystallized from 95% ethanol to give **3a** in a 78% yield; mp 190°C; IR: 3545, 3330, 2145, 3063, 2915, 2856, 1665, 1177 cm^{-1}; ^1H NMR: δ 11.47 (s, 1H), 10.86 (s, 1H), 9.42 (s, 1H), 8.16 (s, 1H), 6.95–7.88 (m, 10H), 4.10 (s, 1H), 2.25 (s, 3H); ^{13}C NMR: δ 179.3, 167.9, 158.4, 146.4, 133.5, 128.6, 122.3, 119.1, 112.4, 58.5, 18.4; LC-MS: *m/z* 389.13 (M^+). Anal. Calcd for $C_{21}H_{19}N_5OS$: C, 64.76; H, 4.92; N, 17.98. Found: C, 64.76; H, 4.92; N, 17.98.

N-(3-Chloro-2-oxo-4-phenylazetidin-1-yl)-4-(1*H*-indol-3-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamides 4a–o

A mixture of 2-chloroacetyl chloride (0.02 mol), *N'*-benzylidene-4-(1*H*-indol-3-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide **(3a–o**, 0.01 mol) and triethylamine (0.02 mol) was heated under reflux for 4 h, then cooled and poured into ice-cold water. The precipitate was filtered, washed with water, dried and crystallized from DMF/ethanol to give product **4a–o**.

***N*-(3-chloro-2-oxo-4-phenylazetidin-1-yl)-4-(1*H*-indol-3-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (4a)** Yield 80%; mp 172°C; IR: 3530, 3327, 3058, 2928, 2866, 2138, 1784, 1589, 1180, 762 cm^{-1}; ^1H NMR: δ 11.72 (s, 1H) 11.47 (s, 1H), 10.86 (s, 1H), 8.18 (s, 1H), 6.85–7.97 (m, 10H), 5.5 (s, 1H), 5.10 (s, 1H), 4.14 (s, 1H), 2.16 (s, 3H); ^{13}C NMR: δ 180.2, 165.6, 163.2, 159.6, 135.6, 128.5, 124.1, 119.8, 111.1, 106.6, 67.5, 64.9, 59.5, 19.4; LC-MS: *m/z* 465.10 (M^+). Anal. Calcd for $C_{23}H_{20}ClN_5O_2S$: C, 59.29; H, 4.33; N, 15.03. Found: C, 59.17; H, 4.40; N, 15.17.

***N*-(3-Chloro-2-(2-hydroxyphenyl)-4-oxoazetidin-1-yl)-4-(1*H*-indol-3-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (4b)** Yield 65%; mp 170°C; IR: 3545, 3335, 3280, 3053, 2932, 2858, 2147, 1793, 1648, 1161, 744 cm^{-1}; ^1H NMR: δ 11.78 (s, 1H), 11.55 (s, 1H), 10.89 (s, 1H), 9.62 (s, 1H), 8.15 (s, 1H), 6.80–7.91(m, 9H), 5.46 (s, 1H), 5.17 (s, 1H), 4.20 (s, 1H), 2.11 (s, 3H); ^{13}C NMR: δ 180.2, 165.2, 163.4, 158.7, 154.4, 136.6, 127.7, 121.7, 115.8, 112.4, 106.9, 67.4, 64.9, 61.5, 59.3, 19.3; LC-MS: *m/z* 481.10 (M^+). Anal. Calcd for $C_{23}H_{20}ClN_5O_3S$: C, 57.32; H, 4.18; N, 14.53. Found: C, 57.44; H, 4.25; N, 14.47.

***N*-(3-Chloro-2-(3-hydroxyphenyl)-4-oxoazetidin-1-yl)-4-(1*H*-indol-3-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (4c)** Yield 61%; mp 196°C; IR: 3538, 3338, 3295, 3061, 2942, 2849, 2137, 1798, 1648, 1168, 750 cm^{-1}; ^1H NMR: δ 11.75 (s, 1H), 11.51 (s, 1H), 10.83 (s, 1H), 9.57 (s, 1H), 8.19 (s, 1H), 6.85–7.97 (m, 9H), 5.52 (s, 1H), 5.25 (s, 1H), 4.24 (s, 1H), 2.13 (s, 3H); ^{13}C NMR: δ 180.4, 165.7, 163.7, 158.4, 153.7, 135.6, 128.2, 122.1, 116.3, 111.1, 106.5, 67.1, 65.2, 59.8, 19.7; LC-MS: *m/z* 481.10 (M^+). Anal. Calcd for $C_{23}H_{20}ClN_5O_3S$: C, 57.32; H, 4.18; N, 14.53. Found: C, 57.28; H, 4.30; N, 14.62.

***N*-(3-Chloro-2-(4-hydroxyphenyl)-4-oxoazetidin-1-yl)-4-(1*H*-indol-3-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (4d)** Yield 63%; mp 185°C; IR: 3526, 3318, 3278, 3061, 2934, 2844, 2126, 1785, 1646, 1156, 742 cm^{-1}; ^1H NMR: δ 11.78 (s, 1H), 11.55 (s, 1H), 10.78 (s, 1H), 9.53 (s, 1H), 8.15 (s, 1H), 6.79–7.87 (m, 9H), 5.46 (s, 1H), 5.20 (s, 1H), 4.27 (s, 1H), 2.17 (s, 3H); ^{13}C NMR: δ 180.9, 164.8, 163.4, 158.6, 153.7, 135.2, 127.7, 121.9, 116.6, 111.5, 106.4, 67.9, 64.5, 58.9, 19.5; LC-MS: *m/z* 481.10 (M^+). Anal. Calcd for $C_{23}H_{20}ClN_5O_3S$: C, 57.32; H, 4.18; N, 14.53. Found: C, 57.48; H, 4.25; N, 14.55.

***N*-(3-Chloro-2-(2-chlorophenyl)-4-oxoazetidin-1-yl)-4-(1*H*-indol-3-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (4e)** Yield 65%; mp 198°C; IR: 3545, 3324, 3066, 2928, 2852, 2135, 1778, 1630, 1172, 760, 605 cm^{-1}; ^1H NMR: δ 11.80 (s, 1H), 11.50 (s, 1H), 10.69 (s, 1H), 8.16 (s, 1H), 6.92–7.70 (m, 9H), 5.43 (s, 1H), 5.25 (s, 1H), 4.21 (s, 1H), 2.12 (s, 3H); ^{13}C NMR: δ 180.3, 165.4, 163.8, 159.5, 143.6, 132.4, 127.5, 123.4, 119.5, 111.3, 106.7, 67.4, 64.1, 58.7, 18.7; LC-MS: *m/z* 499.06 (M^+). Anal. Calcd for $C_{23}H_{19}Cl_2N_5O_2S$: C, 55.21; H, 3.83; N, 14.00. Found: C, 55.38; H, 3.75; N, 13.92.

***N*-(3-Chloro-2-(3-chlorophenyl)-4-oxoazetidin-1-yl)-4-(1*H*-indol-3-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (4f)** Yield 64%; mp 176°C; IR: 3536, 3338, 3054, 2940, 2863, 2144, 1790, 1655, 1163, 778, 680; ^1H NMR: δ 11.84 (s, 1H), 11.53 (s, 1H), 10.64 (s, 1H), 8.18 (s, 1H), 6.95–7.66 (m, 9H), 5.48 (s, 1H), 5.29 (s, 1H), 4.26 (s, 1H), 2.10 (s, 3H); ^{13}C NMR: δ 180.5, 165.6, 163.4, 159.3, 143.2, 132.8, 128.2, 123, 119.8, 111.5, 106.6, 67.6, 64.7, 58.4, 18.6; LC-MS: *m/z* 499.06 (M^+). Anal. Calcd for $C_{23}H_{19}Cl_2N_5O_2S$: C, 55.21; H, 3.83; N, 14.00. Found: C, 55.35; H, 3.94; N, 13.79.

***N*-(3-Chloro-2-(4-chlorophenyl)-4-oxoazetidin-1-yl)-4-(1*H*-indol-3-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (4g)** Yield 67%; mp 224°C; IR: 3530, 3350, 3043, 2952, 2870, 2148, 1778, 1662, 1175, 765, 675 cm^{-1}; ^1H NMR: δ 11.81 (s, 1H), 11.49 (s, 1H), 10.67 (s, 1H), 8.21 (s, 1H), 6.90–7.68 (m, 9H), 5.51 (s, 1H), 5.31 (s, 1H), 4.28 (s, 1H), 2.13 (s, 3H); ^{13}C NMR: δ 180.6, 165.7, 163.3, 158.9, 143.4, 133, 128.5, 123, 119.6, 111.1, 106.8, 67.8, 64.8, 58.3, 18.7; LC-MS: *m/z* 499.06 (M^+). Anal. Calcd for $C_{23}H_{19}Cl_2N_5O_2S$: C, 55.21; H, 3.83; N, 14.00. Found: C, 55.19; H, 3.80; N, 14.04.

***N*-(3-Chloro-2-(2-nitrophenyl)-4-oxoazetidin-1-yl)-4-(1*H*-indol-3-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (4h)** Yield 58%; mp 210°C; IR: 3522, 3357, 3035, 2965, 2882, 2148, 1780, 1650, 1520, 1370, 1171, 759 cm^{-1}; ^1H NMR: δ 11.81 (s, 1H), 11.53 (s, 1H), 10.72 (s, 1H), 8.27 (s, 1H), 6.90–7.68 (m, 9H), 5.46 (s, 1H), 5.04 (s, 1H), 4.22 (s, 1H), 2.15 (s, 3H); ^{13}C NMR: δ 180.7, 165.5, 163.2, 159.4, 147.6, 137.7, 136.4, 127.6, 122.8, 112.3, 106.8, 66.3, 64.7, 58.6, 19.2; LC-MS: *m/z* 510.95 (M^+). Anal. Calcd for $C_{23}H_{19}ClN_6O_4S$: C, 54.07; H, 3.75; N, 16.45. Found: C, 54.19; H, 3.81; N, 16.37.

***N*-(3-Chloro-2-(3-nitrophenyl)-4-oxoazetidin-1-yl)-4-(1*H*-indol-3-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (4i)** Yield 62%; mp 234°C IR: 3538, 3368, 3024, 2955, 2890, 2155, 1775, 1639, 1532, 1357, 1149, 750 cm^{-1}; ^1H NMR: δ 11.78 (s, 1H), 11.55 (s, 1H), 10.69 (s, 1H), 8.22 (s, 1H), 6.82–7.56 (m, 9H), 5.51 (s, 1H), 5.08 (s, 1H), 4.25 (s, 1H), 2.10 (s, 3H); ^{13}C NMR: δ 180.5, 165.3,

162.8, 159.7, 147.3, 137.2, 135.9, 127.8, 122.6, 112.1, 106.3, 66.5, 64.9, 58.3, 19.3; LC-MS: *m/z* 510.95 (M^+). Anal. Calcd for $C_{23}H_{19}ClN_6O_4S$: C, 54.07; H, 3.75; N, 16.45. Found: C, 54.18; H, 3.83; N, 16.52.

***N*-(3-Chloro-2-(4-nitrophenyl)-4-oxoazetidin-1-yl)-4-(1*H*-indol-3-yl)-6-methyl-2-thioxo1,2,3,4-tetrahydropyrimidine-5-carboxamide (4j)** Yield 63%; mp 245°C; IR: 3545, 3376, 3030, 2968, 2878, 2145, 1785, 1645, 1526, 1368, 1158, 740 cm^{-1}; ^1H NMR: δ 11.74 (s, 1H), 11.57 (s, 1H), 10.73 (s, 1H), 8.28 (s, 1H), 6.87–7.62 (m, 9H), 5.55 (s, 1H), 5.05 (s, 1H), 4.28 (s, 1H), 2.11 (s, 3H); ^{13}C NMR: δ 180.1, 165.2, 163.3, 160.4, 147.6, 137.5, 136.4, 127.5, 122.4, 112.3, 106.7, 66.7, 64.6, 58.5, 18.7; LC-MS: *m/z* 510.95 (M^+). Anal. Calcd for $C_{23}H_{19}ClN_6O_4S$: C, 54.07; H, 3.75; N, 16.45. Found: C, 54.18; H, 3.69; N, 16.33.

***N*-(3-Chloro-2-(4-fluorophenyl)-4-oxoazetidin-1-yl)-4-(1*H*-indol-3-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (4k)** Yield 70%; mp 236°C; IR: 3525, 3335, 3052, 2924, 2875, 2140, 1780, 1668, 1155, 1125, 752 cm^{-1}; ^1H NMR: δ 11.79 (s, 1H), 11.45 (s, 1H), 10.67 (s, 1H), 8.19 (s, 1H), 6.98–7.48 (m, 9H), 5.47 (s, 1H), 5.12 (s, 1H), 4.20 (s, 1H), 2.15 (s, 3H); ^{13}C NMR: δ 180.5, 165.7, 162.7, 158.5, 143.7, 132.8, 128.3, 123, 119.4, 112.3, 106.9, 67.6, 64.8, 58.1, 18.4; LC-MS: *m/z* 483.09 (M^+). Anal. Calcd for $C_{23}H_{19}ClFN_5O_2S$: C, 57.08; H, 3.96; N, 14.47. Found: C, 57.21; H, 4.03; N, 14.59.

***N*-(3-Chloro-2-(3-methoxyphenyl)-4-oxoazetidin-1-yl)-4-(1*H*-indol-3-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (4l)** Yield 69%; mp 178°C; IR: 3540, 3336, 3280, 3062, 2934, 2852, 2156, 1770, 1666, 1168, 1110, 750 cm^{-1}; ^1H NMR: δ 11.87 (s, 1H), 11.47 (s, 1H), 10.61 (s, 1H), 6.95–7.60 (m, 9H), 8.24 (s, 1H), 5.57 (s, 1H), 5.36 (s, 1H), 4.28 (s, 1H), 3.75 (s, 3H), 2.13 (s, 3H); ^{13}C NMR: δ 180.1, 165.4, 162.3, 159.4, 135.4, 128.2, 123.7, 119.5, 111.6, 106.3, 67.4, 64.7, 59.3, 55.4, 19.1; LC-MS: *m/z* 495.11 (M^+). Anal. Calcd for $C_{24}H_{22}ClN_5O_3S$: C, 58.12; H, 4.47; N, 14.12. Found: C, 58.19; H, 4.44; N, 14.26.

***N*-(3-Chloro-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl)-4-(1*H*-indol-3-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (4m)** Yield 67%; mp 172°C; IR: 3325, 3266, 3074, 2940, 2865, 2165, 1762, 1655, 1173, 1122, 746 cm^{-1}; ^1H NMR: δ 11.84 (s, 1H), 11.53 (s, 1H), 10.64 (s, 1H), 8.26 (s, 1H), 6.98–7.65 (m, 9H), 5.53 (s, 1H), 5.31 (s, 1H), 4.24 (s, 1H), 3.72 (s, 3H), 2.15 (s, 3H); ^{13}C NMR: δ 180.1, 165.4, 162.3, 159.4, 135.4, 128.2, 123.7, 119.5, 111.6, 106.3, 67.4, 64.5, 59.3, 55.4, 19.1; LC-MS: *m/z* 495.11 (M^+). Anal. Calcd for $C_{24}H_{22}ClN_5O_3S$: C, 58.12; H, 4.47; N, 14.12. Found: C, 58.20; H, 4.60; N, 14.08.

***N*-(3-Chloro-2-oxo-4-(3,4,5-trimethoxyphenyl)azetidin-1-yl)-4-(1*H*-indol-3-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (4n)** Yield 64%; mp 182°C; IR: 3555, 3358, 3062, 2942, 2866, 2145, 1765, 1666, 1154, 1110, 740 cm^{-1}; ^1H NMR: δ 11.83 (s, 1H), 11.44 (s, 1H), 10.57 (s, 1H), 8.22 (s, 1H), 6.91–7.50 (m, 7H), 5.48 (s, 1H), 5.26 (s, 1H), 4.24 (s, 1H), 3.75 (s, 9H), 2.13 (s, 3H); ^{13}C NMR: δ 180.3, 165.6, 162.5, 159.1, 135.7, 127.8, 123.6, 119.6, 111.8, 106.5, 67.6, 64.6, 59.3, 55.2, 18.9; LCMS: *m/z* 555.13 (M^+). Anal. Calcd for $C_{26}H_{26}ClN_5O_5S$: C, 56.16; H, 4.71; N, 12.60. Found: C, 56.28; H, 4.85; N, 12.51.

***N*-(2-(4-Bromophenyl)-3-chloro-4-oxoazetidin-1-yl)-4-(1*H*-indol-3-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (4o)** Yield 62%; mp 209°C; IR: 3545, 3342, 3038, 2924, 2870, 2162, 1788, 1668, 1147, 1178, 735 cm^{-1}; ^1H NMR: δ 11.77 (s, 1H), 11.47 (s, 1H), 8.22 (s, 1H), 6.92–7.54 (m, 9H), 5.42 (s, 1H), 5.13 (s, 1H), 4.22 (s, 1H), 2.13 (s, 3H); ^{13}C NMR: δ 180.2, 165.5, 162.5, 159.1, 143.6, 132.8, 127.9, 123, 119.2, 111.7, 106.2, 67.5, 64.7, 57.8, 18.6; LC-MS: *m/z* 543.01 (M^+). Anal. Calcd for $C_{23}H_{19}BrClN_5O_2S$: C, 50.70; H, 3.52; N, 12.85. Found: C, 50.66; H, 3.48; N, 12.91.

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