Available online at www.ilcpa.pl

International Letters of Chemistry, Physics and Astronomy

17(2) (2014) 168-173 ISSN 2299-3843

Synthesis of novel 2-mercapto-4-(p-aminophenyl sulphonylamino)-6-(aryl)-pyrimidine-5-carboxamide derivatives via the Biginelli reaction

Nayan H. Bhuva*, Vrajlal K. Gothalia, Pankaj M. Singala, Pratik K. Talpara, Viral J. Faldu, Viresh H. Shah

Department of Chemistry, Saurashtra University, Rajkot - 360005, India

*E-mail address: nayanbhuva50@gmail.com

ABSTRACT

Series of 2-mercapto-4-(p-aminophenylsulphonylamino)-6-(aryl)-pyrimidine-5-carboxamide $\mathbf{A_{a-h}}$ were synthesized via the biginelli condensation. 2-mercapto-4-amino-6-(aryl)-pyrimidine-5-carboxamide react with p-acetamidophenylsulphonylchloride in the presence of pyridine **2** to form 2-mercapto-4-(p-acetamidophenylsulphonylamino)-6-(aryl)-pyrimidine-5-carboxamide **3**. It was treated with diluted HCl under reflux afforded 2-mercapto-4-(p-aminophenylsulphonylamino)-6-(aryl)-pyrimidine-5-carboxamide $\mathbf{A_{a-h}}$. The newly synthesized compounds were characterized by elemental analyses, infrared (IR), ^{1}H NMR and ^{13}C NMR spectroscopic investigation.

***Keywords*:** 2-mercapto-4-(p-aminophenylsulphonylamino)-6-(aryl)-pyrimidine-5-carboxamide, Biginelli condensation

1. INTRODUCTION

Pyrimidines have a long and distinguished history extending from the days of their discovery as important constituents of several biological molecules such as nucleic acids, cofactors, various toxins, to their current use in the chemotherapy of AIDS. All these compounds yield great promise for the treatment of retro virus infections in humans. It was soon established that dihydropyrimidine exhibit a similar pharmacological profile to dihydropyridine calcium channel modulators of the nifedipine type and much activity has been observed in this area throughout the 1980s and 1990s[1-4].

More recently, interest has shifted from dihydropyrimidine calcium channel modulators to other biologically active dihydropyrimidine derivatives, e.g. adrenoceptorselective antagonists, useful for the treatment of benign prostatic hyperplasia[5]. Again, the pharmacological activity in the area of a1 adrenergic antagonists is based on activity found earlier in the dihydropyridine series of compounds. The advent of combinatorial chemistry, which has proven particularly useful for multicomponent reactions such as the Biginelli condensation[6], allows the efficient generation of diverse dihydropyrimidine compound

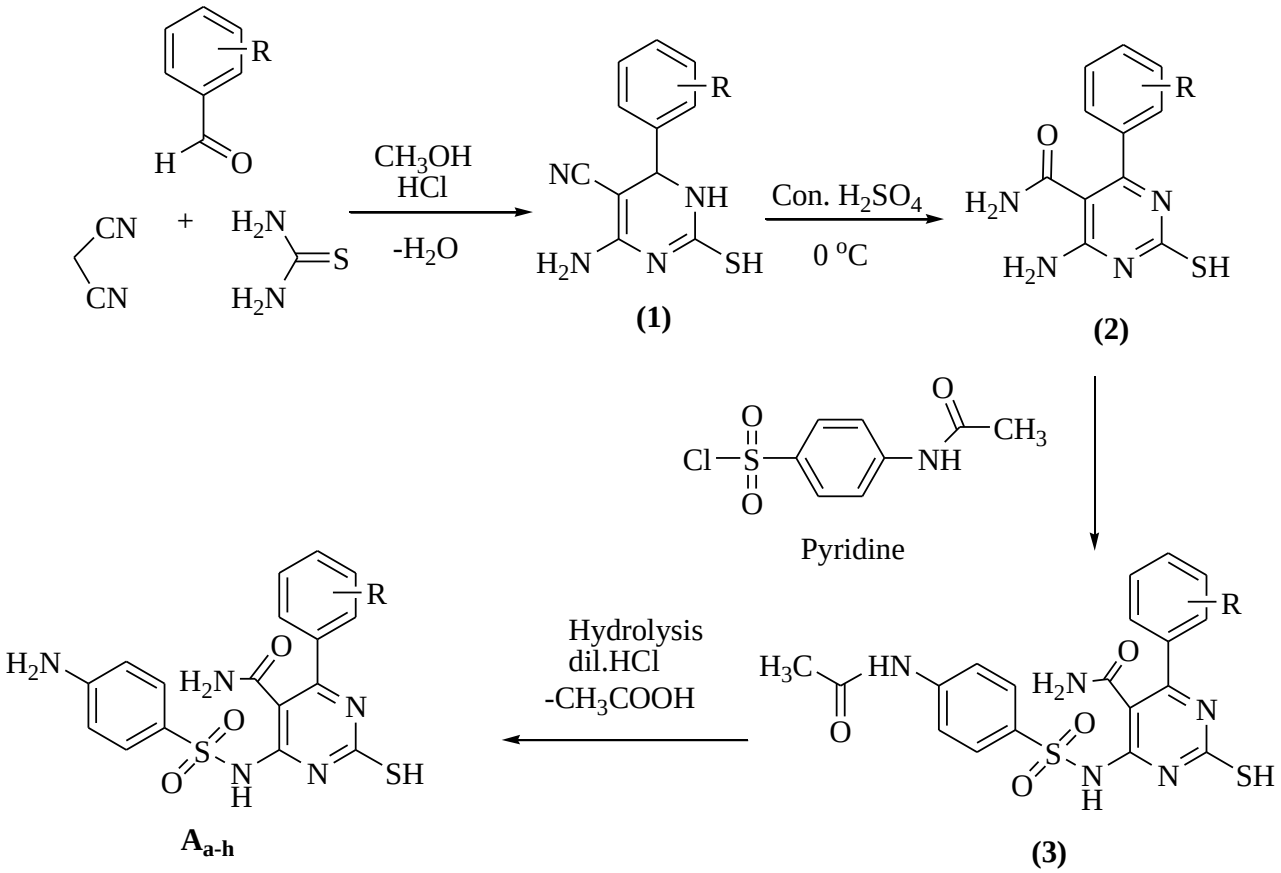
libraries that have been subjected to high throughput screening (HTS) processes. Interesting biological effects have been discovered using HTS techniques. Dihydropyrimidines are not represented in the current clinical antitubercular regimens, suggesting that this class of compounds may target new biochemical mechanisms, potentially allowing treatment of MDR-TB and there are very few investigatory reports on dihydropyrimidines as antitubercular agents[7,8].

Recognizing these facts and in continuation of work on pyrimidine derivatives[9-11], we set upon a programme of making dihydropyrimidine as the template and adding versatile substituents on the various positions of dihydropyrimidine ring.

2. RESULTS AND DISCUSSION

2. 1. Chemistry

The synthetic route for the preparation of pyrimidines derivatives **Aa-h** is summarized in Scheme 1. Various substituted aromatic aldehyde with a range of electron withdrawing and electron donating substituents, *viz*., -H, 2-Cl, 4-Cl, 3-Br, 4-OCH_3, 2-OH, 4-OH and 4-NO_2 reacted with malanonitrile and thiourea by multicomponent reaction is of Biginelli reaction affords dihydropyrimidine (1) which on reaction with Con. H_2SO_4 oxidizes to pyrimidine (2).



R=-H, 2-Cl, 4-Cl, 3-Br, 4-OCH_3, 2-OH, 4-OH and 4-NO_2

All the pyrimidines derivatives **Aa-h** were synthesized by coupling reaction of (2) with p-acetamidophenylsulphonylchloride. The yields of the products were obtained in the range of 45-76 %. Designed series of molecules were characterized by ^{1}H NMR, ^{13}C NMR, and Mass spectrometry.

3. EXPERIMENTAL SECTION / GENERAL PROCEDURES

Melting points of all the compounds are uncorrected and have been recorded by open capillary method. Room temperature, wherever mentioned, normally corresponds to 280 - 330C.

Silica gel-G was used for preparing the TLC plates using different solvent systems. Infra red spectra of all the compounds were scanned on SHIMADZU-FOURIER TRANSFORM INFRA RED (FTIR) - 8400 Spectrophotometer using KBr pellet method. PMR Spectra were recorded on BRUKER Spectrophotometer (300 MHz) using TMS as an internal standard and CDCI3 as solvent. Electron Impact (EI) mass spectra were recorded on GCMSQP2010 Mass Spectrometer. The matrix peaks may appear at m/z 136, 137, 154, 289, 307 in the absence of any metal ions were not considered for mass fragmentations.

Preparation of 2-mercapto-4-amino-5-cyano-6-(aryl)-1,6-dihydropyrimidine (1)
A mixture of Substituted aromatic aldehyde (0.01 M), malononitrile (0.01 M), thiourea (0.01 M) and con. HCl (3 ml) in ethanol (30 ml) was heated under refluxed condition for 4 hrs. Then the reaction mixture was kept at room temperature for 2 hrs. The yellow crystalline product was obtained. The product was isolated and recrystallized from ethanol. Similarly, other compounds (1a-h) were synthesized.

Preparation of 2-mercapto-4-amino-6-(aryl)-pyrimidine-5-carboxamide (2)
A mixture of **(1)** (0.01 M) was dissolved in conc. sulfuric acid (20ml) below 5 °C and kept for 48 hrs. at room temperature. The content was poured into ice cold water and filtered. The product was isolated and crystallized from ethanol. Similarly, other compounds (2a-h) were synthesized.

Preparation of 2-mercapto-4-(p-acetamidophenylsulphonylamino)-6-(aryl)-pyrimidine-5-carboxamide (3)
A mixture of **(2)** (0.01 M) and p-acetamidophenylsulphonylchloride (0.01 M) in pyridine (15 ml) was heated under refluxed condition for 12 hrs. Then the reaction mixture was poured into crushed ice. The product so obtained was recrystallized from ethanol. Similarly, other compounds (3a- h) were synthesized.

Preparation of 2-mercapto-4-(p-aminophenylsulphonylamino)-6-(aryl)-pyrimidine-5-carboxamide (A_{a-h})
A mixture of **(3)** (0.01 M) and con. HCl (4 ml) in ethanol (25 ml) was heated under refluxed condition for 6 hrs. Then the reaction mixture was poured into crushed ice. The product so obtained was recrystallized from ethanol.

2-mercapto-4-(p-aminophenylsulphonylamino)-6-phenyl-pyrimidine-5-carboxamide
(A_a) Yield (47 %), mp 170-172 °C; ^{1}H NMR ($CDCl_3$) δ = 2.79 (s, 1H, -SH), 4.76 (s, 2H, -NH_2), 6.43-6.45 (m, 2H, Ar-H), 7.06 (s, 2H, -NH_2), 7.39-7.42 (m, 3H, Ar-H), 7.42-7.43 (d,

2H, Ar-H, J = 4 Hz), 7.49-7.51 (m, 2H, Ar-H), 7.62 (s, 1H, -NH-); ^{13}C NMR (δ) 178.1, 170.9, 168.8, 167.8, 151.2, 132.8, 129.8, 129.2, 128.7 128.3, 127.1, 116.1, 109.3; Anal. $C_{17}H_{15}N_5O_3S_2$ Calcd: C, 50.86; H, 3.77; N, 17.44; O, 11.96; Found: C, 50.81; H, 3.72; N, 17.39; O, 11.93; MS: m/z 401.

2-mercapto-4-(p-aminophenylsulphonylamino)-6-(2'-chlorophenyl)-pyrimidine-5-carboxamide (A_b)

Yield (49 %), mp 167-169 °C; ^{1}H NMR ($CDCl_3$) δ = 2.77 (s, 1H, -SH), 4.78 (s, 2H, -NH_2), 6.41-6.44 (m, 2H, Ar-H), 7.08 (s, 2H, -NH_2), 7.18-7.21 (d, 2H, Ar-H, J = 12 Hz), 7.34-7.35 (d, 1H, Ar-H, J = 4 Hz), 7.40-7.41 (d, 1H, Ar-H, J = 4 Hz), 7.64 (s, 1H, -NH-) 7.66-7.67 (d, 2H, Ar-H, J = 4 Hz); ^{13}C NMR (δ) 178.2, 168.8, 167.9, 167.2, 151.2, 132.5, 130.3, 130.0, 129.8, 129.4, 128.8, 128.1, 127.3, 116.8, 109.2; Anal. Calcd: $C_{17}H_{14}ClN_5O_3S_2$ C, 46.84; H, 3.24; N, 16.07; O, 11.01; Found: C, 48.86; H, 3.26; N, 16.08, O, 10.97; MS: m/z 435.

2-mercapto-4-(p-aminophenylsulphonylamino)-6-(4'-chlorophenyl)-pyrimidine-5-carboxamide (A_c)

Yield (51 %), mp 145-147 °C; ^{1}H NMR ($CDCl_3$) δ = 2.78 (s, 1H, -SH), 4.78 (s, 2H, -NH_2), 6.45-6.48 (d, 2H, Ar-H, J = 12 Hz), 7.08 (s, 2H, -NH_2), 7.33-7.34 (d, 2H, Ar-H, J = 4 Hz), 7.42-7.43 (d, 2H, Ar-H), 7.60 (s, 1H, -NH-), 7.66-7.67 (d, 2H, Ar-H, J = 4 Hz); ^{13}C NMR (δ) 178.3, 168.7, 168.1, 167.6, 151.4, 134.5, 131.3, 129.8, 129.5, 128.8, 128.2, 116.7, 109.4; Anal. Calcd $C_{17}H_{14}ClN_5O_3S_2$: C, 46.84; H, 3.24; N, 16.07; O, 11.01; Found: C, 48.82; H, 3.28; N, 16.09, O, 10.96; MS: m/z 435.

2-mercapto-4-(p-aminophenylsulphonylamino)-6-(3'-bromophenyl)pyrimidine-5-carboxamide (A_d)

Yield (61 %), mp 139-141 °C; ^{1}H NMR ($CDCl_3$) δ = 2.76 (s, 1H, -SH), 4.77 (s, 2H, -NH_2), 6.41-6.43 (m, 2H, Ar-H), 7.03 (s, 2H, -NH_2), 7.20-7.21 (d, 1H, Ar-H, J = 4 Hz), 7.38-7.41 (d, 2H, Ar-H, J = 12 Hz), 7.64 (s, 1H, -NH-), 7.66-7.69 (m, 3H, Ar-H); ^{13}C NMR (δ) 178.5, 171.5, 168.5, 168.1, 151.5, 133.5, 131.8, 131.2, 129.8, 129.6, 128.3, 126.2, 123.8, 116.5, 109.6; Anal. Calcd $C_{17}H_{14}BrN_5O_3S_2$: C, 42.51; H, 2.94; N, 14.58, O, 9.99; Found: C, 42.56; H, 2.96; N, 14.56, O, 9.96; MS: m/z 480.

2-mercapto-4-(p-aminophenylsulphonylamino)-6-(4'-methoxyphenyl)-pyrimidine-5-carboxamide (A_e)

Yield (48 %), mp 140-142 ºC; ^{1}H NMR ($CDCl_3$) δ = 2.79 (s, 1H, -SH), 3.77 (s, 3H, -OCH_3), 4.79 (s, 2H, -NH_2), 6.43-6.46 (m, 2H, Ar-H), 7.09 (s, 2H, -NH_2), 6.81-6.82 (d, 2H, Ar-H, J = 4 Hz), 7.32-7.33 (d, 2H, Ar-H, J = 4 Hz), 7.64 (s, 1H, -NH-), 7.74-7.75 (m, 2H, Ar-H); ^{13}C NMR (δ) 178.6, 171.7, 168.7, 168.2, 160.8, 151.8, 129.5, 128.4 127.8, 125.2, 116.7, 114.7, 109.8, 55.1; Anal. Calcd: $C_{18}H_{17}N_5O_4S_2$ C, 50.10; H, 3.97; N, 16.23, O, 14.83; Found: C, 50.13; H, 3.98; N, 16.26, O, 14.81; MS: m/z 431.

2-mercapto-4-(p-aminophenylsulphonylamino)-6-(2'-hydroxyphenyl)-pyrimidine-5-carboxamide (A_f)

Yield (53 %), mp 121-123 °C; ^{1}H NMR ($CDCl_3$) δ = 2.76 (s, 1H, -SH), 4.72 (s, 2H, -NH_2), 5.08 (s, 1H, -OH), 6.41-6.43 (d, 2H, Ar-H, J = 8 Hz), 7.04 (s, 2H, -NH_2), 6.82-6.83 (d, 2H, Ar-H, J = 4 Hz), 6.79-6.80 (d, 1H, Ar-H, J = 4 Hz), 6.89-6.90 (d, 1H, Ar-H, J = 4 Hz), 7.04-7.06 (m, 1H, Ar-H), 7.66 (s, 1H, -NH-); ^{13}C NMR (δ) 178.5, 171.4, 168.8, 168.3, 155.5, 151.7, 130.3, 129.8, 128.8, 128.2, 121.8, 120.4, 116.7, 109.8; Anal. Calcd: $C_{17}H_{15}N_5O_4S_2$ C,

48.91; H, 3.62; N, 16.78, O, 15.33; Found: C, 48.86; H, 3.67; N, 16.74, O, 15.29; MS: m/z 417.

2-mercapto-4-(p-aminophenylsulphonylamino)-6-(4'-hydroxyphenyl)-pyrimidine-5-carboxamide (A_g)

Yield (60 %), mp 151-153 °C; ^{1}H NMR ($CDCl_3$) δ = 2.78 (s, 1H, -SH), 4.78 (s, 2H, -NH_2), 5.11 (s, 1H, -OH), 6.41-6.42 (d, 2H, Ar-H, J = 4 Hz), 7.04 (s, 2H, -NH_2), 6.83-6.84 (d, 2H, Ar-H, J = 4 Hz), 6.77-6.78 (d, 1H, Ar-H, J = 4 Hz), 6.89-6.91 (m, 2H, Ar-H), 7.09-7.10 (m, 2H, Ar-H), 7.63 (s, 1H, -NH-); ^{13}C NMR (δ) 178.7, 171.5, 168.7, 168.1, 158.5, 151.7, 129.5, 128.6, 128.0, 125.8, 116.8, 116.1, 109.6; Anal. Calcd for $C_{17}H_{15}N_5O_4S_2$: C, 48.91; H, 3.62; N, 16.78, O, 15.33; Found: C, 48.86; H, 3.67; N, 16.74, O, 15.29; MS: m/z 417.

2-mercapto-4-(p-aminophenylsulphonylamino)-6-(4'-nitrophenyl)-pyrimidine-5-carbocamide (A_h)

Yield (51 %), mp 152-154 °C; ^{1}H NMR ($CDCl_3$) δ = 2.81 (s, 1H, -SH), 4.78 (s, 2H, -NH_2), 6.43-6.44 (d, 2H, Ar-H, J = 4 Hz), 6.87-6.88 (m, 2H, Ar-H), 7.03 (s, 2H, -NH_2), 7.64 (s, 1H, -NH-), 7.84-7.85 (m, 2H, Ar-H), 8.28-8.29 (m, 2H, Ar-H); ^{13}C NMR (δ) 178.6, 171.6, 168.7, 168.0, 151.5, 148.7, 139.5, 129.6, 128.7, 127.9, 121.8, 116.4, 109.8; Anal. Calcd for $C_{17}H_{14}N_6O_5S_2$: C, 45.73; H, 3.16; N, 18.82, O, 17.92; Found: C, 45.78; H, 3.13; N, 18.78, O, 17.94; MS: m/z 446.

4. CONCLUSION

In conclusion, a new class of 2-mercapto-4-(p aminophenylsulphonylamino)-6-(aryl)-pyrimidine-5-carboxamide derivatives were synthesized via the biginelli reaction. The newly synthesized heterocycles interesting lead molecules for further synthetic and biological evaluation. It can be concluded that this class of compounds certainly holds great promise towards the pursuit to discover novel classes of 2-mercapto-4-(p-aminophenylsulphonylamino)-6-(aryl)-pyrimidine-5-carboxamide derivatives. Further studies to acquire more information concerning biological evaluation and structure–activity relationships are in progress.

ACKNOWLEDGEMENTS

We acknowledge DST and UGC, New Delhi, India, for funding and providing instrumental support under FIST and SAP program, respectively.

References

[1] O. Kappe, *Tetrahedron* 49 (1993) 6937-6963.

[2] K. Atwal, C. Rovnyak, J. Schwartz, S. Moreland, A. Hedberg, Z. Gougoutas, F. Malley, M. Floyd, *J. Med. Chem*. 33 (1990) 1510-1515.

[3] S. Atwal, N. Swanson, E. Unger, M. Floyd, S. Moreland, A. Hedberg, C. O'Reilly, *J. Med Chem*. 34 (1991) 806-811.

[4] C. Rovnyak, S. Atwal, A. Hedberg, D. Kimball, S. Moreland, Z. Gougoutas, C. O'Reilly, J. Schwartz, M. F. Malley, *J. Med. Chem*. 35 (1992) 3254-3263.

[5] C. Barrow, G. Nantermet, G. Selnick, L. Glass, E. Rittle, F. Gilbert, G. Steele, F. Homnick, M. Freidinger, W. Ransom, P. Kling, D. Reiss, P. Broten, W. Schorm, L. Chang, S. O'Malley, V. Olah, D. Ellis, A. Barrish, K. Kassahun, P. Leppert, D. Nagarathnam, C. Forray, *J. Med. Chem*. 43 (2000) 2703-2718.

[6] C. O. Kappe, *Acc. Chem. Res.* 33 (2000) 879-888.

[7] J. Modha, N. Datta, H. Parekh, *II Farmaco* 56 (2001) 641.

[8] P. Zalavadiya, S. Tala, J.Akbari, H. Joshi, *Arch. Pharm* 342 (2009) 469.

[9] A. Trivedi, A. Siddiqui, V. Shah, *ARKIVOC* 2 (2008) 210.

[10] A. Trivedi, D. Dodiya, N. Ravat, V. Shah, *ARKIVOC* 11 (2008) 131.

[11] A. Trivedi, D. Dodiya, J. Surani, H. Mathukia, N. Ravat, V. Shah, *Arch. Pharm*. 34 (2008) 435.

(Received 10 June 2014; accepted 24 June 2014)