A four-component modified Biginelli reaction: A novel approach for C-2 functionalized dihydropyrimidines

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Abstract: A novel four component modified Biginelli reaction for the synthesis of C-2 functionalized dihydropyrimidines has been established. The approach uses assembly of less explored acetyl acetone with aromatic aldehyde, thiourea and dimethyl sulphate to construct a novel 5-acetyl 2-methylthio dihydropyrimidine system which works as an efficient well-designed intermediate for generating C-2 modified Biginelli libraries with nitrogen nucleophiles. Phenyl hydrazine, semicarbazide and aryl semicarbazides are successfully used as N-nucleophiles to generate C-2 functionalized dihydropyrimidine derivatives which fulfil the demands of active pharmacophore. Time economy, step economy and a single pot reaction with moderate to excellent yield are the major advantages of this novel method.

Key words: Biginelli reaction; Green synthesis; 4-MCR; 2-Methylthio-1,4-DHPMs; N-nucleophiles
1. Introduction

The synthesis of structurally diverse compounds has gained prime importance to generate molecular libraries in the drug discovery process. The focused issues for the novel developed reaction are the generation of these molecular libraries with excluding the drawbacks of classical reactions such as step-by-step process, tedious workup, use of toxic/expensive reagents/solvents/catalysts, long cyclisation period, and poor yield. Multicomponent reactions (MCR) are the hottest area in organic synthesis to generate scaffolds of drug like candidates [1,2]. Many pharmacophores have been generated from MCRs in medicinal chemistry, including praziquantel, nifedipine, and clopidogrel, to name a few [3,4]. Biginelli reaction, as a 3-CR was conceptualized in 1893 [5] and it gives simplicity of the reaction to generate dihydropyrimidines (DHPMs) with varied pharmacophores. From common organic reagents as well as the structural complexity with all six positions of pyrimidine nucleus, (Figure 1a) amenable to multiple chemical decorations, yielding a large library of compounds. The current surge of interest in this area in the last two decades is largely due to the diligent work of Kappe and his group [6,7]. Dihydropyrimidines (DHPMs) are the N-based heterocycle obtained from Biginelli MCR and have shown remarkable pharmacological activities [8–10]. The discovery of monastrol (Figure 1b) with its pharmacological activities in 1999 was a watershed moment [11,12]. Another fillip to Biginelli reaction (and other MCRs) was provided by the advent of green chemistry as a defining protocol for organic synthesis. The major attribute of MCR include, atom economy, step economy as well as saving energy and time resulting from simple work-up procedures [13–15].

A survey of recent literature revealed that modifications at the N1, C2 and N3 are particularly productive in offering drug-like candidates. Looking towards the libraries
generated by the classical Biginelli reaction and the number of C2 modified DHPM derivatives showed tremendous scope for medicinal chemistry in the last decade [16]. In our earlier work on DHPMs [17,18], we noticed working on DHPM areas deserve more effort. As revealed in the 2004 review of Kappe and several subsequent reviews, there has been abundant activity in DHPM-2-oxo/2-thio/2-amino with C5-ester. Unarguably, the activity spectrum of these 5-ester substituted DHPM – Monastrol led to the flood of publications on them, both DHPM-2-one and 2-thione. We also noticed that a handful of papers have been reported on 5-acetyl DHPMs. It appears to enrich the 5-acetyl DHPM chemistry since they too display useful activities such as, anticancer, calcium channel blocker, antiviral, anti-inflammatory, antitubercular, antioxidant and antibacterial activities [9,10,19–21]. We also noticed that 5-acetyl DHPMs are conspicuously absent in many review articles and are less explored.

The 2-methylthio function has potential for a variety of nucleophilic displacements leading to biologically useful drug candidates. In this regard, current report highlights utility of this substrate by using few selected N-nucleophiles, viz. hydrazine hydrate, phenyl hydrazine, aryl semicarbazides which will function as a lead for designing of new drug targets [16,22,23].

2. Materials and methods

2.1 General: All chemicals and reagents (AR) were procured from commercial sources. Melting points were determined by calibrated digital melting point apparatus (Make- Labline). TLC analysis was carried out on precoated Silica gel 60 F254 aluminum plates procured from Merck, Germany and spots were visualized by UV light and/or by iodine vapors. Fourier-transform infrared (FT-IR) spectra for all the synthesized intermediates and final compounds were recorded on a JASCO 4100 FTIR
spectrophotometer in the range of 4000-5000 cm⁻¹. Proton nuclear magnetic resonance (¹H NMR) spectra and carbon nuclear magnetic resonance (¹³C NMR) spectra were scanned using Bruker Avance Neo 500MHz spectrometer using DMSO-d₆/CDCl₃ as solvent. Chemical shift (δ) values are reported in ppm with TMS as an internal standard. Mass spectra were recorded on a Synapt-XS using the TOF MS ES+ method.

2.2 Synthesis

General procedure for synthesis of 1-(6-Methyl-2-methylsulfanyl-4-phenyl-1,4-dihydro-pyrimidin-5-yl)-ethanone: 5a

The mixture of benzaldehyde (1a, 1.01 mL, 0.01 mol), acetyl acetone (2, 1.03 mL, 0.01 mol) and thiourea (3, 0.91 g, 0.012 mol) was transferred to a reaction flask and the flask was cooled to 0-5°C in an ice bath. Dimethyl sulphate (4, 1.5 mL, 0.012 mol) was added drop wise over 10 minutes. The temperature rose to 60-65°C as a result of the ferocious reaction. Once the vigorous reaction ceased, 10 mL of ethanol was added and the reaction mixture was refluxed for 3-4 hours, along with stirring. The progress of reaction was monitored by TLC. The reaction mixture was cooled to 0°C and triturated with crushed ice and cold water. The solid separated was filtered off and washed with cold ethanol followed by ether. The crude product obtained was crystallized from hot ethanol to obtain compound 5a.

Similarly, compounds 5b-e were obtained by using aryl aldehydes viz. 3-hydroxy-4-methoxybenzaldehyde, 4-nitrobenzaldehyde, 4-chlorobenzaldehyde and 2-hydroxy benzaldehyde respectively with acetyl acetone, thiourea and dimethyl sulphate by following similar reaction protocols.

1-(6-Methyl-2-methylsulfanyl-4-phenyl-1,4-dihydro-pyrimidin-5-yl)-ethanone, (5a)

Yield: 78%, Ochre yellow solid; mp- 128-129°C; Rf- 0.52 (Benzene: Ethyl acetate, 7:3).
**FTIR (KBr, $u_{max}$/cm$^{-1}$):** 3278 (sec. NH), 3194 (Ar. CH), 3027 (Ali. CH), 1699 (C=O), 1616 (C=N), 1455 (Ar. C=O), 1327 (C-N).

**$^1$H-NMR: (500MHz, DMSO):** $\delta$ 2.15 (s, 3H, C$_6$-CH$_3$), $\delta$ 2.24 (s, 3H-SCH$_3$), $\delta$ 2.35 (s, 3H, CO-CH$_3$) $\delta_{5.29-5.30}$ (s, 1H, C$_4$-H), $\delta$ 7.09-7.46 (m, Ar.-CH, 5H), $\delta$10.28 (s, 1H, -NH).

**$^{13}$C-NMR: (500 MHz, DMSO):** $\delta$ 194.67 (C=O), 173 (C=N), 126-139 (Ar. C=C), 110.36 (C=C), 53.68 (C$_4$), 52.77 (S-CH$_3$), 30.31 (CO-CH$_3$), 18.15 (C$_6$-CH$_3$). ESI-MS: m/z calcd. for C$_{14}$H$_{16}$N$_2$OS 260.4 found 264.4 [M+4]$^+$

1-[4-(4-hydroxy-3-methoxyphenyl)-6-methyl-2-(methylsulfanyl)-1,4-dihydropyrimidin-5-yl]ethenone, (5b) Yield: 70%, Brown solid, mp- 171-172$^\circ$; Rf-0.24 (Benzene: Ethyl acetate, 7:3). **FTIR (KBr, $u_{max}$/cm$^{-1}$):** 3436 (-OH) 3290 (sec. NH), 3189, (Ar. CH), 3035 (Ali. -CH) 1711 (C=O), 1631 (C=N), 1512, 1454 (Ar C=C), 1326 (C-N), 1384 (C-O); $^1$H-NMR: (500MHz, DMSO): $\delta$ 2.11 (s, 3H, C$_6$-CH$_3$), $\delta$ 2.28 (s, 3H-SCH$_3$), $\delta$ 2.32 (s, 3H, CO-CH$_3$), $\delta$ 5.20-5.21 (s, 1H, C$_4$-H), $\delta$ 6.57-6.85 (m, Ar.-CH, 3H), $\delta$ 9.03 (s, OH), 9.65 (s, 1H, -NH), $\delta$10.20 (s, 1H, -NH). $^{13}$C-NMR: (500 MHz, DMSO): $\delta$ 194.98 (C=O), 173.59 (C=N), 115-147 (Ar C=C), 110.02, 111.18 (C=C), 55.48 (C$_4$), 53.62 (S-CH$_3$), 30.03 (CO-CH$_3$), 18.00 (C$_6$-CH$_3$)

1-[6-methyl-2-(methylsulfanyl)-4-(4-nitrophenyl)-1,4-dihydropyrimidin-5-yl]ethanone, (5c) Yield: 87%, Yellow grey solid, mp-192-193$^\circ$; Rf-0.50 (Benzene: Ethyl acetate, 7:3). **FTIR (KBr, $u_{max}$/cm$^{-1}$):** 3279 (sec. NH), 3176 (Ar. CH), 3024 (Ali. CH), 1709 (C=O), 1699 (C=N), 1464, 1418 (Ar C=C), 1347 (C-N), 762 (C-Cl)

1-[4-(4-Chloro-phenyl)-6-methyl-2-methylsulfanyl-1,4-dihydropyrimidin-5-yl]ethanone, (5d) Yield: 82%, buff solid; mp-177-178$^\circ$; Rf- 0.45 (Benzene: Ethyl acetate, 7:3). **FTIR (KBr, $u_{max}$/cm$^{-1}$):** 3279 (sec. NH), 3176 (Ar. CH), 3024 (Ali. CH), 1709 (C=O), 1619 (C=N), 1490, 1455 (Ar. C=C), 1327 (C-N), 762 (C-Cl)

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1-[4-(3-hydroxyphenyl)-6-methyl-2-(methylsulfanyl)-1,4-dihydropyrimidin-5-yl]-ethenone, (5e) Yield: 78%, Occur yellow solid, mp- 176-177°C; (Benzene: Ethyl acetate, 7:3) Rf-0.28 IR (KBr, $\nu_{max}$/cm$^{-1}$): 3450 (OH), 3296 (sec. NH), 3183, (Ar. CH), 3068 (Ali. -CH), 1719 (C=O), 1631 (C=N), 1509, 1445 (Ar. C=C), 1325 (C-N), 1380 (C-O)

General procedure for synthesis of 1-(2-hydrazinyl-6-methyl-4-phenyl-1,4-dihydropyrimidin-5-yl) ethanone, (6a)

To 10ml ethanolic solution of 5a (260mg,1mmol), hydrazine hydrate (75mg, 1.5mmol) in 10ml ethanol was added drop wise and mixture was stirred under reflux conditions. The completion of reaction was monitored by TLC (2-4hrs). After the completion of reaction, crude mass obtained was cooled to room temperature and poured on to crushed ice. Obtained product was filtered off, washed with ether, dried and recrystallized using ethanol to give product 6a.

Similarly, compounds 6b-e were obtained by using phenyl hydrazine/semicarbazide/aryl thiosemicarbazides.

1-(2-hydrazinyl-6-methyl-4-phenyl-1,4-dihydropyrimidin-5-yl) ethanone, (6a)

Yield: 81%, Buff solid, mp- 152-153°C; Rf = 0.56 (Benzene: Ethyl acetate, 7:3); FTIR (KBr, $\nu_{max}$/cm$^{-1}$): 3432 (pri. NH$_2$), 3283 (sec. NH), 3192 (Ar. CH), 3025 (Ali. CH), 1701 (C=O), 1607 (C=N), 1454 (Ar C=C), 1330 (C-N), 1184, 1115 (N-N). $^1$H-NMR: (500MHz, DMSO-d$_6$): δ 2.15 (s, 3H, C$_6$-CH$_3$), δ 2.34 (s, 3H, CO-CH$_3$), δ 5.31 (s, 1H, C$_4$-H), δ 7.23-7.36 (m, Ar-CH, 5H), δ 9.78 (s, 1H, -NH), δ 10.29 (s, 1H, -NH), δ 12.11 (s, 2H, -NH). $^{13}$C-NMR: (500MHz, DMSO-d$_6$): δ 194.66 (C=O), 173.98 (C=N), 126-144 (Ar C=C), 110.36 (C=C), 53.68 (C$_4$), 30.31 (CO-CH$_3$), 18.15 (C$_6$-CH$_3$). ESI-MS: m/z calcd. for C$_{13}$H$_{16}$N$_4$O; 244.29 found 246 [M+2]$^+$
1-[6-methyl-4-phenyl-2-(2-phenylhydrazinyl)-1,4-dihydropyrimidin-5-yl]ethanone

(6b) Yield: 51%, Buff solid; mp- 117-118°C; Rf = 0.6 (Benzene: Ethyl acetate, 7:3);

FTIR (KBr, $\mu_{\text{max}}$/cm$^{-1}$): 3356 (sec. NH), 3196, 3100 (Ar. CH), 3026 (Ali. CH), 1712 (C=O), 1634 (C=N), 1600, 1585, 1495, 1455 (Ar C=C), 1339 (C-N), 1190, 1143, 1110 (N-N).

$^1$H-NMR: (500 MHz, DMSO-d$_6$): δ 1.97 (s, 3H, C$_6$-CH$_3$), δ 2.07 (s, 3H, CO-CH$_3$), δ5.30 (s, 1H, C$_4$-H), δ 6.65-7.51 (m, Ar-CH, 10H), δ 8.93 (s, 1H, -NH), δ9.18 (s, 1H, -NH), δ 9.77 (s, 1H, -NH).

$^{13}$C-NMR: (500 MHz, DMSO-d$_6$): δ 194.23 (C=O), 173.11 (C=N), 124-142 (Ar C=C), 112.40, 111.15 (C=C), 55.87 (C$_4$), 16.97 (CO-CH$_3$), 16.27 (C$_6$-CH$_3$).

ESI-MS: m/z calcd. for C$_{19}$H$_{20}$N$_4$O; 320 found 324 [M+4]$^+$

2-(5-acetyl-6-methyl-4-phenyl-1,4-dihydropyrimidin-2-yl)hydrazinecarboxamide

(6c) Yield: 88%, Light brown solid; mp- 190-192°C; Rf- 0.33 (Benzene: Ethyl acetate, 7:3);

FTIR (KBr, $\mu_{\text{max}}$/cm$^{-1}$): 3400 (pri. NH$_2$), 3217 (sec. NH), 3083 (Ar. CH), 1715 (keto C=O), 1681 (Amide C=O), 1632 (C=N), 1602, 1575, 1492 (Ar C=C), 1383 (C-N), 1182, 1113 (N-N) $^1$H-NMR: (500 MHz, DMSO-d$_6$): δ 2.11 (s, 3H, C$_6$-CH$_3$), δ 2.31 (s, 3H, CO-CH$_3$), δ 5.28-5.29 (s, 1H, C$_4$-H), δ 6.78-7.72 (m, Ar-CH, 9H), δ 9.21 (s,1H,-NH), δ10.02 (s,1H,-NH), δ 9.81(s,1H, -NH), δ7.97(s,1H, -NH).

$^{13}$C-NMR: (500 MHz, DMSO-d$_6$): δ 194.20 (C=O), δ 167.46 (C=N), δ 126.48-144.21 (Ar C=C), δ 109.71 (C=C), δ 55.87 (C$_4$), δ 31.48 (CO-CH$_3$), δ 18.97 (C$_6$-CH$_3$) ESI-MS: m/z calcd. for C$_{14}$H$_{17}$N$_5$O$_2$ 287.31 found 287 [M$^+$]

1-[6-Methyl-4-(4-nitro-phenyl)-2-(N'-phenyl-hydrazino)-1,4-dihydro-pyrimidin-5-yl]-ethanone (6d) Yield: 92%, Red brown solid; mp- 121-122°C; Rf= 0.56 (Benzene: Ethyl acetate; 7:3);

FTIR (KBr, $\mu_{\text{max}}$/cm$^{-1}$): 3397 (sec. NH), 3108 (Ar. CH), 3077 (Ali. CH), 1708 (C=O), 1632 (C=N), 1599, 1559, 1455 (Ar C=C), 1345 (C-N), 1186, 1108 (N-N), 1520 (C-NO$_2$).

$^1$H-NMR: (500 MHz, DMSO-d$_6$): δ 1.98 (s, 3H, C$_6$-CH$_3$), δ 2.07
(s, 3H, CO-CH₃), δ 5.45 (s, 1H, C₄-H), δ 6.67-7.96 (m, Ar-CH, 9H), δ 9.03 (s, 1H, -NH), δ 9.39 (s, 1H, -NH), δ 9.81 (s, 1H, -NH), δ 9.91 (s, 1H, -NH). ¹³C-NMR: (500 MHz, DMSO-d₆): δ 194.23 (C=O), 173.34 (C=N), 123.11-146.75 (Ar C=C), 112.50, 110.51(C=C), 55.34 (C₄), 17.14 (CO-CH₃), 11.83 (C₆-CH₃). ESI-MS: m/z calcd. for C₁₉H₁₉N₅O₃; 365.5 found 363.15 [M-2]⁺

2-[5-acetyl-4-(4-chlorophenyl)-6-methyl-1,4-dihydropyrimidin-2-yl]-N-(4-chlorophenyl)-hydrazine-carboxamide (6e) Yield: 89%, Yellow buff solid; mp- 156-157°C; Rf= 0.5 (Benzene: Ethyl acetate: 7:3); FTIR (KBr, υmax/cm⁻¹): 3425, 3313 (pri. NH₂), 3215 (sec. NH), 3000 (Ar. CH), 1689 (keto C=O), 1653 (Amide C=O), 1611 (C=N), 1587, 1550, 1491. 1455 (Ar C=C), 1357 (C-N), 1182, 1117 (N=N).¹H-NMR: (500 MHz, DMSO-d₆): δ 2.13 (s, 3H, C₆-CH₃), δ 2.19 (s, 3H, CO-CH₃) δ 5.31 (s, 1H, C₄-H), δ 5.93 (s, 1H -NH) δ 7.24-7.46 (m, Ar-CH, 9H), δ 8.69 (s, 1H, -NH), δ 9.80 (s, 1H, -NH), δ 10.36 (s, 1H, -NH). ¹³C-NMR: (500 MHz, DMSO-d₆): δ 194.57 (C=O), δ 174.15 (C=N), 155.78 (CO-NH) δ 124.44-144.82 (Ar C=C), δ 110.26 (C=C), δ 52.99 (C₄), δ 30.41 (CO-CH₃), δ 18.23 (C₆-CH₃). ESI-MS: m/z calcd. for C₂₀H₁₉Cl₂N₅O₂; 432.30 found 437.21 [M+4]⁺

3. Results and Discussion

In hitherto reported literature, these 5-acetyl 2-methylthio DHPM derivatives have been obtained by initial synthesis of the corresponding thione by classical Biginelli reaction, followed by its conversion to the S-methyl derivatives by using methyl iodide or dimethyl sulphate [3,16,22,24] (Scheme a). The Atwal approach uses 3-CR to generate S-methyl function at C2 position using S-methyl iso-thiourea with poor yield. Also, this S-methyl iso-thiourea needs to be synthesized from thiourea and dimethyl sulphate, which increases one step for synthesis [25]. (Scheme b). Another route involves use of
the classical Biginelli reaction followed by addition of POCl₃ to generate 2-chloro group in DHPMs [26] which subsequently reacted with N/O/C- nucleophiles to generate scaffolds of DHPM compounds. While various routes were studied, we envisioned that greening the process may be attempted in more than one aspect and thus, scripted to run the reaction using a novel 4-component approach.

We first carried out the reaction with aryl aldehyde, acetyl acetone and thiourea to get the 5-acetyl DHPM-2-thione and treated it with Me₂SO₄ rather than methyl iodide (as a greener choice), followed by the classical approach, i.e. Scheme a. It worked well. Further, the modification has been done by the Atwal approach using aryl aldehyde, acetyl acetone, and S-methyl iso-thiourea i.e., scheme b as a 3-component reaction to obtain 5-acetyl-2-methylthio DHPMs, but this showed poor yield as compared to Scheme a.

To continue work on DHPMs, a simpler and more elegant a novel 4-MCR method was developed for synthesizing 5-acetyl-2-methyl thio DHPMs in a single pot, single step synthesis using aryl aldehyde, acetyl acetone, thiourea, and Me₂SO₄ in good to excellent yield. It too worked well with comparable yields. We then reasoned that designing a 4-component reaction could offer a much better protocol. The reaction of aryl aldehydes 1a-e, acetylacetone (1,3-dicarbonyl compound) 2, thiourea 3 and dimethyl sulphate 6 was attempted in a one pot reaction to get 5a-e in a single step. (Table 1, Novel 4-MCR approach). After adding dimethyl sulphate, vigorous reaction was noted and the temperature of reaction increased up to 60-65 °C. Once the vigorous reaction had ceased, ethanol was added to the reaction mixture, which was then stirred with reflux to complete the reaction.
To our delight, the paradigms gave an acceptable yield for 4-CR. The structure was fully confirmed with analysis/spectral data. Repeating the protocol with other aldehydes confirmed the reliability of the reactions. The general applicability of this 4-component reaction created our new series of 5-acetyl-2-methylthio DHPMs and further processed to replace S-methylthio group with N-nucleophiles viz. hydrazine hydrate, phenyl hydrazine, semicarbazide and aryl semicarbazide offers C-2 functionalized novel DHPM-nucleophile molecular hybrids. Among the synthesized series of 5-acetyl-2-methylthio DHPMs, selected compounds 5a, 5c, and 5d produced a series of newly designed target compounds 6a-e after treatment with various nucleophiles (Table 2). We have successfully synthesized hybrids of C2 functionalized DHPMs with N-nucleophiles using the S-methylthio system as an intermediate compound. These compounds were also fully characterized. By using this approach, assorted C2 functionalized DHPM libraries can be generated using N/O nucleophiles as well. These experiments illustrate a greener approach to obtain C2 substituted-DHPM derivatives of versatile bioactivity. Work on these lines is in progress in our labs.

To propose an idea about the mechanism, several observations have been made which provide a clue to the probable pathway. The reaction involves post modification of the Biginelli DHPMs using acetyl acetone, thiourea, aromatic aldehyde and dimethyl sulphate as a one-pot 4CR. There are two plausible reaction mechanisms, the first one is, the initial formation of Biginelli thione, which subsequently reacts with dimethyl sulphate to offer 2-methylthio DHPMs. The second possibility includes initial reaction of S-methylation of thiourea to give S-methyl iso-thiourea which itself participates in the Biginelli reaction. By considering various observations, the reaction pathway can be proposed as follows-
When the Acetyl acetone, S-methyl iso-thiourea and aryl aldehyde are mixed, no exothermic reactions are observed. When aromatic aldehyde, ethyl acetoacetate and thiourea were mixed with ethanol, reaction did not proceed. When all four reactants, are mixed together, the exothermic reaction was noted, due to formation of S-methyl iso-thiourea, S-MITU. (Confirmed with TLC). Due to rise in temperature, reaction gets initiated. Exothermic reaction (60-65°C) was due to formation of S-MITU from thiourea and dimethyl sulphate. The reaction is quite exothermic and needs to be controlled [27]. Thus, an assumption can be obtained from the above observations, that the reaction follows the second route for the synthesis of 2-methylthio DHPMs i.e. the S-MITU formation is the first step followed by the Biginelli with the established protocol [28]. The next step is the step of the nucleophilic substitution reaction. After addition of N-nucleophiles, to 5-acetyl 2-methylthio DHPM derivatives, a peculiar odour of methyl mercaptan, CH$_3$SH (odour of rotten cabbage) was reported [29]. This confirms the elimination of CH$_3$SH. This signifies the probable mechanism i.e. replacement of S-methyl function with nucleophile, Figure 2.

Improvements in % yield, time economy, step economy and mild reaction conditions, are the key features of the novel MCR. The reported classical approaches to generate C2 functionalised DHPMs involve 3-4 step synthesis to reach final products along with use of toxic reagents like POCl$_3$ and methyl iodide. This novel 4-CR method is advantageous over the earlier reported methods in relation to number of steps, time and avoiding use of non-greener agents such as POCl$_3$. The method also uses dimethyl sulphate as a methylating agent, instead of the expensive, unstable compound methyl iodide which most researchers used earlier [3,16,22,24,30]. Thus, newly designed MCR also avoids the use of these toxic/expensive reagents, which are some added benefits of
this novel approach. The 2-methylthio system in DHPMs has proven its scope as a versatile intermediate for generation of drug like molecules by reaction with N/O-nucleophiles [9,16]. In this regard, we have reported use of 2-methylthio DHPMs reaction with N-nucleophiles which will be screened as an active pharmacological motif. A preliminary investigation is under way at NCI, USA for anticancer screening. In comparison, we used a greener and more economical reaction protocol for synthesis of C-2 functionalised DHPM libraries. All the compounds were screened for FT-IR analysis and the presence of functional groups was confirmed. Prototype structures of compounds from 2-methylthio DHPMs series, viz. compounds 5a, 5b and C-2 functionalised DHPMs 6a-e were confirmed through $^1$H NMR, $^{13}$C NMR and mass spectroscopy. The analysis of spectroscopic data confirms the structures of newly synthesized molecules. [Refer Supplementary information Figure: 1S-21S]

The synthesized substrate (C-2 functionalized DHPM i.e. 2-methylthio dihydropyrimidine) has diverse scope for generation of libraries. The synthesis of novel 5-acetyl 2-methylthio DHPM derivatives were reported for the first time via a novel four component modified Biginelli reaction. Modified novel reaction was also compared with earlier reported classical Biginelli and Atwal modified reaction. In comparison to earlier reported reaction protocols, novel method allows one pot, single step for generation of intermediate i.e. 5-acetyl 2-methylthio dihydropyrimidine. Thus, novel method demonstrates more benefits over earlier reported reaction protocols.

4. Discussion

In continuation of our interest in DHPM derivatives, herein we report an efficient and novel method for the synthesis of 5-acetyl 2-methylthio DHPMs. The method allows more efficient, time-saving, one pot and single step reaction with moderate to excellent
yield. The importance of 2-methylthio function in DHPMs was emphasized because it serves as a good leaving group and can react with N/O-nucleophiles. This led to the synthesis of C2-functionalsed DHPMs with use of selected N-nucleophiles, and the conjugates formed may fulfil the demand of active pharmacophores. Use of one pot 4-MCR increases efficiency of synthesis and incorporation of N-nucleophiles introduces diverse complexity in the DHPM nucleus which will be the potential future targets (drug discovery pipeline) for development of APIs.

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Conflicts of Interest: The authors declare no conflicts of interests.

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1943.


**Figure 1.** a- General structure of Biginelli adduct; b: Monastrol structure
Figure 2. Proposed reaction mechanism
Scheme 1a: Synthesis of 5-acetyl-2-methylthio DHPMs via Classical Biginelli reaction

Scheme 1b: Synthesis of 5-acetyl-2-methylthio DHPMs via Atwal approach

Scheme 1. Synthesis of 5-acetyl-2-methylthio DHPMs via earlier approaches
Table 1. Synthesis of 5-acetyl-2-methylthio DHPMs via novel 4-MCR approach

![Chemical structure diagram](image)

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<td>78</td>
<td>176-177</td>
</tr>
</tbody>
</table>

a Solvent system: Benzene: Ethyl acetate (7:3); Visualizing agent: I₂ vapors: yellow spots, / short UV 254 nm: purple spots
**Table 2.** Synthesis of C2 functionalised DHPMs with N-nucleophiles

<table>
<thead>
<tr>
<th>Entry</th>
<th>Code</th>
<th>R&lt;sub&gt;1&lt;/sub&gt;</th>
<th>Nu-</th>
<th>Time(h)</th>
<th>Rf&lt;sup&gt;a&lt;/sup&gt;</th>
<th>% Yield</th>
<th>mp (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>6a</td>
<td>-H</td>
<td>-NHNH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>2.5</td>
<td>0.56</td>
<td>81</td>
<td>152-153</td>
</tr>
<tr>
<td>7</td>
<td>6b</td>
<td>-H</td>
<td>-NHNHPH</td>
<td>4</td>
<td>0.6</td>
<td>51</td>
<td>117-118</td>
</tr>
<tr>
<td>8</td>
<td>6c</td>
<td>-H</td>
<td>-NHNH C(O)NH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>4</td>
<td>0.33</td>
<td>88</td>
<td>191-192</td>
</tr>
<tr>
<td>9</td>
<td>6d</td>
<td>4-NO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>-NHNHPH</td>
<td>4.5</td>
<td>0.56</td>
<td>92</td>
<td>121-122</td>
</tr>
<tr>
<td>10</td>
<td>6e</td>
<td>4-Cl</td>
<td>NHNHC(O)NH (4-Cl)Ph</td>
<td>4</td>
<td>0.50</td>
<td>89</td>
<td>156-157</td>
</tr>
</tbody>
</table>

<sup>a</sup> Solvent system: Benzene: Ethyl acetate (7:3); Visualizing agent: I<sub>2</sub> vapors: Yellow spots, Short UV 254 nm: purple spots, Nu`= -NHNH<sub>2</sub>; -NHNHPH; -NHNHC(O)NH<sub>2</sub> - NHNHC(O)NH-(4-Cl) Ph.
Supplementary Information:

Prototype intermediate compounds and all final compounds are characterized by FT-IR, $^1$H-NMR, $^{13}$C NMR and mass spectrometry. Presence of absorption band in the range at 1696-1720 cm$^{-1}$ reveals the presence of keto carbonyl in the structure. Ureide N-H band was located at 3290-3278 cm$^{-1}$ and C=N is confirmed by presence of absorption band at 1607-1636 cm$^{-1}$ in all 5a-e and 6a-e. Presence of N-N bond in 6a-e is confirmed by presence of strong absorption band at 1105-1120 cm$^{-1}$ whereas absorption band at 3400-3500 cm$^{-1}$ confirms the presence of primary amine in compound 6a and 6e. Absorption band at 1653-1681 cm$^{-1}$ shows presence of amide carbonyl in compounds 6c and 6e. In $^1$H NMR spectra, two singlet $\delta$ 1.97-2.15ppm, $\delta$ 2.20-2.35ppm designates the methyl proton at C-6 and acetyl proton at C-5 position respectively. Similarly, a singlet at $\delta$ 5.5.20-5.31 ppm is attributed to the C-4 proton of DHPM ring. Appearance of singlet due to S-Methyl at $\delta$ 2.25 ppm in all series 5 compounds, disappearance of S-methyl and appearance of extra -NH singlet in compounds 6a-e represents displacement of S-methyl by N-nucleophiles. Presence of three -NH peaks at $\delta$ 9.78, 10.29, 12.11 ppm in 6a represents two -NH proton and -NH$_2$ proton peaks respectively. Also, singlet at $\delta$ 8.93, 9.18 and 9.77 ppm represent three -NH peaks in 6b and 6d. For compounds substituted with thiosemicarbazide as a nucleophile 6c showed three -NH peaks at $\delta$ 7.97, 9.21, 9.81 ppm and -NH$_2$ peak at $\delta$10.02 ppm. In all compounds, a multiplet at $\delta$ 6.57-7.72 ppm reveals identity of aromatic protons. In $^{13}$C NMR, $\delta$ 18.5, 30.31, 55-58, 110, 125-150, 173 and 194 ppm show presence of C6-CH$_3$, keto-CH$_3$, C$_4$-carbon, C=C, Ar. C=C, C=N and C=O respectively. Presence of S-methyl is confirmed by presence of $\delta$ 52-53 ppm in compound 5a and 5b. Absence S-methyl group in series of compounds 6a-e confirms the displacement of S-methyl with N-nucleophiles. Molecular ion peaks, base peaks and further fragments of Mass analysis shows structural resemblance with molecular weight of compounds.
Figure 1S. 1-(6-Methyl-2-methylsulfanyl-4-phenyl-1,4-dihydro-pyrimidin-5-yl)-ethanone, (5a)

$^1$H-NMR: (novel MCR approach)
Figure 2S. $^{13}$C-NMR: 1-(6-Methyl-2-methylsulfanyl-4-phenyl-1,4-dihydro-pyrimidin-5-yl)-ethanone (5a)

13CPD DMSO [D:\Spectra] nmr 9

BRUKER
AVANCE NEO
500 MHz NMR SPECTROMETER
SAIF, PANJAB UNIVERSITY,
CHANDIGARH

Current Data Parameters
NAME: Jun29-2020
EXPNO: 91
PROCNO: 1

F2 - Acquisition Parameters
Data: 20200629
Time: 14.09 h
DISTRO: Avance Neo 500
PHCNO: 213470_0333 (C)
PULPROG: zgpg30
TD: 65536
SOLVENT: DMSO
NS: 1024
DS: 4
SNH: 37337.035 Hz
FIDRES: 1.130281 Hz
AQ: 0.8847360 sec
RG: 101
DN: 13.500 usec
DE: 5.00 usec
TE: 297.0 K
D1: 2.00000000 sec
D11: 0.00000000 sec
TD0: 1
SFO1: 125.7804233 MHz
NUC1: 13C
P0: 3.33 usec
P1: 10.00 usec
P1M1: 75.50099701 MHz
SFO2: 500.1720007 MHz
NUC2: 1H
CFQPMR[2] wALT65
PCPD2: 80.00 usec
P1M2: 0.3441001 MHz
P1M3: 0.1700000 MHz

F2 - Processing parameters
S1: 32768
SF: 125.7804233 MHz
NSW: EM
SSB: 0
LB: 1.00 Hz
PC: 1.40
Figure 3S.

ESI-MS: 1-(6-Methyl-2-methylsulfanyl-4-phenyl-1,4-dihydro-pyrimidin-5-yl)-ethanone (5a)
Figure 4S. ESI-MS: 1-(6-Methyl-2-methylsulfanyl-4-phenyl-1,4-dihydro-pyrimidin-5-yl)-ethanone (5a)
**Figure 5S.** $^1$H-NMR: 1-[4-(4-hydroxy-3-methoxyphenyl)-6-methyl-2-(methylsulfanyl)-1,4-dihydropyrimidin-5-yl]ethenone, (5b)

1H-8scan DMSO {D:\Spectra} nmr 10
Figure 6S. $^{13}$C-NMR : (5b)

15D
C$^{13}$CPD DMSO (D:\Spectra) nmr 10

220 200 180 160 140 120 100 80 60 40 20 ppm

30
Figure 7S.

\textbf{\textsuperscript{1}H-NMR:} 1-(2-hydrazinyl-6-methyl-4-phenyl-1,4-dihydropyrimidin-5-yl) ethenone, (6a)

1H \_8\text{scan DMSO [D:\Spectra] nmr 11}

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<th>13.01</th>
<th>12.88</th>
<th>12.12</th>
<th>8.66</th>
<th>8.33</th>
<th>8.23</th>
<th>7.91</th>
<th>7.80</th>
<th>7.70</th>
<th>7.57</th>
<th>7.44</th>
<th>7.32</th>
<th>7.21</th>
<th>7.09</th>
<th>6.98</th>
<th>6.89</th>
<th>6.78</th>
<th>6.68</th>
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<tbody>
<tr>
<td>6a</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
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Current Data Parameters

- **NAME**: Jun29-2020
- **EXPNO**: 110
- **PROCNO**: 1

**F2 - Acquisition Parameters**
- **Date_**: 20200629
- **Time**: 14.14 h
- **INSTRUM**: Avance Neo 500
- **PROBHD**: Z119470_0333
- **PULPROG**: zg30
- **TD**: 65536
- **SOLVENT**: DMSO
- **NS**: 16
- **DS**: 0
- **SNR**: 14926.883 Hz
- **AQ**: 2.222228 sec
- **BG**: 33.0939
- **DW**: 34.000 usec
- **DE**: 6.78 usec
- **DS**: 1.00000000 sec
- **TD**: 1
- **SFO1**: 500.170004 MHz
- **NUC1**: 1H
- **P0**: 3.33 usec
- **P1**: 10.00 usec
- **PFW1**: 22.0230072 W

**F2 - Processing parameters**
- **ST**: 65536
- **SF**: 500.170004 MHz
- **NCW**: 16
- **SSB**: 0
- **LB**: 0.30 Hz
- **PC**: 1.00
Figure 8S. $^{13}$C-NMR: 1-(2-hydrazinyl-6-methyl-4-phenyl-1,4-dihydropyrimidin-5-yl) ethenone, (6a)
Figure 9S. ESI-MS: 1-(2-hydrazinyl-6-methyl-4-phenyl-1,4-dihydropyrimidin-5-yl) ethenone, (6a)
**Figure 10S.**

**1H-NMR:** 1-[6-methyl-4-phenyl-2-(2-phenylhydrazinyl)-1,4-dihydropyrimidin-5-yl]ethenone (6b)

|------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|

**Current Data Parameters**
- **NAME:** Jun29-2020
- **EXPNO:** 120
- **PROCNO:** 1

**F2 - Acquisition Parameters**
- **Date:** 20200629
- **Time:** 15.46 h
- **INSTRUM:** Avance Neo 500
- **PROBHD:** Z119470_0333
- **TD:** 65536
- **SOLVENT:** DMSO
- **NS:** 16
- **DS:** 0
- **SWH:** 14705.883 Hz
- **FIDRES:** 0.448788 Hz
- **RG:** 95.7854
- **D1:** 1.00000000 sec
- **D2:** 297.6 K
- **D0:** 1.00000000 sec
- **TP:** 500.1700035 MHz
- **H1C1:** 180
- **F0:** 3.33 usec
- **F1:** 10.00 usec
- **PLW1:** 22.02300072 W

**F2 - Processing parameters**
- **DS:** 6536
- **DF:** 500.1700035 MHz
- **DW:** 0.30 Hz
- **PC:** 1.00
Figure 11S. $^{13}$C-NMR: 1-[6-methyl-4-phenyl-2-(2-phenylhydrazinyl)-1,4-dihydropyrimidin-5-yl]ethenone (6b)

17B
C$^{13}$CPD DMSO (D:\Spectra) nmr 12

Current Data Parameters
NAME: Jun29-2020
EXPNO: 121
PROCNO: 1

F2 - Acquisition Parameters
Date_ 20200629
Time 15.35 h

F2 - Processing parameters
SI 32768
SF 125.7679203 MHz

BRUKER
AVANCE NEO
500 MHz NMR SPECTROMETER
SAIF, PANJAB UNIVERSITY,
CHANDIGARH

SAIF, PANJAB UNIVERSITY,
CHANDIGARH

AVANCE NEO
500 MHz NMR SPECTROMETER
SAIF, PANJAB UNIVERSITY,
CHANDIGARH

AVANCE NEO
500 MHz NMR SPECTROMETER
SAIF, PANJAB UNIVERSITY,
CHANDIGARH

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CHANDIGARH

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AVANCE NEO
500 MHz NMR SPECTROMETER
SAIF, PANJAB UNIVERSITY,
CHANDIGARH

AVANCE NEO
500 MHz NMR SPECTROMETER
SAIF, PANJAB UNIVERSITY,
Figure 12S. ESI-MS: 1-[6-methyl-4-phenyl-2-(2-phenylhydrazinyl)-1,4-dihydropyrimidin-5-yl]ethenone (6b)
Figure 13S. 2-(5-acetyl-6-methyl-4-phenyl-1,4-dihydropyrimidin-2-yl)hydrazinecarboxamide (6c)

$^1$H-NMR:

HIN-6
1H_8scan DMSO \( \text{[D:\Spectra]} \) nmr 52

Current Data Parameters
NAME Jan26-2021
EXPNO 520
PROCNO 1

F2 - Acquisition Parameters
Data... 20210127
Time 9.43 h
INSTRUM Avance Neo 500
PROBHD Z114470_0333
PULPREG zg30
TD 65536
SOLVENT DMSO
NS 8
DS 0
SNR 14705.883 Hz
FIDRES 0.448788 Hz
AQ 2.2282240 sec
RG 23.9816
DM 36.000 usec
DE 6.79 usec
DI 0.1068500 sec
D1 1.00000000 sec
T00 1
SP01 500.1730885 MHz
HCC1 1 Hz
P0 3.33 usec
P1 10.00 usec
PLM1 20.93000031 W

F2 - Processing Parameters
SI 65536
SF 500.1699934 MHz
MOD 0
SSB 0
LB 0.30 Hz
GB 0
FC 1.00
Figure 14S.

$^{13}$C-NMR: $2$-(5-acetyl-6-methyl-4-phenyl-1,4-dihydropyrimidin-2-yl)hydrazinecarboxamide (6c)

HIN-6
C13CPD DMSO (D:\Spectra) nmr 52

BRUKER
AVANCE NEO
500 MHz NMR SPECTROMETER
SAIF, PANJAB UNIVERSITY,
CHANDIGARH

Current Data Parameters
NAME       Jan26-2021
EXPNO      521
PROCNO     1

F2 - Acquisition Parameters
Date_      20210127
Time       14.65 h
INSTRUM     Avance Neo 500
PROBHD      Z119470_0333 (
PULPROG     zgpg30
TD          65536
SOLVENT     DMSO
NS          512

F2 - Processing parameters
SI          32768
SF          125.7678973 MHz
SSB        0
LB          1.00 Hz
PC          1.40

HIN-6
C13CPD DMSO {D:\Spectra} nmr 52

BRUKER
AVANCE NEO
500 MHz NMR SPECTROMETER
SAIF, PANJAB UNIVERSITY,
CHANDIGARH

Current Data Parameters
NAME       Jan26-2021
EXPNO      521
PROCNO     1

F2 - Acquisition Parameters
Date_      20210127
Time       14.65 h
INSTRUM     Avance Neo 500
PROBHD      Z119470_0333 (
PULPROG     zgpg30
TD          65536
SOLVENT     DMSO
NS          512

F2 - Processing parameters
SI          32768
SF          125.7678973 MHz
SSB        0
LB          1.00 Hz
PC          1.40
Figure 15S.

ESI-MS: 2-(5-acetyl-6-methyl-4-phenyl-1,4-dihydropyrimidin-2-yl)hydrazinecarboxamide (6c)
Figure 16S:

$^1$H-NMR: 1-[6-Methyl-4-(4-nitro-phenyl)-2-(N'-phenyl-hydrazino)-1,4-dihydro-pyrimidin-5-yl]-ethanone

(6d)

HIN-5

1H_8scan DMSO {D:\Spectra} nmr 51

BRUKER
AVANCE NEO
500 MHz NMR
SPECTROMETER
SAIF, P.U.

Current Data Parameters
NAME Jan26-2021
EXPNO 510
PROCNO 1

F2 - Acquisition Parameters
Date_ 20210127
Time 9.41 h
INSTRUM Avance Neo 500
PROBHD 2119470_0333
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 8
DS
SMH 14705.883 Hz
TDRES 0.448788 Hz
AQ 2.2282240 sec
RG 32.4379
DE 6.79 usec
TE 295.4 K
TOO 1.00000000 sec
SFO1 500.1730885 MHz
NUC1 1H
P0 3.33 usec
P1 10.00 usec
PLM1 20.93000031 W

F2 - Processing parameters
SI 65536
SF 500.1699952 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
Figure 17S. $^{13}$C-NMR: (6d)

**HIN-5**
Cl3CPD DMSO (D:\Spectra) nmr 51

### BRUKER
AVANCE NEO
500 MHz NMR SPECTROMETER
SAIF, PANJAB UNIVERSITY,
CHANDIGARH

**Current Data Parameters**
NAME: Jan26-2021
EXPNO: 511
PROCNO: 1

**F2 - Acquisition Parameters**
Date: 20210127
Time: 10.16 h

**INSTRUM**: Avance Neo 500
**PROBHD**: Z119470_0333
**PULPROG**: zgpg30
**TD**: 65536
**SOLVENT**: DMSO
**NS**: 512
**DS**: 4
**SN**: 37027.635 Hz
**TDRES**: 1.196281 Hz
**RG**: 101
**DN**: 13.500 ussec
**DE**: 0.50 ussec
**TE**: 380.2 K
**D1**: 0.0.0000000 sec
**D1L**: 0.0.0000000 sec
**TD0**: 25.780423 MHz
**MIC1**: 13C
**P0**: 3.33 ussec
**P1**: 10.00 ussec
**SFO1**: 125.7679148 MHz
**NUC1**: 13C
**CPDPD1**: 83.1449984 W
**CPDPD2**: 83.1449984 W
**CPDPD3**: 83.1449984 W

**F2 - Processing parameters**
**SI**: 32768
**SF**: 15.767016 MHz
**MEN**: 1.0 Hz
**GR**: 0
**IL**: 1.0 Hz
**PC**: 1.40
Figure 18S. ESI-MS: (6d)
Figure 19S.

\(^1\)H-NMR: 2-[5-acetyl-4-(4-chlorophenyl)-6-methyl-1,4-dihydropyrimidin-2-yl]-N-(4-chlorophenyl)-hydrazine-carboxamide  (6e)

HIN-7

BRUKER
AVANCE NEO
500 MHz NMR
SPECTROMETER
SAIF, P.U.

Current Data Parameters
NAME Jan26-2021
EXPNO 530
PROCNO 1

F2 - Acquisition Parameters
Date_ 20210127
Time 9.45 h
INSTRUM Avance Neo 500
PULPROG zg30
TD 65536
SOLVENT DMSO

F2 - Processing parameters
SI 65536
SF 500.1730885 MHz
WDW EM
SSB 0
LB 0.30 Hz
PC 1.00

HIN-7
1H_8scan DMSO \{D:\Spectra\} nmr 53
Figure 20S. $^{13}$C-NMR: (6e)

HIN-7
C13CPD DMSO (D:\Spectra) nmr 53

BRUKER
AVANCE NEO
500 MHz NMR SPECTROMETER
SAIF, PANJAB UNIVERSITY, CHANDIGARH
Current Data Parameters
NAME Jan26-2021
EXPNO 531
PROCNO 1

F2 - Acquisition Parameters
Date_ 20210127
Time 11.10 h
INSTRUM Avance Neo 500
PROBHD 1119470_0333
PULPROG zgpg30
TD 65536
SOLVENT DMSO
DS 512
DS 4
SN 37037.035 Hz
FDRES 1.158201 Hz
SR 0.8847360 sec
RG 101
DN 13.500 usec
DE 6.50 usec
TE 390.2 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 125.7804231 MHz
NUC1 13C
P0 3.33 usec
P1 10.00 usec
SF02 83.1409884 MHz
SF03 500.1722007 MHz
NUC2 1H
CPDPRG[2] waltz65
PCPD2 80.00 usec
PD1 20.93000031 W
PD12 0.5200000 W
PD13 0.6649000 W

F2 - Processing parameters
SI 32768
SF 125.7804231 MHz
NEW 1.0 Hz
LB 0
GB 0
CP 1.40
Figure 21S. ESI-MS: (6e)