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Design, Synthesis and Pharmacological Evaluation of Some Novel Dihydropyrimidin-2 One Derivatives

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This work describes the synthesis of sixteen new 3,4-dihydropyrimidinones using derivatives of imidazolidin-4-one. FT-IR, Lc-Ms/Ms, and proton and carbon NMR were among the spectral instruments used to determine and analytically characterise the physical properties of the synthesised 3,4-DHPM and DHPMT derivatives. According to the current study, compounds with a -OH group are not the only ones that can demonstrate a high degree of efficacy; compounds with -OCH3, -CH3, and -Cl groups can also demonstrate action efficiently. Furthermore, the conjugated system—that is, the 3,4-dihydropyrimidinone ring coupled to an amide linkage—or the presence of multiple labile hydrogen atoms joined to a nitrogen atom may be the cause of the compounds' capacity to scavenge radicals. The latter would have further supported the compound's stabilisation. The antifungal, analgesic, and antibacterial properties of a few

chosen title compounds are examined.

1. Introduction

Anything that destroys or stops the growth of microorganisms like bacteria, fungus, or protozoa is known as an anti-microbial agent. Antimicrobial medications either eradicate microorganisms or stop them from growing. Pasteur and Joubert's findings that one species of bacteria might inhibit the growth of another marked the beginning of the history of antimicrobials. At the time, they were unaware that the other bacteria were creating an antibiotic, which was the reason why one of them had failed to develop. [1, 2] Naturally, in today's popular usage, the term "antibiotic" refers to practically any medication that aims to eradicate a bacterial illness from your body. Antibiotics are only one type of antimicrobial; synthetic chemicals are also included. Microorganisms have, however, evolved to be resistant to earlier antimicrobial agents as a result of the discovery of antimicrobials. [3, 4] The previous antimicrobial technology relied on either heavy metals or poisons, which might not have killed the microorganisms entirely. Instead, the microbes might have changed, survived, and developed resistance to the heavy metals or poisons [5].

In both biological and pharmacological processes, heterocyclic molecules are crucial. Since heterocycles are a fundamental structural component of many therapeutic compounds, significant efforts have been undertaken to create better synthetic techniques for this structure. [6, 7] In biological applications, pyrimidine-based heterocycles are the most intriguing of all the heterocycles. Pyrimidines linked to thiopheno moiety has been reported in the literature for many years. [8, 9] Many of them have been utilised as pharmaceuticals on the market, and it has been discovered that they have a wide range of biological activities. Figure 1 highlights some of the structures of the active medicinal ingredients. [10]

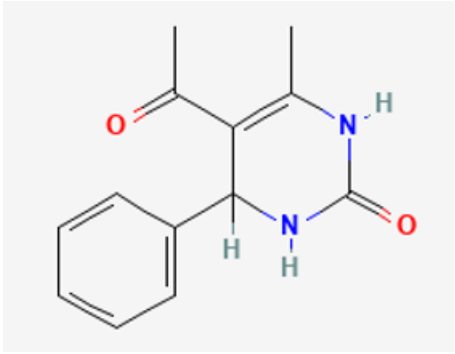


Figure 1: Structure of 3, 4 Dihydropyrimidin-2 One (3,4-DHPM)

2. MATERIALS AND METHODS

Chemistry: All of the chemicals and solvents used were purchased from Sigma-Aldrich in India and were of AR grade. Thin layer chromatography (TLC) was used to track the reaction's development. Using ethyl acetate and hexane as the solvent system, TLC was carried out on Merck silica gel on TLC aluminium foil, and it was visualised in a UV chamber. Q stands for

quartet; m for multiple; d for doublet; t for triplet; and IR for singlet. A Jeol JMS-D 300 mass spectrometer running at 70 eV was used to perform liquid chromatography–mass spectrometry (LC-MS). A Thermo Finnigan FLASH FA 1112 CHN analyser was used to do elemental analysis.

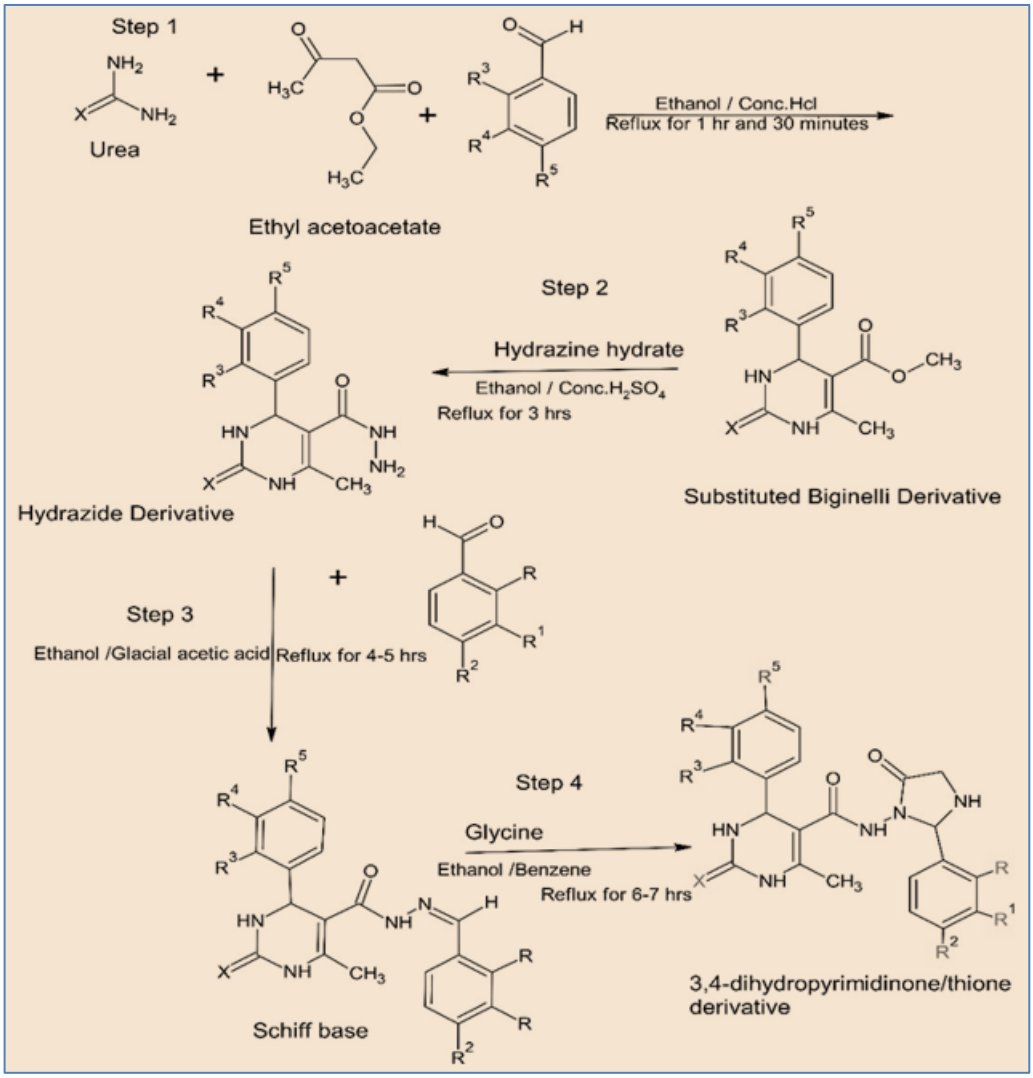
Synthesis of (3,4-DHPM or DHPMT) or Biginelli derivatives from aromatic aldehydes: The one-pot approach was used to synthesise 3,4-DHPM and DHPMT derivatives (1–16) [11, 12]. Following the synthesis of the Biginelli compound from an aromatic aldehyde (step 1), the step 1 product was converted into its hydrazide derivatives using hydrazine hydrate (step 2), and the resultant compound from step 2 was treated with an aromatic aldehyde to transform it into its Schiff base (step 3) [13]. This reaction is a four-step process. Lastly, the Schiff base was treated with the amino acid glycine to produce 3,4-dihydropyrimidinone (its thione analogue) or Biginelli derivatives (step 4). [14].

Step 1: A 500 ml round-bottom flask was filled with 0.1 mol of aromatic aldehydes and 0.1 mol of ethyl acetoacetate (β-keto ester), which were then dissolved in 25 ml of ethyl alcohol that contained 3–4 drops of strong hydrochloric acid and 0.15 mol of urea or thiourea [15]. An electric water bath was used to reflux this for one hour and thirty minutes. The liquid combination was allowed to cool to room temperature before being periodically agitated and then transferred into a 500 ml beaker along with 100–150 ml of ice-cold water. In order to extract the Biginelli chemical, the mixture was filtered and dried after being left at room temperature for the entire night. Alcohol was used for recrystallisation, and TLC verified the final product. [16, 17]

Step 2: After being moved to a 500 ml round-bottom flask, the synthesised Biginelli compound (0.1 mol) was mixed with 0.1 mol of hydrazine hydrate and dissolved with 20 ml of ethyl alcohol and three to four drops of strong sulphuric acid. The product was then obtained by evaporation after refluxing it for roughly three hours on an electric water bath. Ultimately, alcohol was used to recrystallise it, and TLC verified the results. [18]

Step 3: Twenty millilitres of ethyl alcohol and five millilitres of glacial acetic acid were added to a round-bottom flask along with the synthesised carbohydrazide derivative (0.01 mol) and aromatic aldehyde (0.01 mol). After cooling and refluxing for four to five hours on an electric water bath, the liquid was moved, stirring, into a 500 ml beaker filled with 100 to 150 ml of ice-cold water. The product was later obtained by filtering and drying it. Alcohol was used for recrystallisation, and TLC verified the final product. [19, 20]

Step 4: Glycine (0.01 mol) and the synthesised Schiff base (0.01 mol) from the previous step were dissolved in a 500 ml RBF containing benzene and ethyl alcohol. On an electric water bath, it refluxed for roughly six to seven hours. The reaction mixture was cooled and then, while being continuously stirred, moved to a 500 ml beaker filled with 100–150 ml of ice-cold water. After filtering and drying, the product was obtained. Alcohol was utilised for the recrystallisation process, and the result was verified using TLC plates. [21, 22, 23]



Scheme 1: Synthesis of 3, 4 Dihydropyrimidin-2 One derivatives [24]

Pharmacological Activity

Antibacterial activity: Gram-positive bacteria Bacillus subtilis (ATCC 65433) and Staphylococcus aureus (ATCC 26323), as well as Gram-negative bacteria Escherichia coli (ATCC 32288) and Pseudomonas aeruginosa (ATCC 15142), were tested for the antibacterial activity of the synthesised compounds using a cup plate method using Hi-Media agar medium. When compared to the reference compounds, the evaluated compounds showed mild to moderate antibacterial activity against all microbes. [25, 26, 27]

Antifungal activity: Using a filter paper disc technique, the antifungal activity of the test compounds was evaluated at 50 and 100 µg/ml against two distinct fungal strains, Aspergillus niger and Candida albicans. The zone of inhibition was measured in millimetres during a 48-hour incubation period. The conventional medication was glieofulvin, while the control was

dimethylformamide. [28, 29]

Analgesic activity: Three minutes after the acetic acid solution injection, the number of abdominal constrictions was counted for 20 minutes in order to evaluate the analgesic response. Groups 1 through 10 were given the test compounds at a dose of 100 mg/kg body weight, while the eleventh group was given the usual medication at the same dose. [28] After an hour, the acetic acid solution was injected intraperitoneally, and beginning three minutes after the injection, many abdominal constrictions were recorded for twenty minutes. Table 5 presents the findings of calculating the analgesic activity as the percentage of maximum achievable impact. The institution's ethical committee granted permission to undertake in vivo analgesic activity on animals. [30, 31, 32]

3. RESULTS AND DISCUSSION

The Biginelli compound, as shown in Scheme 1, was formed by allowing a range of substituted aromatic aldehydes, β-keto esters, and carbamide (urea)/thio-carbamide (thiourea) to undergo chemical reactions and various nucleophilic addition reactions. This produced the corresponding 3,4-dihydropyrimidinone/thione derivatives. As shown in Table 1, the compounds 1–16 were synthesised in four steps and then recrystallised. To verify the product generated, analytical TLC plates were employed. Table 2 lists the physical characteristics of the produced derivatives, including their molecular weight, colour, and appearance as well as their melting point, yield, and Rf value.

Table 1: The list of the synthesized compounds

Derivatives	X	R	R^1	R^2	R^3	R^4	R^5
4a	O	H	H	OH	H	H	H
4b	O	OH	H	H	NO_2	H	H
4c	O	OH	H	H	H	H	CH_3
4d	O	H	Cl	H	OH	H	H
4e	O	H	H	Cl	OH	H	H
4f	S	H	Cl	H	H	OCH_3	OH
4g	O	OH	H	H	H	H	OH
4h	S	H	Cl	H	Cl	H	H
4i	O	H	H	Cl	H	H	H
4j	S	H	H	OCH_3	H	H	CH_3
4k	O	Cl	H	H	H	Cl	H
4l	O	H	Cl	H	H	Cl	H
4m	S	H	H	OH	H	Cl	H
4n	O	NO_2	H	H	H	H	OCH3
4o	O	NO_2	H	H	H	H	Cl
4p	O	H	H	OCH_3	H	H	CH_3

Table 2: Physical parameters of the synthesized compounds

Compound	Molecular Weight	Colour and appearance	% Yield	Melting Point	Rf Value
4a	407.42	Reddish brown	64	187	0.67
4b	425.86	Light orange	60	186	0.68
4c	470.87	Dark brown	66	181	0.55
4d	441.87	Dark yellow	61	176	0.78
4e	421.5	Light reddish brown	58	187	0.23
4f	487.96	Dark Orange	63	221	0.47
4g	460.31	Yellowish orange	67	181	0.65

4h	476.38	Whitish yellow	68	151	0.59
4i	451.54	Dark brownish red	67	167	0.72
4j	441.87	Dark red	49	231	0.70
4k	423.42	Brownish red	69	205	0.64
4l	460.31	Reddish Black	55	183	0.49
4m	457.93	Reddish orange	67	185	0.61
4n	466.44	Yellowish orange	54	177	0.52
4o	452.42	Yellowish Brown	63	189	0.53
4p	405.45	Dark orange	55	175	0.79

Because of NH, CN, and C=O, compound 4d's infrared spectra showed stretching bands at 3,350, 2,220, and 1,670 cm−1, respectively. The parent molecule 3's 1H NMR spectra in DMSO showed a singlet at δ 3.2 and a multiplet at δ 8.2–7.2 towards N-methyl protons and three aromatic protons, respectively. NH and NH2 have two distinct signals at δ 3.4 and 2.4, respectively. The compound's molecular ion peak, which corresponds to its molecular weight, was seen in its mass spectrum at m/z 441.

The NH, CN, and C=O groups in compound 4i caused peaks in its infrared spectra to appear at 3,074, 2,216, and 1,679 cm−1, respectively. The same compound's 1H NMR spectrum was recorded in DMSO; three aromatic protons were represented by the multiplet at 7.3–8.3, two NH protons by 2.4 and 4.0, a COCH3 proton by 2.6, and three N-methyl protons by a singlet at 3.5. The emergence of a molecular ion signal at m/z 451 (M+1) in 4a's mass spectrum provided additional confirmation of its structure.

Compound 4l's infrared spectra showed peaks at 3,113, 2,224, 1,671, and 1,551 cm−1 that were attributed to the NH, CN, C=O, and CH=N groups, respectively. When the identical compound's 1H NMR spectra was recorded in DMSO, it showed a peak at δ 3.4 that corresponded to one amine proton, a multiplet between δ 7.1 and 8.5 that corresponded to eight aromatic protons, and a singlet at 2.1 that corresponded to three N-CH3 protons. The emergence of a molecular ion signal at m/z 460 (M+1) in 5a's mass spectrum provided additional confirmation of its structure.

The experimental section now includes the whole experimental protocol and analytical data for the chemicals listed above. IR, 1H NMR, LC-MS, and elemental analysis data have all been used to clarify the structures of all the synthesised compounds. The findings of tests conducted on a few of the chosen compounds for their analgesic, antifungal, and antibacterial properties have been discussed.

Pharmacological Activity: When compared to the usual medications, the investigated substances showed substantial to moderate antibacterial effectiveness against all pathogens (Table 3). All of the bacterial strains were significantly inhibited by compounds 4l. The antifungal activity of compound 4l was equivalent to that of a reference drug (Table 4). Comparing compounds 4l to a reference drug, significant analgesic efficacy was observed (Table 5).

Table 3. Antibacterial activity of test compounds 4a-4p against Gram-positive and Gram-negative organisms in comparison with controls.

Der	Zone of Inhibition (mm)							
	S. aureus		B. subtilis		E. coli		P. aeruginosa	
	100 µg/ml	50 µg/ml	50 µg/ml	100 µg/ml	50 µg/ml	100 µg/ml	50 µg/ml	100 µg/ml
4a	14	16	13	15	10	13	11	14

4b	10	12	15	20	13	19	17	23
4c	11	16	14	17	10	14	10	13
4d	14	20	18	23	10	14	14	20
4e	15	21	16	21	15	18	20	25
4f	10	14	14	20	12	17	19	23
4g	11	13	12	15	15	18	17	19
4h	14	16	13	15	10	13	11	14
4i	12	10	15	18	13	19	13	19
4j	14	16	13	15	10	13	11	14
4k	10	14	15	19	13	19	18	20
4l	14	16	13	15	10	13	11	14
4m	13	21	18	23	10	14	15	22
4n	15	21	16	21	15	18	20	25
4o	11	14	14	20	12	18	19	23
4p	12	13	12	17	15	18	18	22
DMF	-	-	-	-	-	-	-	-
Penicillin	-	15	20	16	22	-	-	-
Streptomycin	-					21	26	20

Table 4. Antifungal activity of test compounds 4a-4p in comparison with controls.

Derivatives	Zone of Inhibition (mm)			
	C. albicans		A. niger	
	50 µg/ml	100 µg/ml	50 µg/ml	100 µg/ml
4a	15	19	13	17
4b	21	25	20	25
4c	15	19	23	21
4d	15	16	18	21
4e	18	21	14	17
4f	19	21	15	19
4g	11	19	12	18
4h	12	16	18	22
4i	13	15	12	19
4j	15	19	13	17
4k	21	25	20	25
4l	16	21	18	21
4m	12	15	18	17
4n	18	21	14	17
4o	11	15	15	17
4p	11	18	11	16
DMF	-	-	-	-
Griseofulvin	21	24	24	23

Table 5. Analgesic activity of test compounds 4a-4p in comparison with controls

Derivatives	Mean no. of Writhings ± SEM	Percentage protection
4a	20.83 ± 2.43	54.89
4b	18.42 ± 1.84	59.80
4c	20.84 ± 2.16	54.11
4d	17.57 ± 1.69	61.16
4e	16.84 ± 1.54	63.27
4f	18.09 ± 1.64	60.05
4g	23.51 ± 2.94	48.84
4h	19.65 ± 1.65	55.52
4i	11.99 ± 1.27	73.83
4j	20.83 ± 2.43	54.54
4k	18.42 ± 1.84	59.80
4l	15.91 ± 2.84	65.21
4m	17.85 ± 1.97	60.42
4n	16.99 ± 1.34	62.78
4o	18.55 ± 2.45	55.27

4p	18.99 ± 1.65	59.64
Tween 80	45.83 ± 3.66	-
Aspirin	11.99 ± 1.27	73.83

4. CONCLUSION

Using substituted aromatic aldehydes with β-keto esters and carbamides (urea/thiourea), a scaffold-based library comprising 16 (3, 4 Dihydropyrimidin-2 One) derivatives was created. Hydrazine hydrate and glycine were then added in subsequent steps involving different nucleophilic addition reactions. According to the results of this study, molecules having electron-donating groups like -OCH3, -CH3, and -Cl. Against every bacterial strain, title compounds 4l shown strong antibacterial action. Test compound 4l demonstrated antifungal activity that was equivalent to that of the standard compound. When compared to a standard drug, title compounds 4l demonstrated significant analgesic efficacy.

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