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# Synthesis of S-alkyl/S-benzyl-1,4-dihydropyrimidines and evaluation of their biological activity

**Priyanka Pathak**

*Department of Chemistry, D. A. V. College, Chandigarh, India*

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**ABSTRACT**

*Dihydropyrimidines are associated with wide range of biological activities. Keeping this in view 6-phenyl-4-substituted phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-carboxylic acid ethyl ester were prepared under microwave irradiations. These were converted to S-alky/S-benzyl-1,4- dihydropyrimidines for synthesizing biologically active molecules with improved activity. These are regarded as aza-analog of nifedipine. These compounds were screened for their anti-hypertensive activity. All the synthesized compounds have been characterized on basis of their spectral data.*

**Keywords**: substituted 1,4-dihydropyrimidines, microwave irradiation, smooth muscle relaxant.

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## INTRODUCTION

Biginelli reaction is acid-catalyzed condensation of ethyl acetoacetate, benzaldehyde, and urea in ethanol by refluxing the mixture resulting in formation of 3,4-dihydropyrimidin-2(1*H*)-one. Recently much advanced techniques were introduced in classical reactions with modification in reaction conditions which resulted in introduction of new methods. Microwave assisted reactions are one such type which are gaining much interest as they save reaction time and at the same time produce good yield so biological screening of compounds can be carried out with much efficacy. Chemistry of pyrimidines and dihydropyrimidines appears very interesting and challenging to researchers owing to the broad range of biologically active compounds reported in past. Pyrimidine derivatives play a crucial role in biological activities as their ring system is present in several vitamins, enzymes and nucleic acids. These dihydropyrimidines show anti-microbial [1, 2], anti-inflammatory [3] and anti-ulcer activities [4]. Dihydropyrimidines have close structutural relationship to dihydropyridines. Dihydropyrimidines are commonly described as potent mimics of dihydropyridine calcium channel blockers [5], nifedipine. These calcium channel blockers mainly affect arterial vascular smooth muscle and lower blood pressure by causing vasodilation. These are used in treatment of various cardiovascular disorders [6]. Calcium channel blockers are mainly used in hypertension, angina and cardiac arrhythmias [7]. Biological activities of 1,4-dihydropyridine of nifedipine type are clinically proven. In view of this dihydropyrimidines were synthesized with improved activity than its aza-anlog, nifedipine.

## EXPERIMENTAL SECTION

Materials: Ethyl benzoyl acetate, aromatic aldehydes, ethanol, benzyl chloride, butyl bromide, NaOH, dimethyl sulphate, diethyl sulphate, conc HCl, thiourea.

Melting points are uncorrected and were determined in open capillaries. $^1$H NMR spectra were recorded on BRUKER ADVANCE II 400 NMR Spectrometer. The IR spectra were recorded on Perkin Elmer spectrum RX IFT-IR System. The mass spectra were obtained on JEOL 5x102/DA-6000 mass spectrometer. The microwave irradiated reactions were performed in domestic household microwave oven Samsung M1777N.

Synthesis of 6-phenyl-4-substituted phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-carboxylic acid ethyl ester

A mixture of ethyl benzoyl acetate (0.015 mole 2.4 g), thiourea (0.01 mole, 0.76 g), substituted aromatic aldehyde (0.01 mole), ethanol (5 ml) as energy transfer medium and HCl (0.5 ml) as a catalyst was irradiated in domestic microwave oven for 4 to 5 minutes. The reaction conditions were optimized. The reaction mixture was allowed to stand for 24-36 hours at room temperature. The solid separated was filtered under reduced pressure and recrystallised from methanol (Scheme 1). The reaction was followed by TLC and maximum yield was obtained at 30% microwave power level. Tetrahydropyrimidines were prepared by substituting different aromatic aldehydes (Table-1). The spectral data of compound (2a): $^1$H NMR ($CDCl_3$ + DMSO) δ: 9.2 (s, 1H, -NH), 8.8 (s, 1H, -NH), 6.8-7.5 (m, Ar-H), 5.3 (s, 1H, 4-CH), 3.8 (q, 2H, -O$\underline{CH_2}$-$CH_3$), 3.87 (s, 3H, -$OCH_3$), 0.8 (t, 3H, -$OCH_2\underline{CH_3}$). IR (Nujol) cm$^{-1}$: 3312 (O-H str.), 3150 (sec N-H str.), 1676 (C = O str. of ester), 1568 (C=C str. of aromatic ring), 1335 (C-N vib), 1134 (C=S str). Mass Fragments m/z: 384 (59.0%), 355 (54.04%), 311 (98%), 338 (16.65%), 324 (2.21%), 233 (15.39%), 187 (16.4%), 103 (100.0%), 77 (84%), 51 (43%). These thiones were converted to their enol derivatives (Table-2).

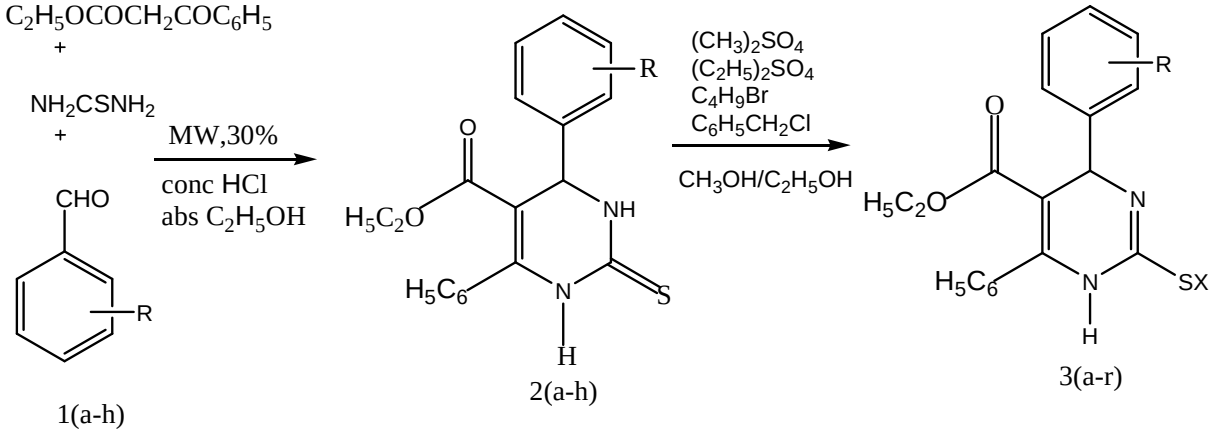
Synthesis of 6-phenyl-4-substituted phenyl-2S-methyl/ethyl-1,4-dihydropyrimidin-5-carboxylic acid ethyl ester
To tetrahydropyrimidine 2 (0.004 mole) which was dissolved in methanol was added NaOH solution which was prepared by dissolving NaOH (0.160 g) in water (2 ml). The mixture was cooled. To this mixture dimethyl sulphate (0.004 mole, 0.5 ml) or diethyl sulphate (0.004 mole, 0.6 ml) was added drop wise while stirring the reaction mixture continuously. Then the reaction mixture was refluxed for 3 hours (Scheme-1). The reaction mixture was cooled and poured over crushed ice. Solid separated was filtered under reduced pressure, dried and recrystallised from methanol. The spectral data of compound (3d): $^1$H NMR ($CDCl_3$ + DMSO) δ: 9.1 (s, 1H, -NH), 7.3-7.8 (m, Ar-H), 5.6 (s, 1H, 4-CH), 3.8 (q, 2H,-O$\underline{CH_2}CH_3$), 2.9 (s, 3H, S-$CH_3$), 0.8 (t, 3H,-O $CH_2\underline{CH_3}$). IR (KBr) cm$^{-1}$: 3171 (sec N-H str), 2970 (aromatic C-H str.), 1695 (C=O str. of ester), 1568 (C=C skeletal vib of aromatic ring), 1458 (C-N vib). Mass Fragments m/z: 381 (2.83 %), 352 (8.26 %), 308 (11.25 %), 259 (78.1 %), 231 (33.9 %), 187 (3.46 %), 122 (1.58 %), 76 (100.0%).

(3f): $^1$H NMR ($CDCl_3$ + DMSO) δ: 9.1 (s, 1H, -NH), 8.6 (s, 1H, -OH), 6.8-7.5 (m, Ar-H) 5.4 (s, 1H, 4-CH), 4.1 (m, 1H of S-$CH_2$), 3.9 (s, 3H, -$OCH_3$), 3.8 (q, 2H, -O $\underline{CH_2}$-$CH_3$), 3.3 (m, 1H of S-$CH_2$), 1.4 (t, 3H, S-$CH_2\underline{CH_3}$), 0.8 (t, 3H, -O $CH_2$-$\underline{CH_3}$). IR (KBr) cm: 3312 (O-H str), 3150 (sec N-H str.), 2954 (asym C-H str), 2924 (sym C-H str), 1676 (C=O str. of ester), 1452 (C=C str), 1373 (C-N vib), 1272 (C-O str). Mass Fragments m/z: 412 (0.99 %), 384 (12.08 %), 355 (14.71 %), 339 (5.92%), 337 (3.12 %), 311 (33.07 %), 103 (97.32 %), 77 (100.0%), 51 (57.72 %).

Synthesis of 6-phenyl-4-substituted phenyl-2S-benzyl-1,4-dihydropyrimidin-5-carboxylic acid ethyl ester
To tetrahydropyrimidine 2 (0.004 mole) which was dissolved in alcohol (5 ml), benzyl chloride (0.5 ml, 0.004 mole) was added and the reaction mixture was refluxed for 5 hours (Scheme-1). The mixture was cooled at room temperature. The solid separated was filtered under reduced pressure and recrystallised from ethanol. The spectral data of (3j): $^1$H NMR ($CDCl_3$ + DMSO) δ: 12.0 (s, 1H, -NH), 6.7-7.4 (m, Ar-H), 6.5(s, 1H, -OH), 5.8 (s, 1H, 4-CH), 4.8 (d, 1H of S-$CH_2$), 4.1 (d, 1H of S-$CH_2$), 3.8 (q, 2H, -O$\underline{CH_2}CH_3$), 0.8 (t, 3H,-$OCH_2\underline{CH_3}$). IR (KBr) cm$^{-1}$: 3500 (O-H str), 3265 (sec N-H str), 2962 (asym C-H str), 2812 (sym C-H str), 1715 (C=O str. of carbonyl gp.), 1520 (C=C str), 1220 (C-N vib), 1085 (C-O str).

Synthesis of 6-phenyl-4-substituted phenyl-2S-butyl-1,4-dihydropyrimidin-5-carboxylic acid ethyl ester
A mixture of tetrahydropyrimidine 2 (0.004 mole), butyl bromide (0.5 ml, 0.004 mole) and absolute alcohol (5 ml) was refluxed for 5 hours. The product was allowed to separate at room temperature. After 36-40 hours the product separated was filtered and recrystallised from methanol. The spectral data of (3n): $^1$H NMR ($CDCl_3$ + DMSO) δ: 11.3 (s, 1H, -NH), 10.7 (s, 1H, -OH), 6.8-7.4 (m, Ar-H), 5.9 (s, 1H, 4-CH), 3.9 (s, 3H, -$OCH_3$), 3.8 (q, 2H, -O $\underline{CH_2}CH_3$), 3.6 (m,1H of S-$CH_2$), 3.1 (m, 1H of S-$CH_2$), 1.2-1.4 (m, 4H, -S-$CH_2$-$\underline{CH_2}$-$\underline{CH_2}$-$CH_3$ of S-butyl), 0.9 (t, 3H, -$CH_3$ of S-butyl), 0.7 (t, 3H, -O $CH_2\underline{CH_3}$). IR (KBr) cm$^{-1}$:3508 (O-H str), 3289 (sec N-H str), 2957 (asym C-H str), 2800 (sym C-H str.), 1718 (C=O str. of ester carbonyl gp.), 1513 (C=C str.), 1215 (C-N vib), 1088 (C-O str).

Mass Fragments m/z: 440 (4.45%), 411 (5.8%), 383 (12.8%), 367 (16.34%), 317 (13.35%), 278 (1.83%), 89 (9.39%), 57 (58.7%), 41 (100%).




R= 2(a)4OH,3$OCH_3$(b)H(c)2$NO_2$(d)3$NO_2$
(e)4$NO_2$(f)2,3-(O-$CH_2$-O)(g)4-$OCH_3$(h)2OH

X=$CH_3$,$C_2H_5$,$CH_2(CH_2)_2CH_3$,$CH_2C_6H_5$

SHEME-1

**TABLE – 1 PHYSICAL CHARACTERIZATION DATA OF $2_{a-h}$**

| 2a-h | R | Time(min) | M.Pt(°C) | Yield(%) |
|---|---|---|---|---|
| $2_a$ | 4-OH, 3-$OCH_3$ | 4.0 | 227°C | 90% |
| $2_b$ | -H | 5.0 | 188°C | 86% |
| $2_c$ | 2-$NO_2$ | 4.5 | 238°C | 82% |
| $2_d$ | 3-$NO_2$ | 4.5 | 230°C | 84% |
| $2_e$ | 4-$NO_2$ | 4.5 | 234°C | 87% |
| $2_f$ | 2,3-(O-$CH_2$-O) | 4.0 | 192°C | 72% |
| $2_g$ | 4-$OCH_3$ | 5.0 | 168°C | 69% |
| $2_h$ | 2-OH | 4.0 | 215°C | 71% |

**TABLE – 2 PHYSICAL CHARACTERIZATION DATA OF (3a-r)**

| 3a-r | R | X | Time(hrs) | M.Pt(°C) | Yield(%) |
|---|---|---|---|---|---|
| $3_a$ | 2-$NO_2$ | $CH_3$ | 3.0 | 168°C | 66% |
| $3_b$ | H | $CH_3$ | 3.0 | 159°C | 59% |
| $3_c$ | (4-OH,3-$OCH_3$) | $CH_3$ | 3.0 | 107°C | 52% |
| $3_d$ | 3-$NO_2$ | $CH_3$ | 3.0 | 121°C | 58% |
| $3_e$ | 4-$NO_2$ | $CH_3$ | 3.0 | 105°C | 56% |
| $3_f$ | (4-OH,3-$OCH_3$) | $C_2H_5$ | 3.0 | 208°C | 62% |
| $3_g$ | 3-$NO_2$ | $C_2H_5$ | 3.0 | 184°C | 55% |
| $3_h$ | 4-$OCH_3$ | $C_2H_5$ | 3.0 | 117°C | 51% |
| $3_i$ | 4-$NO_2$ | $C_2H_5$ | 3.0 | 191°C | 50% |
| $3_j$ | (4-OH,3-$OCH_3$) | $CH_2$-$C_6H_5$ | 5.0 | 140°C | 64% |
| $3_k$ | 2,3-(O-$CH_2$-O) | $CH_2$-$C_6H_5$ | 5.0 | 148°C | 54% |
| $3_l$ | 4-$NO_2$ | $CH_2$-$C_6H_5$ | 5.0 | 166°C | 61% |
| $3_m$ | 4-$OCH_3$ | $CH_2$-$C_6H_5$ | 5.0 | 157°C | 59% |
| $3_n$ | (4-OH,3-$OCH_3$) | $C_4H_9$ | 5.0 | 170°C | 67% |
| $3_o$ | H | $C_4H_9$ | 5.0 | 138°C | 56% |
| $3_p$ | 2-$NO_2$ | $C_4H_9$ | 5.0 | 160°C | 62% |
| $3_q$ | 4-$NO_2$ | $C_4H_9$ | 5.0 | 179°C | 59% |
| $3_r$ | 4-$OCH_3$ | $C_4H_9$ | 5.0 | 142°C | 57% |

## RESULTS AND DISCUSSION

Experiments were carried out on rat uterus [8] and rabbit heart [9]. Nifedipine was used as a standard drug for comparison. The activity is reported by measuring $IC_{50}$ values of these compounds on rat uterus and nifedipine was taken as standard drug for comparison. The molar dose which produces 50% relaxation is taken as $IC_{50}$ (inhibitory concentration). To study $K^+$ induced contractions experiments were conducted on female albino rats. Priming was done 24 hours prior to every experiment, by administration of diethylstilbestrol (DES), 0.1 mg/kg body weight, subcutaneously. Dissection was done and preparation mounted in De Jalon solution as per the method described by Ghosh [10]. Fine suspensions of the test compound in 1% carboxymethylcellulose were added in geometric doses (0.1, 0.2, 0.4, 0.8, 1.6) so as to obtain a cumulative dose response curve. Mean relaxing effect of increasing doses of compounds on $K^+$ induced contractions of isolated rat uterus were observed. The active compounds produced a dose dependent relaxant effect. 2f showed mean percentage inhibition 100% at bath conc of 128 μg/ml and 3k showed mean percentage inhibition 100 % at bath conc of 256 μg/ml. $IC_{50}$ in rat uterus for compound 2f is $1.38 \times 10^{-4}$ M and for compound 3k is $1.17 \times 10^{-4}$ M. It was found that all these compounds have dose dependent relaxant effect on the $K^+$ induced contractions of isolated rat uterus.

To see the effect on rabbit heart it was mounted as per the methods described by Burn [11] and Perry [12]. The heart was mounted in the Langedorff's assembly, perfused with oxygenated Ringer Locke solution at 37ºC. The effect of the test compounds on heart rate, amplitude and coronary flow was compared. There was significant increase in amplitude and coronary flow of these compounds at all doses (except for small decrease in amplitude in 3k at dose of 80 μg/ml). As these compounds cause increase in coronary flow as well as increase in amplitude, these compounds can be useful in conditions like congestive heart failure.

The stereochemical relationship between the aryl group and the dihydropyridine ring was found to be one of the factor affecting biological activity [13]. In the receptor bound conformation it has been proposed that the substituted aryl ring is positioned axially, perpendicular to and bisecting the boat like dihydropyridine or dihydropyrimidine ring [14] with 4-aryl substituent adopting synperiplanar (relative to $C_4$-H) orientation. It was presented that only left hand side of dihydropyridine or dihydropyrimidine to be essential for activity.

In the work carried out S-alkyl/S-benzyl derivative of 4-aryl-1,4-dihydropyrimidne is present on right side of boat shaped conformation. The right hand side cannot be ignored as changes on right hand side also changes activity to considerable extent.

## CONCLUSION

1,4-dihydropyrimidines were synthesized with phenyl group at position 6. All compounds were characterized on basis of IR, NMR and mass spectral data. This work shows that the compounds synthesized possess smooth muscle relaxing property like calcium channel blockers and their effective usage for congestive heart failure as they show increase in coronary flow and amplitude of rabbit heart. Nifedipine cannot be used in congestive heart failure as it decreases the force of contraction of heart.

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