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Research Article

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Synthesis of 1,4-dihydropyrimidines and their pharmacological role for congestive heart failure

Priyanka Pathak

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

ABSTRACT

Dihydropyrimidines are described as potent mimics of dihydropyridine calcium channel blockers. They are regarded as aza-analog of nifedipine related dihydropyridines. Tetrahydropyrimidines were prepared under microwave irradiations and were converted to S-alkyl-1,4-dihydropyrimidines. All synthesized compounds were characterized on basis of their spectral data. Synthesized compounds were tested on rat uterus and rabbit heart. These compounds show smooth muscle relaxing property on rat uterus and increase in coronary flow and amplitude of rabbit heart. These can be used in conditions like congestive heart failure unlike nifedipine which cannot be useful in such conditions.

Keywords: Tetrahydropyrimidines, dihydropyrimidines, anti-hypertensive, congestive heart failure.

INTRODUCTION

Pyrimidines have played an important role in medicinal chemistry. Pyrimidine derivatives [1, 2, 3] show wide range of pharmacological activities. These act as Central Nervous System depressant [4] and show anaesthetic [5], anti-convulsant [6], anti-bacterial [7, 8] and anti-viral [9] activities. Due to their biological importance these compounds have been the subject of considerable synthetic activity. The pyrimidine nucleus [10, 11, 12] occurs in a considerable number of natural products which are of vital importance to living organisms. In recent years much interest had been focused on aza-anologs of dihydropyridines such as dihydropyrimidines which shows a very similar pharmacological profile to classical dihydropyridine calcium channel modulators like nifedipine. Dihydropyrimidines possess coronary vasodilating activity [13, 14] because of their proven clinical activity in cardiovascular [15] medicine. These are available for treatment of various cardiovascular diseases [16, 17, 18]. These 4-Aryl-1,4-dihydropyridines were introduced into clinical medicine in 1975 and since then these have become indispensable for the treatment of cardiovascular diseases such as hypertension, cardiac arrhythmias or angina. In addition to their proven clinical utility in cardiovascular medicine, 1,4-dihydropyridines [19] are used as biological tool for study of voltage activated calcium channel structure and function [20]. In the plan of work that was carried out the main concern was synthesis of dihydropyrimidines and their derivatives which possess anti-anginal and vasodilator activities. Over the past few years several lead compounds have been developed which is superior in potency and duration of antihypertensive activity to classical dihydropyridine drugs and compare favourably with second generation analogues such as amlodipine and nicardipine.

EXPERIMENTAL SECTION

Materials: Benzoyl acetone, aromatic aldehydes, NaOH, dimethyl sulphate, diethyl sulphate, benzylchloride, butyl bromide, conc HCl, thiourea, ethanol.

Melting points are uncorrected and were determined in open capillaries. Thin layer chromatography was performed on Silica gel G (Merck). ^{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. For all the reactions chemicals of BDH standard were used. All solvents were distilled before use.

Synthesis of 5-benzoyl-6-methyl-4-substituted phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine:
A mixture of benzoyl acetone (0.015 mole 2.4 g), thiourea (0.01 mole, 0.76 g) and substituted aromatic aldehyde (0.01 mole) using ethanol (5 ml) as energy transfer medium and HCl (0.5 ml) as a catalyst were 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. The spectral data of compound 2a (Table-1) is as follows:

^{1}H NMR ($CDCl_3$ + DMSO) δ: 8.8 (s, 1H, -NH), 8.5 (s, 1H, -NH), 6.8-7.9 (m, 9H, Ar-H), 4.5 (s, 1H, -OH), 4.1 (s, 1H, 4-CH), 1.8 (s, 3H, 6-CH_3), also OH and NH protons got exchanged with D_2O. IR (Nujol) cm^{-1}: 3380 (O-H str.), 3208 (sec N-H str.), 3071 (aromatic C-H str.), 1669 (C=O str.), 1547 (C=C str.), 1449 (C=C str.), 1224 (C=S str.). Mass fragments m/z: 324 (100%), 309 (60%), 307 (21%), 231 (17%), 219 (40%), 105 (91%), 77 (60%).

Synthesis of 5-benzoyl-6-methyl-4-substituted phenyl-2-Smethyl/ethyl-1,4-dihydropyrimidine:
To tetrahydropyrimidine (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 3b and 3d (Table 2) are as follows:

(3b) ^{1}H NMR ($CDCl_3$+DMSO) δ: 10.9 (s, 1H, -NH), 7.3-7.6 (m, Ar-H), 5.8 (s, 1H, 4-CH), 2.7 (s, 3H, S-CH_3), 1.9 (s, 3H, 6-CH_3). IR (KBr) cm^{-1}: 3130 (sec N-H str.), 2945 (C-H str.), 1670 (C=O str.), 1590 (C=C str.), 1445 (C=C str.), 1350 (C-N vib). Mass Fragments m/z: 321 (40.8%), 245 (30.6%), 130 (4.1%), 115 (7.3%), 105 (100%), 77 (80.9%).

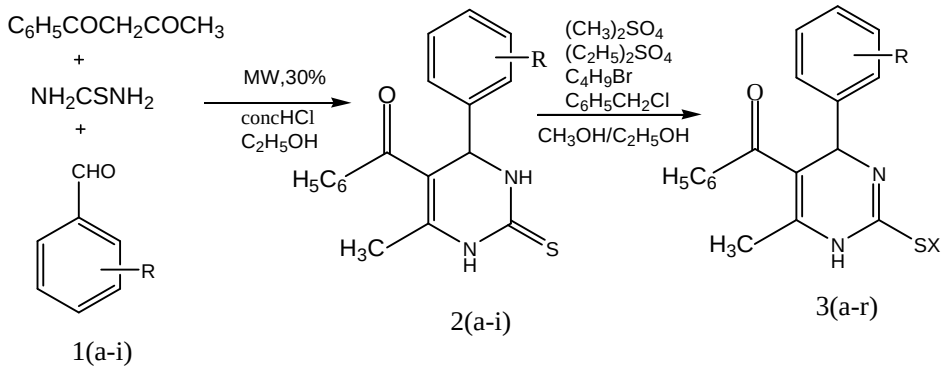
(3d) ^{1}H NMR ($CDCl_3$+DMSO) δ: 10.8 (s, 1H, -NH), 10.7 (s, 1H, -OH), 6.9-8.0 (m, 9H, Ar-H), 4.3 (s, 1H, 4-CH), 3.0-3.4 (m, 2H, -S$\underline{CH_2}$-CH_3), 1.8 (s, 3H, 6-CH_3), 1.2 (t, 3H,-SCH_2-$\underline{CH_3}$). IR (KBr) cm^{-1}: 3200 (sec N-H str), 3066 (O-H str), 2947 (C-H str.), 1685 (C=O str.), 1595 (C=C str.), 1484 (C=C str), 1392 (C-N vib). Mass Fragments m/z: 380 (5.0%), 363 (2.3%), 352 (48.5%), 335 (30.6%), 323 (20.4%), 275 (5.0%), 259 (20.9%), 105 (100.0%), 77 (62.6%).

Synthesis of 5-benzoyl-6-methyl-4-substituted phenyl-2-S-benzyl-1,4-dihydropyrimidine:
To tetrahydropyrimidine (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. The mixture was cooled at room temperature. The solid separated was filtered under reduced pressure and recrystallised from ethanol. The spectral data of 3m (Table 2) is:

^{1}H NMR ($CDCl_3$+DMSO) δ: 10.9 (s, 1H, -NH), 8.1 (s, 1H, -OH), 6.6-7.5(m, 13H, Ar-H), 5.7 (s, 1H, 4-CH), 4.9 (d, 1H, -SCH_2), 4.5 (d, 1H, S-CH_2), 1.9 (s, 3H, 6-CH_3). IR (KBr) cm^{-1}: 3282 (O-H str), 3180 (sec N-H str), 3030 (C-H str.), 1678 (C=O str.), 1521 (C=C str.), 1451 (C=C str), 1274 (C-N vib), 1032 (C-O str). Mass Fragments m/z: 411 (0.93%), 367 (2.67%), 123 (6.0%), 105 (9.2%), 91 (100%), 77 (22.7%).

Synthesis of 5-benzoyl-6-methyl-4-substituted phenyl-2-S-butyl-1, 4-dihydropyrimidine:
A mixture of powdered tetrahydropyrimidine (0.004 mole), butyl bromide (0.5 ml, 0.004 mole) and absolute alcohol (5 ml) was refluxed for 5 hours (Scheme-1). The product was allowed to separate at room temperature. After 36-40 hours the product separated was filtered under reduced pressure and recrystallised from methanol. The spectral data of 3q (Table 2) is as follows:

^{1}H NMR ($CDCl_3$+DMSO) δ:10.7 (s, 1H, -NH), 10.3 (s, 1H, -OH), 6.7-7.8 (m, 9H), 5.3 (s, 1H, 4-CH), 3.2 (m, 1H of S-CH_2), 3.6 (m, 1H of S-CH_2), 1.9 (s, 3H, 6-CH_3), 1.2-1.5 (m, S-CH_2-CH_2-CH_2-CH_3), 0.8 (t, 3H, -CH_3 of S-CH_2-CH_2-CH_2-CH_3). IR (KBr) cm^{-1}: 3280 (O-H str.), 3066 (sec. N-H str.), 2928 (aromatic C-H str.), 1685 (C=O str.), 1595 (C=C str.).



SCHEME 1

TABLE – 1 PHYSICAL CHARACTERIZATION DATA OF 2a-i

2a-i	R	Time(min)	M.Pt°C	Yield(%)
2_a	2-OH	4.0	240-241°C	89%
2_b	2-NO_2	4.5	208-209°C	75%
2_c	-H	5.0	228-230°C	79%
2_d	4-OH, 3-OCH_3	5.0	213-214°C	82%
2_e	3-NO_2	4.5	224-226°C	78%
2_f	4-NO_2	4.5	234-235°C	80%
2_g	2,4-(Cl)	5.0	204-205°C	69%
2_h	2,3-(O-CH_2-O)	4.0	186-187°C	70%
2_i	4-OCH_3	4.5	170-172°C	71%

TABLE – 2 PHYSICAL CHARACTERIZATION DATA OF 3_{a-r}

3a-r	R	X	Time(hrs)	M.Pt(°C)	Yield(%)
3_a	2-OH	CH_3	3.0	194-195°C	65%
3_b	-H	CH_3	3.0	151-152°C	62%
3_c	-H	C_2H_5	3.0	168-170°C	67%
3_d	2-OH	C_2H_5	3.0	159-160°C	64%
3_e	3-NO_2	C_2H_5	3.0	109-110°C	59%
3_f	4-NO_2	C_2H_5	3.0	118-120°C	56%
3_g	2,4-(Cl)	C_2H_5	3.0	124-125°C	52%
3_h	2-OH	CH_2-C_6H_5	5.0	152-154°C	63%
3_i	2,4-(Cl)	CH_2-C_6H_5	5.0	182-183°C	61%
3_j	2-NO_2	CH_2-C_6H_5	5.0	168-169°C	64%
3_k	3-NO_2	CH_2-C_6H_5	5.0	205-207°C	58%
3_l	4-NO_2	CH_2-C_6H_5	5.0	196-198°C	56%
3_m	4-OH,3-OCH_3	CH_2-C_6H_5	5.0	161-162°C	59%
3_n	-H	CH_2-C_6H_5	5.0	185-187°C	58%
3_o	4-NO_2	C_4H_9	5.0	178-179°C	55%
3_p	3-NO_2	C_4H_9	5.0	180-181°C	57%
3_q	2-OH	C_4H_9	5.0	124-125°C	61%
3_r	-H	C_4H_9	5.0	190-192°C	55%

The ultraviolet spectra of S-butyl, S-ethyl, S-methyl and S-benzyl did not show any bathochromic shift which would have been possible if the two double bonds in pyrimidine ring got conjugated in preparation of these derivatives. Further confirmation of the structure was done through PMR, IR and Mass spectral data which is completely in line with fragmentation of S-derivatives.

RESULTS AND DISCUSSION

To study the biological activity, experiments were conducted on rat uterus and rabbit heart. Nifedipine was used as a standard drug for comparison. The activity is reported by measuring IC_{50} values of these compounds on rat uterus. Female albino rats were used. Each rat was administered diethyl stilbesterol (DES) 0.2 mg/Kg body weight, subcutaneously. Each uterine horn was mounted in an organ bath containing Dejalon solution as described by Ghosh [21]. A suspension of investigational compound was individually prepared in 1% carboxy methyl cellulose. This suspension was added to bath in geometric doses (0.1, 0.2, 0.4, 0.8, 1.6) so as to obtain a cumulative dose response curve. The active compounds produced a dose dependent relaxant effect. The molar dose which produced 50% relaxation was taken as IC_{50} (inhibitory concentration).

Mean percentage inhibition caused by compound 3b at doses of 16 μg/ml, 32 μg/ml, 64 μg/ml was 44.3%, 93.9% and 100% respectively. For compound 3j mean percentage inhibition at doses of 16 μg/ml, 32 μg/ml, 64 μg/ml, 128 μg/ml was 23.9%, 82.6%, 94.6% and 100% respectively. For compound 3q mean percentage inhibition at similar doses was 7.69%, 60.84%, 92.30% and 100% respectively. IC_{50} in rat uterus for compound 3b is 0.53×10^{-4} M, for compound 3j is 0.52×10^{-4} M., for compound 3q is 0.74×10^{-5} M. It was found all these compounds have dose dependent relaxant effect on the K^+ induced contractions of isolated rat uterus.

The rabbit heart was mounted as per the methods described by Burn [22] and Perry [23]. The heart was mounted in the Langedorff's assembly and perfused with oxygenated Ringer Locke solution at 37ºC. The effect of the test compound on amplitude and coronary flow of isolated perfused rabbit heart was observed. There was significant increase in amplitude and coronary flow of compound IIIb, IIIj and IIIq at all doses. 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.

CONCLUSION

These compounds were found to have relaxing effect on the isolated rat uterus thus these compounds show smooth muscle relaxing property like that of known calcium channel blockers. There is increase in amplitude and coronary flow of isolated rabbit heart. So these compounds may be useful in the patients of congestive heart failure. The same property occurs in the medicine digoxin which is used by the patients of congestive heart failure while channel blockers like nifedipine decrease the force of contraction of heart so they cannot be useful in such conditions.

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REFERENCES

[1] KS Atwal; G Rovnyak; SD Kimball; DM Floyd; S Moreland; BN Swanson; JZ Gougoutas; J Schwartz; KM Smillie and MF Malley. *J. Med. Chem*., **1990**, 33(9), 2629-2635.
[2] H Cho; K Shima; M Hayashimatrsu; Y Ohnaka; A Mizuno; Y Takeuchi. *J. Org. Chem*., **1985**, 50, 4427.
[3] GJ Grover; D Dzwonczyk; DM McMullen; CS Normadinan; PG Sleph and S Moreland. *J. Cardiovasc. Pharmacol*, **1995**, 26(2), 289-294
[4] RR Astik; JN Acharya; GB Joshi and KA Thaker. *J. Indian Chem. Soc*. **1976**, 53, 272.
[5] AR Surrey. *J. Am Chem Soc*. **1949**, 71, 3354-3356.
[6] HD Troutman and LM Long. *J. Am Chem. Soc*. **1948**, 70, 346.
[7] NC Desai; HK Shukla; NA Langalia. and KA Thaker. *J. Indian Chem Soc*., **1984**, 71, 711.
[8] SB Kalaiya and AR Parik. *J. Indian Chem. Soc*. **1987**, 64, 172-175.
[9] AK Sengupta and AK Pandey, A.K. *J. Indian Chem. Soc*. **1988**, 65, 142.
[10] AU Siddiqui; AH Siddiqui and TS Ramaiah. *J. Indian Chem. Soc*, **1994**, 71, 107.

[11] M Kidwai, Y Goel; P Kumar and K Kumar. *Indian J. Chem*., **1997**, 36B, 782.
[12] RH Udupi; GV Suresh; SR Ramachandra and AR Bhart. *J. Indian Chem. Soc*., **2000**, 77, 302.
[13] K Folkers; HJ Harwood and TB Johnson. *J. Am. Chem. Soc*. **1932**, 54(9), 3751-3758.
[14] DJ Triggle. *J. Cardiovasc. Pharmacol*., **1989**, 27, 628.
[15] K Folkers. *J. Am. Chem. Soc*, **1936**, 58, 1558-1560.
[16] DJ Triggle. *Chirality*, **1996**, 8, 35-38.
[17] P Bellemann. *Innovative Approaches in Drug Research*. Elsevier. Amsterdam, **1986**, 23-46.
[18] F Bossert and W Vater. *Med. Res. Rev*., **1989**, 9, 291.
[19] RA Janis; PJ Silverand and DJ Triggle. *Adv. Drug. Res*., **1987**, 16, 309.
[20] S Goldman and J Stoltefuss. *Angew. Chem*., **1991**, 103, 1587-1605.
[21] MN Ghosh. Fundamentals of Experimental Pharmacology, 2nd edition, Scientific Book Agency, Calcutta, **1984**, 3-5, 22-23, 92-93.
[22] JH Burn. Practical Pharmacology, Blackwell Scientific Publication, Oxford, **1952**, 7-12, 25 and 30.
[23] WLM Perry. Pharmacological Experiments on Isolated Preparation, 2nd edition, E. & S. Livingstone, Edinburgh, **1970**, 116.