Microwave-assisted synthesis of some novel 1,4-dihydropyrimidine derivatives of biological interest

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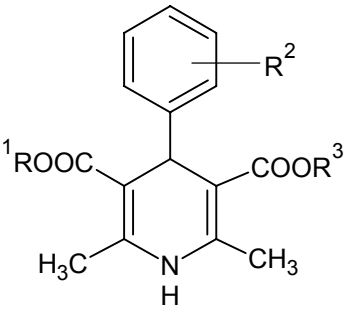
Abstract

Dihydropyrimidines are associated with broad spectrum of biological activities. In view of this 5-benzoyl-6-methyl-4-substituted phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidines were prepared under microwave radiations, and these tetrahydropyrimidines were then converted to S-alkyl-1,4-dihydropyrimidines. Synthesised compounds have been tested for anti-hypertensive activity and have shown some new results about structure-activity relationship.

Keywords: 1,4-Dihydropyrimidine, Antihypertensive compounds, aza-analogs of nifedipine, Microwave assisted synthesis

Introduction

Dihydropyrimidines represent a heterocyclic system with remarkable pharmacological efficiency and are described as potent mimics of dihydropyridine calcium channel blockers[1-4] e.g. Nifedipine (1). These compounds were first introduced into clinical medicine in 1975. Even today these medicines are used for the treatment of cardiovascular diseases.[5] Dihydropyrimidines of type 2 also showed similar activity with some new results when properly modified.[6-8,12]



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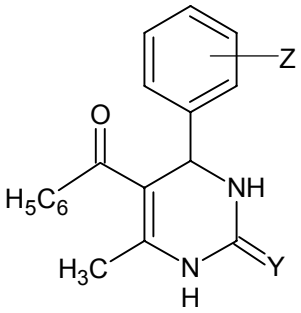

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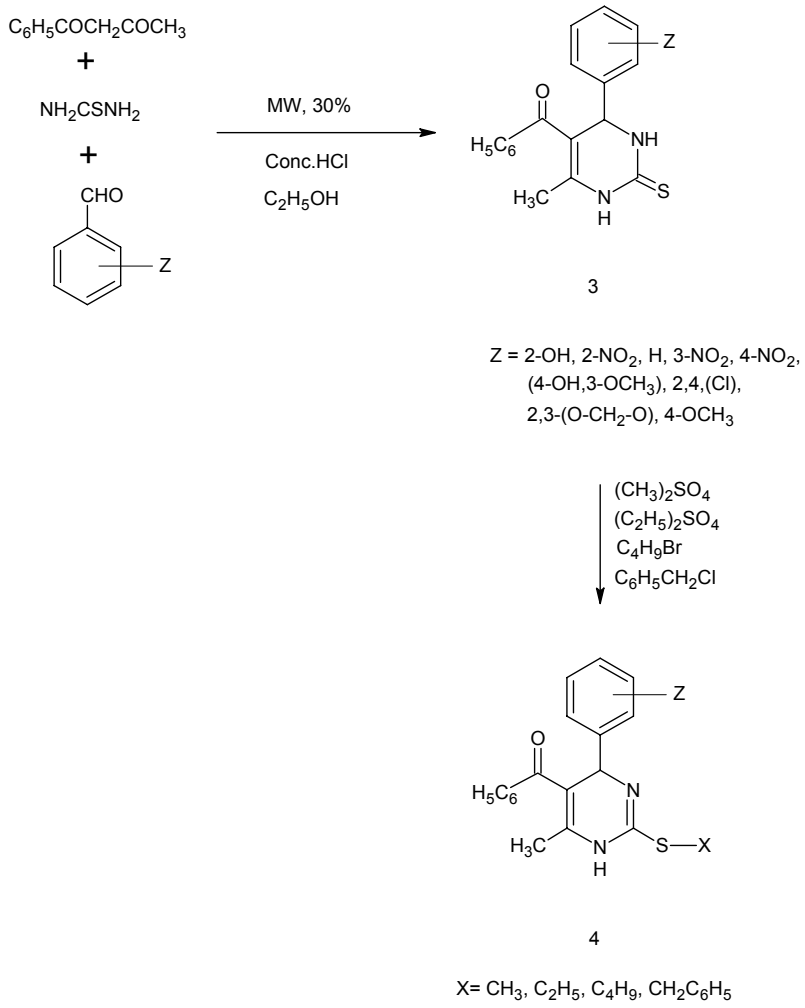
Y=O,S

Results and Discussion

As a correlation has been observed between the pharmacological activity of this class of calcium channel antagonist and the magnitude at 1,4-dihydro ring puckering. The observed ring distortions were found to be influenced to a great extent by the position of substituent in the 4-phenyl ring and the inter ring bond.[9] In receptor bound conformation[10] it has been presented that the changes on right hand side(R.H.S.) of the molecule do not affect the activity and hence the substitution on the right hand side was termed non-essential. But contrary to the earlier[10] report it has been proved by our laboratory[11,13] that one cannot ignore the structural details at the right-hand side also. These observations have increased our interest to synthesize some dihydropyrimidines 4 that can act as valuable substitutes for nifedipine. The changes were made in the substituents at position 2 and 5 of the pyrimidine ring.

The acid catalysed condensation of aromatic aldehyde, benzoyl acetone and thiourea was carried out in an open borosil glassbeaker. Ethanol was used as energy transfer media and the reaction mixture was irradiated in a domestic microwave oven for 4 to 5 minutes. The reaction conditions were optimized. The reaction was followed by TLC, and maximum yield was obtained at 30% microwave power level. Scheme – 1 shows the synthetic methodology leading towards novel types of conformationally restricted dihydropyrimidine derivatives of Table-1 and Table-2.



Scheme 1

Table 1. Synthesis of 5-benzoyl-6-methyl-4-substituted phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine

3a-i	Z	Time (minutes)	M-P^{0}C	% yield
3a	2-OH	4.0	240-241	89
3b	2-NO_2	4.5	208-209	75
3c	H	5.0	228-230	79
3d	4-OH, 3-OCH_3	5.0	213-214	82
3e	3-NO_2	4.5	224-226	78
3f	4NO_2	4.5	234-235	80
3g	2,4-(Cl)	5.0	204-205	69
3h	2,3-(O-CH_2-O)	4	186-187	70
3i	4-OCH_3	4.5	170-172	71

Table 2. Synthesis of 5-benzoyl-6-methyl-4-substituted phenyl-2-S-alkyl-1, 4-dihydropyrimidine

4a-r	Z	X	Time (hrs)	M-P^{0}C	Yield %
4a	2-OH	CH_3	3.0	194-195	65
4b	H	CH_3	3.0	151-152	62
4c	H	C_2H_5	3.0	168-170	67
4d	2-OH	C_2H_5	3.0	159-160	64
4e	3-NO_2	C_2H_5	3.0	109-110	59
4f	4-NO_2	C_2H_5	3.0	118-120	56
4g	2,4-(Cl)	C_2H_5	3.0	124-125	52
4h	2-OH	CH_2-C_6H_5	5.0	152-154	63
4i	2,4-(Cl)	CH_2-C_6H_5	5.0	182-183	61
4j	2-NO_2	$CH_2C_6H_5$	5.0	168-169	64
4k	3-NO_2	CH_2-C_6H_5	5.0	205-207	58
4l	4-NO_2	CH_2-C_6H_5	5.0	196-198	56
4m	4-OH, 3-OCH_3	CH_2-C_6H_5	5.0	161-162	59
4n	H	CH_2-C_6H_5	5.0	185-187	58
4o	4-NO_2	C_4H_9	5.0	178-179	55
4p	3-NO_2	C_4H_9	5.0	180-181	57
4q	2-OH	C_4H_9	5.0	124-125	61
4r	H	C_4H_9	5.0	190-192	55

Experimental Section

General Procedures. Melting points are uncorrected and were recorded in liquid paraffin-bath using open end capillaries. Thin layer chromatography was performed on Silicagel G (Merck). ^{1}H NMR spectra were recorded on AL-300F (Bruker), FTPMR Spectrometer. The IR spectra were recorded on Perkin-Elmer spectrum RX IFT-IR System. The mass spectra were obtained on a JEOL 5x102/DA-6000 mass spectrometer. All the compounds gave satisfactory elemental analysis within ±0.4% of theoretical values. The microwave irradiated reactions were performed in domestic household microwave oven Samsung M1777N. Characterisation data of the compounds are given in table 3.

Table 3. Characterization data of the synthesized compounds

Comp.	^{1}H NMR (δ, ppm); Mass
4a	10.7 (s, 1H, NH), 10.5 (s, 1H, -OH), 6.9-7.9 (m, 9H, Ar-H) 4.2 (s, 1H, 4-CH), 2.5 (s, 3H, S-CH_3), 1.8 (s, 3H, 6-CH_3) m/z 338 (94.5%) M^+, 321 (40.8%), 245 (30.6%), 233 (33.7%) 105 (100%), 77 (80.9%)
4b	10.9 (s, 1H, NH), 7.3-7.6 (m, 10H, Ar-H), 5.8 (s, 1H, 4-CH), 2.7 (s, 3H, S-CH_3), 1.9 (s, 3H, 6-CH_3) m/z 321 (40.8%) M^+, 245 (30.6%), 130 (4.1%), 115 (7.3%), 105 (100%), 77 (80.9%)
4c	11.0 (s, 1H, NH), 7.3-7.6 (m, 10H, Ar-H), 5.8 (s, 1H, 4-CH), 3.5 (m, 1H, S-CH), 3.4 (m, 1H, S-CH), 1.9 (s, 3H, 6-CH_3), 1.2-1.3 (t, 3H, S-CH_2-CH_3) m/z 334 (100%) M^+, 319 (22.3%), 231 (36.9%), 169 (7.9%); 153 (2.7%), 105 (44.3%), 77 (43.0%)
4d	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, SCH_2-CH_3), 1.8 (s, 3H, 6-CH_3), 1.2 (t, 3H, S-CH_2-CH_3) m/z 380 (5.0%) M^+, 363 (2.3%), 352 (48.5%), 335 (30.6%), 323 (20.4%), 275 (5.0%), 259 (20.9%), 105 (100%), 77 (62.6%)
4m	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, S-CH_2), 4.5 (d, 1H, S-CH_2), 1.9 (s, 3H, 6-CH_3), 3.7 (s, 3H, OCH_3) m/z 411 (0.93%), 367 (2.67%), 123 (6.0%), 105 (9.2%), 91 (100%), 77 (22.7%)
4n	10.7 (s, 1H, NH), 6.4-7.2 (m, 15H Ar-H), 5.1 (s, 1H, 4-CH), 4.6 (d, 1H, S-CH_2), 4.2 (d, 1H, -SCH_2), 1.7 (s, 3H, 6CH_3) m/z 398 M^+
4o	10.8 (s, 1H, NH), 6.7-7.6 (m, 9H Ar-H), 5.8 (s, 1H, 4-CH), 3.7 (m, 1H of S-CH_2), 3.2 (m, 1H of S-CH_2), 2.0 (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) m/z 409M^+
4r	10.7 (s, 1H, NH), 7.3-7.5 (m, 10H, Ar-H), 5.8 (s, 1H, 4-CH), 3.6 (m, 1H of S-CH_2), 3.2 (m, 1H, S-CH_2), 2.1 (s, 3H, 6-CH_3), 1.3-1.5 (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) m/z 364M^+

General procedure for 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) were subjected to microwave heating for 4-5 minutes using ethanol (5 ml) as energy transfer medium and HCl (0.5 ml) as a catalyst. In most cases the reaction on long standing for 24-36 hrs, afforded product 3a-i which was filtered under reduced pressure and recrystallised out of methanol.

3(a) ^{1}H NMR (300 MHz $CDCl_3$+DMSO) : δ8.8 (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) Mass fragments m/z : 324 (100%

M^+), 309 (60%), 307 (21%), 231 (17%), 219 (40%), 105 (91%) and 77 (60%). 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.).

General procedure for synthesis of 5-benzoyl-6-methyl-4-substituted phenyl-2-S-methyl/ethyl-1, 4-dihydropyrimidine

To tetrahydropyrimidine (0.004 mole) 3 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 dropwise while stirring the reaction mixture continuously. Then the reaction mixture was refluxed for 3 hrs. The reaction mixture was cooled and poured over crushed ice. Solid separated was filtered under reduced pressure, dried and recrystallised from methanol to give 4a-g. Spectral data are given in Table 3.

General procedure for synthesis of 5-benzoyl-6-methyl-4-substituted phenyl-2-*S*-benzyl-1, 4-dihydropyrimidine

To tetrahydropyrimidine 3 (0.004 mole) dissolved in alcohol (5 ml) was added benzyl chloride (0.5 ml, 0.004 mole) and the reaction mixture was refluxed for 5 hrs. The mixture was cooled at room temperature. The solid separated was filtered and recrystallised from ethanol to give 4h-n. Spectral data given in Table 3.

General procedure for synthesis of 5-benzoyl-6-methyl-4-substituted phenyl-2-S-butyl-1, 4-dihydropyrimidine

A mixture of powdered tetrahydropyrimidine 3 (0.004 mole), butyl bromide (0.5 ml, 0.004 mole) and absolute alcohol (5 ml) was refluxed for 5 hrs. Then the product was allowed to separate at room temperature. After a long standing of 36-40 hrs., the product separated was filtered under reduced pressure and recrystallised from methanol to give 4o-r. Spectral data is given in Table 3.

Biological activity

To study the biological activity, experiments were conducted on rat uterus and rabbit heart. Compounds 4b, 4j and 4q were screened for calcium channel blocking activity. Nifedipine was used as a standard drug for comparison. The activity is reported by measuring IC_{50} (inhibitory concentration, μg/mL) values of these compounds on female albino rat uterus. The results are presented in Table 4.

Table 4. Antihypertensive activity of synthesized compounds

Comp.	IC_{50} (Inhibitory concentration μg/mL)
4b	17 μg/ml
4j	22 μg/ml
4q	28 μg/ml

Potent Ca^{2+} channel blocking activity was found in this series of compounds-S-methyl derivative is the most potent calcium channel blocker as it has lowest IC_{50} value as is evident from Table 4.

In rabbit heart 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 (CHF) while other calcium channel blockers like nifedipine decrease the force of contraction of heart so cannot be useful in such conditions. The same property appears in commonly known drug digoxin.

Conclusions

On comparing S-methyl derivative of 1, 4-dihydropyrimidine with nifedipine, it has been found that it is most potent and S-methyl moiety is present on right side of the boat shaped conformation. This shows that one cannot ignore the structural details at right hand side as reported earlier.

Substitution with 2-NO_2, 2-OH in aromatic ring also changes biological activity.

When benzoyl group was substituted at position 5; it increased the force of contraction of heart, which made these compounds useful in congestive heart failure conditions.

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