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Synthesis of 4-(2-Methylthiazol-4-yl)-Hexahydroquinoline and 1,4-Dihydropyrimidin Derivatives

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Abstract

A series of new hexahydroquinoline and 1,4-dihydropyrimidine derivatives were synthesized. Condensation of 2-methyl- thiazole-4-carboxaldehyde (1) with 1,3-cyclohexanedione and alkyl 3- aminocrotonate afforded 4-(2-methyl-thiazol-4-yl)-hexahydroquinoline while condensation of aldehyde (1) with benzoyl acetone and thiourea gave 1,4-dihydropyrimidine derivatives. The stereochemistry of 1,4-dihydropyrimidine derivatives were studied using ^{1}HNMR.

Keywords: 1,4-Hexahydroquinoline; 1,4-Dihydropyrimidines; Thiazoles; 1,4-Dihydropyridine

Introduction

A major problem in chemotherapy of cancer is the development of resistance against anti tumor chemotherapy in many malignancies [1]. The introduction of potent Multi Drug Resistance (MDR) reversal agents such as NIK-250, N276-9, Nicardipine (Figure 1), and other 1,4-dihydropyridines (DHPs) stimulated the synthesis of novel dihydropyridine (DHP) derivatives [2].

1,4-dihydropyridines were classically prepared by the Hantzsch reaction [3] (Scheme1), in which the mixture of an aldehyde, β-dicarbonyl compound, and ammonia (or ammonium acetate) were refluxed in an alcohol for 12 to 36 hours. Later several methods were developed for the preparation of dihydropyridines in which an aldehyde was used as a source of substituent in the 4-position [4-7]. According to the *in vitro* study, a series of 1,4-dihydropyridines were introduced as MDR reversal agents that 2-methylthiazole ring was substituted at 4-position of DHP ring (Fig. 1, D). Also, a series of hexahydroquinolines derivatives showed MDR reversal properties on the culture media of S. aureus [9]. As a part of our ongoing program to design new DHPs [8-13], we report the synthesis of 1, 4-dihydropyridines having a substituted thiazoyl moiety in the 4-position from the corresponding 2-methylthiazol-4-carboxaldehyde. Furthermore a new series of 1,4-dihydropyrimidine derivatives containing a thiazole moiety in the 4-position are prepared *via* a Bginelli reaction.

Materials and Methods

Melting points were determined with a Reichert-Jung

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hot-stage microscope and are uncorrected. ^{1}H-NMR spectra were recorded on a 500 MHz Bruker spectrometer using $CDCl_3$ or DMSO-d_6 as solvent. Chemical shifts are reported in ppm relative to TMS as internal standard. Infrared spectra were acquired on a Nicolet Magna 550-FT spectrometer. Elemental microanalyses were within ± 0.4% of the theoretical values for C, H and N.

Aldehyde **1** was prepared as reported [7].

General procedure for the preparation of alkyl 2-methyl-5-oxo-4-(2-methyl-thiazol-4-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (3a-e)

A solution of aldehyde **1** (5 mmol), 1,3-dicyclohexanone (5 mmol), glacial acetic acid (0.5 mL), piperidine (0.2 ml) and benzene (50 mL) was refluxed for 24 h during which the water was removed via a Dean-Stark trap. Benzene was removed under reduced pressure. Alkyl aminocrotonate (5 mmol) and 20 ml of methanol were added. The solution was refluxed for 24 hours. After cooling, the precipitate was removed and recrystallized from methanol.

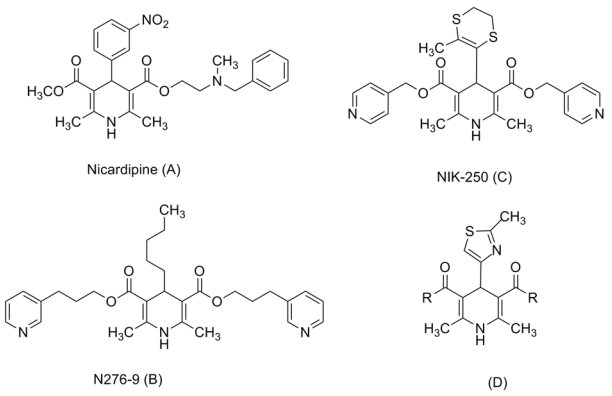
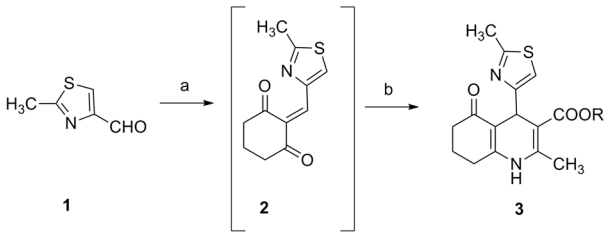


Figure 1. Structure of A) Nicardipine, B) N276-9, C) NIK-250 and D.



Scheme 1. The Pathway for the synthesis of 4-(2-methyl-thiazol-4-yl) derivatives (**3a-e**). Reagent and conditions: (a) 1,3-Cyclohexanedione, (b) Alkyl aminocrotonate.

Methyl2-methyl-4-(2-methylthiazol-4-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3carboxylate (3a)

Yield: 70%. m.p: 267-270 °C ; IR(KBr) ν cm^{-1}: 3265 (NH), 1697 (CO), 1650 (CO), 1630, 1507 (C=C); ^{1}HNMR($CDCl_3$) δ (ppm); 1.8-2.2 (m, 2H), 2.26 (s, 3H, CH_3), 2.60-2.90 (m, 4H), 2.64 (s, 3H, CH_3-thiazole), 3.63 (s, 3H, OCH_3), 5.34 (s, 1H, H_4), 7.06 (s, 1H, H-thiazole), 9.2 (bs, 1H, NH). Anal. Calcd. for $C_{16}H_{18}N_2O_3S$: C, 60.36; H, 5.70; N, 8.80. Found: C, 60.42; H, 5.86; N, 8.61.

Ethyl 2-methyl -4-(2-methylthiazol-4-yl)-5-oxo-1,4,5,6,7,8- hexahydroquinoline-3-carboxylate (3b)

Yield: 60 %. m.p: 230-232 °C ; IR(KBr): ν cm^{-1}: 3440 (NH), 1693 (CO), 1650 (CO), 1626, 1504 (C=C); ^{1}HNMR($CDCl_3$) δ (ppm); 1.21 (t , J = 7.5 Hz , 3H , CH_3), 1.8-2.1 (m, 2H), 2.26 (s, 3H, CH_3), 2.30-2.60 (m, 4H), 2.68 (s, 3H, CH_3-thiazole), 4.03 (q, J = 7.5 Hz , 2H, CH_2), 5.35 (s, 1H, H_4), 7.09 (s, 1H, H-thiazole), 9.4 (bs, 1H, NH). Anal. Calcd. for $C_{17}H_{20}N_2O_3S$: C, 61.42; H, 6.06; N, 8.43. Found : C, 61.57; H, 6.25; N, 8.60.

Isopropyl 2-methyl -4-(2-methylthiazol-4-yl)-5-oxo-1,4,5,6,7,8- hexahydroquinoline-3-carboxylate (3c)

Yield: 27 % . m.p: 189-192 °C ; IR(KBr) ν cm^{-1}: 3458 (NH), 1693 (CO), 1652 (CO), 1622, 1509 (C=C); ^{1}HNMR($CDCl_3$) δ (ppm): 1.12 (d, J=7Hz , 3H , CH_3), 1.25 (d, J=7.0 Hz, 3H, CH_3), 1.8-2 (m, 2H), 2.26 (s, 3H, CH_3), 2.30-2.45 (m, 4H), 2.65 (s, 3H, CH_3-thiazole), 4.95 (sep. J=7.0 Hz, 1H , -$CH(CH_3)_2$), 5.35 (s, 1H, H_4), 7.10 (s, 1H, H-thiazole), 9.55 (bs, 1H, NH). Anal. Calcd. for $C_{18}H_{22}N_2O_3S$: C, 62.40; H, 6.40; N, 8.09. Found : C, 62.53; H, 6.22; N, 8.19.

Butyl 2-methyl -4-(2-methylthiazol-4-yl)-5-oxo-1,4,5,6,7,8- hexahydroquinoline-3-carboxylate (3d)

Yield: 13 %. m.p: 145-147 °C ; IR(KBr) ν cm^{-1}: 3450 (NH), 1708 (CO), 1693 (CO), 1627 (C=C); ^{1}HNMR($CDCl_3$) δ (ppm): 0.95 (t, J=7.5Hz , 3H, CH_3), 1.22-1.6 (m, 4H), 1.8-2 (m, 2H), 2.25 (s, 3H, CH_3), 2.36-2.45 (m, 4H), 2.60 (s, 3H, CH_3-thiazole), 4.05 (t, J=7.5 Hz , 2H, OCH_2), 5.25 (s, 1H, H_4), 6.95 (s, 1H, H-thiazole), 8.1 (bs, 1H, NH). Anal. Calcd. for $C_{19}H_{24}N_2O_3S$: C, 63.31; H, 6.71; N, 7.77. Found : C, 63.42; H, 6.63; N, 7.71.

Benzyl 2-methyl -4-(2-methylthiazol-4-yl)-5-oxo-1,4,5,6,7,8- hexahydroquinoline-3carboxylate (3e)

Yield: 28 %. m.p: 241-243 °C ; IR(KBr) ν cm^{-1}:

3170 (NH), 1734(CO), 1693 (CO), 1639 (C=C); ^{1}HNMR($CDCl_3$) δ (ppm): 1.8-2.0 (m, 2H, CH_2), 2.25 (s, 3H, CH_3), 2.40-2.65 (m, 4H, CH_2), 2.63 (s, 3H, CH_3-thiazole), 5.10 (2d, 2H, phenyl-CH_2-O), 5.34 (s, 1H, H_4), 6.92 (s, 1H, H-thiazole), 7.26-7.34 (m, 5H, phenyl), 9.2 (bs, 1H, NH). Anal. Calcd. for $C_{22}H_{22}N_2O_3S$: C, 66.98; H, 5.62; N, 7.10. Found : C, 66.76; H, 5.82; N, 7.32.

(6-Methyl-4-(2-methylthiazol-4-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)(phenyl) methanone (6)

A solution of aldehyde **1** (10 mmol), benzoylacetone **4** (10 mmol), concentrated H_2SO_4 (0.1 mL), thiourea **5** (1mmol) and methanol (50 ml) was refluxed for 24 h. The mixture was cooled and the precipitates were collected and crystallized from methanol to give 1.05 g (82%) of **6**.

m.p: 231-233 °C; IR(KBr) ν cm^{-1} : 3316, 3165 (NH), 1611 (CO), 1600, 1565 (C=C), 1200(C=S); ^{1}HNMR(DMSO-d_6) δ (ppm): 1.65 (s, 3H, CH_3), 2.60 (s, 3H, CH_3-thiazole), 5.40 (s. 1H, H_4), 7.12 (s, 1H, H-thiazole), 7.25-7.45 (m, 5H, phenyl), 9.6 (bs, 1H, NH), 10.25 (bs, 1H, NH). Anal. Calcd. for $C_{16}H_{15}N_3OS_2$: C, 58.33; H, 4.59; N, 12.76. Found : C, 58.45; H, 4.73; N, 12.67.

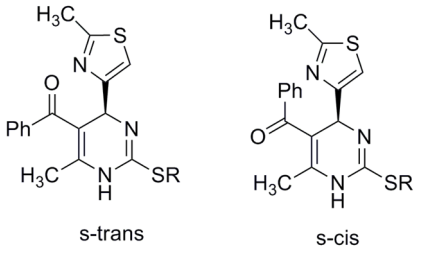
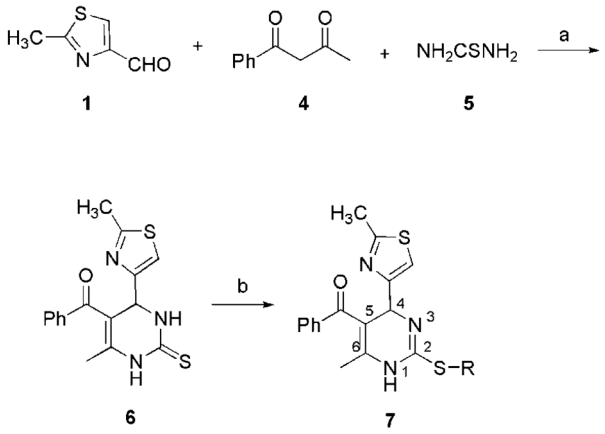


Figure 2. Conformational of dihydropyrimidines.



Scheme 2. The pathway for the synthesis of 4-(2-methyl-thiazol-4-yl)-dihydropyrimidine derivatives (**7a-d**). Reagent and conditions: (a) H^+/CH_3OH, (b) Alkyl iodide.

General procedure for preparation of (6-Methyl-4-(2-methylthiazol-4-yl)-2-(alkylthio)-1,4-dihydropyrimidin-5-yl)(phenyl) methanone (7a-d)

To a stirring solution of compound **6** (10 mmol) in acetone (50 ml), alkyl iodide (12 mmol) and triethylamine (1ml) were added and the mixture was stirred for 24 hours at room temperature. The solvent was removed under reduced pressure. The residue was crystallized from methanol or purified by column chromatography (CH_2Cl_2: EtOAc).

(6-Methyl-4-(2-methylthiazol-4-yl)-2-(methylthio)-1,4-dihydropyrimidin-5-yl)(phenyl)methanone (7a)

Yield: 99 %. m.p: 186-189 ^{o}C ; IR(KBr) ν cm^{-1}: 3453 (NH), 1715 and 1663 (CO), 1610, 1514 (C=C); ^{1}HNMR(DMSO) δ (ppm): 1.78 (s, 3H, CH_3), 2.65 (s, 3H, CH_3), 2.75 (s, 3H, CH_3), 5.7 (s, 1H, H_4), 7.45 (s, 1H, H-thiazole), 7.4-7.55 (m, 2H), 7.6-7.68 (m, 1H), 7.68-7.7 (m, 2H), 11.5 (bs, 1H, NH). Anal. Calcd. for $C_{17}H_{17}N_3OS_2$: C, 59.45; H, 4.99; N, 12.23. Found C, 59.36; H, 4.77; N, 12.38.

(6-methyl-4-(2-methylthiazol-4-yl)-2-(ethylthio)-1,4-dihydropyrimidin-5-yl)(phenyl)methanone (7b)

Yield: 77 %. m.p: 139-142 ^{o}C ; IR(KBr) ν cm^{-1}: 3473 (NH), 1711 and 1648 (CO), 1613 (C=C); ^{1}HNMR($CDCl_3$) δ (ppm): 1.3-1.36 (two t, *J*=8Hz, 3H), 1.85 and 1.92 (two s, 3H, CH_3), 2.62 and 2.64 (two s, 3H, CH_3-thiazole), 3.01-3.06 and 3.19-3.24 (two m, 2H, SCH_2), 5.65 and 5.85 (two s, 1H, H_4) 6.92 and 6.95 (two s, 1H, H-thiazole), 7.35-7.45 (m, 2H), 7.49-7.55 (m, 1H), 7.65-7.7 (m, 2H), 8.6 (bs, 1H, NH). Anal. Calcd. for $C_{18}H_{19}N_3OS_2$: C, 60.47; H, 5.36; N, 11.75. Found C, 60.53; H, 5.45; N, 11.66.

(6-Methyl-4-(2-methylthiazol-4-yl)-2-(n-propylthio)-1,4-dihydropyrimidin-5-yl)(phenyl)methanone (7c)

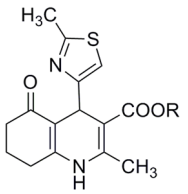
Yield: 62 %. m.p: 224-226 °C ; IR(KBr) ν cm^{-1}: 3319 (NH), 1714 and 1678 (CO), 1639, 1608 (C=C); ^{1}HNMR($CDCl_3$) δ (ppm): 1.3 (t, *J*=7.5Hz, 3H, CH_3), 1.65-1.71 (m, 2H, CH_2), 1.9 (s, 3H, CH_3), 2.61 and 2.63 (two s, 3H, CH_3-thiazole), 2.9-3.1 and 3.1-3.2 (two m, 2H, SCH_2), 5.7 and 5.9 (two s, 1H, H_4), 6.25 and 6.45

(two bs, 1H, NH), 6.78 and 6.95 (two s, 1H, H-thiazole), 7.35-7.41 (m, 2H), 7.45-7.50 (m, 1H), 7.65-7.7 (m, 2H). Anal. Calcd. for $C_{19}H_{21}N_3OS_2$: C, 61.42; H, 5.70; N, 11.31. Found C, 61.52; H, 5.78; N, 11.23.

(6-methyl-4-(2-methylthiazol-4yl)-2-(isopenthylthio)-1,4-dihydropyrimidin-5-yl)(phenyl)methanone (7d)

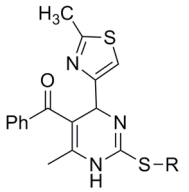
Yield: 39%. m.p: 237-239 °C ; IR(KBr) ν cm^{-1}: 3318 (NH), 1715 and 1674 (CO), 1637, 1602 (C=C); ^{1}HNMR($CDCl_3$) δ (ppm): 0.91-1.14 (m, 2×CH_3), 1.35-1.41 (m, 2H, CH_2), 1.68-1.71 (m, 1H, $CH(CH_3)_2$), 1.89 (s, 3H, CH_3), 2.63 (s, 3H, CH_3-thiazole), 3.15-3.2 and 3.28-3.35 (two m, 2H, SCH_2), 5.60 and 5.66 (two s, 1H, H_4), 5.66 (bs, 1H, NH), 6.92 (s, 1H, H-thiazole), 7.35-7.40 (m, 2H), 7.40-7.50 (m, 1H), 7.65-7.7 (m, 2H). Anal. Calcd. for $C_{21}H_{25}N_3OS_2$: C, 63.12; H, 6.31; N, 10.52. Found C, 63.22; H, 6.25; N, 10.38.

Table 1. Physical data for compound **3a-e**



Compounds	R	Yield%	mp °C
3a	Methyl	70 %	267-270
3b	Ethyl	60 %	230-232
3c	*i*-propyl	27 %	189-192
3d	*n*-butyl	13 %	145-147
3e	Benzyl	28 %	241-243

Table 2. Physical data for compound **7a-d**



Compounds	R	Yield%	mp °C
7a	Methyl	99 %	186-189
7b	Ethyl	77 %	139-142
7c	*n*-propyl	62 %	224-226
7d	*iso*-penthyl	39 %	237-239

Result and Discussion

According to the previous reports, several syntheses of 1,4-Dihydropyridine have been reported. Most of the symmetrical 1,4-Dihydropyridine-3,5-diesters were prepared by the well known Hantzsch reaction [3]. For asymmetrical analogues, a modified method was developed by Meyer et al. in which first an aldehyde was condensed with a β-dicarbonyl compound and then the ring was closed using alkyl 3-aminocrotonate [14]. Recently the preparation of 1,4-dihydropyridines under solvent free conditions was reported [15]. The condensation reaction between aldehyde and 1,3-cyclohexandion in the solid state by grinding has also been reported [16]. In our case however the latter procedures were also unsuccessful. We could prepare the compounds **3** through the modified method of Hantzsch reaction (Scheme 1, Table 1).

Pyrimidine derivatives were prepared using microwave-assisted solution or solid phase synthesis. A reaction condition was reported for preparing pyrimidine derivatives using an aldehyde, thiourea and β-ketocarbonyl compound in the presence of trimethylsilylchloride under microwave irradiation [17].

We have shown that the reaction of aldehyde **1** with benzoyl acetone and thiourea in methanol under reflux condition gave compound **6** in good yield. Alkylation of compound **6** with alkyl iodides in acetone gave **7a-d** in 39-99 % yield (Scheme 2, Table 2).

Many X-ray structural analysis and calculation of 1,4-dihydropyrimidine ring conformation showed preference for the boat form of the 1,4-dihydropyridine ring conformation with the 4-aryl substituent in the pseudo axial position and orthogonal to the plane of the dihydropyrimidine ring [18,19]. Further conformation could be visualized involving orientation of carbonyl group (Figure 2). The carbonyl group at C-5 is considered to be cis if its CO eclipses the adjacent double bound of the dihydropyrimidine ring (s-cis) and trans if its carbonyl group is oriented anti to the adjacent double bound (s-trans).

A looking the ^{1}HNMR data for compound **7a-d** shows an interesting output in stereochemistry of 1,4-dihydropyrimidine ring. In ^{1}HNMR spectra of **7b** for CH_3CH_2 group, CH_3 group at 6-position of dihydropyrimidine ring, CH_3 of thiazole ring, H4 and H-thiazole ring showed two different signals that could be referred to the existence of two orientation of CO group. In addition, when ^{1}HNMR spectra was acquired in DMSO, the spectra showed a simple resonance for the above mentioned protons. In DMSO either a fast equilibrium between two conformers (s-cis and s-trans) exist or one conformer is more stable than the other.

Acknowledgements

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